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Analgesic Activity of some 1-Phenyl-3-aryl-5-(4-(butanoloxy) phenyl) 1*H*-pyrazoles

ANJU GOYAL[1] AND SANDEEP JAIN[2]*

[1]Chitkara College of Pharmacy, Rajpura, Patiala-140401 (Punjab), INDIA

[2]Drug Discovery and Research Laboratory, Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology, Hisar-125001 (Haryana), INDIA

Email: drsjain1969@yahoo.co.in

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Abstract: A series of analgesic activity of synthesised 1 -Phenyl-3-aryl-5-(4-(butanoloxy) phenyl) 1H-pyrazoles were synthesized from chalcones and screened for their *in vitro* analgesic activity. Chalcones *i.e.*,1-aryl-3-(4-hydroxyphenyl) prop-2-en-1-ones, **1** on reaction with phenyl hydrazine in presence of acetic acid and few drops of hydrochloric acid furnished the corresponding 1-phenyl-3-aryl-5-(4-hydroxyphenyl)-1*H*-pyrazoles **2** which on further reaction with 4-chloroalkanol yielded the title compounds **3**. These compounds were characterized by CHN analyses, IR, mass and ^{1}H NMR spectral data. All the novel synthesised 1-Phenyl-3-aryl-5-(4-(butanoloxy) phenyl) 1H-pyrazoles were evaluated pharmacologically for their analgesic activity and the title synthesised compounds exhibited significant results as compared to standard drug.

Keywords: Chalcones, 1*H*-pyrazoles, analgesic activity

1. INTRODUCTION

The most pervasive, frightening, and important symptom of injury, and much of disease, is pain. Pain should be considered a syndrome of highly unpleasant sensations rather than a symptom. Clinically pain is classified into two distinct types: acute and chronic. Acute pain is a set of unpleasant and emotional experiences often culminating in behavioural responses. Acute pain is, invariably, produced by disease, injury, noxious chemicals, or some physical stimulation (e.g. heat). Chronic pain, by its persistent and pathological form, appears to

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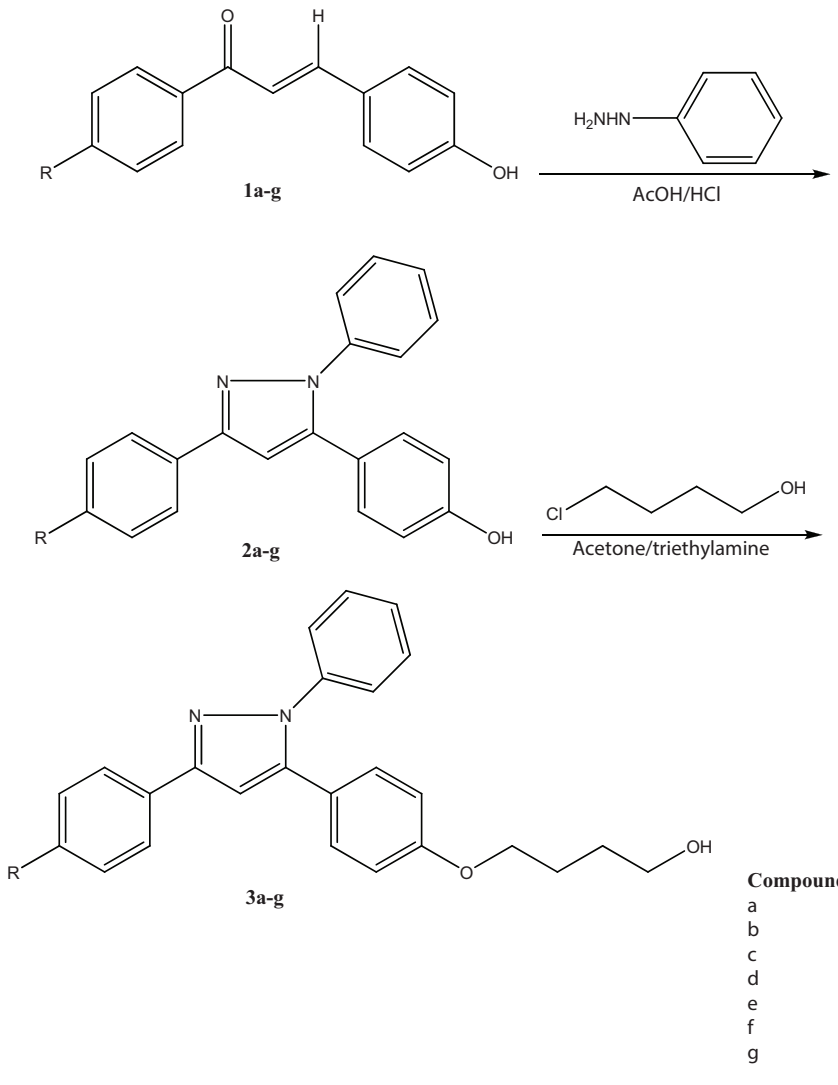
have no biological function. It imposes physical, emotional, and social stresses of severe magnitudes (Abdel-Hafez *et al*., 2009). Heterocyclic compounds continue to create a center of attention due to their various biological activities. Amongst the five membered heterocles, pyrazoles have been found to exhibit wide application in the field of medicinal and pharmaceutical chemistry. In recent years, progressively more concentration has been given to the synthesis of pyrazole derivatives for the development of new antibacterial agents. Pyrazole derivatives have been reported to possess diverse biological activities such as antibacterial as suggested (Vogel, 2008); (Abdel-Aziz, *et al.,* 2009), antifungal (Khalifa M.M., 2008), herbicidal (Chen and Li, 2000), insecticidal (Musad, 2011), anti-inflammatory, anticonvulsant (Goyal, 2012; Jain, 2013), anti-tumor, anti-oxidant (Jain et al., 2012) and so on. These reports prompted us to undertake the synthesis of some more 1*H*-pyrazoles bearing phenoxy alkanol moiety. The synthesized compounds were characterized on the basis of elemental analysis, IR, ^{1}H NMR and mass spectral data. All the novel synthesised 1-Phenyl-3-aryl-5-(4-(butanoloxy)phenyl) 1H-pyrazoles were evaluated pharmacologically for their analgesic activity and exhibited significant results as compared to standard drug.

2. EXPERIMENTAL

Chalcones **1a–g** were synthesized by a base-catalyzed Claisen-Schmidt condensation reaction of appropriately substituted acetophenones and 4-hydroxy benzaldehyde suggested by Youssef *et al.,* 2010 and 1-phenyl-3-aryl-5-(4-hydroxyphenyl)-1*H*-pyrazoles **2a–g** were prepared from the chalcones **1a–g** following the procedure described in the literature (Suwito *et al.,* 2014) as shown in **scheme 1.** The purity of all the synthesized compounds was checked by thin layer chromatography on silica gel G as a stationary phase and different solvent systems as a mobile phase using iodine vapors as detecting agent. Melting points were determined by the Tempo melting point determination apparatus in open capillary tubes and are uncorrected. Infrared spectra were recorded on Shimadzu 8000 FTIR Spectrophotometer in KBr phase. Proton NMR spectra were done on Bruker Avance II 400 NMR Spectrometer using tetra-methyl silane as internal standard. Mass spectra of the compounds were carried out on Waters Micromass Q-Tof Micro Mass Spectrometer using electrospray ionization (ESI) technique. Elemental analyses were carried out on Perkin Elmer 2400 CHN Elemental Analyser.

General Procedure for the Synthesis of 1-phenyl-3-aryl-5-(4-(4-butanoloxy phenyl)-1H-pyrazoles (3a–g). 1-phenyl-3-aryl-5-(4-hydroxy phenyl)-1*H*-pyrazoles (2a–g 0.01 M) and 4-chlorobutanol (0.01 M) were refluxed in acetone (50 mL) in the presence of tri-ethylamine (0.01 M) for



Compound	R
a	H
b	CH_3
c	OCH_3
d	Cl
e	Br
f	F
g	NO_2

Scheme 1: Synthesis of 1-Phenyl-3-aryl-5-(4-(4-butanoloxy)phenyl-1*H*-pyrazoles.

about four hours. Excess of solvent was removed under reduced pressure. The residue thus obtained was washed thoroughly with cold distilled water, dried, and then re-crystallized from ethanol. The physical and analytical data of the synthesized title compounds are given as follows.

1, 3-Diphenyl-5-(4-(4-butanoloxy) phenyl)-1H-pyrazole (3a): Yield: 76%; m.p.: 81-83 °C; IR (KBr, cm^{-1}): 3340 (O–H), 3070 (aromatic C–H *str*), 2916 (C–H), 1465, (CH_2), 1255 (C–O–C), 1071 (C–O), 830, 732 & 690 (aromatic C–H *def*); ^{1}HNMR ($CDCl_3$): δ (ppm) 8.05-7.09 (m, 14H, Ar**H**), 7.02 (s, 1H, =C**H**–), 4.08-4.06 (t, 2H, HO–CH_2–CH_2–CH_2–C**H**$_2$–O–Ar), 3.69 (s, 1H, O–**H**), 3.53-3.51 (t, 2H, HO–C**H**$_2$–CH_2–CH_2–CH_2–O–Ar), 1.89-1.87 (quin, 2H, HO–CH_2–CH_2–C**H**$_2$–CH_2–O–Ar), 1.57-1.53 (quin, 2H, HO–CH_2–**CH**$_2$–CH_2–CH_2–O–Ar); MS, m/z (%): 385 $[M+H]^+$ (100%). Anal.: Calcd. for $C_{25}H_{24}N_2O_2$: C, 78.10; H, 6.29; N, 7.29. Found: C, 78.16; H, 2.22; N, 7.21.

1-Phenyl-3-(4-methyl phenyl)-5-(4-(4-butanoloxy) phenyl)-1H-pyrazole (3b): Yield: 69%; m.p.: 87-89 °C; IR (KBr, cm^{-1}): 3339 (O–H), 3065 (aromatic C–H *str*), 2919 (C–H), 1465, (CH_2), 1255 (C–O–C), 1070 (C–O), 832, 730 & 690 (aromatic C–H *def*); ^{1}HNMR ($CDCl_3$): δ (ppm) 7.67-7.08 (m, 13H, Ar**H**), 7.01 (s, 1H, =C**H**–), 4.08-4.06 (t, 2H, HO–CH_2–CH_2–CH_2–C**H**$_2$–O–Ar), 3.69 (s, 1H, O–**H**), 3.53-3.51 (t, 2H, HO–C**H**$_2$–CH_2–CH_2–CH_2–O–Ar), 2.34 (s, 3H, C**H**$_3$–Ar), 1.89-1.87 (quin, 2H, HO–CH_2–CH_2–C**H**$_2$–CH_2–O–Ar), 1.57-1.53 (quin, 2H, HO–CH_2–**CH**$_2$–CH_2–CH_2–O–Ar); MS, m/z (%): 399 $[M+H]^+$ (100%). Anal.: Calcd. for $C_{26}H_{26}N_2O_2$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.30; H, 6.51; N, 7.09.

1-Phenyl-3-(4-methoxy phenyl)-5-(4-(4-butanoloxy) phenyl)-1H-pyrazole (3c): Yield: 71%; m.p.: 93-95 °C; IR (KBr, cm^{-1}): 3343 (O–H), 3065 (aromatic C–H str), 2916 (C–H), 1465, (CH_2), 1255 (C–O–C), 1068 (C–O), 832, 735 & 693 (aromatic C–H def); ^{1}HNMR ($CDCl_3$): δ (ppm) 7.64-7.07 (m, 13H, Ar**H**), 7.02 (s, 1H, =C**H**–), 4.08-4.06 (t, 2H, HO–CH_2–CH_2–CH_2–C**H**$_2$–O–Ar), 3.83 (s, 3H, C**H**$_3$O–Ar), 3.70 (s, 1H, O–**H**), 3.53-3.51 (t, 2H, HO–C**H**$_2$–CH_2–CH_2–CH_2–O–Ar), 1.89-1.87 (quin, 2H, HO–CH_2–CH_2–C**H**$_2$–CH_2–O–Ar), 1.57-1.53 (quin, 2H, HO–CH_2–**CH**$_2$–CH_2–CH_2–O–Ar); MS, m/z (%): 415 $[M+H]^+$ (100%). Anal.: Calcd. for $C_{26}H_{26}N_2O_3$: C, 75.34; H, 6.32; N, 6.76. Found: C, 75.39; H, 6.38; N, 6.71.

1-Phenyl-3-(4-chloro phenyl)-5-(4-(4-butanoloxy) phenyl)-1H-pyrazole (3d): Yield: 77%; m.p.: 83-85 °C; IR (KBr, cm^{-1}): 3336 (O–H), 3061 (aromatic C–H *str*), 2916 (C–H), 1465, (CH_2), 1255 (C–O–C), 1066 (C–O), 832, 730 & 690 (aromatic C–H *def*); ^{1}HNMR ($CDCl_3$): δ (ppm) 8.01-7.07 (m, 13H, Ar**H**), 7.01 (s, 1H, =C**H**–), 4.08-4.06 (t, 2H, HO–CH_2–CH_2–CH_2–C**H**$_2$–O–Ar), 3.70 (s, 1H, O–**H**), 3.53-3.51 (t, 2H, HO–C**H**$_2$–CH_2–CH_2–CH_2–O–Ar), 1.89-1.87 (quin, 2H, HO–CH_2–CH_2–C**H**$_2$–CH_2–O–Ar), 1.57-1.53 (quin, 2H, HO–CH_2–**CH**$_2$–CH_2–CH_2–O–Ar); MS, m/z (%): 419 $[M+H]^+$ (100%), 421 $[M+2+H]^+$ (35%).Anal.: Calcd. for $C_{25}H_{23}ClN_2O_2$: C, 71.68; H, 5.53; 8.46; N, 6.69. Found: C, 71.61; H, 5.58; N, 6.62.

1-Phenyl-3-(4-bromo phenyl)-5-(4-(4-butanoloxy) phenyl)-1H-pyrazole(3e): Yield: 76%; m.p.: 95-97 °C; IR (KBr, cm^{-1}): 3337 (O–H), 3066 (aromatic C–H *str*), 2919 (C–H), 1465, (CH_2), 1256 (C–O–C), 1072 (C–O), 832, 732 & 695 (aromatic C–H *def*); ^{1}HNMR ($CDCl_3$): δ (ppm) 7.79-7.08 (m, 13H, Ar**H**), 7.01 (s, 1H, =C**H**–), 4.08-4.06 (t, 2H, HO–CH_2–CH_2–CH_2–C**H**$_2$–O–Ar), 3.68 (s, 1H, O–**H**), 3.53-3.51 (t, 2H, HO–C**H**$_2$–CH_2–CH_2–CH_2–O–Ar), 1.89-1.87 (quin, 2H, HO–CH_2–CH_2–C**H**$_2$–CH_2–O–Ar), 1.57-1.53 (quin, 2H, HO–CH_2–**CH**$_2$–CH_2–CH_2–O–Ar); MS, m/z (%): 463 $[M+H]^+$ (100%), 465 $[M+2+H]^+$ (98%). Anal.: Calcd. for $C_{25}H_{23}BrN_2O_2$: C, 64.80; H, 5.00; N, 6.05. Found: C, 64.87; H, 5.06; N, 6.10.

1-Phenyl-3-(4-fluoro phenyl)-5-(4-(4-butanoloxy) phenyl)-1H-pyrazole (3f): Yield: 74%; m.p.: 91-92 °C; IR (KBr, cm^{-1}): 3340 (O–H), 3073 (aromatic C–H *str*), 2917 (C–H), 1465, (CH_2), 1255 (C–O–C), 1070 (C–O), 830, 730 & 692 (aromatic C–H *def*); ^{1}HNMR ($CDCl_3$): δ (ppm) 8.15-7.08 (m, 13H, Ar**H**), 7.02 (s, 1H, =C**H**–), 4.08-4.06 (t, 2H, HO–CH_2–CH_2–CH_2–C**H**$_2$–O–Ar), 3.69 (s, 1H, O–**H**), 3.53-3.51 (t, 2H, HO–C**H**$_2$–CH_2–CH_2–CH_2–O–Ar), 1.89-1.87 (quin, 2H, HO–CH_2–CH_2–C**H**$_2$–CH_2–O–Ar), 1.57-1.53 (quin, 2H, HO–CH_2–**CH**$_2$–CH_2–CH_2–O–Ar); MS, m/z (%): 403 $[M+H]^+$ (100%). Anal.: Calcd. for $C_{25}H_{23}FN_2O_2$: C, 74.61; H, 5.76; N, 6.96. Found: C, 74.67; H, 5.71; N, 6.90.

1-Phenyl-3-(4-nitrophenyl)-5-(4-(4-butanoloxy) phenyl)-1H-pyrazole (3g): Yield: 72%; m.p.: 87-88 °C; IR (KBr, cm^{-1}): 3342 (O–H), 3065 (aromatic C–H *str*), 2918 (C–H), 1465, (CH_2), 1255 (C–O–C), 1070 (C–O), 832, 735 & 690 (aromatic C–H *def*); ^{1}HNMR ($CDCl_3$): δ (ppm) 8.35-7.08 (m, 13H, Ar**H**), 7.01 (s, 1H, =C**H**–), 4.08-4.06 (t, 2H, HO–CH_2–CH_2–CH_2–C**H**$_2$–O–Ar), 3.70 (s, 1H, O–**H**), 3.53-3.51 (t, 2H, HO–C**H**$_2$–CH_2–CH_2–CH_2–O–Ar), 1.89-1.87 (quin, 2H, HO–CH_2–CH_2–C**H**$_2$–CH_2–O–Ar), 1.57-1.53 (quin, 2H, HO–CH_2–**CH**$_2$–CH_2–CH_2–O–Ar); MS, m/z (%): 430 $[M+H]^+$ (100%). Anal.: Calcd. for $C_{25}H_{23}N_3O_4$: C, 69.92; H, 5.40; N, 9.78. Found: C, 69.98; H, 5.47; N, 9.72.

Analgesic Activity. The experimental protocol was approved by the institutional animal ethical committee and care of the animals was done as per the guidelines of Committee (Chitkara College of Pharmacy) for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environment and Forests, Government of India (Reg. No.1181/ab/08/CPCSEA). Wistar rats of either sex weighing 170-230g obtained from the Department of Livestock Production and Management, Guru Angad Dev Veterinary and Animal Sciences University, Ludhiana**,** India maintained on standard laboratory diet (Ashirwad Feeds Ltd., Chandigarh, India).

The analgesic activity of the synthesized title compounds was evaluated by using tail-flick method in albino wistar mice (170-230g) of either sex.

Phenylbutazone was used as a standard drug. A dose of 100 mg/kg body weight was given orally as suspension of tween 80 (1% w/v, in distilled water). The response time was observed after 15 min, 30 min, 45 min and 60 min. post administration of drug. Percentage of Analgesic Activity (PAA) was calculated by the following formula.

$$PAA = (T_2 - T_1 / T_1) \times 100$$

Where T_1 and T_2 are the reaction time in seconds before and after treatment of drug(s) respectively. Data were statistically analysed and all the title compounds showed significant analgesic activity ($P < 0.001$).

3. RESULTS AND DISCUSSION

Chemistry. The syntheses of 1-phenyl-3-aryl-5-(4-(4-butanoloxy) phenyl) 1*H*-pyrazoles were achieved following the steps outlined in the scheme 1. Chalcones *i.e.*, 1-aryl-3-(4-hydroxyphenyl) prop-2-en-1-ones, **1** were prepared by the reaction of 4-hydroxy benzaldehyde with substituted acetophenones following the Claisen-Schmidt reaction. The chalcones **1** then on refluxing with phenyl hydrazine in the presence of acetic acid and few drops of hydrochloric acid furnished 1-phenyl-3-aryl-5-(4-hydroxyphenyl)-1*H*-pyrazoles **2**. 4-Chlorobutanol reacted with **2** in the presence of triethyl amine to give the **3**. All the compounds were obtained in good yield. These compounds were characterized on the basis of elemental and spectral analyses. IR spectra of each compound showed a band for O–H stretching vibrations for intermolecular hydrogen bonding near 3340 cm^{-1} while the C–O stretching vibrations for primary alcohols were observed in the range of 1075-1066 cm^{-1}. C–O–C stretching vibrations for aryl alkyl ether were appeared at 1255 cm^{-1}. The C–H stretching vibrations for methylene groups were appeared in the range of 2916-2919 cm^{-1} whereas bending vibrations for methylene scissoring were observed constantly at 1465 cm^{-1}. Aromatic C–H stretching vibrations were observed in the range of 3073-3061 cm^{-1} whereas aromatic C–H bending vibrations were appeared below 900 cm^{-1}. In case of ^1H NMR, the chemical shift value for the O–**H** group was observed in the range of 3.70-3.68 δ (ppm) and appeared as singlet (s). Aromatic protons appeared as multiplet (m) in the range of 8.35-7.07 δ (ppm). The methine proton of the pyrazole nucleus absorbed at 7.02-7.01 δ (ppm) and appeared as singlet (s). The methylene protons adjacent to the O–H group [HO–C**H**$_2$–CH_2–CH_2–CH_2–O–Ar] were appeared as triplet (t) in the range of 3.53-3.51 δ (ppm) whereas the methylene protons adjacent to the O–Ar group [HO–CH_2–CH_2–CH_2–C**H**$_2$–O–Ar] were observed at 4.08-4.06 δ (ppm) and appeared as triplet (t). The central methylene protons which are

Table 1. *In Vitro* Analgesic Activity of 1-phenyl-3-(4-(4-butanoloxy) phenyl)-5-aryl-1*H*-pyrazoles (3a-g).

Compound Code No.	Normal reaction time (seconds) (Mean ± SEM)	Change in reaction time (seconds) (Mean ± SEM)		% Analgesic Activity (Mean ± SD)	
		After 02 h	After 04 h	After 02 h	After o4 h
3a	3.5 ± 0.14	2.4± 0.09	3.2± 0.3	142.72± 0.08	116..78± 0.07
3b	3.8± 0.42	2.56± 0.09	1.79± 0.09	138.90± 0.09	135.84±0.087
3c	3.6 ± 0.15	2.25± 0.09	1.79± 0.75	146.30±0.067	146.17± 0.06
3d	3 ± 0.07	2.1 ± 0.034	1.27± 0.87	155.69±0.42	106.8±0.056
3e	3.36 ± 0.05	4.10± 0.08	1.70± 0.056	134±0.045	130.7± 0.07
3f	3 ± 0.07	3.39±0.076	1.70± 0.45	119.09±0.054	155.8±0.056
3g	2.88 ± 0.08	3.40±0.043	1.58± 0.10	118.85± 0.12	160.12± 0.08
Control	4.74± 0.09	4.91± 0.03	4.91± 0.04	16± 0.06	15± 0.078
Phenyl-butazone	3.2± 0.04	3.8± 0.06	4.8± 0.05	119.83± 0.08	110± 0.098

nearer to the O–H group appeared as quintet (quin) at 1.57-1.53 δ (ppm) and those are nearer to O–Ar group appeared at 1.89-1.87 δ (ppm) respectively. Aromatic methyl and methoxy protons were observed at 2.34 δ (ppm) and 3.83 δ (ppm) respectively as singlet (s). All the title compounds showed $[M+H]^+$ of 100% intensity as the molecular ion peak. Compound containing chlorine showed isotopic peak at $[M+2+H]^+$ of about 35% intensity to that of parent ion peak whereas bromo derivative showed isotopic peak at $[M+2+H]^+$ of about equal intensity. The results of elemental analyses were found in good agreement with the calculated values.

Analgesic activity. All the novel synthesised series, 1-Phenyl-3-aryl-5-(4-(butanoloxy)phenyl) 1H-pyrazoles (3a-3g), were evaluated pharmacologically for their analgesic activity and some of them exhibited significant results as compared to standard drug.

It was also observed that the activity was also affected by the substituents present on the phenyl ring attached to position -3 and position-5 of the pyrazole nucleus. The order of activity was found to be in the following manner:

$$-Br > -Cl > -CH_3 > -H > -CH_3O > -NO_2$$

The title compounds (3d) containing chlorophenyl group attached to position-5 of the pyrazole nucleus were found to be most active and the compounds having nitro (3g) phenyl group were found to be least active.

4. CONCLUSION

Present study describes the synthesis of a series of 1-phenyl-3-aryl-5-(4-(4-butanoloxy) phenyl)-1*H*-pyrazoles starting from the chalcones. The compounds were characterized by modern analytical techniques such as CHN analyses, IR, Mass and proton NMR spectra. The analgesic activity of the synthesized title compounds was evaluated by using tail-flick method in albino wistar mice (170-230g) of either sex.

Data were statistically analysed and all the title compounds showed significant analgesic activity ($P < 0.001$).

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