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SYNTHESIS, SPECTRAL STUDIES AND ANTIMICROBIAL ACTIVITY OF SCHIFF BASE DERIVATIVES CONTAINING IMIDAZOLE NUCLEUS

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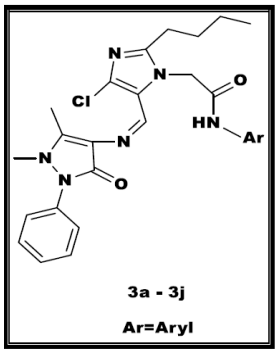
ABSTARACT

The Schiff base derivatives of **(3a-3j)** were synthesized by the condensation of Amide derivatives with 4-amino-5-keto-2,3-dimethyl-1-N-phenyl pyrazole in the presence of glacial acetic acid. The structures of newly synthesized compounds were confirmed based on ^{1}H- NMR, mass spectra, and IR data. All the newly synthesized compounds were screened for their antibacterial activity against Gram +ve Bacteria *Bacillus subtilis*, *Staphylococcus aureus*, and Gram –ve Bacteria *Escherichia coli*, *Pseudomonas aeruginosa* and Fungi *Aspergillus niger*.

Graphical Abstract



KEYWORDS: Schiff base derivatives, Anti-microbial activity.

INTRODUCTION

Imidazole, which is a heterocyclic and a 1,3-diazole, is classified as an alkaloid.[1] Clotrimazole and Miconazole are the two imidazole drugs introduced as topical antimycotics

on the market.[2,3] Losartan potassium is a medication that acts as an antihypertensive agent taken orally[4–6] Losartan's synthesis requires 2-butyl-5-chloro-4- formyl-3H-imidazole which isone of its essential intermediates.[7,8] A primary amine and an aldehyde or ketone condense to form a Schiff base with an imine functional group.[8,9] Hugo Schiff reported it for the first timealmost 150 years back (1864), and went on to refer to him as Schiff going forward. Schiff base derivatives possesses remarkable pharmaceutical importance and biological activities. Schiff base derivatives have been reported to be active Anti-malarial activity[10], Anticancer activity[11,12], Anti-tumor activity[13], Anti-convulsant activity[14,15], Antimicrobial activity[16], Anthelmintic activity[17], Antifungal activity[18], Anti-rheumatics activity[19] etc. On the basis of these results prompted us to synthesized some new Schiff base derivatives. This paper outlinesthe synthesis of Schiff base derivatives **3a-3j**. It includes a study on their biological activities. The antimicrobial activity was determined by the cup plate method at a concentration of 50 μg/ml using DMSO as a solvent.[20]

I. EXPERIMENTAL

All the chemicals used in the reaction Sigma-Aldrich. Thin-layer chromatography (TLC) using precoated silica gel GF254 plates from E-Merck Co. was used to monitor the reactions, and UV light exposure allowed the chemicals to be observed. The melting points of synthesized compounds were measured in open glass capillaries are uncorrected. Tetramethylsilane was used as an internal standard for the ^{1}H NMR spectra of the synthesized compounds, which were recorded on a Bruker 400-MHz NMR spectrometer in DMSO-d6 solvent. The compound's IR spectra were recorded using the KBr pellet technique on the SHIMADZU-FTIR-8400 spectrophotometer. A water mass spectrometer was used to record the mass spectra.

General synthesis of 2-Chloro-1-*N*-(4-methoxy phenyl) Ethanamide. (1b)

To a solution of 4-methoxy aniline (5 mmol, 1 equiv.) in acetone, chloroacetyl chloride (5 mmol, 1 equiv.) was added dropwise, and the resulting mixture was stirred for 15 min at room temperature. The reaction mixture was poured onto crushed ice and solid intermediate product fell out, which was isolated by simple vacuum filtration wash with hexane. The productwas used without further purification.m.p.122˚C; Yield 85 %.

($C_9H_{10}ClNO_2$; Required: C, 54.15 %; H, 5.05 %; Cl, 17.76 %; N, 7.02 %; O, 16.03%; found : C, 54.12 %; H, 5.02 %; Cl, 17.72 %; N, 6.97 %; O, 16.01%)

Simillarly, other 2-Chloro-1-*N*-aryl ethanamides compounds have been synthesized. The Compounds (1a-1j) were reported in *BMC Chemistry* **volume 17**, Article number: 66 (2023) DOI: 10.1186/s13065-023-00973-8

General synthesis of 2-(2'-n-butyl-4'-chloro-5'-Carboxaldo-1'H- imidazol-1'-yl)-N-(4''-methoxy) ethanamide. (2b)

The compound (2b) have been synthesized by the reaction of 2-n-butyl-4-chloro-1H-imidazole-5-carbaldehyde with 2-chloro-1-N-(4-methoxyphenyl) ethanamide (1 equi) acetonitrile as a solvent in presence of K_2CO_3 (2 equi). The reaction mass was refluxed continuously for 4-5 hr . TLC was used to monitor the reaction in a 7:3 hexane:ethyl acetate mixture. The reaction mass was quenched in ice once all the starting materials had been used up on TLC, and the white precipitate was then recovered via a filter and washed with methanol to yield the pure product as an off-white powder. M.P. :102 °C ; Yield : 82 %.

Spectral analysis : IR(KBr pallet) in CM-3354,3203,3051,2945,2871,1679,1619,1551,1462,1413,1244,1177,762,743.1H NMR(DMSO, 400.1 MHz) in δ PPM: 10.44 (Singlet, 1H of -NH) ,9.75 (Singlet, 1H of -CH), 7.4 (Doublet, 2H –CH),6.8 (Doublet, 2H –CH),4.67 (Singlet, 2H –CH2), 3.8 (Singlet, 3H –OCH3),2.8 (Triplet, 2H –CH2),1.5 (Multiplet, 2H –CH2),1.3(Multiplet, 2H –CH2),0.9 (triplet, 3H –CH3), 4H aromatic).MS: at M/Z = 349. Analytical calculated for Molecular formula $C_{17}H_{20}ClN_3O_3$; Required: C, 58.37 %; H, 5.76 %; Cl, 10.13 %; N, 12.01 %; O, 13.72 % found : C, 58.34 %; H, 5.74 %; Cl, 10.11 %; N, 12.0 %; O, 13.72 %.

Similarly, other 2-(2'-n-butyl-4'-chloro-5'-Carboxaldo-1'H- imidazol-1'-yl)-N-aryl ethanamides were synthesized. Amide derivatives physical data and antimicrobial activities was published in *International journal of Research and analytical reviews* (P- ISSN 2349-5138) **2023**, 10(4), 69-76. DOI: http://doi.one/10.1729/Journal.36639.

General procedure for the synthesis of 2-{2'-n-butyl-4'-chloro-5'-[(1''',5'''-dimethyl-3'''-oxo-2'''-phenyl pyrazolyl)4'''-yl]imino methylene}-1'H- (imidazol-1'-yl)-N-(4''''-methoxyphenyl) ethanamide. (3b)

The reaction of 2-(2'-n-butyl-4'-chloro-5'-carboxaldo-1'H-imidazol-1'-yl)-N-(4''- methoxy phenyl) ethanamide (1 equi) with 4-amino-5-keto-2,3-dimethyl-1-N-phenyl pyrazole (1 equi) in the presence of methanol and catalytic amount of Glacial acetic acid . TLC was used to

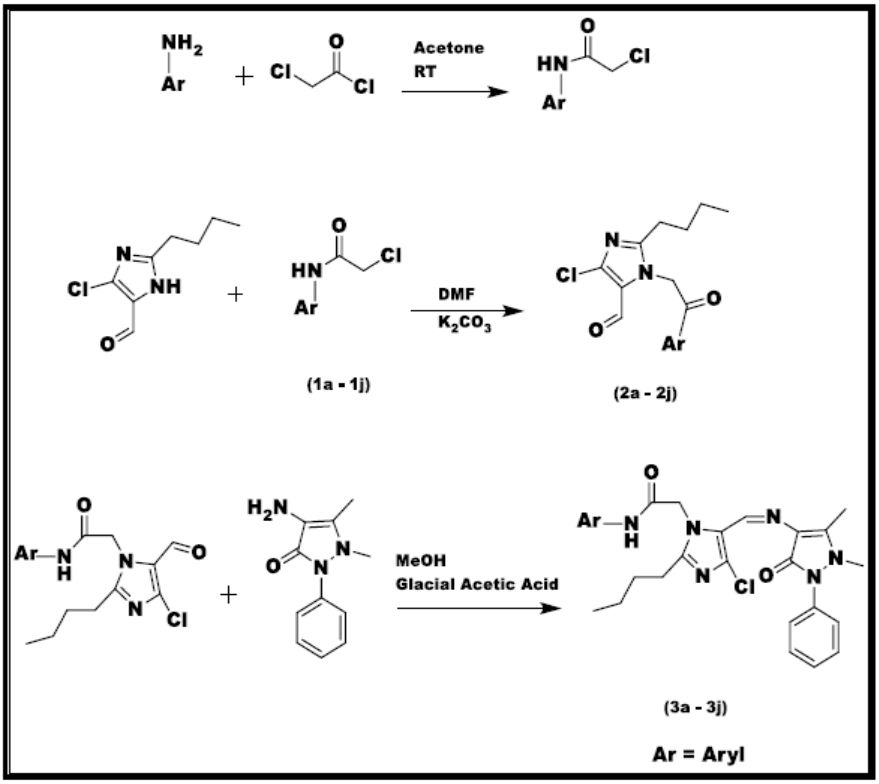
monitor the reaction in a 7:3 hexane:ethyl acetate mixture. After competition of the reaction, reaction mixture was quenched in ice once all the starting materials had been used up on TLC, and the white precipitate was then recovered via a filter and washed with methanol toyield the pure product as an off-white. m.p.154˚C, Yield 72 %.

Spectral analysis: IR(KBr pallet) in CM^{-} 3276 (N-H str. Imidazole), 3067 (C-H str. Aromatic), 2933(C-H Asym. Alkane), 2870(C-H Sym. Alkane), 1669 (C=O str. Ketone), 1632 (C=N str. Imidazole),1550(C-N str. Imidazole),1550(C=C Str. Aromatic),1457(C-H Def. Alkane),1244(C-O-C Ether),767(C- Cl Halide).^{1}H NMR(DMSO, 400MHz) in δ PPM: 10.19 (Singlet, 1H of -NH), 9.54 (Singlet, 1H of -CH), 7.53(Doublet, 4H of –CH),7.38 (Doublet, 4H –CH),6.91(Doublet, 1H –CH),7.3(Doublet,2H –CH),7.1 (Doublet, 2H –CH),7.0 (Doublet,1H –CH),5.3(Singlet,2H–CH_2), 3.73 (Singlet, 3H –OCH_3),3.11 (Singlet, 3H CH_3),2.68 (Triplet, 2H – CH_2),2.28(Singlet,3H - CH_3),1.67 (Multiplet, 2H -CH_2), 1.41(Multiplet, 2H -CH_2),0.93 (Singlet, 3H CH_2). MW = 535. Analytical calculated for Molecular formula $C_{28}H_{31}ClN_6O_3$ is Calcd C: 62.86 %, H: 5.84%, Cl: 6.63 %, N:15.71 %, O:8.97 Found C: 62.84 %, H: 5.81 %, Cl: 6.60 %, N:15.68 %, O:8.94 Similarally, other 2-{2'-n-butyl-4'-chloro-5'-[(1'",5'"-dimethyl-3'"-oxo-2'"-phenyl pyrazolyl)4'"-yl]imino methylene}-1'H- (imidazol-1'-yl)-N-aryl ethanamides were prepared. The physical data are recorded in Table no.:-1.

Table 1: Physical and Analytical data of 2-{2'-n-butyl-4'-chloro-5'-[(1''',5'''- dimethyl-3'''-oxo-2'''-phenyl pyrazolyl)4'''-yl]imino methylene}-1'H- (imidazol-1'- yl)-N-aryl ethanamides. (3a – 3j).

Sr No	-Ar	Molecular Formula	M. W	M. P	Yield	% of Nitrogen	
						Calcd	Found
3a	C_6H_5-	$C_{27}H_{29}ClN_6O^2$	505	148	69	16.64	16.62
3b	4-OCH_3-C_6H_4-	$C_{28}H^{31}ClN_6O_3$	535	154	72	15.71	15.68
3c	4-Cl-C_6H_4-	$C_{27}H_{28}Cl_2N_6O_2$	539	155	64	15.58	15.52
3d	4-Br-C_6H_4-	$C_{27}H_{28}BrClN_6O_2$	583	167	58	14.39	14.33
3e	2-NO2-C^6H^4-	$C_{27}H_{28}ClN_7O_4$	550	158	62	17.83	17.81
3f	2,4$(CH_3)_2$-C_6H^3-	$C_{29}H_{33}ClN_6O_2$	533	150	55	15.77	15.72
3g	3-Cl,2-CH_3-C_6H_3-	$C_{28}H_{30}Cl_2N_6O_2$	553	162	64	15.18	15.15
3h	2,5$(Cl)_2$-C_6H_3-	$C_{27}H_{27}Cl_3N_6O_2$	573	165	58	14.64	14.60
3i	2-CH_3,5-NO_2-C_6H_3-	$C_{28}H_{30}ClN_7O_4$	564	160	55	17.38	17.35
3j	5-Cl, 2-NO_2-C_6H_3-	$C_{27}H_{27}Cl_2N_7O_4$	584	168	60	16.78	16.74
Zone of Inhibition measured in mm.							

II. REACTION SCHEME



Scheme 1: The synthetic scheme for the preparation of compounds (3a-3j).

III. RESULTS AND DISCUSSION

Scheme 1 shows the synthetic pathway used to produce the Amide derivatives **2a–2j** and Schiff base derivatives **3a–3j**. The compounds **1a-1j** were synthesized by reacting substituted Aniline with chloroacetyl chloride in the presence of Acetone. The Amide derivatives **2a–2j** were prepared by condensation the condensation with 2-n-butyl-4-chloro-1H-imidazole-5-carbaldehyde with 2-Chloro-1-N-aryl ethanamides in the presence of K2CO3. After recrystallization from methanol, all corresponding chalcones were obtained in 76–88% yield. The Schiff base derivatives **3a–3j** were prepared from Amide derivatives **2a–2j** by reacting with 4-amino-5-keto-2,3-dimethyl-1-N-phenyl pyrazole in the presence of glacial acetic acid. The isolated products obtained Schiff base derivatives in 55-72 % yield. The structures of all newly synthesized compounds **3a–3j** were assigned based on spectral data such as IR, ^{1}H-NMR, and mass spectra.

Antimicrobial Activity

The antimicrobial activity was determined by the cup plate method at a concentration of 50 µg/ml using DMSO as a solvent. The activity was taken by Gram-positive bacteria *Staphylococcus aureus, Bacillus subtilis*, Gram-negative bacteria *Escherichia coli*,

Pseudomonas aeruginosa, and anti-fungal activity against *Aspergillus niger*. The zone of inhibition was measured in mm. The antibacterial activity was compared with the known standard drugs, viz, Streptomycin, Ampicillin, and anti-fungal activity was compared with known standard drugs viz. Nystatin. The zone of inhibition activity results of compounds **(3a-3j)** are shown in Table No. 2 comparable antimicrobial activity represented in Table 3.

Table 2: Antimicrobial Activity of 2-{2'-n-butyl-4'-chloro-5'-[(1''',5'''-dimethyl-3'''-oxo-2'''-phenyl pyrazolyl)4'''-yl]imino methylene}-1'H- (imidazol-1'-yl)-N-aryl ethanamides. (3a – 3j).

Compd	Ar	Antibacterial Activity				Anti Fungal Activity
		Gram +ve bacteria		Gram -ve bacteria		
		B.subtilis	*S. aureus*	*E.coli*	*P. aeruginosa*	*A.niger*
3a	C_6H_5-	20	13	7	8	9
3b	4-OCH_3-C_6H_4-	19	9	11	9	14
3c	4-Cl-C_6H_4-	18	11	11	18	18
3d	4-Br-C_6H_4-	18	9	10	7	11
3e	2-NO_2-C_6H_4-	19	6	13	14	7
3f	2,4$(CH_3)_2$-C_6H_3-	21	7	13	11	10
3g	3-Cl,2-CH_3-C_6H_3-	18	9	10	12	11
3h	2,5$(Cl)_2$-C_6H_3-	19	11	9	17	20
3i	2-CH_3,5-NO_2-C_6H_3-	16	8	12	12	13
3j	5-Cl, 2-NO_2-C_6H_3-	22	10	9	8	9

Table 3: Compounds (3a-3j) showing comparable antimicrobial activity with known standard drugs.

Compounds	Antibacterial activity				Anti fungal activity
	Gram +ve bacteria		Gram -ve bacteria		
	B. subtilis	*S. aureus*	*E. coli*	*P.aeruginosa*	*A. niger*
(3a-3j)	3a	3a	3e	3c	3b
	3f	3c	3f	3e	3c
	3h	3h	3i	3h	3h
	3j	-	-	-	3i
Activity of Known Standard Drugs:					
Streptomycin (50µg/ml)	26	27	28	20	0
Ampicillin (50µg/ml)	25	26	26	19	0
Nystatin 50 µg/ml)	0	-	-	-	22
Zone of Inhibition measured in mm.					

IV. CONCLUSION

In summary, in the present work we have developed 2-{2'-n-butyl-4'-chloro-5'-[(1''',5'''-dimethyl-3'''-oxo-2'''-phenyl pyrazolyl)4'''-yl]imino methylene}-1'H- (imidazol-1'-yl)-N- aryl ethanamides. **(3a – 3j)** were synthesized and characterized based on their physical andspectral

data. Schiff base derivatives **(3a - 3j)** have been synthesized and some of the compounds **3a,3e,3f.3h,3i,3j** showed good to remarkable antibacterial and antifungal activity which are compared to known standard drugs e.g. Streptomycin, Ampicillin, Nystatin at the same concentration (50 µg/ml), which are represented in the table-3.

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VI. REFERENCES

1. Beltran-Hortelano, I.; Alcolea, V.; Font, M.; Pérez-Silanes, S. *European journal of medicinal chemistry*, 2020; *206:* 112692.
2. Yamaguchi, H.; Iwata, K. *Sabouraudia: Journal of Medical and Veterinary Mycology*, 1979; *17*(3): 311–322.
3. Aldewachi, H. S.; Gurram, A. *International Journal of Pharmaceutical Sciences Review and Research*, 2013; *20*(1): 153–158.
4. Heeb, N. V.; Benner, S. A. *Tetrahedron letters*, 1994; *35*(19): 3045–3048.
5. Gaba, M.; Mohan, C. *Medicinal Chemistry Research*, 2016; *25:* 173–210.
6. Tippannanavar, M.; Verma, A.; Kumar, R.; Gogoi, R.; Kundu, *Journal of agricultural and food chemistry*, 2020; *68*(16): 4566–4578.
7. Carini, D. J.; Duncia, J. V.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Pierce, M. E.; Price, W. A.; Santella III, J. B.; Wells, G. J. *Journal of medicinal chemistry*, 1991; *34*(8): 2525–2547.
8. Moutevelis-Minakakis, P.; Gianni, M.; Stougiannou, H.; Zoumpoulakis, P.; Zoga, A.; Vlahakos, A.; Iliodromitis, E.; Mavromoustakos, T. *Bioorganic & medicinal chemistry letters*, 2003; *13*(10): 1737–1740.
9. De, S.; Jain, A.; Barman, P. *ChemistrySelect*, 2022; *7*(7): e202104334.
10. Sharma, M.; Chauhan, K.; Srivastava, R. K.; Singh, S. V.; Srivastava, K.; Saxena, J. K.; Puri, S. K.; Chauhan, P. M. *Chemical biology & drug design*, 2014; *84*(2): 175–181.
11. Howsaui, H. B.; Basaleh, A. S.; Abdellattif, M. H.; Hassan, W. M.; Hussien, M.A. *Biomolecules*, 2021; *11*(8): 1138.
12. Poonia, K.; Siddiqui, S.; Arshad, M.; Kumar, D. *Spectrochimica Acta Part A: Molecular*

and Biomolecular Spectroscopy, 2016; *155:* 146–154.

13. Hassan, A. S.; Awad, H. M.; Magd-El-Din, A. A.; Hafez, T. S. *Medicinal Chemistry Research*, 2018; *27:* 915–927.
14. Hajare, R.; Polshettiwar, S. *Int. J. Chem. Pharm. Sci.*, 2013; *1*(3): 199–207.
15. Mahapatra, D. K.; Bharti, S. K. *Life sciences*, 2016; *148:* 154–172.
16. Saini, L.; Jain, A.; Bhadoriya, U. *Asian Journal of Pharmacy and Life Science ISSN.*, 2011; *2231:* 4423.
17. Mathew, B.; Vakketh, S. S.; Kumar, S. S. *Der Pharma Chem.*, 2010; *2*(5): 337–343.
18. Magalhães, T.; da Silva, C.; Dos Santos, L.; Santos, D.; Silva, L.; Fuchs, B.; Mylonakis, E.; Martins, C.; de Resende-Stoianoff, M.; de Fátima, Â. *Letters in Applied Microbiology*, 2020; *71*(5): 490–497.
19. Rakesh, K.; Manukumar, H.; Gowda, D. C. *Bioorganic & medicinal chemistry letters*, 2015; *25*(5): 1072–1077.
20. Barry, A.; Lasner, R. *Antimicrobial agents and chemotherapy*, 1976; *9*(3): 549–550.