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ORIGINAL ARTICLE

SYNTHESIS AND ANTIMICROBIAL SCREENING OF MANNICH BASES OF IMIDAZO[1,2-A]PYRIDINE

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ABSTRACT

Prompted by the varied biological activities of imidazo[1,2-a]pyridines and Mannich bases, a series of Mannich bases were prepared by condensing 2-(4- bromophenyl)imidazo[1,2-a]pyridine with different secondary amines and formaldehyde in the presence of acid catalyst. The structures of these novel 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.

KEY WORDS: Imidazo[1,2-a]pyridine**;** Mannich bases; antifungal activity; antibacterial activity.

INTRODUCTION

Bridge nitrogen containing fused heterocycles represents important building blocks in both natural and synthetic bioactive compounds which have been shown to possess diverse therapeutic activities[1]. The chemistry of imidazo[1,2-a]pyridines has been intensively investigated since the beginning of the last century. This area is still of great interest, mainly due to important biological activity of these molecules. Imidazo[1,2-a]pyridines have significant importance in the pharmaceutical industry owing to their 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]. More recently, the photo physics of these compounds was studied by Araki and co-workers, who discovered their strong solid-state emission. The design and characterization of compounds that undergo ESIPT continues to engage the interest of scientists throughout the world because of the wide applications of this phenomenon to such systems as laser dyes, fluorescence sensors, and molecular switches[11]. A variety of synthetic methods have been reported for the preparation of substituted imidazo[1,2-a]pyridines[12].

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.

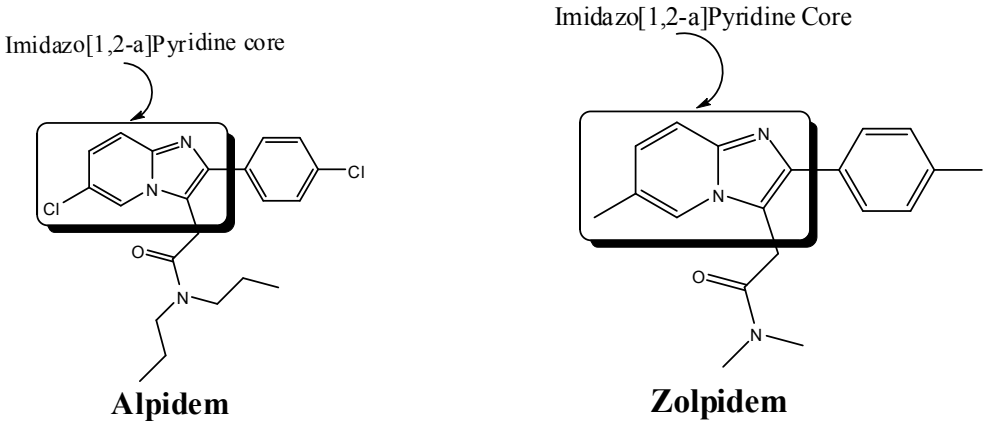


Figure-1

Synthesis of Mannich bases using Mannich reaction posse an opportune method for the introduction of basic aminoalkyl chain in various substrate, since Mannich bases constitute one of the most widely utilized classes of drugs due to their highly therapeutic index in humans.

Some important Drugs in markets having Mannich Base as key structure are as follow:

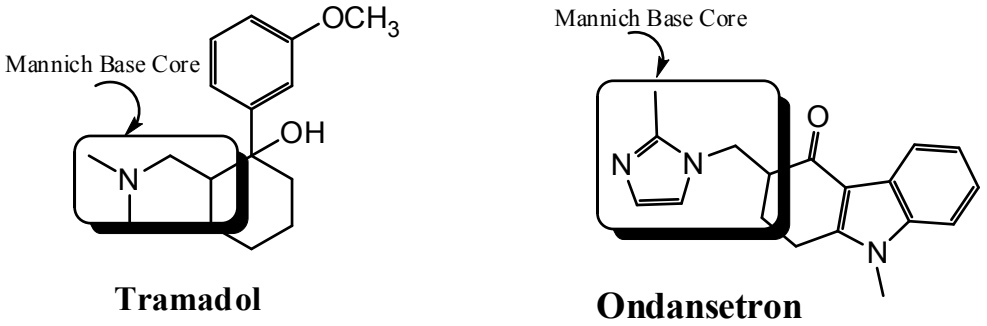
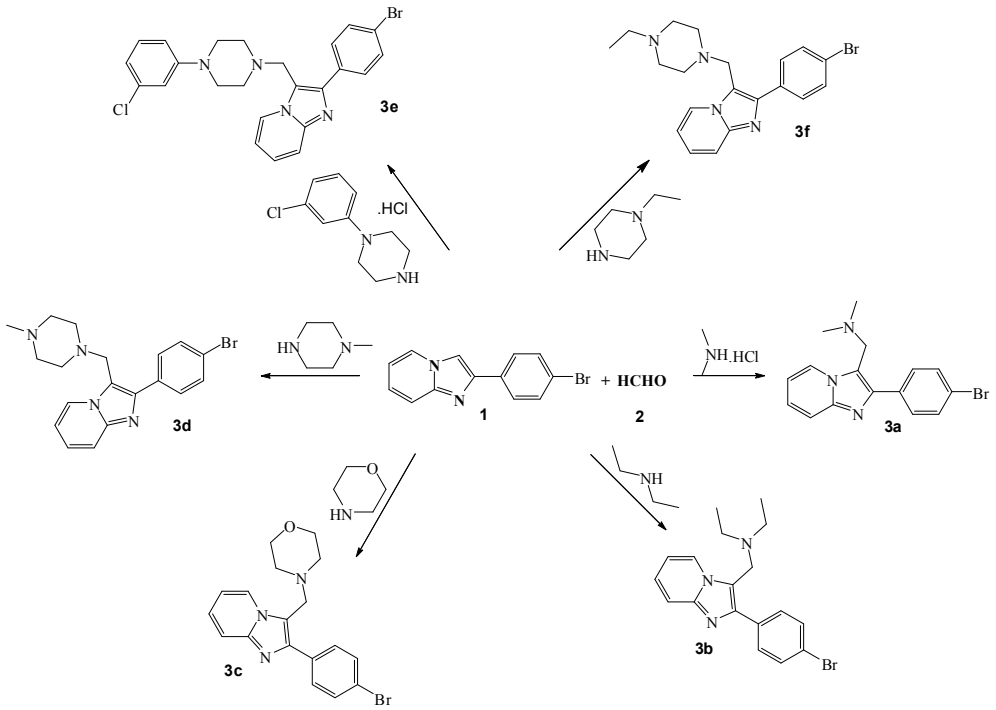


Figure-2

It was envisaged that the two pharmacophores if linked together would generate novel molecular templates which are likely to exhibit interesting biological properties. Owing to the importance and in continuation of our work on developments of newer methods for biologically important molecules. We were designed and synthesized various Mannich bases containing imidazo[1,2,a] pyridine nucleus. **(Scheme 1)**



Scheme 1. Reagents and Condition: (a) Methanol, Cat. HCl, Reflux for 6-8 hrs

Table No. 1 Synthesis of Mannich bases of imidazo[1,2,a] Pyridine

Entry	Compound	Mol. Formula	Mol. weight	M.P. (^oC)	Yield (%)
1	3a	$C_{16}H_{16}BrN_3$	330.22	160-163	55
2	3b	$C_{18}H_{20}BrN_3$	358.28	210-212	60
3	3c	$C_{18}H_{18}BrN_3$	372.26	140-143	60
4	3d	$C_{19}H_{21}BrN_4$	385.30	122-124	60
5	3e	$C_{24}H_{22}BrClN_4$	481.82	180-182	68
6	3f	$C_{20}H_{23}BrN_4$	399.33	120-123	65

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 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 Mannich bases of Imidazo[1,2,a] Pyridine: A mixture of equimolar quantities of imidazo[1,2-a]Pyridine (0.5 mmol), secondary amine (0.5mmol) and formaldehyde (0.5mmol) in methanol were refluxed for 6-8 hrs in presence of catalytic amount of hydrochloric acid. Reaction was monitored by TLC. After completion of reaction, the reaction mass

was cooled to 0-5 ^{o}C in freeze overnight. Reaction mass was poured in ice cold water and filtered off to obtain desired product and washed with chilled ethanol. The resulting product was purified by column chromatography on silica gel (Merck, 60–120 mesh, ethyl acetate–hexane) to afford pure product**.**

SPECTRAL DATA OF REPRESENTATIVE COMPOUND:

1-(2(4-bromophenyl)Imidazo[1,2-a]pyridine-3-yl)-N,N-dimethylmethaneamin (3a): White Solid, IR (KBr): 3070, 1597, 1525, 1495, 1422, 1205, 650 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.23(d, 1H), 7.68(d, J=8Hz, 2H), 7.62(d, J=8Hz, 2H), 7.40(d, 1H), 7.18(dd, 1H), 6.80(dd, 1H), 3.53(s, 2H), 3.28(t, 4H), 1.65(t, 4H); LCMS(ESI): m/z 332.22(M+2)

1-(2(4-bromophenyl)Imidazo[1,2-a]pyridine-3-yl)-N,N-diethylethaneamine (3b): Yellow Solid, IR (KBr): 3080, 1597, 1520, 1500, 1420, 1200, 650 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.48(d, 1H), 7.65(d, J=8 Hz, 2H), 7.62(d, J=8Hz, 2H), 7.40(d, 1H), 7.20(dd, 1H), 6.80(dd, 1H), 3.55(s, 2H), 2.44(q, 4H), 1.02(t, 6H); LCMS(ESI): m/z 360.28(M+2)

4-(2(4-bromophenyl)Imidazo[1,2-a]pyridin-3-yl)-methyl)morpholine(3c): White Solid, IR (KBr): 3060, 1597, 1530, 1488, 1423, 1242, 1206, 650 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.11(d, 1H), 7.68(d, J=8Hz, 2H), 7.62(d, J=8Hz, 2H), 7.40(d, 1H), 7.18(dd, 1H), 6.80(dd, 1H), 3.53(s, 2H), 3.28(t, 4H), 1.65(t, 4H); LCMS(ESI): m/z 374.26(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 No. 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 No. 3**

Table No. 2 Antibacterial activity of synthesized compound

Comp. No.	*In vitro activity*- zone of inhibition in mm			
	B. coccus	*S. aureus*	*Aerogenes*	*P. aeruginosa*
3a	12	11	13	11
3b	13	17	11	16
3c	16	14	18	14
3d	14	18	14	19
3e	12	13	19	15
3f	15	14	12	13
Amoxicillin	25	25	20	21
Ciprofloxacin	20	15	22	16

Table No. 3 Antifungal activity of synthesized compound

Comp. No.	*In vitro activity*- zone of inhibition in mm
	A. niger
3a	12
3b	14
3c	13
3d	22
3e	19
3f	17
Greseofulvin	26

RESULTS AND DISCUSSION

A series of Mannich bases **(3a-3f)** were prepared by condensing 2-(4- bromophenyl) imidazo[1,2-a]pyridine with different secondary amines and formaldehyde in the presence of acid catalyst **(Scheme-1 and Table-1)**. The structures of newly synthesized compounds characterized by IR, 1H NMR, Mass and physical data.

The formation of Mannich bases (**3a-3f**) was confirmed by IR and NMR spectra. The presence of a band around 1200-1206 cm^{-1} due to C-N stretch and band around 1420-1423 cm^{-1} show CH_2 stretch. The characteristic band at 1597 cm^{-1} shows C=N stretch in imidazo[1,2-a]pyridine ring. The appearance of characteristic band 3060-3080cm^{-1} and near 1520-1530cm^{-1} due to aromatic C-H and C=C stretch respectively. The band at 650 cm^{-1} shows halide C-Br stretch.

In 1H NMR spectrum of Mannich bases doublet in range at δ 8.11-8.48 (1H) suggested the presence of protons adjacent to bridge nitrogen in imidazo[1,2-a]pyridine ring. and singlet in between δ 3.53- 3.55 shows the presence of CH_2 group.

Newly synthesized compounds were evaluated for their antibacterial screening against *B. coccus, S. aureus, P. aeruginosa* and *Aerogenes*. All compounds **(3a-3f)** shows moderate activity against *B.coccus*. Compounds **3b** and **3d** showed maximum zone of inhibition against bacteria *S. aureus* and *P. aeruginosa.* Compounds **3c** and **3e** shows maximum zone of inhibition against *Aerogenes* but less than standard used for screening.

Compound **3d** 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** and **3d** showed maximum zone of inhibition against bacteria *S. aureus* and *P. aeruginosa*. Compound **3d** 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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