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Original article

Microwave synthesis, characterization and bio-efficacy evaluation of novel chalcone based 6-carbethoxy-2-cyclohexen-1-one and 2H-indazol-3-ol derivatives

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ABSTRACT

Novel chalcone based 6-carbethoxy-2-cyclohexen-1-one and 2H-indazol-3-ol derivatives were synthesized and characterized by using spectral techniques like IR, ^{1}H NMR, ^{13}C NMR, COSY, DEPT, and GC-MS. All these compounds were screened for anti-fungal, anti-bacterial and anti-oxidant activity. Cyclohexenone derivatives, in general, showed better anti-fungal and anti-bacterial activity than parent chalcones. Whereas, all the Indazole derivatives showed very good anti-oxidant activity and some were also found to be active as anti-bacterial agent. Among the screened compounds, **15** was found to be most active as anti-fungal agent (against *Rhizoctonia solani*, $LC_{50} = 2.36$ μg mL^{-1}), **15b** was found to be most active anti-bacterial agent (against *Klebsiella pneumonia*, MIC = 24.68 μg mL^{-1}) and **14b** emerged as most active anti-oxidant ($IC_{50} = 19.81$ μg mL^{-1}).

1. Introduction

Due to stringent and growing environmental regulations, the chemical industry needs the development of more eco-compatible synthetic methodologies and consequently a detailed re-examination of the important synthetic processes [1]. In recent decades, microwave heating has taken an incontestable place in analytical and organic laboratories practice as a very effective and non-polluting method of activation.

Microwave irradiation leads to large reduction in reaction time, enhancement in conversion, and sometimes [2,3] in selectivity with several advantages of the environmental approach, termed green chemistry. The solvent-free Microwave assisted reactions [4] have gained popularity as they provide potentialities to work with open vessels and enhanced possibility of up-scaling the reactions on preparative scale [4–6].

Chalcone is a generic term for the compounds bearing the 1, 3-diphenyl-prop-2-en-1-one framework [7]. Under homogeneous conditions, these compounds are usually prepared by base or acid catalyzed aldol condensation between aromatic aldehydes and ketones. Chalcones represent an important class of compounds due to their chemical flexibility, as synthons for the production of five- and six-member ring systems [8,9] for example Pyrazoles [10], Pyrazolines [11], isoxazolines [12], aurones [13], pyrimidine [14], falvanones [15] and di-aryl cyclohexenones [16]. The biological activities of chalcones are equally wide ranging [17–20]. In fact, not many structural templates can claim association with such a diverse range of pharmacological activities, among which anti-microbial [21], anti-leishmanial [22], anti-malarial [23], anti-fungal [24], anti-viral [25], anti-inflammatory [26], cytotoxicity [27], anti-tumor [28], nematicidal [29] and anti-oxidant [30] are widely cited.

From a chemical point of view, an important feature of chalcones and their hetero-analogs is the ability to act as activated unsaturated systems in conjugated addition reactions of carbanions in the presence of basic catalysts [31,32]. This type of reaction is more commonly used for the preparation of 3,5-diaryl-6-carbethoxycyclohexenones via Michael addition of ethyl

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acetoacetate [33–35]. The mentioned cyclohexenones are efficient synthons in building spiranic compounds [36] or intermediates in the synthesis of fused heterocycles such as benzoselenadiazoles and benzothiadiazoles [37], benzopyrazoles and benzisoxazoles [38,39], carbazole derivatives [40], and 2H-indazoles [41].

The anti-bacterial, anti-fungal, anti-cancer and anti-tubercular activities of di-arylcyclohexenone derivatives were also reported [42,43].

Wide spectrum of biological activities has been reported for indazoles and they have increasingly attracted the attention in pharmaceutical field due to various interesting bioactivity against different targets [44,45].

In the quest for biologically more potent anti-microbial and anti-oxidant agents and to increase the molecular diversity, we envisioned to design and synthesize the chalcone based 6-Carbethoxy-2-cyclohexen-1-one and 2H-Indazol-3-ol Derivatives through a simple, efficient and environment friendly method which utilizes the approach of "*Green chemistry*".

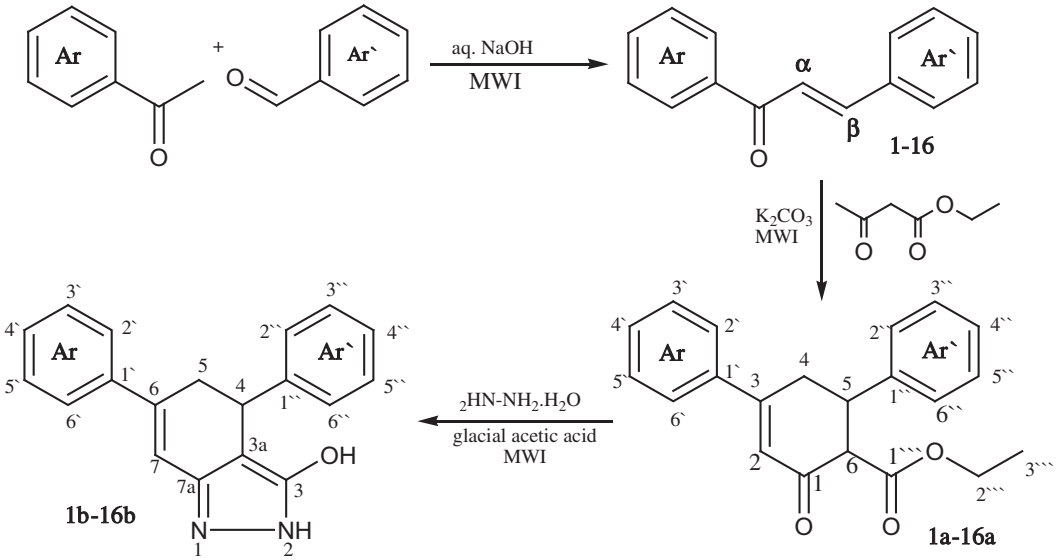
2. Results and discussion

2.1. Chemistry

Chalcones (**1**–**16**) were prepared from substituted acetophenones and benzaldehydes using aq. NaOH under microwave irradiation. The chalcones were then condensed with ethyl acetoacetate using K_2CO_3, under microwave irradiation to give cyclohexenones (**1a**–**16a**). These cyclohexenones were then condensed with hydrazine hydrate in presence of glacial acetic acid under microwave irradiation to afford 2H-indazol-3-ols (**1b**–**16b**) (Scheme 1). All the cyclohexenone and indazole derivatives were characterized by elemental analysis, IR, ^{1}H NMR, ^{13}C NMR, COSY, DEPT, and GC-MS.

Claisen-Schmidt condensation method for the synthesis of chalcones is very attractive since it specifically generates the *trans* (E)-isomer [8,46,47]. Signals for two vinylic protons in the structure of chalcones appear as two doublets in aromatic region of ^{1}H NMR spectra, and their coupling constant (J) showed that all chalcones were geometrically pure and with *trans*-configuration ($J_{H\alpha-H\beta}$ = 15.50–16.50 Hz). Aromatic protons appear between δ 6.9 and 8.1. In ^{13}C NMR, a signal at around δ 190 confirms the presence of carbonyl group. Signal for α and β carbons appear at around δ 145 and 120 respectively. Aromatic carbons appear at around δ 120–140. The IR spectrum supported the NMR data showing the characteristic band for C]O at 1655–1660 and C]C Ar at around 1600 and 1475 cm^{-1}.

The cyclo-condensation of ethyl acetoacetate with chalcones leads to the generation of two chiral centers at C-5 and C-6 in the structure of cyclohexenones. As the explored reaction is not stereo selective, both configurations of the chiral carbon atoms are expected to be noticed in the synthesized cyclohexenones, which would result in a mixture of diastereomers. No attempt to separate the diastereomeric cyclohexenones was undertaken, and the cyclo-condensation products have been characterized in the form of the mixture originated from the synthesis. The IR spectra of these compounds revealed a sharp strong absorption band above 1700 cm^{-1} that can be correlated with the presence of the ester function in the structure of cyclohexenones. Furthermore, another sharp strong absorption band was noticed at approximately 1660 cm^{-1} and was assigned to the carbonyl group conjugated with a carbon–carbon double bond. No other absorption band could be evidenced in the region of the IR spectrum associated with the stretching vibrations of the carbonyl group, thus excluding the intermediate Michael adduct having an extra carbonyl group. The ^{1}H NMR spectra substantiated the results of the IR analysis. The characteristic signals of an ethyl ester moiety (a triplet at chemical shift values of about δ 1 and a quartet at around δ 4) confirmed the presence of the ester group in the structure of cyclohexenones. The characteristic signal in the ^{1}H NMR spectrum was however the singlet of the vinylic proton of the cyclohexenone ring, that appeared at approximately δ 6.5 and confirming that the intramolecular cyclo-condensation, subsequent to the Michael addition, actually took place. The two protons at C-4, being non-equivalent, appeared as two different signals, the axial proton appeared as double of double-doublet at around δ 2.95 showing both germinal coupling, vicinal coupling and long range ^{1}H–^{1}H coupling and the equatorial proton appeared as double-doublet at around δ 3.05, showing germinal and vicinal couplings. The signals for the protons at C-5 and C-6 appeared as a multiplet at around δ 3.7. Vinylic proton at C-2 appeared as doublet at around δ 6.5 and aromatic protons appeared between δ 6.7 and 7.8. COSY spectrum of cyclohexenones confirmed the long range ^{1}H–^{1}H coupling between axial proton at C-4 and vinylic proton at C-2. ^{13}C NMR also



Scheme 1. General method for the synthesis of cyclohexenone and indazole derivatives.