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Efficient ultrasound-assisted synthesis, spectroscopic, crystallographic and biological investigations of pyrazole-appended quinolinyl chalcones

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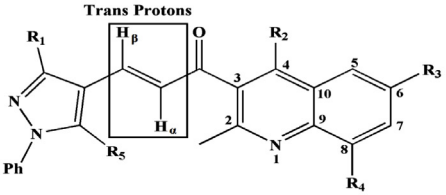
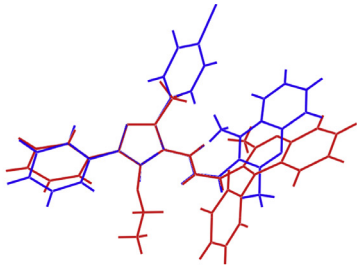
HIGHLIGHTS

- Synthesis of pyrazole appended quinoline chalcones.
- Spectral, crystallographic and biological properties of chalcones.
- E-configuration about the C=C bond established *via* ^{1}H NMR & X-ray crystallography.
- Antibacterial and antifungal studies showed promising activity of quinoline chalcones.

GRAPHICAL ABSTRACT

Two series of new quinolinyl chalcones containing a pyrazole group, have been synthesized by Claisen–Schmidt condensation under ultrasonic method. These compounds show promising anti-microbial and anti-oxidant activity.





R_1 = CH_3, C_6H_5, *4*-BrC_6H_4, *4*-$OCH_3C_6H_4$; R_2 = H, CH_3, C_6H_5, *2*-ClC_6H_4
R_3 = H, Cl, Br, NO_2; R_4 = H, Br; R_5 = H, OCH_2CH_3.

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ABSTRACT

Two series of new quinolinyl chalcones containing a pyrazole group, **3a–f** and **4a–r**, have been synthesized by Claisen–Schmidt condensation of the derivatives of 2-methyl-3-acetylquinoline with either substituted 1,3-diphenyl-1H-pyrazole-4-carbaldehyde or 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde in 76–93% yield under ultrasonic method. The compounds were characterized using IR, ^{1}H NMR and ESI-MS spectroscopic methods and, for representative compounds, by X-ray crystallography. An E-configuration about the C=C ethylene bond has been established via ^{1}H NMR spectroscopy and X-ray crystallography. These compounds show promising anti-microbial properties, with **4a** and **3e** being the most potent against bacterial and fungal strains, respectively and the methoxy substituted compounds showed moderate anti-oxidant activity.

Introduction

Chalcones and their derivatives are known for their wide range of applications in the field of pharmaceutics and also in the manufacture of pesticides, cosmetics, etc. [1,2]. For example, they have been found to act as anti-inflammatory, analgesic, anti-platelet, anti-ulcerative, anti-malarial, anti-cancer, anti-viral, anti-leishmanial, antioxidant, anti-tubercular, anti-hyperglycemic and anti-tumour agents [3,4]. In terms of putative biological mechanisms of action, reports indicate chalcone derivatives inhibit the release of chemical mediators [5], tyrosinase [6], leukotriene B4 [7] and aldose reductase [8]. In addition, chalcones separated by bichromophoric moieties, such as a vinyl chain and a carbonyl group, were found to be effective photosensitive materials and to exhibit

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potential nonlinear optical (NLO) properties [9,10]. Metal chelates of chalcones are found to be effective catalysts and potential anticancer agents [11,12].

Nitrogen heterocycles are of special interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activities, such as anti-bacterial, anti-fungal, anti-viral and anti-inflammatory, and also demonstrate distinctive optical properties [13]. Quinolines, which form a part of the structure of many alkaloids, are an important class of nitrogen heterocyclic compounds that display versatile biological activity [14]. They are found to form the basis of many drugs used in the treatment of cancer and inflammatory diseases [15]. Their high lipophilicity and conformational rigidity together with metabolic stability and oral bioavailability [16], lead to the study of these heterocycles for therapeutic purposes. Studies reveal that incorporation of a pyrazole moiety into various heterocyclic ring systems results in useful molecules from the biological point of view [17,18]. Thus, many pyrazole derivatives are reported to have a broad spectrum of biological activities, such as anti-inflammatory, anti-fungal, herbicidal, anti-viral and are A3 adenosine receptor antagonists [13,17,18]. Several drugs, including Celecoxib® [19] and Rimonabant® [20], utilize pyrazole in their molecular core [21].

Compared to conventional methods, ultrasound irradiation is considered as a clean and useful technique in organic synthesis as the procedure can be more convenient and is cost effective [22,23]. A large number of organic reactions can be carried out in higher yield, short reaction time and/or milder conditions under ultrasonic irradiation. In this way, ultrasound has proved extremely useful in the synthesis of a wide range of organic, inorganic and nanostructured materials [24,25]. The introduction of high-power ultrasound waves (i.e. sound energy with frequencies in the range 15 kHz to 1 MHz) into liquid reaction mixtures is known to cause a variety of chemical transformations.

Herein, the synthesis by conventional (CON) and ultrasonic (US) synthetic methods of two new series of pyrazole-appended quinolinyl chalcones, **3a–f** and **4a–r**, featuring pyrazole and quinoline linked via a chalcone unit (Fig. 1), are reported. Spectroscopic properties and biological activities of the synthesized compounds are described as well as the crystal structures of representative compounds (**3c** and **4h**; the latter as a hydrate). The synthetic pathway of target molecules is shown in Scheme 1.

Chemistry

The precursors of the title pyrazole-appended quinoline chalcones were derivatives of 2-methyl-3-acetylquinoline and of pyrazole-4-carboxaldehyde. Derivatives of pyrazole-4-carboxaldehyde, **1a–d**, were obtained in good yield by a modified Vilsmeier–Haack formylation of the corresponding acetophenone phenylhydrazone and 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole [26–29] and the derivatives of 2-methyl-3-acetylquinoline, **2a–f**, were synthesized by Friedlander cyclization of substituted 2-aminobenzophenone, 2-aminobenzaldehyde or 2-aminoacetophenone with acetylacetone in acidic medium [30–33]. The synthesis of pyrazolyl–quinoline chalcone derivatives, **3a–f** and **4a–r**, were carried out by a Claisen–Schmidt condensation of substituted 2-methyl-3-acetylquinolines (where R_2 = H, CH_3, C_6H_5 or 2-ClC_6H_4, R_3 = H, Br, Cl or NO_2 and R_4 = H or Br) with the corresponding substituted pyrazole-4-carboxaldehyde (where R_1 = CH_3, C_6H_5, 4-BrC_6H_4 or 4-OCH_3-C_6H_4) using KOH as catalyst in ethanol at room temperature (Table 1). In the condensation reactions of **1a** with **2a–f**, on using ethanol as the solvent, pyrazolyl–quinoline chalcone derivatives **3a–f** were obtained where the original pyrazolyl-bound chloro atom was substituted by an ethoxy group.

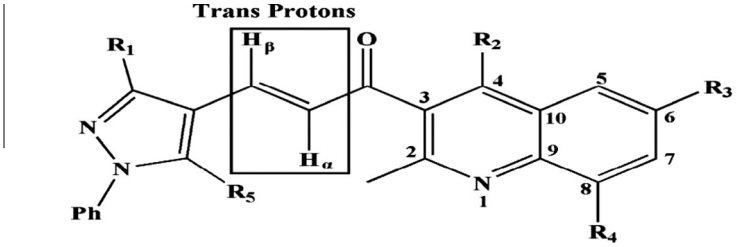
The reaction time for the conventionally synthesized chalcones is 12 h, while reaction time for the synthesis by ultrasonic method is 15 min. The purity and yield of the product by ultrasound method was found to be better than conventionally synthesized ones. It is observed that the variation of reaction temperature had a considerable influence on the yield of the product. All reactions were normally carried out at 30–35 °C. On increasing the reaction temperature to 45 °C, a drastic reduction in the yield was noted.

The effect of the catalyst on the yield of chalcones **3a** and **4a** was also studied. As shown in Table 2, the catalytic effect of K_2CO_3, KOH, NaOH and EtONa are listed. It was found that KOH was the most effective of those evaluated. For example, under the same reaction conditions, when KOH was used as the catalyst, the yields were 76% and 90% for **3a** and **4a**, respectively, whereas when K_2CO_3, NaOH or EtONa were used as the catalyst, the yields were less than 61% and 66% for **3a** and **4a**, respectively. The study also showed that the molar ratio of potassium hydroxide to starting materials also had a significant effect on the yield of compounds **3a–f** and **4a–r**, with the optimum molar ratio of starting materials to potassium hydroxide being 1:0.75.

Results and discussion

Spectral characterisation

The absorption data of compounds **3a–f** and **4a–r** were recorded in dichloromethane solution (concentration 10^{-5} M) and the results are collated in Table 3. Two or more absorption bands were observed in the linear absorption spectra of all molecules in the wavelength range 229–347 nm. The spectra bear a close resemblance owing to the similarity in structure. As noted from Table 3 (and Supplementary material Fig. S1), the maximum absorption band for compounds **3a–f**, having an electron-donating methyl group in the 3-position of the pyrazole ring, is blue shifted compared with compounds **4a–r** which have an aromatic ring in the corresponding 3-position. By contrast, it is observed that the



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R_3 = H, Cl, Br, NO_2; R_4 = H, Br; R_5 = H, OCH_2CH_3.

Fig. 1. Molecular structure of pyrazolyl-quinolinyl chalcone derivatives.