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Microwave-Assisted Synthesis of Some Hybrid Molecules Derived from Morpholine and Investigation of Their Antimicrobial Activities

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2*H*-1,2,4-triazol-3(4*H*)-one compound was obtained starting from 4-(2-fluoro-4-nitrophenyl)morpholine via several steps. Then, these compounds were converted to the corresponding fluoroquinolone hybrids via one pot three component Mannich reaction. Moreover, the synthesis of eleven compounds, which can be considered as conazole analogues, was performed starting from 1,2,4-triazole-3-one compounds via three steps by either conventional or microwave mediated conditions. The effect of different solvents and microwave power on microwave prompted reactions was examined as well.

The synthesized compounds were screened for their antimicrobial activities, and some of them were found to possess good to moderate activity.

Introduction

In the last two decades, fungal infections have become a continuous and serious threat to human health and life. Infections caused by fungi, which are the heterotrophic eukaryotic organisms using almost any surface for their growth are classified into three groups incorporating (1) allergic reactions to fungal proteins (2), toxic reactions to toxins present in certain fungi and (3) infections(mycoses). Many fungal infections are caused by opportunistic pathogens that may be endogenous (Candida infections) or acquired from the environment (Cryptococcus, Aspergillus infections). Invasive fungal infections and dermatomycoses produced by fungal organisms constitute the other type of fungal infections mostly emerging in the individuals with increased vulnerability such as neonates, cancer patients receiving chemotherapy, organ transplant patients, and burns patients, apart from those with acquired immune deficiency syndrome (AIDS). Other risk factors include the long term use of corticosteroid and antibiotics, diabetes, lesions of epidermis and dermis, malnutrition, neutropenia and surgery.[1–7]

Beside fungal infections, certain bacterial diseases have become potential threat to human health and these bacterial diseases yet have not been overcome. Literature survey revealed that, more than one-third of the world populations are infected by bacterial pathogens and nearly two million people per year die due to these infections.[8] The overuse and misuse of common antibiotics has resulted in resistance in certain bacteria and the human pathogen no longer response to these clinically used antibiotics, although significant progress has been made for the treatment and control of microbial infections by introducing new strategies and combinatorial therapy. The alarming rates of emerging and reemerging microbial threats coupled with increasing antibacterial resistance have emphasized the urgent need for new and more effective antibacterial agents with high safety profile.[9–14]

Among the nitrogen containing heterocyclic compounds, *N*-functionalizedmorpholines apparently have gained considerable importance owing to their varied biological properties including antidiabetic,[15] antiemetic,[16] platelet aggregation inhibitors, antihyperlipoproteinemics[15] bronchodilators, growth stimulants[17] and antidepressants.[18] These were also used in the treatment of inflammatory diseases, pain, migraine and asthma.[19] Recently, some morpholine derivatives possessing antimicrobial activity have been synthesized in our laboratory.[20,21]

Other *N*-containing heterocycle, triazole constitutes another important bioactive nucleus in the field of medicinal chemistry[22–26] the therapeutic effects of 1,2,4-triazole and containing compounds have been well studied for a number of pathological conditions including inflammation, cancer, pain, tuberculosis or hypertension.[27–30] Ribavirin, rizatriptan, alprazolam, vorozole, letrozole, and anastrozole are the best examples of drugs containing 1,2,4-triazole moiety.[31–33] Among azole-based drugs, conazoles, such as itraconazole, fluconazole,

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voriconazole, posaconazole and ravuconazole constitute a major class being used for the treatment of fungal infections[34–36] (figure 1).

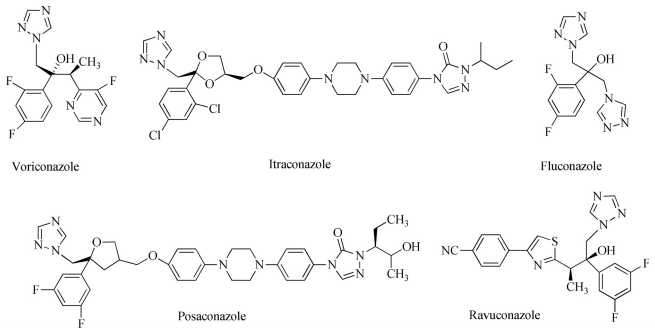


Figure 1. Some known azole class antifungals.

Fluoroquinolone antibacterial agents constitute a fastgrowing group of antibiotics; various derivatives were synthesized and tested for their antimicrobial activities. The new generations of fluoroquinolones achieved significant improvement in potency, spectrum and physicochemical properties.[37] Several compounds with broad spectrum antibacterial activity have been introduced by the *N*-4 substitution of piperazin on fluoroquinolones,[38,39] some of which have been studied in our laboratory.[30] Also, isatineMannich bases of gatifloxacin, a floroquinolone class antibacterial have been obtained as potent anticancer agents.[40]

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. Themodification of structural units in the existing drugs or the synthesis of their novel analogues has become one of most promising and applied strategy aiming to overcome drug resistance. Some reasons, such as not including the discovery of new scaffolds or validation of novel biological targets, which require difficult and time-consuming work, have made this procedure attractive.[41–43] It has been reported that the compounds 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.[44]

Microwave-assisted organic synthesis has also received great attention due to some advantages including reduction of reaction times, minimization of by-products and increased yields. So the application of microwaves has become a particularly attractive way for the preparation of key intermediates and new bioactive molecules.[15,30]

In this study focused on the design, eco friendly synthesis and antimicrobial evaluation of new azole class antifungals.

Moreover, the synthesis of morpholine-azole-fluoroquinolone hybrids were intended as well, based on pharmacophores hybridization. Morpholine scaffold was selected as the key

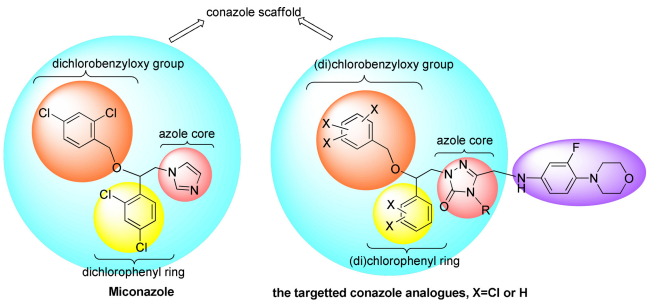


Figure 2. The schematic representation of the relationship between the structures of miconazole and the synthesized conazole analogues.

prototype structural unit and the integration of morpholine skeleton, azole and fluoroquinolonepharmacophoreswith different mode of action in the one molecular frame was performed as shown in figure 3 with the aim to prepare new antibacterial

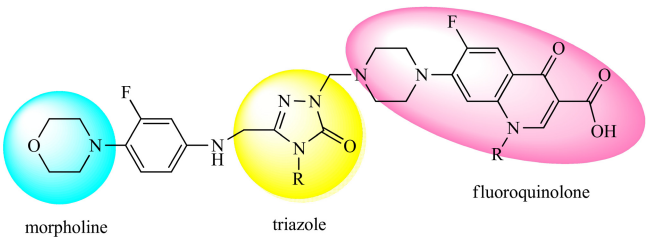


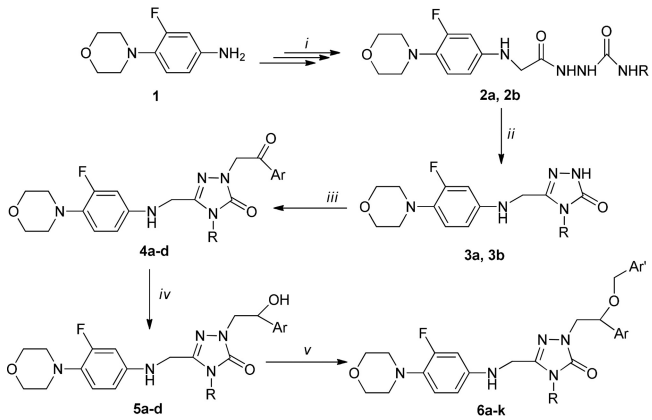
Figure 3. General representation of the target compounds

agents with preferably therapeutic profile having less tendency to antibacterial resistance.

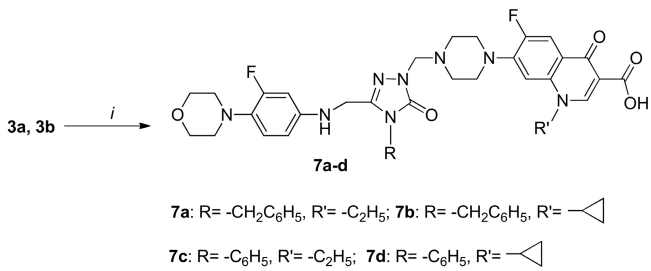
Results and Discussion

Chemistry

The synthetic strategies adopted to obtain the target compounds are depicted in Schemes 1 and 2, and the substituents on compounds **2–6** were presented in table 1. In the present study, the synthesis of compound **1** was performed following the procedure reported by us earlier.[45] Compounds**3a** and **3b** were synthesized starting from compound **1** via two steps by conventional and microwave irradiated techniques. This idea originated from the aim to obtain an active hydrogen compound with biological activity that can be used as an intermediate for further condensation reactions leading to the formation of new bioactive products. Moreover, this heterocycle which constitutes one of active part of azole class antifungal is necessary for the construction of new conazole analogues targeted in the present study. In order to optimize the method, microwave (MW) irradiation was applied at different power values of 100, 150 and 200 W and the progress of reaction was monitored by TLC. The complete conversion of the starting carboxamide (**2a, 2b**) was observed after micro-



Scheme 1. Reaction and conditions: *i*: DCM, benzylisocyanate (for **2a**) or phenylisocyanate (for **2b**), rtor 80 W MW; *ii*: NaOH, EtOH-H_2O, reflux or 150 W MW; *iii*: 2-bromo-1-(4-chlorophenyl)ethanone or 2-chloro-1-(2,4-dichlorophenyl)ethanone, NaOEt, reflux or 175 W MW; *iv*: $NaBH_4$, EtOH, reflux; *v*: 2,6-dichlorobenzylchloride, 2,4-dichlorobenzylchloride or 4-chlorobenzylchloride, THF, NaH, reflux or 200 W MW.



Scheme 2. *i*: Ciprofloxacine or norfloxacine, DMF, HCHO, rt or 50 W MW.

Table 1. Substituents on compounds **2–6**.

Comp. No.	R	Ar	Ar′
2a	$-CH_2C_6H_5$	-	-
2b	$-C_6H_5$	-	-
3a	$-CH_2C_6H_5$	-	-
3b	$-C_6H_5$	-	-
4a	$-CH_2C_6H_5$	$-C_6H_4Cl$(*-4*)	-
4b	$-C_6H_5$	$-C_6H_4Cl$(*-4*)	-
4c	$-CH_2C_6H_5$	$-C_6H_3Cl_2$(*-2,4*)	-
4d	$-C_6H_5$	$-C_6H_4Cl$(*-2,4*)	-
5a	$-CH_2C_6H_5$	$-C_6H_4Cl$(*-4*)	-
5b	$-C_6H_5$	$-C_6H_4Cl$(*-4*)	-
5c	$-CH_2C_6H_5$	$-C_6H_3Cl_2$(*-2,4*)	-
5d	$-C_6H_5$	$-C_6H_4Cl$(*-2,4*)	-
6a	$-CH_2C_6H_5$	$-C_6H_4Cl$(*-4*)	$-C_6H_4Cl$(*-4*)
6b	$-C_6H_5$	$-C_6H_4Cl$(*-4*)	$-C_6H_4Cl$(*-4*)
6c	$-CH_2C_6H_5$	$-C_6H_4Cl$(*-4*)	$-C_6H_3Cl_2$(*-2,4*)
6d	$-C_6H_5$	$-C_6H_4Cl$(*-4*)	$-C_6H_3Cl_2$(*-2,4*)
6e	$-CH_2C_6H_5$	$-C_6H_4Cl$(*-4*)	$-C_6H_3Cl_2$(*-2,6*)
6f	$-C_6H_5$	$-C_6H_3Cl_2$(*-2,4*)	$-C_6H_4Cl$(*-4*)
6 g	$-CH_2C_6H_5$	$-C_6H_3Cl_2$(*-2,4*)	$-C_6H_4Cl$(*-4*)
6 h	$-C_6H_5$	$-C_6H_3Cl_2$(*-2,4*)	$-C_6H_3Cl_2$(*-2,4*)
6j	$-CH_2C_6H_5$	$-C_6H_3Cl_2$(*-2,4*)	$-C_6H_3Cl_2$(*-2,4*)
6k	$-C_6H_5$	$-C_6H_3Cl_2$(*-2,4*)	$-C_6H_3Cl_2$(*-2,6*)
6 l	$-CH_2C_6H_5$	$-C_6H_3Cl_2$(*-2,4*)	$-C_6H_3Cl_2$(*-2,6*)

wave irradiation at 150 W for 15 min. It is noteworthy to underline that shorter reaction time or lower microwave energy power caused to lower conversion rate, while increasing reaction time or MW power resulted in decomposition of the target product as revealed by TLC analysis.

Compared to the classical method, microwave mediated method supplied an alternative route with much shorter reaction duration and better yield for the synthesis of compounds **3a** and **3b**. These compounds (**3a, 3b**) were characterized by the presence of NH band at 3286 or 3289 cm^{-1} in the FT-IR spectra. This proton was resonated between 8.66-8.99 ppm in the ^{1}H NMR spectra as D_2O exchangeable singlet. Moreover these compounds displayed elemental analysis results confirming the proposed structures.

The treatment of 1,2,4-triazole-3-one (**3a,b**) with 2-bromo-1-(4-chlorophenyl)ethanone (for**4a, 4b**) or 2-chloro-1-(2,4-dichlorophenyl)ethanone (for **4c, 4d**) produced compounds **4a–d.** Two methods including conventional heating under reflux conditions (Method 1) and MW irradiated method (Method 2) were used for the preparation of **4a–d**. The obtained results revealed that the latter technique supplied more useful procedure with much shorter reaction duration of 15 min. while conventional method requires 6 hours. In the method 2, higher temperatures than 150 °C or higher microwave energy than 175 W resulted in a decrease in yields of compounds **4a–d** or completely decomposition.

The support for the formation of the targeted compounds, **4a–d** is the appearance of [M + H], [M + H_2O], [M + K + 2H]ion peaks at corresponding *m/z* values confirming their molecular masses; and these compounds gave elemental analysis results consistent with the proposed structures. The reduction of exocyclic carbonyl function of compounds **4a–d** to alcohol was achieved in the presence of $NaBH_4$ in ethanol using both conventional and MW irradiated methods. For MW mediated reactions leading to the formation of compounds **5a–d**, the production of compound **5b** was selected as model and the effects of various reaction parameters, including solvent, temperature, time and MW power were examined on the model reaction, and the results are summarized in (Table 2).

The obtained results showed that the MW irradiation supplied more suitable method with shorter reaction time and improved yields. The FT-IR and ^{1}H NMR spectra of these compounds displayed signal originated from -OH proton (exchangeable with D_2O) between 4.02–5.28 ppm, while no signal due to carbonyl function was present in the FT-IR spectra. In addition, compounds **5a–d** gave Mass spectral data and elemental analysis consistent with the assigned structures.

The synthesis of compounds **6a–k,** which were regarded as new analogs of azole class antifungals was achieved by treatment of compounds **5a–d** with chlorinated benzyl chlorides, namely 4-chloro-, 2,4-dichloro- and 2,6-dichlorobenzyl chlorides in the presence of NaH under MW-mediated and conventional conditions. In order to improve the MW conditions, the reaction leading to the formation of **6b** was selected as a model reaction and the effects of several parameters including time, power and solvent were examined. The best conditions were obtained with 10 minutes of MW

Table 2. Optimization of the model reaction conditions for compounds **4b–6b**.

Entry	Time (min)	Power (W)	Yield (%)	Temperature (°C)	Solvent
Comp 4b					
1	18	200	97	175	EtOH
2	14	175	98	150	EtOH
3	20	150	96	125	EtOH
4	16	125	97	100	EtOH
5	10	100	90	100	EtOH
6	10	100	92	125	EtOH
Comp 5b					
1	6	200	97	150	EtOH
2	8	150	99	150	EtOH
3	10	200	93	150	THF
4	4	150	96	100	THF
5	10	200	74	150	MeCN
6	10	200	81	200	MeCN
Comp 6b					
1	25	100	65	100	EtOH
2	25	100	53	100	THF
3	25	100	60	100	MeCN
4	27	100	50	100	DCM
5	15	150	71	100	EtOH
6	17	150	77	100	THF
7	16	150	69	100	MeCN
8	18	150	68	100	DCM
9	10	200	65	100	EtOH
10	10	200	70	100	THF
11	10	200	73	100	MeCN
12	8	200	40	100	DCM

irradiation at 200 W in MeCN. After optimization of the conditions for the preparation of **6b**, the synthesis of the remaining compounds **6** was carried out. Comparison of two methods, conventional and MW irradiated procedures showed that with the use of MW irradiation provided more efficient and green way for the synthesis of compounds **6a–k** with the better reaction yields and much shorter reaction times. In the NMR spectra of compounds **6a–k**, the number of signals and their chemical shifts are in accordance with the assigned structures. In the ^{1}H NMR and ^{13}C NMR spectra, additional signals corresponding to the substituted (di)chlorobenzyloxy group were recorded at the related chemical shift values while ^{1}H NMR spectra of these compounds showed the disappearance of the characteristic band of -OH function. Moreover, the preparation of conazole analogs was verified by registration of their mass spectra which were in accordance with their molecular masses and the elemental analysis data (carbon, hydrogen and nitrogen) were ±0.4% of the theoretical values.

Compounds **3a** and **3b** were subjected to a Mannich reaction with norfloxacine and ciprofloxacine in the presence of formaldehyde solution under conventional and also MW irradiated conditions. The method with MW irradiation provided more useful way with improved reaction yields and shorter reaction times. This idea originated from the intend to introduce the fluorophenylenmorpholine nucleus to fluoroquinolone skeleton with the aim to obtain antimicrobial agents with improved properties including broader spectrum, less tendency to resistance, less toxic side effects etc. No signal representing the existence of NH group is present in the FT-IR and ^{1}H NMR spectra of compounds **7a–d,** while the splitting patterns of remaining protons of spectra were as expected, according to the structures. The ^{13}C NMR spectra were also as expected. Moreover, [M + Na], [M + 1], [M + K] or [M + H_2O]ion peaks were observed at the related *m/z* values supporting the proposed structures of compounds **7a–d** (Scheme 2). In addition, these compounds gave reasonable elemental analysis data.

Antimicrobial activity

Most of the compounds synthesized in the present study exhibited activity on the test compounds (table 3, only positive results were presented). Among them, **7a–d**, which contain a fluoroquinolone nucleus in their structures, demonstrated excellent activities on Gram positive and Gram negative

Table 3. Screening for the activity of newly synthesized compounds

Comp No	Microorganismsand Minimal InhibitoryConcentrations (μg/mL) Ec	Yp	Pa	Sa	Ef	Bc	Ms	Ca	Sc
2a	-	-	-	250	-	-	31.25	-	-
2b	-	-	-	-	-	-	-	-	-
3a	-	-	-	-	-	-	-	-	-
3b	-	-	-	-	-	-	-	-	-
4a	0.24	-	-	-	-	-	-	125	125
4b	-	-	-	-	-	-	-	-	-
4c	0.24	-	-	-	-	-	-	125	125
4d	<0.24	<0.24	<0.24	<0.24	<0.24	<0.24	-	500	-
5a	0.24	-	-	-	-	-	-	125	125
5b	-	-	-	-	-	-	-	-	-
5c	0.24	-	-	-	-	-	-	125	125
7a	<0.24	<0.24	<0.24	<0.24	<0.24	<0.24	-	125	500
7b	<0.24	<0.24	<0.24	<0.24	<0.24	<0.24	-	-	-
7c	<0.24	<0.24	<0.24	<0.24	<0.24	<0.24	-	125	-
7d	<0.24	<0.24	<0.24	<0.24	<0.24	<0.24	-	500	-
Amp.	10	18	>128	10	35	15			
Strep.							4		
Flu								<8	<8

bacteria of the test microorganisms with the mic values <0.24 μg/mL. The carboamides, **2a, 2b,** and triazoles, **3a, 3b,** which were obtained from intramolecular cyclisation of **2a, 2b**, displayed selective activity on a Gram positive coccal bacterium, *Staphylococcus aureus* (Sa), and *Mycobacterium smegmatis* (Ms), atipical tuberculosis factor leading to morbidity and mortality. A remarkable antifungal activity was observed for **4a–d** and **7a–d** with the MIC values varying between 8–31.2 μg/mL.

Ec: Escherichia coli ATCC 25922, Yp: Yersinia pseudotuberculosisATCC 911, Pa: Pseudomonas aeruginosaATCC 43288, Sa: Staphylococcus aureus ATCC 25923, Ef: Enterococcus faecalis ATCC 29212, Bc: Bacillus cereus 702 Roma, Ms: Mycobacterium smegmatis ATCC607, Ca: Candida albicans ATCC 60193, Saccharomyces cerevisiae RSKK 251, Amp.: Ampicillin, Str.: Streptomycin (—): Flu.: Fluconazole, (—): no activity.

Antimicrobial Activity Assessment

The test microorganisms were obtained from the Hifzissihha Institute of RefikSaydam (Ankara, Turkey) and were as follows: *Escherichia coli* (*E. coli*) ATCC35218, *Yersinia pseudotuberculosis (Y. pseudotuberculosis*) ATCC911, *Pseudomonas aeruginosa* (*P.aeruginosa*) ATCC43288, *Enterococcus faecalis*(*E. faecalis*) ATCC29212, *Staphylococcus aureus*(*S. aureus*)ATCC25923, *Bacillus cereus* (*B. cereus)* 709 Roma, *Mycobacterium smegmatis* (*M. smegmatis*) ATCC607, *Candida albicans*(*C. albicans*)ATCC60193 and *Saccharomyces cerevisiae* (*S. cerevisia*) RSKK 251. All the newly synthesized compounds were weighed and dissolved in hexane to prepare extract stock solution of 20.000 microgram/milliliter (μg/mL).

The antimicrobial effects of the substances were tested quantitatively in respective broth media by using double microdilution and the minimal inhibition concentration (MIC) values (μg/mL) were determined. The antibacterial and antifungal assays were performed in Mueller-Hinton broth (MH) (Difco, Detroit, MI) at pH.7.3 and buffered Yeast Nitrogen Base (Difco, Detroit, MI) at pH 7.0, respectively. The micro dilution test plates were incubated for 18–24 h at 35 °C. Brain Heart Infusion broth (BHI) (Difco, Detriot, MI) was used for *M. smegmatis,* and incubated for 48–72 h at 35 °C [46]. Ampicillin (10 μg) and fluconazole (5μg) 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.

CONCLUSION

This study reports the successful synthesis of some new hybrid compounds starting from 4-(2-fluoro-4-nitrophenyl)morpholine. Two methods have been used to synthesize these new compounds: conventional and microwave. Microwave synthesis was a more effective way of synthesizing the targeted compounds.Moreover, the effect of acid catalyst on Mannich reactions was investigated. The antimicrobial activity screening studies were also performed in the study. The antimicrobial screening suggests that the compounds containing norfloxacin or ciprofloxacin nucleus displayed excellent antimicrobial activity.The experimental data of the synthesized compounds can be seen in the supporting information part.

Supporting Information Summary:

The experimental section is provided in the supporting information.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Antimicrobial activity · conazole · fluoroquinolone · microwave · morpholine · 1,2,4-triazole

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