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A Facile Synthesis and the Study of Some New Chalcones for Analgesic and Anti-Inflammatory Activity

Visagaperumal Dhanapal[1,2*], Chilukodi Gopinath[1], Bodepudi Ashajothi[1], Jayakumar Ramalingam[3], Anbalagan Navaneetha Raman[4]

1.Department of Pharmaceutical Chemistry, Bapatla College of Pharmacy, Bapatla, Andhra Pradesh, India

2.Department of Pharmacy, Acharya Nagarjuna University, Guntur, Andhra Pradesh, India

3.Technical department, Astra Zeneca India Pharma limited, Bellary road, Yalahanka, Bangalore, Karnataka, India

4.Department of Pharmaceutical Chemistry, Pydah College of Pharmacy, Kakinada, Andhra Pradesh, India

ABSTRACT

Some chalcones (**2a-2n**) were synthesized by the condensation of various substituted benzaldehydes and unsubstituted/4-bromo acetophenone by using Claisen-Schmidt condensation. This is a comparative study of synthesizing compounds by conventional as well as non-conventional microwave irradiation in a commercially modified microwave oven. The research is focused on the remarkable reaction rate enhancement by the use of various non-conventional microwave irradiations which minimizes the time and solvents in reactions. Variety of functional groups such as nitro, chloro, dimethylamino, methoxy and methyl survived under the reaction conditions. The structures of newly synthesized compounds have been established on the basis of IR, ^{1}H NMR spectral data and elemental analysis. The synthesized compounds were screened for analgesic and anti-inflammatory activity.

Keywords: 4-bromoacetophenone, chalcone, analgesic, anti-inflammatory

*Corresponding Author Email: vishak_dr@yahoo.co.in

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INTRODUCTION

After the introduction of acetylsalicyclic acid into medical use the first adverse reaction to it was reported in 1902 by Hirschberg[1]. A number of compounds possessing analgesic and anti-inflammatory property were designated as NSAIDS possessed the inhibition of Cyclooxygenase enzymes (COX) as the main mechanism of action. COX enzymes participate in the metabolism arachidonic acid that results in the producton of potent inflammatory mediators such as prostaglandins and thromboxaness. Two isoenzymes of COX, COX-1 (constitutive form) and COX-2 (inducible form) were found. Classical NSAIDs inhibit both isoenzymes and because of this gastrointolerance is produced due to the decreased production of prostaglandins. Selective COX-2 inhibitors exhibited better gastric tolerance but it was associated with severe cardiovascular events that led to recommendation for careful utilization for patients with existing vascular diseases[2,3].

Chalcones are the aromatic ketones belonging to 1,3-diaryl-2-propen-1-ones. Chemically, they consist of open-chain flavonoids in which the two aromatic rings are joined by a three-carbon α,β-unsaturated carbonyl system[4]. The chemistry of chalcones generated intensive scientific studies throughout the world, especially interesting for their biological applications. The compounds with backbone of chalcones have been reported to possess various biological activities such as antimicrobial[5], anti-inflammatory[6], analgesic[7], antiplatelet[8], antiulcerative[9], antimalarial[10], anticancer[11-16], antiviral[17], antileishmanial[18], antioxidant[19], antitubercular[20], anti-hyperglycemic[21] activities. Chalcones synthesized can be used as intermediates for synthesizing various heterocyclic compounds. The main method for the synthesis of chalcones is the classical Claisen-Schmidt condensation in the presence of aqueous alkali[22,23], $Ba(OH)_2$, ultrasound irradiation[24]. However many of this methods suffered from harsh reaction conditions, toxic reagents, strong acidic/basic conditions, prolonged reaction time, poor yield and low selectivity. Although, several modification have been made to counter these problems. There is still a need for the development of selective and better strategies for the synthesis of α, β- unsaturated carbonyl compounds. Recently, microwave radiation has gained the attention of chemists due to its unique advantages, such as shorter reaction times, cleaner reaction products, higher yields and better selectivity, being a valuable alternative to accomplish more efficient syntheses of a variety of organic compounds with a considerable simplicity of operation and milder reaction conditions, when combined with the solvent-free approach, as it provides an opportunity to work with open vessels[25,26] Keeping in view of these findings, herein we had described the synthesis of chalcones under microwave irradiation and compared with conventional method.

MATERIAL AND METHODS

All solvents used were of laboratory grade and were obtained from SD fine chemicals (Mumbai, India), Merck (Mumbai, India) and Loba Chemie. Melting points were determined in open glass capillary tubes and were uncorrected. Compounds were routinely checked for their purity on Silica gel G (Merck) thin layer chromatography (TLC) plates. Iodine chamber and UV lamp were used for visualization of TLC spots. The IR spectra were recorded in KBr pellets on FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on Bruker DPX-300 NMR spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard. The chemical shifts were reported in ppm scale. All reactions were carried out in a commercially available LG microwave oven (MB-3947C) having a maximum power output of 800 W operating at 2450 MHz.

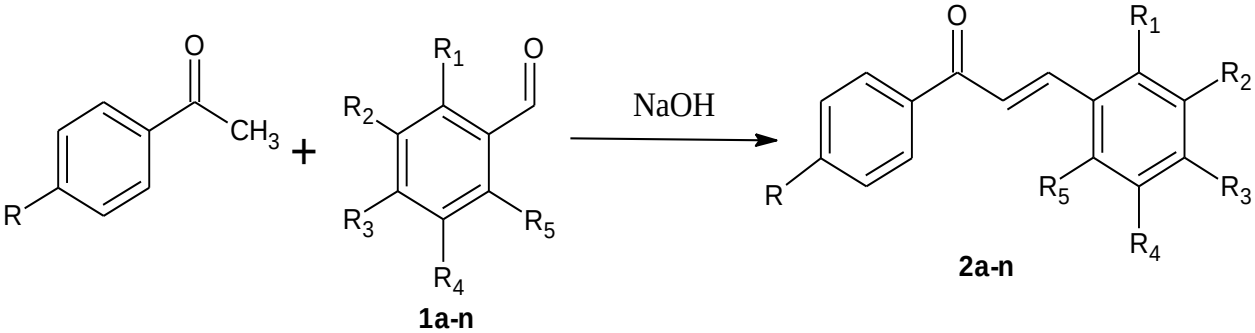
Synthesis of Chalcones

Conventional method

Equimolar quantities of substituted benzaldehydes (0.01 mol) and unsubstituted/4-bromoacetophenone (0.01 mol) were dissolved in minimum quantity of alcohol with 3-4 drops of concentrated sodium hydroxide. The solution was stirred with magnetic stirrer for 2-3 h and was placed overnight in a refrigerator. The mixture was then cooled, filtered, washed, dried in air and recrystallized from ethanol.

Microwave method

An equimolar mixture of unsubstituted/4-bromoacetophenone and substituted benzaldehydes dissolved in minimum amount of ethanol and NaOH were placed in a conical flask. The conical flask was covered with a funnel and then the flask was taken in a domestic microwave oven. The reaction mixture was irradiated under 160-320 watt microwave irradiation for 60-120 sec. The progress of the reaction was monitored by TLC for every 30 sec. Then the reaction mixture was cooled and the obtained solid was recrystallized from ethanol.



Scheme: Synthesis of chalcone derivatives

Animals

Adult albino mice of both sexes weighing 20–25 g were fasted for 12–24 h and used for the assessment of the analgesic activity. Adult male albino rats weighing 150–180 g were fasted for 12 h and used for the evaluation of the anti-inflammatory activity. All animals were obtained from the animal house of Bapatla College of Pharmacy, Bapatla. Animals were allowed free access to water and fed with standard diet. The research was conducted in accordance with the ethical rules on animal experimentation, approved by the Ethical Committee of Bapatla College of Pharmacy, Bapatla.

Analgesic activity

The synthesized compounds were used for evaluating their analgesic activity in acetic acid induced writhing response in albino mice following the method of Turner[27] and Collier[28] et al. Seventy two mice were selected and divided into 16 groups (six in each group), starved for 16 h and pretreated as follows: the first group which served as a positive control was orally received 1% CMC in appropriate volumes. The second to eleventh groups were receiving the aqueous suspension of synthesized compounds while the last group received diclofenac sodium. The test compounds were administered orally at the dose level of 200 mg/kg and Diclofenac sodium at the dose of 10 mg/kg (p.o.) was administered as standard drug for comparison. After 30 min, each mouse was administered 1% of an aqueous solution of acetic acid (10 mL/kg) and the mice were then placed in transparent boxes for observation. The number of writhes was counted for 15 min after acetic acid injection at 30, 60 and 90 min. The number of writhes in each treated group was compared to that of a control group. The number of writhing was recorded and the percentage protection was calculated using the following ratio and the results are presented in table-3:

$$\% \text{ Protection} = [(\text{Control mean} - \text{Treated mean}) / \text{Control mean}] \times 100\%$$

Anti-inflammatory activity

The anti-inflammatory activity was evaluated by using carrageenean-induced rat paw oedema model[29]. In this the animals were divided into groups (control, reference and test groups) each of 6 animals. Acute inflammation was produced by subplantar injection of 0.05 mL of 1 % suspension of carrageenean in saline into the plantar tissue of one (right) hind paw of the rat, one hour after oral administration of the test compound at dose levels of 200 mg kg^{-1}. The control group received equal volume of saline into the other (left) hind paw. The reference group was orally administered with indomethacin (10 mg kg^{-1}) suspended in saline as reference drugs. The average mass of oedema was calculated for control, reference and the test groups after drug

administration. The percentage of inhibition of oedema was evaluated as per Winter et al[30]. The results were analyzed for statistical significance (expressed as mean ±SEM) between the zero hour administrations with other durations for the treated groups using one-way ANOVA followed by multiple comparisons by Dunnett's tests.

Acute toxicity:

Acute toxicity tests were performed according to the organization of economic co-operation and development (OECD) guideline for testing of chemicals. Acute toxicity of chalcone derivatives was determined in Wister albino mice. Each group of 3 animals was fasted for 24 hours prior to the administration of the test compounds. The test compounds are administered orally in doses up to 2000 mg/kg by suspending in 1% C.M.C solution and were kept under observation for period of 14 days.

Statistical analysis

The data was expressed as Mean ± SEM (standard error of mean). Analysis of variance (ANOVA) followed by Dunnett test was used to statistically analyze the data. P values less than 0.001 ($P<0.001$), 0.01 ($P<0.01$), 0.05 ($P<0.05$) were considered as significant.

RESULTS AND DISCUSSION

Spectral data:

1,3-Diphenylpropenone (2a)

IR-Spectrum (KBr), cm^{-1}: 3030 (C-H aromatic), 1664 (C=O), 1598 (C=C). ^{1}H-NMR spectrum (δ, ppm): 7.77 (d, 1Hα), 8.08 (d, 1Hβ), 7.4–8 (m, 10H, Ar-H).

3-(4-Methylphenyl)-1-phenylpropenone (2e) IR-Spectrum (KBr), cm^{-1}: 3021 (C-H aromatic), 1674 (C=O), 1591 (C=C). ^{1}H-NMR spectrum (δ, ppm): 2.98 (s, 3H, CH_3), 7.59 (d, 1Hα), 8.11 (d, 1Hβ), 7.56–8.01 (m, 9H, Ar-H).

3-(4-Dimethylaminophenyl)-1-phenylpropenone (2h) IR-Spectrum (KBr), cm^{-1}: 3038 (C-H aromatic), 1669 (C=O), 1608 (C=C). ^{1}H-NMR spectrum (δ, ppm): 2.84 (s, 6H, $N(CH_3)_2$), 7.79 (d, 1Hα), 8.18 (d, 1Hβ), 7.49–8.02 (m, 9H, Ar-H).

1-(4-bromophenyl)-3-phenylprop-2-en-1-one (2j)

IR (cm^{-1}) ν_{max}: 3065 (CH), 1658 (C=O), 1598 (C=C arm). ^{1}H NMR (δ ppm): 7.56 (d, 1Hα), 7.91 (d, 1Hβ), 7.30- 8.01 (m, 10H, ArH).

1-(4-bromophenyl)-3-(4-chlorophenyl)prop-2-en-1-one (2k)

IR (cm^{-1}) ν_{max}: 3003 (Ar CH), 2937 (CH), 1593 (C=O), 1510 (C=C arm), (C-Br). ^{1}H NMR (δ ppm): 7.40 (d, 1Hα), 7.82 (d, 1Hβ), 7.48-7.99 (m, 9H, ArH).

1-(4-bromophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (2l)

IR (cm^{-1}) ν_{max}: 3015 (Ar CH), 2965 (CH), 1658 (C=O), 1592 (C=C arm). ^{1}H NMR (δ ppm):3.8 (s, 3H, OCH_3),7.43 (d, 1Hα),7.81 (d, 1Hβ), 6.96–7.95 (m, 9H, Ar-H).

1-(4-bromophenyl)-3-(3-nitrophenyl)prop-2-en-1-one (2m)

IR (cm^{-1}) ν_{max}: 3088 (Ar CH), 1665 (C=O), 1527 (C=C arm). ^{1}H NMR (δ ppm): 7.42 (d, 1Hα), 7.85 (d, 1Hβ), 7.69-8.44 (m, 9H, ArH).

1-(4-bromophenyl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one (2n)

IR(cm^{-1}) ν_{max}: 3046 (Ar CH), 1656 (C=O), 1562 (C=C arm), (C-Br). ^{1}H NMR (δ ppm): 2.96 (s, 6H, $N(CH_3)_2$, 7.56 (d, 1Hα), 8.02 (d, 1Hβ), 7.44-7.79 (m, 9H, ArH).

The synthesis of the chalcones was accomplished according to the Claisen-Schmidt condensation of unsubstituted/4-hydroxyacetophenone with appropriate substituted aromatic aldehyde under microwave irradiation and conventional method, as indicated in Scheme and Table 1. The corresponding reactions proceeded smoothly and given good to excellent yields (80-96%) in microwave method when compared conventional method which had the yield of 71-93%. An important feature of this procedure is the survival of variety of functional groups such as nitro, chloro, dimethylamino, methoxy and methyl under the reaction conditions. The structures of the products were deduced from their IR and ^{1}H NMR spectral data. For example the IR spectrum of compound **2a-2n** exhibited characteristic band absorption for conjugated C=O group in the region of 1593-1674 cm^{-1}. The absorptions bands at around 1593-1674 cm^{-1} were assigned to the existing of C=C. Similarly, the peaks in ^{1}H NMR spectra of the synthesized compounds were in accordance with assigned structures.

Table-1. Physical data for the chalcones (2a-2n)

S no	R	R_1	R_2	R_3	R_4	R_5	MF	MW	mp (^{0}C)	Yield (%) Conventional	Microwave
2a	H	H	H	H	H	H	$C_{15}H_{12}O$	208	56-57	75	82
2b	H	Cl	H	H	H	H	$C_{15}H_{11}ClO$	243	53-54	78	87
2c	H	H	H	Cl	H	H	$C_{15}H_{11}ClO$	243	206	71	83
2d	H	H	H	OCH_3	H	H	$C_{16}H_{14}O_2$	238	55	79	85
2e	H	H	H	CH_3	H	H	$C_{16}H_{14}O$	222	102	77	88
2f	H	H	H	NO_2	H	H	$C_{15}H_{11}NO_3$	253	146	74	80
2g	H	H	NO_2	H	H	H	$C_{15}H_{11}NO_3$	253	159	93	96
2h	H	H	H	$N(CH_3)_2$	H	H	$C_{17}H_{17}NO$	251	112	75	94
2i	H	H	OCH_3	OCH_3	OCH_3	H	$C_{18}H_{18}O_4$	298	>300	72	82
2j	Br	H	H	H	H	H	$C_{15}H_{11}BrO$	287	115	91	95
2k	Br	H	H	Cl	H	H	$C_{15}H_{10}BrClO$	322	192	88	92
2l	Br	H	H	OCH_3	H	H	$C_{16}H_{13}BrO_2$	317	156	85	90
2m	Br	H	NO_2	H	H	H	$C_{15}H_{10}BrNO$	332	138	81	95
2n	Br	H	H	$N(CH_3)_2$	H	H	$C_{17}H_{16}BrNO$	330	131	72	91

Table 2. Analgesic effect of selected investigated compounds

S.no	Mean value ± S.E.M at different time interval (in seconds)			% Analgesia at	
	30 min	60 min	90 min	60 min	90 min
2a	4.333±0.6146	4.333±0.7601	4.833±0.7932	27.78	23.68
2b	4.167±0.6009	4.333±0.6667	5±0.9661	27.78	21.05
2c	4.333±0.8819	4.5±0.8466	4.667±0.6146	41.67	26.31
2d	4.5±1.176	4.833±0.9458	5.167±0.8333	19.45	18.41
2e	4.167±0.7032	4.333±0.8433	4.667±0.8819	27.88	26.31
2f	4.5±0.4282	4.667±0.8028	5.167±0.7032	22.22	18.41
2g	4.167±0.4773	4.667±0.7601	5.5±0.7638	22.22	13.15
2h	4±0.5774	4.333±0.7149	4.667±0.6667	27.78	26.31
2i	5.167±0.7032	4.5±0.9574	5.667±1.022	41.67	10.52
2j	5.167±0.7923	5.5±0.4282	6±0.9661	8.33	5.26
2k	4.833±0.6009	5.5±0.7638	6.167±0.9458	8.33	2.62
2l	4.833±1.014	5.333±0.5578	5.883±1.078	11.11	8.33
2m	5.167±0.4773	5.333±0.6146	5.667±0.6667	11.11	10.52
2n	5±0.7303	5.167±0.7032	5.667±0.8433	13.83	10.52
Diclofenac sodium	2.667±0.4216	2.333±0.4216	2.667±0.4944 *	61.12	57.88

Significance levels(*P< 0.05) compared with their control (ANOVA followed by Dunnett's test).

Each value represents ± SEM (n = 6)

Table 3 Anti-inflammatory effects of selected investigated compounds

S.no	Paw volume measured after				% inhibition at	
	30 min	1 h	2 h	3 h	2 hr	3 hr
2a	0.35±0.08851	0.8167±0.1167	1.15±0.1176	1.25±0.07638	20.69	15.71
2b	0.4±0.05774	0. ±0.139	1.233±0.09888	1.383±0.1078	14.97	6.74
2c	0.4±0.06325	0.8667±0.1333	0.9333±0.07601*	1.133±0.1647*	35.63	23.6
2d	0.4333±0.1145	0.7833±0.08774	1.183±0.1014	1.2±0.177	18.41	15.71
2e	0.3±0.07303	0.7833±0.1302	1.217±0.08724	1.3±0.1673	16.09	12.34
2f	0.35±0.09916	0.8333±0.1054	1.283±0.1515	1.4±0.1592	11.52	5.59
2g	0.35±0.07638	0.7667±0.09545	1.3±0.139	1.45±0.1232	10.34	2.22
2h	0.3667±0.08819	0.9±0.1592	1.367±0.1382	1.4±0.07303	5.72	5.59
2i	0.4±0.07303	0.95±0.09916	1.033±0.1202	1.45±0.1384	28.76	2.22
2j	0.4333±0.9545	0.9833±0.07923	1.15±0.07638	1.383±0.09804	20.69	6.74
2k	0.25±0.05627	0.85±0.1176	1.233±0.08819	1.45±0.1057	14.97	2.22
2l	0.35±0.09916	0.7167±0.2072	1.367±0.08819	1.433±0.1282	5.72	3.37
2m	0.25±0.05627	0.8667±0.09189	1.25±0.1232	1.417±0.1078	13.79	4.45
2n	0.25±0.06191	0.8667±0.5507	1.183±0.1447	1.433±0.1706	18.41	3.37
Indomethacin	0.2833±0.06009	0.55±0.1176**	0.6833±0.09458**	0.6667±0.1606***	52.87	55.04

Significance levels *P< 0.05, **P< 0.01, ***P<0.001 compared with respective control (ANOVA followed by Dunnett's test). Each value represents ± SEM (n = 6).

The analgesic activity was evaluated by acetic acid induced writhing method. The percent protection in mice brought about by administration of the drugs is shown in Table 2. The

compounds used for screening showed analgesic activity in the range of 8.33 to 41.67% with acetic acid induced writhing method as compared to 57.88% protection with diclofenac sodium. Compounds (**2a-2n**) were further tested for anti-inflammatory activity with the same dose as used for analgesic activity. The anti-inflammatory activity of compounds was carried out at an oral dose relative to 10 mg/kg of indomethacin. The percent edema inhibition relative to control was measured after 1 h, 2 h and 3 h of the treatment. The inhibition of swelling in carrageenan induced edema in rat paw brought about by oral administration of the drug is shown in Table 3. All the synthesized compounds tested for anti-inflammatory activity had shown the inhibition of edema ranging from 5.72 to 35.63%. The statistical significance testing using one way analysis of variance (ANOVA) followed by Dunnett's test showed that the anti-inflammatory activity of indomethacin and all the newly synthesized compounds were slightly effective in comparison with the standard.

CONCLUSION

In this work, the synthesis of chalcones using microwave irradiation and compared with conventional method was demonstrated. The use of microwave for synthesis has shown the advantages like high yields, relatively short reaction times, low cost, simple experimental and as isolation procedures. The activity data obtained in this study will be certainly useful to go for further research for drug designing and also for heterocyclic moieties.

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