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SYNTHESIS, SPECTRAL CHARACTERIZATION AND BIOLOGICAL SCREENING OF SOME NEWLY SYNTHESIZED IMIDAZOLES

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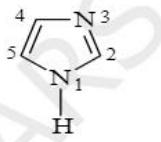
ABSTRACT

Di & tri substituted imidazoles were prepared by condensing phenylglyoxal with different aryl aldehydes in presence of ammonium acetate and glacial acetic acid. All the di and tri substituted imidazoles were characterized by spectral analysis i.e. ^{1}HNMR and Mass spectral data. All the synthetic compounds were screened for there anti-inflammatory and anti bacterial activity.

Keywords: Imidazole, Phenyl glyoxal, anti-inflammatory and anti microbial.

1. INTRODUCTION

Imidazole is a planar five-member ring system with three carbon and two nitrogen atoms in 1st and 3rd positions. The systematic name for the compound is 1, 3-diazole, one of the annular nitrogen bears a hydrogen atom and can be regarded as pyrrole type nitrogen.



Imidazole was prepared in 1858 from glyoxal and ammonia since then several approaches are available for synthesis of imidazole.

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Reaction between a α-halo ketone and amidine, dehydrogenation of imidazolones in the presence of sulphur and Radiszewski synthesis are some of the commonly used method for preparation of imidazole. Literature revels that Imidazoles have been identified as anthelmintic[1-2], antifilarial agent, anti-inflammatory[3] (specific COX-2 inhibitor[4]), antiviral[5], anti-cancer[6], anti-bacterial[7], anti-fungal[8], anti tubercular[9], lipo-oxygenase inhibitor[10], anti-depressant[11] and now they are also known for their anti ulcer activity.

Other then there pharmacological action they also function as dyestuffs catalysts and polymerizing agents. 2-nitro imidazole (azomycin) and 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole (metronidazole) are anti

bacterial agent with particular applications as trichomonacide. Along with metronidazole other nitroimidazoles (misonidazole, metrazole and clotrimazole) are important anti cancer drugs. Two imidazolines priscol and privine are valuable vasodialating and vasoconstricting drugs. With reference to these imidazoles were prepared by reacting phenyl glyoxal with different aryl aldehydes. The starting material phenyl glyoxal were prepared by refluxing via stirring dioxane, selenium dioxide and acetophenone.

Melting points were determined in capillaries in liquid paraffin and are uncorrected. Purity of the compounds was checked with TLC. ^{1}H NMR spectra were recorded on Bruker DRX-300 (300 MHz FT NMR) spectrometer using TMS as an internal standard (chemical shift value are expressed in ppm). Mass spectra were recorded on JEOL5x102/DA-6000 Mass spectrometer.

2. Synthesis of Phenylglyoxal (I)

Compound **1** was prepared by stirring dioxane (300 ml), pure selenium dioxide (0.5mol.) and water (10 ml) in a 500 ml round bottom flask, heat the mixture to 50-55°C and stir until the solid has dissolved then add acetophenone (0.5 mol.) in one lot. Reflux the mixture with stirring for 4 hrs after about 2 hrs solution become clear and little further precipitation of selenium is observed. Decant the hot solution from the precipitate and remove the dioxane and water by distillation. The yield of pure phenylglyoxal (yellow liquid) is 48 gm (72 %), Rf value - 0.77, m.p. - 54°C.

Step-II

Synthesis of 2, 4- Disubstituted imidazoles (IIa-e) from (I)

Compound **I** (0.025 mol.) was refluxed with different arylaldehydes (0.025 mol.) in glacial acetic acid (50 ml) with ammonium acetate (10 gm) in round bottom flask for about 5 hrs. After refluxing the mixture was cooled to room temperature and was poured in to 200 ml cold water. The precipitate was filtered and dried. The filtrate obtained was made alkaline to litmus paper by adding excess of ammonia. TLC checked purity of the compound.

Step-III

Synthesis of 1, 2, 4- Trisubstituted imidazoles (IIIa-e) from (IIa-e)

Compound **II (a-e)** (0.01 mol.) was suspended in tetrahydrofuran (20 ml) and was refluxed with excess of chlorobenzene (2 ml) in the presence of 2 to 3 drops of triethylamine for 8 hrs. Completion of the reaction was

determined by TLC. After refluxing, acetone was added to the reaction mixture and was kept in room temperature for over night. Later the precipitate formed was filtered and recrystallised with ethanol. Physical characteristics of the synthesized compounds were recorded in table-1.

2.1Anti-inflammatory activity:

All the synthesized derivatives of di & tri substituted imidazoles were screened for there anti-inflammatory activity by carrageenan induced rat paw edema method[12] in albino rats at a dose of 10 mg/kg body weight the test compound were made into homogeneous suspension with distilled water and 1% CMC solution and were administered orally. The percentage inhibition was noted at the end of first and third hour of administration of carrageenan. Carrageenan induced paw edema method of the test compound was compared with known standard drug (indomethacin).

2.2 Anti microbial activity:

All the synthesized compounds were screened *in vitro* for their anti bacterial and anti fungal activity at the concentration of 100 and 200 µgm/ ml against gram +ve (*bacillus subtillis*, MTCC-441), gram –ve (*E. coli*, MTCC-40) organism in anti bacterial and *Candida albicans* (MTCC-183),*Aspergillus flaveous* (MTCC-871) organism in anti fungal activity by cup plate method[13] using DMF as solvent. After 24 and 48 hrs of incubation at 37°C in anti bacterial and anti fungal activity respectively, the zone of inhibition was measured in mm. Ofloxacin and voriconazole were taken as standard drug in anti bacterial and anti fungal activity in a dose of 20 µgm/ ml concentration.

3. Result and Discussion

Physical properties and spectral data of the synthesized compounds were recorded in table-1 and table-2 respectively. Results of anti-inflammatory activity were recorded in table-3. Among the synthesized compounds, compound VIII, IX and XI show significant anti-inflammatory activity. These compounds show 42.18 %, 44.00 % and 38.28 % inhibition respectively. Result of anti microbial activity was recorded in table-4. Compounds III, IV. V, IX, X, XI show good activity against ***E. coli,*** compound V show good activity against ***B. subtilis,*** compound VIII show good activity against ***C. albicans*** and compound II, III, IX, X and XI show good activity against ***A. flaveous*** .

Table-1 Physical characteristics of the synthesized compounds.

Code	Compound name	R	R′	R″	% Yield	Rf value	M.P. (˚C)
II	2,4- Dipheylimidazole	H	H	H	69	0.79	168
III	1,2,4- Triphenyl imidazole	$-C_6H_5$	H	H	42	0.73	180
IV	2-(2- Chlorophenyl) –4-phenylimidazole	H	H	H	62	0.68	183
V	2-(2- Chlorophenyl) –1,4-diphenyl imidazole	$-C_6H_5$	2-Cl	H	54	0.78	207
VI	2-(3- Chloro phenyl) –4- phenyl Imidazole	H	3-Cl	H	32	0.67	193
VII	2-(3- Chlorophenyl) –1,4- diphenyl imidazole	$-C_6H_5$	3-Cl	H	36	0.78	215
VIII	2-(4- Chloro phenyl) –4-phenylimidazole	H	4- Cl	H	58	0.63	170
IX	2-(4- Chlorophenyl) –1,4- diphenyl imidazole	$-C_6H_5$	4-Cl	H	60	0.54	189
X	2-(4- Fluoro phenyl) –4- phenyl imidazole	H	4-F	H	65	0.69	197
XI	2- (4-Fluorophenyl) –1,4- diphenyl imidazole	$-C_6H_5$	4-F	H	55	0.81	221

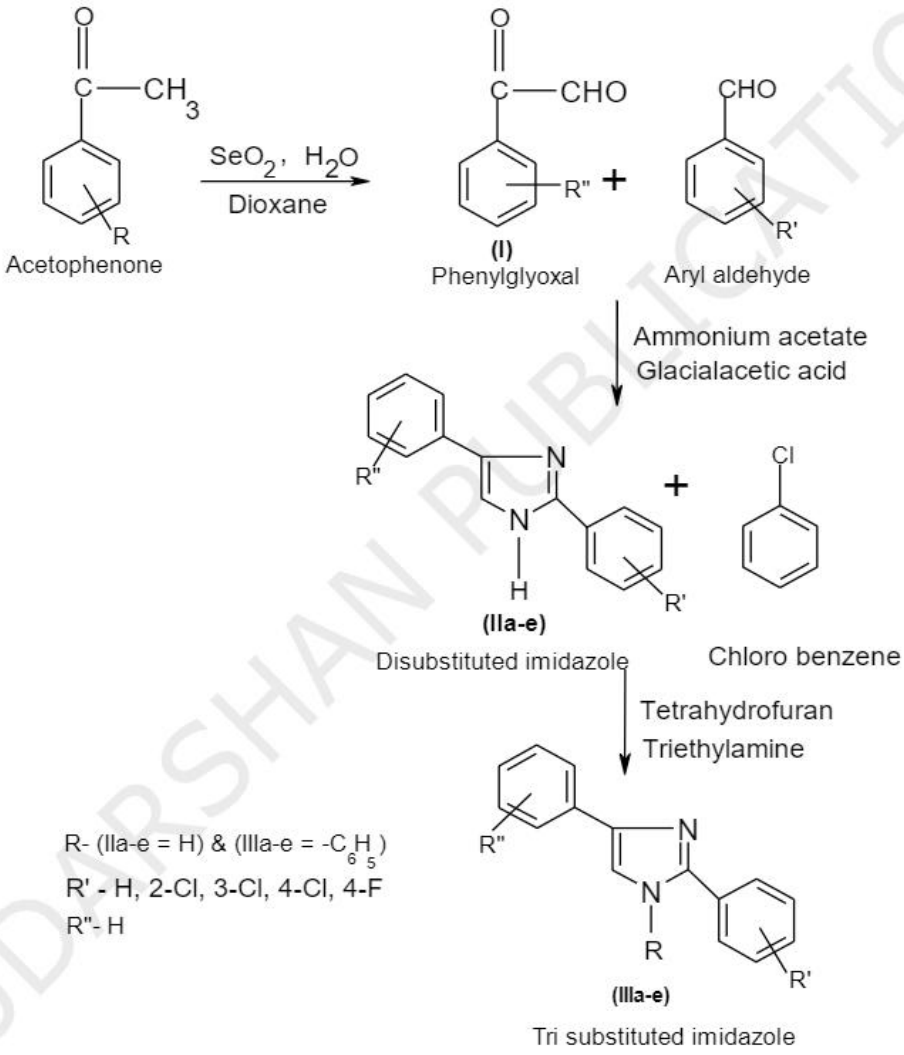
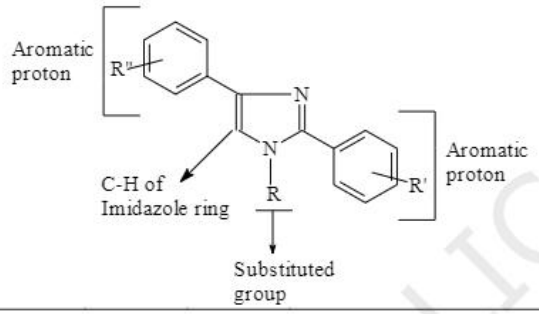


Table-2 Spectral data of synthesized compounds.



Code	Compound name	R	R′	R″	NMR spectral data
I	2,4- Dipheylimidazole	H	H	H	7.35 (d, 2H,H3′, 5′), 7.42 (m, 3H,H-4′, 2″, 6″), 7.51(m, 1H,H-4″), 7.67 (s, 1H, 5 imidazole), H-7.93 (d, 2H,H-3″, 5″), 10.03 (s, 1H,N-H)
III	1,2,4- Triphenyl imidazole	$-C_6H_5$	H	H	7.24-7.81 (m, 15H, H- aromatic proton), 7.94 (s, 1H, H-5)
IV	2-(2- Chlorophenyl) –4-phenylimidazole	H	H	H	7.36-7.91 (m, 9H,H-aromatic proton), 7.62 (s, 1H, H-5), 10.31 (s, 1H, N-H)
V	2-(2- Chlorophenyl) –1,4-diphenyl imidazole	$-C_6H_5$	2-Cl	H	7.24-7.91 (m, 14H, H- aromatic proton), 8.32(s, 1H, H-5)
VI	2-(3- Chloro phenyl) –4- phenyl Imidazole	H	3-Cl	H	7.33-7.52 (m, H5, H-4′, 5′, 2″, 4″, 6″), 7.61 (s, 1H,H-5), 7.95-8.03 (m, 4H,H-2′, 6′, 3″, 5″), 10.36 (s, 1H,N-H)
VII	2-(3- Chlorophenyl) –1,4- diphenyl imidazole	$-C_6H_5$	3-Cl	H	7.24-7.49 (m, aromatic protons), 7.93 (s, 1H,H-5)
VIII	2-(4- Chloro phenyl) –4- phenylimidazole	H	4- Cl	H	7.10 (s, 1H,H-5 imidazole), 7.41(m, 3H,H-3″, 4″, 5″),7.52 (d, 2H, H-2″, 6″), 7.58(d, 2H,H-2′, 6′), 8.04(d, 2H,H-3′, 5′), 8.21(s, 1H,N-H)
IX	2-(4- Chlorophenyl) –1,4- diphenyl imidazole	$-C_6H_5$	4-Cl	H	7.21-7.56(m, aromatic protons), 8.01 (s, 1H,H-5)
X	2-(4- Fluoro phenyl) –4- phenyl imidazole	H	4-F	H	7.18 (d, 2H,H-3′, 5′), 7.43-7.51 (m, 3H,H-2″, 4″, 6″), 7.64 (s, 1H, H-5), 7.95 (d, 2H,H-3″, 5″), 8.16 (d, 2H,H-2′, 6′),10.25 (s, 1H,N-H)
XI	2- (4-Fluorophenyl) –1,4- diphenyl imidazole	$-C_6H_5$	4-F	H	7.27-7.61 (m, aromatic protons), 7.97 (s, 1H,H-5)

Mass fragmentation pattern of synthesized compound II

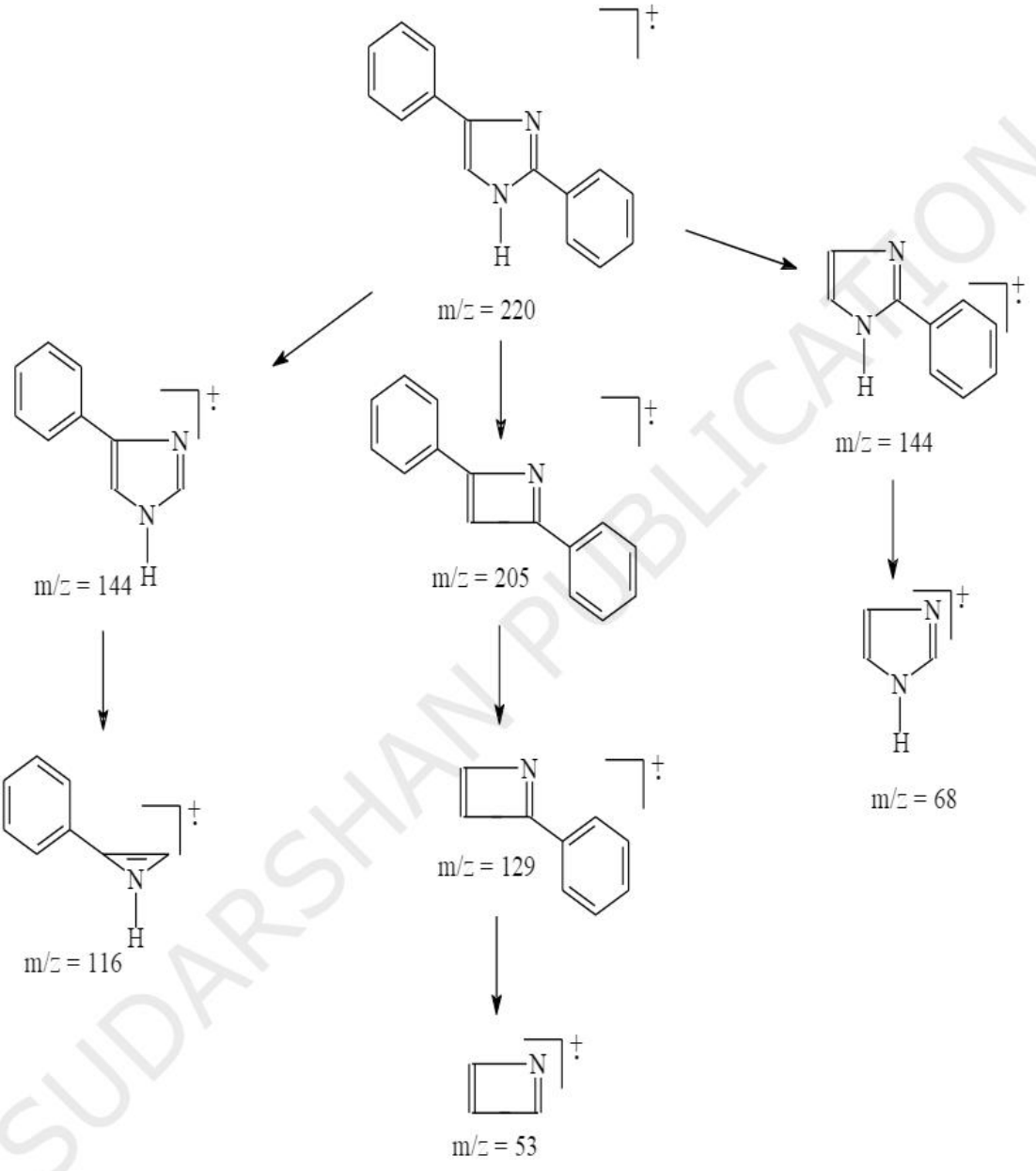


Table-3 Anti-inflammatory activity of synthesized compounds.

Compound Code	% Inhibition ± SEM (After 3 hrs)
Indomethacin	68.48 ± 1.18**
Control	1.28±0.18
II	29.68 ± 0.75**
III	30.46 ± 1.02**
IV	25.26 ± 1.45**
V	18.13±1.72
VI	23.62±1.39**
VII	14.21±1.53
VIII	42.18 ± 2.37**
IX	44.00 ± 1.11**
X	32.0 ± 0.83**
XI	38.28 ± 0.92**

#Relative to standard and data were analyzed by ANOVA followed by dunnett's multiple comparison test for n=6; **P value < 0.01.

Table-4 Anti-microbial activity of synthesized imidazole compounds.

Compounds	Conc. (µg\ml)	Diameter of Zone of Inhibition (mm)			
		E. coli	*B. subtilis*	*C. albicans*	*A. flaveous*
Voriconazole	20	--	--	27	31
Ofloxacin	20	27	29	--	--
DMF	--	12	12	12	12
II	100	13	14	12	16
	200	17	17	16	20
III	100	12	12	13	15
	200	18	16	15	21
IV	100	13	12	12	12
	200	19	17	17	18
V	100	12	12	12	12
	200	19	25	17	17
VI	100	10	11	12	11
	200	16	15	15	16
VII	100	10	10	12	11
	200	16	14	15	15
VIII	100	14	14	13	19
	200	17	16	22	13
IX	100	12	12	12	18
	200	18	15	16	22
X	100	13	12	14	24
	200	18	16	16	28
XI	100	12	10	12	24
	200	19	15	17	26

Bibliography:

1. Kapoor, V.K.; Dubey, S.; Mahindroo, N.; Indian Journal of chemistry, Vol.39B, January2000, pp. 27-30.
2. Takakura, Y.; Takagi, A.; Hashida, M.; Sezaki, H.; int. J. Pharm, 37, 1987, 135.
3. Breslin, H.J.; Cai, C.; Miskowski,T.A.; Coutinho, S.V.; Zhang, Sui-Po,; Pamela, H.; Bioorganic and Medicinal Chemistry Letters 16 (2006) 2505-2508.
4. Yadav, M.R.; Puntambekar, D.S.; Sarathy, K.P.; Vengurlekar, S.; Giridhar, R.; Indian Journal of Chemistry., Vol. 45B, Febrary2005, pp. 475-482.
5. Cheng, J.; Xie, J.; Luo, X.; Bioorganic and Med. Chem. Lett. 15(2), 2005, 267.
6. Nair, S.C.; Pannikar, B.; Pannikar, K.R., Cancer Letters, 1991, 60, pp. 253-258.

7. Khabnadideh, S.; rezaei, Z.; Khalafi-Nezhad, A.; Bahrinajafi, R.; Mohamadi, R.; Farrokhroz.; Bioorganic and Med. Chem. Lett. 13 (2003) 2863-2865.
8. Matysiak, J.; Niewiadomy,A.; Macik-Niewiadomy, G.; Krajewska-Kulak, E.; IL Farmaco 58 (2003) 455-461.
9. Narayanan, S.; Vangapandu, S.; Jain, R.; Bioorg. Med. Chem. Lett. 11 (2001) 1133-1136.
10. Ahmed, S.; Smith, L.H.; Nicholls, P.J.; Whomsley, R.; Cariuk, P.; Drug des. Discov. 1995. 13: 27-41.
11. Volke, V.; Soosaar, A.; Koks, S.; Bourin, M.; Mannisto, P.T.; Vasar, E.; Psychopharmacology (Berl) 1997; 131: 399-405.
12. Winter, C.A., Risley, E.A. and Nuss, G.W., Proc. Soc. Exp. Biol. Med. 1962,111, 544-547.
13. Murray, P.R., Baron, E.J., Pfallar,M. A., Tenover, F.C. and Yolken, R.H., Mannual of clinical microbiology, Am. Soc. Microbilo. Washington,DC,(1995).

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