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Synthesis and Characterization of SomeBiologically Potent 2-(2-butyl-4-chloro-1H-imidazol-5-yl)-4H-chromen-4-onederivatives.

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ABSTRACT

In the present investigation, a series of novel chromone derivatives containing imidazole moiety has been synthesized. The condensation of 2-butyl-4-chloro-1H-imidazole-5-carbaldehyde with various substituted o-hydroxy acetophenones in the presence of 40% KOH in PEG- 400 gives the chalcones. Oxidative cyclisation of chalcones withcatalytic amount of iodine in the presence of DMSO gives chromones. Chalcones and Chromones were obtained in satisfactory yield.The structure of intermediate and titled compounds was confirmed by spectral tools.
Keywords: Chalcones, Chromones, O-Hydroxyacetophenones, Imidazole, PEG-400

I. INTRODUCTION

Owing to interesting chemistry and various bioactivities, heterocycles are of prime importance for synthetic and medicinal chemists. Extensive studies are being carried out for designing potential pharmaceuticals. Chalcones are α,β-unsaturated carbonyl compounds and are used as intermediates for the synthesis of various heterocyclic compounds. Chalcones are well known precursor for the synthesis of various biologically important heterocycles[1-4].Chalcones belong to flavanoid family displayed an impressive array of biological activities[5].Chalcones exhibits different biological activities such as anti-inflammatory, anti-invasive, antimalarial, antitumor, anti-diabetic, cytotoxic and chemoprotective[6-10]etc.Imidazole is a part of essential amino acid histidine, biotin, and alkaloids. Recently, certain imidazole based compounds were reported to possess antimicrobial activities[11,12]. It is alsoreported that, imidazole derivatives are gained synthetic interest in recent yearsdue to their broad spectrum of biological properties[13-16].

By the synthetic point of view chromones are important in thesynthesis of the variety of heterocyclic compounds. Naturally, chromones are mostly in theform of 2-phenyl chromones called as iso-flavones those arefound in fruits and vegetables[17,18].In the plant kingdom, Chromone-4-ones, a class of naturally occurring compound, are widely distributed.Chromones and other related ring systems have plenty ofinteresting biological activities. Literature survey displayed thatchromone compounds possess various physiological andbiological properties and thus found use in medicine[19].Chromone compounds have considerable interest in the pastdecades[20]. A series of sulfonamide chromones areinhibitors of carbonic anhydrase, show in vitro antibacterialand antifungal activity[21-22]. Duringthe last decades the 5-hydroxy-2-styrilchromone were derivedfrom the green algae [chrysophaeum] against leukemia cells.Chromones substituted at 2-position has been shown to possessvarious activities. Few of the chromones have potentialantirhythmic activity such as HIV-integrase inhibition[23].Few of them showed anti-cancer, anti-tumour, anti-ulceractivities[24-25]. Synthesis of flavones (Chromones) and theirderivatives has considerable attention due to their significantbiocidal and pharmaceutical effects.

A synthesis is termed ideal if it relies on use of a green solventsuch as water, supercritical CO_2 or low-boiling liquid polymerssuch as polyethylene glycols(PEG's). Recently PEG-400 emerged as analternative green solvent with unique properties such as thermalstability, commercial availability, nonvolatility, miscibility witha number of organic solvents, and recyclability[26]. PEGs overcome the toxiceffects of solvents on the

environment. Therefore, we prepare chalconesusing KOH in PEG-400 as green solvent.

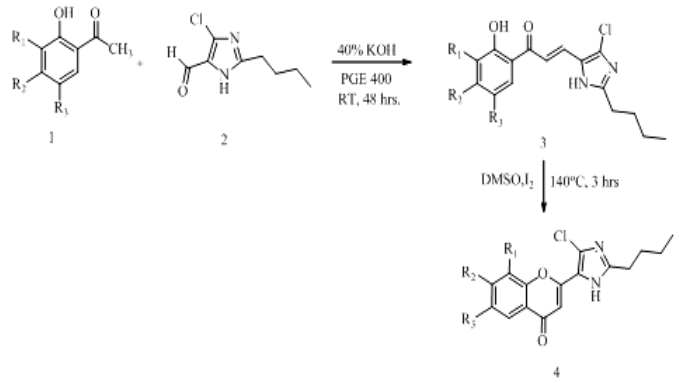
II. Methods & Material

All melting points were recorded in an open capillary tube in liquid paraffin bath and are uncorrected (Table-1). The purity and the progress of the reaction were routinely monitored by TLC. The product was purified by recrystallization technique.

IR spectra were recorded on Perkin-Elmer FTIR spectrum-2 with ATR-single Refl. ZnSe technology. ^{1}HNMR spectra were recorded on BRUKER-ADVANCE II 400 MH_z spectrometer in $CDCl_3$ and DMSO-d_6 as solvent and TMS as internal standard. Peak values are shown in δ ppm. Mass spectra were obtained by Finnegan mass spectrometer. TLC was performed on pre-coated silica-gel plates and was observed under UV light. All the synthesized compounds gave satisfactory elemental analysis.

In the present investigation a series of novel chromones derivatives containing imidazole moiety has been synthesized. The precursor,i.e. substituted *o*-hydroxy acetophenones, were prepared by fries rearrangement[27].The condensation of *o*-hydroxy acetophenones (**1**) with 2-butyl-4-chloro-1*H*-imidazole-5-carbaldehyde (**2**) in presence of 40% KOH in PEG-400 as a green reaction medium gives the chalcones (**3**). Oxidative cyclization of chalcones with catalytic amount of iodine in presence of DMSO gives chromones (**4**).

The structure of synthesized compound was confirmed by spectral analysis.Outline of synthesis of 2-(2-butyl-4-chloro-1*H*-imidazol-5-yl)-4*H*-chromen-4-one is summarized in Scheme 1.



Scheme 1

General Procedure for Synthesis of Chalcones (3a-3f):

Equimolar amount of substituted *o*-hydroxy acetophenones and 2-butyl-4-chloro-1*H*-imidazole-5-carbaldehyde were taken in 100 ml RB flask with minimum amount of PEG-400. To this mixture KOH solution (40%) was added drop wise and stirred for 1 hr. Progresses of reaction were monitored by TLC. After completion of the reaction, the mixtures were poured into crushed ice and acidify with conc. HCl. Solid thus obtained were separated by filtration and recrystallized from proper solvent to get chalcones (**3**).

3a: IRcm^{-1}:3557.3 (O-H stretching), 3133.9 (N-H stretching), 2960, 2930 (CH_3 stretching), 1635.38 (conjugated C=O group), 1554 (aromatic ring), 648, 782 (C-Cl bond stretching). ^{1}H NMR:0.85 δ (t, 3H, 7.28 Hz), 1.34 δ (m, 2H, 7 Hz), 1.8 δ (quintet, 2H, 7.4 Hz), 2.73 δ (t, 2H, 7.4 Hz), 2.23 δ (s, 3H)7.82 δ (d, 1H,16 Hz), 6.90 δ (d, 1H,16 Hz), 7.51 δ (d, 2H,8 Hz), 7.28 δ (t, 1H,8 Hz), 11.40 δ(s, 1H, O-H proton), 12.76 δ (s, 1H, N-H proton).MS: M+1 as m/z= 319.1.

Synthesis of 2-(2-butyl-4-chloro-1H-imidazol-5-yl)-4H-chromen-4-one (4a-4f):

Chalcone **(3)** was dissolved in 5ml DMSO. To this reaction mixture catalytic amount of I_2 was added. Contents were heated at 140 ^{o}C for 3 hours. Then the reaction mixture were poured over crushed ice containing 3-4 gm sodium thiosulphate to eliminate the unreacted I_2. The solid thus obtained was washed with cold water. The product obtained was recrystallized from alcohol to afford pure chromone **(4).**

4a: IRcm^{-1}:3139.8 (-N-H stretching), 3101-2872.4 (-CH_3 stretching), 1618.28(conjugated C=O group), 1544-1573.85 (aromatic C-H stretching), 629.32-817.04 (C-Cl stretching), 1034.07(C-O stretching). ^{1}H NMR: 0.91 δ (t, 3H, 7 Hz), 1.35 δ (m, 2H,7 Hz), 1.67 δ (quintet, 2H,7 Hz), 2.67 δ (t, 2H,7 Hz), 2.40 δ (s, 1H), 6.69 δ (s, 1H), 7.48 δ (d,1H,7.4 Hz), 7.56 δ (d, 1H, 7.4Hz), 7.79 δ (s, 1H), 12.96 δ (s, 1H), MS: M+1 as m/z= 317.1

III. Results and Discussion

The Claisen-Schmidt condensation is an important C-C bond formation for the synthesis of Chalcones. It is generally carried out by the using strong bases such as NaOH or KOH in polar solvents (MeOH or DMF). In present study, PEG-400 is used as a recyclable reaction solvent to obtain 1,3-diaryl-2-propen-1-ones with good to excellent yields[28].

First, we attempted condensation of various substituted*o*-hydroxy acetophenone with 2-butyl-4-chloro-5-formyl-imidazole using PEG-400 as a reaction solvent under alkaline condition. The reaction was completed within 1 h and the corresponding product was obtained upto 95% yield. The purity of the compounds waschecked by thin layer chromatography and structures of the synthesized products wereconfirmed by their spectral analysis.

Chalcone **3a** shows characteristic band at 1635 cm^{-1}indicats the presence of α, β- unsaturated >C=O group (Fig. 1).^{1}H NMR spectra of chalcone **3a** showed characteristic doublet signals at 7.82δdue to olefinic proton αH, J≈15.98Hz and 6.90 δ due to olefinic proton βH, J≈15.98Hz indicating the trans geometry.The phenolicproton (2'-OH) was observed as a singlet at 11.40 δdue to hydrogen bondingwith the adjacent carbonyl group(Figure 2). Mass spectra of compound **3a** satisfies molecular formula frommolecular ion peaks. Also it confirms the isotopic abundances of –Cl as 3:1 (Figure 3).

IR spectra of chromone showed characteristic bands at 1618.28 cm^{-1}due >C=O stretching vibrations. Lowering of normal >C=O frequency was observed due tothe presence of -C=C stretching in chromones(Fig. 4). ^{1}H NMR spectra of the compounds showedcharacteristic singlet signals at 6.69δ due to olefinicprotons. The –NH proton was observed as a singlet at 12.96δ, while other aromatic and aliphatic protons were foundat expected regions(Fig. 5). The mass spectra of compounds **4a** showed molecular ion peakscorresponding to their molecular formula. Besides the molecular ion peak [M+], thecompounds showed [M+1] (isotopic abundances), which confirmed the presence ofhalogen groups in respective compounds. The base peak was seen at m/z 317(Figure 6).

Table 1. The physical constants of prepared compounds (3a-f) and (4a-f)

Compound	Substituent			M. P.(°C)	Yield (%)
	R_1	R_2	R_3		
3a	H	H	CH_3	264	93
3b	H	CH_3	H	194	90
3c	H	CH_3	Cl	178	92
3d	H	H	Cl	218	95
3e	H	Cl	H	224	91
3f	Cl	H	Cl	186	94
4a	H	H	CH_3	282	74
4b	H	CH_3	H	228	70
4c	H	CH_3	Cl	192	72
4d	H	H	Cl	236	81
4e	H	Cl	H	232	75
4f	Cl	H	Cl	192	78

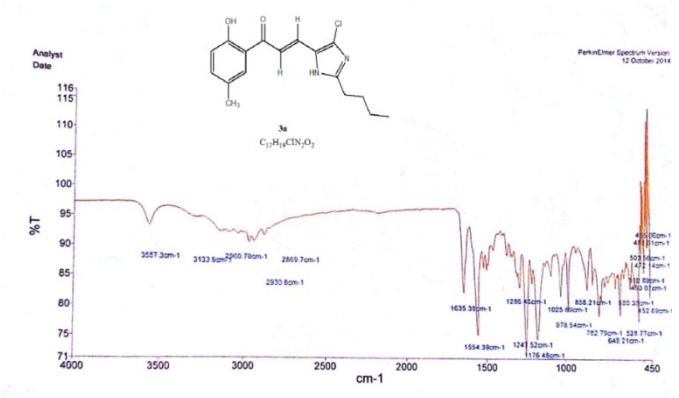


Figure 1. IR Spectra of compound **3a**

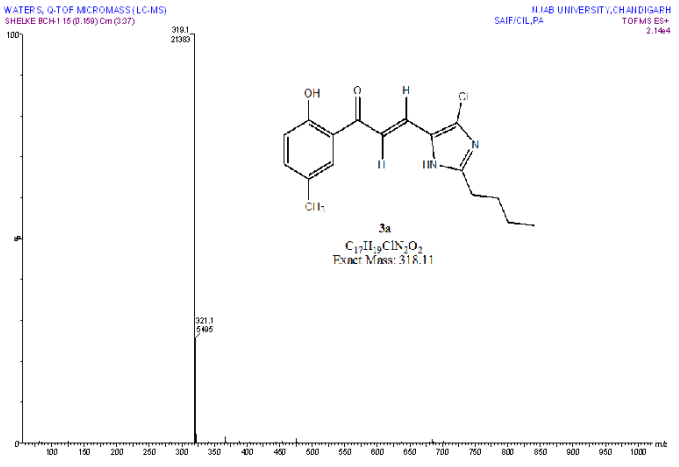


Figure 2. Mass Spectra of compound**3a**

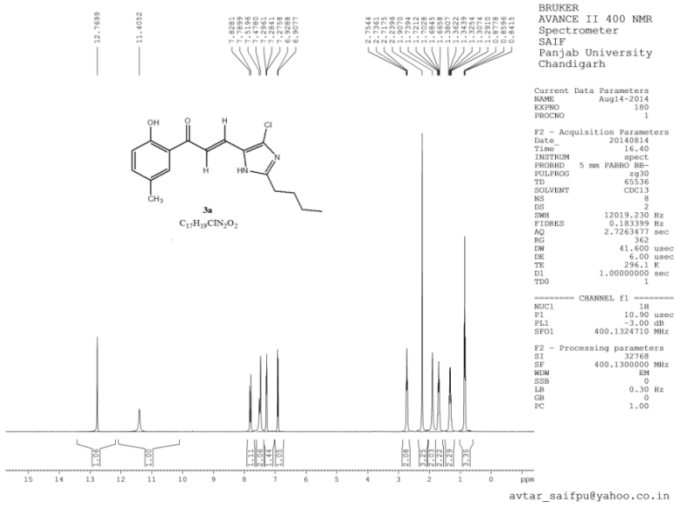


Figure 3. ^{1}H NMR of compound **3a**

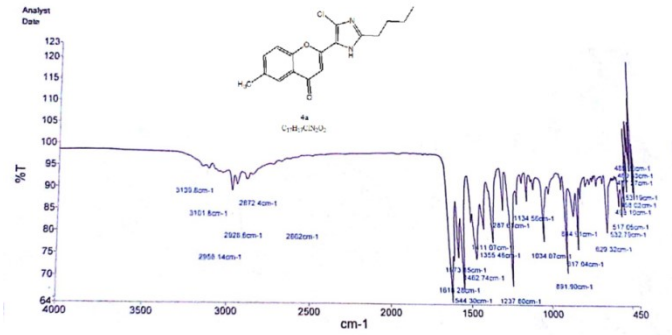


Figure 4. IR Spectra of compound **4a**

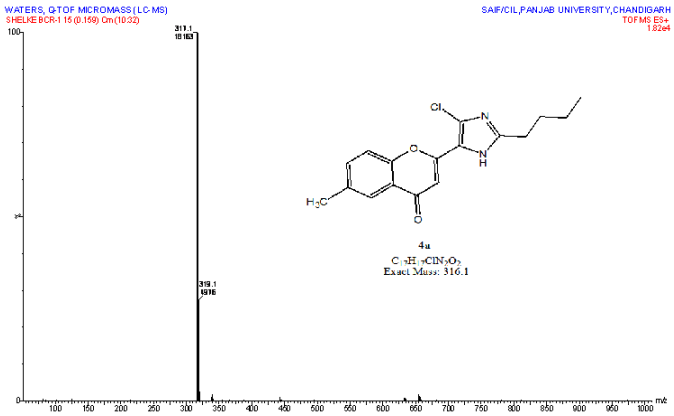


Figure 5. Mass Spectra of compound **4a**

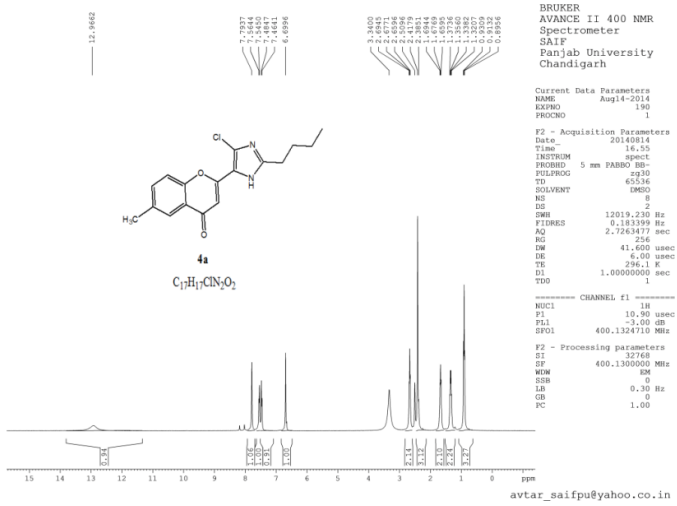


Figure 6. ^{1}H NMR of compound **4a**

IV. Conclusion

The present investigation reports the synthesis of 2-(2-butyl-4-chloro-1H-imidazol-5-yl)-4H-chromen-4-one derivatives by oxidative cyclisation of chalcones with catalytic amount of iodine in the presence of DMSO.The structures of synthesized chromone derivatives were established by the satisfactoryspectral analysis.

V. Acknowledgement

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