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Microwave Irradiated and Conventional Synthesis, Antibacterial Activity Evaluation Studies of Indole-Azole-Fluoroquinolone and Indole-Azole Hybrids

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Abstract: Tryptamine was converted to the corresponding 1,2,4-triazole, 1,3,4-oxadiazole, 5-oxo-1,3-thia(oxa)zolidine and 5-(4-chlorophenyl)-1,3-thia(oxa)zole derivatives via several steps. 1,3,4-oxadiazole and 1,2,4-triazoles were then converted to the corresponding Mannich bases containing fluoroquinolone core using a one-pot three-components procedure. Conventional and microwave-assisted methods were applied for all syntheses. All the newly synthesized compounds were screened for their antibacterial and most of them were found to have good-moderate antibacterial activity.

Keywords: Indole, hybrid compound, multicomponent, microwave, antibacterial activity.

Introduction

The increasing community- and hospital-acquired infectious diseases caused by resistant bacteria to most classes of antibacterial drugs resulted in a pressing and urgent need for designing of new antibiotic candidates. The declaration of The European Centre for Disease Prevention and Control (ECDC) reporting “Every year, the infections caused by resistant bacteria gives rise to 25,000 deaths with a cost of over 1.5 billion Euro because of healthcare spending and labor losses in the Europa” reveals that this is a public health problem with also socio-economic losses [1-5].

In recent years, to overcome the drug resistance problem, the concept of hybrid molecules, which contain two or more pharmacophore groups binding together covalently in one molecular framework, has been introduced in the medicinal chemistry field. These compounds that are obtained by molecular hybridization of several pharmacophore groups, act by inhibiting two or more conventional targets simultaneously, and this multiple target strategy has resulted in the development of a number of bioactive hybrid molecules with desired pharmacokinetic profile, therapeutic index and more importantly less tendency to resistance [6-11].

Heterocyclic compounds accepted as medicinally important products have given a new direction to new drug design and discovery studies. 1,2,4-Triazole, 1,3,4-oxadiazole and 1,3-thiazole derivatives which attract great attention by synthetic and medicinal chemists due to their distinct structures have been regarded as useful tools for drug discovery processes [12-14]. The compounds containing these heterocyclic units in their structures have been reported to possess a wide range of biological activities, such as antibacterial, antitubercular, antiviral, analgesic,

antioxidant, anticancer etc [15-18]. Another class of bioactive compounds, indoles exhibit several biological activities with high bioavailability and relatively low toxicity. Indole unit constitutes a part of several natural compounds isolated from marine creatures, medicinal plants or microorganisms. Although a number of studies devoted on the modifications of indole unit were reported, there are only a few studies about indole-azole hybrids. Based on the pharmacodynamic principle of superposition, it is accepted that the indole hybrids containing 1,3,4-oxadiazole and 1,2,4-triazole units at the position 3 exhibit efficient antibacterial activity [19, 20].

In the anti-infective chemotherapy field, fluoroquinolones which target two type II bacterial topoisomerase enzymes, DNA gyrase and/or topoisomerase IV, constitute a large and constantly expanding group of synthetic antibiotics. They have been attracting major interest due to broad-spectrum of activity towards both Gram (-) and Gram (+) bacteria by inhibiting bacterial DNA replication, and their chemotherapeutic efficacy [8-11]. In the concept containing the synthesis of new analogs or modifying existing drug compounds, new fluoroquinolones including large substituent at the position 7 were reported by several research groups [7, 21-25]. Microwave assisted techniques were reported to be more effective in terms of environment, reaction time, high yields, ease of work-up and isolation of products. Moreover, the environmentally polluting solvents with high boiling points which are often expensive, toxic, difficult to remove are not necessary most of the microwave assisted synthesis [26].

Recently, multicomponent reactions (MCRs) have received considerable attention by synthetic organic and medicinal chemists for the construction of complex molecules having biological activity. When compared with conventional organic reactions and

maximal structural complexity MCRs have some superior properties including high conversion rate, minimal reaction time and structural complexity. Thus, MCRs are also considered as green chemical processes [27]. Among these, Mannich reaction, a one pot three-component condensation reaction, provide synthetically and biologically important β -aminoalkylated compounds, which are important intermediates for the construction of various nitrogen-containing natural products and pharmaceuticals [28].

Thus, based on the aforementioned statements, this study focused on the design, ecofriendly synthesis,

and antibacterial activity evaluation of new indole-azole-fluoroquinolone hybrids based on pharmacophores hybridization. Indole scaffold was selected as the key prototype structural unit and the integration of indole skeleton, azole and fluoroquinolone pharmacophores we attempted to conventional and MW mediated green synthesizes of new indole-azole hybrid scaffold in the one molecular frame was performed as shown in figure 1 with the aim to prepare new antibacterial agents with preferably therapeutic profile having less tendency to antibacterial resistance.

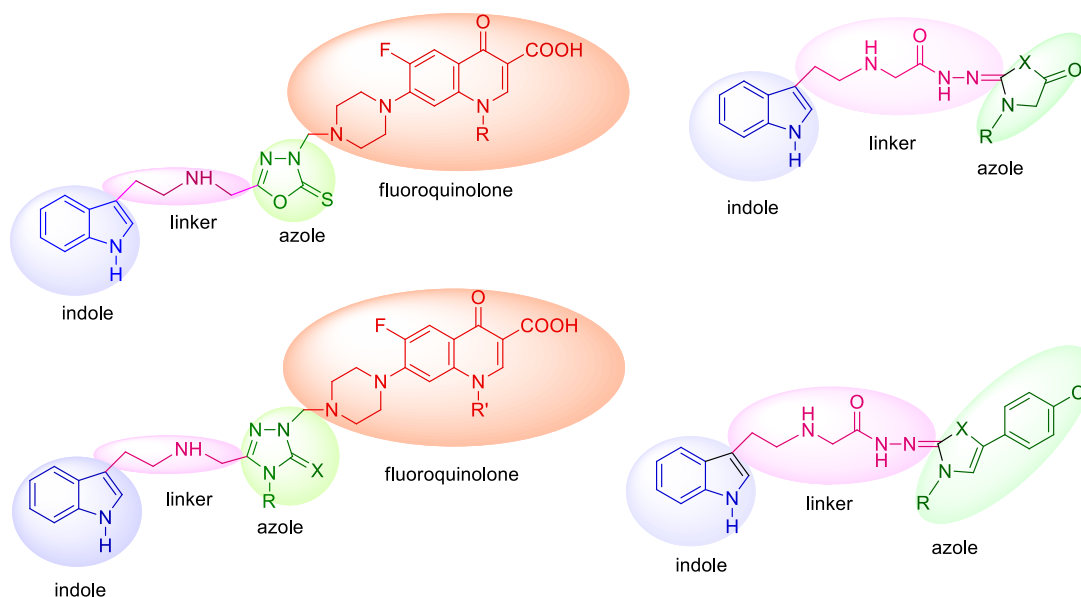


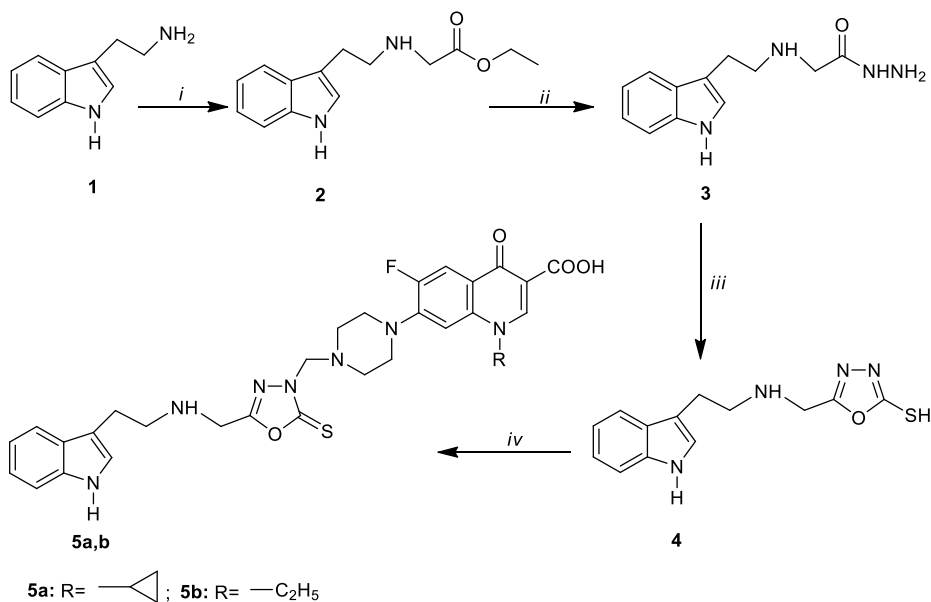
Figure 1. the targeted new hybrid drug candidates

Results and Discussion

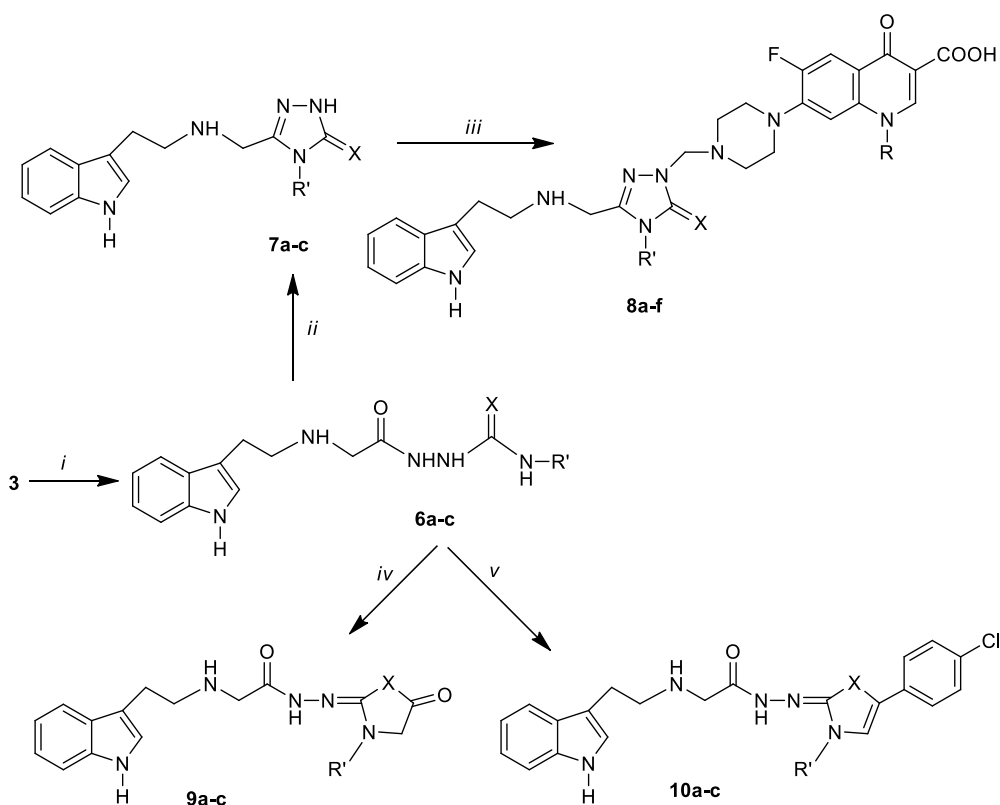
Chemistry

In this study, we attempted to conventional and MW mediated green synthesise of new indole-azole-fluoroquinolone hybrids as possible drug candidates with antibacterial activity. On the basis of ^1H , ^{13}C NMR, FT IR and EI-MS data, the structure of


the target products was established. All synthesized compounds were checked for purity and identity using elemental analysis. The MICs against clinically important Gram-negative and Gram positive pathogens were determined as well. The synthetic methodologies adopted to obtain the target compounds were depicted in Scheme 1 and Scheme 2.



Scheme 1. Reaction and conditions for the preparation of compounds 2-5. *i:* BrCH₂CO₂Et, THF, Et₃N, 24 h rt or MW (180 W), 10 min; *ii:* H₂NNH₂, H₂O, ref 15 h or MW (220 W) 6 min; *iii:* CS₂, KOH, EtOH, ref, 8 h or MW (250 W), 10 min; *iv:* norfloxacin or ciprofloxacin, HCHO, InCl₃, rt, 24 h or MW (100 W), InCl₃, 7 min.



6a, 7a, 8a, 8b, 9a, 10a: X=O, R' = -C₆H₅; **6b, 7b, 8c, 8d, 9b, 10b:** X=S, R' = -C₆H₅;

6c, 7c, 8e, 8f, 9c, 10c: X=S, R' = -CH₂C₆H₅; **8a, 8c, 8e:** R =  ; **8b, 8d, 8f:** R = -C₂H₅

Scheme 2. Synthetic pathway for the preparation of compounds 6-10. *i:* benzylisothiocyanate, phenylis(thio)cyanate, DCM, rt, 24 h or MW (150 W), 8 min; *ii:* NaOH+H₂O, ref. 6 h or MW (200 W), 18 min; *iii:* norfloxacin, ciprofloxacin, HCHO, InCl₃, DMF, rt 24 h or MW (100 W), InCl₃, 7 min; *iv:* BrCH₂CO₂Et, NaOAc, EtOH, ref 18 h or MW (180 W), 17 min; *v:* BrCH₂C₆H₄Cl(4-), NaOAc, EtOH, ref, 17-20 h or MW (200 W) 22 min.

The treatment of the starting compound, tryptamine [2-(1*H*-indol-3-yl)ethanamine], which was selected considering its biological importance [29-33], with ethyl bromoacetate to give ethyl 2-[2-(1*H*-indol-3-yl)ethylamino]acetate (**2**) was carried out under conventional and also microwave (MW) irradiated conditions with a view to maximizing the yield of the product and minimizing the reaction time. With the assessing of MW irradiated method, the yield of the reaction was improved to good level (87 %), however, more significantly, the reaction time for complete consumption of starting materials was lowered from 18 h with conventional stirring to a remarkable 10 min. Moreover, MW irradiated method with no solvent supplied more ecofriendly way. The structure compound **2** was confirmed by the disappearance of broad singlet for NH₂ and the presence of triplet at the region 1.90-1.93 ppm and a quartet at 2.85-2.89 ppm due to the presence of ethyl group protons in the ¹H NMR spectrum of compound **2**. This group appeared at 14.68 ppm (CH₃) and 61.18 ppm (CH₂) in the ¹³C NMR spectrum. Further, in the FT IR, the appearance of the stretching band due to C=O group at the region 1619 cm⁻¹ confirmed the formation of ester (**2**). The substitution of ester group by hydrazide generated 2-[2-(1*H*-indol-3-yl)ethylamino]acetohydrazide (**3**), which were confirmed by the appearance of broad signal for -NHNH₂ group in FT IR. Further, the protons of hydrazide function appeared at 3.93 (NH₂) and 10.94 ppm (NH) as D₂O exchangeable singlets confirming the formation of hydrazide. In order to optimize microwave (MW) irradiation conditions, MW was applied at different power values of 120 and 150 W without any solvent, while the conventional synthesis of compound **3** required ethanol as reaction solvent. The complete conversion of the compound **2** in best yield was observed after microwave irradiation at 220

W maximum power for 6 min. Higher MW power or longer reaction time caused to lower yields. Compound **3** gave the corresponding 1,3,4-oxadiazole derivative (**4**) upon the treatment with carbon disulfide in basic media. The ¹³C NMR observations revealed the appearance 1,3,4-oxadiazole C-2 and C-5 carbons at the region 166.19 ppm and 163.99 ppm confirming the formation of 1,3,4-oxadiazole [34, 35]. The stretching band characteristic for SH absorption was seen at 2921 cm⁻¹ in the FT IR spectrum. The signal observed at 13.69 ppm in the ¹H NMR spectrum was attributed the SH proton. On the other hand, the treatment of compound **3** with alkyliso(thio)cyanates produced the corresponding hydrazinecarbo(thio)amides (**6a-c**) with both conventional and MW irradiated method. In the conventional method, the reaction yielding compounds **6a-c** completed in 24 h in DCM with 86-91 % yield, while reaction time was 8 min with the yield 97-99 %. The structures of hydrazinecarbo(thio)amides were confirmed by the presence of additional signals at the related chemical shift values originated from alkyliso(thio)cyanate moiety. This compound exhibited mass fragmental and elemental analysis data confirming the assigned structures.

The basic treatment of compounds **6a-c** produced the corresponding 1,2,4-triazoles (**7a-c**), which can be considered as important tools for further condensation reactions leading to the formation of new bioactive molecules. The reaction was carried out in water-ethanol as a none toxic ecofriendly solvent mixture under reflux and also microwave conditions. With the use of MW conditions, higher yields and lower reaction times were assessed. Microwave irradiation decreased the reaction time from 6 h to 18 min and increased the yields from 56-63 % to 93-97 %. The optimum reaction condition was assessed at 200 W maximum power (Table 1).

Table 1. Time, Power and yield data for compounds **2-4**, **6a-c** and **7a-c**, **9a-c** and **10a-c**.

Comp.	Microwave irradiation Method			Conventional method	
	time (min)	Power (W)	Yield (%)	Time (h)	Yield (%)
2	10	180	87	24	69
3	6	220	97	15	70
4	10	250	96	8	73
5a	7	100	90	24	70
5b	7	100	92	24	70
6a	8	150	99	24	91
6b	8	150	97	24	91
6c	8	150	99	24	86
7a	18	200	93	6	61
7b	18	200	95	6	63
7c	18	200	97	6	56
9a	17	180	71	18	63
9b	17	180	63	18	57

9c	17	180	66	18	48
10a	22	200	72	18	45
10b	22	200	75	17	51
10c	22	200	73	20	49

The FT IR spectra of compounds **7a-c** have -C=S or C=O and -NH stretching bands at 1223-1284 cm^{-1} , 1683 cm^{-1} and 3163-3397 cm^{-1} , respectively. In the ^1H NMR spectra, resonances assigned to the -NH proton on 1,2,4-triazole ring were detected at 10.34-11.40 ppm (NH) which are supported by the literature findings^[36-40]. ^{13}C NMR spectra of these compounds have resonances of triazole C-5 and C-3 at 156.63-181.79 ppm and 153.21-171.51 ppm, respectively. The one-pot, three-component Mannich type reaction of compounds **4** and **7a-c** with norfloxacin and ciprofloxacin, which are fluoroquinolone class antibiotics, yielded the indole-azole-fluoroquinolone hybrids as new drug candidates (**5a,b** and **8a-f**) with best antibacterial activity. This reaction proceeds via the formation of immonium salt which subsequently attacks the *N*-1 of triazole or oxadiazole *N*-3 giving rise to the corresponding Mannich bases. In the preliminary experiment, to optimize the conditions for this condensation, the synthesis of compound **8a** was selected as model reaction and various reaction parameters including time, solvent and MW power

were screened on the model reaction (Table 2). With the aim to provide further improvement for this synthetic approach, the model reaction was also performed in the presence of polar solvents including THF, H_2O , EtOH, and DMF, however, the best result was assessed in solvent free media and the corresponding product was obtained in nearly quantitative yields within 10 min (Table 2, entry 10) in model reaction under microwave irradiation. Secondly, the effect of different catalyst on the reaction yield was screened (Table 2). For this purpose, several Bronsted and Lewis acids including *p*-TSA, FeCl_3 , InCl_3 , HCl were examined in the optimized reaction conditions (Table 2, entry 10) and completion of the reaction was monitored by TLC. The screening studies exhibited that the character of solvent and catalyst has no important influence on the reaction yield. Even so, quite good yields with 83% were obtained with InCl_3 (Table 2, entry 14). Furthermore, the TLC analysis showed that the duration of the reaction with catalyst was shorter 3 minutes than the non-catalytic reaction (Table 2, entry 14).

Table 2. Optimization of the model reaction conditions for compound **8a**.

Entry	Time (min)	Power (W)	Yield (%)	Solvent	Catalyst (10%)
1	20	200	66	THF	-
2	15	150	54	THF	-
3	20	150	75	EtOH	-
4	15	200	53	EtOH	-
5	10	100	42	H_2O	-
6	18	150	36	H_2O	-
7	10	100	63	DMF	-
8	15	100	58	DMF	-
9	15	120	75	-	-
10	10	100	78	-	-
11	8	100	79	-	<i>p</i> -TSA
12	8	100	79	-	FeCl_3
13	7	100	80	-	HCl
14	7	100	83	-	InCl_3

In comparison with the long refluxing time in hazardous solvent, microwave irradiation provided more efficient and green way for one pot Mannich type condensation with relatively higher product yield. The number of signals and their chemical shifts are in accordance with the assigned structures for the Mannich bases. In the ^1H and ^{13}C NMR spectra, additional signals corresponding to norfloxacin or

ciprofloxacin skeleton were recorded at the related chemical shift values, while the spectra of these compounds showed the disappearance of the characteristic bands of triazole (or oxadiazole)-NH. Moreover, the preparation of Mannich bases was verified by registration of their mass spectrums which were in accordance with their molecular masses and the

elemental analysis data (carbon, hydrogen and nitrogen)

Until today, several methods have been developed for the preparation of 1,3-thiazoles, however, Hantzsch synthesis containing the reaction of α -halogenocarbonyl components with the compounds including a thioamide function is the procedure most often referred to. According to the accepted mechanism, the attack of sulfur atom of thioamide, which is present in its ene- thiole form to the halogen atom of carbonyl compound, and this attack is followed by HBr and H₂O elimination, which leads to the 1,3thiazole ring formation [36].

As different from the classical Hantzsch reaction, the fact that hydrazinecarbo(thio)amides synthesized in the present study (**6a-c**) have more than one nucleophilic center and 2-bromo-1-(4-chlorophenyl)ethanone, that is the carbonyl component in this reaction has two position for nucleophilic attacks, can cause the formation of different structural isomers; each of them can exist as their individual *E* and *Z* geometrical. [3, 4, 37-40].

In our previous studies [37, 38, 40], to identify the exact structure of type of compounds **10a-c**, full geometric optimization of the possible isomer products was obtained by DFT/B3LYP (density functional theory with B3LYP-the hybrid Becke's three parameter functional and Lee-Yang-Parr exchange-correlation potential) method with the 6-31G (d,p) basis set and

were $\pm 0.4\%$ of the theoretical values.

the structure of the molecules was also investigated in detail. According to the obtained results [37, 38], the most stable product is *Z* geometrical isomer with the calculated relative energy 0.000 kcal mol⁻¹. Therefore, thermodynamically, the formation of *Z* isomers is more favorable. Similar case is present for compounds **9a-c**.

Antibacterial activity

All newly synthesized compounds were screened for their antibacterial activity and the results obtained were submitted in Table 3. Most of the compounds synthesized in the present study exhibited activity on the test microorganisms. Among them, **5a,b** and **8a-f** and which contain a fluoroquinolone nucleus in their structures, demonstrated excellent activities on Gram positive and Gram negative bacteria of the test microorganisms with the mic values <0.24 $\mu\text{g/mL}$. Compound **4**, **6c** and **7c** demonstrated activity against *Mycobacterium smegmatis*(Ms), an atypical tuberculosis factor, with the mic values 62.5 $\mu\text{g/mL}$. No important activity was observed for the remaining compounds. According to the results presented in Table 3, it can be concluded that the superior antibacterial activity of compounds **5a,b** and **8a-f** is due to the presence of fluoroquinolone core in their structures.

Table 3. Screening for antibacterial activity of the newly synthesized compounds.

Comp. No	Microorganisms and Minimal Inhibitory Concentration ($\mu\text{g/mL}$)						
	Ec	Yp	Pa	Sa	Ef	Bc	Ms
2	-	-	-	250	-	-	-
3	250	-	-	-	-	-	-
4	250	-	-	250	-	-	62.5
5a	<0.24	<0.24	<0.24	<0.24	<0.24	<0.24	-
5b	<0.24	<0.24	<0.24	<0.24	<0.24	<0.24	-
6a	-	-	-	-	-	-	-
6b	-	-	-	-	-	-	-
6c	250	-	-	-	-	-	62.5
7a	-	-	-	-	-	-	-
7b	-	-	-	-	-	-	-
7c	-	-	-	-	-	-	62.5
8a	<0.24	<0.24	<0.24	<0.24	<0.24	<0.24	<0.24
8b	<0.24	<0.24	<0.24	<0.24	<0.24	<0.24	<0.24
8c	<0.24	<0.24	<0.24	<0.24	<0.24	<0.24	<0.24
8d	<0.24	<0.24	<0.24	<0.24	<0.24	<0.24	<0.24
8e	<0.24	<0.24	<0.24	<0.24	<0.24	<0.24	<0.24
8f	<0.24	<0.24	<0.24	<0.24	<0.24	<0.24	<0.24
9a	125	-	500	-	-	-	-
9c	-	-	-	-	-	-	-
10a	125	-	500	-	-	-	-
10c	500	-	500	-	-	-	-
Amp.	10	18	> 128	10	35	15	-
Strep.	-	-	-	-	-	-	4
Norf.	<0.24	<0.24	<0.24	<0.24	<0.24	<0.24	<0.24

Ec: *Escherichia coli* ATCC 25922, Yp: *Yersinia pseudotuberculosis* ATCC 911, Pa: *Pseudomonas aeruginosa* ATCC 43288, Sa: *Staphylococcus aureus* ATCC 25923, Ef: *Enterococcus faecalis* ATCC 29212, Bc: *Bacillus cereus* 702 Roma, Ms: *Mycobacterium smegmatis* ATCC607, *Saccharomyces cerevisiae* RSKK 251, Amp.: Ampicillin, Str.: Streptomycin, Norf.: Norfloxacin, (—): no activity.

Conclusion

This study reports the conventional and successfully developed microwave assisted synthesis of some new hybrid molecules containing several heterocyclic moieties having importance for biological activity. As compared with traditional method, microwave irradiation provided more efficient and clean procedure leading to the formation of the target compounds. Hence, we combined all these potential chemotherapeutic units, namely indole, 1,3,4-oxadiazole, 1,2,4-triazole, fluoroquinolone and/or 1,3-thiazole moieties. with the aim to obtain new drug candidates with antibacterial activity. The antimicrobial screening suggested that the compounds containing fluoroquinolone core exhibited excellent activities against most of the test microorganisms.

Materials and Methods

Chemistry

All the chemicals were purchased 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 aluminium sheets. The mobile phase was ethyl acetate/diethyl ether 1:1 and detection was made using UV light. FT-IR spectra were recorded as potassium bromide pellets using a Perkin Elmer 1600 series FTIR spectrometer. ^1H NMR and ^{13}C NMR spectra were registered in DMSO- d_6 on a Bruker Avance II 400 MHz NMR spectrometer (400.13 MHz for ^1H 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. All the compounds gave C, H, and N analyses within $\pm 0.4\%$ of the theoretical values. The mass spectra were obtained on a Quattro EI-MS (70 eV) instrument. Physical parameters for synthetic procedures were given in Table 1.

Ethyl 2-(2-(1H-indol-3-yl)ethylamino)acetate (2)

Method 1. To a solution of the corresponding compound **1** (10 mmol) in tetrahydrofuran, triethylamine (20 mmol) and ethyl bromoacetate (10 mmol) were added and the mixture was stirred at room temperature for 24 hours. The precipitate was removed by filtration and the resulting solution was evaporated under reduced pressure to dryness. The crude product obtained was purified by column chromatography (silica gel, hexane/ethyl acetate 7:3).

Method 2. The mixture of ethyl bromoacetate (10 mmol), compound **1** (10 mmol) and triethylamine (20 mmol) was irradiated in monomod microwave reactor

in closed vessel with pressure control (Table 1). The crude product obtained was purified by column chromatography (silica gel, hexane/ethyl acetate 7:3). FT-IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 3243 (NH), 1732 and 1619 (C=O), 1117 (C-O). ^1H NMR (DMSO- d_6 , δ ppm): 1.90-1.93 (3H, m, CH_3), 2.85-2.89 (4H, m, 2CH_2), 3.31 (2H, s, CH_2), 3.51 (2H, s, CH_2), 6.96-7.09 (3H, m, arH), 7.37 (1H, d, $J = 8.0$ Hz, arH), 7.53 (1H, d, $J = 8.0$ Hz, CH), 10.85 (2H, s, 2NH). ^{13}C NMR (DMSO- d_6 , δ ppm): 14.68 (CH_3), 45.48 (CH_2), 52.14 (CH_2), 61.18 (CH_2), 69.90 (CH_2), arC: [101.42 (CH), 104.99 (CH), 108.45 (CH), 121.10 (CH), 122.19 (CH), 130.23 (C), 145.75 (C), 154.49 (C)], 172.11 (C=O). EI MS m/z (%): 130.80 (100), 195.88 (68), 152.83 (64), 196.89 (54), 124.80 (43), 162.84 (42), 208.90 (38), 190.94 (37), 210.90 (23), 283.05 ($[\text{M}+2+\text{K}]^+$, 19).

2-(2-(1H-Indol-3-yl)ethylamino)acetohydrazide (3)

Method 1. A solution of compound **2** (10 mmol) in ethanol was refluxed with hydrazine hydrate (25 mmol) for 15 h. The crude product obtained was purified by column chromatography (silica gel, hexane/ethyl acetate 7:3).

Method 2. The solution of compound **2** (10 mmol) in hydrazine hydrate (25 mmol) was irradiated in a monomod microwave reactor in closed vessel with the pressure control (Table 1). The crude product obtained was purified by column chromatography (silica gel, hexane/ethyl acetate 7:3).

FT-IR (ν_{max} , cm^{-1}): 3259 (NH_2+3NH), 3052 (aromatic CH), 1666 (C=O). ^1H NMR (DMSO- d_6 , δ ppm): 2.74 (2H, d, $J = 4.0$ Hz, CH_2), 2.77-2.81 (2H, m, CH_2), 3.13 (2H, s, CH_2), 3.93 (2H, brs, NH_2), 6.94-6.98 (1H, m, arH), 6.99-7.07 (1H, m, arH), 7.12-7.33 (1H, m, arH), 7.35 (1H, s, arH), 7.51 (1H, d, $J = 8.0$ Hz, CH), 10.82 (2H, s, 2NH), 10.94 (1H, s, NH). ^{13}C NMR (DMSO- d_6 , δ ppm): 50.03 ($\text{CH}_2\text{-NH}$), 51.26 (CH_2), 57.97 (CH_2), 111.80 (CH), arC: [118.66 (CH), 118.76 (CH), 121.33 (CH), 123.01 (CH), 127.72 (C), 136.70 (C), 169.85 (C)], 170.86 (C=O). EI MS m/z (%): 144.18 (100), 233.29 ($[\text{M}+1]^+$, 21), 117.27 (18), 145.31 (12).

5-[[2-(1H-Indol-3-yl)ethylamino]methyl]-1,3,4-oxadiazole-2-thiol (4)

Method 1. CS_2 (10 mmol) was added to the solution of compound **3** (10 mmol) in ethanol-water (1:1) and the mixture was refluxed in the presence of KOH (10 mmol) for 8 h. Then, the resulting solution was cooled to room temperature and acidified to pH 4 with 37% HCl. The solid precipitate was collected by filtration and recrystallized from methanol to give the pure compound.

Method 2. The mixture of compound **3** (10 mmol), CS_2 (10 mmol) and KOH (10 mmol) in ethanol-water (1:1) was irradiated in monomod microwave reactor in closed vessel with pressure control (Table 1). Then, the

resulting solution was cooled to room temperature and acidified to pH 4 with 37% HCl. This was collected by filtration and recrystallized from methanol to give the pure compound. FT-IR ($\nu_{\max}/\text{cm}^{-1}$): 3247 (NH), 2921 (SH), 1456 (C=N). $^1\text{H NMR}$ (DMSO- d_6 , δ ppm): 1.07 (2H, s, CH₂), 3.15 (2H, s, CH₂), 3.95 (2H, s, CH₂), 6.99-7.06 (3H, m, arH), 7.08-7.17 (1H, m, arH), 7.34 (1H, d, $J=8.0$ Hz, CH), 10.85 (1H, s, NH), 10.90 (1H, s, NH), 13.69 (1H, s, SH). $^{13}\text{C NMR}$ (DMSO- d_6 , δ ppm): 45.32 (CH₂), 46.42 (CH₂), 50.27 (CH₂), arC: [110.43 (C), 112.03 (CH), 118.89 (CH), 121.57 (CH), 123.28 (CH), 123.62 (CH), 127.57 (C), 136.71 (C)], 163.99 (oxadiazole C-5), 166.19 (oxadiazole C-2). EI MS m/z (%): 144.31 (100), 117.21 (34), 119.21 (21), 145.31 (12).

General Method for The Synthesis of Compounds **5a**, **5b**

Method 1. To a solution of corresponding compound **4** (10 mmol) in dimethyl formamide containing InCl₃ (1 mmol), ciprofloxacin (for **5a**) or norfloxacin (for **5b**) (10 mmol) was added and the mixture was stirred at room temperature in the presence of formaldehyde (30 mmol) for 24 h. The solid precipitate was filtered off, washed with water and recrystallized from dimethyl sulfoxide:water (1:1) to give the desired compound.

Method 2. The mixture consisting of compound **4** (10 mmol), ciprofloxacin (for **5a**) or norfloxacin (for **5b**), formaldehyde (30 mmol) and InCl₃ (1 mmol) was irradiated in monomod microwave reactor in closed vessel with pressure control at 100 W maximum power for 7 min. The obtained solid was washed with water and recrystallized from dimethyl sulfoxide:water (1:1) to give the desired compound.

7-[4-[(5-[(2-(1H-Indol-3-yl)ethylamino)methyl]-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)methyl]piperazin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**5a**). M.p. 183-185 °C. FT-IR (ν_{\max} , cm^{-1}): 3058 (aromatic CH), 1717 (C=O), 1664 (C=O), 1225 (C=S). $^1\text{H NMR}$ (DMSO- d_6 , δ ppm): 1.13 (2H, s, CH₂), 1.27 (2H, s, CH₂), 2.73 (4H, s, 2CH₂), 2.89 (4H, s, 2CH₂), 3.27 (2H, s, CH₂), 3.75 (2H, s, CH₂), 3.93 (2H, s, CH₂), 4.96 (2H, s, CH₂), 5.11 (1H, s, CH), 7.03-7.33 (3H, m, arH), 7.45-7.95 (3H, m, arH), 8.61 (2H, s, 2CH), 11.05 (2H, s, 2NH), 15.12 (1H, s, OH). $^{13}\text{C NMR}$ (DMSO- d_6 , δ ppm): 17.99 (2CH₂), 40.61 (2CH₂), 49.72 (2CH₂), 49.88 (2CH₂), 67.71 (2CH₂), 106.82 (CH), 107.17 (CH), 111.15 (CH), arC: [107.17 (2CH), 111.15 (CH), 118.63 (CH), 119.49 (CH), 121.87 (CH), 127.93 (C), 137.45 (C), 139.46 (C), 145.49 (C), 148.26 and 150.60 (C, d, $J_{C-F}=234.0$ Hz), 152.10 (C), 154.55 (C), 162.78 (C)], 148.10 (quinolone CH), 162.78 (oxadiazole C-2), 167.20 (oxadiazole C-5), 176.67 (C=O). EI MS m/z (%): 675.46 (100), 676.47 (50), 602.40 (36), 618.35 [(M+1), 35]⁺, 646.39 (19).

7-[4-[(5-[(2-(1H-Indol-3-yl)ethylamino)methyl]-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)methyl] piperazin-1-

yl]-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**5b**). Mp. 181-183 °C. FT-IR (ν_{\max} , cm^{-1}): 3058 (aromatic CH), 1711 (C=O), 1664 (C=O), 1234 (C=S). $^1\text{H NMR}$ (DMSO- d_6 , δ ppm): 1.35 (3H, s, CH₃), 2.67 (4H, s, 2CH₂), 2.89 (4H, s, 2CH₂), 2.27 (2H, s, CH₂), 3.95 (2H, s, CH₂), 4.53 (4H, s, 2CH₂), 4.96 (2H, s, CH₂), 7.05-7.18 (3H, m, arH), 7.57-7.60 (2H, m, arH), 7.95 (1H, s, arH), 8.86 (2H, s, 2CH), 11.00 (2H, s, 2NH), 15.30 (1H, s, OH). $^{13}\text{C NMR}$ (DMSO- d_6 , δ ppm): 14.73 (CH₃), 45.20 (CH₂), 47.85 (CH₂), 49.48 (2CH₂), 49.89 (2CH₂), 66.90 (2CH₂), 70.80 (CH₂), 106.30 (CH), 107.51 (C), 111.00 (CH), arC: [111.44 (CH), 111.67 (CH), 118.93 (CH), 119.64 (CH), 121.85 (CH), 122.10 (CH), 128.03 (C), 137.49 (C), 139.10 (C), 140.87 (C), 145.77 and 147.80 (C, d, $J_{C-F}=203.0$ Hz), 151.99 (C), 154.47 (C)], 148.79 (quinolone CH), 162.78 (oxadiazole C-5), 163.91 (oxadiazole C-2), 166.55 (C=O), 176.52 (C=O). EI MS m/z (%): 651.38 (100), 663.40 [(M+K+H₂O+1)⁺, 56], 652.38 (40), 576.42 (31), 664.33 (25), 695.37 (19).

General Method for The Synthesis of Compounds **6a-c**

Method 1. Benzylisothiocyanate (for **6c**), phenylisothiocyanate (for **6a**) or phenylisocyanate (for **6b**) (10 mmol) was added to the solution of compound **3** (10 mmol) in dried DCM drop wise and the mixture was stirred at room temperature for 24 h. The solid precipitate was collected by filtration and recrystallized from ethanol to afford the desired compound.

Method 2. Benzylisothiocyanate (for **6c**), phenylisocyanate (for **6a**) or phenylisothiocyanate (for **6b**) (10 mmol) was added to the solution of compound **3** (10 mmol) in dried DCM drop wise and the mixture was irradiated in monomod microwave reactor in closed vessel with the pressure control (Table 1). On cooling it to room temperature, a solid appeared. The crude product was recrystallized from acetone:diethyl ether (1:2, v/v) to give the desired product.

2-([2-(1H-Indol-3-yl)ethyl]amino)acetyl)-N-phenylhydrazinecarboxamide (**6a**). Mp. 255-256 °C. FT-IR (ν_{\max} , cm^{-1}): 3345 (5NH), 3044 (aromatic CH), 1770 and 1709 (2C=O). $^1\text{H NMR}$ (DMSO- d_6 , δ ppm): 3.01-3.04 (2H, m, CH₂), 3.58-3.68 (2H, m, CH₂), 4.17 (2H, s, CH₂), 7.03 (2H, d, $J=8.0$ Hz, arH), 7.10-7.26 (1H, m, arH), 7.33-7.40 (4H, m, arH), 7.46-7.50 (2H, m, arH), 7.59 (1H, d, $J=4.0$ Hz, CH), 10.90 (5H, s, 5NH). $^{13}\text{C NMR}$ (DMSO- d_6 , δ ppm): 23.72 (CH₂), 43.61 (CH₂), 50.08 (CH₂), arC: [111.42 (C), 111.96 (CH), 118.57 (CH), 118.85 (CH), 121.52 (CH), 123.43 (CH), 127.07 (2CH), 127.60 (C), 128.21 (2CH), 129.19 (CH), 132.76 (C), 136.74 (C)], 155.62 and 169.87 (2C=O). EI MS m/z (%): 339.51 [(M+2)⁺, 100], 358.47 (84), 358.28 (78), 302.66 (68), 308.98 (62), 359.41 (60), 342.58 (50), 361.41 (34), 378.55 (31), 343.52 (30).

2-([2-(1H-Indol-3-yl)ethyl]amino)acetyl)-N-phenylhydrazinecarbothioamide (**6b**). Mp. 148-149 °C. FT-IR (ν_{\max} , cm^{-1}): 3201 and 2989 (4NH), 1704 (C=O),

1210 (C=S). ¹H NMR (DMSO-*d*₆, δ ppm): 3.11 (2H, t, *J*= 16.0 Hz, CH₂), 4.04 (2H, t, *J*= 16.0 Hz, CH₂), 4.37 (2H, s, CH₂), 7.03-7.27 (2H, m, arH), 7.30-7.32 (3H, m, arH), 7.37 (1H, s, arH), 7.46-7.51 (3H, m, arH), 7.66 (1H, d, *J*= 4.0 Hz, CH), 10.94 (5H, s, 5NH). ¹³C NMR (DMSO-*d*₆, δ ppm): 22.80 (CH₂), 47.87 (CH₂), 53.37 (CH₂), 111.08 (C), 112.01 (CH), arC: [118.95 (3CH), 121.61 (2CH), 123.55 (2CH), 127.61 (C), 129.07 (2CH), 134.39 (C), 136.74 (C)], 171.11 (C=O), 181.88 (C=S). EI MS *m/z* (%): 368.29 (100), 369.36 (30).

N-Benzyl-2-({2-(1*H*-indol-3-yl)ethylamino}acetyl)hydrazinecarbothioamide (**6c**). Mp. 148-149°C. FT-IR (ν_{max}/cm⁻¹): 3374 and 3281 (5NH), 3061 (aromatic CH), 1732 (C=O), 1232 (C=S). ¹H NMR (DMSO-*d*₆, δ ppm): 3.09-3.06 (2H, m, CH₂), 4.00 (2H, t, *J*=8.0 Hz, CH₂), 4.28 (2H, s, CH₂), 4.79 (2H, d, *J*=4.0 Hz, CH₂), 6.98-7.09 (1H, m, arH), 7.23-7.29 (1H, m, arH), 7.32-7.37 (6H, m, arH), 7.60 (1H, m, arH), 8.68 (1H, brs, CH), 10.05 (2H, s, 2NH), 10.91 (3H, s, 3NH). ¹³C NMR (DMSO-*d*₆, δ ppm): 22.88 (CH₂), 44.75 (CH₂), 47.00 (CH₂), 52.82 (CH₂), 111.10 (CH), 127.97 (C), arC: [123.51 (CH), 127.19 (CH), 127.55 (CH), 127.78 (CH), 127.83 (CH), 128.60 (2CH), 128.61 (2CH), 136.81 (C), 139.90 (C), 152.17 (C)], 171.68 (C=O), 181.90 (C=S). EI MS *m/z* (%): 144.17 (100), 174.27 (40), 214.31 (31), 117.27 (30), 143.17 (28), 359.41 (12), 420.48 ([M+K]⁺, 11).

General Method for The Synthesis of Compounds **7a-c**

Method 1. The solution of the corresponding compound **6a-c** (10 mmol) in ethanol:water (1:1) was refluxed in the presence 100 mL of 2 % NaOH for 6 h. Then the resulting solution was cooled to room temperature and acidified to pH 4 with 37% HCl. The precipitate formed was filtered off, washed with water, and recrystallized from ethyl acetate to afford the desired compound.

Method 2. The mixture of the corresponding compound **6a-c** (10 mmol) and 2 % NaOH (100 mL) was irradiated in monomod microwave reactor in closed vessel with the pressure control (Table 1). Upon acidification of reaction content to pH 7 with 37% HCl, a white solid appeared. This crude product was filtered off, washed with water and recrystallized from ethyl acetate to afford the desired product.

3-{{2-(1*H*-Indol-3-yl)ethylamino}methyl}-4-phenyl-1*H*-1,2,4-triazole-5(4*H*)-one (**7a**). Mp. 135-136°C. FT-IR (ν_{max}/cm⁻¹): 3397 and 3275 (2NH), 3057 (aromatic CH), 1683 (C=O). ¹H NMR (DMSO-*d*₆, δ ppm): 2.99-3.02 (2H, m, CH₂), 4.35 (4H, brs, 2CH₂), 7.01-7.15 (5H, m, arH), 7.37 (2H, d, *J*=8.0 Hz, arH), 7.55 (2H, d, *J*=8.0 Hz, arH), 9.24 (1H, s, CH), 10.91 (2H, s, 2NH), 11.40 (1H, s, NH). ¹³C NMR (DMSO-*d*₆, δ ppm): 51.41 (CH₂), 66.71 (2CH₂), 107.02 (CH), arC: [107.27 (CH), 114.68 (CH), 118.73 (2CH), 119.85 (CH), 122.33 (2CH), 129.22 (2CH), 135.53 (C), 135.63 (C), 140.07 (C), 152.96 (C)], 155.42 (triazole C-3), 156.63 (triazole

C-5). EI MS *m/z* (%): 468.34 (100), 446.38 (43), 469.40 (31), 447.51 (17), 353.34 ([M+H₂O+2]⁺, 10).

3-{{2-(1*H*-Indol-3-yl)ethylamino}methyl}-4-phenyl-1*H*-1,2,4-triazole-5(4*H*)-thione (**7b**). Mp. 135-136°C. FT-IR (ν_{max}/cm⁻¹): 3161 (2NH), 3061 (aromatic CH), 1284 (C=S). ¹H NMR (DMSO-*d*₆, δ ppm): 3.07 (2H, t, *J*= 16.0 Hz, CH₂), 4.53 (2H, s, CH₂), 4.71-4.73 (2H, d, *J*=8.0 Hz, CH₂), 7.22 (1H, brs, arH), 7.29-7.30 (1H, m, arH), 7.31-7.37 (7H, m, arH), 7.66 (1H, d, *J*= 4.0 Hz, CH), 8.29 (1H, s, NH), 8.75 (1H, s, NH), 10.90 (1H, s, NH). ¹³C NMR (DMSO-*d*₆, δ ppm): 46.43 (CH₂), 50.29 (CH₂), 52.84 (CH₂), arC: [112.02 (CH), 115.07 (CH), 118.67 (CH), 118.94 (CH), 121.51 (CH), 123.49 (CH), 123.72 (CH), 127.22 (C), 127.57 (2CH), 128.74 (CH), 136.77 (C), 163.99 (C), 168.63 (C)], 171.51 (triazole C-3), 181.79 (triazole C-5). EI MS *m/z* (%): 361.41 (100), 364.29 (33), 372.30 ([M+Na]⁺, 31), 356.28 (20), 332.32 (18).

3-{{2-(1*H*-Indol-3-yl)ethylamino}methyl}-4-benzyl-1*H*-1,2,4-triazole-5(4*H*)-thione (**7c**). Mp. 135-136°C. FT-IR (ν_{max}/cm⁻¹): 3296 and 3239 (3NH), 3061 (aromatic CH), 1587 (C=N), 1223 (C=S). ¹H NMR (DMSO-*d*₆, δ ppm): 2.00 (8H, d, *J*=8.0 Hz, 4CH₂), 7.17 (2H, d, *J*=8.0 Hz, arH), 7.33 (3H, t, *J*=8.0 Hz, arH), 7.59 (4H, d, *J*=8.0 Hz, arH), 9.83 (1H, s, CH), 10.34 (2H, s, 3NH). ¹³C NMR (DMSO-*d*₆, δ ppm): 18.35 (CH₂), 22.27 (CH₂), 23.68 (CH₂), 25.51 (CH₂), 128.48 (CH), arC: [118.26 (2C), 129.08 (CH), 129.15 (CH), 129.25 (CH), 129.29 (CH), 129.40 (CH), 129.86 (CH), 130.00 (CH), 130.45 (CH), 130.53 (CH), 139.53 (2C)], 153.21 (triazole C-3), 176.82 (triazole C-5). EI MS *m/z* (%): 360.47 (100), 368.42 (49), 361.54 (36), 381.50 (34), 370.42 (13).

General Method for The Synthesis of Compounds **8a-f**

Method 1. To a solution of corresponding compound **7** (10 mmol) in dimethyl formamide containing InCl₃ (1 mmol), ciprofloxacin (for **8a**, **8c**, **8e**) or norfloxacin (for **8b**, **8c**, **8f**) (10 mmol) was added and the mixture was stirred at room temperature in the presence of formaldehyde (30 mmol) for 24 h. The solid precipitate was collected by filtration, washed with water and recrystallized from dimethylsulfoxide:water (1:1) to give the desired compound.

Method 2. The mixture consisting of the corresponding compound **7** (10 mmol), ciprofloxacin (for **8a**, **8c**, **8e**) or norfloxacin (for **8b**, **8c**, **8f**) (10 mmol), formaldehyde (30 mmol) and InCl₃ (1 mmol) was irradiated in monomod microwave reactor in closed vessel with the pressure control with 100 W maximum power for 7 min. The solid obtained was washed with water and recrystallized from ethyl acetate to give the desired compound.

7-{4-[(3-[(2-(1*H*-Indol-3-yl)ethylamino)methyl]-5-oxo-4-phenyl-4,5-dihydro-1,2,4-triazol-1-yl)methyl]piperazin-1-yl}-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**8a**). Mp.

183-185°C. FT-IR (ν_{\max} , cm^{-1}): 3269 (NH), 3063 (aromatic CH), 1719 (C=O), 1664 (C=O), 1599 (C=N). ^1H NMR (DMSO- d_6 , δ ppm): 1.18 (2H, s, CH_2), 1.31 (2H, s, CH_2), 2.09 (2H, s, CH_2), 2.70 (2H, s, CH_2), 2.73 (2H, s, CH_2), 2.89 (2H, s, CH_2), 3.71 (2H, s, CH_2), 3.82 (2H, s, CH_2), 4.58-4.62 (2H, m, CH_2), 4.91 (2H, s, CH_2), 6.97 (2H, s, arH), 7.25-7.29 (4H, m, arH), 7.48-7.62 (4H, m, arH), 7.89 (1H, s, arH), 8.66 (3H, d, $J=4.0$ Hz, 3CH), 9.34 (1H, s, NH), 10.60 (1H, s, NH), 15.21 (1H, s, OH). ^{13}C NMR (DMSO- d_6 , δ ppm): 8.02 (CH_2), 43.96 (CH_2), 48.39 (CH_2), 49.80 (CH_2), 49.96 (CH_2), 50.20 (CH_2), 63.05 (CH_2), 72.10 (CH_2), 75.17 (CH_2), 82.41 (CH_2), 119.89 (2CH), 120.12 (CH), arC: [120.22 (CH), 120.29 (CH), 120.37 (CH), 120.60 (CH), 120.90 (CH), 123.26 (CH), 128.80 (CH), 128.83 (2CH), 128.88 (2CH), 128.96 (C), 129.13 (C), 139.62 (C), 139.92 (2C), 140.85 (C), 152.86 and 154.05 (C, d, $J_{\text{C-F}}=119.0$ Hz), 154.37 (2C)], 154.71 (triazole C-3), 155.43 (triazole C-5), 166.38 (C=O), 176.83 (C=O). EI MS m/z (%): 685.56 (100), 685.81 (81), 684.31 (62), 675.52 (48), 699.37 [(M+Na), 25] $^+$, 717.51 [(M+K), 21] $^+$, 676.71 [(M), 15] $^+$.

7-[4-[(3-[(2-(1H-Indol-3-yl)ethylamino)methyl]-5-oxo-4-phenyl-4,5-dihydro-1,2,4-triazol-1-yl)methyl]piperazin-1-yl]-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (8b). Mp. 178-180°C. FT-IR (ν_{\max} , cm^{-1}): 3266 (NH), 3063 (aromatic CH), 1708 (C=O), 1663 (C=O), 1598 (C=N). ^1H NMR (DMSO- d_6 , δ ppm): 1.41 (3H, d, $J=4.0$ Hz, CH_3), 2.73 (4H, s, 2 CH_2), 2.89 (6H, s, 3 CH_2), 3.75 (4H, s, 2 CH_2), 4.59 (4H, s, 2 CH_2), 7.01-7.25 (3H, m, arH), 7.26-7.29 (4H, m, arH), 7.50 (4H, s, arH), 7.89 (2H, s, CH), 8.94 (1H, s, NH), 10.50 (1H, s, NH), 15.35 (1H, s, OH). ^{13}C NMR (DMSO- d_6 , δ ppm): 14.80 (CH_3), 36.24 (CH_2), 44.02 (CH_2), 61.31 (CH_2), 63.05 (CH_2), 72.11 (CH_2), 79.96 (2 CH_2), 82.41 (2 CH_2), 107.59 (2CH), arC: [120.14 (CH), 120.29 (CH), 120.37 (CH), 128.79 (2CH), 128.83 (3CH), 128.96 (3CH), 137.63 (2C), 139.57 (2C), 139.73 (2C), 140.85 (2C), 152.10 and 154.37 (C, d, $J_{\text{C-F}}=227.0$ Hz)], 154.60 (triazole C-3), 155.42 (triazole C-5), 166.56 (C=O), 176.62 (C=O). EI MS m/z (%): 685.56 (100), 686.63 (48), 688.45 [(M+Na) $^+$, 28], 683.49 [(M+H $_2$ O) $^+$, 17].

7-[4-[(3-[(2-(1H-Indol-3-yl)ethylamino)methyl]-4-phenyl-5-thioxo-4,5-dihydro-1,2,4-triazol-1-yl)methyl]piperazin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (8c). Mp. 188-189 °C. FT-IR (ν_{\max} , cm^{-1}): 3262 (OH), 3198 (NH), 3128 (NH), 3053 (aromatic CH), 1717 (C=O), 1663 (C=O), 1545 (C=N). ^1H NMR (DMSO- d_6 , δ ppm): 1.16 (2H, d, $J=8.0$ Hz, CH_2), 1.30 (2H, d, $J=8.0$ Hz, CH_2), 2.72 (2H, s, CH_2), 2.88 (2H, s, CH_2), 3.04 (2H, s, CH_2), 3.46 (2H, s, CH_2), 4.62 (2H, s, CH_2), 4.75 (2H, s, CH_2), 5.16 (2H, s, CH_2), 5.37 (4H, s, 2 CH_2), 7.23 (4H, d, $J=8.0$ Hz, arH), 7.48- 7.58 (7H, m, arH), 8.62 (1H, s, CH), 8.64 (1H, s, CH), 8.89 (1H, s, CH), 9.27 (1H, s, NH), 9.38 (1H, s, NH), 15.20 (1H, s, OH). ^{13}C NMR (DMSO- d_6 , δ ppm): 8.03 (CH_2), 31.24 (CH_2), 36.24

(CH_2), 36.28 (CH_2), 49.93 (CH_2), 50.11 (2 CH_2), 66.17 (2 CH_2), 68.77 (2 CH_2), 106.91 (CH), 111.25 (CH), arC: [111.48 (CH), 117.71 and 117.76 (CH, d, $J=5.0$ Hz), 118.39 (CH), 118.50 (C), 121.47 (CH), 122.15 (CH), 125.55 (C), 128.44 and 128.83 (CH, d, $J=39.0$ Hz), 129.11 (CH), 129.94 (2CH), 130.04 (CH), 130.12 (CH), 133.56 (C), 139.59 (C), 140.29 (2C), 147.68 and 150.01 (C, d, $J_{\text{C-F}}=233.0$ Hz), 162.77 (2C)], 148.36 (quinolone CH), 166.38 (triazole C-3), 166.94 (triazole C-5), 171.57 (C=O), 176.77 (C=O). EI MS m/z (%): 512.20 (100), 693.74 [(M+1) $^+$, 85], 631.85 (73), 378.72 (60), 436.90 (34).

7-[4-[(3-[(2-(1H-Indol-3-yl)ethylamino)methyl]-4-phenyl-5-thioxo-4,5-dihydro-1,2,4-triazol-1-yl)methyl]piperazin-1-yl]-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (8d). Mp. 180-181 °C. FT-IR (ν_{\max} , cm^{-1}): 3262 (OH), 3198 (NH), 3128 (NH), 3053 (aromatic CH), 1717 (C=O), 1663 (C=O), 1545 (C=N). ^1H NMR (DMSO- d_6 , δ ppm): 1.39 (3H, t, $J=8.0$ Hz, CH_3), 2.73 (2H, s, CH_2), 2.88 (4H, s, 2 CH_2), 3.03 (4H, s, 2 CH_2), 3.34 (2H, s, CH_2), 4.55 (4H, t, $J=4.0$ Hz, 2 CH_2), 5.16 (2H, s, CH_2), 6.93-7.87 (11H, m, arH), 7.89 (1H, s, CH), 7.95 (1H, s, CH), 8.48 (1H, s, NH), 8.93 (1H, s, NH), 15.35 (1H, s, OH). ^{13}C NMR (DMSO- d_6 , δ ppm): 14.76 (CH_3), 44.94 (CH_2), 49.52 (CH_2), 50.03 (CH_2), 50.15 (2 CH_2), 51.07 (2 CH_2), 68.77 (2 CH_2), 107.52 (CH), arC: [111.48 (CH), 111.48 (CH), 111.71 and 111.76 (CH, d, $J=5.0$ Hz), 118.49 (CH), 119.68 (CH), 122.27 and 122.14 (CH, d, $J=13.0$ Hz), 124.06 (CH), 125.04 (CH), 125.73 (CH), 126.42 (CH), 126.53 (CH), 133.55 (2C), 137.61 (2C), 140.29 (2C), 145.91 (2C), 148.84 and 150.92 (C, d, $J_{\text{C-F}}=208$ Hz)], 147.67 (quinolone CH), 152.05 (triazole C-3), 166.57 (triazole C-5), 166.92 (C=O), 176.58 (C=O). EI MS m/z (%): 577.26 (100), 430.25 (86), 412.38 (73), 681.20 [(M+1) $^+$, 65], 612.45 (39).

7-[4-[(3-[(2-(1H-Indol-3-yl)ethylamino)methyl]-4-benzyl-5-thioxo-4,5-dihydro-1,2,4-triazol-1-yl)methyl]piperazin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (8e). Mp. 191-193°C. FT-IR (ν_{\max} , cm^{-1}): 3260 (NH), 3070 (aromatic CH), 1718 (C=O), 1666 (C=O). ^1H NMR (DMSO- d_6 , δ ppm): 1.17 (2H, d, $J=20.0$ Hz, CH_2), 1.27-1.32 (2H, m, CH_2), 2.75 (4H, s, 2 CH_2), 2.87 (4H, s, 2 CH_2), 3.28 (2H, s, CH_2), 4.29 (2H, s, CH_2), 4.76 (2H, d, $J=4.0$ Hz, CH_2), 4.89 (2H, s, CH_2), 4.98 (2H, s, CH_2), 6.48 (1H, s, arH), 7.02 (1H, s, arH), 7.22-7.25 (6H, s, arH), 7.30 (3H, d, $J=4.0$ Hz, arH), 7.95 (1H, s, CH), 8.63 (1H, s, CH), 8.66 (1H, s, CH), 8.98 (1H, s, NH), 11.43 (1H, s, NH), 15.21 (1H, s, OH). ^{13}C NMR (DMSO- d_6 , δ ppm): 8.02 (CH_2), 22.62 (CH_2), 31.24 (CH_2), 36.24 (CH_2), 44.73 (CH_2), 46.99 (CH_2), 47.57 (CH_2), 48.37 (CH_2), 49.90 (CH_2), 51.09 (CH_2), 52.87 (CH_2), 106.82 (CH), 107.19 (CH), arC: [110.83 (CH), 111.28 (CH), 127.18 (CH), 127.79 (CH), 127.82 (CH), 127.95 (CH), 128.48 (C), 128.57 (CH), 128.79 (2CH), 128.91 (2CH), 134.21 (C), 136.77 (C), 136.69 (C), 143.68 and 145.60 (C, d, $J_{\text{C-F}}=192.0$ Hz), 169.79 (2C),

166.39 (2C), 148.41 (quinolone CH), 171.65 (triazole C-3), 176.80 (triazole C-5), 178.49 (C=O), 181.92 (C=O). EI MS m/z (%): 735.53 (100), 715.32 (97), 736.41 (93), 697.61 (82), 715.19 (81), 719.40 (80), 731.45 (78), 706.09 ($[M]^+$, 55), 707.60 ($[M+1]^+$, 44), 729.44 ($[M+Na]^+$, 33), 724.48 ($[M+H_2O]^+$, 31).

7-{4-[(3-[(2-(1*H*-Indol-3-yl)ethylamino)methyl]-4-benzyl-5-thioxo-4,5-dihydro-1,2,4-triazol-1-yl)methyl]piperazin-1-yl}-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**8f**). Mp. 189-190°C. FT-IR (ν_{max} , cm^{-1}): 3281 (NH), 3067 (aromatic CH), 1716 (C=O), 1667 (C=O). 1H NMR (DMSO- d_6 , δ ppm): 1.36-1.44 (3H, m, CH₃), 2.51 (2H, s, CH₂), 2.69 (2H, s, CH₂), 2.73 (2H, s, CH₂), 2.89 (2H, s, CH₂), 4.30 (2H, s, CH₂), 4.58 (2H, s, CH₂), 4.75 (2H, d, $J=8.0$ Hz, CH₂), 4.89 (2H, s, CH₂), 4.98 (4H, s, 2CH₂), 7.18-7.28 (8H, m, arH), 7.30 (1H, d, $J=4.0$ Hz, arH), 7.89-7.95 (2H, m, arH), 8.91 (1H, s, CH), 8.95 (1H, s, CH), 11.42 (2H, s, NH), 15.35 (1H, s, OH). ^{13}C NMR (DMSO- d_6 , δ ppm): 14.72 (CH₃), 46.98 (CH₂), 49.54 (CH₂), 49.99 (CH₂), 51.08 (CH₂), 52.85 (2CH₂), 79.95 (2CH₂), 80.07 (2CH₂), 111.49 (CH), arC: [107.52 and 107.55 (C, d, $J=3.0$ Hz), 111.72 (CH), 118.90 (CH), 119.41 (CH), 119.66 and 119.74 (C, d, $J=8.0$ Hz), 127.17 (CH), 127.44 (CH), 127.62 (CH), 127.74 (CH), 127.78 (CH), 127.81 (CH), 127.95 (CH), 128.23 and 128.48 (CH, d, $J=25.0$ Hz), 162.78 (2C), 148.80 and 150.87 (C, d, $J_C-F=207.0$ Hz), 171.65 (2C), 176.61 (2C)], 148.92 (quinolone CH), 176.61 (triazole C-3), 178.49 (triazole C-5), 181.92 (2C=O). EI MS m/z (%): 685.56 (100), 703.26 (74), 681.29 (73), 651.29 (68), 663.34 (50), 604.14 (49), 695.35 ($[M+1]^+$, 22).

General Method for The Synthesis of Compounds **9a-c**

Method 1. A mixture of compound **6** (10 mmol) and ethyl bromoacetate (10 mmol) in absolute ethanol was allowed to reflux in the presence of dried sodium acetate (50 mmol) for 18 h. The reaction mixture was then cooled to room temperature and the salt was separated by filtration. After the solvent was removed under reduced pressure, a solid appeared. This crude product was recrystallized from acetone-water (1:1) to afford the desired product.

Method 2. A mixture of compound **6** (10 mmol) and ethyl bromoacetate (10 mmol) and dried sodium acetate (50 mmol) was irradiated in monomod microwave reactor in closed vessel with pressure control (Table 1). The solid obtained was treated with 50 mL of water, the precipitate was collected by filtration and recrystallized from acetone-water (1:1) to afford the desired product.

2-[[2-(1*H*-Indol-3-yl)ethyl]amino]-*N'*-(5-oxo-3-phenyloxazolidin-2-ylidene)aceto hydrazide (**9a**). Mp. 152-153°C. FT-IR (ν_{max} , cm^{-1}): 3211 (NH), 3092 (aromatic CH), 1595 (C=N), 1693 (C=O), 1720 (C=O), 1241 (C-O). 1H NMR (DMSO- d_6 , δ ppm): 2.10 (2H, s, CH₂), 3.03 (2H, s, CH₂), 3.67 (2H, s, CH₂), 4.11 (2H, s, CH₂), 6.50-6.72 (2H, m, arH), 7.10-7.28 (3H, m, arH),

7.35-7.45 (4H, m, arH), 8.10 (1H, s, CH), 9.20 (1H, s, NH), 10.10 (2H, s, 2NH). ^{13}C NMR (DMSO- d_6 , δ ppm): 23.70 (CH₂), 43.61 (CH₂), 50.08 (2CH₂), 111.42 (C), 111.95 (CH), arC: [114.37 (CH), 116.15 (CH), 118.56 (CH), 118.85 (CH), 118.96 (CH), 121.51 (CH), 122.33 (CH), 123.42 (CH), 127.06 (CH), 136.73 (C), 140.14 (C), 155.62 (C), 156.52 (C)], 169.87 (2C=O). EI MS m/z (%): 378.12 (100), 563.78 (83), 496.21 (75), 414.52 ($[M+Na]^+$, 66), 217.52 (36).

2-[[2-(1*H*-Indol-3-yl)ethyl]amino]-*N'*-(3-phenyl-5-oxothiazolidin-2-ylidene)aceto hydrazide (**9b**). Mp. 134-136°C. FT-IR (ν_{max} , cm^{-1}): 3309 (NH), 3109 (aromatic CH), 1727 (C=O). 1H NMR (DMSO- d_6 , δ ppm): 1.28 (2H, s, CH₂), 1.45 (2H, s, CH₂), 4.01 (2H, s, CH₂), 3.53 (2H, s, CH₂+H₂O), 7.30-7.42 (3H, m, arH), 7.43-7.49 (3H, m, arH), 7.51 (3H, s, arH), 10.77 (1H, s, CH), 10.89 (3H, s, 3NH). ^{13}C NMR (DMSO- d_6 , δ ppm): 18.71 (CH₂), 24.86 (CH₂), 32.55 (CH₂), 39.20 (CH₂), 111.99 (CH), arC: [118.63 (CH), 123.54 (CH), 124.67 (CH), 128.44 (CH), 128.81 (CH), 129.05 (CH), 129.20 (CH), 129.26 (2CH), 140.11 (C), 141.76 (C), 143.82 (C), 150.77 (C), 161.41 (C)], 172.21 (2C=O). EI MS m/z (%): 427.36 (100), 447.44 (70), 429.49 ($[M+Na]^+$, 67), 425.29 (51), 44 1.37 (48), 433.43 (45), 434.43(28).

2-[[2-(1*H*-Indol-3-yl)ethyl]amino]-*N'*-(3-benzyl-5-oxothiazolidin-2-ylidene)aceto hydrazide (**9c**). Mp. 132-134°C. FT-IR (ν_{max} , cm^{-1}): 3289 (NH), 3032 (aromatic CH), 1709 (C=O), 1599 (C=N). 1H NMR (DMSO- d_6 , δ ppm): 3.10 (2H, s, CH₂), 4.28 (2H, s, CH₂), 4.81 (2H, d, $J=12.0$ Hz, CH₂), 4.91 (2H, s, CH₂), 5.14 (2H, s, CH₂), 6.97- 7.08 (1H, m, arH), 7.22-7.27 (1H, m, arH), 7.29-7.59 (7H, m, arH), 7.61 (1H, s, CH), 9.52 (2H, s, 2NH), 10.91 (1H, s, NH). ^{13}C NMR (DMSO- d_6 , δ ppm): 25.22 (CH₂), 39.76 (CH₂), 41.76 (CH₂), 45.78 (CH₂), 52.60 (CH₂), 110.95 (C), 111.97 (CH), arC: [121.56 (CH), 123.50 (CH), 127.77 (CH), 127.95 (CH), 128.04 (CH), 128.09 (CH), 128.70 (CH), 128.73 (CH), 128.82 (CH), 136.35 (C), 136.80 (C), 150.11 (C), 171.69 (C), 172.23 (C)], 181.89 (2C=O). EI MS m/z (%): 360.47 (100), 447.44 (95), 327.31 (65), 323.31 (58), 283.20 (55), 381.43 (51), 355.28 (38).

General Method for The Synthesis of Compounds **10a-c**

Method 1. A mixture of the corresponding compound **6** (10 mmol) and 2-bromo-1-(4-chlorophenyl)ethanone (10 mmol) in absolute ethanol was allowed to reflux in the presence of dried sodium acetate (50 mmol) for 17-20 h. The reaction mixture was then cooled to room temperature and the salt was separated by filtration. After the solvent was removed under reduced pressure, an oily product obtained. This was extracted with 15 mL of ethyl acetate three times. The organic layer was dried on Na₂SO₄ and evaporated under reduced pressure. The obtained crude product was recrystallized from acetone: petroleum ether (1:1).

Method 2. A mixture of the corresponding compound **6** (10 mmol), 2-bromo-1-(4-chlorophenyl)ethanone (10 mmol) and dried sodium acetate (50 mmol) in absolute

ethanol was irradiated in monomod microwave reactor in closed vessel with pressure control (Table 1). The solid obtained was treated with 50 mL of water, the precipitate was collected by filtration and recrystallized from acetone-petroleum ether (1:1) to afford the desired product.

2-[[2-(1*H*-Indol-3-yl)ethyl]amino]-*N*'-[5-(4-chlorophenyl)-3-phenyl-oxazol-2(3*H*)-ylidene]acetohydrazide (**10a**). Mp.141-142°C. (Method 2), FT-IR (ν_{\max} , cm^{-1}): 3294 (NH), 3092 (aromatic CH), 1595 (C=N), 1698 (C=O), 1241 (C-O). ^1H NMR (DMSO- d_6 , δ ppm): 2.15 (2H, s, CH₂), 3.10 (2H, s, CH₂), 5.45 (2H, s, CH₂), 6.95 (3H, s, arH), 7.25 (5H, s, arH), 7.49 (5H, s, arH), 7.97 (2H, s, 2CH), 8.76 (2H, s, 2NH), 9.80 (1H, s, NH). ^{13}C NMR (DMSO- d_6 , δ ppm): 23.70 (CH₂), 48.25 (CH₂), 66.82 (CH₂), 114.34 (2CH), arC: [118.94 (2CH), 122.31 (2CH), 127.06 (2CH), 129.07 (2CH), 129.52 (2CH), 130.16 (3CH), 140.14 (2C), 156.49 (2C), 160.31 (2C), 161.4 (2C)], 169.18 (C=O). EI MS m/z (%): 312.25 (100), 547.36 (78), 296.34 (65), 486.23 ([M+1]⁺, 51).

2-[[2-(1*H*-Indol-3-yl)ethyl]amino]-*N*'-[3-phenyl-5-(4-chlorophenyl)thiazol-2(3*H*)-ylidene] acetohydrazide (**10b**). Mp.137-138°C. FT-IR (ν_{\max} , cm^{-1}): 3319 (NH), 3049 (aromatic CH), 1712 (C=O). ^1H NMR (DMSO- d_6 , δ ppm): 2.15 (2H, s, CH₂), 2.70 (2H, s, CH₂), 5.46 (2H, s, CH₂), 6.57 (1H, s, arH), 7.15-7.35 (11H, m, arH), 7.65 (1H, s, arH), 10.93 (2H, s, 2CH), 11.10 (1H, s, NH), 11.70 (1H, s, NH), 12.66 (1H, s, NH). ^{13}C NMR (DMSO- d_6 , δ ppm): 31.15 (CH₂), 66.83 (2CH₂), 102.26 (CH), 116.77 (CH), arC: [127.88 (CH), 128.85 (CH), 128.79 (CH), 128.92 (CH), 129.14 (CH), 129.52 (2CH), 130.12 (2CH), 130.17 (2CH), 131.42 (2CH), 138.34 (2C), 159.63 (2C), 160.75 (2C), 170.33 (2C)], 192.46 (C=O). EI MS m/z (%): 427.36 (100), 447.44 (70), 452.49 ([M+Na]⁺, 67), 425.29 (51), 44 1.37 (48), 433.43 (45), 434.43(28).

2-[[2-(1*H*-Indol-3-yl)ethyl]amino]-*N*'-[3-benzyl-5-(4-chlorophenyl)thiazol-2(3*H*)-ylidene] acetohydrazide (**10c**). Mp.148-150°C. FT-IR (ν_{\max} , cm^{-1}): 3217 (NH), 3086 (aromatic CH), 1590 (C=N). ^1H NMR (DMSO- d_6 , δ ppm): 4.37 (2H, d, $J=4.0$ Hz, CH₂), 4.91 (2H, s, CH₂), 5.46 (4H, s, 2CH₂), 7.19-7.59 (8H, m, arH), 7.64 (5H, d, $J=8.0$ Hz, arH), 10.92 (1H, s, CH), 12.21 (1H, s, CH), 12.37 (3H, s, 3NH). ^{13}C NMR (DMSO- d_6 , δ ppm): 44.73 (CH₂), 52.85 (CH₂), 66.83 (2CH₂), 110.95 (C), 111.97 (CH), 118.62 (CH), arC: [118.89 (CH), 121.55 (CH), 127.96 (CH), 128.53 (CH), 128.77 (CH), 128.80 (CH), 128.91 (CH), 129.03 (2CH), 129.52 (2CH), 130.17 (2CH), 136.72 (2C), 140.85 (C), 150.36 (C), 171.68 (C), 181.88 (2C)], 191.45 (C=O). EI MS m/z (%): 612.54 (100), 554.78 ([M+K]⁺, 65), 502.57 (51), 378.56 (45).

Antibacterial Activity Assessment

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. aeruginosa*) ATCC43288, *Enterococcus faecalis* (*E. faecalis*) ATCC29212, *Staphylococcus aureus* (*S. aureus*) ATCC25923, *Bacillus cereus* (*B. cereus*) 709 Roma, *Mycobacterium smegmatis* (*M. smegmatis*) ATCC607. All the newly synthesized compounds were weighed and dissolved in dimethyl sulfoxide to prepare extract stock solution of 20.000 microgram/milliliter ($\mu\text{g}/\text{mL}$). The antibacterial effects of the substances were tested quantitatively in respective broth media by using double microdilution and the minimal inhibition concentration (MIC) values ($\mu\text{g}/\text{mL}$) 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, Detroit, MI) was used for *M. smegmatis*, and incubated for 48-72 h at 35 °C [41]. 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. The results obtained were presented in Table 3.

Conflict of Interest

The authors declare that there is not conflict of interest in the present study.

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