SYNTHESIS AND CHARACTERIZATION OF SOME PYRAZOLINE DERIVATIVES OF AZA-INDOLIZINE ANALOGUE AS ANTIMICROBIAL AGENT

N.N. Kansagara , V. R. Dangar, and V. R. Shah*

Department of Chemistry, Kamani Science college,
Amreli-365601 Gujarat, India
Email: vrdangar@gmail.com

ABSTRACT

Different pyrazoline derivatives were synthesized by cyclization of substituted chalcones with phenyl hydrazine in basic conditions. Some new 1-Aryl-3-[6-methyl-2-(4-methylphenyl) imidazo [1,2-*a*] pyridin-3-yl]prop-2-ene-1-ones (**1a-l**) and 3-(3-Aryl-1-phenyl-4,5-dihydro-1*H*-pyrazol-5-yl)-6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridines (**2a-l**) were prepared. All the prepared compounds were characterized by their spectral (I.R., N.M.R., Mass) data and screened for their antimicrobial activities.

Key words : Chalcones, Phenyl pyrazolines , Antimicrobial activities.

INTRODUCTION

With the biodynamic activities of chalcones and it is a good synthon for various heterocyclic rings, the interest has been focused on the synthesis of new chalcones[1]. Chalcones are potential biocides because some naturally occurring antibiotics[2] and showing their biological activity in the presence of the αβ-unsaturated carbonyl group[3]. Pyrazoline derivatives [4-6] have been found to possess wide range of therapeutic activity such as Cardiovascular[7] ,. Diuretic[8] , Fungicidal[9], Herbicidal[10] , Antimicrobial , Analgesic[11] ,Bactericidal[12-13] , Antiallergic[14] , Anticonvulsant[15], Antidiabetic[16], Antiinflammatory[17].

Chalcones and pyrazolines have been proved to be the most useful framework for biological activities[18-20]. Both have attracted attention of medicinal chemists for both with regard to heterocyclic chemistry and the pharmacological activities associated with them. This inspired us to synthesize 1-Aryl-3-[6-methyl-2-(4-methylphenyl) imidazo [1,2-*a*] pyridin-3-yl]prop-2-ene-1-ones (1a-l) and 3-(3-Aryl-1-phenyl-4,5-dihydro-1*H*-pyrazol-5-yl)-6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridines(2a-l).

The structure of synthesized compounds were assigned based on Elemental analysis , I.R. ^{1}H-NMR and Mass spectral data. The antimicrobial activity was assayed by using the cup-plate agar diffusion method [21] by measuring the zone of inhibition in mm. All the compounds were screened *in vitro* for their antimicrobial activities [22] against varieties of bacterial strains such Gram positive bacteria : *Staphylococcus aureus & Bacillus subtilis and* Gram negative bacteria : *Pseudomonas aeruginosa & E. coli* , fungi *Aspergillus niger* at 40 µg concentration. Standard drugs like Amoxicillin, Benzyl Penicillin,Ciprofloxacin, Erythromycin, Griseofulvin were used for comparison purpose (Table-1).

Experimental Section:

Melting points were taken in open capillary tubes are uncorrected. IR spectra (cm^{-1}) were recorded on SHIMADZU FTIR 8400 Spectrophotometer and ^{1}H-NMR spectra on Bruker spectrometer (200 MHz) using TMS as an internal standard, chemical shift in δ ppm.

Preparation of 1-Aryl-3-[6-methyl-2-(4-methylphenyl) imidazo[1,2-*a*]pyridin-3-yl]prop-2-ene-1-ones:

6-Methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde 2.5g (0.01mol) was dissolved in 25 ml methanol at room temperature. p-Methoxy acetophenone 1.40g (0.01mol) and 0.2 ml 40% sodium hydroxide solution was added. Stirred the content at room temperature for 24 hrs then filtered it and washed with chilled methanol. Yield 76 %, m. p. 200 ^oC, Elemental Analysis Calcd for $C_{25}H_{22}N_2O_2$,Requires : C-78.51%, H-5.80%, N-7.32%, Found : C-78.40%, H-5.72%, O-7.35%.

1-Aryl-3-[6-methyl-2-(4-methylphenyl) imidazo[1,2-*a*]pyridin-3-yl]prop-2-ene-1-ones:

IR(KBr) : ν 2966(Alkane,-CH-str.asym.), 2876(Alkane,-CH-str.sym.),1453 (Alkane,-CH-def.asym.), 1352(Alkane, C-H o.o.p. def.asym.) ,3061(Aromatic,C-H-str), 1503(Aromatic, C=C, str.),1610(Imidazo[1,2-a],C=N str.), 1110 (Pyridine, C-N) 1682(α,β-unsatd. ketone, C=O str.) , 1536 (Vinyl, C=C str.) cm^{-1}; ^{1}H-NMR ($CDCl_3$) : δ 2.41 & 2.43 (s,6H, Ar-CH_3), 3.85, (s,3H,Ar-OCH_3) , 7.40 & 7.48 (d,2H,-CH=CH-, J=15.6 Hz), 6.91-8.25(m,14H, Ar-H) , Mass m/z 382 , M.F.: $C25H22O_2N2$.

Preparation of 3-(3-Aryl-1-phenyl-4,5-dihydro-1*H*-pyrazol-5-yl)-6-methyl-2-(4-methylphenyl) imidazo[1,2-*a*]pyridines :

A mixture of 1-(2,4-Dichlorophenyl)-3-[6-methyl-2-(4-methylphenyl) imidazo[1,2-*a*] pyridin-3-yl]prop-2-ene-1-one 4.21gm (0.01 mol), phenyl hydrazine 1.18gm (0.01 mol) and basic catalyst piperidine in 25ml methanol was refluxed for 28hrs.Rreaction mass was poured into chilled water. Product was filtered and dried. it was recrystallized from ethanol. Yield 54 %, m.p.146 ^oC, Elemental Analysis Calculated for C30H24Cl2N4 Requires : C-70.45%, H-4.73%, N-10.95%, Found : C-70.34%, H-

4.75%, N-10.93%. Similarly other 3-(3-Aryl-1-phenyl-4,5-dihydro-1H-pyrazol-5-yl)-6-methyl-2-

(4-methylphenyl)imidazo [1,2-a]pyridines were prepared. The physical data are recorded in table no.1

3-(3-Aryl-1-phenyl-4,5-dihydro-1*H*-pyrazol-5-yl)-6-methyl-2-(4-methylphenyl)imidazo [1,2-*a*]pyridines :

IR(KBr) : ν 2943(Alkane, C-H str.(asym.)), 2843(Alkane, C-H str.(sym.)), 1433(Alkane, C-H def.(asym.)), 1388(Alkane, C-H def.(sym.)), 704(C-Cl str.); 1596 (Imidazo, C=N str.) , 1124(pyridine, C-N str.), 3028(Aromatic,C-H str.), 1500(Aromatic,C=C str.), 1062 & 817(Aromatic, C-H i.p.(def.)), cm^{-1}; ^{1}H-NMR ($CDCl_3$) : δ 2.24 & 2.42 (s,6H, Ar-CH_3), 3.63 & 4.09 (d, 2H,py-H, J=10.4 Hz) , 5.90-5.96 (t,1H,pyr-Ar-H), 6.77-7.86 (m,21H, Ar-H) .Mass m/z 511 . M.F.: C30H24Cl2N4 .

Results and Discussion:

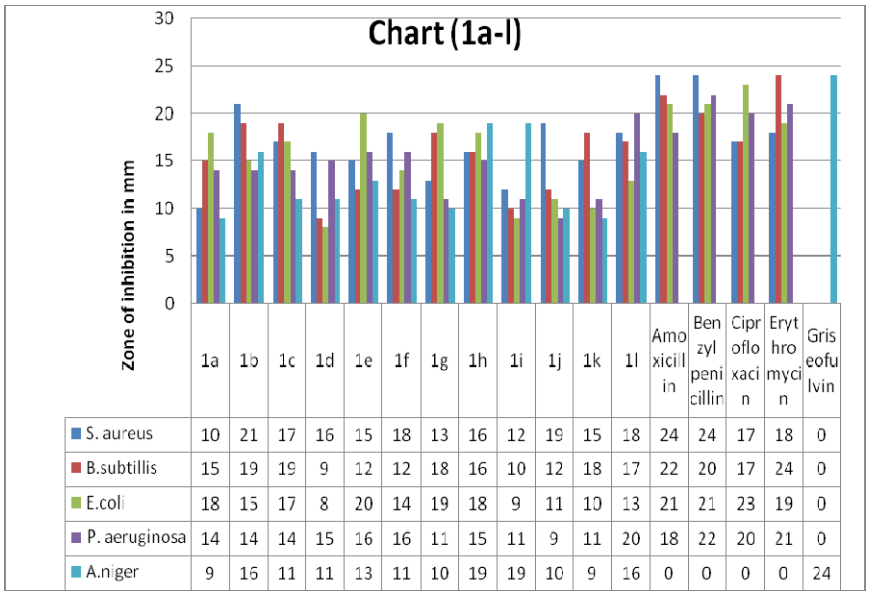
The synthesis of 1-Aryl-3-[6-methyl-2-(4-methylphenyl) imidazo [1,2-*a*] pyridin-3-yl]prop-2-ene-1-ones (1a-l) and 3-(3-Aryl-1-phenyl-4,5-dihydro-1*H*-pyrazol-5-yl)-6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridines(2a-l) was carried out in two steps, first by the condensation of 6-Methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde with different aromatic acetophenone in presence base catalyst to give chalcone derivatives (1a-l), which in next step were refluxed with phenyl hydrazine and glacial acetic acid to yield Aza-indolizine derivatives (2a-l). (scheme-1).

The formulas of the selected compounds were confirmed by the elemental analysis and their structures were determined by IR ,^{1} H-NMR , and mass spectral data.

Table-1

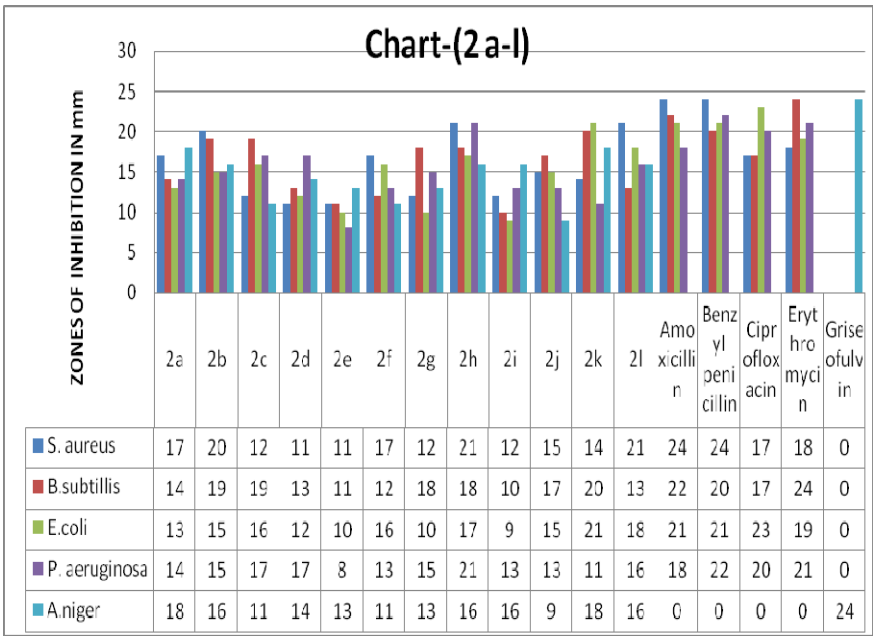
Characterization data of the compounds (1a-l) and (2a-l)

compd no.	R	Molecular formula	Mole. Wt.	M.P. (^{0}C)	Nitrogen %	
					Calcd.	Found
1a	-C_6H_5	C24H20N2O	352	178	7.75	7.71
1b	4-Cl-C6H4-	C24H19ClN2O	386.5	172	7.24	7.28
1c	2,4-(Cl)2-C6H3-	C24H18Cl2N2O	421	205	6.65	6.54
1d	4-NO2-C6H4-	C24H19N3O3	397	208	10.57	10.55
1e	4-OCH3-C6H4-	C25H22N2O2	382	200	7.32	7.29
1f	4-CH3-C6H4-	C25H22N2O	366	196	7.65	7.60
1g	4-OH-3-OCH3-C6H3-	C25H22N2O3	398	148	7.03	7.08
1h	4-Br-C6H4-	C24H19BrN2O	431	175	6.49	6.42
1i	2-OH-C6H4-	C24H20N2O2	368	135	7.60	7.68
1j	4-OH-C6H4-	C24H20N2O2	368	145	7.60	7.58
1k	4-NH2-C6H4-	C24H21N3O	367	180	11.44	11.42
1l	2-C4H3S-	C24H18N2OS	358	248	7.82	7.78
2a	-C_6H_5	C30H26N4	442	121	12.66	12.64
2b	4-Cl-C6H4-	C30H25ClN4	476.6	151	11.75	11.73
2c	2,4-(Cl)2-C6H3-	C30H24Cl2N4	458	220	12.22	12.30
2d	4-NO2-C6H4-	C30H25N5O2	487	225	14.37	14.30
2e	4-OCH3-C6H4-	C31H28N4O	472	146	11.86	11.79
2f	4-CH3-C6H4-	C31H28N4	456	dec.115	12.28	12.32
2g	4-OH-3-OCH3-C6H3-	C31H28N4O2	488	132	11.47	11.44
2h	4-Br-C6H4-	C30H25BrN4	521	dec.150	10.74	10.70
2i	2-OH-C6H4-	C30H26N4O	458	90	12.22	12.20
2j	4-OH-C6H4-	C30H26N4O	458	145	12.22	12.18
2k	4-NH2-C6H4-	C30H27N5	457	210	15.31	15.27
2l	2-C4H3S-	C28H24N4S	448	140	12.50	12.41



	1a	1b	1c	1d	1e	1f	1g	1h	1i	1j	1k	1l	Amoxicillin	Benzyl penicillin	Ciprofloxacin	Erythromycin	Griseofulvin
S. aureus	10	21	17	16	15	18	13	16	12	19	15	18	24	24	17	18	0
B.subtillis	15	19	19	9	12	12	18	16	10	12	18	17	22	20	17	24	0
E.coli	18	15	17	8	20	14	19	18	9	11	10	13	21	21	23	19	0
P. aeruginosa	14	14	14	15	16	16	11	15	11	9	11	20	18	22	20	21	0
A.niger	9	16	11	11	13	11	10	19	19	10	9	16	0	0	0	0	24

Figure.1: Antimicobial activity of (1a-l)



	2a	2b	2c	2d	2e	2f	2g	2h	2i	2j	2k	2l	Amoxicillin	Benzyl penicillin	Ciprofloxacin	Erythromycin	Griseofulvin
S. aureus	17	20	12	11	11	17	12	21	12	15	14	21	24	24	17	18	0
B.subtillis	14	19	19	13	11	12	18	18	10	17	20	13	22	20	17	24	0
E.coli	13	15	16	12	10	16	10	17	9	15	21	18	21	21	23	19	0
P. aeruginosa	14	15	17	17	8	13	15	21	13	13	11	16	18	22	20	21	0
A.niger	18	16	11	14	13	11	13	16	16	9	18	16	0	0	0	0	24

Figure.2: Antimicobial activity of (2a-l)

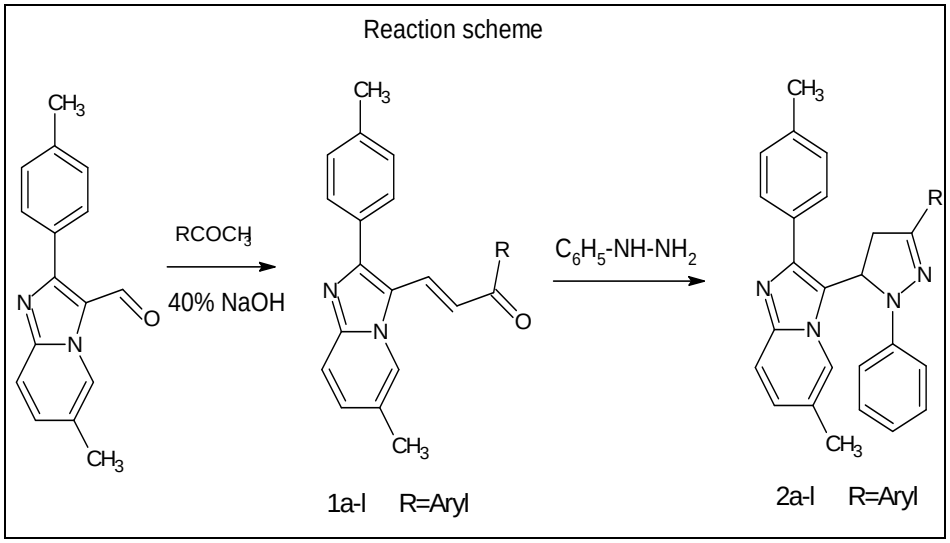
ANTIBACTERIAL ACTIVITY

It has been observed from the microbiological data that all compounds (1a-l) and (2a-l) were found to be mild to moderately active against Gram positive and Gram negative bacterial strains. How ever the maximum activity was observed in compounds (**1b**), (**1j**), (**2h**), (**2k**) against *S.aureus*. The significant activity was observed in compounds (**1b**), (**1c**), (**2b**), (**2c**) against *B.subtilis*. However, the compounds (**1e**), (**1g**), (**2k**), (**2l**), were shown significant activity against *E. coli*. The compounds (1e), (**1f**), (**2d**), and (**2h**) were comparatively more effective against *P.aeruginosa*. The remaining Chalcone and Pyrazoline derivatives possess moderate to mild activity against all four bacterial species.

ANTIFUNGAL ACTIVITY

The antifungal data revealed that compounds were least toxic to the fungal strain. However mild activity was shown by the compounds (**1h**), (**1i**), (**2a**), (**2k**), against *A.niger***.** All other compounds exhibit mild to moderate antifungal activity against *A.niger*. The antibacterial activity was compared with standard drug viz. Amoxicillin, Benzyl penicillin, Ciprofloxacin, Erythromycin and antifungal activity was compared with standard drug viz. Griseofulvin.

Scheme-1



Reagents and conditions: i: Methanol, basic media,stirred,24-hours . ii) Piperidine ,reflux 28-hours.

CONCLUSION

The present study leads to a convenient synthetic method for the synthesis of new compounds. These were characterized by IR, NMR, Mass spectrometry study and elemental analyses. The substrates were obtained in good yield in basic conditions. Which show significant antibacterial and antifungal activity. Further investigation with appropriate structural modification of the above compounds may result in therapeutically useful products.

ACKNOWLEDGEMENT

The authors are thankful to authorities of Kamani Science College, Amreli for providing research facilities and we are also thankful to Department of Chemistry Saurashtra University Rajkot for I.R., elemental analysis. Authors are also thankful to CSMCRI, Bhavnagar for providing ^{1}H NMR spectral analysis and Mass spectral analysis of the compounds.

REFERENCES

[1] S. V. Kostanecki and J. Tambor; Chem. Ber., 32, 1921 (1899).
[2] Inamori Y. et al.; Chem. Pharm. Bull., 39(6), 1604 (1991); Chem. Abstr., 115, 105547c (1991).
[3] Nelson George L.; U.S. US 4,338,499 (Cl. 568-343; CO7C49/597), 06 Jul (1982), Appl. 250, 366, 02 Apr (1981); 7 pp.;
[4] V. R. Dangar and V. R. Shah ; The Inter. Journal. Of Sci. & Tech. , P-6,vol-2 Issue-1,Jan.-2014.
[5] Fahmy A. M. ,Hussan M., Khalt A. A., Ahmedi R. A.; Rev. Roum-Chim., 33(7), 755-61 (1988); Chem. Abstr., 111, 77898 (1989).
[6] V. R. Dangar and V. R. Shah ; Sci.Revs.Chem.Commun:4(1) 2014 P-31-37.
[7] Marmo E. , Caputi A. P. and Cataldi S.; Farmaco Ed. Prat., 28(3), 132 (1973); Chem. Abstr., 79, 13501v (1973).
[8] Zalgislaw K., and Seffan V.; Acta. Pol. Pharm., 36(6), 645 (1979); Chem. Abstr., 93, 204525e (1980).
[9] Fathalla O. A., Awad S. M., Mohamed M. S.; Arch. Pharm. Res., 28(11), 1205-1212 (2005).
[10] Wellinga K.,Eussen H. H., Jacobus; Eur. Pat. Ep. 269 141 (Cl C07D 231/06) (1988); Chem. Abstr., 110, 8204 (1989).
[11] Delay Francois (Fermenich S. A.) Patent Schrift (Switz); Chem. Abstr., 117, 90276f (1992).
[12] Bowden K., Dal P. A.and Shah C. K.; J. Chem. Res. Synop., 12, 2801 (1990); Chem. Abstr., 114, 160570m (1991).
[13] Kalluraya Balakrishna, Chimabalkar R., Rai G., Gururaja R., Shenoy S.; J. Indian Coun. Chemi., 18(2), 39-43 (2001); Chem. Abstr., 138, 238061 (2003).
[14] Roman B.; Pharmazie, 45, 214 (1990).
[15] Ruhoglu O., Ozdemir Z., Bilgin A. A.; Arzneimittelforschung, 55(8), 431-436 (2005).
[16] Garg H. G. and Singh P. P. ; J. Chem. Soc., 2, 1141 (1936).
[17] Hsieh, Hasin, Kaw, Lee-Tai-Hua Wang, Jih-Pyang. Wang. et al.;Chem. Abstr., 128, 225684n (1998).
[18] P. M. S. Chauhan and S. K. Srivastava, Curr. Med. Chem., 8, 1535 (2001).
[19] M. Balasubramanian and J. G. Keay, in Comprehensive Heterocyclic Chemistry II A. R. Katritzky and C. W. Rees (Eds.) Pergamon Press, New York, Vol. 5 (1996) p. 245.
[20] F. S. Yates, in Comprehensive Heterocyclic Chemistry; A. J. Boulton and A. McKillop, (Eds.), Pergamon Press, New York, Vol. 2, Chapter 2.09 (1984).
[21] Barry A.L.; The antimicrobial susceptibility test, principle and practices, edited by , Illus les and FebigerPhiladelphia pa, USA (1976),180;Biol Abstr, 64, 25183 (1976).
[22] Panda J. Srinivas S. V., Rao M. E.; J. Indian Chem. Soc., 79(9), 770-1 (2002); Chem. Abstr., 138, 153499n (2003).