Microwave-Assisted, Solvent-Free and Parallel Synthesis of Some Novel Substituted Imidazoles of Biological Interest

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Solvent free microwave assisted synthesis of some novel substituted imidazoles of biological interest is reported. First, primary aromatic or heteryl amine was condensed with aryl or heteryl aldehydes to afford corresponding Schiff's base. The Schiff's base further on treatment with ammonium acetate (NH_4OAC) and isatin using silica gel as the solid support, yielded the corresponding aryl imidazoles. In this paper a comparative study between the developed microwave method and conventional method is described. The synthesized compounds were analyzed by physical and analytical data. The synthesized compounds were evaluated for their antibacterial, anthelmintic, short-term anticancer and antitubercular activity. All the synthesized substituted imidazoles have shown good antibacterial activity against gram negative bacterial strains *Klebsiella pneumoniae* and *Escherichia coli* and moderate to good anthelmintic activity. The synthesized imidazole derivative possessed significant cytotoxic activity against Ehrlich's ascites carcinoma (EAC) cell lines. None of the compounds exhibited prominent antitubercular activity.

Key words aryl imidazole; anticancer activity; anthelmintic activity

A survey of the pertinent literature reveals that aryl imidazoles have been found to possess a wide spectrum of biological activity such as antibacterial,[1] antirheumatoid arthritis,[2] antitubercular,[3] antiviral,[4] antiepileptic,[5] anti-inflammatory[6] and anticancer activities.[7—9] Since, we have made an attempt to synthesize and screen aryl imidazoles which are incorporated with some antibacterial pharmacophores such as sulphanilamide, its bioisoester PABA (*p*-aminobenzoic acid), INH (isoniazid) and *p*-amino phenol by using both microwave assisted synthesis as well as conventional synthetic method and screened them as potential antibacterial, anticancer, anthelmintic and antitubercular agents.

It has been revealed from the literature that imidazoles fused with indole nucleus possess various biological activities[10—12] including anticancer activity especially against breast cancer.

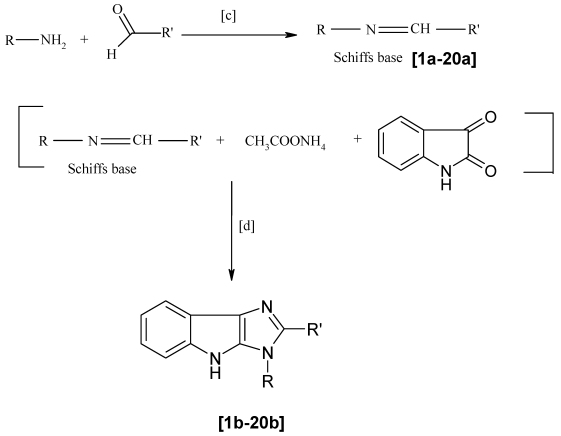
In 1858, Debus reported the reaction between glyoxal and ammonia, ever since this reaction became a novel route to the synthesis of imidazoles.[13] Later, a number of articles have described the synthesis of imidazoles and their medicinal significance.[14—22]

In the last decade, microwave assisted organic synthesis (MAOS) have become a new and quickly growing area in the synthetic organic chemistry.[23,24] This synthetic technique is based on the empirical observation that some organic reactions proceed much faster and with higher yields under microwave irradiation as compared to conventional heating. In many cases reactions that normally require many hours at reflux temperature under classical conditions can be completed within several minutes or even seconds in a microwave oven. Recent simplifications of MORE (microwave organic reaction enhancement) technique have increased safety and practical utility of the microwave oven for their use in organic laboratories without any modification. An eco-friendly method is an important salient feature of MORE chemistry, since it requires no solvent (dry media synthesis) or very little solvent as energy transfer medium.

Results and Discussion

The results and discussion pertaining to the synthesis of Schiff's bases and finally substituted imidazoles are as follows:

First, the primary aromatic or heteroarylamine was condensed with aryl or heteryl aldehydes afforded the corresponding Schiff's base.[25] To prepare aryl imidazoles, the Schiff's base was further treated with ammonium acetate and isatin (cyclization steps involving diketone) in the presence of glacial acetic acid as a solvent, gave a corresponding aryl imidazoles **1b**—**20b** (Chart 1). On the basis of above facts (as depicted in the introduction) that the novel series of synthesized derivative of aryl imidazoles containing indole moiety may yield compounds with high therapeutic potential. All the synthesized compounds were analyzed by TLC, mp, FT-IR, ^{1}H-NMR, ^{13}C-NMR, MASS and elemental analysis. Microwave irradiation was done using microwave oven supplied by catalyst microwave synthesis system, model: CATA-2R. The microwave assisted parallel synthesis was performed under solvent free conditions using activated silica gel



Preparation of substituted imidazoles. [c] Conv; AcOH, Reflux 5-6 h. MW; Activated silica gel, 1000 W, 8 min. [d] Ammonium acetate, Conv; Reflux 12-15 h. MW; 1000 W, 14-22 min.

Chart 1

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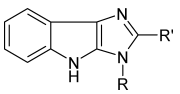
1000 W. Schiff's base formation was completed after 8 min of microwave irradiation, whereas aryl imidazoles formed between 14—22 min of microwave irradiation. We are of the opinion that the acidic nature of silica gel would have enhanced this process particularly during dehydration steps. The list of synthesized compounds and the comparative yield statement between microwave and conventional method is as shown in Table 1.

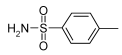
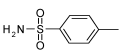
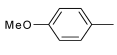
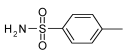
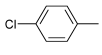
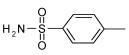
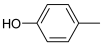
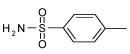
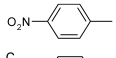
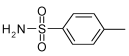
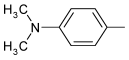
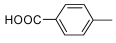
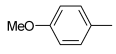
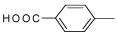
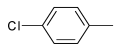
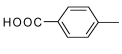
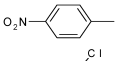
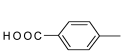
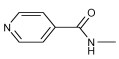
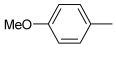
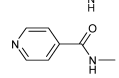
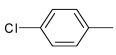
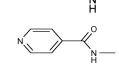
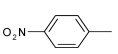
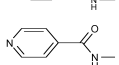
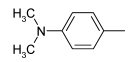
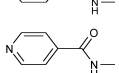
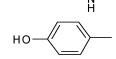
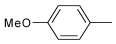
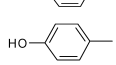
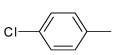
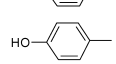
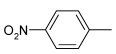
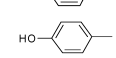
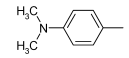
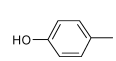
The microwave method was found to be better than conventional method in terms of reaction time, yield and relatively simple method to perform parallel synthesis. Thus, this methodology becomes an efficient strategy for the rapid synthesis of aryl imidazoles, selectively.

The ^{1}H-NMR showed a characteristic peak for NH_2 between 6.22—6.39 δ ppm for compounds containing sulphanilamide **1b**—**6b** and characteristic peak for COOH was observed between 11.13—11.96 δ ppm for compounds containing PABA (*p*-aminobenzoic acid) **7b**—**10b**. A characteristic peak for NH was observed between 8.31—9.28 δ ppm for compounds containing INH (isoniazid) **11b**—**15b**. A characteristic peak for OH was observed between 8.58—8.76 δ ppm for compounds containing *p*-amino phenol **16b**—**20b**.

All the synthesized imidazoles incorporated with chemotherapeutic pharmacophores were evaluated for their *in vitro* antibacterial activity against two-gram positive bacte-

Table 1. Data of All Synthesized Aryl Imidazoles Compounds Screened against EAC Cell Line



Comp. no.	R	R′	Reaction time		Yield (%)[a]		mp (°C)	CTC_{50}[c] (μg/ml)
			MW[b] (min)	Conventional (h)	MW	Conventional		
1b			14	13	89	61	130	262.50
2b			16	13	83	58	180	275.50
3b			15	14	86	67	185	400.00
4b			20	15	90	62	205	380.00
5b			22	15	91	63	180	31.25
6b			21	15	88	61	220	420.00
7b			19	15	93	72	212	91.61
8b			17	14	81	77	183	360.00
9b			14	13	90	50	240	143.67
10b			16	12	89	45	251	114.00
11b			19	14	78	55	191	322.47
12b			21	13	78	67	149	50.32
13b			15	15	67	56	188	380.00
14b			18	13	76	49	201	198.50
15b			19	13	81	56	205	50.00
16b			21	14	82	60	221	94.63
17b			13	15	75	58	223	>500
18b			12	14	77	45	263	360.34
19b			14	12	84	50	256	350.00
20b			13	11	83	52	262	31.25

a) Isolated yield. *b*) Microwave irradiation. *c*) The cytotoxic concentration (which inhibited 50 % of total cells).

Table 2. Antibacterial Data of All Synthesized Aryl Imidazoles Compounds Screened against Various Bacterial Strains

Compound	Diameter of zone of inhibition (mm) Bacterial strains			
	Gram (+ve)		Gram (−ve)	
	S. aureus	*B. subtilis*	*E. coli*	*K. pneumoniae*
1b	5.9 (50)	6.9 (50)	7.2 (50)	8.1 (50)
2b	5.1 (25)	5.5 (25)	8.1 (50)	8.9 (50)
3b	8.6 (25)	8.4 (25)	9.2 (12.5)	9.5 (12.5)
4b	13.1 (50)	12.5 (25)	11.9 (25)	12.5 (6.2)
5b	9.1 (25)	8.8 (50)	7.6 (100)	7.8 (100)
6b	5.7 (100)	5.9 (100)	6.6 (50)	6.9 (50)
7b	12.5 (50)	12.1 (25)	11.9 (25)	11.6 (25)
8b	11.9 (50)	11.3 (25)	10.9 (100)	10.7 (50)
9b	12.1 (25)	13.8 (50)	14.3 (25)	12.5 (50)
10b	13.1 (25)	12.3 (25)	15.4 (12.5)	11.8 (25)
11b	11.2 (50)	12.4 (25)	13.5 (12.5)	9.1 (50)
12b	6.2 (100)	7.2 (100)	9.2 (50)	7.5 (50)
13b	7.2 (100)	8.7 (50)	10.2 (50)	10.3 (25)
14b	10.3 (25)	12.4 (12.5)	14.5 (6.2)	13.3 (12.5)
15b	12.3 (50)	13.6 (25)	14.6 (25)	14.6 (25)
16b	9.1 (100)	8.3 (100)	9.1 (50)	10.2 (25)
17b	6.1 (100)	7.4 (100)	8.3 (50)	6.9 (50)
18b	7.3 (100)	7.4 (100)	9.5 (50)	9.7 (50)
19b	13.2 (25)	14.5 (12.5)	14.6 (12.5)	11.5 (25)
20b	12.4 (25)	12.7 (25)	13.1 (50)	11.1 (50)
Control	—	—	—	—
Ciprofloxacin	18 (12.5)	19 (6)	19 (12.5)	17 (6)

Values in bracket are MIC values ($\mu g\,ml^{-1}$).

Table 3. Anthelmintic Activity of All Synthesized Aryl Imidazoles Compounds Screened against Various Earthworm Species

Compound	Earthworm species			
	M. konkanensis		*P. corethruses*	
	Mean paralyzing time (min)[a)]	Mean death time (min)[a)]	Mean paralyzing time (min)[a)]	Mean death time (min)[a)]
1b	28.38±0.52	40.58±0.59	35.57±1.26	50.26±1.02
2b	13.54±0.83	22.18±1.28	17.47±1.47	29.02±1.18
3b	13.73±1.90	22.73±0.49	17.52±2.23	29.58±1.63
4b	36.10±0.23	65.13±0.92	57.62±1.90	82.30±0.49
5b	16.22±0.37	25.56±0.72	20.65±1.25	32.22±1.29
6b	26.66±1.46	35.22±0.94	31.98±1.17	43.76±0.41
7b	11.28±0.62	20.03±1.34	13.76±0.51	21.72±0.45
8b	26.22±0.67	35.54±0.90	30.34±1.12	42.56±1.40
9b	25.50±0.34	34.12±0.87	29.83±1.45	41.53±1.67
10b	09.44±0.56	17.49±0.72	14.34±0.69	26.21±0.54
11b	36.78±0.21	62.48±0.91	49.35±1.65	72.24±1.02
12b	27.67±0.17	36.48±1.95	31.38±0.74	42.45±1.55
13b	12.22±0.32	18.12±0.34	13.56±0.67	19.57±0.53
14b	22.12±0.84	30.12±0.31	26.12±1.12	35.43±0.52
15b	10.12±0.13	15.56±0.81	17.12±0.32	21.17±0.13
16b	35.12±0.72	40.15±0.12	42.13±0.19	52.19±0.16
17b	10.56±0.19	18.16±0.29	13.56±0.81	20.22±0.89
18b	16.34±0.65	24.75±0.67	21.87±1.56	28.23±0.45
19b	12.34±1.12	20.45±2.23	15.34±0.12	24.12±0.23
20b	23.12±0.23	27.83±1.23	12.32±0.49	17.23±0.34
Control	—	—	—	—
Mebendazole	12.22±0.54	20.12±0.76	17.45±1.23	28.76±1.06

a) Data are given as mean±S.D. ($n=3$).

ria such as *Bacillus subtilis* and *Staphylococcus aureus* and two gram negative bacteria such as *Escherichia coli* and *Klebsiella pneumoniae*. Almost all the newly synthesized substituted imidazoles showed good antibacterial activity against gram negative bacterial strains *Escherichia coli* and *Klebsiella pneumonia*. The results of antibacterial studies are presented in Table 2.

Anticancer activity of the synthesized compounds was evaluated by determining the percentage growth inhibition of Erlich's ascites carcinoma (EAC) cells by tryphan blue dye exclusion technique. Compounds **5b**, **7b**, **12b**, **15b**, **16b** and **20b** showed good anticancer activity with CTC_{50} (cytotoxic concentration). The CTC_{50} values of the newly synthesized imidazoles are shown in Table 1. Presence of phenolic group in compound **16b** and **20b** significantly affect activity due to the binding capability to the cytoplasmic hormone receptors.[26)] Compound **5b** containing sulfur in its structure decreases the melting temperature of DNA in EAC cells and thereby showing significant activity. Presence of carboxylic acid and its amide also increases the potential of compound **7b** and **12b**.

All the newly synthesized imidazole derivatives showed moderate to good anthelmintic activity at 2 mg ml^{-1} in Tween 80 (0.5%) and distilled water. Compounds **7b**, **10b**, **13b**, **15b** and **17b** were found to be most active possessing more activity against *M. konkanensis* and *P. corethruses* in comparison to standard drug (mebendazole). Presence of amide group (–CONH) in compounds **13b** and **15b** make them more potent with low toxicity and several times more potent than Mebendazole. Substituents at R′ (2nd) position was introduced to prevent metabolic inactivation. Presence of carboxylic and hydroxyl group in compound **10b** and **17b** make them devoid of side effects. Hydroxyl and carboxyl group are responsible for inhibition of respiration and blocking glucose absorption by the intestinal adult worms. The results of anthelmintic studies are tabulated in Table 3.

All the synthesized compounds were evaluated for their possible antimycobacterial activity toward strain of *M. tuberculosis* $H_{37}Rv$ strain sensitive to isoniazid. Middlebrook (MB) 7H10 agar medium was used for testing antitubercular activity. The minimum inhibitory concentration (MIC) determination was performed from 1 to 25 μg/ml concentrations. But, no compound exhibited MIC below 25 μg/ml concentration including the aryl imidazoles containing isoniazid moiety.

Experimental

Materials and Methods The laboratory grade chemicals and reagents were used to synthesize all the reported compounds. The melting points were determined in open capillaries and are uncorrected. The temperatures are expressed in °C and are uncorrected. The IR spectra of newly synthesized compounds were recorded on Perkin-Elmer Infrared-283 FTIR spectrometer by KBr pellet technique and are expressed in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra were recorded on Bruker DRX-300 (300 MHz, FT-NMR) spectrophotometer using tetramethylsilane (TMS) as an internal standard, $CDCl_3$ and DMSO as a solvents. Mass spectrum was obtained using LC-MS (Shimadzu-2010AT) under electro spray ionization (ESI) technique and elemental analysis was performed using Elemental Vario EL III, Carlo-Erba 1108. TLC was performed to monitor the reactions and to determine the purity of products on a precoated aluminum plates using 10% methanol in chloroform or 20% ethyl acetate in chloroform as a mobile phase.

General Procedure for the Preparation of Schiff's Bases (1a—20a). Conventional Method Equimolar amounts (0.01 M) of primary aromatic amine and aromatic aldehyde were transferred to a 250 ml flat bottom flask containing 15 ml glacial acetic acid and refluxed for 6 h. The reaction mixture was allowed to cool to give product. The reactions were monitored through thin layer chromatography (TLC). The completed reactions were

taken directly for the preparation of aryl imidazoles.

Microwave Method Equimolar amounts (0.01 M) of primary aromatic amine and aromatic aldehyde were transferred to a clean and dry mortar, triturated to form uniform mixture. The reaction mixture was then transferred to a 100 ml beaker containing 2 g of activated silica gel. All the beakers containing different reaction mixtures were also kept inside the microwave oven and then microwave irradiation was carried out at 1000 W power for about 8 min. Intermittent cooling was done after every 60 s of microwave irradiation. During intermittent cooling, the reaction mixtures were thoroughly mixed. The reactions were monitored through TLC. The products so obtained were taken directly for the preparation of aryl imidazoles.

General Procedure for the Preparation of Aryl Imidazoles by Solid Phase, Solvent Free, Multicomponent Reaction (1b—20b). Conventional Method Isatin (0.01 M) was transferred along with excess of ammonium acetate (0.1 M) into a flask containing the Schiff's base (*ca.* 0.01 M) obtained by conventional procedure. The reaction mixture was stirred and refluxed on heating plate with magnetic stirrer for about 12—15 h. The reaction was monitored through TLC.

The reaction mixture was poured into 250 ml of water to remove ammonium acetate and acetic acid then it was filtered and dried in hot air oven. The crude product was washed with 2×10 ml of benzene to remove traces of any unreacted isatin and products were recrystallized by ethyl acetate.

Microwave Method This reaction was carried out in a parallel synthetic way as shown in Chart 1. Isatin (0.01 M) was transferred along with excess of ammonium acetate (0.1 M) in to a dry mortar containing the Schiff's base (*ca.* 0.01 M) obtained in the previous microwave procedure. Triturate to become a uniform mixture. The reaction mixture was then transferred to 100 ml beaker. Like this all other beakers containing different reaction mixtures were kept inside the microwave oven in a circle and then microwave irradiation was carried out at 1000 W power for about 14—22 min. Intermittent cooling was done after every 60 s of microwave irradiation. During intermittent cooling, the reaction mixtures were thoroughly mixed. The reactions were monitored through TLC. The reaction mixtures were withdrawn from microwave oven soon after the reaction is completed based on TLC data at regular intervals.

The completed and cooled reaction mixture was poured in to 250 ml of water to remove ammonium acetate and acetic acid, filtered and dried it in hot air oven. The crude product was washed with 2×10 ml of benzene to remove traces of any unreacted isatin, further extracted with ethyl acetate. The ethyl acetate was heated, filtered in hot condition and allowed to cool. The solid crystals formed were collected by filtration and dried under vacuum.

The analytical and spectral data of final compounds are given in the following text.

4-(2-Phenylimidazo[4,5-*b*]indol-3(4*H*)-yl)benzenesulfonamide (1b) White crystals. ^{1}H-NMR ($CDCl_3$-d_6, ppm) δ: 6.25 (2H, bs, NH_2, D_2O exchangeable), 7.12—8.35 (13H, m, Ar-H), 8.75 (1H, bs, NH, D_2O exchangeable). ^{13}C-NMR δ: 110.5, 118.5, 119.4 (2C), 120.5, 123.3 (2C), 123.8, 126.4 (2C), 127.8 (2C), 128.2, 129.9 (2C), 130.1, 134.9, 136.1, 139.7, 140.8, 145.5. IR (KBr) cm^{-1}: 3322 (N–H), 3120 (C–H), 1625 (C=C), 1570 (C=N), 1280 (C–N), 1148 (SO), 1075 (C–S). MS (*m*/*z*): 387.80, 388 $(M+H)^+$, 312.35, 309.37, 233.28, 157.19. *Anal.* Calcd for $C_{21}H_{16}N_4O_2S$: C, 64.93; H, 4.15; N, 14.42; S, 8.25. Found: C, 64.90; H, 4.30; N, 14.26; S, 8.35.

4-[2-(4-Methoxyphenyl)imidazo[4,5-*b*]indol-3(4*H*)-yl]benzenesulfonamide (2b) White amorphous solid. ^{1}H-NMR ($CDCl_3$-d_6, ppm) δ: 3.11 (3H, s, OCH_3), 6.22 (2H, bs, NH_2, D_2O exchangeable), 7.05—8.32 (12H, m, Ar-H), 8.82 (1H, bs, NH, D_2O exchangeable). ^{13}C-NMR δ: 55.3, 111.3, 116.1 (2C), 119.8, 120.5 (2C), 121.4, 121.8 (2C), 122.9, 123.3, 126.1 (2C), 126.5 (2C), 135.5, 135.6, 138.1, 140.9, 143.7, 161.3. IR (KBr) cm^{-1}: 3350 (N–H), 3032 (C–H), 1621 (C=C), 1575 (C=N), 1271 (C–N), 1143 (SO), 1070 (C–S). MS (*m*/*z*): 417.50, 418 $(M+H)^+$, 339.40, 312.35, 263.30, 156.92. *Anal.* Calcd for $C_{22}H_{18}N_4O_3S$: C, 63.14; H, 4.34; N, 13.39; S, 7.66. Found: C, 63.20; H, 4.20; N, 13.20; S, 7.60.

4-[2-(4-Chlorophenyl)imidazo[4,5-*b*]indol-3(4*H*)-yl]benzenesulfonamide (3b) Pale yellow crystals. ^{1}H-NMR ($CDCl_3$-d_6, ppm) δ: 6.31 (2H, bs, NH_2, D_2O exchangeable), 7.07—8.13 (12H, m, Ar-H), 8.63 (1H, bs, NH, D_2O exchangeable). ^{13}C-NMR δ: 110.5, 118.5, 119.4 (2C), 120.5, 123.3 (2C), 123.8, 126.4 (2C), 127.8 (2C), 128.2, 129.9 (2C), 130.1, 134.9, 136.1, 139.7, 140.8, 145.5. IR (KBr) cm^{-1}: 3352 (N–H), 1625 (C=C), 1568 (C=N), 1285 (C–N), 1131 (SO), 691 (C–Cl), 1065 (C–S). MS (*m*/*z*): 422.90, 422 $(M-H)^-$, 343.82, 312.35, 267.72, 157.19. *Anal.* Calcd for $C_{21}H_{15}ClN_4O_2S$: C, 59.64; H, 3.58; Cl, 8.38; N, 13.25; S, 7.58. Found: C, 59.60; H, 3.50; Cl, 8.30; N, 13.36; S, 7.66.

4-[2-(4-Hydroxyphenyl)imidazo[4,5-*b*]indol-3(4*H*)-yl]benzenesulfonamide (4b) White crystals. ^{1}H-NMR ($CDCl_3$-d_6, ppm) δ: 6.39 (2H, bs, NH_2, D_2O exchangeable), 7.11—8.13 (12H, m, Ar-H), 8.66 (1H, s, OH); 8.99 (1H, bs, NH, D_2O exchangeable). ^{13}C-NMR δ: 110.7, 115.8 (2C), 118.8, 120.5 (2C), 121.9, 122.5 (2C), 123.1, 124.5, 127.7 (2C), 128.1 (2C), 134.8, 135.9, 139.5, 140.1, 144.2, 158.9. IR (KBr) cm^{-1}: 3405 (O–H), 3312 (N–H), 1622 (C=C), 1563 (C=N), 1278 (C–N), 1123 (SO), 1061 (C–S). MS (*m*/*z*): 403.75, 404 $(M+H)^+$, 325.37, 312.35, 249.27, 157.76. *Anal.* Calcd for $C_{21}H_{16}N_4O_3S$: C, 62.36; H, 3.99; N, 13.85; S, 7.93. Found: C, 62.49; H, 3.80; N, 13.75; S, 7.85.

4-[2-(4-Nitrophenyl)imidazo[4,5-*b*]indol-3(4*H*)-yl]benzenesulfonamide (5b) Pale yellow crystals. ^{1}H-NMR ($CDCl_3$-d_6, ppm) δ: 6.22 (2H, bs, NH_2, D_2O exchangeable), 7.11—8.22 (12H, m, Ar-H), 8.69 (1H, bs, NH, D_2O exchangeable). ^{13}C-NMR δ: 110.4, 118.9, 120.6 (2C), 121.9 (2C), 122.1, 123.1 (2C), 124.6, 128.7 (2C), 129.2 (2C), 134.9, 135.9, 136.2, 138.8, 140.1, 144.2, 147.8. IR (KBr) cm^{-1}: 3339 (N–H), 1619 (C=C), 1567 (C=N), 1462 (NO_2) 1279 (C–N), 1134 (SO), 1065 (C–S). MS (*m*/*z*): 432.95, 433 $(M+H)^+$, 354.37, 312.35, 278.27, 157.12, 78.11. *Anal.* Calcd for $C_{21}H_{15}N_5O_4S$: C, 58.19; H, 3.49; N, 16.16; S, 7.40. Found: C, 58.30; H, 3.52; N, 16.25; S, 7.52.

4-[2-(4-Dimethylaminophenyl)imidazo[4,5-*b*]indol-3(4*H*)-yl]benzenesulfonamide (6b) Yellow amorphous solid. ^{1}H-NMR ($CDCl_3$-d_6, ppm) δ: 6.26 (2H, bs, NH_2, D_2O exchangeable), 2.32 [(6H, s, $(CH_3)_2$], 7.12—8.32 (12H, m, Ar-H), 8.71 (1H, bs, NH, D_2O exchangeable). ^{13}C-NMR δ: 39.5 (2C), 111.4, 113.8 (2C), 118.6, 119.7 (2C), 120.3, 121.9, 123.8 (2C), 124.6, 127.9 (2C), 128.1 (2C), 134.8, 136.2, 138.9, 140.1, 144.1, 149.3. IR (KBr) cm^{-1}: 3382 (N–H), 2965 (C–H), 1619 (C=C), 1576 (C=N), 1283 (C–N), 1135 (SO), 1065 (C–S). MS (*m*/*z*): 430.45, 431 $(M+H)^+$, 352.44, 312.35, 276.34, 157.19. *Anal.* Calcd for $C_{23}H_{21}N_5O_2S$: C, 64.02; H, 4.91; N, 16.23; S, 7.43. Found: C, 64.15; H, 4.80; N, 16.12; S, 7.50.

4-[2-(4-Methoxyphenyl)imidazo[4,5-*b*]indol-3(4*H*)-yl]benzoic Acid (7b) White crystals. ^{1}H-NMR ($CDCl_3$-d_6, ppm) δ: 2.91 (3H, bs, OCH_3), 7.15—8.34 (12H, m, Ar-H), 8.82 (1H, bs, NH, D_2O exchangeable), 11.34 (1H, s, COOH). ^{13}C-NMR δ: 55.6, 111.2, 114.1 (2C), 118.5, 119.6 (2C), 121.8, 122.1 (2C), 122.9, 124.6, 127.9 (2C), 129.1, 130.8 (2C), 134.9, 136.1, 141.9, 144.1, 159.9, 168.1. IR (KBr) cm^{-1}: 3350 (N–H), 3032 (C–H), 1665 (C=O), 1621 (C=C), 1575 (C=N), 1271 (C–N). MS (*m*/*z*): 382.76, 383 $(M+H)^+$, 339.40, 263.30, 227.28, 157.18, 108.14. *Anal.* Calcd for $C_{23}H_{17}N_3O_3$: C, 72.05; H, 4.47; N, 10.96. Found: C, 71.95; H, 4.48; N, 10.91.

4-[2-(4-Chlorophenyl)imidazo[4,5-*b*]indol-3(4*H*)-yl]benzoic Acid (8b) White redish amorphous solid. ^{1}H-NMR ($CDCl_3$-d_6, ppm) δ: 6.52—7.70 (12H, m, Ar-H), 8.82 (1H, s, NH, D_2O exchangeable), 11.25 (1H, s, COOH). ^{13}C-NMR δ: 110.5, 119.6, 119.8 (2C), 121.7, 122.7 (2C), 124.8, 127.1, 127.7 (2C), 129.2, 129.6 (2C), 131.9 (2C), 134.9, 135.3, 136.9, 141.9, 144.5, 170.1. IR (KBr) cm^{-1}: 3309 (N–H), 3054 (C–H), 1685.48 (C=O), 1540 (N=C), 1519 (C=C), 1257 (C–N), 698 (C–Cl). MS (*m*/*z*): 386.78, 387 $(M+H)^+$, 343.82, 277.28, 267.72, 157.18, 112.56. *Anal.* Calcd for $C_{22}H_{14}ClN_3O_2$: C, 68.13; H, 3.64; Cl, 9.14; N, 10.83. Found: C, 68.11; H, 3.62; Cl, 9.11; N, 10.82.

4-[2-(4-Nitrophenyl)imidazo[4,5-*b*]indol-3(4*H*)-yl]benzoic Acid (9b) Cream color crystals. ^{1}H-NMR ($CDCl_3$-d_6, ppm) δ: 6.52—7.61 (12H, m, Ar-H), 8.82 (1H, s, NH, D_2O exchangeable), 11.13 (1H, s, COOH). ^{13}C-NMR δ: 110.9, 118.8, 120.4 (2C), 122.0 (2C), 122.7, 122.9 (2C), 123.6, 127.7 (2C), 129.1, 131.9 (2C), 135.8, 136.0, 136.8, 141.8, 144.1, 147.9, 168.7. IR (KBr) cm^{-1}: 3381 (N–H), 3020 (C–H), 1640 (C=N), 1619.91 (C=O), 1463.71 (NO_2). MS (*m*/*z*): 397.80, 398 $(M+H)^+$, 354.37, 278.27, 277.28, 157.18, 123.11. *Anal.* Calcd for $C_{22}H_{14}N_4O_4$: C, 66.33; H, 3.54; N, 14.06. Found: C, 66.30; H, 3.52; N, 14.02.

4-[2-(2,6-Dichlorophenyl)imidazo[4,5-*b*]indol-3(4*H*)-yl]benzoic Acid (10b) Yellow crystals. ^{1}H-NMR ($CDCl_3$-d_6, ppm) δ: 6.52—7.70 (12H, m, Ar-H), 8.98 (1H, s, NH, D_2O exchangeable), 11.96 (1H, s, COOH). ^{13}C-NMR δ: 111.8, 119.7, 120.5 (2C), 121.8, 122.1 (2C), 123.8, 126.8 (2C), 129.6, 130.8 (2C), 132.3, 135.1 (2C), 136.1, 136.9, 137.8, 142.1, 144.7, 168.1. IR (KBr) cm^{-1}: 3325 (N–H), 3050 (C–H), 1686 (C=O), 1570 (C=N), 1520 (C=C), 1250 (C–N), 670 (C–Cl). MS (*m*/*z*): 421.90, 422 $(M+H)^+$. 378.20, 302.17, 277.28, 157.18, 146.89. *Anal.* Calcd for $C_{22}H_{13}Cl_2N_3O_2$: C, 62.58; H, 3.10; Cl, 16.79; N, 9.95. Found: C, 62.49; H, 3.22; Cl, 16.61; N, 9.62.

***N*-[2-(4-Methoxyphenyl)imidazo[4,5-*b*]indol-3(4*H*)-yl]isonicotinamide (11b)** White crystals. ^{1}H-NMR ($CDCl_3$-d_6, ppm) δ: 2.39 (3H, s, OCH_3), 7.05—8.12 (12H, m, Ar-H), 8.31 (1H, bs, NH, D_2O exchangeable), 10.24 (1H, bs, NH, D_2O exchangeable). ^{13}C-NMR δ: 54.1, 110.9, 113.9 (2C), 118.3, 120.7 (2C), 122.1, 122.9 (2C), 123.4, 123.9, 128.1 (2C), 134.9, 135.6, 136.8, 141.0, 150.0 (2C), 159.9, 165.8. IR (KBr) cm^{-1}: 3395 (N–H), 3029

(C–H), 1695 (C=O), 1545 (C=N), 1503 (C=C), 1234 (C–N). MS (*m*/*z*): 383.60, 383 $(M-H)^-$, 353.39, 277.29, 263.30, 157.18, 122.13. *Anal.* Calcd for $C_{22}H_{17}N_5O_2$: C, 68.92; H, 4.47; N, 18.27. Found: C, 68.78; H, 4.53; N, 18.20.

***N*-[2-(4-Chlorophenyl)imidazo[4,5-*b*]indol-3(4*H*)-yl]isonicotinamide (12b)** Redish white crystals. ^{1}H-NMR ($CDCl_3$-d_6, ppm) δ: 7.11—8.19 (12H, m, Ar-H), 9.01 (1H, bs, NH, D_2O exchangeable), 10.34 (1H, bs, NH, D_2O exchangeable). ^{13}C-NMR δ: 111.3, 118.7, 120.3 (2C), 122.5, 122.9 (2C), 124.5, 128.9, 129.1, 129.5 (2C), 134.6, 135.1, 136.4, 136.8, 140.7 (2C), 149.5 (2C), 166.4. IR (KBr) cm^{-1}: 3390 (N–H), 3032 (C–H), 1701 (C=O), 1565 (C=N), 1515 (C=C), 1223 (C–N); 705 (C–Cl). MS (*m*/*z*): 386.70, 387 $(M+H)^+$, 353.39, 277.29, 267.72, 157.18, 122.13. *Anal.* Calcd for $C_{21}H_{14}ClN_5O$: C, 65.04; H, 3.64; Cl, 9.14; N, 18.06. Found: C, 65.14; H, 3.66; Cl, 9.21; N, 18.11.

***N*-[2-(4-Nitrophenyl)imidazo[4,5-*b*]indol-3(4*H*)-yl]isonicotinamide (13b)** Off white crystals. ^{1}H-NMR ($CDCl_3$-d_6, ppm) δ: 7.21—8.35 (12H, m, Ar-H), 9.06 (1H, bs, NH, D_2O exchangeable), 10.29 (1H, bs, NH, D_2O exchangeable). ^{13}C-NMR δ: 110.7, 118.5, 119.7 (2C), 120.9 (2C), 121.9, 123.0 (2C), 124.5, 128.9 (2C), 134.7, 135.5, 136.1, 136.9, 140.5, 147.9, 149.0 (2C), 164.4. IR (KBr) cm^{-1}: 3323 (N–H), 3031 (C–H), 1705 (C=O), 1556 (C=N), 1498 (C=C), 1230 (C–N). MS (*m*/*z*): 397.90, 398 $(M+H)^+$, 353.39, 278.27, 277.29, 122.13. *Anal.* Calcd for $C_{21}H_{14}N_6O_3$: C, 63.31; H, 3.54; N, 21.10. Found: C, 63.19; H, 3.53; N, 21.20.

***N*-[2-[4-(Dimethylamino)phenyl]imidazo[4,5-*b*]indol-3(4*H*)-yl]isonicotinamide (14b)** Brown amorphous solid. ^{1}H-NMR ($CDCl_3$-d_6, ppm) δ: 2.32 [(6H, s, $(CH_3)_2$], 7.02—8.32 (12H, m, Ar-H), 8.95 (1H, bs, NH, D_2O exchangeable), 10.65 (1H, bs, NH, D_2O exchangeable). ^{13}C-NMR δ: 38.6 (2C), 110.7, 114.9 (2C), 119.4, 119.9 (2C), 120.6, 121.9, 122.1 (2C), 123.6, 129.1 (2C), 135.7, 136.4, 136.9, 141.2, 148.6, 149.2 (2C), 165.3. IR (KBr) cm^{-1}: 3353 (N–H), 3056 (C–H), 1701 (C=O), 1578 (C=N), 1520 (C=C), 1230 (C–N). MS (*m*/*z*): 395.86, 396 $(M+H)^+$, 387.95, 339.40, 312, 309.05, 263, 156.92. *Anal.* Calcd for $C_{23}H_{20}N_6O$: C, 69.68; H, 5.08; N, 21.20. Found: C, 69.58; H, 5.03; N, 21.27.

***N*-[2-(2,6-Dichlorophenyl)imidazo[4,5-*b*]indol-3(4*H*)-yl]isonicotinamide (15b)** Pale white crystals. ^{1}H-NMR ($CDCl_3$-d_6, ppm) δ: 7.16—8.33 (11H, m, Ar-H), 9.28 (1H, bs, NH, D_2O exchangeable), 10.56 (1H, bs, NH, D_2O exchangeable). ^{13}C-NMR δ: 110.7, 118.6, 119.6 (2C), 121.8, 122.1 (2C), 124.0, 126.6 (2C), 130.8, 133.1 (2C), 135.1, 136.1, 136.9, 137.2, 139.5, 149.1 (2C), 167.1. IR (KBr) cm^{-1}: 3235 (N–H), 3050 (C–H), 1699 (C=O), 1563 (C=N), 1534 (C=C), 1227 (C–N), 671 (C–Cl). MS (*m*/*z*): 421.90, 422 $(M+H)^+$, 353.39, 302.17, 277.29, 157.18, 122.13. *Anal.* Calcd for $C_{21}H_{13}Cl_2N_5O$: C, 59.73; H, 3.10; Cl, 16.79; N, 16.59. Found: C, 59.68; H, 3.13; Cl, 16.61; N, 16.55.

4-[2-(4-Methoxyphenyl)imidazo[4,5-*b*]indol-3(4*H*)-yl]phenol (16b) White crystals. ^{1}H-NMR ($CDCl_3$-d_6, ppm) δ: 2.34 (3H, s, OCH_3), 7.09—8.18 (12H, m, Ar-H), 8.66 (1H, s, OH), 9.34 (1H, bs, NH, D_2O exchangeable). ^{13}C-NMR δ: 56.1, 110.9, 114.2 (2C), 117.1 (2C), 119.2, 120.4 (2C), 121.9, 122.8, 123.3 (2C), 124.5, 128.6 (2C), 129.5, 135.1, 135.9, 145.1, 158.5, 160.3. IR (KBr) cm^{-1}: 3435 (O–H), 3311 (N–H), 3034 (C–H), 1589 (C=N), 1551 (C=C), 1231 (C–N). MS (*m*/*z*): 354.60, 355 $(M+H)^+$, 325.37, 263.30, 249.27, 157.18. *Anal.* Calcd for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.82. Found: C, 74.45; H, 4.77; N, 11.76.

4-[2-(4-Chlorophenyl)imidazo[4,5-*b*]indol-3(4*H*)-yl]phenol (17b) Bright yellow amorphous solid. ^{1}H-NMR ($CDCl_3$-d_6, ppm) δ: 7.01—8.05 (12H, m, Ar-H), 8.74 (1H, s, OH), 9.43 (1H, bs, NH, D_2O exchangeable). ^{13}C-NMR δ: 110.7, 117.1 (2C), 118.5, 120.6 (2C), 122.0, 123.1 (2C), 124.8, 127.9, 128.3 (2C), 129.0 (2C), 130.4, 134.6, 135.9, 136.7, 144.3, 160.0. IR (KBr) cm^{-1}: 3454 (O–H), 3391 (N–H), 3095 (C–H), 1556 (C=N), 1501 (C=C), 1252 (C–N); 697 (C–Cl). MS (*m*/*z*): 358.75, 359 $(M+H)^+$, 325.37, 267.72, 249.27, 112.56. *Anal.* Calcd for $C_{21}H_{14}ClN_3O$: C, 70.10; H, 3.92; Cl, 9.85; N, 11.68. Found: C, 69.98; H, 3.83; Cl, 9.79; N, 11.55.

4-[2-(4-Nitrophenyl)imidazo[4,5-*b*]indol-3(4*H*)-yl]phenol (18b) White crystals. ^{1}H-NMR ($CDCl_3$-d_6, ppm) δ: 7.13—8.24 (12H, m, Ar-H), 8.58 (1H, s, OH), 9.65 (1H, bs, NH, D_2O exchangeable). ^{13}C-NMR δ: 111.3, 115.6 (2C), 118.7, 120.0 (2C), 120.9 (2C), 122.6, 123.2 (2C), 124.6, 129.1 (2C), 130.6, 134.9, 136.1, 136.9, 145.0, 148.4, 156.7. IR (KBr) cm^{-1}: 3419 (O–H), 3364 (N–H), 3042 (C–H), 1590 (C=N), 1531 (C=C), 1245 (C–N). MS (*m*/*z*): 369.68, 370 $(M+H)^+$, 325.37, 278.27, 249.27, 157.12. *Anal.* Calcd for $C_{21}H_{14}N_4O_3$: C, 68.10; H, 3.81; N, 15.13. Found: C, 68.20; H, 3.83; N, 15.24.

4-[2-[4-(Dimethylamino)phenyl]imidazo[4,5-*b*]indol-3(4*H*)-yl]phenol (19b) White amorphous solid. ^{1}H-NMR (DMSO-d_6, ppm) δ: 2.65 [(6H, s, $(CH_3)_2$], 7.19—8.45 (12H, m, Ar-H), 8.67 (1H, s, OH), 9.89 (1H, bs, NH, D_2O exchangeable). ^{13}C-NMR δ: 38.5 (2C), 110.7, 113.9 (2C), 116.1 (2C), 118.8, 120.5 (2C), 121.0, 122.5, 123.3 (2C), 124.8, 128.0 (2C), 129.5, 134.8, 136.7, 144.1, 150.3, 157.3. IR (KBr) cm^{-1}: 3411 (O–H), 3397 (N–H), 3046 (C–H), 1549 (C=N), 1534 (C=C), 1221 (C–N). MS (*m*/*z*): 368.50, 368 $(M-H)^-$, 325.37, 276.34, 249.27, 157.18. *Anal.* Calcd for $C_{23}H_{20}N_4O$: C, 74.98; H, 5.47; Cl, 15.21; N, 16.59. Found: C, 74.91; H, 5.41; Cl, 15.12; N, 16.55.

4-[2-(2,6-Dichlorophenyl)imidazo[4,5-*b*]indol-3(4*H*)-yl]phenol (20b) White crystals. ^{1}H-NMR ($CDCl_3$-d_6, ppm) δ: 7.01—8.12 (11H, m, Ar-H), 8.76 (1H, s, OH), 9.76 (1H, bs, NH, D_2O exchangeable). ^{13}C-NMR δ: 111.6, 116.1 (2C), 118.8, 120.6 (2C), 122.2, 123.2 (2C), 124.0, 126.9 (2C), 129.7, 130.9, 133.9 (2C), 134.8, 135.7, 137.1, 144.2, 156.9. IR (KBr) cm^{-1}: 3434 (O–H), 3321 (N–H), 3056 (C–H), 1578 (C=N), 1525 (C=C), 1234 (C–N), 1167 (C–Cl). MS (*m*/*z*): 393.50, 394 $(M+H)^+$, 325.37, 302.17, 157.18, 146.92. *Anal.* Calcd for $C_{21}H_{13}Cl_2N_3O$: C, 63.98; H, 3.32; Cl, 17.98; N, 10.66. Found: C, 63.90; H, 3.23; Cl, 17.81; N, 10.55.

Antibacterial Studies The synthesized imidazole derivatives were screened for their antibacterial activity against two gram positive bacterial strains *B. subtilis* (NCIM 2063), *S. aureus* (NCIM 2079) and two gram negative bacterial strains *K. pneumonia* (NCIM 2087), *E. coli* (NCIM 2065) by using modified Kirby–Bauer disc diffusion method.[27,28] Minimum inhibitory concentration (MIC) values of test compounds were determined by tube dilution technique.[29] All the synthesized compounds were dissolved separately to prepare a stock solution of 1 mg ml^{-1} using *N*,*N*-dimethylformamide (DMF). Stock solution was aseptically transferred and suitably diluted with sterile broth medium to have seven different concentrations of each test compound ranging from 200 to 3.1 μg ml^{-1} in different test tubes. All the tubes were inoculated with one loopful of one of the test bacteria. The process was repeated with different test bacteria and different samples. Tubes inoculated with bacterial cultures were incubated at 37 °C for 18 h and the presence/absence of growth of the bacteria was observed. From these results, MIC of each test compound was determined against each test bacterium. A spore suspension in sterile distilled water was prepared from 5-d old culture of the test bacteria growing on nutrient broth media. About 20 ml of the growth medium was transferred into sterilized petri plates and inoculated with 1.5 ml of the spore suspension (spore concentration 6×10^4 spores ml^{-1}). Filter paper disks of 6 mm diameter and 2 mm thickness were sterilized by autoclaving at 121 °C (15 psi) for 15 min. Each petri plate was divided into five equal portions along the diameter to place one disc. Three discs of test sample were placed on three portions together with one disc with reference drug ciprofloxacin and a disk impregnated with the solvent (DMF) as negative control. Test sample and reference drugs were tested at the concentration of 10 μg ml^{-1}. The petri plates inoculated with bacterial cultures were incubated at 37 °C for 18 h. Diameters of the zones of inhibition (mm) were measured and the average diameters for test sample were calculated in triplicate sets. The diameters obtained for the test sample were compared with that produced by the standard drug ciprofloxacin.

Anticancer Activity Anticancer activities of the synthesized compounds were assessed by determining the percentage inhibition of EAC cells by tryphan blue dye exclusion technique according to the standard procedure.[30—32] We checked anticancer activity of all the synthesized compounds at the concentration of 500, 250, 125, 62.5, 31.25 μg/ml. The percentage growth inhibition was calculated by using the following formula: % growth inhibition=[(total cells−live cells)×100]/total cells.

The CTC_{50} values were calculated by plotting the graph between concentration *versus* percentage growth inhibition and by bisecting concentration at the 50% growth inhibition. The synthesized aryl imidazoles and their CTC_{50} values are as shown in Table 1. Cyclophosphamide was used as standard drug (CTC_{50}, 12 μg/ml).

Anthelmintic Studies Anthelmintic activity studies were carried out against two different species of earthworms *M. konkanensis* (ICARBC 211) and *P. corethruses* (ICARBC 408) by Garg and Atal method[33] at 2 mg ml^{-1} concentration. Suspensions of samples were prepared 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 reference drug, mebendazole, was prepared with the same concentration in a similar way. Three sets of five earthworms of almost similar sizes (2 inch in length) were placed in Petri plates of 4 inch diameter containing 50 ml of suspension of test sample and reference drug at RT. Another set of five earthworms was kept as control in 50 ml suspension of distilled water and Tween 80 (0.5%). The paralyzing and death times were noted and their mean was calculated for triplicate sets. The death time was ascertained by placing the earthworms in warm water (50 °C) which stimulated the movement, if the worm was alive.

Antitubercular Activity Middlebrook (MB) 7H10 agar medium was used for testing of antitubercular activity of the compounds. Culture of *M. tuberculosis* $H_{37}Rv$ grown on Lowenstein–Jensen (L–J) was harvested in saline containing 0.05% Tween-80 and used according to the standard procedure.[34,35] The minimum concentration of the drug or compounds that completely inhibited the growth of different mycobacterium was recorded as minimum inhibitory concentration (MIC) with respect to the used inoculum. The MIC for test compounds was performed up to 25 μg/ml concentrations. Isoniazid (INH) was used as a standard drug (MIC, 21 μg/ml).

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