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A convenient 'one-pot' synthesis and *in vitro* microbiological evaluation of novel 2,7-diaryl-[1,4]-diazepan-5-ones

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Abstract

A convenient method for the 'one-pot' synthesis of novel target molecule 2,7-diaryl-[1,4]-diazepan-5-ones from the respective 2,6-diaryl-piperidin-4-ones was catalyzed by $NaHSO_4.Al_2O_3$ heterogeneous catalyst in dry media under microwave irradiation in solvent-free conditions. Moreover, the catalyst could be recovered and re-used up to 4 times after washing with ethyl acetate. They were evaluated for potential antibacterial activity against *Staphylococcus aureus, β-Haemolytic streptococcus, Vibreo cholerae, Salmonella typhii, Escherichia coli, Klebsiella pneumonia, Pseudomonas* and antifungal activity against *Aspergillus flavus, Aspergillus fumigatus, Mucor, Candida albicans* and *Rhizopus*. Structure-Activity Relationship (SAR) led to the conclusion that, of all the compounds **25–32** tested, compound **30** exerted strong *in vitro* antibacterial activity against *S. aureus, S. typhii*, and *Pseudomonas* and all the compounds **25–32** were less active against *E. coli,* whereas all the compounds **25–32** displayed potent *in vitro* antifungal activity against all the fungal strains used, except compound **30**, which was more effectual against *Mucor*.

Keywords: *2,7-diaryl-[1,4]-diazepan-5-ones, $NaHSO_4.Al_2O_3$ Heterogeneous Catalyst, Green Chemistry, Antibacterial activity, Antifungal activity*

Introduction

Over the past decades, the incidence of systemic microbial infections has been increasing dramatically due to an increase in the number of immuno-compromised hosts [1]. The increasing incidence of bacterial resistance to a large number of antibacterial agents such as glycopeptides (vancomycin, inhibition cell walls synthesis), sulfonamide drugs (inhibitors of tetrahydrofolate synthesis), β-lactam antibiotics (penicillins and cephalosporins), nitroimidazoles and quinolones (DNA inhibitors), tetracyclins, chloramphenicol and macrolides (erythromycin, inhibiting protein synthesis) is becoming a major concern [2]. For the past several years, vancomycin has been considered the last line of defense as an agent against Gram-positive infections and no alternative drugs are available for treating diseases that have become resistant to vancomycin [3]. Patients undergoing organ transplants, anticancer chemotherapy or long term treatment with antimicrobial agents and patients with AIDS are immunosuppressed and very susceptible to life threatening systemic fungal infections such as Candidiasis, cryptococcosis and aspergillosis. Antifungal azoles, fluconazole and itraconazole which are strong orally active inhibitors of lanosterol 14a-demethylase (cytochrome *P*45014DM) have been widely used in antifungal chemotherapy. Reports are available on the developments of resistance to currently available antifungal azoles in *Candida* spp.,

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as well as clinical failures in the treatment of fungal infections [4–7]. Furthermore, most of the present antifungal drugs are not effective against invasive aspergillosis and the only drug of choice in such patients is the injectable amphotericin B. Some examples of 1,2,4-triazole based antibacterial and antifungal drugs are estazolam [8,9], alprazolam [10] and rizatriptane [11]. These observations place new emphasis on the need to search for alternative new and more effective antimicrobial agents with a broad spectrum. Recently, we expanded the synthesis of 2,6-diarylpiperidin-4-one derivatives [12–16] with a view to incorporating various other bioactive heterocyclic nucleui such as selenadiazoles, and thiadiazoles for evaluation of their associated antibacterial and antifungal activities. Synthesis of molecules, which are novel yet still resembling known biologically active molecules by virtue of the presence of some critical structural features, is an essential component in the search for new leads in a drug design programme. Antibiotics such as penicillins and cephalosporins have an amide group. Novel bioactive natural compounds [17] are synthesized by the conversion of ketones into amides, since the amide group is an important pharmacophore. Consequently in the interest of above, we planned to synthesize the novel bioactive target molecule, 2,7-diaryl-[1,4]-diazepan-5-one, which has the key functional amide group - present.

Microwave irradiation (MWI) has become an established tool in organic synthesis, because of the rate enhancements, higher yields, and often, improved selectivity, with respect to conventional reaction conditions [18–23]. In recent years, solvent –free reactions using either organic or inorganic solid supports have received increasing attention [24]. There are several advantages to performing synthesis in dry media: (i) short reaction times, (ii) increased safety, (iii) economic advantages due to the absence of solvent. In addition, solvent free MWI processes are also clean and efficient.

The challenge in chemistry to develop practical processes, reaction media, conditions and/or utility of materials based on the concept of green chemistry is one of the important issues in the scientific community [25]. Owing to our interest in synthesizing fascinating pharmacological and therapeutically important compounds under solid-state reaction conditions [26–28], we attempted and succeeded in using neutral alumina supported sodium hydrogen sulphate ($NaHSO_4.Al_2O_3$) [29], as a heterogeneous catalyst for the one-pot conversion of ketones to amides. This prompted us to continue our work on the application of $NaHSO_4.Al_2O_3$ heterogeneous catalyst for the 'one-pot' synthesis of the novel target molecule 2,7-diaryl-[1,4]-diazepan-5-ones from the respective 2,6-diaryl-piperidin-4-ones in dry media under microwave irradiation in solvent-free conditions.

Experimental

Microbiology

Materials. All the bacterial strains namely Staphylococcus aureus, β-Haemolytic streptococcus, Vibreo cholerae, Salmonella typhii, Escherichia coli, Klebsiella pneumonia, Pseudomonas and fungal strains namely Aspergillus flavus, Aspergillus fumigatus, Mucor, Candida albicans, Rhizopus were obtained from the Faculty of Medicine, Annamalai University, Annamalainagar-608 002, Tamil Nadu, India.

In vitro *antibacterial and antifungal activity*. The *in vitro* activities of the compounds were tested in Sabourauds dextrose broth (SDB) (Hi-media, Mumbai) for fungi and nutrient broth (NB) (Hi-media, Mumbai) for bacteria by the Disc Diffusion method [33]. The respective hydrochlorides of the test compounds **25**–**32** were dissolved in water to obtain 1 mg mL^{-1} stock solution and different concentrations (100, 200, 500 ppm) were prepared. Seeded broth (broth containing microbial spores) was prepared in NB from 24 h old bacterial cultures on nutrient agar (Hi-media, Mumbai) at 37 ± 1°C while fungal spores from 1 to 7 days old Sabourauds agar (Hi-media, Mumbai) slant cultures were suspended in SDB. Sterile paper disc of 5 mm diameter were saturated with the three different concentrations and placed in each seeded agar plate. The petri plates were incubated in a BOD incubator at 37°C for bacteria and at 28°C for fungi. The zone of inhibition was recorded by visual observations after 24 h inhibition for bacteria and after 72–96 h inhibition for fungi. Moreover, the zone of inhibition was measured by excluding the diameter of the paper disc. Ciprofloxacin was used as a standard for bacteria and fluconazole for fungi under analogous conditions.

Chemistry

TLC was used to assess the reactions and the purity of the products. Melting points were taken in open capillaries and were uncorrected. IR spectra were recorded in KBr (pellet) on a Nicolet-Avatar–360 FT-IR spectrophotometer and noteworthy absorption values (cm^{-1}) alone are listed. ^{1}H-NMR spectra were recorded at 300 MHz on a Bruker AV 300 spectrometer using $CDCl_3$ as solvent and TMS as internal standard. The APCI + ve mass spectra were recorded on a Shimazdu LCMS-QP8000α LC MS spectrometer. Satisfactory microanalysis was obtained on a Carlo Erba 1106 CHN analyzer. A conventional (*unmodified*) domestic microwave oven equipped with a turntable (LG, MG-395 WA, 230V ~ 50 Hz, 760 W) was used for the irradiation. By adopting the

literature precedent [34], 2,6-diarylpiperidin-4-ones (**9–16**) were prepared by the condensation of the appropriate ketones, aldehydes and ammonium acetate in a 1:2:1 ratio.

*Preparation of 2,7-diphenyl-[1,4]-diazepan-5-one (**25**).* In a 100 mL borosil beaker, 2,6-diphenylpiperidin-4-one (**9**) (0.1 mol) and $NH_2OH.HCl$ (0.3 mmol) were mixed thoroughly with $NaHSO_4.Al_2O_3$ catalyst (150 mg), and the reactions were irradiated at 320W for 150 s. The mixture was removed from the oven, cooled and shaken with ethyl acetate (40 mL) and the catalyst removed by filtration. The filtrate was concentrated and the residue was subjected to column chromatography over silica gel using benzene [CARE-CARCINOGEN]:$CHCl_3$ (1.2:0.8) as eluent to afford the corresponding product (**25**) as a crystalline solid. IR (KBr) (cm^{-1}): 3447, 3311, 3082, 2927, 2792, 1671; MS (m/z): 267 (M^+) (M.F. $C_{17}H_{18}N_2O$); ^{1}H NMR (δ ppm): 2.11 (s, 1H, H_1), 2.65–2.69 (d, 1H, H_{6e}, J = −14.10), 3.00–3.34 (m, 2H, H_{3e} & H_{6a}), 3.58–3.82 (m, 1H, H_{3a}), 4.02–4.05 (d, 2H, H_2, J = 9.0), 4.12–4.16 (d, 2H, H_7, J = 10.2), 6.16 (s, 1H, H_4), 7.26–7.45 (m, 10H, Harom.).

Compounds **26–32** were synthesized similarly.

*3-Methyl-2,7-diphenyl-[1,4]-diazepan-5-one (**26**).* IR (KBr) (cm^{-1}): 3302, 3207, 3082, 2925, 2880, 2852, 1667; MS (m/z): 281 M^+ (M.F. $C_{18}H_{20}N_2O$); ^{1}H NMR (δ ppm): 0.61–0.90 (d, 3H, CH_3), 2.07 (s, 1H, H_1), 2.63–2.68 (d, 1H, H_{6e}, J = −14.1), 3.11–3.19 (t, 1H, H_{6a}), 3.81–3.84 (m, 1H, H_{3a}), 3.69–3.71 (d, 2H, H_2, J = 7.8), 4.12–4.15 (d, 2H, H_7, J = 10.8), 5.82 (s, 1H, H_4), 7.26–7.38 (m, 10H, Harom.).

*3-Ethyl-2,7-diphenyl-[1,4]-diazepan-5-one (**27**).* IR (KBr) (cm^{-1}): 3308, 3224, 3061, 2978, 2929, 2881, 2852, 1663; MS (m/z): 295 M^+ (M.F. $C_{19}H_{22}N_2O$); ^{1}H NMR (δ ppm): 0.61–0.89 (t, 3H, CH_3), 1.01–1.21 (m, 2H, CH_2), 2.03 (s, 1H, H_1), 2.63–2.67 (d, 1H, H_{6e}, J = −13.8), 3.11–3.18 (t, 1H, H_{6a}), 3.61–3.69 (m, 1H, H_{3a}), 3.75–3.79 (d, 2H, H_2, J = 7.5), 4.12–4.15 (d, 2H, H_7, J = 10.5), 5.76 (s, 1H, H_4), 7.21–7.42 (m, 10H, Harom.).

*3-Isopropyl-2,7-diphenyl-[1,4]-diazepan-5-one (**28**).* IR (KBr) (cm^{-1}): 3590, 3399, 3060, 2972, 2847, 2840, 2837, 1650; MS (m/z): 309 M^+ (M.F. $C_{20}H_{24}N_2O$); ^{1}H NMR (δ ppm): 0.93–0.97 (d, 6H, CH_3), 1.58–1.62 (m, 1H, CH), 2.07 (s, 1H, H_1), 2.62–2.66 (d, 1H, H_{6e}, J = −14.2), 3.14–3.18 (t, 1H, H_{6a}), 3.59–3.63 (m, 1H, H_{3a}), 3.93–3.97 (d, 2H, H_2, J = 7.6), 4.08–4.12 (d, 2H, H_7, J = 10.4), 5.74 (s, 1H, H_4), 7.28–7.45 (m, 10H, Harom.).

*3,6-Dimethyl-2,7-diphenyl-[1,4]-diazepan-5-one (**29**).* IR (KBr) (cm^{-1}): 3446, 3333, 3081, 2979, 2934, 2821, 1661; MS (m/z): 295 M^+ (M.F. $C_{19}H_{22}N_2O$); ^{1}H NMR (δ ppm): 0.72–0.82 (d, 6H, CH_3), 2.08 (s, 1H, H_1), 3.05–3.15 (m, 1H, H_{6e}), 3.87–3.91 (m, 1H, H_{3a}), 3.64–3.68 (d, 2H, H_2, J = 7.9), 3.79–3.81 (d, 2H, H_7, J = 8.9), 5.69 (s, 1H, H_4), 7.21–7.38 (m, 10H, Harom.).

*2,7-Bis(2-chloro-phenyl)-[1,4]-diazepan-5-one (**30**).* IR (KBr) (cm^{-1}): 3449, 3316, 3089, 2932, 2798, 1675; MS (m/z): 336 (M^+) (M.F. $C_{17}H_{16}Cl_2N_2O$); ^{1}H NMR (δ ppm): 2.18 (s, 1H, H_1), 2.68–2.72 (d, 1H, H_{6e}, J = −14.2), 3.26–3.30 (m, 2H, H_{3e} & H_{6a}), 3.79–3.83 (m, 1H, H_{3a}), 4.57–4.61 (d, 2H, H_2, J = 8.9), 4.68–4.72 (d, 2H, H_7, J = 10.2), 6.21 (s, 1H, H_4), 7.40–7.81 (m, 8H, Harom.).

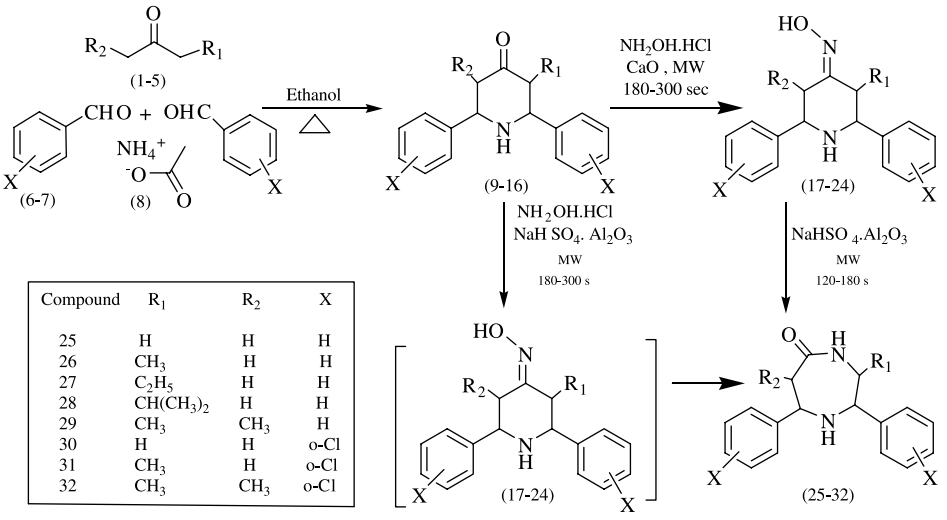
*2,7-Bis(2-chloro-phenyl)-3-methyl[1,4]-diazepan-5-one (**31**).* IR (KBr) (cm^{-1}): 3308, 3212, 3087, 2928, 2885, 2857, 1669; MS (m/z): 350 M^+ (M.F. $C_{18}H_{18}Cl_2N_2O$); ^{1}H NMR (δ ppm): 0.91–0.99 (d, 3H, CH_3), 2.17 (s, 1H, H_1), 2.69–2.73 (d, 1H, H_{6e}, J = −14.2), 3.20–3.24 (t, 1H, H_{6a}), 3.90–3.94 (m, 1H, H_{3a}), 4.49–4.53 (d, 2H, H_2, J = 7.6), 4.70–4.74 (d, 2H, H_7, J = 10.5), 5.89 (s, 1H, H_4), 7.41–7.70 (m, 8H, Harom.).

*2,7-Bis(2-chloro-phenyl)-3,6-dimethyl[1,4]-diazepan-5-one (**32**).* IR (KBr) (cm^{-1}): 3449, 3337, 3089, 2983, 2939, 2827, 1669; MS (m/z):364 M^+ (M.F. $C_{19}H_{20}Cl_2N_2O$); ^{1}H NMR (δ ppm): 0.85–0.95 (d, 6H, CH_3), 2.18 (s, 1H, H_1), 3.19–3.23 (m, 1H, H_{6e}), 3.93–3.97 (m, 1H, H_{3a}), 4.49–4.53 (d, 2H, H_2, J = 7.8), 4.61–4.65 (d, 2H, H_7, J = 8.7), 5.79 (s, 1H, H_4), 7.41–7.80 (m, 8H, Harom.).

Chemistry

Treatment of 2,6-diarylpiperidin-4-ones with hydroxylamine hydrochloride together with a catalytic amount of $NaHSO_4.Al_2O_3$ afforded the corresponding 2,7-diaryl-[1,4]-diazepan-5-ones in high yields in dry media under MW irradiation without any of the environmental disadvantages of using toxic reagents like sodium azide [30]. The $NaHSO_4.Al_2O_3$ catalyst was shown to be one of the most efficient MW absorbers with a very high specificity to MW heating and was able to reach a temperature of 120°C after 5 minutes irradiation in a domestic oven (320 W). The 1:1 ratio of $NaHSO_4.Al_2O_3$ catalyst to substrate is the most acceptable ratio in terms of efficiency and safety; a power level of 320 watts is the most suitable one. The product was separated using ethyl acetate and purified by column chromatography. The schematic representation and analytical data for the synthesized compounds **25–32** are given in Scheme 1 and Table I, respectively.

The conversion of 2,6-diarylpiperidin-4-ones into 2,7-diaryl-[1,4]-diazepan-5-ones by this method is believed to follow the Beckmann rearrangement. In the first step, 2,6-diarylpiperidin-4-ones are



Compound	R_1	R_2	X
25	H	H	H
26	CH_3	H	H
27	C_2H_5	H	H
28	$CH(CH_3)_2$	H	H
29	CH_3	CH_3	H
30	H	H	o-Cl
31	CH_3	H	o-Cl
32	CH_3	CH_3	o-Cl

Scheme 1. A convenient synthesis of some novel 2,7-diaryl-[1,4]-diazepan-5-ones (25–32).

Table I. Reaction conditions and analytical data for compounds 25–32[a].

Compound[a]	R_1	R_2	X	Reaction time (s)	Yield[b] (%)	m.p. (°C)
25	H	H	H	150	90	169
26	CH_3	H	H	120	95	183
27[c]	C_2H_5	H	H	170	83	189
28[c]	$CH(CH_3)_2$	H	H	300	90	187
29	CH_3	CH_3	H	250	95	181
30	H	H	*o*—Cl	180	90	210
31	CH_3	H	*o*—Cl	150	93	202
32	CH_3	CH_3	*o*—Cl	280	89	195

[a]The microanalysis values for C, H and N were within ± 0.4% of the theoretical values; [b]Yields of isolated products; [c]Reference [32].

converted to their respective oximes and rapidly rearrange to give 2,7-diaryl-[1,4]-diazepan-5-ones in the second step. The attempt to isolate the respective oximes from the reaction mixture was unsuccessful.

The formations of 2,7-diaryl-[1,4]-diazepan-5-ones *via* the oximes was confirmed by the same kind of reactions carried out using $NaHSO_4.Al_2O_3$ catalyst and 2,6-diarylpiperidin-4-one oximes (**17–24**) [31], under microwave irradiation. The products formed from the above two methods were found to be identical.

*Re-use of $NaHSO_4.Al_2O_3$ heterogeneous catalyst in the synthesis of 3-methyl-2,7-diphenyl-[1,4]-diazepan-5-one (**26**).* $NaHSO_4.Al_2O_3$ heterogeneous catalyst can be recovered and re-used up to four times (Figure 1) by washing with ethyl acetate after each use and then activating it in an oven at 120°C for 1 h prior to use, thus rendering the process more economical and green. (Figure 2).

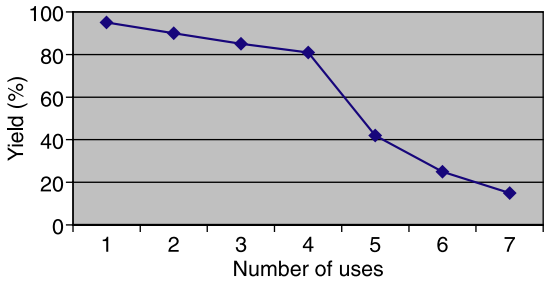


Figure 1. Re-use of $NaHSO_4.Al_2O_3$ in the synthesis of 3-methyl-2,7-diphenyl-[1,4]-diazepan-5-one (26). The reaction was carried out in a domestic microwave oven operating at 320W.

Results and discussion

Antibacterial activity

All the synthesized novel target molecule 2,7-diaryl-[1,4]-diazepan-5-ones **25–32** were tested for their antibacterial activity *in vitro* against *Staphylococcus*

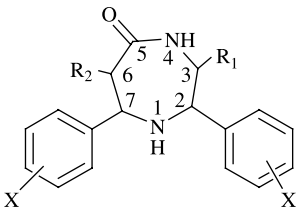


Figure 2. Numbering of **25–32**.

aureus, β-H. streptococcus, V. cholerae, S. typhii, E. coli, K. pneumonia and *Pseudomonas*. Ciprofloxacin was used as a standard drug. The zone of inhibition (mm) values are shown in Table II.

In general all the synthesized novel 2,7-diaryl-[1,4]-diazepan-5-ones **25**–**32** exerted a wide range of modest antibacterial activity *in vitro* against the tested organisms, their activity decreasing upon dilution. All the compounds were less active against *Escherichia coli* and more active against *Staphylococcus aureus, Salmonella typhii and Pseudomonas.* Introduction of an alkyl groups at C_3/C_6 position in compounds **26–29**, **31** and **32** did not influence much the biological activities. However, among the chloro-substituted compounds **30–32**, 2,7-*bis*(2-chloro-phenyl)-[1,4]-diazepan-5-one (**30**), was the most effective compound.

Table II. *In vitro* antibacterial activity of compounds 25–32.

Compounds	DIAMETER OF THE ZONE OF INHIBITION																					
	Staphylococcus aureus			β-Heamolytic streptococcus			Vibreo cholerae			Salmonella typhii			Escherichia coli			Klebsiella pneumonia			Pseudomonas		
	100	200	500	100	200	500	100	200	500	100	200	500	100	200	500	100	200	500	100	200	500
	(ppm)			(ppm)			(ppm)			(ppm)			(ppm)			(ppm)			(ppm)		
25	20	23	25	21	23	26	20	21	23	21	23	24	15	16	18	21	24	28	23	25	27
26	23	24	26	21	23	25	19	20	23	20	22	25	13	15	17	26	27	29	24	26	28
27	21	23	25	20	23	25	20	22	24	21	23	25	15	17	18	22	25	27	24	26	28
28	22	25	27	22	24	26	20	22	24	22	24	26	16	17	19	25	26	28	26	27	29
29	20	23	26	20	22	25	18	20	23	20	23	25	16	17	20	25	27	29	24	26	28
30	21	24	29	22	24	27	21	21	25	22	24	27	17	18	21	22	25	29	24	26	29
31	24	25	28	22	24	26	20	21	24	21	23	26	14	17	19	26	27	28	25	27	28
32	21	24	27	21	23	26	19	21	23	21	24	26	17	18	19	26	26	27	25	26	27
Ciprofloxacin		25			28			23			22			24			26			23	

Antifungal activity

The *in vitro* antifungal activity of the synthesized novel heterocyclic compounds **25**–**32** was studied against certain fungal strains viz., *A. flavus, A. fumigatus, Mucor, C. albicans* and *Rhizopus.* Fluconazole was used as a standard drug. The zone of inhibition (mm) values are shown in Table III. Generally all the synthesized compounds exerted a wide range of modest *in vitro* antifungal activity against all the tested organisms, their activity decreasing upon dilution. Of the chloro-substituted compounds **30–32**, 2,7-*bis*(2-chloro-phenyl)-[1,4]-diazepan-5-one (**30**) was the most active compound. Moreover, of all the compounds tested, **30** was the most effective against *Mucor.*

Conclusion

Examination of the *in vitro* antibacterial and antifungal activity profiles for the differently substituted novel 2,7-diaryl-[1,4]-diazepan-5-ones against the tested bacterial and fungal strains, provides a structure-activity relationship, which may be summarized as follows:

The nature of the substituent on the phenyl ring viz., chloro moiety is determinant for the nature and extent of the activity of the synthesized compounds, which might an influence on their inhibiting mechanism of action. Although this is unknown, these observations may promote further developments of our research in this field. Which may lead to compounds with a better pharmacological profile than standard drugs and serve as templates for the construction of better drugs to combat bacterial and fungal infection.

Table III. In vitro antifungal activity of compounds 25–32.

	DIAMETER OF THE ZONE OF INHIBITION														
	Aspergillus flavus			Aspergillus fumigatus			Mucor			Candida albicans			Rhizopus		
Compounds	100	200	500	100	200	500	100	200	500	100	200	500	100	200	500
	(ppm)			(ppm)			(ppm)			(ppm)			(ppm)		
25	21	23	25	20	22	24	23	25	27	18	19	21	10	12	14
26	20	24	26	20	22	24	21	23	26	18	19	22	08	10	13
27	19	21	24	20	22	25	21	23	25	17	18	20	11	13	15
28	18	20	23	20	22	25	22	24	26	17	19	21	10	12	14
29	21	23	25	20	22	24	20	23	25	18	20	22	08	10	13
30	22	25	27	22	23	26	23	26	29	18	20	24	11	15	18
31	21	24	26	20	22	25	22	23	27	19	20	21	10	12	16
32	21	24	25	21	22	25	21	24	24	18	21	21	11	13	15
Fluconazole	20 ± 0.5 zone of inhibition against all the test fungi														

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