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Synthesis, structural aspects and antimicrobial activity of novel chiral β-keto amides

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ABSTRACT

Practical, stereoselective synthetic methods were applied to the preparation of a series of ten chiral β-keto amides. The antimicrobial activity of these compounds with respect to S. aureus, B.sutilis, E. coli and C.albicans was evaluated. It was found that of 3-(4-fluorophenyl)-N-[(S)-1-cyclohexylethyl]-3-oxopropanamide suppressed the growth of test microbes, with a minimum inhibitory concentration of 125 μg/ml against B.subtilis, S.aureus and 3-(4-chlorophenyl)-3-oxo-N-[(R)-1-phenylethyl]propanamide with a minimum inhibitory concentration of 125 □g/ml against E. coli and C.albicans. The other tested compounds were significantly less active.

Keywords: β-keto esters, chiral β-keto amides, antibacterial, antifungal

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INTRODUCTION

The World Health Organisation (WHO) in 2005 ranked infections as the leading are the leading infectious cause of death in all ages, worldwide [1].

Key community and hospital bacterial disease burdens include pediatric infections and multiple drug resistance in both Gram-positive and Gram-negative organisms [2].

An increasing prevalence of antibiotic resistance has led to the progressive decrease in the effectiveness of narrow-spectrum agents and to an increase in difficult-to-treat infections. More than ever, selection of most appropriate antibiotic therapy has become a challenge for clinicians [3].

β-Keto amides [4-8] are versatile intermediates for the synthesis of several heterocycles: 3-acyltetramic acids [9], pyrans, [10] alkaloids [11], lactams and spirolactams [12], azetidin- 2-ones [13], as well as several 3-hydroxyisothiazol bioisosteres of glutamic acid and analogs of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor agonist [14]. Some β-keto amides have been converted into □-keto amides, a class of compounds related with a wide variety of biologically relevant systems [15].

In addition to that, many biologically active compounds contain β-keto amide fragments in their structure [16] and various amide derivatives were synthesized and explored for their antimicrobial [17]-[18].

A series of quinoline carboxamide derivatives have also been evaluated for positive inotropic activity [19], as potential radio ligands in the neurodegeneration systems [20] and antiviral against acyclovir resistant herpes simplex virus [21].
Various 2- substituted amide derivatives of benzofuran are reported as potent orexin receptor antagonist [22] and anti hyperlipidemic agents [23].

Literature survey reveals that various amide derivatives show antimicrobial as well as central nervous system (CNS) activities, however, the antimicrobial activity of chiral β-keto amides is still insufficiently studied.

In continuation of our research aimed toward the preparation of natural and non-natural compounds of biomedical importance [24-25] and in connection with ongoing investigations on the synthesis and reactivity of β-keto esters [26-30] it seemed interesting to study the reaction of β-keto esters with different commercially available chiral amines and to evaluate the antimicrobial activity of the prepared compounds.

EXPERIMENTAL SECTION

Chemistry

Reagent grade chemicals and solvents were purchased from commercial supplier and used without purification. TLC was performed on silica gel F254 plates (Merck). Silica gel (100-200 mesh) was used for column chromatographic purification. Melting points are uncorrected and were measured in open capillary tubes, using a Rolex melting point apparatus. IR spectra were recorded as KBr pellets on Perkin Elmer RX spectrometer. ^{1}H NMR and ^{13}C NMR spectral data were recorded on Advance Bruker 300 spectrometer (300 MHz) with $CDCl_3$ as solvent and TMS as internal standard. *J* values are in Hz.

The β-keto ester **2** (314 mg, 1 mmol) was dissolved in toluene (10 mL). A chiral amine in toluene (20 mL) was heated at 110 °C for 5 h. After cooling, the solution was diluted with toluene, and the product was extracted with ether and the organic phase was washed with brine, dried with anhydrous potassium carbonate and evaporated. The product was purified by column chromatography (SiO_2, cyclohexane/AcOEt, 50:50) to provide the corresponding β-keto amides **3**.

_N_-[(_S_)-1-cyclohexylethyl]-3-oxo-3-phenylpropanamide (3a)
Yield: 72%; white powder; mp 115 Cº; ^{1}H NMR ($CDCl_3$, 300 MHz, 27 ºC): δ=7.94 (d, *J*= 8, 4 Hz, 2H), 7.51 (m, 1H), 7.31 (m, 2H), 6.95 (d, NH), 3.92 (s, 2H), 3.76 – 3.87(m, 1H), 1.62–1.71 (m, 5H), 1.04–1.32 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz, 27 ºC): δ=196.0, 164.3, 135.6, 133.5, 130.0, 128.3, 128.0, 127.9, 125.1, 49.1, 44.9, 42.4, 28.5, 28.3, 25.8, 28.6, 17.5, 17.3.

_N_-[(_S_)-1-cyclohexylethyl]-3-(4-methylphenyl)-3-oxopropanamide (3b)
Yield: 70%; white powder; mp 121 C º; ^{1}H NMR ($CDCl_3$, 300 MHz, 27 ºC): δ =7.88 (d, *J*= 8,4, 2H), 7.26 (d, *J* = 8.7, 2H), 7.0 (d, NH), 3.90 (s, 2H), 3.84 – 3.87 (m, 1H), 2.42 (s, 3H), 1.62–1.74 (m, 5H), 1.04–1.32 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz, 27 ºC): δ =196.1, 164.9, 145.0, 133.8, 129.5, 128.6, 49.6, 45.3, 42.9, 29.04, 28.8, 26.3, 26.1, 21.6, 17.7.

3-(4-chlorophenyl)-_N_-[(_S_)-1-cyclohexylethyl]-3-oxopropanamide (3c)
Yield: 68%; white crystals, mp 150 C º; ^{1}H NMR ($CDCl_3$, 300 MHz, 27 ºC): δ =7.94 (d, *J*= 8.4 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 6.81 (d, NH), 3.91 (s, 2H), 3.85 – 3.96(m, 1H), 1.66–1.74 (m, 5H), 0.9–1.35 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz, 27 ºC): δ =194.5, 163.9, 140.1, 134.0, 129.5, 128.6, 49.3, 45.4, 42.4, 28.5, 28.3, 25.8, 25.6, 17.2.

_N_-[(_S_)-1-cyclohexylethyl]-3-(4-fluorophenyl)-3-oxopropanamide (3d)
Yield: 63%; white powder, mp 127 C º; ^{1}H NMR ($CDCl_3$, 300 MHz, 27 ºC): δ = 6.38–7.43 (m, 2H), 6.42–6.54 (m, 2H), 6.15 (d, NH), 3.23 (s, 2H), 3.18 – 3.22(m, 1H), 1.01–1.2 (m, 5H), 0.57–0.78 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz, 27 ºC): δ =194.1, 167.5, 164.0, 130.9, 130.8, 115.6, 115.3, 49.2, 45.8, 42.9, 28.5, 28.3, 25.8, 25.6, 17.2.

3-(4-bromophenyl)-_N_-[(_R_)-1-cyclohexylethyl]-3-oxopropanamide (3j)
Yield: 69%; white powder, mp 136 C º; ^{1}H NMR ($CDCl_3$, 300 MHz, 27 ºC): δ =7.85 (d, *J*= 8.4, 2H), 7.58 (d, *J*= 8.4 Hz, 2H), 6.76 (d, NH), 3.91 (s, 2H), 3.83 – 3.97 (m, 1H), 1.60–1.73 (m, 5H), 1.14–1.35 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz, 27 ºC): δ =195.3, 164.3, 134.9, 132.2, 131.6, 130.1, 129.4, 127.2, 49.8, 45.8, 42.9, 29.0, 28.8, 26.3, 26.1, 18.0, 17.7.

3-oxo-3-phenyl-*N*-[(*R*)-1-phenylethyl]propanamide (3g)
Yield : 74%; white powder, mp 150 C °; ^{1}H NMR ($CDCl_3$, 300 MHz, 27 °C): δ = 8.02–7.99 (d, *J*= 7,8 Hz, 2H), 7.72 (d, NH), 7.33–7.65 (m, 8H), 5.13 (m, 1H), 3.96 (d, *J* = 5.1 Hz, 2H), 1.52 (d, *J* = 6.9 Hz, 3H) ; ^{13}C NMR ($CDCl_3$, 75 MHz, 27 °C): δ = 195.7, 164.2, 142.6, 135.7, 133.5, 128.3, 128.1, 128.0, 127.9, 126.8, 125.5, 125.2, 48.5, 48.0, 44.7, 21.6, 21.4.

IR (KBr): ν = 3328νcm^{-1} (ν_{NH}), 2984 cm^{-1} (ν_{C-H}), 1719 cm^{-1} ($\nu_{C=O}$), 1638 cm^{-1} ($\nu_{C=O}$), 1523 cm^{-1} ($\nu_{C=C}$). $[\alpha]_D^{22}$ +46.4 (c= 0.87, $CHCl_3$).

3-(4-methylphenyl)-3-oxo-*N*-[(*R*)-1-phenylethyl]propanamide (3h)
Yield: 75%; yellow powder, mp 119 C °; ^{1}H NMR ($CDCl_3$, 300 MHz, 27 °C): δ = 7.86–7.88 (d, *J*= 8, 4 Hz, 2H), 7.54 (d, NH), 7.16–7.34 (m, 7H), 5.10 (m, 1H), 3.90 (d, *J* = 6 Hz, 2H), 2.41 (s, 3H), 1.48 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, 27 °C): δ = 195.8, 164.9, 145.1, 143.1, 133.7, 129.5, 129.1, 128.69, 128.65, 127.4, 127.2, 126.0, 125.6, 49.0, 48.4, 45.1, 22.1, 21.9, 21.7, 21.4.

IR (KBr): ν = 3321νcm^{-1} (ν_{NH}), 2978 cm^{-1} (ν_{C-H}), 1712 cm^{-1} ($\nu_{C=O}$), 1638 cm^{-1} ($\nu_{C=O}$), 1530 cm^{-1} ($\nu_{C=C}$).

3-(4-fluorophenyl)-3-oxo-*N*-[(*R*)-1-phenylethyl]propanamide (3f)
Yield: 67%; white crystals, mp 113 C °; ^{1}H NMR ($CDCl_3$, 300 MHz, 27 °C): δ = 8 (t, *J* = 8.4 Hz, 2H), 7.7 (s, NH), 7.07–7.36 (m, 7H), 5.11 (m, 1H), 3.85 (d, *J* = 4.8 Hz, 2H), 1.51 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, 27 °C): δ = 194.4, 168.0, 164.6, 143.0, 132.6, 131.4, 131.3, 128.6, 127.3, 126.0, 116.1, 115.9, 49.1, 45.5, 22.0.

3-(4-chlorophenyl)-3-oxo-*N*-[(*R*)-1-phenylethyl]propanamide (3i)
Yield: 71%, white crystals, mp 137 C °; ^{1}H NMR ($CDCl_3$, 300 MHz, 27 °C): δ = 7.93–7.96 (d, *J*= 8, 4 Hz, 2H), 7.65 (d, NH), 7.29–7.49 (m, 7H), 5.11 (m, 1H), 3.92 (d, *J* = 4.2 Hz, 2H), 1.51 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, 27 °C): δ = 194.3, 163.9, 142.4, 140.2, 133.9, 129.5, 128.7, 128.1, 126.8, 125.5, 48.6, 45.1, 21.5.

IR (KBr): ν = 3275νcm^{-1} (ν_{NH}), 2972 cm^{-1} (ν_{C-H}), 1700 cm^{-1} ($\nu_{C=O}$), 1645 cm^{-1} ($\nu_{C=O}$), 1551 cm^{-1} ($\nu_{C=C}$).

***N*-[(*S*)-1-(naphthalen-2-yl) ethyl]-3-oxo-3-phenylpropanamide (3e)**
Yield: 74%; white powder, mp 141 C °; ^{1}H NMR ($CDCl_3$, 300 MHz, 27 °C): δ = 7.25–8.09 (m, 12H), 7.76 (d, NH), 5.94 (m, 1H), 3.86 (d, *J* = 5.1 Hz, 2H), 1.65 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, 27 °C): δ = 196.0, 164.6, 138.3, 136.1, 134.0, 133.9, 130.9, 128.8, 128.7, 128.5, 128.4, 128.2, 126.4, 125.9, 125.7, 125.2, 123.2, 122.4, 45.4, 45.0, 21.1, 20.9.

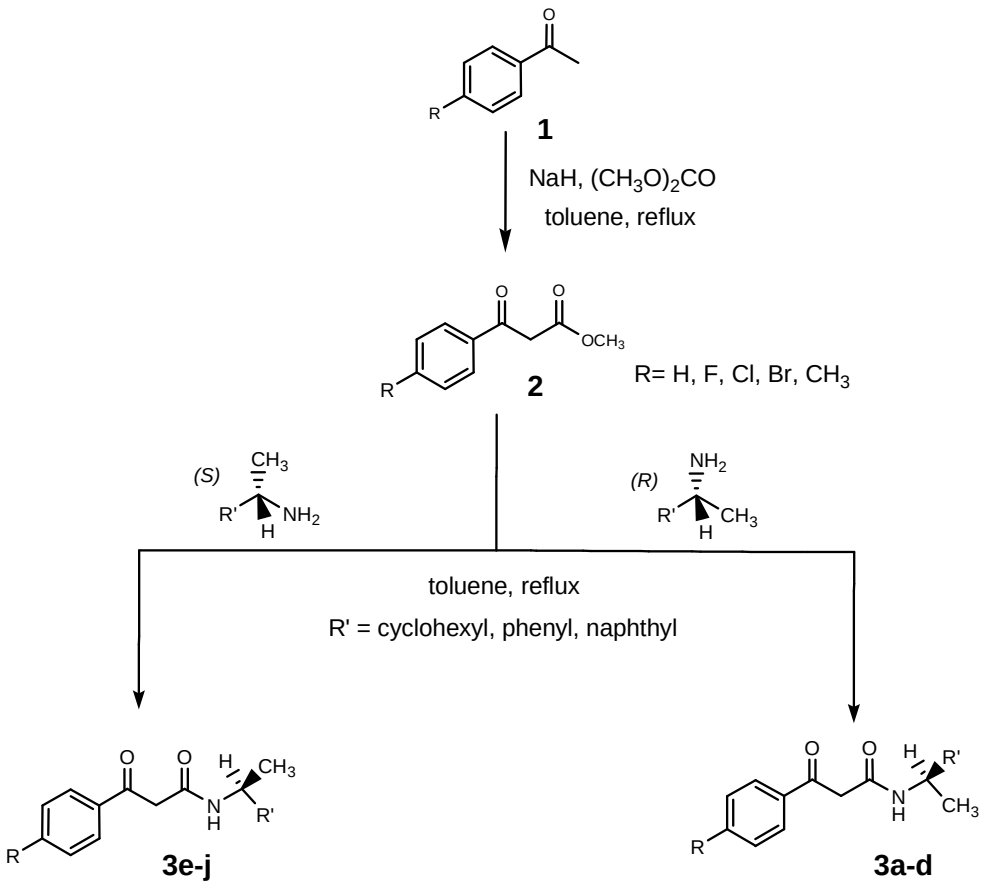
IR (KBr): ν = 3289 cm^{-1} (ν_{NH}), 2972 cm^{-1} (ν_{C-H}), 1706 cm^{-1} ($\nu_{C=O}$), 1639 cm^{-1} ($\nu_{C=O}$), 1545 cm^{-1} ($\nu_{C=C}$).

Antimicrobial and Antifungal Assays
The bacteria were cultivated in tryptic soy broth (TSB) or agar (Sigma) at the appropriated temperature (30°C or 37°C) of the strain. Yeast was cultured on malt extract broth (MEB) or agar (Fluka,) at 28°C. Inocula were prepared by adjusting the turbidity of each bacterial and yeast cultures to reach an optical comparison to that of a 0·5 McFarland standard, corresponding to approx. 1–5 ×10^5 CFU ml^{-1}.

Minimal inhibitory concentrations (MICs) [17, 18], minimal bactericidal concentrations (MBCs) [19], and minimal fungicidal concentration (MFCs) [20] were determined by NCCLS (2000) broth macrodilution method. DMSO was used as a blank exhibited no activity against any of the used strains. Further dilutions were, then, performed using two fold dilution in TSB for bacteria and MEB for fungi.

RESULTS AND DISCUSSION

Chemistry
The starting β-keto esters **2** were prepared from the commercially available acetophenone derivatives **1** in the presence of sodium hydride and dimethyl carbonate, as previously described [29] (Scheme 1).



Scheme 1. Synthesis of chiral β-keto amides 3a–j

3a : R= H ; R'= cyclohexyl
3b : R= CH_3 ; R'= cyclohexyl
3c : R= Cl ; R'= cyclohexyl
3d : R= F ; R'= cyclohexyl
3e : R= H ; R'= naphthyl
3f : R= F ; R'= phenyl
3g : R= H ; R'= phenyl
3h : R= CH_3 ; R'= phenyl
3i : R= Cl ; R'= phenyl
3j : R= Br ; R'= cyclohexyl

The β-keto amides **3** were synthesized by reacting β-keto esters **2** with different commercially available chiral amines in refluxing non-polar solvents such as toluene.

The resulting products were obtained in good yields and the results are summarized in table 1.

Table 1. Isolated yields of compounds 3 obtained according to scheme 1

Entry	R	R'	Substrate (configuration)	Yield(%)	m.p (°C)
1	H-	C_6H_{11}	**3a (*S*)**	72%	115
2	CH_3-	C_6H_{11}	**3b (*S*)**	70%	121
3	Cl-	C_6H_{11}	**3c (*S*)**	68%	150
4	F-	C_6H_{11}	**3d (*S*)**	63%	127
5	H-	$C_{10}H_7$	**3e (*S*)**	74%	141
6	F-	C_6H_5	**3f (*R*)**	67%	113
7	H-	C_6H_5	**3g (*R*)**	74%	150
8	CH_3-	C_6H_5	**3h (*R*)**	75%	119
9	Cl-	C_6H_5	**3i (*R*)**	71%	137
10	Br-	C_6H_{11}	**3j (*R*)**	69%	136

Interestingly, the stereogenic center did not undergo any racemization. A single crystal X-ray crystal structure was obtained for 3-(4-chlorophenyl)-3-oxo-*N*-[(*S*)-1-phenylethyl] propanamide **3i** (Figure 1).

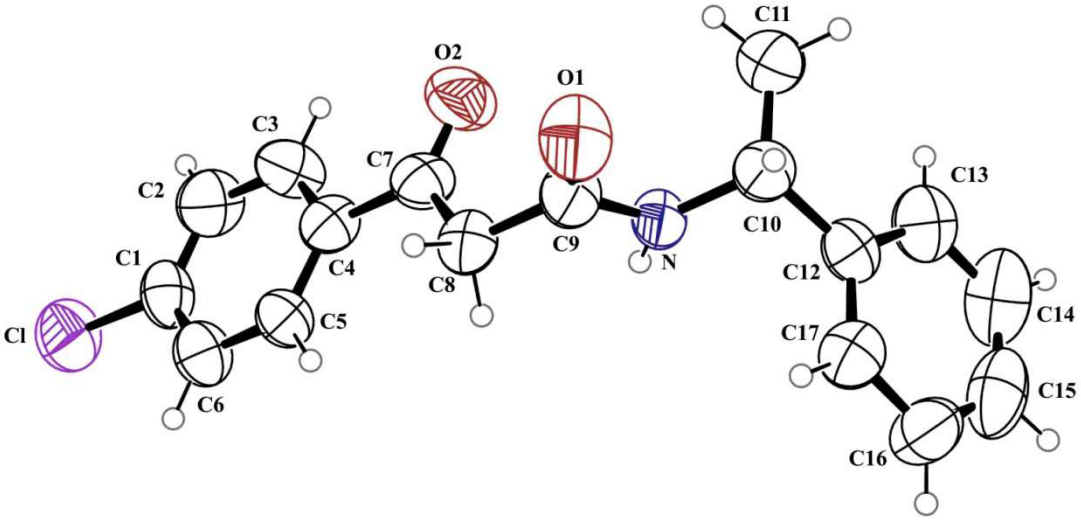


Figure 1. The Crystal Structure of 3-(4-chlorophenyl)-3-oxo-*N*-[(*R*)-1-phenylethyl]propanamide ORTEP drawing [31]

All the compounds were characterized by, ^{1}H NMR, ^{13}C NMR, and IR spectra.

IR spectrum of **2c** exhibited bands at 1710 and 1757 cm^{-1} for ketone carbonyl and ester group respectively. In ^{1}H NMR of **2c** singlet at δ 3.98 for three protons confirmed the presence of OCH_3 group and singlet at δ 3.8 for two protons indicated CH_2 group. The carbon signals at 191-175 ppm are assigned to ketone C=O and the amide C=O groups.

After amidation, in ^{1}H NMR of **3c**, the disappearance of peak at δ 3.98 and broad peak appears at δ 6.81 ppm corresponding to amide CONH proton. The carbon signals at 194.5 and 163.9 ppm are assigned to ketone C=O group and the amide C=O group respectively, No significant changes are observed for the aromatic moieties in the ^{1}H and ^{13}C NMR spectra.

Antimicrobial activity

The newly synthesized compounds were tested for their antibacterial and antifungal activities. The tested compounds were evaluated for their antifungal activity against *Candida albicans* (ATCC90028). The antibacterial activity was evaluated against Gram-positive: *Bacillis subtilis* (ATCC 6059), *Staphylococcus aureus* (ATCC 25923) and Gram-negative *Escherichia coli* (ATCC 25922). Cefazol and Flucanazole were taken as standards respectively for the antifungal and antibacterial activity. The antimicrobial activity of the chiral β-keto amides are listed in table 2.

Table 2. Minimal inhibitory concentration (MIC, µg /mL) of the newly synthesized compounds

Compound no.	MIC µg mL^{-1}			
	Gram(+) bacteria		Gram(-) bacteria	FUNGI
	S. aureus	*B.subtilis*	*E. coli*	*C. albicans*
3a	250	250	250	250
3b	500	250	250	250
3c	250	250	250	250
3d	125	125	250	250
3e	250	250	250	250
3f	250	250	250	250
3g	250	250	250	250
3h	250	250	250	250
3i	250	250	125	125
3j	500	250	250	250
Cefazol	250	250	250	NA
Flucanazole	NA	NA	NA	250

"NA": no activity.

Table 3. The Minimum Bactericidal Concentration (MBC) and Minimum Fungicidal Concentration (MFC) of three newly synthesized compounds (NCCLS, 2002)

Compound no.	MBC (µg/mL) *E. coli*	MFC (µg/mL) *C. albicans*
3d	NA	250
3e	250	NA
3i	NA	250
Cefazol	250	NA
Flucanazole	NA	250

"NA": No Activity.

The obtained data revealed that most of the compounds showed a potent antimicrobial activity against the used microorganisms (Table 2). In fact, all compounds -excepting **3d** and **3j**- showed a strong antibacterial activity essentially against *S. aureus* which MICs are less than 256 µg mL^{-1} (table 2). Rao et al. [3] established that antibiotics activity against *S. aureus* required MICs up to 256 µg mL^{-1}. Moreover, these compounds revealed powerful antibacterial activity against Gram-negative bacteria and fungi. In the contrary of some researcher's results, MICs values are similar both for Gram-positive, Gram-negative bacteria and also for fungi. In effect, Yangui et al. established that MICs values generally were higher for fungi than for bacteria and Gram-positive are more sensitive than Gram-negative bacteria [32].

Results of Table 3 showed that, **3d**, **3e** and **3i** exhibited bactericide and fungicide effects. Indeed, the MICs are equal to the MBCs values (Table 2 and 3), while the other compounds showed rather, an inhibitory effect since MBCs are higher than MICs (data not shown). In fact, these compounds possess a bacteriostatic effect because the MBC/MIC ratio is greater than one.

It is more attractive to speculate the observation that the result of the antimicrobial activity of the various derivatives appeared to be related the nature of substituents on the phenyl ring.

The compound **3d**, showed effective activity against both *S.aureus* and *B.subtilis* (MIC= 125 µg /mL). Moreover, compound **3i**, with chloro-phenyl group showed a good activity against *E. coli* (MIC= 125 µg /mL). Further, the compounds **3c**, **3e**, **3f** and **3g** were found moderate activity against all the tested organisms at a MIC 250 µg /mL. The compound **3b** having CH_3 substituent on the phenyl ring were found less active with (MIC 500 µg /mL) against *S.aureus*.

It is obvious from the analysis of activity results that electron withdrawing groups such as chloro- and fluoro-group these have strong effects in determining the antibacterial activity. This observation is supported by the highest activity shown by the compound **3i** with (MIC, 125 µg /mL) against both the Gram-negative bacterial strains and fungi. Thus, we hypothesize that the presence of electron withdrawing groups such as chloro- and fluoro-group and with electron releasing groups such as CH_3 has significant effect on antibacterial activity.

This could result from increased lipophilicity associated with chloro phenyl group have higher biological activities because the increased lipophilicity facilitates penetration and transport as well as protection of the compound from metabolism. It is apparent that there is a positive correlation between anti-*Candidal* activity and electronegative functional groups like chloro, bromo and fluoro [33]. The hydrophobicity balance was already proved to be important in such series to obtain anti *Candida* activity [34].

CONCLUSION

In the present work series of ten new β-keto amides were synthesized and screened for their antimicrobial activity as well as their MIC against ATCC microorganisms (Gram-positive and Gram-negative bacteria and fungus). The most lipophilic compounds bearing p-chlorophenyl, fluorophenyl substitution were more active than the compounds bearing methylphenyl. Compound **3i** was the most effective compound against *C. albicans* (MIC, 125 µg /mL). This outcome confirms that p-chlorophenyl substitution have a considerable influence on anti-Candidal activity. The present results may be used as key steps for the construction of novel chemical entities with better pharmacological profiles than standard drugs. These compounds can also be explored for orexin receptor antagonist activity.

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[31] CCDC 1060095 contains crystallographic data for 3-(4-chlorophenyl)-3-oxo-*N*-[(*R*)-1-phenylethyl]propanamide. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44 1223336033; e-mail: deposit_reply@ccdc.cam.ac.uk, https://www.ccdc.cam.ac.uk/deposit). The molecular formula = C_{17} H_{16} C_{l1} N_1 O_2, belongs to an monoclinic system, space group = P 1 21 1, parameters of the unit cell are: a = 4.677 (3) Å, b = 10.839 (8) Å, c = 15.373 (10) Å, β = 92.975, Z = 4.
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