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Synthesis, antimicrobial and antifungal screening of novel chalcones containing imidazo[1,2-a] pyridine nucleus

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ABSTRACT

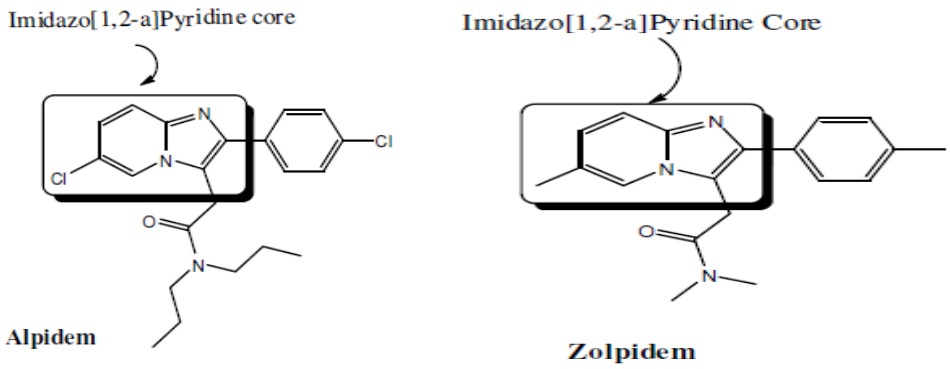
A series of chalcones were prepared by reacting various 2-(phenyl) imidazo [1,2-a] pyridine-3-carbaldehyde with acetophenones in the presence of alcoholic alkali. The structure elucidation of synthesized compounds has been done on the basis of elemental analysis, infrared and 1H nuclear magnetic resonance spectroscopy and further supported by Mass spectrometry. All the compounds have been evaluated for their in vitro biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards Aspergillus niger at a concentration of 40µg/ml. The biological activities of synthesized compounds were compared with standard drugs.

Keywords: Imidazo [1, 2-a] pyridine; Imidazo [1,2-a]pyridine-3-carbaldehyde chalcones; antifungal activity; antibacterial activity.

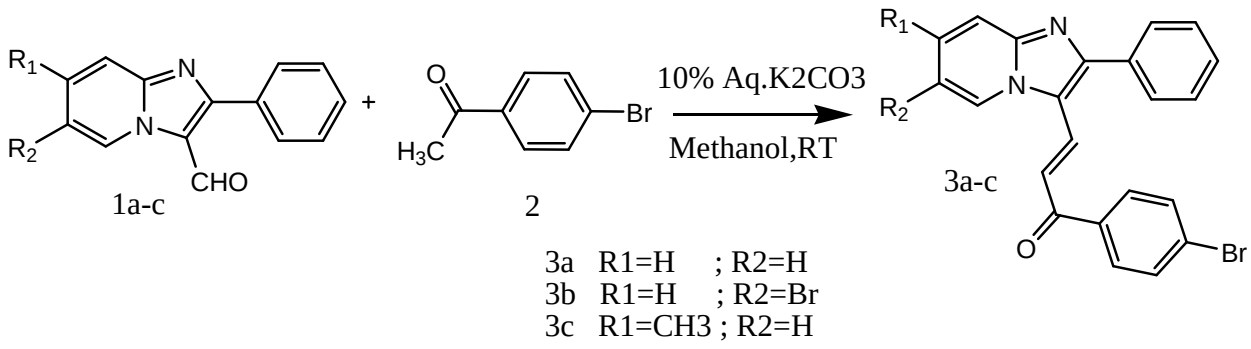
INTRODUCTION

Synthesis of new compound with appropriate therapeutic importance is a major challenge in medicinal chemistry. Recently, imidazo [1,2-a] pyridines have significant importance in the pharmaceutical industry[1] owing to their various interesting biological activity displayed over a broad range of therapeutic classes; these molecules exhibit antiviral [2], anti-inflammatory [3], analgesic, antipyretic, antiulcer, and antibacterial[4] properties. They are also β-amyloid formation inhibitors, GABA and benzodiazepine receptor agonists [5]and cardiotonic agents [6]. Drug formulations containing imidazo [1,2-a]pyridine that are currently available on the market include Alpidem (anxiolytic)[7], Zolpidem (hypnotic)[8]and olprinone (PDE-3 inhibitor)[9].

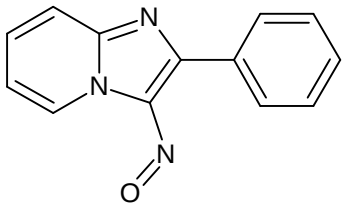
The non-benzodiazepines are generally used as sedatives, anticonvulsants, hypnotics, anxiolytics and muscle relaxants as they show less adverse effects compared to classical benzodiazepines [10]. In fact, imidazopyridines are the major class of non-benzodiazepines, acting upon various central nervous systems (CNS) disorders. Several imidazo [1,2-a]pyridine nucleus already in market which include Alpidem has sedative and anxiolytic properties and Zolpidem is a hypnotic drug. Both Alpidem and Zolpidem have higher affinity for benzodiazepine-1 than for benzodiazepine-2 receptors and their interaction with various receptors has been reported [11]. Some imidazo [1,2-a] pyridine containing drugs are as follow:



Chalcones are well known intermediates for synthesizing various heterocyclic compounds. The compounds with backbone of chalcones have been reported to possess various biological activities such as antibacterial [12], anti-inflammatory [13], anti-malarial [14], antioxidant [15], anti-HIV [16], and anti- tubercular [17]. The presence of a reactive α,β- unsaturated keto function in chalcones was found to be responsible for their anti-inflammatory activity. It was envisaged that the two pharmacophores if linked together would generate novel molecular templates which are likely to exhibit interesting biological properties. We were designed and synthesized various chalcone containing imidazo [1,2-a] pyridine nucleus and compared with 3-nitroso-2-phenylimidazo[1,2-a]pyridine .



Scheme1: Reagents and Condition: Methanol, 10% Aq. K2CO3, RT for 6-8 hrs



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Scheme 2:3-nitroso-2-phenylimidazo[1,2-a]pyridine

Table-1 :Synthesis of Chalcone containing Imidazo [1,2,a] Pyridine nucleus

Entry	Compound	Mol. Formula	Mol. weight	M.P. (ºC)	Yield (%)
1	3a	$C_{22}H_{15}OBrN_2$	403,27	168°C	**38,5 %**
2	3b	$C_{22}H_{14}OBr_2N_2$	482,16	228 °C	**38,88** %
3	3c	$C_{23}H_{17}OBrN_2$	417,29	194 °C	**61,3** %

MATERIALS AND METHODS

Experimental:

All commercially available chemicals and reagents were purchased from Aldrich and used without further purification. All the solvents were dried and distilled before use. The melting points were measured on a Tottoli apparatus and are uncorrected; The IR spectra of synthesized compounds were recorded on un Perkin-Elmer FT Pargamon 1000 PC Spectrophotometer using potassium bromide. The 1H NMR were recorded in $CDCl_3$ or DMSO-

d6 using NMR Bruker Avance DPX 300 MHz spectrometer and chemical shifts are reported as parts per million (ppm) using tetramethylsilane (TMS) as an internal standard and Mass spectra have been recorded on Perkin-Elmer SCIEX API 3000 model . Reactions were monitored using thin layer chromatography (TLC) carried out on Merck silica gel 60 F254 precoated aluminium plates. The visualization was achieved under UV light or staining with I2. Chromatographic separations were achieved on silica gel columns (Merck, 60–120 mesh) using gradient of hexanes/ethyl acetate as eluent.

General procedure for the preparation of Chalcone of Imidazo [1,2,a] Pyridine nucleus:
Substituted 2-(phenyl) Imidazo [1, 2-a] pyridine carbaldehyde (0,45mmol; 1eq) dissolved in 20ml of Methanol and to this 10% aqueous K2CO3 (1 ml) solution were added and stirred for 15-20 minutes at room temperature. To this P-Bromoacetophenone(0,45 mmol ; 1eq) were added. Stirred the above reaction mass for 6-8 hours at room temperature. Reaction was monitored by TLC. After completion of reaction, reaction mass was poured in ice cold water and neutralized with acetic acid, filtered off to obtain desired product. The resulting product was purified by column chromatography on silica gel (Merck, 60–120 mesh, ethyl acetate–hexane, 2:8) to afford pure product.

Spectral data of representative compound:(2E)-1-(4-bromophenyl)-3-(2-phenyl H-Imidazo[1,2-a]pyridin-3-yl) prop-2-en-1-one (3a): Yellow Solid, IR (KBr/Cm^{-1}): 3030, 1650, 1590, 1565, 1280, 1000, 810,740,690 Cm^{-1}; **1H RMN, 300 MHz** (CDCl3) δ**ppm :**7,06 (1H ; H6 ; t) ; 7,38 (1H ; Hc ; d) ; 7,43 (2H ; HPhe ; m) ; 7,51 (2H ; Hphe;d) ; 7,61 (2H ; H8-He ; dd) ; 7,76 (5H ; HPhe ; m) ; 8,2 (1H ; Hd ; d) ;8,53 (1H;H5;d)

MS (spray ionique): m/z = 403; 405 (M+2)

Spectral data of representative compound:(2E)-3-(6-bromo-2-phenyl H-Imidazo[1,2-a]pyridin-3-yl)-1-(4-Bromophenyl)prop-2-en-1-one (3b):
Yellow Solid, IR (KBr/Cm^{-1}):: 3030, 1680, 1650, 1590, 1275, 1200, 1080,1000,780,750, 690cm-1; **1H RMN, 300 MHz**(CDCl3) δ**ppm :**7,22 (1H ,**H**ph,t) ; 7,38 (1H ; **H_7** ; d) ; 7,43 (2H ; **H**ph ; m) ; 7,51 (1H ; CH=C**H**;d) ; 7,61 (2H ; **H**ph ; dd) ; 7,76 (5H ; HPhe ; m);7,92(1H,**H_8**,d) ; 8,1 (1H ; C**H**=C ; d) ;8,33 (1H;H5;S);

MS (spray ionique): m/z = 482; (M+2)

Spectral data of representative compound :(2E)-1-(4-bromophenyl)-3-(7-methyl-2-phenyl H-Imidazo [1,2-a]pyridin-3-yl) prop-2-en-1-one (3c): Yellow Solid, IR (KBr/Cm^{-1}): 1650, 1560, 1270, 1230, 1030, 690cm-1; **RMN 1H, 300 MHz** (CDCl3) δ**ppm**2,49 (3H ; C**H3**; s) ; 6,94 (1H ; **H6** ; d) ; 7,34 (1H ; **He** ; d) ; 7,5 (3H ;**Hphe b,b',c**m) ; 7,59 (3H ; **H8-Ha,a'** ; m) ; 7,77 (4H ; **HPhe** ; m) ; 8,15 (1H ; **Hd**; d) ; 8,42 (1H;**H5;**d).

RMN 13C, 75, 47 MHz (CDCl3) δ**ppm**21, 5 (**CH_3**) ; 116,35(**C3**) ; 116,6 (**C8**) ; 117,23 (**C5**) ; 124,68 (**C6**);127,68(**Ce**);128,89(2**Cph**);129,30(**Cph**);129,5(2**Cph**);129,77(2**Cph**);130,2(**Cph);**131,92(**2Cph**);133,2(**C**);137 ,05(**C**); 139,57(**C**) ;147,41 (**C**) ;188,39 (**C=O**)

SM (spray ionique) : m/z = 417,29 ; 419,10 (M+2)

Antibacterial and antifungal activity
1. Determination of the antibacterial activity:
The antibacterial activity against E. coli (DH5α strain) has been determined in liquid medium (LB, Laury Broth) using the phenol red indicator (32661, Riedel-de Haen). The bacterial isolate was cultivated overnight at 37°C under aeration. Then, a fraction of the overnight culture containing roughly 1x106 bacterial cells were used to inoculate the test tube.

Table .2 Antimicrobial activity of the compounds evaluated against *E. coli*
(+): Active ; (-): Not active.

Concentrations / Compounds	1 mM	2 mM
3a	-	-
3b	-	-
3c	-	-
4	-	-

After inoculation, the test tube containing the compound and the phenol red indicator was incubated at 37°C. Twenty four hours later, the bacterial overgrowth was determined by visual observation as the culture become turbid. Bacterial overgrowth was also determined by the color change of the culture from pink-red to orange and then

yellow following the acidification of the medium. In the presence of a compound with antibacterial activity, the culture stays limpid and the phenol red indicator remains pink-red. Each test was repeated three times at least [18].The antibacterial screening results are compiled in table2.

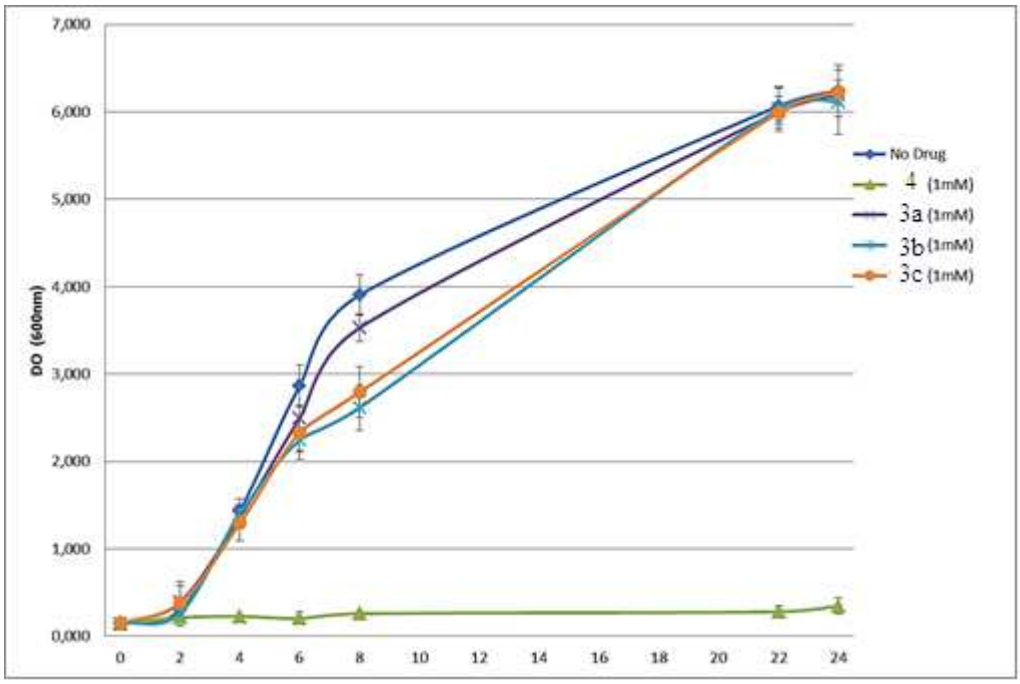

Figure 1A. Cultures of *S. cerevisiae* were grown in the presence of the compounds
Optical density was measured every 2 hours to follow cell growth.

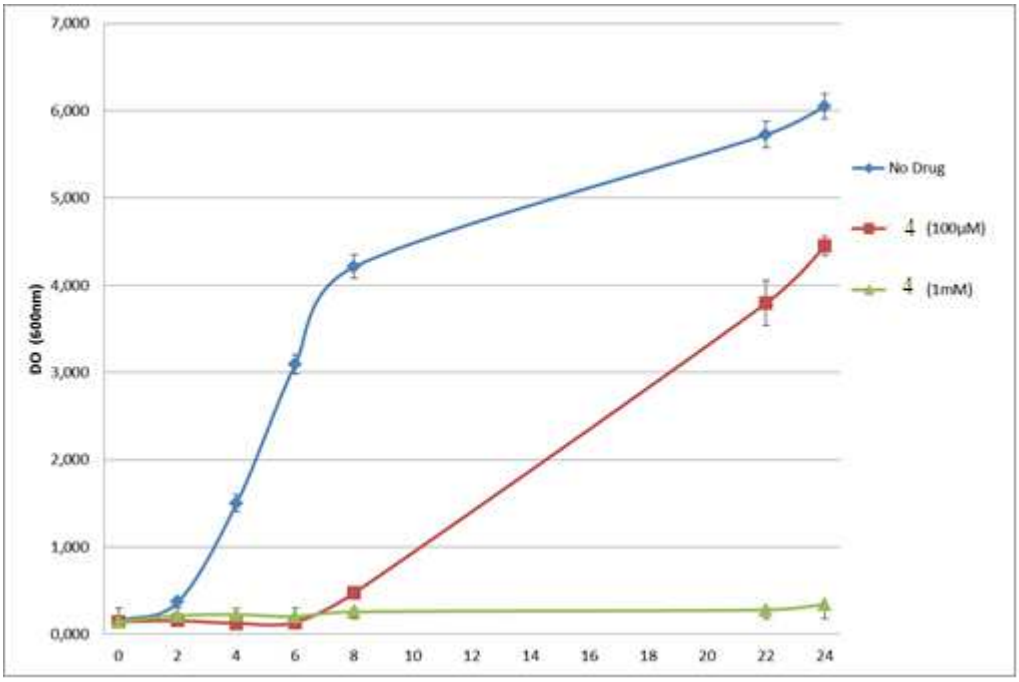

Figure 1B. Cultures of *S. cerevisiae* were grown in the presence of the compounds

2. Determination of the antifungal activity:

The yeast (*Saccharomyces cerevisiae*) strain BY4741 [19; 20] was used in the growth rate study. Growth rate of yeast cells was measured as the optical density of cells at 600 nm as a function of time (hours) in rich medium. Yeast cells were diluted from an overnight culture to an O.D. (600 nm) of ~0.08 and allowed to grow until the O.D. (600 nm) reached ~0.14, ensuring that the cells were in logarithmic phase. Drug was then added and growth rate was

measured. All compounds were diluted in 100% DMSO, and all assays, including the "no drug" control, contained 1% DMSO. Optical density was measured every 2 hours to follow cell growth.

RESULTS AND DISCUSSION

A series of chalcones (3a-3c) were prepared by reacting various substituted 2-(phenyl) imidazo [1, 2-a] pyridine-3-carbaldehyde with P-bromoacetophenones in the presence of alkali (scheme-1and table-1). The structures of newly synthesized compounds characterized by IR, 1H NMR, 13C NMR, Mass and physical data. The formation of chalcones (3a-3c) was confirmed by IR and NMR spectra. The presence of a band around 1560 cm-1 due to C=C stretch. The appearance of characteristic band at 1650cm-1is due to carbonyl C=O stretch. The band at 690 cm-1 shows halide C-Br stretch. In 1H NMR spectrum of chalcones doublet at δ 8.48(3H) suggested the presence of protons behind nitrogenin imidazo [1, 2-a] pyridine ring and singlet at 2,49(3H) shows -Synthesized compounds were evaluated for their antibacterial screening against B. coccus, S. aureus, P. aeruginosa and Aerogenes.

We first evaluated the compounds for their antibacterial activity against E. coli as described in Materials and methods. Compounds 3a, 3b and 3c showed no antibacterial activity when they were used at 1mM. Even higher concentrations of these compounds (2 mM) did not inhibit growth.

Regarding the antifungal activity compounds were tested for toxicity against the budding yeast (S. cerevisiae) cells. Cells were cultured in the presence of 1 mM of each compound and assayed for growth inhibition in liquid culture as described in Materials and methods. A weak activity was registered after 8h of incubation for 3b and 3c. But the three compounds (3a, 3b and 3c) were not toxic to yeast cells after 22-24h of incubation (Figure 1A).

A strong antifungal activity was registered for 4 compound during all time of incubation; and even if the concentration is decreased to 0,1 mM (Figure 1B), this strong activity was observed after 8h for being moderate in the final of the test.

For 3b and 3c compounds, a weak activity was registered after 8h of incubation. But the three compounds (3a, 3b and 3c) were not toxic to yeast cells after 22-24h of incubation (Figure 1A)

CONCLUSION

The structures of synthesized compounds were confirmed by IR,NMR spectroscopy, and MS. Investigation of antibacterial and antifungal screening data revealed that the compounds showed no antibacterial activity when they were used at 1mM.The three compounds (3a, 3b and 3c) were not toxic to yeast cells after 22-24h of incubationNiger. Further bioassay, optimization and structure-activity relationship of the title compounds are underway.

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