International Journal of Pharmaceutical Chemistry

ISSN: 2249-734X (Online)
Journal DOI:10.7439/ijpc
CODEN:IJPCI4 (American Chemical Society)

Research Article

Synthesis and Antimicrobial Evaluation of Some Chalcone Derivatives of 3-Cinnamoyl-4-hydroxy-6-methyl-2-pyrones

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Abstract

In an effort to develop antimicrobial agents, a series of chalcone derivatives of 3- cinnamoyl-4-hydroxy-6-methyl-2-pyrones were synthesized by base catalyzed condensation of 3-acetyl-4-hydroxy-6-methyl-2-keto-2*H*-pyran (DHA) with different aromatic aldehydes. The synthesized compounds were characterized by means of their IR, and ^{1}HNMR spectra's. The synthesized compounds were tested for their antibacterial and antifungal activities.

Key words: chalcone, 3-cinnamoyl-4-hydroxy-6-methyl-2-pyrones, dehydroacetic acid, antibacterial, antifungal activity.

1. Introduction

Chalcones are probably the most widely used intermediates for synthesizing various heterocyclic ring systems. Chalcones 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 exhibit association with such a wide range of pharmacological activities among which cytotoxicity[2] antitumor[3], anti-inflammatory[4], antiplasmodial[5], immunosuppression[6], antioxidant[7], antibacterial[8], antifungal[9], and antiprotozoal are widely cited[10]. They also possess antiviral[11], antimalarial[12], antiulcerative[13] and antihyperglycemic[14] activities. Chalcones are used as aldose reductase[15], leukotriene B_4[16] and tyrosinase[17] inhibitors. The presence of reactive a,b-unsaturated keto function in chalcone 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 have important feature 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) also shows promising antifungal[18], antibacterial[19] and antiprotozoal activities[20].

The present work deals with the synthesis of chalcones of dehydroacetic acid with different aromatic aldehydes. 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.

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2. Experimental

2.1. General: Melting points were determined in open capillary and are uncorrected. The IR Spectra were recorded on Shimadzu FT IR / Perkin Elmer RX FT-IR Spectrometer using potassium bromide pellets, ^{1}H NMR spectra 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 of S.A.I.F. Panjab University, Chandigarh. Purity of compounds was checked by thin layer chromatographic technique**.**

2.2. General Procedure for the synthesis of Substituted 3-Cinnamoyl-4-hydroxy-6-methyl-2-pyrones: A mixture of 10 mmol of dehydroacetic acid **1**, 10 mmol of aromatic aldehyde **2** and 8- 10 drops of piperedine as a catalyst was dissolved in 30 ml of chloroform solvent. The reaction mixture was refluxed for a reaction time 8 hours. The reaction mixture was distilled out to remove the azeotropic mixture produced during the reaction. After the complete separation of azeotropic mixture, the remaining chloroform was slowly evaporated to give a solid crude product which was recrystallise from suitable solvent to give the crystals of the corresponding product **3** in good to excellent yield.

2.3. IR, ^{1}HNMR and Mass Spectral data of 1-(4-hydroxy-6-methyl-2-oxa-2H-pyran-3-yl)-3-phenyl-2-propenone (3a): IR (cm^{-1}, KBr): 3356 (OH), 2940 (CH_3), 1710 (lactone C=O), 1649 (C=O), 1620 (CH=CH). ^{1}H NMR ($CDCl_3$,d,ppm): 17.7 (s,1H, D_2O exchangeable, OH); 8.21-8.25 (dd,1H *J*= 9.75,=CHAr); 7.90-7.94 (dd,1H, *J*= 9.75, -C=OCH); 7.68 (m,2H,Ar-H); 7.45 (m,2H,Ar-H); 6.16 (s,1H,C^{5}H); 2.30 (s,3H,CH_3). Mass m/z: M+ 256, M+1 257.

2.4. IR and ^{1}HNMR Spectral data of 1-(4-hydroxy-6-methyl-2-oxa-2H-pyran-3-yl)-3-(4-hydroxyphenyl)-2-propenone (3c): IR (cm^{-1}, KBr): 3266 (OH), 1697 (lactone C=O), 1647 (C=O), 1603 (CH=CH). ^{1}H NMR ($CDCl_3$,d,ppm): 18.1 (s,1H,D_2O exchangeable, OH); 8.20-8.24 (dd,1H, *J*= 9.75, =CHAr); 7.95-7.99 (dd,1H, *J*= 9.85,-C=OCH); 7.62 (m,2H,Ar-H); 6.89 (m,2H,Ar-H); 5.97 (s,1H,C^{5}H); 5.55 (s,1H,OH); 2.19 (s,3H,CH_3).

2.5. IR, ^{1}HNMR and Mass Spectral data of 1-(4-hydroxy-6-methyl-2-oxa-2H-pyran-3-yl)-3-(2-hydroxyphenyl)-2-propenone (3d): IR (cm^{-1}, KBr): 3226 (OH), 1689 (lactone C=O), 1647 (C=O), 1615 (CH=CH). ^{1}H NMR ($CDCl_3$,d,ppm): 18.1 (s,1H,D_2O exchangeable, OH); 8.20-8.24 (dd,1H,=CHAr); 7.95 (m,1H,Ar-H); 7.63-7.65 (d,1H,C=OCH); 7.02 (m,3H,Ar-H); 5.97 (s,1H,C^{5}H); 5.55 (s,1H,OH); 2.19 (s,3H,CH_3). Mass m/z: M 272.

2.3. IR and ^{1}HNMR Spectral data of 1-(4-hydroxy-6-methyl-2-oxa-2H-pyran-3-yl)-3-(4-bromoyphenyl)-2-propenone (3e): IR (cm^{-1}, KBr): 3105 (OH), 1708 (lactone C=O), 1624 (C=O), 1597 (CH=CH). ^{1}H NMR (DMSO,d,ppm): 8.33-8.37 (dd,1H,=CHAr); 8.30 (d,2H,Ar-H); 7.96-7.97 (d,1H,-C=OCH); 7.91-7.93 (d,2H,Ar-H); 6.18 (s,1H,C^{5}H); 2.33 (s,3H,CH_3).

3. Result and discussion

The Chalcones of dehydroacetic acid were synthesized by Claisen-Schmith condensation in good to excellent yields (**Scheme 1**). All of the synthesized compounds exhibit antibacterial and antifungal activity. The structures of all the compounds were established from IR and ^{1}HNMR spectral analysis. The IR spectrum of compounds **3a, 3d** and **3e** showed a broad band for OH group at 3356 cm^{-1}, 3216 cm^{-1} and 3105cm^{-1} and sharp and strong band at 1710 cm^{-1}, 1689 cm^{-1} and 1708 cm^{-1} for lactone carbonyl group. Another sharp band observes at 1649 cm^{-1}, 1647 cm^{-1} and 1624 cm^{-1} due to the presence of carbonyl group and at 1620 cm^{-1}, 1615 cm^{-1} and 1597 cm^{-1} for the carban-carban double bond of a,b-unsaturated chalcone system. The ^{1}HNMR spectra of **3a, 3d and 3e** showed a characteristic singlet due to C^5-H proton around d 6.16, 5.97 and 6.18 ppm for lactone unit. We also noted the olefinic protons of reactive a,b-unsaturated keto function occurs as doublet around d 7.90-7.94 (*J*= 9.75) and 8.21-8.25 (*J*= 9.75), d 7.93-7.97 (*J*= 8.0) and 8.33-8.37 (*J*= 8.3) for 3a and 3e (Figure1). A broad singlet around d 17.7 and 18.1 due to D_2O exchangeable OH group of lactone unit.

Scheme 1: **Synthesis of chalcone derivatives of 3-Cinnamoyl-4-hydroxy-6-methyl-2-pyrones**

Figure 1: ^{1}HNMR spectrum of 3a

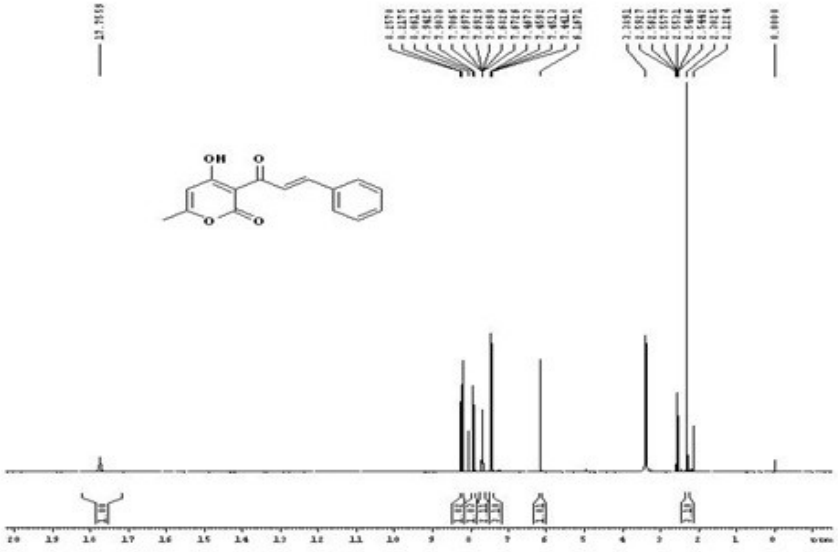
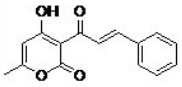
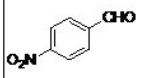
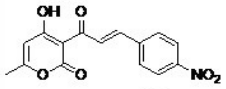
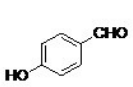
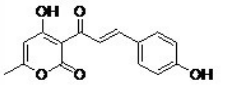
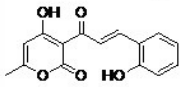
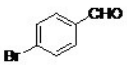
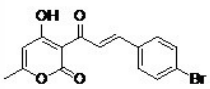
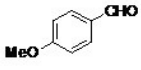
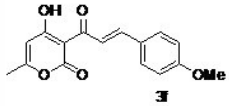


Table 1: Percentage yield and melting points of Substituted 3-Cinnamoyl-4-hydroxy-6-methyl-2-pyrones.

Entry	X	Product	Yield %	M.P ^{0}C
1		 3a	69	130-132
2		 3b	74	245-246
3		 3c	81	260-262
4		 3d	65	197-198
5		 3e	68	211-212
6		 3f	71	196-197

3.1. Antimicrobial Activity: The synthesized compounds are screened for their antibacterial activity against two gram positive bacteria viz; *Bacillus subtilis, Staphylococcus aureus* and two gram negative bacteria viz; *Escherichia coli*, *Salmonella typhi* by using agar cup method[21]. 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 mg/ 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 2a.

The compounds screened 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 compound 5mg each in 5mL of dimethylsulfoxide at a concentration of 1000 mg/ mL was used for screening. A reference / standard Griseofulvin used as –ve standerd and dimethylsulfoxide as a control which did not reveal any inhibition. The results of antifungal activities of the screened compounds are given in Table 2b.

4. Conclusion

In conclusion, we have synthesized chalcones from starting material 3-acetyl-4hydroxy-6-methyl-2-keto-2H-pyran.The newly synthesizes chalcone derivatives were fully characterized by spectral analysis. Morever, we studied the biological importance of synthesized compounds by screening their antimicrobial activity against four fungi [*Aspergillus niger, Penicillium chrysogenium, Fusarium moneliform and Aspergillus Flavors*] and two Gram +ve *[Bacillus subtilis, Staphylococcus aureus]* as well as two Gram –ve *[Escherichia coli*, *Salmonella typhi]* bacteria. Compounds **3a** and **3d** shows excellent antibacterial activity against all the test microorganism except *Salmonella typhi.*Compound **3a** was more potent antibacterial than the reference drug showed highest inhibitiom zone 14 mm against *Escherichia coli* than reference Penicillin 13 mm. Compounds **3c** and **3e** were inactive against all the test microorganism. Compounds **3a, 3c, 3d** and **3e** exhibited the high antifungal against all test microorganism except **3c** and **3d** against *Aspergillus niger, Penicillium chrysogenium.*

Acknowledgements

The author N.P. Shaikh is thankful to the UGC, New Delhi, for providing Maulana Azad National Fellowship (Junior Research Fellowship) and Principal, Rajarshi Shahu Mahavidhyalaya, Latur for providing all necessary research facilities to carry out this work.

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