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GREEN SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL EVALUATION OF SOME PIPERAZINE BENZENAMINE IMINO DERIVATIVES

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ABSTRACT:
The interaction of piperazine benzenamine (**A**) and substituted benzaldehyde (**B**) *via* a greener approach resulted in the synthesis of their imino derivatives (**C1 – C6**). The compound **A** was synthesized by green method using water as a solvent. The resultant compounds were characterized by elemental analysis, ^{1}H-NMR, IR spectral studies.
The *in-vitro* antimicrobial activities of all the final compounds have proven that they are active against bacterial strains *S. aureus*, *E. coli* and fungal strains *C. albicans*, *A. niger*.

KEYWORDS: Imines, Green synthesis, Piperazine, Antibacterial activities, Antifungal activities.

INTRODUCTION:

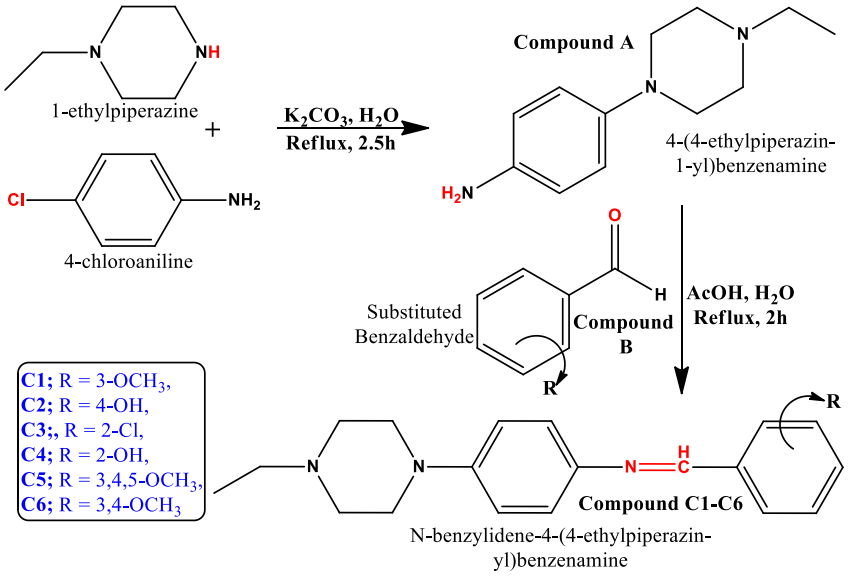
Imines (containing >C=N- group) are typically prepared by the condensation of primary amines and aldehydes or ketones; where the carbonyl group (C=O) gets replaced by the imine group.[i-iii] They have been of particular interest for a long time in pharmaceutical and medicinal applications owing to their diversified biological significance such as anti-inflammatory,[iv-v] antimicrobial,[vi] analgesic,[iv, vii] antitubercular,[viii] anticancer,[ix] anticonvulsant,[x] antioxidant,[xi] and many more. It has been evident that the N-atom of the imino centre is associated with the formation of a H-bond with the active centers and disrupts the normal cell processes.[xii, xiii] The imino-metal complexes on the other hand, have been widely investigated for their herbicidal and anticancer significance.[xiv, xv]
Looking at the variety and numerous applications of imino moieties in different fields of chemistry, there has always been an interest in developing economical, efficient, greener and feasible methods for their synthesis.[xvi-xxiii] In addition to the aforementioned findings; in this research paper, we report the green synthesis and *in-vitro* antimicrobial evaluation of some imino compounds derived from piperazine benzenamine and substituted benzaldehyde. The synthesized analogues have eventually showed appreciable activities against the bacterial and fungal strains for which they were investigated.

EXPERIMENTAL:

All the chemicals and reagents (procured from Sigma Aldrich/Merck) were used as such without further purification. Carbon, Nitrogen and Hydrogen were analyzed on a Perkin-Elmer C, H, N and S II series 2400 analyzer. IR spectra were recorded using KBr pellet method on a Spectrum Version: 10.4.00 - Perkin Elmer FTIR spectrophotometer in the range 4000-400 cm^{-1}. ^{1}H-NMR spectra were recorded for the synthesized compounds using TMS as the internal reference on Bruker Ascend 300 MHz system in d_6-DMSO. Melting points were determined using an electric melting point apparatus and were uncorrected. The IR studies were carried out at *MNIT*, *Jaipur*; whereas ^{1}H-NMR studies were carried out at *Therachem Research Medilab, Jaipur*. Biological activities were carried out at *Seminal Applied Sciences Pvt. Ltd., Jaipur* and *Dr. B. Lal Clinical Laboratory Pvt. Ltd. - CIRD, Jaipur*

Synthesis of Piperazine benzenamine (Compound A; Scheme 1)

N-ethylpiperazine (0.01 mole) and 4-chloroaniline (0.01 mole) were mixed with K_2CO_3 (0.01 mole) in water (10 ml) and the contents were refluxed for about 2.5 hrs. The resultant mixture was then cooled to room temperature. The precipitated powdered solid compound (**A**) was filtered, washed twice with cold water and dried; observed melting point 109-110°C (Yield: 94%).



Scheme 1. Green Synthesis of Imino derivatives of Piperazine benzenamine

Synthesis of Imino derivatives (C1-C6; Scheme 1)

Piperazine benzenamine (A, 0.1 mole), substituted benzaldehyde (0.1 mole) and 2-3 drops of glacial acetic acid in water (20 ml) were mixed and refluxed for about 2 hrs. The resultant mixture was then cooled to room temperature. The precipitated powdered solid compounds (**C1-C6**) were filtered, washed twice with cold water and dried.

RESULT AND DISCUSSION

All the resultant final compounds (**C1-C6**) were found to be insoluble in water. They were found to be thermally stable and were obtained in 77-91% yield. Physical and analytical observations are listed in Table 1.

Table 1

Physical and Analytical data for the synthesized compounds **C1-C6**

S. N.	Compound	Molecular Formula	M.P. (°C)	Yield (%)	Elemental Analysis % Found (% calcd.)		
					C	H	N
1	**C1** (R = 3-OCH_3)	$C_{20}H_{25}N_3O$	144-146°C	85%	73.98 (74.27)	7.86 (7.79)	13.09 (12.99)
2	**C2** (R = 4-OH)	$C_{19}H_{23}N_3O$	126-127°C	77%	73.59 (73.76)	7.38 (7.49)	13.73 (13.58)
3	**C3** (R = 2-Cl)	$C_{19}H_{22}ClN_3$	98-100°C	89%	69.67 (69.61)	6.59 (6.76)	12.64 (12.82)
4	**C4** (R = 2-OH)	$C_{19}H_{23}N_3O$	133-135°C	91%	73.68 (73.76)	7.62 (7.49)	13.71 (13.58)
5	**C5** (R = 3,4,5-OCH_3)	$C_{22}H_{29}N_3O_3$	149-151°C	87%	68.74 (68.90)	7.53 (7.62)	10.82 (10.96)
6	**C6** (R = 3,4-OCH_3)	$C_{21}H_{27}N_3O_2$	143-145°C	84%	71.24 (71.36)	7.43 (7.70)	11.95 (11.89)

IR Spectra (Table 2)

IR Spectra of the synthesized analogues were observed in the definite region of 4000-400 cm^{-1}. These spectra were analyzed depending on some key peaks as recorded. The signals in the region 3035-2945 cm^{-1} in spectra of derivatives **C1-C6** have been accounted for ν(C–H). The peaks recorded in the spectra in the region 1560-1530 cm^{-1} are attributed to ν(>C=N) of the synthesized analogues which depicts the formation of imino bond.[xxiv-xxvi] Furthermore, peaks observed in spectra of derivatives **C1**, **C5** and **C6** in the region 1225-1200 cm^{-1} can be assigned to ν(C-O-C) of the methoxy group.

Table 2

IR spectral readings for the synthesized compounds **C1-C6**

S. N.	Compound	υ(C-H)	υ(C=N)	υ(C-O-C)	υ(C-Cl)
1	**C1** (R = 3-OCH_3)	3035	1535	1225	---
2	**C2** (R = 4-OH)	2945	1530	---	---
3	**C3** (R = 2-Cl)	2995	1560	---	620
4	**C4** (R = 2-OH)	2975	1545	---	---
5	**C5** (R = 3,4,5-OCH_3)	3000	1540	1205	---
6	**C6** (R = 3,4-OCH_3)	3025	1550	1200	---

^{1}H-NMR Spectra (Table 3)

The presence of signals observed in 8.51-8.28 ppm region in the proton spectra of all the synthesized compounds can be attributed to N=CH group; which clearly implies the formation of imino bond. Additionally, signals observed in 6.86-6.39 ppm region are assigned to aromatic protons in the proton spectra of these compounds. Signals observed in 3.84-3.76 ppm region have been assigned to the methoxy (-OMe) protons in compounds **C1**, **C5** and **C6**.

Table 3

^{1}H-NMR spectral readings for the synthesized compounds **C1-C6**

S. N.	Compound	^{1}H NMR (300 MHz, Me_2SO–d_6)
1	**C1** (R = 3-OCH_3)	δ 8.44 (s, 1H), 6.86 (m, 8H), 3.84 (s, 3H), 3.70 (s, 4H), 3.24 (s, 4H), 2.38 (m, 2H), 1.02 (t, 3H)
2	**C2** (R = 4-OH)	δ 8.29 (s, 1H), 6.72 (m, 8H), 5.26 (s, 1H), 3.54 (s, 4H), 3.28 (s, 4H), 2.34 (m, 2H), 1.11 (t, 3H)
3	**C3** (R = 2-Cl)	δ 8.51 (s, 1H), 6.69 (m, 8H), 3.56 (s, 4H), 3.37 (s, 4H), 2.41 (m, 2H), 1.17 (t, 3H)
4	**C4** (R = 2-OH)	δ 8.42 (s, 1H), 6.47 (m, 8H), 5.48 (s, 1H), 3.45 (s, 4H), 3.21 (s, 4H), 2.33 (m, 2H), 1.29 (t, 3H)
5	**C5** (R = 3,4,5-OCH_3)	δ 8.28 (s, 1H), 6.39 (m, 8H), 3.77 (s, 9H), 3.64 (s, 4H), 3.32 (s, 4H), 2.32 (m, 2H), 1.10 (t, 3H)
6	**C6** (R = 3,4-OCH_3)	δ 8.36 (s, 1H), 6.50 (m, 8H), 3.76 (s, 6H), 3.57 (s, 4H), 3.26 (s, 4H), 2.31 (m, 2H), 1.22 (t, 3H)

Antimicrobial Evaluation (Table 4, Figure 1)

The synthesized analogs were evaluated for their antimicrobial activities against gram-positive bacterial strain (*S. aureus* ATCC 25923), gram-negative bacterial strain (*E. coli* ATCC 8739) and fungal strains (*C. albicans* ATCC 14053 and *A. niger* ATCC 1015). For this purpose; Ciprofloxacin was used as the control drug for antibacterial activity and Nystatin for antifungal activity.[xxvii, xxviii]

Antibacterial evaluation of the synthesized imino derivatives (**C1-C6**) reveals that they show appreciable activities against both *S. aureus* and *E. coli*. Compound **C2** (R = 4-OH) showed the best activity against both the bacterial strains compared to the other analogues. When tested against the fungal strains; it was observed that analogue **C4** (R = 2-OH) proved to be better as compared to the other analogues. It may be suggested here that the high activities of **C2** and **C4** can be attributed to the hydroxy group (-OH) which may interact *via* H-bonding with the strains. Overall; it was found that the analogues showed better antibacterial significance compared to their antifungal activities.

Table 4
Antimicrobial activity results for the synthesized compounds C1-C6

S. N.	Compound	MIC concentrations (ug/ml)		MIC concentrations (ug/ml)	
		Gram positive bacterial strain	Gram negative bacterial strain	Fungal Strains	
		S. aureus ATCC 25923	*E. coli* ATCC 8739	*C. albicans* ATCC 14053	*A. niger* ATCC 1015
1	**C1**	425	225	475	525
2	**C2**	175	100	275	325
3	**C3**	475	470	550	450
4	**C4**	450	125	175	200
5	**C5**	525	225	500	550
6	**C6**	550	225	525	525
7	**Ciprofloxacin**	50	25		
8	**Nystatin**			100	100

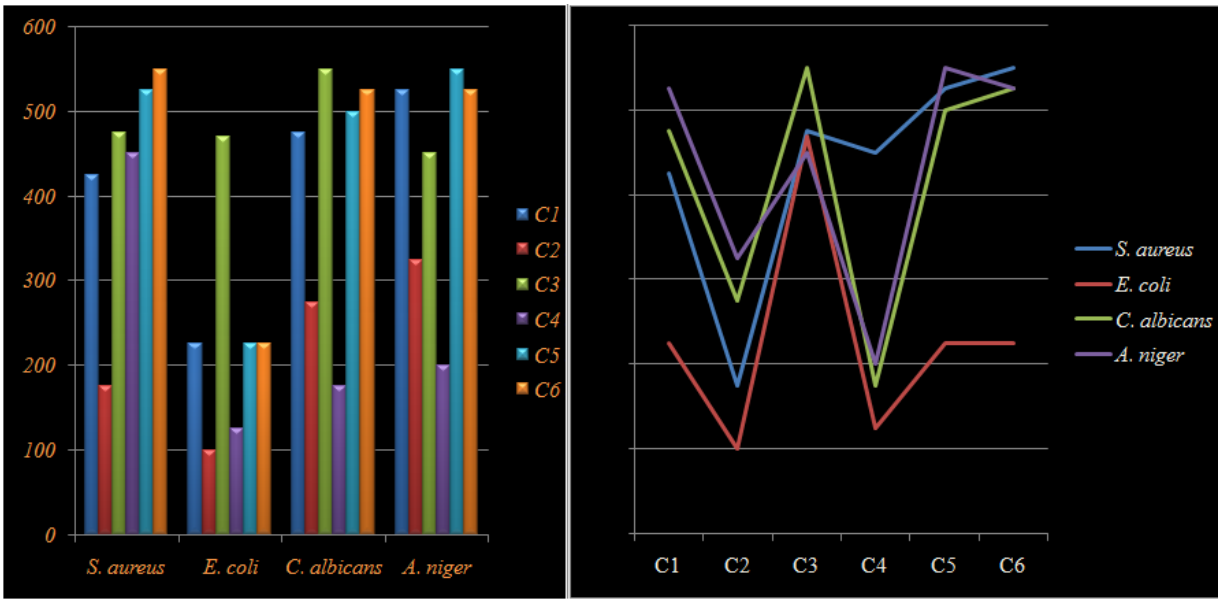


Figure 1(a & b). Antimicrobial activities of synthesized compounds **C1-C6**
(Y-axis stands for MIC data in µg/ml)

CONCLUSION

In the presented work; green synthesis of some imino derivatives obtained from piperazine benzenamine and substituted benzaldehyde; have been reported. All of these synthesized analogues were analyzed based on their elemental analysis, ^{1}H-NMR, IR spectral studies. The antimicrobial evaluation of these compounds demonstrates their significant biological activities against *S. aureus*, *E. coli*, *C. albicans* and *A. niger*.

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REFRENCES

i. Cimerman Z.; Miljanic, S. and Galic N.; "Schiff bases derived from aminopyridines as spectrofluorimetric analytical reagents"; Croat. Chem. Acta; 2000, **73**, 81.
ii. Wittig G. and Hesse A.; "Directed Aldol Condensations: β-phenylcinnamaldehyde"; Organic Syntheses; 1970, **50**, 66.
iii. Bigelow L.A. and Eatough H.; "Benzalaniline"; Organic Syntheses; 1928, **8**, 22.
iv. Sondhi S.M.; Singh N.; Kumar A.; Lozach O. and Meijer L; "Synthesis, anti- inflammatory, analgesic and kinase (CDK-1, CDK-5 and GSK-3) inhibition activity evaluation of benzimidazole/benzoxazole derivatives and some Schiff 's bases"; Bioorg. Med. Chem.; 2006, **14**, 3758.
v. Chandramouli C.; Shivanand M.R.; Nayanbhai T.B.; Bheemachari B. and Udupi R.H.; "Synthesis and biological screening of certain new triazole schiff bases and their derivatives bearing substituted benzothiazole moiety"; J. Chem. Pharm. Res.; 2012, **4**, 1151.
vi. Venkatesh P.; "Synthesis, characterization and antimicrobial activity of various schiff bases complexes of Zn(II) and Cu(II) ions"; Asian Journal of Pharmaceutical and Health Sciences; 2011, **1**, 8.
vii. Chinnasamy R.P.; Sundararajan R. and Govindaraj S.; "Synthesis, characterization, and analgesic activity of novel schiff base of isatin derivatives"; J. Adv. Pharm. Technol. Res.; 2010, **1**, 342.
viii. Aboul-Fadl T.; Mohammed F.A.H. and Hassan E.A.; "Synthesis, antitubercular activity and pharmacokinetic studies of some Schiff bases derived from 1- alkylisatin and isonicotinic acid hydrazide (INH)"; Arch. Pharmacal. Res.; 2003, **26**, 778.
ix. Murray J.H. and Harding M.M.; "Organometallic Anticancer Agents: The Effect of the Central Metal and Halide Ligands on the Interaction of Metallocene Dihalides Cp_2MX_2 with Nucleic Acid Constituents"; J. Med. Chem.; 1994, **37**, 1936.
x. Chaubey A.K. and Pandeya S.N.; "Synthesis & anticonvulsant activity (Chemo Shock)of Schiff and Mannich bases of Isatin derivatives with 2-Amino pyridine (mechanism of action)"; Int. J. PharmTech Res.; 2012, **4**, 590.
xi. Wei D.; Li N.; Lu G. and Yao K.; "Synthesis, catalytic and biological activity of novel dinuclear copper complex with Schiff base"; Science in China Series B; 2006, **49**, 225.
xii. Venugopala K.N. and Jayashree B.S.; "Synthesis of carboxamides of 2 -amino-4 - (6-bromo-3-coumarinyl) thiazole as analgesic and antiinflammatory agents"; Indian Journal of Heterocyclic Chemistry, 2003, **12**, 307.
xiii. Vashi K. and Naik H.B.; "Synthesis of novel Schiff base and azetidinone derivatives and their antibacterial activity"; Journal of Chemistry; 2004, **1**, Article ID 158924.
xiv. Cozzi P.G.; "Metal–Salen Schiff base complexes in catalysis: practical aspects"; Chem. Soc. Rev.; 2004, **33**, 410.
xv. Chandra S. and Sangeetika J.; "EPR and electronic spectral studies on copper (II) complexes of some NO donor ligands" J. Indian Chem. Soc.; 2004, **81**, 203.
xvi. Xu J.; Zhuang R.; Bao L.; Tang G. and Zhao Y.; "KOH-mediated transition metal-free synthesis of imines from alcohols and amines"; Green Chemistry, 2012, **14**, 2384.

xvii. Patil R.D. and Adimurthy S.; "Catalytic Methods for Imine Synthesis" Asian J. Org. Chem.; 2013, **2**, 726.
xviii. Yadav G. and Mani J.V.; "Green Synthesis of Schiff Bases by Using Natural Acid Catalysts"; Int. J. Sci. Res.; 2015, **4**, 121.
xix. Sharma D. and Nag P.; "In-vitro antifungal evaluation of some Cu and Ni complexes"; Res. J. Pharm. Technol.; 2022, **1**, 24.
xx. Reeves J.T.; Visco M.D.; Marsini M.A.; Grinberg N.; Busacca C.A.; Mattson A.E. and Senanayake C.H.; "A General Method for Imine Formation Using $B(OCH_2CF_3)_3$"; Org. Lett., 2015, **17**, 2442.
xxi. Lv X.; Zhou Y.; Zhang A.; Zhou L. and Zeng Q.; "A straightforward green synthesis of *N*-(*tert*-butylsulfinyl)imines"; Toxicol. Environ. Chem.; 2015, **98**, 1155.
xxii. Adams M.R.; Tien C.H.; Huchenski B.S.N.; Ferguson M.J. and Speed A.W.H.; "Diazaphospholene Precatalysts for Imine and Conjugate Reductions"; AngewandteChemie International Edition; 2017, **56**, 1.
xxiii. Illán J.A.M.; Miguel D.R.S.; Franco C.; Imaz I.; Maspoch D.; Luis J.P. and Zamora F.; "Green synthesis of imine-based covalent organic frameworks in water"; Chem. Commun.; 2020, **56**, 6704.
xxiv. Sharma D. and Nag P.; "Synthesis, Characterization and Preliminary Antifungal Activity of Some Co(II) and Zn(II) Complexes Derived from Oximes of 2-Acetyl Aromatic Heterocycles"; Orbital; 2021, **1**, 48.
xxv. Zuo Z.; Liu J.; Nan J.; Fan L.; Sun W.; Wang Y. and Luan X. "Highly Stereoselective Synthesis of Imine-Containing Dibenzo[*b*,*d*]azepines by a Palladium(II)-Catalyzed [5+2] Oxidative Annulation of *o*-Arylanilines with Alkynes"; AngewandteChemie International Edition; 2015, **54**, 15385.
xxvi. Nag P. and Sharma D.; "Synthesis, Characterization and Antifungal Evaluation of Some Novel Mo(VI) Complexes"; Rev. Roum. Chim.; 2021, **64**, 331.
xxvii. Patel AB.; "Investigation of the antibacterial activity of new quinazoline derivatives against methicillin and quinolone resistant Staphylococcus aureus"; Journal of Chemical Research; 2020, **44**, 315.
xxviii. Brown D.F.J. and Kothari D.; "Comparison of antibiotic discs from different sources"; J. Clin. Pathol. (London); 1975, **28**, 779.

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