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Research Article

CHALCONE DERIVATIVES; THEIR EFFICIENT ORGANOCATALYSED SYNTHESIS AND BIOLOGICAL APPLICATIONS

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ABSTRACT

Different proline derived organocatalyts were tried to bring about the Michael addition reaction between benzylidene-acetone and 4-hydroxy coumarin as model reaction. The yield of the Michael adduct (**1a**) was tried to improve by the variation of mol% of catalysts and solvents. The maximum yield was obtained for 20 mol% Organocatalyst **A** in DCM while TFA was used as a cocatalyst. At these optimized reaction conditions six other derivatives of 4-hydroxycoumarin with substituted α,β unsaturated ketones were synthesized. Maximum yield of product were obtained when methyl and phenyl groups were selected as a substituent's on α, β unsaturated ketones. The synthesized compounds were characterized by using EI-MS, ^{1}H-NMR and ^{13}C-NMR spectroscopic techniques. These compounds were evaluated for their antimicrobial activities by Filter paper disc diffusion methods. The compound 4a showed maximum %inhibition against *Candidaalbicans* at concentration of 1000 µg/mol while the compound 7a has shown excellent activity against *Aspergilusflavus and Candidaalbicans* at both low and high concentrations. The compound 7a also showed excellent antibacterial activities against *Escherichia coli* and *Acetobecoracceti* at both 500 µg/mol and 1000 µg/mol. The results of antimicrobial activities proved these compounds to be biologically active and may be investigated as new drugs in future.

Keywords: Synthesis, Organocatalysts, Antifungal, Antibacterial.

INTRODUCTION

The role of organocatalysts in the field of organic synthesis is versatile. Organocatalysis is the technique to bring about easy and convenient chemical reactions with inexpensive and readily available organic compounds. Such reactions are friendly benign [1]. Michael addition reactions are mostly catalyzed by organic moieties and number of organic compounds have been synthesized [2] as potent organocatalysts. Warfarin is an example of such compounds synthesized by using different organocatalysts. It is an anticoagulant drug and is prepared by carbon carbon bond formation between 4-hydroxycoumarin and α,β unsaturated ketones [3]. Synthesis of Warfarin using different amines is one of most successful Michael addition reactions [4-5]. Although the reaction was accelerated by number of different organocatalysts but the synthesis in terms of its analogues is limited. The organocatalysts have improved the yield and enantioselectivity of the warfarin. The previous reactions were carried out by using 4-hydroxycoumarin and α,β unsaturated ketones [6-10]. The current research is based on the use of new organocatalysts in the Michael addition reactions between 4-hydroxy coumarinsand α, β unsaturated ketones as well as chalcones.

α,β unsaturated ketones and chalcones are the resourceful organic compounds. Chalcones are 1,3-diphenyl-2-propene-1-one. In chalcones three carbon atoms are linked by α, β unsaturated carbonyl system [11]. Chalcones and α, β unsaturated ketones act as Michael accepters in Michael addition reactions. Naturally occurring chalcones are present in edible plants and they are the building frameworks of many flavonoids and iso-flavonoids [12]. Chalcones has played a broad spectrum of pharmacological activities. The derivatives of chalcones are more potent than their precursors. Most of the derivatives exhibit antibacterial [13-14], anti-inflammatory [15-16], antifungal [17-18], antimicrobial [19-20] and anticancer [21-22] activities. The progress in the synthesized derivatives of chalcones as well as the advances in organocatalysis has motivated us to synthesize new derivatives of chalcones in the presence of organic moities. The organocatalysed Michael reactions were brought about between chalcones and β-dicarbonyl system. The organocatayst used were proline derived amides. This catalytic scheme was tried for the first time for chalcones and β- dicarbonyl system. Earlier research has shown such type of reactions between nitroalkanes and chalcones[23-25]. The reported catalysts gave moderate to excellent yields of the products and have also shown excellent antimicrobial activities. This strategy will be helpful in future because a number of such compounds can be synthesized with high yield and enantioselectivity.

MATERIALS AND METHODS

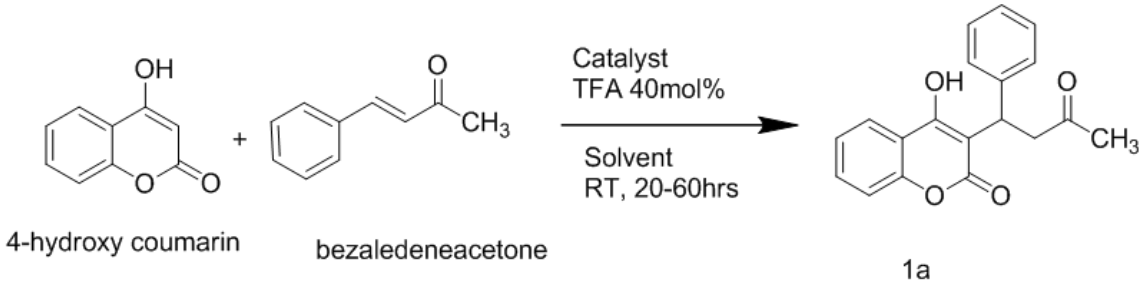
Instruments and chemicals

The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 or $CDCl_3$ solvent on Advance Bruker 400 MHz spectrophotometers using tetramethylsilane (TMS) as an internal reference. Mass spectras were recorded on JEOL MSRoute. Melting points were determined in a capillary tube using a Gallenkamp (UK) electrothermal melting point apparatus. The progress of the reaction was monitored by Thin Layer Chromatography using precoated silica gel plates (aluminum sheets, layer thickness 0.2mm, HF-254, Riedel-de-Haen). Following solvents systems were used for the separation of compounds on chromatograms: n-hexane/ethylacetate (7:3), pet. ether/ethylacetate (6:4), chloroform/methanol (9:1). Chromatograms were detected by UV light (254 and 360 nm) and vanillin spray. The vanillin spray was prepared by dissolving 2grm vanillin in 2ml H_2SO_4 and 100ml absolute ethanol.

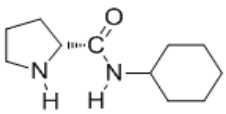
General procedure of synthesis

Synthesis of compound 1a and optimization of reaction conditions

The compound 1a was synthesized at different reaction conditions. The reaction conditions were optimized by varying mol% of catalyst and solvents. Their results were summarized in table1. 10-30mol% of catalyst **A to E** were tried to increase the yield of **1a**. Dichloromethane (DCM) and tetrahydrofuran (THF) with different combination of co-catalysts TFA and Et_3N were also used to improve the yield. Generally 0.16mmol (0.0626g) of 4-hydroxycoumarin and 0.1mmol (0.0145g) of α,β unsaturated ketones (bezylideneacetone), 10-30 mol% catalysts **A** to **E** were dissolved in 20ml of dry dichloromethane in round bottom flask. 40 mol% of TFA/Et_3N were also added in the reaction mixture. This reaction mixture was stirred at room temperature for different time intervals till the completion of reactions. The progress of the reactions were monitored by TLC visualized under UV lamp and developed in vanillin spray. The product gave blue spot in vanillin with α,β unsaturated ketones. When there was not further significant increase in concentration of product, the final product was purified by column chromatography. The columns were packed in silica gel in n-hexane or pet ether. Elution was made with increasing concentration of ethyleacetate in n-hexane: ethyleacetate mixture.

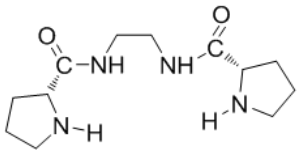


Scheme 1: Scheme of synthesis of compounds



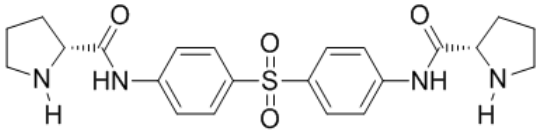
Catalyst A

N-{1-[(2R)-pyrrolidin-2-yl]ethenyl}cyclohexanamine



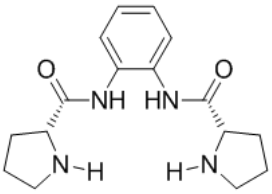
Catalyst B

(2R,2'R)-N,N'-(ethane-1,2-diyl)bis(pyrrolidine-2-carboxamide)



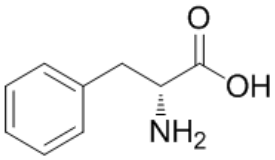
Catalyst C

(2R,2'R)-N,N'-(sulfonylbis(4,1-phenylene)bis(pyrrolidine-2-carboxamide)



Catalyst D

(2R2'R)-N,N'-(ethane-1,2-phenylene)bis(pyrrolidine-2-carboxamide)



Catalyst E

(2R)-2-amino-3-phenylpropanoic acid

Fig. 1: Structures of organocatalysts used

Table1: Optimization of reaction conditions

S. No.	Catalyst	Catalyst (mol%)	Co-catalyst	Solvent	Yield (%)
01	A	20	TFA	DCM	82
02	B	20	TFA	DCM	64
03	C	20	TFA	DCM	75
04	D	20	TFA	DCM	79
05	E	20	TFA	DCM	NR
06	A	20	Et_3N	DCM	44
07	A	20	TFA	THF	81.5
08	A	10	TFA	DCM	38
09	A	30	TFA	DCM	80

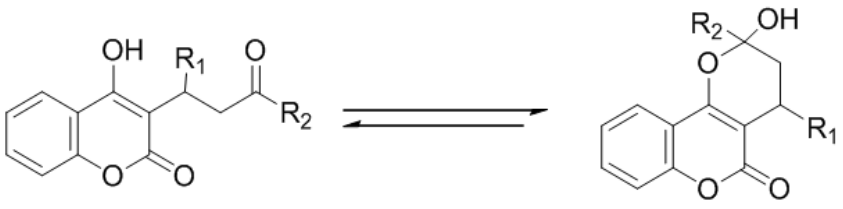


Fig. 2: Keto enol tautomeric forms of synthesized compounds

Synthesis of compounds 2a-7a

The conditions for maximum yield were optimized in the above reaction scheme 1 and then are used for the synthesis of compound 2a-7a as given in scheme 2. Six more compounds were synthesized by mixing 4-hydroxycoumarin (0.16mmol), different types of α, β unsaturated ketones or chalcones (0.1mmol) and 20% of catalyst **A** in 20ml of dry dichloromethane in round bottom flask in the presence of 40 mol% of TFA. The reaction mixtures were stirred at room temperature and progress of the reactions were monitored by TLC visualized under UV lamp and developed in vanillin spray. The characteristic dark green spot of chalcones in vanillin increase with time till the completion of the reaction.

The final product was purified by column chromatography, packed in silica gel in n-hexane/ pet ether and the percentage yields were calculated. Elution was made with increasing concentration of increasing concentration of ethylacetate in n-hexane:ethylacetate. The synthesis of different derivative is shown in scheme 2.

Scheme 2: Synthesis of compounds 1a-7a at optimized conditions

Antimicrobial Activities

Antifungal and antibacterial activities of the synthesized compounds were carried out by disc diffusion method [25]. All the human pathogens including fungi and bacteria were procured from Pakistan Institute of Medical Sciences. The media used for fungal and bacterial growth were purchased from Sigma Aldrich suppliers.

The antifungal assay was done against two fungal strains, *Aspergillus flavus* and *Candida albicans.* Sabouraud dextrose agar (SDA) was used to grow fungus for inoculums preparations. Discs measuring 6.25 mm in diameter were punched from Whatman No.1 filter paper.

Media was prepared by dissolving Sabouraud dextrose agar 6.5gm /100ml in distilled water. Contents were dissolved and were autoclaved at 121^{o}C for 20 minutes. After sterilization media is poured on sterile plates under LFC and allowed to solidify. After solidification the plates were pre-incubated at 37^{o}C for 24 hours to confirm sterility .The plates showing no growth were then used for antifungal activity studies. The disk diffusion method was used for testifying the antibacterial activity as well. The antibacterial assay was done against *Escherichia coli, Acetobacter aceti, Staphylococcus aureus, Klebsilla pneumonia and Pseudomonas aeruginosa.* These bacteria were maintained on nutrient agar medium at 4^{o}C. Nutrient agar was used to grow bacteria for inoculums preparations. Media was prepared by dissolving nutrient agar 2.9gm/100ml in distilled water. Contents were dissolved and autoclaved at 121^{o}C for 20 minutes. After sterilization media was poured on sterile plates under LFC and allowed to solidify. After solidification the plates were pre-incubated at 37^{o}C for 24 hours to confirm sterility. The plates showing no growth were then used for anti-bacterial activity testing. The stock solutions of synthesized compounds were prepared in DMSO at two different concentrations, one of 500µg/mol and other of 1000µg/mol. The results of antimicrobial screening are summarized in table2 and table3.

RESULTS AND DISCUSSIONS

Chemical Part

The Michael addition reactions were carried out using different types of organocatalysts (A-E). The data concluded that maximum yield i.e. 82% was obtained for compound 1a by using catalyst A at 20 mol% ratio and TFA (40 mol%) as a co-catalyst in dichloromethane as shown in Table 1.This result suggested that small size of catalyst and polar solvent dichloromethane favored the completion of reaction. By changing the catalyst type or the amount of catalyst reduces the yield. Similarly, the change of TFA by Et_3N also changes the % yield of the product.

These optimized conditions were used for the synthesis of six more derivatives of chalcones derivatives as shown in Table 2.

Table 2: Physical properties of structural compounds 1a-7a

Compound code	R1	R2	Molecular formula	Molecular weight	Yield %	Melting point ^{0}C
1a	Ph	CH_3	$C_{18}H_{14}O_4$	308	82	161
2a	4-0CH_3Ph	CH_3	$C_{20}H_{18}O_5$	338	85	172
3a	Ph	Ph	$C_{24}H_{16}O_4$	370	95	183
4a	4-0CH_3 Ph	Ph	$C_{25}H_{18}O_5$	400	92	188
5a	4-Br Ph	Ph	$C_{24}H_{15}O_4Br$	448	79	196-198
6a	4-Cl Ph	Ph	$C_{24}H_{15}O_4Cl$	406	64	183-184
7a	4-N$(CH_3)_2$Ph	Ph	$C_{26}H_{21}O_4N$	415	73	178-179

The data in Table 2 shows the synthesized compounds at optimized conditions along with physical parameters. The data shows that maximum product yield was obtained for the first follow by third set of reactants. In first case one "R" group is small methyl group and other one is symmetrical phenyl. In case of third set of reactants, both groups were symmetrical phenyl. In rest of combinations the "R" groups on reactants are substituted phenyl and due to these substitutions the symmetry is lost. The loss of symmetry results in the reduction of yield as shown in the Table 2. The structures of the synthesized compounds were confirmed by NMR and MS analysis.

Spectral Data

The structures of the synthesized compounds were determined on the basis of ^{1}H-NMR, ^{13}C- NMR and EI-MS are as follows.

1a: 3-hydroxy-3-(3-oxo-1-phenylbutyl)-2H-chromen-2-one

^{1}H-NMR (400MHz, $CDCl_3$) δ (ppm): 10.2 (bs, 1H), 7.7 (d, 1.0H, j=7.2Hz), 7.65 (d, 0.85H, 7.8Hz), 7.45 (dd, 2.0H. J=8.0Hz), 7.19-7.35 (m, 5H), 4.29 (dd, J=3.2, 6.8 Hz, 1.0H), 4.15 (dd, J=2.4, 10.0Hz, 1.0H), 3.0 (bs, 1.0H), 2.44-2.56 (m, 2H), 2.27 (s, 1.3H), 1.95-2.04 (m, 2H), 1.54 (s, 1H).^{13}C- NMR (360MHz,$CDCl_3$) δ (ppm): 162, 161.5, 159.6, 158.6, 153.0, 152.9, 143.2, 141.5, 131.7, 131.5, 129.2, 128.6, 127.9, 127.2, 123.95, 123.8, 123.6, 122.68, 116.67, 116.56, 115.8, 115.5, 104.26, 100.46, 98.9, 45.18, 42.47, 39.97, 35.35, 34.8, 34.11, 30.04, 29.7, 28.3, 27.8.ESI-HRMS: Calculated for $C_{19}H_{20}O_4$: 308.2

2a: 3-hydroxy-3-[3-oxo-1-(4-methoxyphenyl)butyl]-2H-chromen-2-one

^{1}H-NMR (360MHz, $CDCl_3$) δ (ppm): 10.0 (bs, 1H), 7.5 (s, 1.0H), 7.4 (s, 1.30H), 7.3-7.4 (m, 2.35H), 6.80-6.88 (m, 4.27H), 4.24-4.26 (m, 1.0H),

4.10-4.15 (m, 0.92H), 4.1 (s, 6.0H), 3.4-3.7 (m, 1.4H), 2.4 (s, 7.21H).^{13}C- NMR (360MHz,$CDCl_3$) δ (ppm): 172,161.5,159.7, 159.0, 152.8, 152.6, 143.2, , 141.5, 131.9, 131.4, 128.9, 128.4, 127.8, 126.9, 126.3, 123.87, 123.8, 123.5, 122.9, 122.6, 116.5, 116.2, 115.8, 115.5, 103.9, 100.5, 99.1, 60.42, 42.6, 40.1, 35.2, 34.8, 27.8, 27.3, 20.98.ESI-HRMS: Calculated for $C_{20}H_{18}O_5$: 338

3a: 4-hydroxy-3-(3-oxo-1,3-diphenylpropyl)-2*H*-chromen-2-one

^{1}H-NMR (400MHz, $CDCl_3$) δ (ppm): 9.9 (bs, 1H), 8.06 (d, 1.0H, J=7.6Hz), 7.96 (dd, 1.0H, 7.5, 10.1Hz), 7.6 (t, 1.23H. J=8.0Hz), 7.42-7.49 (m, 3H), 7.39 (d, J=2.8H), 7.18-7.3 (m, 5H), 4.93 (d, J=3.2, 1.2H), 4.46 (q, J=2.4, 1.2H), 3.80 (d, J=6.1, 1.0H), 2.44-2.56 (m, 2H), 2.27 (s, 1.3H), 1.95-2.04 (m, 2H), 1.54 (s, 1H).^{13}C-NMR, 202,162,161, 152, 139.0, 135, 134, 132, 131, 129, 128.8, 128.6, 127, 126, 125, 123, 122, 116, 44, 35. ESI-HRMS: Calculated for $C_{24}H_{16}O_4$: 370

4a: 4-hydroxy-3-[1-(4-methoxyphenyl)-3-oxo-3-phenylpropyl]-2*H*-chromen-2-one

^{1}H-NMR (400MHz, $CDCl_3$) δ (ppm): 9.78 (bs, 1H), 8.06 (d, 1.0H, J=7.6Hz), 7.94 (t, 1.0H, 5.4Hz), 7.58-7.62 (m, 1H), 7.42-7.49 (m, 3H), 7.39-7.47 (m, 3H), 7.18-7.27 (m, 2H,), 6.82 (d, J=3.6, 2H) 4.88 (d, J=3.2, 1H), 4.44 (q, J=6.6, 1.2H), 3.70 (s, 3.0H).^{13}C-NMR, 202,162,160, 158, 152, 135, 134, 131, 129, 128.8, 128.6, 128.2, 127, 125, 124, 123, 122, 116, 114, 108, 77, 55, 44, 33.60. ESI-HRMS: Calculated for $C_{25}H_{18}O_5$: 400

5a: 3-[1-(4-bromophenyl)-3-oxo-3-phenylpropyl]-4-hydroxy-2*H*-chromen-2-one

^{1}H-NMR (400MHz, $CDCl_3$) δ (ppm): 9.01(bs, 1H), 8.01 (dd, 1.0H, J_1=9Hz, J_2=3Hz), 7.72 (dd, 2H, 7.5, J_1=4.5Hz, J_2=3Hz), 7.533-7.598 (m, 1H), 7.42-7.49 (m, 3H), 7.39-7.50 (m, 5H), 7.18-7.3 (m, 1H), 5.78 (d, H, J=4.8Hz, 1H), 4.67 (dd, J_1=2.1Hz, J_2=4.9Hz, 1H).^{13}C-NMR, 202,182,181, 168, 156.0, 135, 133, 129.5, 128.8, 128.6, 127, 126, 125, 123, 120, 118, 44, 35. ESI-HRMS: Calculated for $C_{24}H_{15}O_4Br$: 448

6a: 3-[1-(4-chlorophenyl)-3-oxo-3-phenylpropyl]-4-hydroxy-2*H*-chromen-2-one

^{1}H-NMR (400MHz, $CDCl_3$) δ (ppm): 10.0 (bs, 1H), 7.82(bs, 1H), 7.83 (d, 2.0H, J=8.4Hz), 7.68 (d, 2H, J=8.0Hz), 7.45-7.58 (m, 5H), 7.42-7.49 (m, 3H), 7.34 (d, 3H, J=8.4Hz), 7.18-7.3 (m, 1H), 5.36 (dd, 1H, J_1=9Hz, J_1=4Hz), 4.06-4.20 (m, 2H).^{13}C-NMR, 201,183,178, 170, 166.0, 154, 148, 139.5, 129.8, 128.6, 127, 126, 124, 123, 120, 118, 65, 38. ESI-HRMS: Calculated for $C_{24}H_{15}O_4Cl$: 406

7a: 4-hydroxy- 3-{1-[4-(dimethylamino) phenyl]-3-oxobutyl}-2*H*-chromen-2-one

^{1}H-NMR (400MHz, $CDCl_3$) δ (ppm): 9.78(bs, 1H), 8.06 (d, 2.0H, J=4.5Hz), 7.97 (d, 1H, J=4.8Hz), 7.60 (t, 1H, 4.5H), 7.38-7.48 (m, 3H), 7.31 (d, 2H, J=5.1Hz), 7.12-7.27 (m, 2H), 4.32 (d, 1H, J=5.4Hz), 4.40 (dd, 2H, J_1=11.4Hz, J_2=6Hz).^{13}C-NMR, 119,183,178, 167, 166.0, 158, 147, 139, 136, 128, 127, 125, 124, 122, 120, 118, 66, 38. ESI-HRMS: Calculated for $C_{26}H_{21}O_4N$: 415

The inspection of compounds NMR data showed double peaks in ^{1}H-NMR and ^{13}C-NMR. This is mainly due to the existence of keto-enol tautomeric forms. Each compound contains one methylene (-CH_2). DEPT-135 spectras showed two negative peaks for methylene group at very close positions. It further confirms the existence of keto enol tautomerism.

Antimicrobial Part

The results of antimicrobial screening against different fungi and bacteria showed that almost all the synthesized compounds were active against one or more microbes. The compound 4a showed excellent activity against *Candidia albicans* at 1000 µg/mol concentration. The compound 7a showed remarkable antifungal activity. The maximum %inhibition was calculated against *Candidia albicans* and *Aspergillus flavus at both* concentrations i.e 500 µg/mol and 1000 µg/mol. Antibacterial screening results revealed that good to excellent activities were shown by all the synthesized compounds. Compound 7a was a potent antibacterial agent against *Escherichia coli* and *Acetobecor acceti* at both low and high sample concentrations. The compound 3a gave high %inhibition against Acetobector *acceti* at both concentrations. No antibacterial activity was observed for compound 2a against *Aspergillus flavus* and 3a against *Psedumonas aeuroginosa* and *Aspergillus flavus.*The compound 4a was also inactive against *Acetobector acceti , Staphylococcus aureus and Aspergillus flavus.*Compound 5a and 6a did not show %inhibition against *Klesebla pneumonia* and *Candidia albicans.*

Table 3: % Inhibition of synthesized compounds for antifungal screening

Compounds	% Inhibition (*Aspergillus flavus*)		% Inhibition (*Candida albicans*)	
	500µg/mol	1000 µg/mol	500µg/mol	1000 µg/mol
1a	22	43	30	51
2a	18	35	21	60
3a	43	66	37	68
4a	32	67	45	82
5a	52	69	35	70
6a	32	55	29	69
7a	59	71	60	72
Fluconazole	64	78	72	94

Table 4: % Inhibition of synthesized compounds for antibacterial screening

Compounds	%Inhibition *Escherichia coli*		%Inhibition *Acetobecor acceti*		%Inhibition *Staphylococcus aureus*		%Inhibition *Klesebla pneumoniae*		%Inhibition *Psedumonas aeuroginosa*		%Inhibition *Aspergillus flavus*		%Inhibition *Candidia. albicans*	
	500µg/mol	1000µg/mol	500µg/mol	1000µg/mol	500µg/mol	1000µg/mol	500µg/mol	1000µg/mol	500µg/mol	1000µg/mol	500µg/mol	1000µg/mol	500µg/mol	1000µg/mol
1a	31	54	29	58	19	39	26	45	20	43	23	48	25	56
2a	18	32	33	13	35	55	29	8	11	21	-	-	9	15
3a	44	69	24	52	5	17	22	32	-	-	-	-	-	-
4a	29	61	-	-	-	-	12	18	31	51	-	-	35	56
5a	32	43	25	41	11	31	-	-	26	46	14	25	-	-
6a	39	42	18	34	17	33	-	-	22	26	13	19	-	-
7a	54	71	41	62	38	59	32	48	34	49	24	38	25	32
Levofloxacine	64	79	71	83	65	85	58	67	43	68	54	66	74	92

(-) No effect

CONCLUSION

The current research has two important aspects. First is the use of organocatalysts to enhance the yield of Michael adducts. Second is incorporation of versatile chalcones as Michael adducts and their use as potent antimicrobial agents.

On the basis of results obtained from screening of organocatalysts, it is concluded that the catalysts A N [(S)-benzyloxycarbonylprolyl] cyclohexyl amine synthesized all the compounds in good to excellent yields in the presence of cocatalyst, trifluroacetic acid and DCM solvent. These catalysts in chiral form, with different variations of reaction conditions can also be used to enhance the enantioselectivity of the synthesized compounds. Some of the synthesized Michael adducts have shown an excellent antimicrobial activities with ciprofloxacin and fluconazole as reference drugs.

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