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Synthesis, characterization and screening of anti convulsant activity of novel tetra substituted imidazole derivatives

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ABSTRACT

In this study a new tetra substituted imidazole derivatives has been synthesized from the condensation of Benzil, substituted aldehyde, substituted aromatic amine and ammonium acetate in presence of glacial acetic acid at 120-140 ^{o}C. The newly synthesized derivatives has been characterized by various physicochemical techniques such as melting point, TLC, FTIR ^{1}HNMR, and elemental analysis. The synthesized compounds are screened for their anti convulsant activity by PTZ induced convulsion and MES method. The standards used for the method are diazepam and phenytoin respectively.

Keywords: Tetra substituted imidazole, PTZ & MES method, Anti convulsant activity.

INTRODUCTION

Imidazole is a basic nucleus in various drugs. Substitution on the nucleus can produce or alter the pharmacology of the drugs. Rutuja sonawane, Chandrakant Magdum, (2015) [3] done a study on synthesis Anti-convulsant activity and screening of some novel 1, 5 disubstituted-4-chloro 1H imidazole derivatives. The synthesized derivatives were evaluated for anti convulsant activity by PTZ and MES method. This work indicates that halo and alkoxy substituted phenyl ring of imidazole moiety have given impetus to the present investigation and showed favored MES activity as compared to hydroxyl or unsubstituted ring G.Mariappan et al (2013) [2] design synthesis and screened neuro pharmacological activity of dihydro imidazole derivatives. All the compounds were screened for their neuropharmacological activity. Rahul Mishra et al (2012) [4] done a study on synthesis and anti convulsant activity of some novel 2-methyl imidazole derivatives. A novel series of 10 N aryl 2-2 methyl 1H imidazole acteamide with corresponding ωchloro acetanilide in dimethyl formamide and potassium carbonate. The present study was undertaken in an attempt to synthesize some new tetra substituted derivatives of imidazoles by the condensation reaction of benzil, substituted aldehyde, substituted aromatic amine

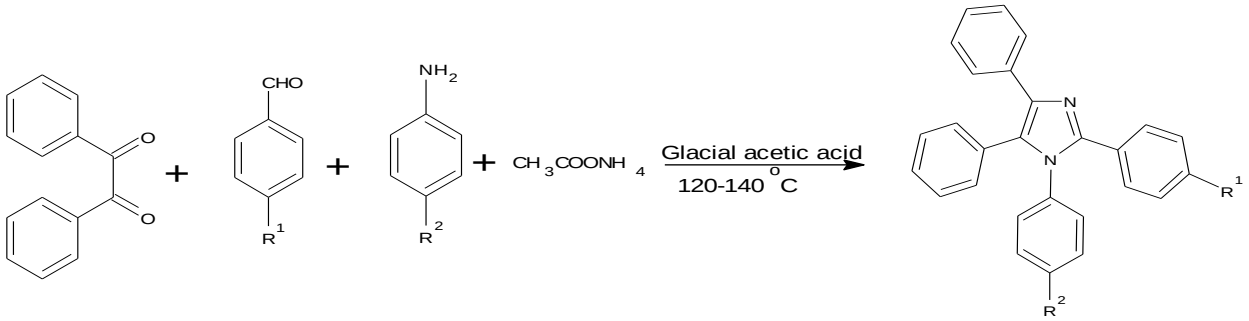
and ammonium acetate in presence of glacial acetic acid at 120-140 ºC

MATERIALS AND METHOD

All the reagents used are commercially available and they are used without further purification. The synthesized compounds were mixed with previously dried KBr and made a disc by pressed pellet technique. Then it is placed in IR spectrophotometer. The peaks obtained in the graph indicate different groups present in the synthesized compounds. ^{1}HNMR Spectroscopy the synthesized compounds are dissolved in $CDCl_3$. This NMR spectrum reveals different type of protons present in a compound, standard used for NMR spectroscopy is TMS. Elemental analysis gives the percentage of carbon, hydrogen, nitrogen and Sulphur present in compound. There will be a calculated percentage and experimental percentage value. The synthesized compounds are screened for their anti convulsant activity by PTZ and MES method in albino rats.

Synthesis of tetra substituted imidazole derivatives

Prepared by condensation of an α dicarbonyl compound, with aromatic substituted amine and an aromatic substituted aldehyde in presence of ammonium acetate and glacial acetic acid at 120-140^{o}C for 3hrs. The completion of reaction was checked out by TLC. The reaction mixture was cooled and poured into ice cold water and neutralized with ammonium hydroxide. The precipitate was filtered washed with water and purified by recrystallizing with ethanol.



Scheme for Synthesis of 1,2,4,5 tetrasubstituted

SCREENING OF ANTI-CONVULSANT ACTIVITY

PTZ induced convulsion method

Rats were divided into 3 groups, each contains 6 animals. Control group is treated with 0.5% tween 80. Standard group is treated with Diazepam (10mg/kg) i.p and test group receive test drug (60mg/kg) orally. After 60mts, administered PTZ (50mg/kg) i.p and note down the onset of convulsion.

Maximal electro shock method

Rats were divided into 3 groups. Each group contains 6 animals. Group 1 considered as control and is treated with alcohol water mixture (2:1) 10ml/kg p.o. The second group is standard treated with 25mg/kg i.p. Third group; test is treated with test compound orally 60mg/kg. After 1 hr an electric current of 150mA for 0.2sec, was given through ear electrodes to induce convulsion. Note down the different phases of convulsion and reduction or abolition in the duration of hind limb extensor phase considered as measure of anti convulsant activity.

RESULT AND DISCUSSION

TABLE 1 Physical data of the title compounds

COMPOUD	R1	R2	Mol. Formula (Mol. Wt.)	M.P(ºC)	YIELD (%)	R_f
M1	4-OH C_6H_5	P-Bromo Aniline	467.356	161	52.28	0.19
M2	4-Cl C_6H_5	P-Bromo Aniline	485.802	150	60.90	0.23

M3	2-C_2H_5 C_6H_5	P-Bromo Aniline	495.409	142	80.00	0.70
M4	4-CH_3 C_6H_5	P-Bromo Aniline	465.383	148	76.75	0.28
M5	4-OCH_3 C_6H_5	P-Bromo Aniline	481.382	145	84.74	0.70
M6	4-OH C_6H_5	P-Fluro Aniline	406.450	225	85.00	0.21
M7	4-Cl C_6H_5	P-Fluro Aniline	424.896	190	76.00	0.89
M8	2-C_2H_5 C_6H_5	P-Fluro Aniline	434.503	179	76.74	0.77
M9	4-CH_3 C_6H_5	P-Fluro Aniline	404.477	180	84.15	0.79
M10	4-OCH_3 C_6H_5	P-Fluro Aniline	420.477	189	73.8	0.57

SPECTRAL DATAS

Compound M1: 4-[1-(4-bromophenyl)-4,5-diphenyl-1*H*imidazol-2-yl]phenol, IR (cm^{-1}) 1258.5(Ar-OH), 3455.7(NH stretching), 1638.6(NH bending), 696.4(C-Br), 834.95(Para substitution.). ^{1}HNMR, 6.939 (OH), 7.262-8.081 (18Ar-H), CHN cal. % C 69.39, H 4.10, N 5.99. Found C 67.99, H 4.80, N 6.09.

Compound M2: 1-(4-bromophenyl)-2-(4-chlorophenyl)-4,5-diphenyl-1*H*-imidazole: IR (cm^{-1}) 1175.4(Ar-Cl), 3459.6(NH stretching), 1638.6(NH bending), 834.95(Para substitution.), 696.4(C-Br). ^{1}HNMR 7.083-7.541 (18Ar-H). CHN cal. % C 66.75, H 3.73, N 5.77. Found C 66,H 4.09, N 5.01.

Compound M3: 1-(4-bromophenyl)-2 (2-ethoxy), 4, 5-triphenyl-1*H*-imidazole. IR (cm^{-1}) 1179.4(aromatic ether group), 3467.5(NH stretching), 1638.6(NH bending), 696.4(C-Br). ^{1}HNMR 2.042-2.109 (5H, CH_2CH_3), 7.092-7.643 (18Ar-H). CHN cal. % C 70.31,H 4.68,N 5.65.Found C 63.44, H 4.06, N 5.87.

Compound M4: 1-(4-bromophenyl)-2(4 methyl), 4,5-triphenyl-1*H*-imidazole. IR (cm^{-1}) 2929.1(Ar-CH_3), 3455.7(NH stretching), 1634.6(NH bending), 696.4(C-Br). ^{1}HNMR 3.980-4.125 (3H, CH_3), 7.01-7.836(18Ar-H). CHN cal. % C 72.26, H 4.55, N 6.02. Found C 71.56, H 4.49, N 6.81.

Compound M5: 1-(4-bromophenyl)-2(4-methoxy),4,5-triphenyl-1*H*-imidazole. IR(cm^{-1}) 2842(OCH_3), 3459.6(NH stretching), 1642.5(NH bending), 700.35(C-Br). ^{1}HNMR 1.238-1.273(3H, CH_3), 7.089-7.983(18Ar-H). CHN cal. % C 69.86, H 4.40, N 5.82. Found C 70.09, H 4.95, N 5.02.

Compound M6: 4-[1-(4-fluorophenyl)-4,5-diphenyl-1*H*-imidazol-2-yl]phenol. IR(cm^{-1}) 1238.6(Ar-OH), 3061.3(NH stretching), 1610.32(NH Bending), 1457.7(C-F), 836.5(Para substitution). ^{1}HNMR 6.649(OH), 7.55-7.987(18Ar-H).). CHN cal. % C 79.79, H 4.71, N 6.89. Found C 78.57, H 4.77, N 6.84.

Compound M7: 2-(4-chlorophenyl)-1-(4-fluorophenyl)-4,5-diphenyl-1*H*-imidazole. IR (cm^{-1}) 1151.7(Ar-Cl), 3459.6(NH stretching), 1634.6(NH bending), 1440.6(C-F stretching), 850.79(Para substitution). ^{1}HNMR 6.942-7.582(18Ar-H). CHN cal. % C 76.32, H 4.27, N 6.59. Found C 74.99, H 3.08, N 5.82.

Compound M8: 1-(4-fluorophenyl)-2,(2-ethoxy)4,5-triphenyl-1*H*-imidazole. IR (cm^{-1}) 1187.3(aromatic ether group), 3455.7(NH stretching), 1642.5(NH bending), 1444.6(C-F stretching). ^{1}HNMR 3.970-4.028(5H, C_2H5) 7.010-7.585(18Ar-H). CHN cal. %C 80.16, H 5.34, N 6.45. Found C 81.97, H 5.92, N 7.21.

CompoundM9: 1-(4-fluorophenyl)-2(4methyl),4,5-triphenyl-1*H*-imidazole. IR(cm^{-1}) 3388.4(NHstretching), 1632.6(NHbending),1440.6(CFStretching).^{1}HNMR 2.0442.315(3H,OCH_3) 7.004-7.590(18Ar-H). CHN cal.% C 83.14,H 5.23, N 6.93. Found C 80.21,H 3.91, N 5.21.

Compound M10: 1-(4-bromophenyl)-2(4-methoxy),4,5-triphenyl-1*H*-imidazole. IR(cm^{-1}) 3443.8(NH stretching), 1642.51(NH bending), 1424.8(C-F stretching). ^{1}HNMR 2.119-3.782(3H, CH_3), 6.990-7.585(18Ar-H). CHN cal. % C 79.98, H 5.03, N 6.66. Found C 79.41,H 5.66, N 7.00.

ANTI CONVULSANT ACTIVITY

Table 2: Anti convulsant activity of M1-M10 by PTZ and MES method

Anti Convulsant Activity				
PTZ Induced Method			MES Method	
Compound	Group	Onset of convulsion (sec)	Group	Tonic extensor phase (sec)

Control	Vehicle	10.67±0.33	Control	49.33±0.33
Std	Std +PTZ	320.12±0.22	Std	10.83±0.30
M1	M1+PTZ	270.45±0.44	M1	20.17±0.30
M2	M2+PTZ	290.67±0.44	M2	12.67±0.33
M3	M3+PTZ	205.98±0.33	M3	39.00±0.33
M4	M4+PTZ	220.09±0.36	M4	35.33±0.47
M5	M5+PTZ	195.33±0.33	M5	34.17±0.47
M6	M6+PTZ	250.98±0.33	M6	34.83±0.30
M7	M7+PTZ	285.5±0.56	M7	12.50±0.22
M8	M8+PTZ	210.17±0.47	M8	36.83±0.30
M9	M9+PTZ	200.53±0.31	M9	35.17±0.30
M10	M10+PTZ	199.17±0.30	M10	35.50±0.22

The anti-convulsant activity of the novel tetra substituted imidazole derivatives against convulsion are tested by observing the onset of duration of convulsion in rat administered with the synthesized compound by PTZ induced convulsion method

The compounds M2 and M7 and shows significant activity with an onset of convulsion time of 290.67, 285.5 sec respectively

The anti-convulsant activity of the novel tetra substituted imidazole derivatives against convulsion are tested by observing the duration of Hind Limb Tonic Extensor Phase of rat administered with the synthesized compound by MES method.

Synthesized novel tetra substituted imidazole derivatives, M2 and M7 showed significant anti-convulsant activity when compared to standard drug phenytoin (20 mg/kg), whereas M3 and M8 did not show any significant activity. Compound M7 showed the maximum activity of 12.5 sec of HLTE Phase

CONCLUSION

Compounds M2 and M7 shows significant activity in both PTZ and MES induced convulsion. This may be due to the presence of halogens at the Para position. Other substituent at Para position does not produce significant activity. Halogens at Para position significantly decline the speeding of seizures.

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