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Synthesis and Antimicrobial screening of Chalcones containing imidazo [1,2-a] pyridine nucleus

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Abstract

A series of chalcones were prepared by reacting various acetophenones with 2-(4-bromophenyl)imidazo[1,2-a]pyridine-3-carbaldehyde in the presence of alcoholic alkali. The structures of these compounds were confirmed on the basis of spectral data. All the title compounds were screened for their antimicrobial activities. The screening data indicated that tested compounds showed good antimicrobial activity.

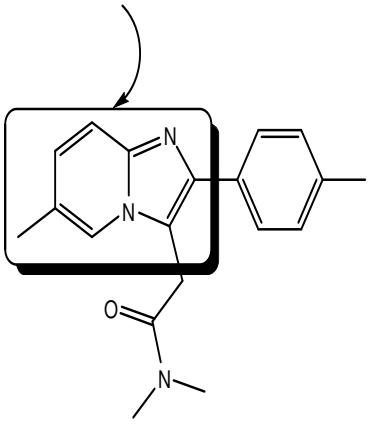
Keywords: Imidazo[1,2-a]pyridine; Imidazo[1,2-a]pyridine-3-carbaldehyde chalcones; antifungal activity; antibacterial activity.

Introduction

Design and 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 (anticytomegalo-zoster and antivaricella-zoster virus)[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]. Acuña and co-workers were the first to report that imidazo[1,2-a]pyridines possessing a 2-hydroxyphenyl substituent at position 2 display excited-state intramolecular proton transfer (ESIPT)[10].

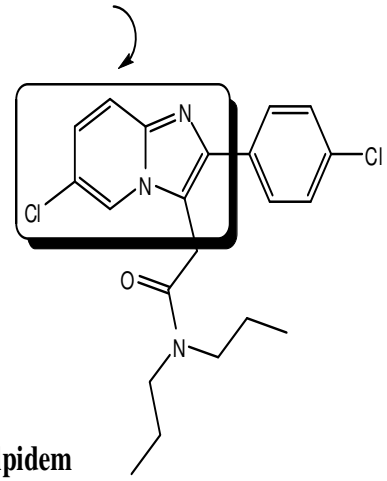
The non-benzodiazepines are generally used as sedatives, anticonvulsants, hypnotics, anxiolytics and muscle relaxants as they show less adverse effects compared to classical benzodiazepines[11]. In fact, imidazopyridines are the major class of non-benzodiazepines, acting upon various central nervous 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[12]. Some imidazo[1,2-a]pyridine containing drugs are as follow:

Imidazo[1,2-a]Pyridine Core



Zolpidem

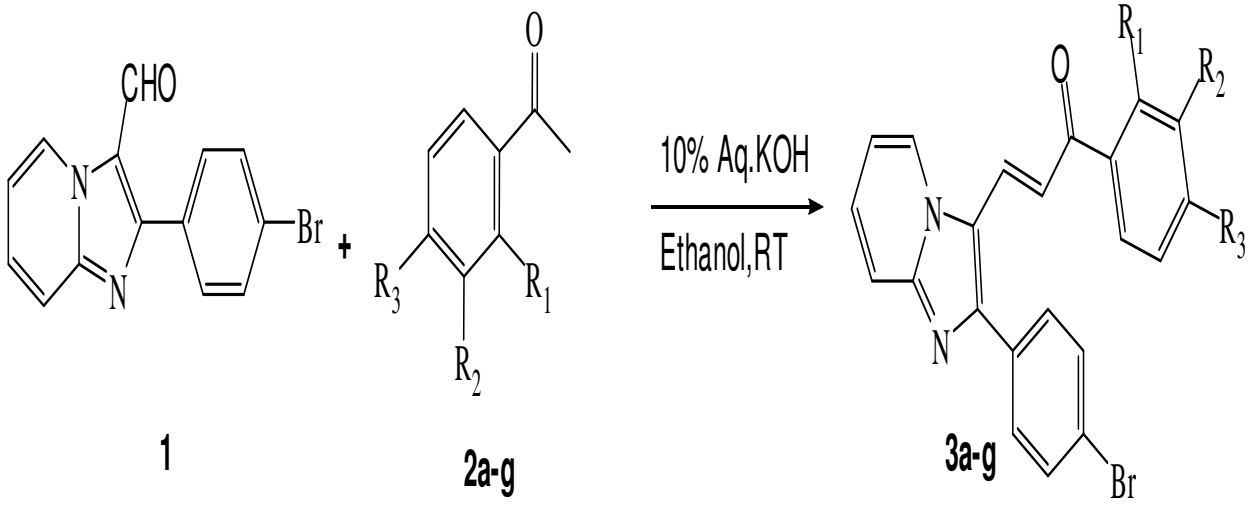
Imidazo[1,2-a]Pyridine core



Alpidem

Further, it is also revealed that, selectivity of imidazo [1,2-a]pyridines towards benzodiazepine receptors can be enhanced by incorporating a 4-halophenyl ring at 2nd position and a hydrophobic unit at 8th position[13]. Inspired by this observation, it has been planned to design new series of imidazo[1,2-a]pyridines containing 4-bromo substituted aryl ring at 2nd position with the expectation of improved pharmacological activity.

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[14], anti-inflammatory[15], anti-malarial[16], antioxidant[17], anti-HIV[18], and antitubercular[19]. 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.



1 2a-g 3a-g

Where, **3a**: R_1=R_2=R_3=H; **3b**: R_1=R_2=H, R_3= -OCH_3
3c: R_1=R_2=H, R_3=Br; **3d**: R_1=R_2=H, R_3=Cl
3e: R_1=H, R_2= -CH_3, R_3= -OH; **3f**: R_1= -OH, R_2=H, R_3= -CH_3
3g: R_1=H, R_2= R_3= -OCH_3

Scheme-1
Reagents and Condition: (a) Ethanol, 10% Aq. KOH, RT for 6-8 hrs

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

Entry	Compound	Mol. Formula	Mol. weight	M.P. (^oC)	Yield (%)
1	3a	$C_{22}H_{15}BrN_2O$	403.27	122-124	65
2	3b	$C_{23}H_{17}BrN_2O_2$	433.30	168-170	70
3	3c	$C_{22}H_{14}Br_2N_2O$	482.17	220-224	68
4	3d	$C_{22}H_{14}BrClN_2O$	437.72	210-212	64
5	3e	$C_{23}H_{17}BrN_2O_2$	433.30	178-180	52
6	3f	$C_{23}H_{17}BrN_2O_2$	433.30	190-192	54
7	3g	$C_{24}H_{19}BrN_2O_3$	463.32	156-158	68

Material 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 determined in open capillary tube and are uncorrected. The IR spectra of synthesized compounds were recorded on Shimadzu 8400-S FT-IR Spectrophotometer using potassium bromide. The 1H NMR were recorded in $CDCl_3$ or DMSO-d_6 using NMR Varian-Mercury 300 MHz spectrometer and chemical shifts are reported as parts per million (ppm) using tetramethylsilane (TMS) as an internal standard. 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 I_2. 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: Acetophenone / Substituted acetophenone (0.5mmol) dissolved in 5ml of ethanol and to this 10% aqueous KOH (1 ml) solution were added and stirred for 15-20 minutes at room temperature. To this mass 2-(4-bromophenyl)Imidazo[1,2-a]Pyridine-3-carbaldehyde 0.5mmol) 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: (E)-3-(2-(4-bromophenyl)Imidazo[1,2-a]pyridine-3-yl)-1-(4-m-ethoxyphenyl) prop-2-en-1-one (3b): Yellow Solid, IR (KBr): 3017, 2864, 1680, 1604, 1570, 1221, 1170, 650cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.48(d, 1H), 8.10(d, J=8Hz, 2H), 7.90(d, 1H), 7.70(d, 4H), 7.55(d, 1H), 7.40(d, 1H), 7.20(t, 1H), 7.10(d, J=8Hz, 2H), 6.80(t, 1H), 3.84(s, 3H); LCMS(ESI): m/z 435.28(M+2)

Antibacterial activity: The purified products were screened for their antibacterial activity using cup-plate agar diffusion method. The nutrient agar broth prepared by the usual method was inoculated aseptically with 0.5 ml of 24 hr. old subcultures of *Bacillus coccus, Staphylococcus aureus, Aerogenes, Pseudomonas aeruginosa* in separate conical flasks at 40-50^{0}C and mixed well by gentle shaking. About 25 ml content of the flask was poured and evenly spreaded in a petridish (13 cm diameter) and allowed to set for 2 hr. The cups (10 mm diameter) were formed by the help of borer in agar medium and filled with 0.04ml (40mg) solution of sample in DMF. The plates were incubated at 37^{0}C for 24 hr. and the control was also maintained with 0.04ml of DMF in a similar manner and the zone of inhibition of the bacterial growth were measured in millimeter and recorded in table- 2.

Antifungal activity: *Aspergillus niger* was employed for testing antifungal activity using cup-plate agar diffusion method. The culture was maintained on sabourauds agar slants sterilized sabourauds agar medium was inoculated with 72 hr. old 0.5ml suspension of fungal spores in a separate flask. About 25 ml of the inoculated medium was evenly spreaded in a Petridish (13cm diameter) and allowed to set for 2 hr. the cups (10mm diameter) were punched. The plates were incubated at 30^{0}C for 48 hr. After the completion of incubation period, the zone of inhibition of growth the form of diameter in mm was measure. Along the test solution in each petridish one cup was filled up with solvent, which acts as control. The zone of inhibition of test solution are recorded in table-3.

Table-2
Antibacterial activity of synthesized compound

Comp. No.	*In vitro activity*- zone of inhibition in mm			
	B. coccus	***S. aureus***	***Aerogenes***	***P. aeruginosa***
3a	18	11	16	15
3b	14	19	13	19
3c	16	14	15	14
3d	13	12	19	12
3e	10	14	12	15
3f	19	13	14	13
3g	13	12	11	12
Amoxicillin	25	25	20	21
Ciprofloxacin	20	15	22	16

Table-3
Antifungal activity of synthesized compound

Comp. No.	*In vitro activity*- zone of inhibition in mm
	A. niger
3a	18
3b	12
3c	13
3d	18
3e	19
3f	20
3g	13
Greseofulvin	26

Results and Discussion

A series of chalcones (3a-3g) were prepared by reacting various substituted acetophenones with 2-(4-bromophenyl)imidazo[1,2-a]pyridine-3-carbaldehyde in the presence of alkali (scheme-1 and table-1). The structures of newly synthesized compounds characterized by IR, 1H NMR, Mass and physical data.

The formation of chalcones (3a-3g) was confirmed by IR and NMR spectra. The presence of a band around 1570 cm^{-1} due to

C=C stretch. The appearance of characteristic band at 1680cm^{-1} is due to carbonyl C=O stretch. The band at 650 cm^{-1} shows halide C-Br stretch. In ^{1}H NMR spectrum of chalcones doublet at δ 8.48(3H) suggested the presence of protons behind nitrogen in imidazo[1,2-a]pyridine ring and singlet at δ 3.84(3H) shows -OCH_3 group proton.

Synthesized compounds were evaluated for their antibacterial screening against *B. coccus, S. aureus, P. aeruginosa* and *Aerogenes.* Compound 3a and 3f shows moderate activity against *B.coccus*. Compound 3b showed maximum zone of inhibition against bacteria *S. aureus* and *P. aeruginosa.* Compound 3d shows maximum zone of inhibition against *Aerogenes* but less than standard used for screening.

Compound 3e and 3f for their antifungal screening shows maximum zone of inhibition against fungi *A. niger* but less than the standard used for screening.

Conclusion

The structures of synthesized compounds were confirmed by IR and NMR spectroscopy. Investigation of antibacterial and antifungal screening data revealed that the compound 3b showed maximum zone of inhibition against bacteria *S. aureus* and *P. aeruginosa* and Compound 3f showed maximum zone of inhibition against fungi *A. niger*. Further bioassay, optimization and structure-activity relationship of the title compounds are underway.

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