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Synthesis of Some Novel Tetra Aryl Imidazoles Compounds: Evaluation of *In-Vitro* Cytotoxicity and Anthelmintic Activity

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ABSTRACT

The imidazole derivatives have potent therapeutic activity against cytotoxicity and parasites. The present study was planned to synthesize novel tetra aryl imidazoles compounds and evaluated for in vitro cytotoxicity and anthelmintic activity. Firstly, 2-amine-4-chloro pyridine was condensed with substituted benzaldehyde to give corresponding Schiff's base. These Schiff's bases further on treatment with ammonium acetic acid derivation and isatin yielded comparing novel tetra aryl imidazoles. The synthesized compounds were examined for in-vitro cytotoxicity and anthelmintic activity. The discoveries showed that all the synthesized novel substituted imidazoles have moderate to great anthelmintic action. They additionally had critical in-vitro cytotoxicity against HEp2 cell lines (Human larynx malignancy cell line) against standard utilizing 5-fluorouracil. The compounds 1b, 2b, 4b, 6b, and 8b had higher anthelmintic action contrasted with standard mebendazole. The synthesized compounds 1b, 2b and 8b had noteworthy in-vitro cytotoxicity against HEp2 cell lines.

Keywords: Tetra acyl imidazoles, Anthelmintic activity, *In-vitro* cytotoxicity

INTRODUCTION

Synthesis of heterocyclic compounds from readily available reagents by simple and efficient method is the major requirements of heterocyclic chemistry. Imidazole-indole joined to frame fresher tetra aryl imidazoles with higher adequacy and low reactions. The most straightforward individual from the azole family is imidazole with atomic recipe $C_3H_4N_2$. The foundational name for the compound is 1, 3 diazoles, one of the annular N having an H particle and can be viewed as a pyrrole type nitrogen and it is dissolvable in polar solvents. It exists in two equal tautomeric structures. The indole having a benzene ring with pyrrole core taken from Isatin which gives connect imidazole to frame more up to date tetra aryl imidazoles. Independently both imidazole and indole core have noteworthy anticancer and antimicrobial agents so we have made to synthesize more up to date tetra aryl imidazole which is a mix of imidazole and indole [1].

A study of the relevant writing uncovers that imidazole subordinates have assorted biological activities freely from their synthetic advantages. They are accounted to show pharmacological activity, for example, antimicrobial [2,3], anthelmintic [4,5], cognitive enhancers [6,7], and anticancer [8-11]. Probably the top-rated treatments today contain this versatile heterocycle in their center structures. Thus, it is hard to think little of the significance of imidazoles in the pharmaceutical business.

In 1858, Debus revealed the response among glyoxal and smelling salts, as far back as this response turned into a novel course to the unions of imidazole subsidiaries. Afterward, various articles have portrayed the unions of different imidazole subordinates [12-22]. In perspective on these perceptions, this examination is, henceforth, centered to research the *in-vitro* cytotoxicity and anthelmintic exercises of combined aryl imidazoles subsidiaries.

MATERIALS AND METHODS

In-vitro Cytotoxicity Studies

Cell cultures were taken from the National center for cell sciences, Puna. HEp-2 cells were grown in Earl's Minimal essential medium supplemented with 2 mM L-glutamine, 10% Fetal Bovine Serum, Penicillin (100 µg/ml), Streptomycin (100 µg/ml) and Amphotericin B (5 µg/ml) and the cells were maintained at 37°C in a humidified atmosphere with 5% CO_2 and subculture 2 times a week. The compound shows significant cytotoxicity activity against these cell lines. Determinations of CTC50 value by SRB assay are given in results.

Anthelmintic Studies

Anthelmintic activity studies were performed against earthworms at 2 mg/ml concentration using Garg and Atal method [23]. Suspensions of samples were produced by triturating synthesized compounds (100 mg) with Tween 80 (0.5%) and distilled water and the resulting mixtures were stirred using a mechanical stirrer for 30 min. The suspensions were diluted to contain 0.2% w/v of the test samples. Suspension of standard medication, mebendazole, was created with a similar focus along these lines. About 3 arrangements of 5 nightcrawlers of practically comparative sizes (2 inches long) were put in Petri plates of 4-inch distance across containing 50 ml of a suspension of test and reference medicate at room temperature. Another arrangement of 5 nightcrawlers was kept as control in 50 ml suspension of refined water and Tween 80 (0.5%). The deadening and demise times were noted and their mean was determined for triplicate sets. The demise time was checked by putting the nightcrawlers in warm water (50°C) which invigorated the development if the worm was alive. Assurance of incapacitating and passing time is given in results.

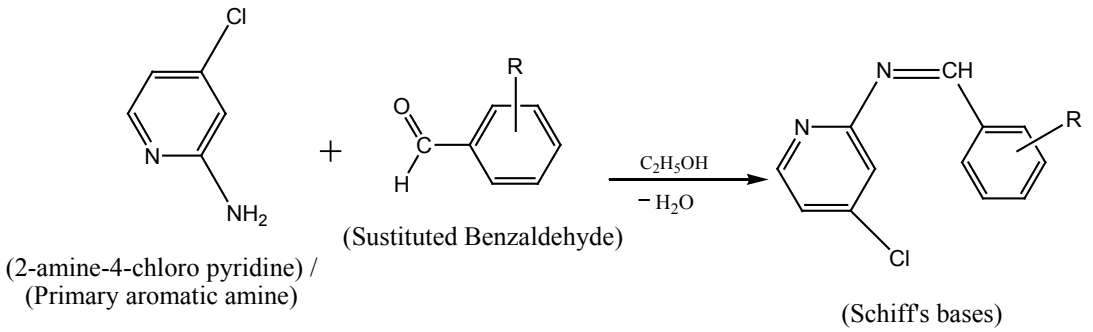
General procedure for the preparation of newer tetra aryl imidazoles was completed in two steps as follows:

General procedure for the preparation of Schiff's bases (1a-8a) Step-I: Same amounts (0.01 M) of 2-Amine-4-chloro-pyridine and substituted benzaldehyde were taken into a 250 ml round bottom flask containing 15 ml of glacial acetic acid and refluxed it for 6 h. The reaction mixture was allowed to cool to give the product. The reactions were monitored through TLC. The finished responses were made legitimately for the step-II.

General procedure for the preparation of Newer imidazoles (1b-8b) Step-II: Isatin (0.01M) was brought with ammonium acetic acid derivation (0.1 M) into a carafe containing the Schiff's base (~ 0.01M) acquired by step-I. The response blend was refluxed with mixing on warming plate with attractive stirrer for around 11-13 h. The response was observed through TLC.

The response blend fell into 250 ml of water to evacuate abundance of ammonium acetic acid derivation and acidic corrosive then it was sifted and dried in tourist oven. The item was washed with 2 × 20 ml of benzene to expel hints of any unreacted isatin and items were recrystallized by ethyl acetic acid derivation give the comparing novel imidazoles 1B-8B (Table 1 and Figure1).

Step-I:



Step-II:

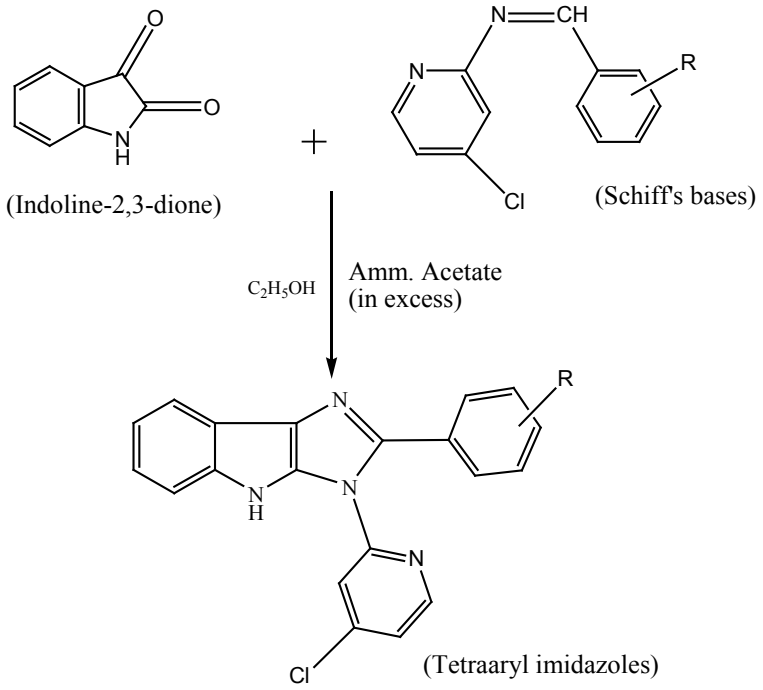


Figure 1 General procedure for the preparation of newer tetra aryl imidazoles

Based on above certainties (as outlined in the presentation) the novel arrangement of an orchestrated subordinate of aryl imidazoles containing Indole moiety may yield mixes with high remedial potential. The more up to date mixes were examined and shown by physical and expository information.

3-(4-Chloropyridin-2-yl)-3,4-dihydro-2-(3-nitrophenyl)imidazo[4,5-b]indole (1B)

Yellow solid, Mp (ºC): 113-114; R_f value: 0.65; IR (KBr): 3323.42 (N-H), 3120.14 (Ar C-H), 1575.09 (C=N), 1270.42 (C-N), 858.67 (C-N stretching for NO_2), 665.21 (C-Cl), cm^{-1}; 1H NMR (DMSO-d6): δ=7.12-8.48 (m, 11H, Ar-H), 10.1 (s, 1H, N-H, D_2O exchangeable) ppm; 13C-NMR δ: 111.1, 116.5, 119.0, 120.1 (2C), 121.1, 122.1, 122.2, 124.1, 125.9, 130.2, 131.6, 133.6, 135.5, 136.4, 141.9, 143.9, 148.9, 151.4, 159.4; MS (ESI) m/z: M+1 peak found, 391.04 (M+1 peak calculated, 391.15); Anal. Calcd. for: C, 61.63; H, 3.10; Cl, 9.10; N, 17.97; O, 8.21. Found: C, 61.59; H, 3.07; Cl, 9.08; N, 17.95; O, 8.18.

2-(3-(4-chloropyridin-2-yl)-3,4-dihydroimidazo[4,5-b]indol-2-yl)phenol (2B)

Yellow solid, Mp (ºC): 117-118; R_f value: 0.74; IR (KBr): 3570.42 (O-H), 3330.71 (N-H), 3070.17 (Ar C-H), 1546.10

(C=N), 1195.78 (C-N), 665.21 (C-Cl), cm^{-1}; 1H NMR (DMSO-d6): δ 7.12-8.48 (m, 12H, Ar-H), 10.1 (s, 1H, N-H, D_2O exchangeable), 4.9 (s, 1H, OH, D_2O exchangeable) ppm; 13C-NMR δ: 111.1, 116.4, 116.5, 118.5, 119.0, 120.1 (2C), 121.9, 122.2, 124.1, 125.9, 128.9, 130.2, 135.5, 136.4, 141.9, 143.9, 151.4, 155.3, 159.4; MS (ESI) m/z: M+1 peak found, 362.05 (M+1 peak calculated, 362.25); Anal. Calcd. for: C, 66.58; H, 3.63; Cl, 9.83; N, 15.53; O, 4.43. Found: C, 66.56; H, 3.61; Cl, 9.80; N, 15.51; O, 4.40.

3-(3-(4-chloropyridin-2-yl)-3,4-dihydroimidazo[4,5-b]indol-2-yl)phenol (3B)

Yellow solid, Mp (ºC): 108-109; R_f value: 0.66; IR (KBr): 3570.42 (O-H), 3330.71 (N-H), 3080.17 (Ar C-H), 1546.10 (C=N), 1195.78 (C-N), 665.21 (C-Cl), cm^{-1}; 1H NMR (DMSO-d6): δ=7.12-8.48 (m, 12H, Ar-H), 10.1 (s, 1H, N-H, D_2O exchangeable), 4.9 (s, 1H, OH, D_2O exchangeable) ppm; 13C-NMR δ: 111.1, 112.9, 115.9, 116.5, 119.0, 120.1 (3C), 122.2, 124.1, 125.9, 130.7, 132.1, 135.5, 136.4, 141.9, 143.9, 151.4, 159.0, 159.4; MS (ESI) m/z: M+1 peak found, 362.05 (M+1 peak calculated, 362.25); Anal. Calcd. for: C, 66.58; H, 3.63; Cl, 9.83; N, 15.53; O, 4.43. Found: C, 66.56; H, 3.61; Cl, 9.80; N, 15.51; O, 4.40.

2-(2-chlorophenyl)-3-(4-chloropyridin-2-yl)-3,4-dihydroimidazo[4,5-b]indole (4B)

Pale solid, Mp (ºC): 127-128; R_f value: 0.61; FTIR (KBr): 3328.83 (N-H), 3083.62 (Ar C-H), 1569.66 (C=N), 1151.42 (C-N), 756.04 (C-Cl) cm^{-1}; 1H NMR (DMSO-d6): δ=7.12-8.48 (m, 12H, Ar-H), 10.1 (s, 1H, N-H, D_2O exchangeable) ppm; 13C-NMR δ: 111.1, 116.5, 119.0, 120.1 (2C), 122.2, 124.1, 125.9, 127.4, 128.9, 129.4, 130.2, 132.3, 135.5, 136.4, 138.5, 141.9, 143.9, 157.4, 159.4; MS (ESI) m/z: M+1 peak found, 380.02 (M+1 peak calculated, 380.8); Anal. Calcd. for: C, 63.34; H, 3.19; Cl, 18.70; N, 14.77. Found: C, 63.31; H, 3.17; Cl, 18.68; N, 14.75.

2-(4-chlorophenyl)-3-(4-chloropyridin-2-yl)-3,4-dihydroimidazo[4,5-b]indole (5B)

Yellow solid, Mp (ºC): 124-125; R_f value: 0.68; FTIR (KBr): 3328.83 (N-H), 3083.62 (Ar C-H), 1569.66 (C=N), 1151.42 (C-N), 756.04 (C-Cl) cm^{-1}; 1H NMR (DMSO-d6): δ=7.12-8.48 (m, 12H, Ar-H), 10.1 (s, 1H, N-H, D_2O exchangeable) ppm; 13C-NMR δ: 111.1, 116.5, 119.0, 120.1 (2C), 122.2, 124.1, 125.9, 128.8, 128.9 (2C), 129.4 (2C), 134.3, 135.5, 136.4, 141.9, 143.9, 151.4, 159.4; MS (ESI) m/z: M+1 peak found, 380.02 (M+1 peak calculated, 380.8); Anal. Calcd. for: C, 63.34; H, 3.19; Cl, 18.70; N, 14.77. Found: C, 63.31; H, 3.17; Cl, 18.68; N, 14.75.

2-(3-chlorophenyl)-3-(4-chloropyridin-2-yl)-3,4-dihydroimidazo[4,5-b]indole (6B)

Pale solid, Mp (ºC): 121-122; R_f value: 0.63; FTIR (KBr): 3328.83 (N-H), 3083.62 (Ar C-H), 1569.66 (C=N), 1151.42 (C-N), 756.04 (C-Cl) cm^{-1}; 1H NMR (DMSO-d6): δ=7.12-8.48 (m, 12H, Ar-H), 10.1 (s, 1H, N-H, D_2O exchangeable) ppm; 13C-NMR δ: 111.1, 116.5, 119.0, 120.1 (2C), 122.2, 124.1, 125.6, 125.9, 127.4, 128.9, 130.7, 132.1, 134.8, 135.5, 136.4, 141.9, 143.9, 151.4, 159.4; MS (ESI) m/z: M+1 peak found, 380.02 (M+1 peak calculated, 380.8); Anal. Calcd. for: C, 63.34; H, 3.19; Cl, 18.70; N, 14.77. Found: C, 63.31; H, 3.17; Cl, 18.68; N, 14.75.

3-(4-chloropyridin-2-yl)-3,4-dihydro-2-(4-nitrophenyl)imidazo[4,5-b]indole (7B)

Yellow solid, Mp (ºC): 110-111; R_f value: 0.57; IR (KBr): 3323.42 (N-H), 3120.14 (Ar C-H), 1575.09 (C=N), 1270.42 (C-N), 858.67 (C-N stretching for NO2), 665.21 (C-Cl), cm^{-1}; 1H NMR (DMSO-d6): δ=7.12-8.48 (m, 11H, Ar-H), 10.1 (s, 1H, N-H, D_2O exchangeable) ppm; 13C-NMR δ: 111.1, 116.5, 119.0, 120.1 (2C), 121.6 (2C), 122.2, 124.1, 125.9, 128.4 (2C), 135.5, 136.4, 136.8, 141.9, 143.9, 148.4, 151.4, 159.4; MS (ESI) m/z: M+1 peak found, 391.04 (M+1 peak calculated, 391.15); Anal. Calcd. for: C, 61.63; H, 3.10; Cl, 9.10; N, 17.97; O, 8.21. Found: C, 61.59; H, 3.07; Cl, 9.08; N, 17.95; O, 8.18.

3-(4-chloropyridin-2-yl)-3,4-dihydro-2-(3-methoxyphenyl)imidazo[4,5-b]indole (8B)

Yellow solid, Mp (ºC): 134-135; R_f value: 0.71; FTIR (KBr): 3350.76 (N-H), 3072.39 (Ar C-H), 2925.81 (Ali. C-O-C), 1593.09 (C=N), 1236.29 (C-N), 665.21 (C-Cl) cm^{-1}; 1H NMR (DMSO-d6): δ=3.7 (s, 3H, OCH_3), 7.12-8.48 (m, 12H, Ar-H), 10.1 (s, 1H, N-H, D_2O exchangeable) ppm; 13C-NMR δ: 55.9, 111.1, 111.3, 114.3, 116.5, 119.0, 119.8, 120.1 (2C), 122.2, 124.1, 125.9, 130.3, 131.7, 135.5, 136.4, 141.9, 143.9, 151.4, 159.4, 161.2; MS (ESI) m/z: M+1 peak found, 376.08 (M+1 peak calculated, 376.38); Anal. Calcd. for: C, 67.29; H, 4.03; Cl, 9.46; N, 14.95; O, 4.27. Found: C, 67.26; H, 4.01; Cl, 9.44; N, 14.92; O, 4.25.

RESULTS AND DISCUSSION

The results and discussion for the synthesis substituted novel Tetra aryl imidazoles are as follows:

Firstly, the 2-amine-4-chloro-pyridine was condensed with substituted benzaldehydes afforded the corresponding Schiff's base. To produce aryl imidazoles, the Schiff's base was further directly reacted with ammonium acetate and isatin (cyclization steps involving diketone) in the presence of glacial acetic acid as a solvent, gave a corresponding novel Tetra aryl imidazoles 1B-8B. Based on writing the novel arrangement of an integrated subsidiary of aryl imidazoles containing Indole moiety may yield mixes with high remedial potential.

Structures of all the recently incorporated Tetra aryl imidazoles were affirmed by FTIR, 1H NMR, and mass spectral examination. The IR spectra of the recently integrated mixes demonstrated the nearness of trademark retention in the locale 3310-3350 cm^{-1} for N-H in NH_2, 3012-3096 cm^{-1} for sweet-smelling C-H extending, 1500-1600 cm^{-1} for C=N extending individually. 1H NMR spectra of blended mixes demonstrated the trademark tops in the area 6.67-7.80 ppm for aromatic protons and 10.1-11.0 ppm for N-H.

Table 1 Data of all synthesized novel tetra aryl imidazoles (1B-8B)

Compound name	R	Molecular Formula	Molecular Weight	Reaction Time (hr)	Yield (%)
1B	3-nitro	$C_{20}H_{12}ClN_5O_2$	389.79	10.5	63
2B	2-hydroxy	$C_{20}H_{13}ClN_4O$	360.08	11.0	56
3B	3-hydroxy	$C_{20}H_{13}ClN_4O$	360.08	10.0	52
4B	2-chloro	$C_{20}H_{12}Cl_2N_4$	379.24	11.5	62
5B	4-chloro	$C_{20}H_{12}Cl_2N_4$	379.24	11.0	58
6B	3-chloro	$C_{20}H_{12}Cl_2N_4$	379.24	12.0	61
7B	4-nitro	$C_{20}H_{12}ClN_5O_2$	389.79	10.0	57
8B	3-methoxy	$C_{21}H_{15}ClN_4O$	374.82	11.5	64

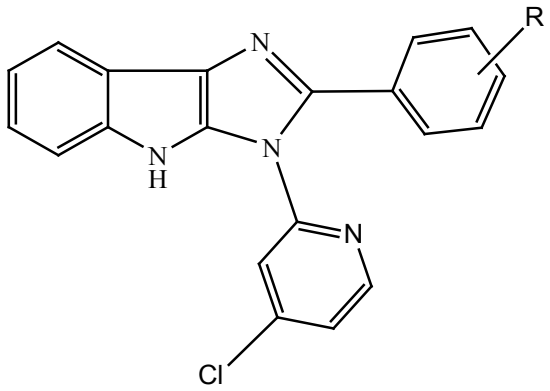


Figure 2 Novel tetra aryl imidazoles structural formula

The synthesized compounds were screened for *in vitro* cytotoxicity examines against HEp2 cell lines by SRB measure. The mixes 1b, 2b, and 8b indicate noteworthy cytotoxicity against HEp2 cell lines in contrast with standard 5-Fluorouracil. The nearness of phenolic bunch in compound 2b and 3b essentially influence movement because of the coupling ability to the cytoplasmic hormone receptors [24]. Compound 7b containing sulfur in its structure diminishes the liquefying temperature of DNA in EAC cells and in this way indicating huge action. The nearness of methoxy bunch additionally builds the possibilities of compound 8b. Mixes 4b, 5b and 6b having the chlorine in their structure demonstrating the mixes progressively lethal as contrast and others. Anticancer activity of all the synthesized compounds at the groupings of 500 mg/ml, 250 mg/ml, 125 mg/ml, 62.5 mg/ml, and 31.25 mg/ml were performed (Table 2 and Figure 2).

Table 2 Determination of CTC50 value by SRB assay of novel tetra aryl imidazoles

S. No	Sample No.	CTC_{50}c value (µg/ml)
1	1B	37.35
2	2B	32.04
3	3B	34.16
4	4B	75.41
5	5B	>140
6	6B	102.04
7	7B	46.11
8	8B	33.32
9	5-Fluorouracil	31.76

Anthelmintic activity of the synthesized novel imidazoles was accomplished against Eudrilus species at 4 mg/ml concentration. All the novel imidazoles indicated significant activity at 100 mg in Tween 80 (0.5%) and refined water. Correlation of anthelmintic information uncovered that subsidiary 1b, 2b, 4b, 6b, and 8b had higher activity in contrast with standard Mebendazole.

Presence of nitro and methoxy group in compounds 1b and 8b make them more potent with low toxicity and several times more potent than Mebendazole. Substituent's at R' position was introduced to prevent metabolic inactivation. Presence of hydroxyl group in compound 2b and 3b make them lack side effects. Hydroxyl and carboxyl group are accountable for inhibition of respiration and blocking glucose absorption by the intestinal adult worms. The overall results are given in Table 3.

Table 3 Anthelmintic activity of synthesized of novel tetra aryl imidazoles

Compound No.	Mean paralyzing time (min)	Mean death time (min)
	Eudrilus species	*Eudrilus species*
1B	18.64 ± 0.50	28.23 ± 0.50
2B	23.04 ± 0.46	28.10 ± 0.46
3B	19.16 ± 0.57	29.88 ± 0.56
4B	16.20 ± 0.50	25.01 ± 0.57
5B	26.51 ± 0.54	37.25 ± 0.74
6B	19.00 ± 1.00	27.54 ± 0.57
7B	26.23 ± 0.76	39.12 ± 0.56
8B	19.24 ± 1.32	28.00 ± 1.02
Control	-	-
Mebendazole	24.83 ± 0.76	29.33 ± 1.52

CONCLUSION

All the novel imidazoles were examined by physical and expository information and assessed for *in-vitro* cytotoxicity and anthelmintic screening. Each synthesized novel imidazoles have indicated moderate to great anthelmintic movement. The compounds 1b, 2b, 4b, 6b, and 8b obtained higher potency in contrast with mebendazole. The synthesized novel imidazoles got huge *in-vitro* cytotoxicity against HEp2 cell lines.

DECLARATIONS

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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