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SYNTHESIS AND MICROBIAL EVALUATION OF SOME NOVEL ETHYL-4-(SUBSTITUTED PHENYL-5-YL)-6-(6-METHOXYNAPTHALEN)-2-OXO-CYCLOHEXA-3-ENE-1-ETHYL CARBOXYLATE DERIVATIVES

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ABSTRACT

Objective:A series of some novel pharmacological active moleculeEthyl-4-(substituted phenyl-5-yl)-6-(6-methoxynapthalen)-2-oxo-cyclohexa-3-ene-1-ethyl carboxylate derivatives were synthesized and evaluated *in vitro* for Antibacterial activity against *staphylococcus aureus, Escherichia coli, Salmonella Typhi, Bacillus subtilis* and antifungal activity against *Aspergillusniger, Aspergillusflavus and Penicilliumchrysogenum,Fusariummoneliforme.*

Methods: The present research work describes the synthesis of Cyclohexenones by Michael addition. In the present investigation first Chalcones and their derivatives have been synthesized. Chalcones, 3-(6-methoxynaphthalen-1-yl)-1-phenylprop-2-en-1-one**(3a-f)** were prepared by the Aldol condensation of substituted acetophenone and 6-methoxy-1-napthaldehyde. Base catalyzed condensation of 3-(6-methoxynaphthalen-1-yl)-1-phenyl prop-2-en-1-one **(3a-f)** with ethyl acetoacetate **(4)** yields corresponding Ethyl-4-(substituted phenyl-5-yl)-6-(6-methoxynapthalen)-2-oxo-cyclohexa-3-ene-1-ethyl carboxylate **(5a-f).**The newly synthesized compounds were characterized on the basis of elemental analysis, spectroscopic studies viz, FT-IR, ^{1}H NMR and mass.

Results: Literature survey reveals that the synthesized pharmacological active molecule i.e. substituted Ethyl-4-(substituted phenyl-5-yl)-6-(6-methoxynapthalen)-2-oxo-cyclohexa-3-ene-1-ethyl carboxylate **(5a-f)**was not reported.

Conclusion: All these newly synthesized compounds were evaluated for their *in vitro* antimicrobial activity. Most of the compounds showed potent activity.

Key Words: Cyclohexenones, Michael addition, ethyl acetoacetate, Chalcones.

INTRODUCTION

Heterocyclic and Medicinal chemistry is the science that deals with designing and discovery of new therapeutic chemicals and their development in medicinal chemistry is useful for society. Drug development is perhaps the most elegant approach for discovering compounds exhibiting high specificity and biological activity[1].

Chemist had designed and synthesized a lot of new heterocyclic derivatives related to this moiety and screened those for different pharmacological activities to obtained a molecule which have good pharmacological activity with least adverse effects. The chalcone is not only synthetically important scaffold but also possesses a wide range of promising biological activities

Chalcone is a generic term used for the compounds that bears, 1, 3-diphenyl-prop-2-en-1-one framework [2]. Under homogeneous conditions, these compounds are usually prepared by base or acid catalyzed Aldol condensation between aromatic aldehydes and ketones. Chalcones represent an important class of compounds due to their chemical flexibility, as synthons.

Chalcones and the corresponding heterocyclic analogs are valuable intermediatesin organic synthesis [3] and exhibit a multitude of biological activities [4].From a chemical point of view, an important feature of chalcones and their hetero analogs is the ability to act as activated unsaturated systems in conjugated addition reactions of carbanions in the presence of basic catalysts [5,6]. This type of reaction may be exploited with the view of obtaining highly functionalized cyclohexene derivatives [7],but is more commonly used for the preparation of 3,5-diaryl-6-carbethoxycyclohexenones *via* Michael addition of ethyl acetoacetate. The mentioned Cyclohexenones are efficient synthons in building spiranic compounds [8] or intermediates in the synthesis of fused heterocycles such as benzoselenadiazoles and benzothiadiazoles [9],benzopyrazoles and benzisoxazoles[10,11]or carbazole derivatives [12].

The Michael reaction of chalcones with active methylenecompounds such as 1,3-dicarbonyls have been the subject of many investigations [13-16]. It is known that a weak base or acid such as Piperidine [17] or phosphorus trichloride [18]often affords open chain adducts, while cyclic products have been obtained in the presence of sodium methoxide [19] or sodium hydroxide [20].Particularly, the products of these cyclic reactions are of interest in terms of their stereochemistry and as starting materials for the synthesis of compounds with possible biological activity [21].These types of reactions may be exploited with the view of obtaining highly functionalized cyclohexene derivatives [22] but are more commonly used for the preparation of 3,5-diaryl-6-carbethoxy-2-cyclohexenones *via* the Michael addition of ethyl acetoacetate with chalcones.

Prompted by all these observations and in continuation of our earlier work on the synthesis and of some chalcones, it was felt worthwhile tosynthesize some 3,5-diaryl-6-carbethoxy-2-cyclohexen-1-ones derivatives.

MATERIALS AND METHODS

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded using Perkin –Elmer spectrometer.^{1}H NMR spectra were recorded on Brucker Advance II 400 spectrometer in DMSO by using TMS as internal standard. Thin layer chromatography was performed with E. Merk precoated TLC plates, silica gel 60F_{254} with thickness of 0.25mm and spots were visualized by irradiation with ultraviolet light (254 nm). Physical constants and analytical data of all the compoundsreported in this paper are summarized in Table 1.

General procedure for the synthesis of 3-(6-methoxynaphthalen-1-yl)-1-(4-substituted phenyl)prop-2-en-1-one(Chalcone)[17] (3a-f).

A mixture of 4-substituted acetophenone**(2a-f)**(0.01mole) and 6-methoxy-1-naphthaldehyde (**2)**(0.01mole) was stirred in methanol (50 mL) and then a solution of 15 mL potassium hydroxide (0.02mole) was added to it. The mixture was kept overnight at room temperature and then it was poured into crushed ice and acidified with dil. hydrochloric acid. The chalcones i.e. [3-(6-methoxynaphthalen-1-yl)-1-(4-substituted phenyl)prop-2-en-1-one] **(3a-f)**precipitate out as solid **(Scheme-I)**. The obtained solid was filtered, washed with water, dried and purified by recrystallization from acetic acid.

General Procedure for Synthesis of 3, 5-diaryl-6-carbethoxy-2-cyclohexen-1-ones 5(a-f)

In a clean & dry round bottom flask 3-(4-chlorophenyl)-1-substituted phenylprop-2-en-1-one (Chalcones) (3 mmol) and ethyl acetoacetate (0.39 g, 0.40 mL, 3 mmol) were refluxed for 2 h in 10-15 mL ethanol in the presence of 0.5 mL 10% NaOH. The reaction mixture was then poured with good stirring into 200 mL ice-cold water and kept at room temperature until the reaction product separated as a solid, which was filtered off and recrystallized from ethanol. The physical constant and yields are recorded in **table-I**.

Antimicrobial activity

All the newly synthesized compounds 5a-f was tested for their antimicrobial activity. The effects of unknown compounds were compared with the standard drug Penicillin for bacteria and Greseofulvin for fungi. Antibacterial activity was performed against *staphylococcus aureus, Escherichia coli, Salmonella Typhi, Bacillus subtilis* and antifungal activity against *Aspergillusniger, Aspergillusflavus and Penicilliumchrysogenum,Fusariummoneliforme.* The antibacterial activity was assayed by cup plate method [23] and antifungal activity was assayed by standard agar disc diffusion method [24].The results are shown in **Table II and III** respectively.

RESULTS AND DISCUSSION

Ethyl-4-(substituted phenyl-5-yl)-6-(6-methoxynapthalen)-2-oxo-cyclohexa-3-ene-1-ethyl carboxylate derivatives**5a-f,** were successfully synthesized as per the scheme-I.The entire synthesized compounds are qualitatively analyzed by running T.L.C. and melting point. Thestructures of the compounds synthesized are confirmed by IR,^{1}HNMR and mass spectral data.

Analytical and spectral data (IR, ^{1}H-NMR) of all synthesized compounds were in full agreement with given structure. The IR spectrum of **5a-f** exhibited two sharp strong absorption bands above 1700 cm^{-1}and near 1650 cm^{-1}, these absorption bands confirm the presence of the ester function and the carbonyl group conjugated with a carbon–carbon double bond, respectively in Cyclohexenones ring. The characteristic signal in the ^{1}HNMRspectra of compounds **5a-f**is the singlet of the vinylic proton in position 3 of the Cyclohexenones ring that occurs at approximately δ 6.55 ppm and confirms that the intramolecular cyclocondensation subsequent to the Michael addition actually took place.

The investigation of antibacterial screening data revealed that compounds **5b,d,f** shows excellent activity against all bacteria, compound **5a,c** shows good activity and compound **5e** shows low activity against most of the bacteria. The investigation of antifungal activity data revealed that compound **6b** show inhibitory effect against all the fungus, compound **5a,c**show inhibitory effect against *Penicilliumchrysogenum and Fusariummoneliforme*, compound **5d,f** show inhibitory effect against *Aspergillusniger, Penicilliumchrysogenum, Aspergillusflavus.* Remaining compounds are inactive against all the fungus.

Table 1: Analytical Data and Elemental Analysis of Compounds 5(a-f)

Compd.	Molecular formula	M.P. ^{0}C	Yield %	Elemental Analysis %C Calcd.	%C Found	% H Calcd.	% H Found
5a	$C_{26}H_{24}O_4$	116	85	77.98	77.78	6.04	6
5b	$C_{26}H_{23}ClO_4$	110	90	71.8	71.6	5.33	5.12
5c	$C_{26}H_{23}BrO_4$	130	87	65.14	65.05	4.84	4.54
5d	$C_{26}H_{23}FO_4$	145	92	74.63	74.43	5.54	5.25
5e	$C_{27}H_{26}O_4$	147	90	78.24	78.1	6.32	6.15
5f	$C_{26}H_{22}Cl_2O_4$	117	80	66.53	66.33	4.72	4.45

Table2: Antibacterial screening results of the compounds 5a-f.

Sr. No.	Compounds	*E.coli*	*Salmonella typhi*	*Staphylococcus aureus*	*Bacillus subtilis*
		Diameter of growth inhibition zone (mm)			
1	**5a**	13	11	15	16
2	**5b**	17	19	26	26
3	**5c**	14	14	21	16
4	**5d**	17	14	20	20
5	**5e**	16	12	10	17
6	**5f**	13	17	22	22
7	**Penicillim**	22	25	35	38
8	**DMSO**	-ve	-ve	-ve	-ve

-ve no antibacterial activity

Spectral data of synthesized compounds (5a-f)

Ethyl-4-(phenyl-5-yl)-6-(6-methoxynapthalen)-2-oxo-cyclohexa-3-ene-1-ethyl carboxylate (5a):IR (KBr pellets Cm^{-1}): 1146.82 (C–O str.), 1514.34 (–CH_2), 1607.51 (C=C), 1732.15 (C=O of α, β-unsaturated ketone), 1735.15 (C=O of ester), 1162 (-OCH_3); ^{1}H NMR (DMSO, 400 MHz) δ 1.06-1.12 (t, 3H, CH_3), 2.56-2.70 (m, 2H, -CH-CH-Ar), 3.23-3.41(m, 2H, CH_2-CHAr), 3.93 (s, 3H, -OCH_3), 4.07- 4.14 (q, 2H, -OCH_2), 6.32 (s, 1H, =CH),8.65-7.20 (m, 11H, Ar-H); Mass (m/z): 400.17(M+1).

Ethyl-4-(4-chlorophenyl-5-yl)-6-(6-methoxynapthalen)-2-oxo-cyclohexa-3-ene-1-ethyl carboxylate (5b):IR (KBr pellets Cm^{-1}): 1140.32 (C–O str.), 1510.14 (–CH_2), 1600.31 (C=C), 1730.10 (C=O of α, β-unsaturated ketone), 1725.15 (C=O of ester), 1160 (-OCH_3); ^{1}H NMR (DMSO, 400 MHz) δ 1.08-1.15 (t, 3H, CH_3), 2.46-2.60 (m, 2H, -CH-CH-Ar), 3.21-3.38(m, 2H, CH_2-CHAr), 3.90 (s, 3H, -OCH_3), 4.06-

4.16 (q, 2H, -OCH_2), 6.30 (s, 1H, =CH),8.60-7.10 (m, 10H, Ar-H); Mass (m/z): 434.13 (M+1).

Table3: Antifungal screening results of the compounds 5a-f.

Sr. No.	Compounds	*Aspergillus Niger*	*Aspergillusflavus*	*Penicillumchrysogenum*	*Fusariummoneliforme*
1	**5a**	-ve	-ve	+ve	-ve
2	**5b**	-ve	-ve	-ve	-ve
3	**5c**	+ve	-ve	-ve	-ve
4	**5d**	-ve	+ve	-ve	-ve
5	**5e**	+ve	RG	+ve	-ve
6	**5f**	-ve	-ve	-ve	-ve
7	**Griseofulvin**	-ve	-ve	-ve	-ve
8	**DMSO**	+ve	+ve	+ve	+ve

-ve No growth Antifungal activity present
+ve Growth Antifungal activity absent
RG Reduced growth

Ethyl-4-(4-bromophenyl-5-yl)-6-(6-methoxynapthalen)-2-oxo-cyclohexa-3-ene-1-ethyl carboxylate (5c):IR (KBr pellets Cm^{-1}): 1145.72 (C–O str.), 1510.14 (–CH_2), 1600.81 (C=C), 1730.10 (C=O of α, β-unsaturated ketone), 1732.10 (C=O of ester), 1152 (-OCH_3); ^1H NMR (DMSO, 400 MHz) δ 1.07-1.12 (t, 3H, CH_3), 2.50-2.80 (m, 2H, -CH-CH-Ar), 3.20-3.40(m, 2H, CH_2-CHAr), 3.89 (s, 3H, -OCH_3), 4.05-4.12 (q, 2H, -OCH_2), 6.28 (s, 1H, =CH),8.62-7.10 (m, 10H, Ar-H); Mass (m/z): 478.08(M+1).

Ethyl-4-(4-flourophenyl-5-yl)-6-(6-methoxynapthalen)-2-oxo-cyclohexa-3-ene-1-ethyl carboxylate (5d):IR (KBr pellets Cm^{-1}): 1136.72 (C–O str.), 1510.14 (–CH_2), 1612.31 (C=C), 1712.11 (C=O of α, β-unsaturated ketone), 1725.25 (C=O of ester), 1160 (-OCH_3); ^1H NMR (DMSO, 400 MHz) δ 1.12-1.20 (t, 3H, CH_3), 2.46-2.65 (m, 2H, -CH-CH-Ar), 3.20-3.38(m, 2H, CH_2-CHAr), 3.93 (s, 3H, -OCH_3), 4.17-4.27 (q, 2H, -OCH_2), 6.31 (s, 1H, =CH),8.70-7.40 (m, 10H, Ar-H); Mass (m/z): 418.46 (M+1).

Ethyl-4-(4-methylphenyl-5-yl)-6-(6-methoxynapthalen)-2-oxo-cyclohexa-3-ene-1-ethyl carboxylate (5e):IR (KBr pellets Cm^{-1}): 1126.12 (C–O str.), 1510.14 (–CH_2), 1618.21 (C=C), 1722.05 (C=O of α, β-unsaturated ketone), 1725.10 (C=O of ester), 1152 (-OCH_3); ^1H NMR (DMSO, 400 MHz) δ 1.10-1.22(t, 3H, CH_3),2.14 (s, 3H, CH_3), 2.46-2.65 (m, 2H, -CH-CH-Ar), 3.22-3.40(m, 2H, CH_2-CHAr), 3.90 (s, 3H, -OCH_3), 4.05- 4.16 (q, 2H, -OCH_2), 6.22 (s, 1H, =CH),8.65-7.22 (m, 10H, Ar-H); Mass (m/z): 414.18 (M+1).

Ethyl-4-(2,4-dichlorophenyl-5-yl)-6-(6-methoxynapthalen)-2-oxo-cyclohexa-3-ene-1-ethyl carboxylate (5f):IR (KBr pellets Cm^{-1}): 1150.82 (C–O str.), 1512.24 (–CH_2), 1627.50 (C=C), 1742.17 (C=O of α, β-unsaturated ketone), 1735.15 (C=O of ester), 1160 (-OCH_3); ^1H NMR (DMSO, 400 MHz) δ 1.11-1.22 (t, 3H, CH_3),2.55-2.68 (m, 2H, -CH-CH-Ar), 3.20-3.41(m, 2H, CH_2-CHAr), 3.95 (s, 3H, -OCH_3), 4.20- 4.45 (q, 2H, -OCH_2), 6.29 (s, 1H, =CH),8.60-7.22 (m, 9H, Ar-H); Mass (m/z): 469.36(M+1).

CONCLUSION

In conclusion, we have reported some novel Ethyl-4-(substituted phenyl-5-yl)-6-(6-methoxynapthalen)-2-oxo-cyclohexa-3-ene-1-ethyl carboxylate derivatives. From the above studies it can be concluded that the synthesized compounds exhibit significant antibacterial activityagainst pathogenic bacteria. Further studies are needed to determine the mode of action of the studied compounds.

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