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SYNTHESIS, CHARACTERIZATION AND ANTI-INFLAMMATORY ACTIVITY OF FUROQUINOLINE CONTAINING CHALCONE DERIVATIVES

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ABSTRACT

In the present work, eight novel 1-(8-methyl-furo[2,3-*b*]quinolin-2yl)ethanone derivatives [IVa-h] were synthesized by clasein schmidt condensation, it is condensation between1-(8-methyl-furo[2,3-*b*]quinolin-2yl)ethanone (ketone) and substituted aryl aldehyde to yield 1-(8-methyl-furo[2,3-*b*]quinolin-2yl)ethanone derivatives [IVa-h] called as chalcones. The structures of the synthesized compounds were characterized on the basis of IR, ^{1}HNMR and Mass spectral data. Among all synthesized compounds only few selected compounds are screened for their anti-inflammatory activity by paw edema method, Diclofenac sodium is employed as a reference standard. From the results it is concluded that, compound IV-b and IV-f exhibited potent, rest of compounds exhibited mild to moderate activity anti-inflammatory activity.

KEYWORDS

Chalcones, 2-Chloro-3-formyl-quinoline, Claisen Schmidt condenstion Furoquinoline derivatives and anti-inflammatory.

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INTRODUCTION

The chemistry of quinoline derivatives has been of increasing interest since many of these compounds have been found usefull as chemotherapeutic agents against malaria[1] parasite and microbes[2]. It also reported that nitrogen and oxygen containing heterocycles are one of the most extensively synthesized and screened compounds as they show diverse pharmacological activities.

Chalcones constitute an important class of natural products belonging to the flavonoid family[3], which have been reported to possess a wide spectrum of biological activities, including anti-bacterial[4], anti-

fungal[5], anti-inflammatory[6], anti tumor[7], and anti-mutagenic[8]. Additionally, some of chalcone derivatives have been found to inhibit several important enzymes in cellular systems, such as xanthine oxidase[9] protein tyrosine kinase[10]. Chalcones are also key precursors in the synthesis of many biologically important heterocycles such as benzothiazepin[11], pyrazolines[12] 1,4-diketones[13] and flavones[14] Hence, the synthesis of chalcones has generated vast interest among organic as well as medicinal chemists.

Hence this inspired us to synthesize 1-(8-methyl-furo[2,3-b]quinolin-2yl)ethanone derivatives and screen for their anti-inflammatory.

MATERIALS AND METHODS

All chemicals used were of analytical grade from, SD Fine. Melting points of all the synthesized compounds were determined by open capillary tube method. These are uncorrected. The purity of all compounds was checked by TLC was run on Silica Gel G plates using Chloroform and Methonol (9:1). Spots were visualized using iodine vapour chamber. IR spectra were recorded on Shimadzu IR spectrophotometer by using KBr pellets technique. ^{1}H-NMR was recorded on Bruker AMX 60 MHz spectrophotometer by using DMSO as solvent.

Synthesis of 2-Chloro-8-methyl quinoline-3-carbaldehyde[15-16] (I)

Dimethyl formamide (0.125 mol, 9.13 gm, 9. 65 ml) was cooled to 0 °C (using freezing moisture) in a flask equipped with a drying tube and phosphorus oxychloride (0.35 mol, 53.55 gm, 32.2 ml) was added drop wise with stirring. To this solution 2-Methyl acetanilide (0.05 mol, 7.45 gm) was added and the contents of the flask were stirred for 15 minutes and the resulting solution was refluxed for 16 hours at 85-90 ^{0}C. The reaction mixture was poured into crushed ice, stirred for 5 minutes and the resulting solid was filtered, washed well with water and dried. Thus compound obtained was purified by recrystallisation from ethyl acetate to yield yellow shiny needle shaped crystals of 2-Chloro-8-methyl quinoline-3-carbaldehyde. Yield 77 %, m.p. 137 ^{0}C.

Synthesis of 2-Hydroxy-8-methylquinoline-3-carbaldehyde (II)

In to a clean round bottomed flask containing a mixture of 2-chloro-8-methylquinoline-3-carbaldehyde (0.01 mol,1.9 gm) and aqueous hydrochloric acid (35 ml, 4 mol) was heated under reflux for 2 hrs and then allowed to cool to room temperature. The reaction mixture was poured on to crushed ice, when 2-Hydroxy-8-methyl quinoline separated as a yellow solid. It was filtered washed with water and dried. It was recrystalised from aqueous acetic acid into yellow silky needles.

Synthesis of 1-(8-methylfuro[2, 3-*b*]quinolin-2yl)ethanone (III):

In to a clean dried round bottomed flask, a mixture of 2-hydroxy-8-methylquinoline-3 carbaldehye (0.1mol, 18.7gm), chloroacetone (0.1 mol, 7.97 ml) in dimethyl formamide (80-90 ml) and anhydrous potassium carbonate (0.1 mol, 1.38 gm) was added and the reaction mixture was stirred for 2 hours at room temperature. The reaction mixture was kept for reflux on water bath for 36 hours at 80-90 ^{0}C, allowed to cool at room temperature and then filtered. The resulting filterate was poured into ice cold water, precipitate thus separated out was filtered, dried and recrystalized from aqueous dimethyl formamide as brown solid powder. Yield 60 %, m.p. 110 ^{0}C.

Synthesis of 1-(8-methylfuro[2,3-*b*]quinolin-2yl)ethanone derivatives[17] (Chalcones) [IVa-h**]**

General procedure

In a clean round bottomed flask, equimolar mixture of 1-(8-methylfuro[2,3-*b*]quinolin-2yl) ethanone (0.01 mol) and different aryl aldehydes (0.01 mol) in ethanol medium (40 ml) in presence aqueous solution of potassium hydroxide (40 %, 15 ml) is stirred continuously for 12-16 hours at room temperature. The reaction mixture was kept overnight at room temperature and then it was poured into 300 ml ice cold water, acidified with dilute Hcl, The solid thus separated was filtered, air dried and recrystalized from aqueous ethanol (Figure No.1). Physical data of synthesized compounds is given in Table No.1.

ANTI-INFLAMMATORY ACTIVITY

Anti-inflammatory activity of selected compounds was evaluated by carrageenan induced rat hind paw edema method[18]. Diclofenac sodium used as a reference standard (100mg/kg) orally 1 hr. Paw. The results obtained were subjected to statistical analysis using ANOVA followed by Turkey-Krammer Multiple Comparison Test. Percentage inhibition of paw volume was calculated by following formula. Results are given in Table No.2.

$$\% \text{ inhibition of edema} = 1 - \left[\frac{Vt}{Vc} \times 100 \right]$$

Where, Vt = mean paw volume of test group.
Vc = mean paw volume of control group.

RESULTS AND DISCUSSION

Anti-inflammatory activity

Anti-inflammatory activity of the selected new compounds was screened by caragennan induced acute rat hind paw edema method. Diclofenac sodium used as standard drug, which showed 71.13 % inhibition.

The results of the anti-inflammatory study reveal that all the four selected compounds have shown significant anti-inflammatory effect which was evident by significant reduction in the paw volume when compared to control group.

Spectral data

IVc: IR (KBr) cm^{-1}: 1681 (C=O), 2947 **(**-CH), 1650 (C=N), 1583(C=C), 1128 (-C-O-C), 3150 (Ar-CH). ^{1}H NMR (DMSO) δ ppm: 1.3 (s, 3H, CH_3), 7.-7.5 (m, 5H, Ar-H), 7.69-7.71(2d, 4H, Ar-H), 7.89 (s, 2H,-CH=CH). ESIMS (m/z): 347 (M^+).

IVd: IR (KBr) cm^{-1}: 1689 C=O), 2928 **(**-CH), 1651 (C=N), 1575 (C=C), 1022 (-C-O-C), 3186 (Ar-CH). ^{1}H NMR (DMSO) δ ppm: 1.45 (s, 3H, CH_3), 2.37 (s, 3H, CH3), 7-7.6 (m, 9H, Ar-H), 7.84 (s, 2H, -CH=CH). ESIMS (m/z): 327(M^+).

IVe: IR (KBr) cm^{-1}: 1658 (C=O), 3036 **(**-CH), 1649 (C=N), 1572 (C=C), 1026 (-C-O-C), 3186 (Ar-CH). ^{1}HNMR (DMSO) δ ppm: 1.2 (s, 3H, CH_3), 5.06(s 1H, Ar-OH) 7.0-7.95 (m, 8H, Ar-H), 8.08 (s, 2H, -CH=CH). ESIMS (m/z): 329 (M^+).

IVf: IR (KBr) cm^{-1}: 1668 (C=O), 2970 **(**-CH), 1650 (C=N), 1575 (C=C), 1166 (-C-O-C), 3100 (Ar-CH). ^{1}HNMR (DMSO) δ ppm: 1.6 (s, 3H, CH_3), 7-7.8 (m, 9H, Ar-H), 7.92 (s, 2H, -CH=CH). ESIMS (m/z): 331(M^+).

IVg: IR (KBr) cm^{-1}: 1662 (C=O), 2929 **(**-CH), 1612 (C=N), 1568 (C=C), 1118 (-C-O-C), 3115 (Ar-CH) ^{1}HNMR (DMSO) δ ppm: 2.1 (s, 3H, CH_3), 3.6(s, 6H, N-(CH_3)2) 7.2-7.9 (m, 9H, Ar-H), 8.1 (s, 2H, -CH=CH). ESIMS (m/z): 356 (M^+) (Figure No.2-4).

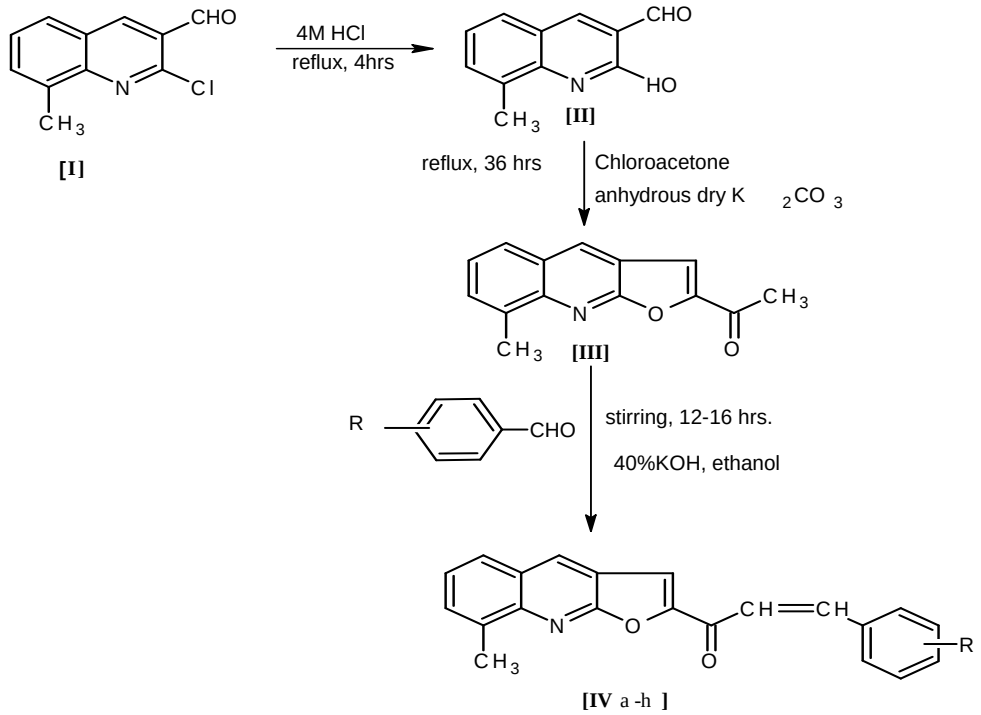
Table No.1: Characterization data of synthesized compounds IVa-h

S.No	Comp. Code	Melting point °C	% Yield	Mol. Formula	M. Wt.
1	**IV**a	268-270	64	$C_{21}H_{15}NO_2$	313
2	**IV**b	160-162	72	$C_{21}H_{14}ClNO_2$	347
3	**IV**c	120-122	68	$C_{21}H_{14}ClNO_2$	347
4	**IV**d	168-170	67	$C_{22}H_{17}NO_2$	327
5	**IV**e	238-240	69	$C_{21}H_{15}NO_3$	329
6	**IV**f	200-202	60	$C_{21}H_{14}FNO_2$	331
7	**IV**g	232-234	55	$C_{23}H_{20}N_2O_2$	356
8	**IV**f	204-206	61	$C_{22}H_{17}NO_3$	343

Table No.2: Results of Anti-inflammatory Activity

S.No	Compound code	Mean difference in Paw volume (ml) ± SE after 3 hr.	Percentage of inhibition
1	Control	0.97 ± 0.05	--
2	Std.	0.28 ± 0.01***	71.13
3	IV-b	0.30 ± 0.02***	69.07
4	IV-d	0.40 ± 0.03*	58.76
5	IV-f	0.32 ± 0.02***	64.92.
6	IV-h	0.50 ± 0.04***	48.45

Values are Mean ± S.E.M., n=5, Where *P<0.05 and ***P<0.001 vs Control.



Compounds	R	R	R	R	R	R	R	R
IV (a-h)	H	4-Cl	3-Cl	4-CH3	2-OH	4-F	4-N(CH_3)$_2$	4-OCH_3

Figure No.1: Synthesis of furoquinoline containing chalcone derivatives

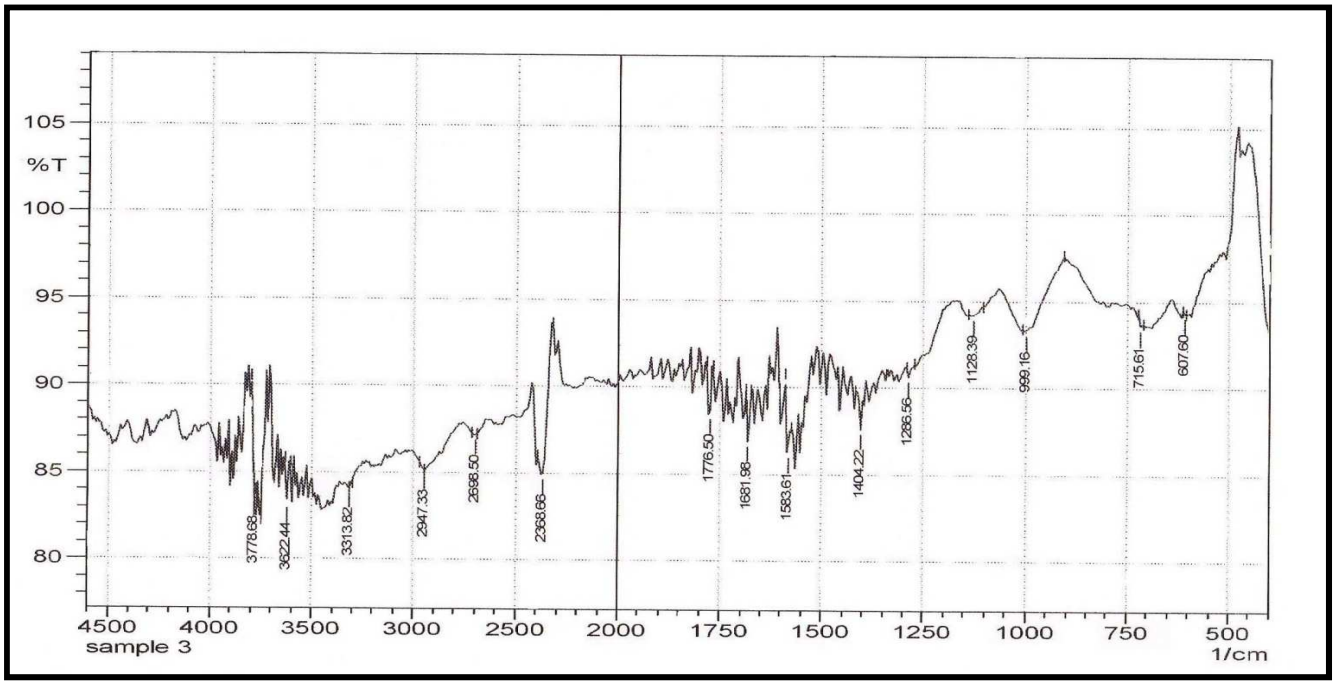


Figure No.2: IR spectrum of compound IV-c

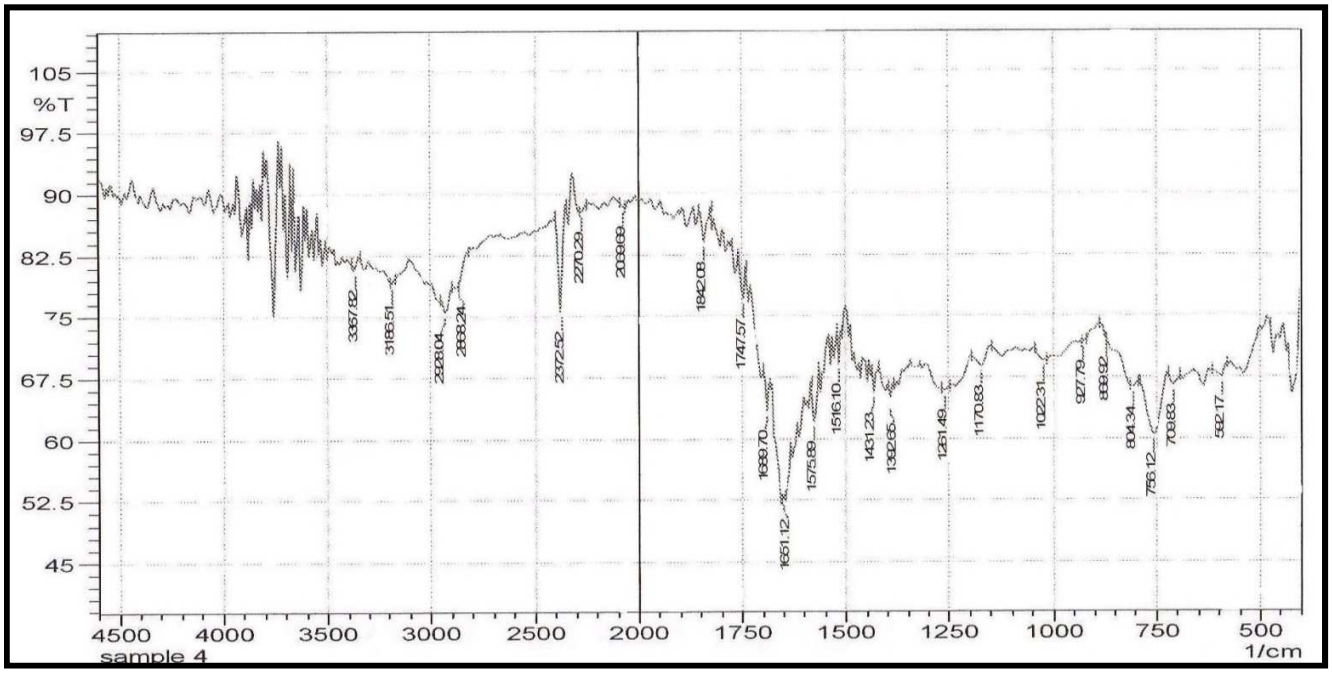


Figure No.3: IR spectrum of compound IV-d

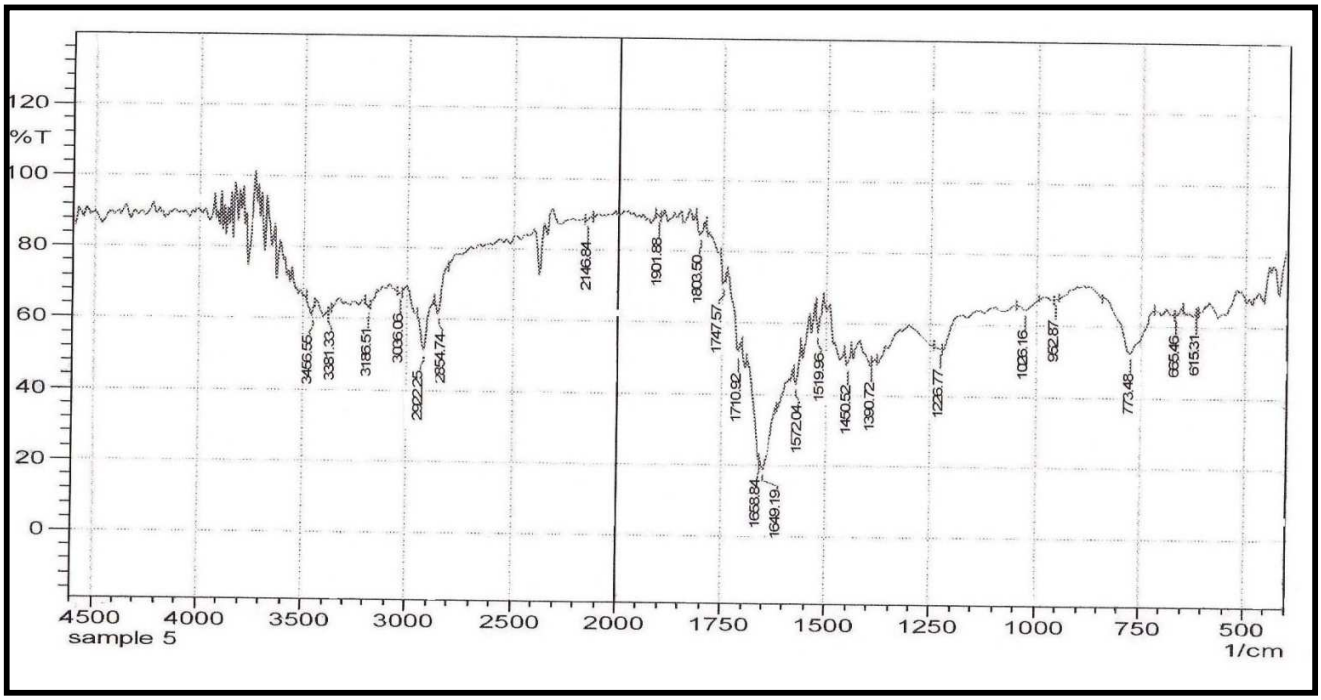


Figure No.4: IR spectrum of compound IV-e

CONCLUSION

Eight novel furoquinoline derivative have been synthesized, characterized by IR, ^{1}HNMR and Mass spectral data and few novel selected compounds **IV**-b**,** d**,** f and h are screened for their anti-inflammatory using paw-odema method, diclofenac employed as a reference standard. From the results obtained it is concluded that compound **IV**-b**, IV**-f shown potent and compound **IV**-d, **IV**-h shown mild to moderate anti-inflammatory activity when compared to control and almost equipotent activity when compared to standard diclofenac sodium.

Compounds **IV**-b and **IV**-f, benzaldehye containing electron withdrawing groups like *p*-chloro and *p*-fluro which may favored potent anti-inflammatory activity when compared to compounds **IV**-d, **IV**-h, electron releasing groups like *p*-methyl, *p*-methoxy. If work is futher continued with different substituted benzaldehyde you may get potent pharmacophore which may promote significant anti-inflammatory activity.

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