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SYNTHESIS AND BIOLOGICAL EVALUATION OF IMIDAZO PYRIDINE DERIVATIVES CONTAINING MORPHOLINE NUCLEUS

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Abstract:

In the present study we have synthesized a series of substituted 3-(morpholin-4-ylmethyl)-2-phenylimidazo [1, 2-a] pyridine derivatives **4(a-o)**. The title compounds were synthesized by the Mannich reaction of imidazo [1, 2-a] pyridines derivatives **3(a-o)**, morpholine and formaldehyde with catalytic amount of acetic acid at reflux temperate. The newly synthesized compounds were well characterized by NMR and LCMS spectroscopic techniques. The synthesized compounds were screened for the antimicrobial and antioxidant activities. From antimicrobial activity results it was found that compounds **4c**, **4e** displayed very good antibacterial against *Staphylococcus aureus* and the compound **4c** showed very good antifungal activity against *Pseudomonas aeruginosa.* Compounds **4f** and **4o** showed promising free radical scavenging activity.

Key words: Imidazole, Pyrimidine, morpholine, Mannich reaction, antimicrobial, antioxidant

Introduction

Heterocyclic compounds hold a special place among pharmaceutically significant natural products and synthetic compounds [i,ii]. Nitrogen heterocycles are abundant in nature and are of great significance to life because their structural subunits exist in many natural products such as vitamins, hormones, antibiotics, and alkaloids as well as pharmaceuticals, herbicides and many more compounds. The remarkable ability of heterocyclic nuclei to serve both as biomimetics and reactive pharmacophores has largely contributed to their unique value as traditional key elements of numerous drugs. In both lead identification and lead optimization processes, there is an acute need for new small organic scaffolds.

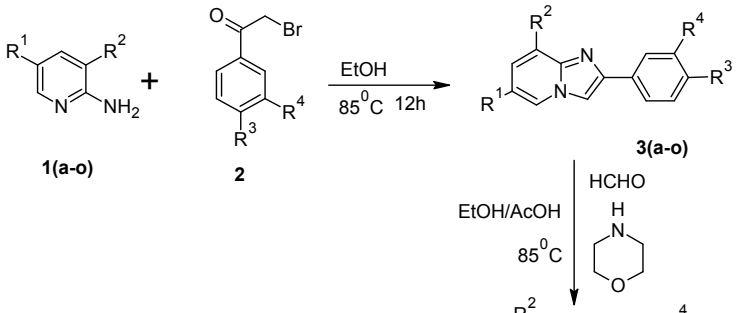
Nitrogen bridgehead-fused heterocycles containing an imidazole ring are common structural motifs in pharmacologically important molecules, with activities spanning a diverse range of targets. Probably, the most widely used heterocyclic system from this group is imidazo-[1, 2-a] pyridine which contained in marketed drugs such as Zolpidem, the benzodiazepine agonist, Olprinone the PDE 3 inhibitor and Zolimidine antiulcer drug as well as other experimental molecules [iii-v].

The heterocyclic compounds play significant role in developing new antimicrobial, anticancer, antimalarial, anticonvulsant agents. Recent observations suggested that, heterocyclic compounds containing nitrogen as heteroatom are very important class of

organic heterocycles, because of their wide application in medicine, agriculture and technology aspects. Among these, 2-phenylimidazo [1,2-a]pyridine derivatives are of significant synthetic interest due to their diverse range of biological activities. Some of them showed pharmacological properties such as anti-inflammatory [vi,vii], aromatase-inhibitors[viii], antibacterial[ix], antifungal[x], antiviral[xi] and analgesic[xii] activities.

Literature shows the presence of morpholine moiety in the compounds is act as the building block in the preparation of Linezolid**,** an antibiotic [xiii] and anticancer agent [xiv].

Promoted by these observations and in continuation our research on biologically active heterocycles [xv-xvii] we hereby reported the synthesis of some new imidazo pyridine derivatives containing morpholine nucleus (**Scheme-1**).



Comp	R^1	R^2	R^3	R^4	Comp	R^1	R^2	R^3	R^4
a	Br	H	Cl	Cl	i	CH_3	H	NO_2	H
b	Br	H	Cl	H	j	CH_3	H	CN	H
c	Br	H	Br	H	k	H	OBz	Cl	Cl
d	Br	H	NO_2	H	l	H	OBz	Cl	H
e	Br	H	CN	H	m	H	OBz	Br	H
f	CH_3	H	Cl	Cl	n	H	OBz	NO_2	H
g	CH_3	H	Cl	H	o	H	OBz	CN	H
h	CH_3	H	Br	H					

Scheme-1 Substituted 3-(morpholin-4-ylmethyl)-2-phenylimidazo [1, 2-a] pyridine derivatives **4(a-o)**.

Experimental section

All the chemicals used were of analytical grade. Melting points were determined on a Bu¨ chi Melting Point B-545 apparatus. Purity of the compounds was checked by TLC on Merck 60 F-254 silica gel plates with visualization by UV-light using ethyl acetate and n-hexane as solvent system. 1H NMR spectra were recorded on Bruker (400 MHz) spectrometer instruments in DMSO-d6 and chemical shifts were recorded in parts per million downfield from tetramethylsilane. Mass spectra were recorded on LC–MS Aglilent 1100 series with MSD (Ion trap) using 0.1% aqueous TFA in acetonitrile system on C18-BDS column for 10 min.

General procedure for the Synthesis of substituted 4-((2-phenylimidazo [1, 2-a] pyridin-3- yl) methyl) morpholine derivatives 4(a-o)

Compounds **3(a-o)** (1 mmol), morpholine (1.2mmol), formaldehyde and catalytic amount of acetic acid was taken in round bottom flask in dry ethanol (8mL) and refluxed for 6-10 hr at 85^{o}C,

the progress of the reaction was monitored by TLC. After completion of reaction, excess of solvent was distilled off and the content was poured into crushed ice with uniform stirring. The product was separated, filtered, dried and recrystallized using ethanol to give compounds **4(a-o)**. The purification of compound was done by chromatography on silica gel using a mixture of ethyl acetate and hexane as an eluent.

6-Bromo-2-(3, 4-dichlorophenyl)-3-(morpholin-4-ylmethyl) imidazo [1, 2-*a*] pyridine (4a)

White solid, Yield- 75 %, m.p. 185-187℃; ^{1}HNMR (400MHz DMSO-d_6,δppm): 8.91 (s, 1H), 8.25 (s, 1H), 7.93-7.43 (m, 4H,Ar-H), 4.02 (s, 2H), 3.54 (b s, 4H), 2.47 (b s, 4H); ^{13}CNMR (400MHz DMSO-d_6, δ ppm): 143.4, 143.1, 135.7, 132.5 131, 130, 128, 126, 125,124,121,118,117, 66, 52,50; MS(LCMS):m/z 441[M], 443 (M+2). Mol. formula; $C_{18}H_{16}BrCl_2N_3O$,

6-Bromo-2-(4-chlorophenyl)-3-(morpholin-4-ylmethyl) imidazo [1,2-*a*]pyridine (4b)

White solid, Yield- 82 %, m.p.157-159°C; ^{1}HNMR (400MHz DMSO-d_6, δ ppm): 8.84 (s, 1H), 7.93--7.42 (m, 6H,Ar-H), 4.01 (s, 2H), 3.52 (b s, 4H), 2.41 (b s, 4H); ^{13}CNMR (400MHz DMSO-d_6, δ ppm): 143.8, 143.1, 133, 132, 130, 129, 128, 126, 118.2, 118.1, 106,66, 52.50; MS(LCMS):m/z 408[M+2]; Mol. formula; $C_{18}H_{17}BrCl_2N_3O$.

6-Bromo-2-(4-bromophenyl)-3-(morpholin-4-ylmethyl) imidazo[1,2-*a*]pyridine (4c)

Off white solid, Yield- 78 %,m.p.176-178℃; ^{1}HNMR (400MHz DMSO-d_6, δ ppm): 8.85 (s, 1H), 7.86-7.84 (d, 2H, *J*=8.4), 7.69-7.66 (d, 2H, *J*=8.8), 7.61-7.59 (d, 1H, *J*=9.2), 7.44-7.41 (d, 1H, *J*=11.2Hz), 4.00 (s, 2H), 3.52 (b s, 4H), 2.41 (b s, 4H); ^{13}C NMR (400MHz DMSO-d_6, δ ppm): 143.8, 143.1, 133, 131, 130, 128, 126, 121, 118.2, 118.1, 106, 66.7, 52.50; MS(LCMS):m/z 451 (M+1), 454 (M+2), Mol. formula; $C_{18}H_{17}BrN_3O$.

6-Bromo-3-(morpholin-4-ylmethyl)-2-(4-nitrophenyl) imidazo[1,2-*a*]pyridine (4d)

White solid ,Yield- 80 %.m.p.188-190°C; ^{1}HNMR (400MHz DMSO-d_6, δ ppm): 8.89 (s, 1H), 8.12 -7.44 (m, 6H, Ar-H), 4.04 (s, 2H), 3.52 (b s, 4H), 2.43 (b s, 4H); ^{13}C NMR (400MHz DMSO-d_6, δ ppm): 146, 143, 139, 132, 129, 128, 126, 119, 118, 110, 106, 66, 52.50; MS(LCMS);m/z-416[M+] Mol.formula;$C_{18}H_{17}BrCl_2N_4O_3$.

4-[6-Bromo-3-(morpholin-4-ylmethyl) imidazo[1,2-*a*]pyridin-2-yl]benzonitrile (4e)

White solid, Yield- 74% m.p. 223-225℃; ^{1}HNMR (400MHz DMSO-d_6, δ ppm): 8.91 (s, 1H), 8.35-8.33 (m, 6H,Ar-H) 4.07 (s, 2H), 3.53 (bs,4H), 2.45 (bs,4H); ^{13}C NMR (400MHz DMSO-d_6, δ ppm): 14.5, 143, 139, 132, 128, 126, 118.7, 118.3, 106, 66, 52.50; MS(LCMS)-397[M], Mol formula; $C_{19}H_{17}BrN_4O$.

2-(3, 4-Dichlorophenyl)-6-methyl-3-(morpholin-4-ylmethyl) imidazo[1,2-*a*]pyridine (4f)

Off white solid. Yield- 76 %,m.p. 157-159℃; ^{1} HNMR (400MHz DMSO-d_6, δ ppm): 8.42 (s, 1H), 8.28 (s, 1H), 7.95- -7.18 (m, 4H), 3.95 (s, 2H), 3.56 (b s, 4H), 2.50 (b s, 4H), 2.35 (s, 3H); ^{13}CNMR (400MHz DMSOd_6, δ ppm): 143, 141, 135, 131.6, 131.1, 130, 128.6, 128.1, 123, 122, 117, 116, 66, 52, 50, 18; MS(LCMS):m/z 376[M]. Mol.formula; $C_{19}H_{19}Cl_2N_3O$.

2-(4-Chlorophenyl)-6-methyl-3-(morpholin-4-ylmethyl) imidazo[1,2-*a*]pyridine (4g)

White solid, Yield- 78% m.p.139-137℃; ^{1}HNMR (400MHz DMSO-d_6, δ ppm): 8.36 (s, 1H), 7.94- 7.15 (m, 6H,Ar-H) 3.94 (s, 1H), 3.53 (b s, 4H), 2.43 (b s, 4H), 2.34 (s, 3H); ^{13}CNMR (400MHz DMSO-d_6, δ ppm): 143, 142, 139, 132, 130, 129, 128, 123, 121, 117,

116, 67, 53, 21; MS(LCMS)m/z 341[M], Mol formula; $C_{19}H_{20}ClN_3O$.

2-(4-Bromophenyl)-6-methyl-3-(morpholin-4-ylmethyl)imidazo[1,2-*a*]pyridine (4h)

Off white solid, Yield- 76%,m.p. 175-177℃; ^{1}HNMR (400MHz DMSO-d_6, δ ppm): 8.37 (s, 1H), 7.88- 7.15 (m, 6H,Ar-H), 3.94 (s, 1H), 3.53 (b s, 4H), 2.43 (b s, 4H), 2.34 (s, 3H); ^{13}CNMR (400MHz DMSO-d_6, δ ppm): 140, 139, 138, 132,131, 130, 129, 128, 123, 121, 117, 116, 67, 53, 21; MS(LCMS):m/z 388[M+2], Mol. Formula; $C_{19}H_{20}BrN_3O$.

6-Methyl-3-(morpholin-4-ylmethyl)-2-(4-nitrophenyl) imidazo[1,2-*a*]pyridine (4i)

Pale Yellow solid, Yield-85 % m.p.; 161-163℃; ^{1}HNMR (400MHz DMSO-d_6, δppm): 8.41 (s, 1H), 8.15-7.19 (m, 6H,Ar-H) 3.98 (s, 2H), 3.32 (b s, 4H), 2.43 (b s, 4H), 2.35 (s, 3H); ^{13}CNMR (400MHz DMSO-d_6, δ ppm): 148, 143, 140, 132,131, 130, 129, 128, 123, 121, 117, 116 67, 53, 21; MS (LCMS):m/z 352[M].Mol formula $C_{19}H_{20}N_4O_3$.

4-(6-Methyl-3-(morpholinomethyl) imidazo [1,2-a] pyridin-2-yl) benzonitrile (4j)

Off white solid, Yield- 80%,m.p. 199-203℃; ^{1}HNMR (400MHz DMSO-d_6, δppm): 8.44 (s, 1H), 8.35-7.21 (m, 6H, Ar-H), 4.02 (s, 2H),3.55 (b s, 4H), 2.48 (b s, 4H), 2.36 (s, 3H); ^{13}CNMR (400MHz DMSO-d_6, δ ppm)143.8, 143.1, 136,133, 132, 130, 129, 128, 126, 119.2, 118.1, 106,66, 52.50,20;MS (LCMS):m/z 332[M+]. Mol.formula; $C_{20}H_{20}N_4O$.

4-((8-(Benzyloxy)-2-(3,4-dichlorophenyl) imidazo [1,2-a] pyridin-3-yl) methyl) morpholine (4k)

Off white solid,Yield-82 % ,m.p. 187-189℃; ^{1}HNMR (400MHz DMSO-d_6, δ ppm): 8.22 (s, 2H), 7.92-7.90 (m, 9H, Ar-H),5.33 (s, 2H),3.54 (s, 2H), 3.32 (b s, 4H), 2.44 (b s, 4H); ^{13}C NMR (DMSOd_6, δ ppm): 147, 140, 139, 136, 135, 31.6, 131.1, 130, 129, 128, 119, 118, 112, 104, 70, 66, 52, 50; MS(LCMS):m/z 468[M+]; Mol. Formula; $C_{25}H_{23}Cl_2N_3O_2$.

4-((8-(Benzyloxy)-2-(4-chlorophenyl) imidazo [1, 2-a] pyridin-3-yl) methyl) morpholine (4l)

Off white solid,Yield-80%,m.p.178-180℃; ^{1}HNMR (400MHz DMSO-d_6, δ ppm): 8.20-6.8 (m, 12H, Ar-H), 5.32 (s, 2H), 3.95 (s, 2H), 3.52 (b s, 4H), 2.41 (b s, 4H); ^{13}CNMR (400MHz DMSOd_6, δ ppm): 147, 136, 133, 132, 130, 128.9, 128.6, 119, 118, 112, 103, 70, 66, 53, 51; MS(LCMS):m/z 434 (M+1), 436(M+2); Mol formula; $C_{25}H_{24}ClN_3O_2$.

4-(8-(Benzyloxy)-2-(4-bromophenyl) imidazo [1,2-a] pyridin-3-yl) methyl) morpholine (4m)

White solid,Yield-70%, m.p. 224-226℃; ^{1}HNMR (400MHz DMSO-d_6, δppm): 8.21-6.82 (m, 12H, Ar-H), 5.36 (s, 2H), 3.95 (s, 2H), 3.52 (bs, 4H), 2.41 (bs, 4H); ^{13}CNMR (400MHz DMSOd_6, δ ppm): 148, 138, 134, 131, 130, 127, 128., 119, 118, 112, 103, 70, 66, 53, 51;MS(LCMS):m/z 478[M+]; Mol. formula; $C_{25}H_{24}BrN_3O_2$.

4-((8-(Benzyloxy)-2-(4-nitrophenyl) imidazo [1,2-a] pyridin-3-yl) methyl) morpholine (4n)

Light yellow solid, Yield-72%, m.p. 236-238℃; ^{1}HNMR (400MHz DMSO-d_6, δ ppm): 8.22-6.83 (m, 12H, Ar-H), 5.33 (s, 2H), 3.99 (s, 2H), 3.52 (b s, 4H), 2.43 (b s, 4); MS(LCMS):m/z 444[M]. Mol. Formula; $C_{25}H_{24}N_4O_4$.

4-(8-(Benzyloxy)-3-(morpholinomethyl) imidazo [1, 2-a] pyridin-2-yl) benzonitrile (4o)

Off white solid,Yield-76%,m.p. 203-205℃; Yield-79%; ^{1}HNMR (400MHz DMSO-d_6, δ

ppm): 8.34-6.85 (m, 12H, Ar-H), 5.33 (s, 2H), 4.02 (s, 2H), 3.31 (b s, 4H), 2.45 (b s, 4); ^{13}CNMR (400MHz DMSOd_6, δ ppm): 147, 136 133, 129,128, 127, 126, 123, 119, 118, 117, 114, 113, 111, 101, 66, 53, 50; MS(LCMS):m/z-444[M+2], Mol. Formula; $C_{26}H_{24}N_4O_2$.

Biological activity

Antimicrobial activity

Antimicrobial activity of the synthesized compounds was tested against five bacterial strains using agar well diffusion method[xviii]. Dimethylsulfoxide (DMSO) was used as solvent control. The bacterial cultures were inoculated on nutrient agar (Merck) and fungal culture was inoculated on Potato Dextrose agar media (20 mL).The test compounds were dissolved in DMSO to get a concentration of 12.79M and 100µl of this sample was loaded into the wells of agar plates directly. Plates inoculated with the bacteria were incubated at 37°C for 24h and the fungal culture was incubated at 25°C for 72 h. All determinations were done in triplicates. The Streptomycin and Fluconazole were used as standard drugs for antibacterial and antifungal activities respectively.

Antioxidant activity

Free radical scavenging activity by DPPH method

Free radical-scavenging capacities of synthesized compounds were determined according to the reported procedure[xix]. The newly synthesized compounds at different concentrations (25-100 µmol/L) were added to each test tube and volume was made up to 4 ml using methanol. To this, 3 ml of 0.004% DPPH in methanol was added and the mixtures were incubated at room temperature under dark condition for 30 min. The absorbance was recorded at 517nm using UV-Visible spectrophotometer (Shimadzu UV-1800, Japan). Butylatedhydroxytoluene (BHT), dissolved in distilled water was used as a reference. Control sample was prepared using the same volume without any compound and BHT, 95% methanol served as blank. Test was performed in triplicate and the results were averaged. Radical scavenging activity was calculated using the formula:

% of radical scavenging activity = $[(A_{control} - A_{test})/A_{control}] \times 100$

Where $A_{control}$ is the absorbance of the control sample (DPPH solution without test sample) and A_{test} is the absorbance of the test sample (DPPH solution + test compound).

Results and discussion

Chemistry

The synthetic route to the title compounds **4(a-o)** is demonstrated in the **Scheme-1.** Compounds **3(a-o)** were prepared by treatment of 2-bromo-1-(3, 4-dichlorophenyl) ethanone (**2)** with different substituted 2-aminopyridines **1(a-o)** using ethanol as a solvent at reflux temperature. Further these compounds were treated with morpholine and formaldehyde with catalytic amount of acetic acid at reflux temperate to yield the target compounds substituted 3-(morpholin-4-ylmethyl)-2-phenylimidazo [1, 2-a] pyridine derivatives **4(a-o).** The method describes an easy and convenient route to furnish a number of imidazo [1, 2-*a*] pyridine derivatives. The method included several advantages short steps, short reaction times and excellent yields.

The structure of compounds **4(a-o)** was confirmed by ^{1}H NMR, ^{13}C NMR and mass spectral studies. In ^{1}HNMR spectrum, compound **4c** showed two triplets at δ 2.41 and 3.52 ppm corresponds to four CH_2 protons of morpholine ring and a singlet at δ 4.00 ppm due to bridgehead CH_2 protons. The aromatic protons of the compound **4c** were appeared between δ 7.43–8.85ppm. The ^{13}CNMR spectrum of compound **4c** showed a signals at δ 66.0 (2C) and 52

(2C) due to four morpholine carbons, a signal at δ 50.0 ppm corresponds to methylene carbon and other signals are in well agreement with the assigned structure. Compound **4c** displayed a molecular ion peak M^+ at m/z 452 corresponding to the molecular mass of the compound and isotopic peak [M+2] at m/z 454.

Antimicrobial activity

The antibacterial and antifungal activity of synthesized compounds was studied comparatively with that of standard drugs Diclofenac (antibacterial) and Fluconazole (antifungal).

Table1. Substituted 3-(morpholin-4-ylmethyl)-2-phenylimidazo [1, 2-a] pyridine derivatives 4(a-o)

The preliminary investigation was done by using agar well diffusion method. The results are tabulated in the **Table 1**. The investigation of antibacterial screening revealed that, test compounds showed varying degree of activity against all the tested microorganisms. Among the tested compounds, compound **4c** and **4e** were found to be most active against all the tested strains and the compounds **4g** and **4h** showed very good activity against all the tested strains.

Comp	Zone of inhibition in mm (mean ±S.D.) n = 3							
	Antibacterial				**Antifungal**			
	***S.a*± S.D**	***K. p* ±S.D***	***S. t*± S.D***	***E.c*± S.D***	***P.a*± S.D***	***S.p*± S.D***	***M.g*± S.D***	***C.a*± S.D***
4a	12±0.20	10±0.10	08±0.30	--	07±0.20	10±0.30	07±0.50	06±0.20
4b	14±0.10	11±0.10	10±0.20	10±0.40	07±0.20	--	09±0.10	08±0.50
4c	28±0.10	24±0.30	22±0.30	23±0.10	21±0.50	16±0.50	27±0.10	15±0.20
4d	04±0.20	--	03±0.30	03±0.50	10±0.10	05±0.10	03±0.20	08±0.20
4e	24±0.30	20±0.10	20±0.10	19±0.40	18±0.20	15±0.20	--	14±0.10
4f	--	--	--	--	03±0.20	01±0.20	05±0.30	04±0.30
4g	19±0.30	18±0.30	17±0.30	18±0.10	16±0.10	13±0.10	--	12±0.20
4h	19±0.30	17±0.30	--	16±0.10	15±0.50	11±0.20	--	10±0.10
4i	18±0.30	17±0.30	--	14±0.20	15±0.20	--	--	12±0.10
4j	16±0.30	13±0.10	15±0.20	13±0.20	10±0.20	--	07±0.50	09±0.20
4k	08±0.30	06±0.20	04±0.10	04±0.20	02±0.30	--	10±0.10	03±0.10
4l	10±0.30	07±0.30	--	06±0.10	07±0.50	03±0.20	09±0.50	03±0.10
4m	15±0.30	12±0.30	14±0.10	12±0.20	09±0.20	--	--	10±0.10
4n	15±0.30	11±0.10	12±0.20	11±0.20	09±0.20	--	--	09±0.20
4o	05±0.30	04±0.20	04±0.10	03±0.20	02±0.30	--	--	03±0.10
Diclofenac	34±0.30	32±0.30	28±0.20	30±0.20	24±0.20	20±0.10	--	--
Fluconazole							34±0.30	22±0.30

The newly synthesized compounds **4(a-o)** were also screened for antifungal activity. The investigation of antifungal screening revealed that, the compound **4c** exhibited very good antifungal activity against both the tested fungal strains and the compound **4e** showed moderate to good activity against *Candida albicans*. Compounds **4(g-i)** and **4(m-o)** were inactive against *Microspora griseous.* The activity of these compounds was found to be concentration dependent.

Antioxidant activity

The investigation of (DPPH) radical scavenging activity (**Table 2**) revealed that, among the tested compounds, compounds **4f**, and **4o** which contains electron withdrawing group(s) on phenyl ring have shown promising antioxidant property when compared to standard. The

incorporation of electron donating group CH_3 (**4h**) on target compounds decreases the antioxidant property. Compounds **4a** and **4n** displayed moderate to good activity. The remaining compounds displayed less activity**.**

Table 2. DPPH assay in % of synthesized compounds **4(a-o)**

Comp	DPPH Assay in %	Comp	DPPH Assay in %
4a	52.5 ±0.45	**4i**	22.5 ±0.45
4b	37.6±0.61	**4j**	37.2±0.26
4c	26.3 ±0.23	**4k**	28.7±0.11
4d	43.3±0.16	**4l**	26.3 ±0.23
4e	38.7±0.35	**4m**	38.6±0.61
4f	67.3±0.12	**4n**	56.2±0.35
4g	32.5 ±0.45	**4o**	78.3±0.16
4h	54.1±0.14	**BHT**	90.42±0.25

Conclusion

We synthesized novel series of imidazo pyridine derivatives containing morpholine nucleus. All the synthesized compounds obtained in moderate to good yield. From the antimicrobial activity results it revealed that, compounds containing two electron withdrawing substituents are responsible for potential antimicrobial activity. In case of antioxidant screening, the presence of both electron withdrawing and electron donating groups (**4f**) and the incorporation of benzene ring to the parent moiety (**4o**) exhibited very good antioxidant activity.

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