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Synthesis, characterization and antimicrobial activity of new chalcones of 3-acetyl 4-hydroxy-6-methyl-2*h*-pyran-2-one

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ABSTRACT

In an effort to develop antimicrobial agents, a series of substituted 3- cinnamoyl-4-hydroxy-6-methyl-2-pyrones were synthesized by base catalyzed condensation of 3-acetyl-4-hydroxy-6-methyl-2-oxa-2*H*-pyran (DHA) with different aromatic or heteroaromatic aldehydes. The synthesized compounds were characterized by means of their IR, ^{1}HNMR, ^{13}CNMR and Mass spectroscopic data. The synthesized compounds were tested for their antibacterial and antifungal activities.

Keywords: Substituted 3-cinnamoyl-4-hydroxy-6-methyl-2-pyrones, Dehydroacetic acid, Antibacterial and antifungal activity.

1. INTRODUCTION

Chalcones are probably the most widely used intermediates for synthesizing various heterocyclic ring systems. Chalcones are a class of compounds that have shown promising therapeutic efficiency for the management of several diseases due to vast array of structural modification[1]. In fact not many structurally diverse compounds show association with such a wide range of pharmacological activities among which cytotoxisity, antitumor, anti-inflammatory, antiplasmodial, immunosuppression, antioxidant[2], antibacterial and antifungal are widely cited[3]. They also possess antiviral[4], antimalarial[5], antiulcerative[6] and antihyperglycemic[7] activities. Chalcones are used as aldose reductase[8], leukotriene B_4[9], and tyrosinase[10] inhibitors. The presence of reactive □□□-unsaturated keto function in chalcones is found to be responsible for their antimicrobial activity, which may be altered depending on the type and position of substituent on the aromatic ring. It is not surprising that the chalcones play an important role in many medicinal agents. The synthesis and reactivity of chalcone derivatives has been a topic of research interest for well over a century. Dehydroacetic acid (DHA) is also shows promising antifungal, antibacterial and antiprotozoal activities[11, 12].

The present work deals with the synthesis of chalcones of dehydroacetic acid with different aromatic and heteroaromatic aldehydes. Their characterization by IR, ^{1}HNMR and mass spectroscopic techniques. The synthesized compounds were screened for their antibacterial activity against two gram positive bacteria viz; *Staphylococcus aureus, Basillus subtilis* and two gram negative bacteria viz; *Escherichia coli*, *Salmonella typhi* and the compounds were also used for antifungal studies against *Aspergillus niger, Penicillium chrysogenium, Fusarium moneliform and Aspergillus Flavus* fungal species. The results are summarized in Table I, IIa and IIb for their percentage yield, melting point and confirm whether there is enhancement in antibacterial and antifungal activity due to the keto function is directly bonded to a C=C group.

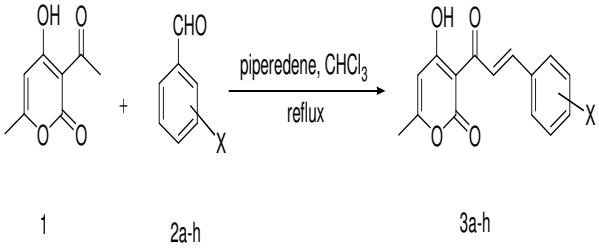
2. EXPERIMENTAL

Melting points were determined in open capillary and are uncorrected. The IR spectra were recorded on Perkin Elmer RX- FT-IR Spectrometer using potassium bromide pellets, ^{1}H NMR were determined on a Bruker Avance II 400 NMR Spectrometer against TMS as internal standard. Mass spectra were recorded on Water micro mass Q-TOF micro analyzer. Purity of compounds was checked by thin layer chromatographic technique.

2.1. General Procedure for the of synthesis Substituted 3-Cinnamoyl-4-hydroxy-6-methyl-2-pyrones (3a-h):

A solution of (10mmol) of dehydroacetic acid, few drops of piperedine and (10mmol) of the

aldehyde in 30 ml of chloroform was refluxed for 8 hours. 10 ml of azeotropic mixture was separated by distillation. Crystals of the product which separated on slow evaporation of the remaining chloroform were collected and recrystallized.



Scheme I: synthesis Substituted 3-Cinnamoyl-4-hydroxy-6-methyl-2-pyrones.

2.2. Spectral Data of substituted 3-Cinnamoyl-4-hydroxy-6-methyl-2-pyrones:

2.2.1. 1-(4-hydroxy-6-methyl-2-oxa-2H-pyran-3-yl)-3-[4-(pyrrolidin-1-yl)phenyl]-2-propenone (3a)

IR (cm^{-1}, KBr): 3396 (OH), 1704 (lactone C=O), 1656 (C=O), 1592 (CH=CH). ^{1}H NMR ($CDCl_3$,δ,ppm): 2.06 (t, 4H, pyr-H); 2.26 (s,3H,CH_3); 2.40 (t, 4H, pyr-H); 5.92 (s,1H,C^5H); 6.58 (s,2H,Ar-H); 7.63 (s,2H,Ar-H); 8.02-8.05 (dd,1H, *J*= 8.02, -C=OCH); 8.10-8.14 (dd,1H, *J*= 8.11, =CHAr); 18.7 (s,1H, D_2O exchangeable, OH). ^{13}CNMR: 20.5, 25.4, 47.8, 103.3, 112.0, 115.6, 120.0, 150.2, 161.6, 167.2, 184.0, 192.0. MASS *m/z:* 325 (M+); 326 (M+1).

2.2.2. -(4-hydroxy-6-methyl-2-oxa-2H-pyran-3-yl)-3-(4-florophenyl)-2-propenone (3c)

IR (cm^{-1}, KBr): 3549 (OH), 1720 (lactone C=O), 1639 (C=O), 1516 (CH=CH). ^{1}H NMR (DMSO,δ,ppm): 2.33 (s,3H,CH_3); 6.16 (s,1H,C^5H); 7.91-7.93 (d,2H,Ar-H); 7.96-7.97 (d,1H,-C=OCH); 8.30 (d,2H,Ar-H); 8.33-8.37 (dd,1H,=CHAr).

2.2.3. 1-(4-hydroxy-6-methyl-2-oxa-2H-pyran-3-yl)-3-(2-chlorophenyl)-2-propenone (3d)

IR (cm^{-1}, KBr): 3552 (OH), 1726 (lactone C=O), 1640 (C=O), 1615 (CH=CH). ^{1}H NMR (DMSO,δ,ppm): 2.30 (s,3H,CH_3); 6.18 (s,1H,C^5H); 7.79 (m,3H,Ar-H); 7.98 (d,1H,-C=OCH); 8.00 (m,1H,Ar-H); 8.91 (d,1H,=CHAr).

2.2.4. 1-(4-hydroxy-6-methyl-2-oxa-2H-pyran-3-yl)-3-(3,4-dihydroxyphenyl)-2-propenone (3f):

IR (cm^{-1}, KBr): 3383 (OH), 1683 (lactone C=O), 1641 (C=O), 1595 (CH=CH). ^{1}H NMR ($CDCl_3$,δ,ppm): 2.24 (s,3H,CH_3); 5.06 (s,2H,OH); 6.09 (s,1H,C^5H); 6.79 (s,1H,Ar-H); 6.97 (s,1H,Ar-H); 7.18 (s,1H,Ar-H); 7.77-7.81 (dd,1H, *J*= 9.85,-C=OCH); 7.96-8.00 (dd,1H, *J*= 9.75, =CHAr); 18.2 (s,1H,D_2O exchangeable, OH).

2.2.5. 1-(4-hydroxy-6-methyl-2-oxa-2H-pyran-3-yl)-3-(3-methyl-4-hydroxyphenyl)-2-propenone (3h):

IR (cm^{-1}, KBr): 3356 (OH), 1710 (lactone C=O), 1649 (C=O), 1620 (CH=CH). ^{1}H NMR ($CDCl_3$,δ,ppm): 2.24 (s,3H,CH_3); 3.85 (s,3H,CH_3); 6.04 (s,1H,C^5H); 6.85 (s,1H,Ar-H); 7.15 (m,2H,Ar-H); 7.83-7.87 (dd,1H, *J*= 9.85,-C=OCH); 7.99-8.03 (dd,1H, *J*= 9.75, =CHAr); 9.64 (s,1H,OH); 18.1 (s,1H,D_2O exchangeable, OH). MASS *m/z*: 287 (M+1).

3. RESULTS AND DISCUSSION

The Claisen-Schmith condensation method was employed for the synthesis of chalcone derivatives by condensing dehydroacetic acid with suitable aldehyde using piperedine as catalyst in chloroform at reflux temperature to yield corresponding chalcone (Scheme I). The structures of all the compounds were established from IR and ^{1}HNMR ^{13}CNMR and mass spectroscopic data. The IR spectrum of compound 3a (Figure 1), 3c, 3f and 3h show a broad band for OH group at 3396 cm^{-1}, 3549 cm^{-1} , 3383 cm^{-1} , 3386 cm^{-1} respectively and sharp and strong band at 1704 cm^{-1}, 1720 cm^{-1} 1683 cm^{-1} and 1710 cm^{-1} for lactone carbonyl group. Another sharp band observed at 1592 cm^{-1} 1516 cm^{-1}, 1595 cm^{-1} and 1620 cm^{-1} due to the presence of carban-carban double bond of -unsaturated chalcone system. The ^{1}HNMR spectra of 3a (Figure 1) showed a characteristic singlet due to C^5-H proton around δ 5.92 ppm for lactone unit. It is also noted that olefinic protons of reactive α,β-unsaturated keto function occurs as doublet around δ 8.02-8.05 (*J*= 8.02) and 8.10-8.14 (*J*= 8.11) respectively. A broad singlet around δ 18.7 due to D_2O exchangeable OH group of lactone unit. The protons of the pyrrolidine unit appeared as two triplets at δ 2.06 and 2.40. The structure of 3a was further confirmed by mass spectrum which showed M+1 at *m/z* 326.

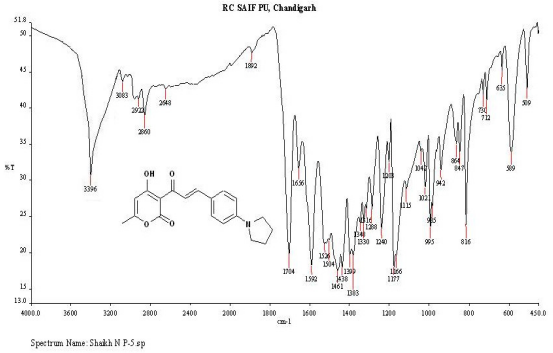


Figure - 1: IR spectrum of compound 3a.

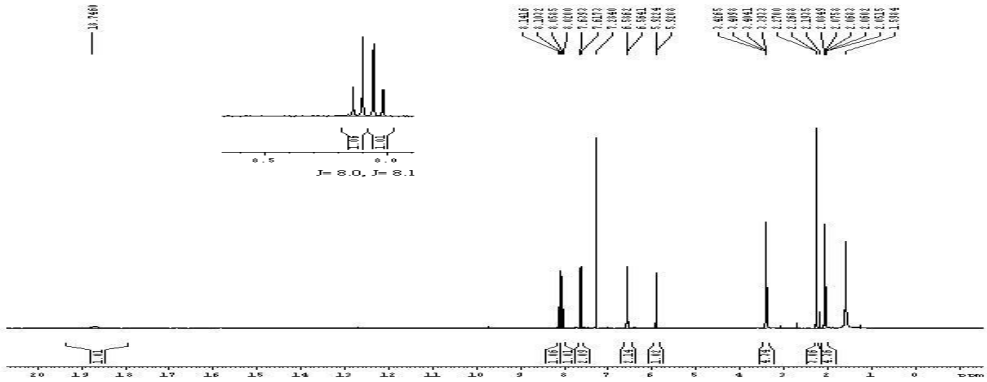


Figure - 2: ^{1}HNMR spectrum of compound 3a

Table - I: Percentage yield and melting points of Substituted 3-Cinnamoyl-4-hydroxy-6-methyl-2-pyrones.

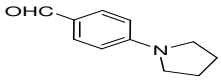
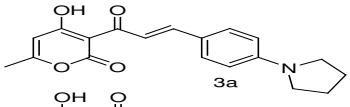
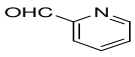
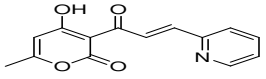
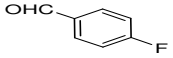
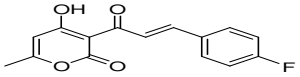
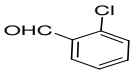
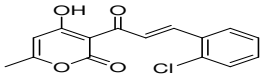
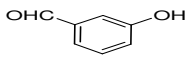
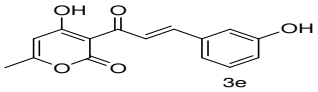
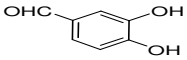
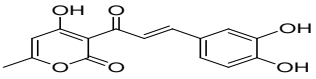
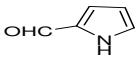
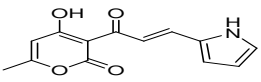
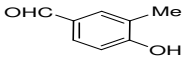
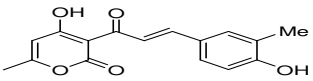
Entry	X	Product 3	Yield %	M.P.^{0}C
1		 3a	71	220-222
2		 3b	68	200-201
3		 3c	74	135-136
4		 3d	65	120-122
5		 3e	62	210-211
6		 3f	79	204-205
7		 3g	66	157-159
8		 3h	73	232-233

Table IIa: Antibacterial activity of 3a, 3d, 3e and 3h compounds

Comound	Zone of inhibition in mm			
	Staphylococcus aureus	*Basillus subtilis*	*Escherichia coli*	*Salmonella typhi*
3a	10	15	14	--
3d	20	16	11	--
3f	19	14	14	11
3h	--	--	--	--
Penicillin	34	17	13	22

-- Indicate no zone of inhibition

Table IIb: Antifungal activity of 3a, 3d, 3e and 3h compounds

Compound	*Aspergillus niger*	*Penicillium chrysogenium*	*Fusarium moneliform*	*Aspergillus Flavus*
3a	RG	RG	RG	RG
3d	RG	-ve	-ve	-ve
3f	-ve	-ve	-ve	
3h	-ve	-ve	-ve	-ve
DMSO +ve control	+ve	+ve	+ve	+ve
Griseofulvin control	-ve	-ve	-ve	-ve

+ve control, -ve control and RG indicate No antifungal activity, Antifungal activity observed and Reduced growth respectively.

3.1. Antimicrobial Activity

The synthesized compounds were screened for their antibacterial activity against two gram positive bacteria viz; *Basillus subtilis, Staphylococcus aureus* and two gram negative bacteria viz; *Escherichia coli*, *Salmonella typhi* by using agar cup method. The agar cup medium was purchased from HI media laboratories Ltd. Mumbai, India. The preparation of nutrient broth, subculture, base layer medium, agar medium and peptone water was done as per standard procedure. The solution of the test compounds were prepared by dissolving 5mg each in 5mL of dimethylsulfoxide at a concentration of 1000 µg/mL. The cups each of 10 mm in diameter were made by scooping out medium with a sterilized cork borer in a Petri dish which was streaked with the organism. The solutions of each test compound (0.1 mL) were added separately in the cups and petri dishes were subsequently incubated. Penicillin was used as standard / reference drug and Dimethyl Sulphoxide as a control which did not reveal any inhibition. Zone of inhibition produced by each compound was measured in mm. The results of antibacterial studies are given in Table IIa.

The compound screenrd for antibacterial activity were also tested for their antifungal activity using potato-dextrose agar (PAD) medium by plate method against *Aspergillus niger, Penicillium chrysogenium, Fusarium moneliform and Aspergillus Flavus* The PAD medium was purchased from HI media laboratories Ltd. Mumbai, India. The preparation of nutrient broth, subculture, base layer medium, agar medium and peptone water was done as per standard procedure. The solution of the test compounds were prepared by a similar procedure described under the antibacterial activity. Each test compounds 5mg was dissolved in 5mL of dimethylsulfoxide at a concentration of 1000 µg/mL A Griseofulvin used as –ve control reference / standard and dimethylsulfoxide as a control which did not reveal any inhibition. The results of antifungal studies are given in Table IIb.

4. CONCLUSION

Majority of the compounds tested showed excellent to good antifungal activity but compound 3a exhibited reduced antifungal activity against all the tested organisms and 3d also shows moderate activity against *Aspergillus niger*. Among the all tested compounds 3a and 3d showed excellent antibacrerial activity against *Basillus subtilis* and *Escherichia coli* and moderate activity against *Staphylococcus aureus.* While 3h compound do not show any inhibition against all the tested organisms and 3f was found to be good antibacterial agent against the entire tested organisms.

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