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Design and Synthesis of 1-(3',5'-bis trifluoromethyl phenyl)-3-(substituted phenyl)-2-propene-1-one as potent antifungal and antibacterial agents

Ch. M. M. Prasada Rao^{*a}, S. A. Rahaman^b, Y. Rajendra Prasad^c, G Eswara Rao^{da}

^aQis College of Pharmacy, Vengamukkala Palem, Ongole, A.P-523272.

^bNirmala college of pharmacy, Atmakur Village, Mangalagiri Mandal, Guntur Dt, A.P - 522 503

^cDepartment of Chemistry, University College of Pharmaceutical Sciences, Andhra University, Visakhapatnam-530 003, (A.P), India

^dNRI College of pharmacy, Pothavarappadu(v), Agiripalli (mandal), Krishna Dist, A.P.

ABSTRACT

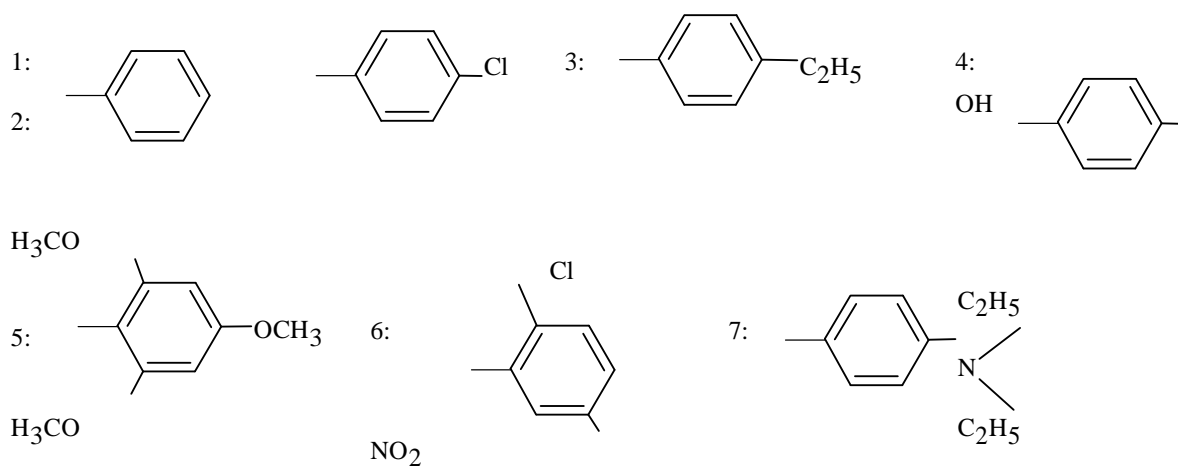
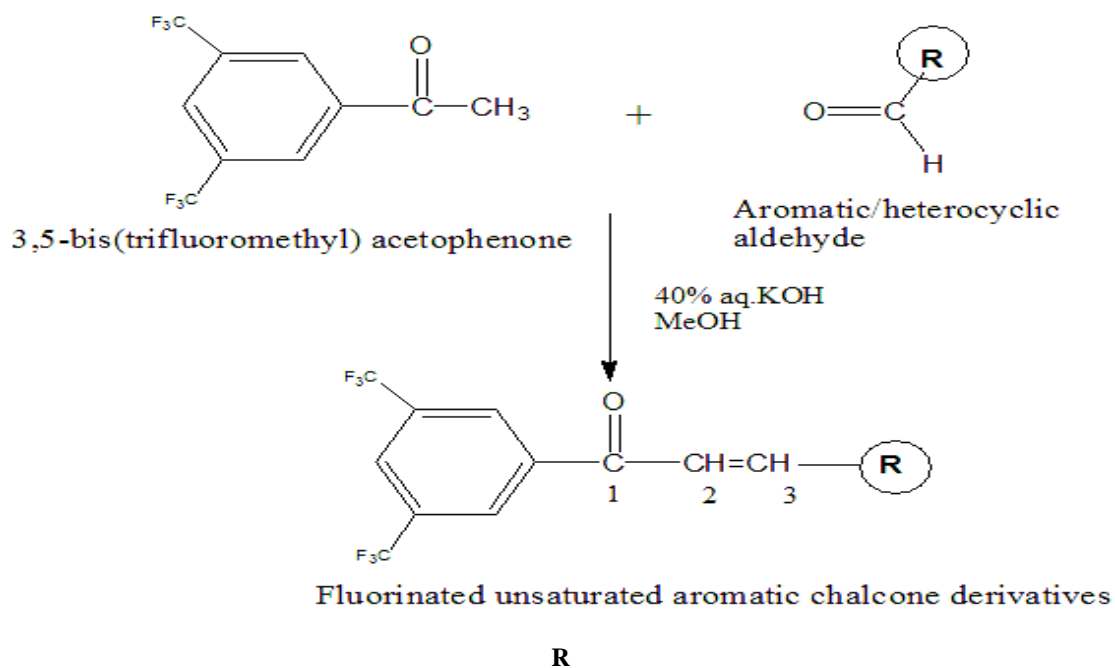
Seven new chalcones were synthesised by Claisen Schmidt condensation using 3,5-bis-trifluoromethyl acetophenone with aromatic aldehydes in dilute ethanolic potassium hydroxide solution at room temperature. All these compounds were characterised by means of their IR, ¹H NMR Spectroscopic data and Elemental analysis. The antibacterial activity of these compounds were evaluated by cup plate method using Streptomycin as standard drug. The obtained zone of inhibition values showed that synthesized compounds are moderately significant. It is evident that the compound TFEA showed maximum antifungal activity when comparable with standard Ketoconazole.

Keywords: Chalcones, Claisen Schmidt, 3,5-bis-trifluoromethyl acetophenone, antibacterial and antifungal activities.

INTRODUCTION

Discovery of novel synthetic heterocyclic compounds are the target of organic scientists to cure the diseases. Hence, novel chalcones were synthesized because it is known to exhibit various biological activities. Chalcones have been reported to possess antioxidant [1-3], antiulcer [4], antimalarial [5,6], antileishmanial [7], anti-inflammatory [8], antitumor [9], antitubercular [10,11] and antibacterial activity [12] and antifungal activity. The presence of a reactive α,β -unsaturated keto functional group in chalcones is found to be responsible for their antimicrobial and other activities, which may be altered depending on the type and position of substituent on the aromatic rings. In the present communication we report the reaction of 3,5-bis-trifluoromethyl acetophenone with different aromatic aldehydes to afford novel chalcones(1-7). The structures of the various synthesized compounds were assigned on the basis of elemental analysis, IR and ¹H NMR spectral data. These compounds were also screened for their antibacterial and antifungal activities.

Scheme 1 synthesis of novel chalcone derivatives



MATERIALS AND METHODS

Melting points were determined on a capillary melting point apparatus and are uncorrected. ^1H NMR spectra was recorded in the indicated solvent on Bruker AV 400 MHz spectrometer using TMS as internal standard. Infrared spectra were recorded in KBr on Perkin-Elmer AC-1 spectrophotometer. Microanalyses were performed on Carlo Erba EA145 1108 element analyzer and were within the $\pm 0.5\%$ of the theoretical values. Column chromatography was performed on silica gel (Merck, 60-120 mesh).

General procedure for the synthesis of new chalcones (1-7):

A mixture of 3,5-bistrifluoromethyl acetophenone (0.001 moles) and aryl aldehyde (0.001 moles) was stirred in methanol (8ml) and to it 5 milli moles of 40% KOH was added [13,14]. The mixture was kept for 24 hrs and it was acidified with 1:1 hydrochloric acid and water then it was filtered through vacuum by washing with water to afford title compounds (Scheme 1). The Characterisation data of these compounds is described in Table 1.

Characterization of synthesized novel chalcone derivatives [15] (1-7):**1-(3',5'-bis trifluoro methyl phenyl)-3-(phenyl)-2-propene-1-one (TFP):**

IR (cm^{-1}) C-H str --- 3131.7, C=O str --- 1678.3, C=C str --- 1600.7; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 7.12 (1H, d, J=8Hz, C-2H), 7.387 (1H, d, J=8Hz, C-3H), 7.268-8.21 (8H, aromatic protons)

1-(3',5'-bis trifluoro methyl phenyl)-3-(4-chloro phenyl)-2-propene-1-one (TFC):

IR (cm^{-1}) C-H str --- 3156.26, C=O str --- 1705.81, C=C str --- 1589.40; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 6.72 (1H, d, J=8Hz, C-2H), 7.25 (1H, d, J=8Hz, C-3H), 7.12-8.4 (7H, aromatic protons)

1-(3',5'-bis trifluoro methyl phenyl)-3-(4-ethyl phenyl)-2-propene-1-one (TFE):

IR (cm^{-1}) C-H str --- 3074.26, C=O str --- 1715.81, C=C str --- 1586; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 7.08 (1H, d, J=8Hz, C-2H), 7.64 (1H, d, J=8Hz, C-3H), 7.4-8.12 (7H, aromatic protons)

1-(3',5'-bis trifluoro methyl phenyl)-3-(4-hydroxy phenyl)-2-propene-1-one (TFH):

IR (cm^{-1}) C-H str --- 3073.6, C=O str --- 1702, C=C str --- 1576, O-H str --- 3550.4; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 7.02 (1H, d, J=8Hz, C-3H), 7.8 (1H, d, J=8Hz, C-2H), 7.2-8.31 (7H, aromatic protons)

1-(3',5'-bis trifluoro methyl phenyl)-3-(2,4,6-trimethoxy phenyl)-2-propene-1-one (TFMC):

IR (cm^{-1}) C-H str --- 3077.3, C=O str --- 1692.15, C=C str --- 1598.67; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 7.836 (1H, d, J=16Hz, C-2H), 8.182 (1H, d, J=16Hz, C-3H), 8.408-8.45 (5H, aromatic protons), 3.883 & 3.925 (9H, -OCH₃ protons)

1-(3',5'-bis trifluoro methyl phenyl)-3-(2-chloro-5-nitro phenyl)-2-propene-1-one (TFNC):

IR (cm^{-1}) C-H str --- 3031.7, C=O str --- 1718.3, C=C str --- 1607.5, N-O str --- 1545.2 & 1486; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 8.211 (1H, d, 3H), 7.530 (1H, d, 2H), 7.935-8.05 (6H, m, aromatic protons)

1-(3',5'-bis trifluoro methyl phenyl)-3-(4-N,N-diethyl amino phenyl)-2-propene-1-one (TFEA):

IR (cm^{-1}) C-H str --- 3085.05, C=O str --- 1705.39, C=C str --- 1575.57; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 6.478 (1H, d, J=8.4Hz, C-3H), 7.09 (1H, d, J=8Hz, C-2), 6.7-7.78 (7H, aromatic protons), 1.115-1.158 (4H, s, CH₂), 0.982 (6H, s, CH₃).

Antibacterial activity of synthesized compounds

The antimicrobial activity was tested by Cup plate method [16,17,18,19] using Mueller-Hinton agar medium was employed to study the preliminary antibacterial activity of novel chalcones (1-7) against *Staphylococcus aureus*, *Bacillus subtilis* and *E.coli*.

Preparation of nutrient agar medium

The agar medium was purchased from HI media Laboratories Ltd., Mumbai, India. Peptone, meat extract and sodium chloride were dissolved in 100 ml of distilled water and the solution was made upto 200 ml by distilled water. The pH of the medium was adjusted to 7.2. Agar was dissolved in above solution. Then the solution was distributed in 20 ml quantities into 50 ml boiling test tubes. They were sterilized in autoclave at temperature of 121⁰c and pressure of 15 lbs/sq.in for 20 minutes.

Procedure

The above medium was inoculated at 1% level with 18 hrs old cultures of the above mentioned test organisms and were transferred into sterile petridishes (6 inch). The medium in the plates was allowed to set at room temperature for about 10 minutes and they were solidify in a refrigerator for 30 minutes. Then three bores were made in each petriplate and respective 1 ml test and standard concentrations of prepared 50µg/ml, 100µg/ml, 250 µg/ ml prepared in DMSO were poured. The plates thus prepared were left to stand in a refrigerator for about 1 hr to allow the test solution for diffusion. Then incubation of the above plates was done for 24 hrs at 37⁰c. The plates were examined for zones of inhibition and the inhibition zone diameters were recorded in table (2).

Antifungal activity of Chalcones

The antifungal activity [20] of new chalcones (1-7) also done in cup plate method using PDA medium against *Aspergillus niger*. The PDA medium was purchased from HI media Laboratories Ltd., Mumbai, India. Preparation of nutrient broth, subculture, base layer medium and PDA medium was done as per the standard procedure. Each test and standard compound (5 mg) was dissolved in 5 ml of dimethyl sulfoxide to attain 1000 µg/ml. From this a serial dilutions of 50 µg/ml, 100 µg/ml, 250 µg/ ml were prepared and they were used for testing. The cups each of 9mm diameter were made by scooping out medium with a sterilized cork borer in a Petri dish which was streaked with the organisms. The solutions of each test compound were added separately in the cups and Petri dishes were subsequently incubated. ketoconazole were used as standard reference drug. Dimethyl Sulphoxide as a control which did not reveal any inhibition. The Zone of inhibitions produced by each compound was measured in mm and the results were presented in Table (3)

Table (1) Physical Data of compounds (1-7)

Compound code	Molecular Formula	Melting point (°C)	% Yield	Elemental Analysis					
				C		H		O	
				Found	Calculated	Found	Calculated	Found	Calculated
TFP	C ₁₇ H ₉ OF ₆	112	85	59.31	58.92	2.9	2.8	4.62	4.58
TFC	C ₁₇ H ₉ OF ₆ Cl	120	82	53.93	53.64	2.44	2.31	4.22	4.20
TFE	C ₁₇ H ₉ OF ₆ Cl	118	86	61.29	60.91	3.79	3.69	4.30	4.28
TFH	C ₁₇ H ₁₀ O ₂ F ₆	126	84	56.68	55.98	2.80	2.75	8.88	8.79
TFMC	C ₂₁ H ₁₉ NOF ₆	133	90	55.31	53.21	3.71	3.64	14.73	14.64
TCNC	C ₂₀ H ₁₆ O ₄ F ₆	124	85	48.19	47.91	1.90	1.83	11.33	11.28
TFEA	C ₂₁ H ₁₉ NOF ₆	122	79	60.72	60.57	4.61	4.54	3.85	3.84

Table (2) zone of inhibitions of antibacterial activity novel chalcones (1-7)

Compound	Zone of inhibition (mm)								
	Staphylococcus Aureus			Bacillus subtilis			Escherichia coli		
	50 µg/ml	100 µg/ml	250 µg/ml	50 µg/ml	100 µg/ml	250 µg/ml	50 µg/ml	100 µg/ml	250 µg/ml
TFP	04	10	14	-	12	14	-	12	16
TFC	08	12	16	-	10	14	12	16	18
TFE	06	10	12	7	10	12	-	10	12
TFH	06	08	12	8	12	14	-	10	14
TFMC	14	18	19	12	15	17	12	17	20
TCNC	10	13	17	10	14	18	10	12	14
TFEA	14	18	24	12	16	20	18	22	24
Streptomycin	19	24	26	18	22	24	20	22	25
Control(DMSO)	-	-	-	-	-	-	-	-	-

- indicates no zone of inhibition

Table (3) zone of inhibitions of antifungal activity of novel chalcones (1-7)

Compound	Zone of inhibition (mm)		
	Aspergillus niger		
	50µg/ml	100µg/ml	250 µg/ml
TFP	04	10	14
TFC	08	12	16
TFE	06	10	12
TFH	06	08	12
TFMC	14	18	20
TCNC	18	18	22
TFEA	12	14	18
KETOCONAZOLE	30	32	34
Control (DMSO)	-	-	-

- no zone of inhibition

RESULTS AND DISCUSSION

Seven novel 1-(3',5'-bis trifluoromethyl phenyl)-3-(substituted phenyl)-2-propene-1-one were designed and synthesized by the condensation of 3,5-bis-trifluoromethyl acetophenone with various aromatic aldehydes in dilute ethanolic potassium hydroxide solution at room temperature. The molecular formulas of the compounds were found by Carlo Erba elemental analyzer. The individual melting points of TFP, TFC, TFE, TFH, TFMC, TCNC and TFEA were determined as 112⁰C, 120⁰C, 118⁰C, 126⁰C, 133⁰C, 124⁰C and 122⁰C respectively. The yields of novel chalcones (1-7) was found to be 79 – 90 % as shown in Table 1.

The obtained compound structures were characterized by its IR and ¹H NMR spectral data. The obtained compounds were screened for antibacterial and antifungal activities at the concentrations of 50, 100 and 250 µg/ml. Among all tested compounds only TFEA (1-(3',5'-bis trifluoro methyl phenyl)-3-(4-N,N-diethyl amino phenyl)-2-propene-1-one) showed maximum zone of inhibition when comparable with standard antibacterial agent Streptomycin due to the presence of electron withdrawing group at para position as shown in Table 2. Whereas in antifungal activity the zone of inhibitions of novel chalcones (1-7) reveals that the compound TCNC (1-(3',5'-bis trifluoro methyl phenyl)-3-(2-chloro-5-nitro phenyl)-2-propene-1-one) showed better activity than other novel chalcones comparable with standard Ketoconazole as shown in Table 3.

CONCLUSION

The screening results revealed that the synthesized phenyl chalcones have showed significant antibacterial and antifungal activity at 50 µg/ml, 100 µg/ml and 250 µg/ml dose level and are comparable to that of standard drug streptomycin.

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