Microwave-Assisted, Solvent-Free, Parallel Syntheses and Elucidation of Reaction Mechanism for the Formation of Some Novel Tetraaryl Imidazoles of Biological Interest

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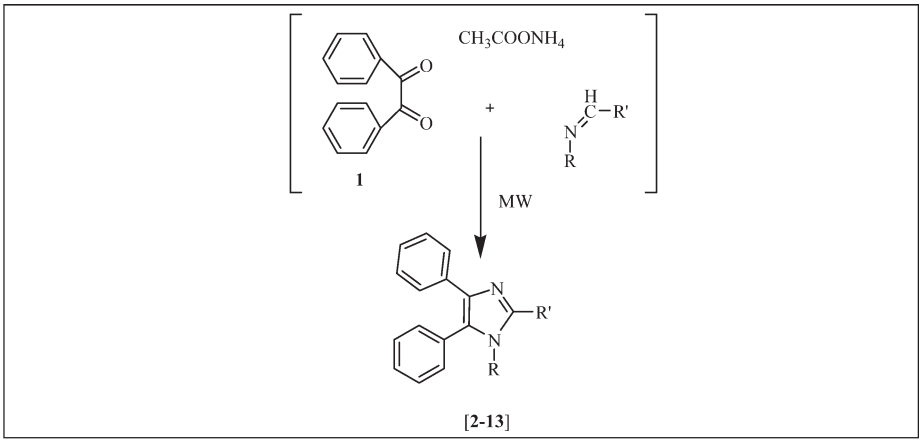

The microwave assisted, solvent free, parallel syntheses of title compounds is described in this protocol. Twelve new tetraaryl imidazoles, which are incorporated with the chemotherapeutic pharmacophores, have been synthesized by adopting one pot multicomponent reaction. Attempt has been made to investigate the mechanism behind the formation of tetraaryl imidazoles by product identification method. The synthesized compounds were analyzed by physical and analytical data. The synthesized compounds were evaluated for their antibacterial, antitubercular, and short-term anticancer activity. Compound **13** was found to be the candidate compound to investigate further for its potential anticancer activity.

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INTRODUCTION

Syntheses of heterocyclic compounds from readily available reagents by simple and efficient methods are the major requirements of heterocyclic chemistry. A survey of the pertinent literature reveals that, tetraaryl imidazoles possess diverse biological activities apart from their synthetic interests [1–3]. They are reported to exhibit pharmacological activities such as antirheumatoid arthritis [4], antituberculosis [5], antiHIV [6], antiepileptic [7], and anticancer activity [8,9]. Some of the best-selling therapies today contain this versatile heterocycle in their core structures. Therefore, it would be difficult to underestimate the importance of imidazoles in the pharmaceutical industry. Structurally, imidazole shows all the typical properties of an aromatic ring system.

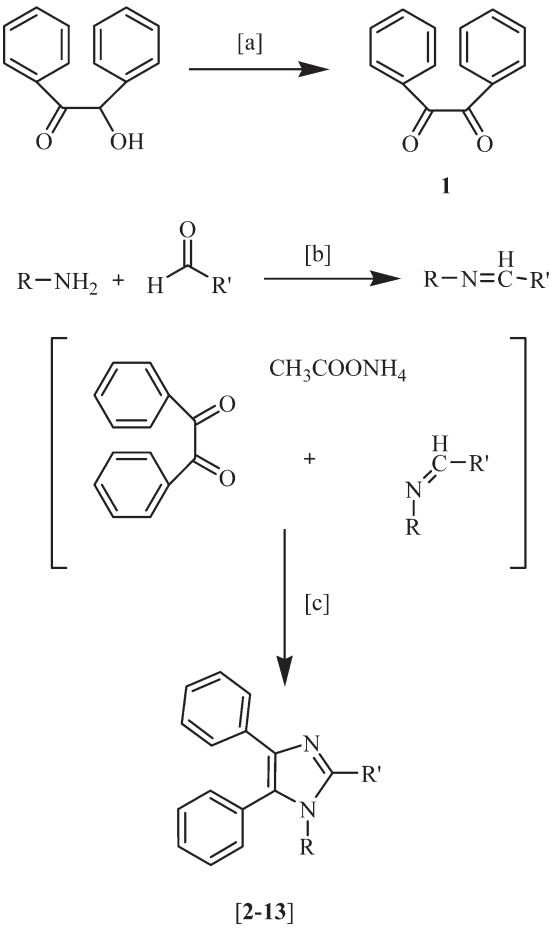
In 1858, Debus reported the reaction between glyoxal and ammonia, ever since this reaction became a novel route to the syntheses of imidazoles [10]. Later, a number of articles have described the syntheses of various imidazoles [11–19].

On the basis of the above observations, we have sought to synthesize novel tetraaryl imidazoles which are incorporated with the chemotherapeutic pharmacophores such as sulphanilamide, its bioisoster PABA (*p*-aminobenzoic acid) and INH (isoniazid) as possible antibacterial, antitubercular, or anticancer agents.

RESULTS AND DISCUSSION

Benzoin on oxidation gave Benzil **1** (Scheme 1). In an attempt to search for oxidizing agent to oxidize a mono ketone to diketone, we tried using oxidizing agents such as aluminium nitrate, cerric ammonium sulphate, ferric ammonium sulphate, potassium nitrate, and sodium nitrite. Among these oxidizing agents, only sodium nitrite was able to oxidize mono ketone to

Scheme 1. Preparation of tetraaryl imidazoles. (a) $NaNO_2$, AcOH, reflux for 50 min. (b) Conv; AcOH, Reflux 5-6 h. MW; Activated silica gel, 1000 W, 8 min. (c) Conv; Ammonium acetate, Reflux 12-15 h. MW; Ammonium acetate, 1000 W, 14–23 min.



diketone efficiently in the presence of glacial acetic acid as a solvent. In the literature [20], nitric acid and lead nitrate were used to oxidize benzoin to benzil taking 1.5 h for completing reaction, involving a nasty brown nitrogenous gas evolution. The same reaction using sodium nitrite just takes 50 min for completion. The yield of benzil was better when compared with the existing oxidizing agents and the brown nitrogenous gas evolution was also been reduced.

The primary aromatic or heteroarylamine was condensed with aryl or heteroaryl aldehydes to afford the corresponding Schiff's base. Schiff's base was further treated with ammonium acetate and benzil in the presence of glacial acetic acid as a solvent, gave the corresponding tetraaryl imidazoles (**2-13**) according to Scheme 1. The microwave assisted parallel syntheses were performed under solvent-free conditions using activated silica gel at the full power of 1000 W. Schiff's base formation was completed after 8 min of microwave irradiation, whereas tetraaryl imidazoles formed after 14–23 min of microwave irradiation.

We have an opinion that, the acidic nature of silica gel would have enhanced this reaction particularly during dehydration steps. All the synthesized compounds were analyzed by TLC, mp, IR, ^{1}H NMR, MASS, and elemental analysis. The ^{1}H NMR showed a characteristic peak for NH between 8.77 and 8.86 δ ppm for compounds containing INH (**2-4**). A characteristic peak for NH_2 was observed between 6.57 and 6.82 δ ppm for compounds containing sulphanilamide (**5-9**). A characteristic peak for COOH was observed between 12.94 and 13.04 δ ppm for compounds containing PABA (**10-13**).

Initially, we tried to synthesize the tetraaryl imidazoles by adopting a one-pot single-step multicomponent reaction by both conventional and microwave method [21–23], involving primary aromatic amine, aldehyde, benzyl, and ammonium acetate as shown in Scheme 2.

However, the above reaction gave triaryl imidazole in addition to the tetraaryl imidazole with incorporated aryl amine in a yield ratio of 3:1, respectively. This result indicated that, the formation of triaryl imidazole is relatively easy when compared with tetraaryl imidazole. To improve the yield of tetraaryl imidazoles and to synthesize them selectively, we have modified the procedure according to the Scheme 1. Hence, for this reason we prepared the Schiff's bases first and then taken further to the cyclization step involving equivalent amount of diketone and excess of ammonium acetate. The list of synthesized compounds and the comparative yield statement between microwave and conventional method is as shown in Table 1.

Scheme 2. (a) Multicomponent reaction, Conv; Glacial acetic acid, reflux 12–15 h, MW; 1000 W, 14–23 min.

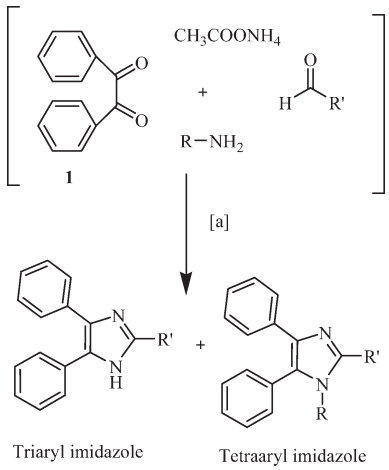
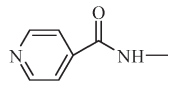
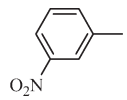
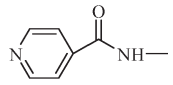
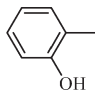
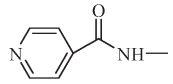
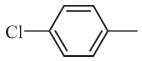
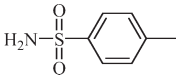
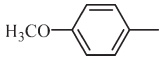
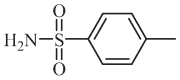
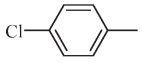
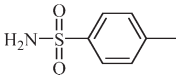
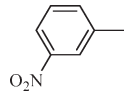
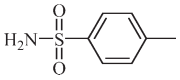
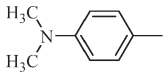
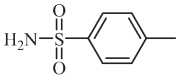
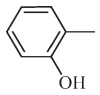
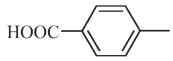
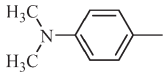
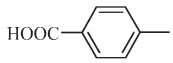
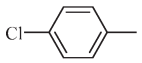
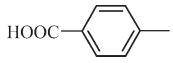
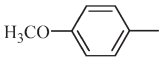
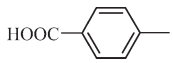
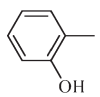


Table 1

Physical and analytical data of compounds **2-13**

Compound	R	R′	Reaction time		Yield (%)[a]		CTC_{50}[c] (μg/mL)
			MW[b] (min)	Conven (h)	MW	Conven	
2			14	13	89	61	190.26
3			16	13	83	58	>500
4			15	14	86	67	500
5			20	15	90	62	>500
6			22	15	91	63	>500
7			21	15	88	61	>500
8			19	15	93	72	>500
9			17	14	81	77	438.50
10			22	15	92	90	>500
11			21	15	86	86	>500
12			20	13	97	88	>500
13			23	15	84	71	94.63

[a] Isolated yield.
[b] Microwave irradiation (Whirlpool™ domestic microwave oven).
[c] The cytotoxic concentration (which inhibited 50% growth of total cells).

To understand the reaction mechanism, we performed a couple of experiments to find out the possible intermediates formed during the formation of tetraaryl imidazoles [24]. The experiments were designed to identify the intermediates under similar reaction conditions as follows,

1. Benzil with ammonium acetate
2. Benzil with PABA
3. PABA with anisaldehyde
4. Ammonium acetate with anisaldehyde
5. Product of experiment 3 with benzil and excess of ammonium acetate.

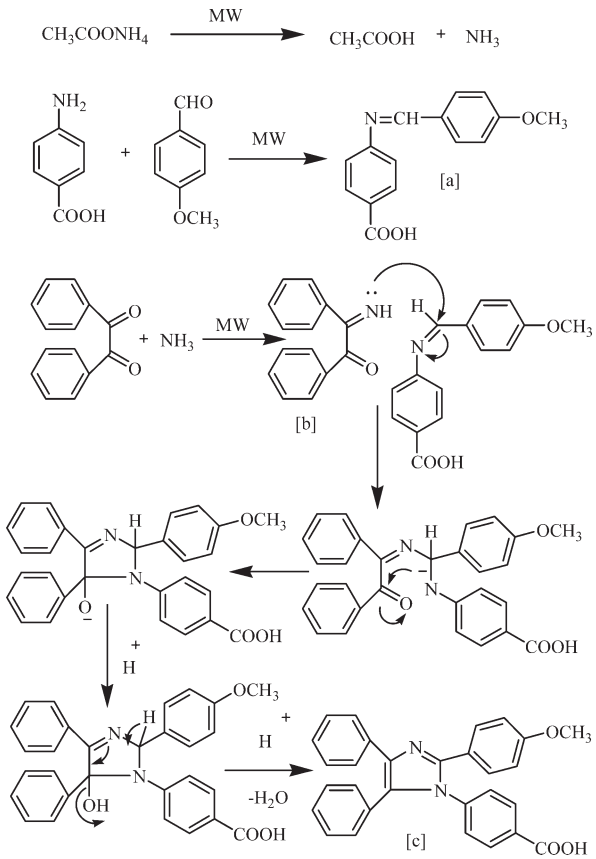
The reaction mixtures were irradiated with microwaves for 8 min and directly fed to the mass spectrometry to find out the intermediates formed under APCI (atmospheric pressure chemical ionization) technique. The reaction mixture of experiment 1 showed a molecular ion peak at 209.0 confirming the formation of mono imine and another molecular ion peak at 208.0 for a di imine. TLC also showed one spot each for mono imine and di imine. Further, isolated yield ratio was found to be 7:1 for the mono imine and di imine, respectively. This experiment indicated that, mono imine formation is favored over the di imine. The reaction mixture of experiment 2 showed the molecular ion peak at 329.1. However, the isolated yield was found to be just 4%. This result indicates that the formation of Schiffs base from diketone is quite difficult in this reaction. Probably, the steric crowding around the diketone (benzil) and less reactivity of aromatic amine may not have favored the formation of Schiff's base. The reaction mixture of experiment 3 showed a molecular ion peak at 255.0 confirming the formation of Schiff's base between aldehyde and aromatic amine, the TLC showed a clear single spot. The isolated yield was found to be about 98%. The reaction mixture of experiment 4 showed a molecular ion peak at 135.0 indicating formation of imine. But, we could not isolate the product, which may be because of its instability or its being formed in very low quantities. The reaction mixture of experiment 5 showed a molecular ion peak at 444.95 confirming the formation of tetraaryl imidazole and no peak was observed for triaryl imidazole. The TLC showed single spot for the formation of tetraaryl imidazole and isolated yield was found to be 99%. The experiment 5 clearly indicates that the Schiffs base formation between aldehyde and aromatic amine is more likely during the formation of tetraaryl imidazole. In contrast to this, the experiment 2 results reveal that possibility of Schiffs bases formation between aryl amine and diketone is less likely under this set of reactants and provided reaction conditions. All the above experiments were conducted by both conventional and microwave method. Acetic acid was used as a solvent in conventional method, whereas activated silica gel was used in the microwave method. By the conventional method all the above reaction mixtures were refluxed for 10 h. The observations were found to be same under both the methods.

In addition to the above experiments, we stopped the reaction between benzil, anisaldehyde, PABA, and ammonium acetate at the half way stage under both microwave and conventional methods. The reaction mixtures were directly fed to the mass spectromet. Presence of triaryl imidazole, tetraaryl imidazole, and product of experiment 1 and 3 was observed.

All the above experimental results revealed the possible intermediates formed during the formation of title compounds. The possible motive or driving force for this reaction would be the formation of relatively more stable imidazole ring system. On the basis of these facts the possible mechanism may be postulated as shown in the Scheme 3.

Even though, protocol and postulated mechanism for the formation of triaryl imidazoles is reported by

Scheme 3. (a) Schiff's base, (b) Imine, (c) Tetraaryl imidazole.



Siddiqui [25] recently in the year 2005. The present protocol and postulated mechanism for the formation of tetraaryl imidazoles attempts to give the better insight based on the experimental facts. We differ from their postulated mechanism by saying; imine formation will be favored between diketone and ammonia, rather between aldehyde and ammonia. The reason for this as already explained in the results of experiment 4. However, further studies are required to come to any hard core conclusion.

All the synthesized tetraaryl imidazoles incorporated with chemotherapeutic pharmacophores were evaluated for their *in vitro* antibacterial activity against two-gram positive bacteriae such as *B. subtilis* and *S. aureus* and two gram negative bacteriae *E. coli* and *K. pneumoniae*. Only compound no **13** exhibited a moderate activity with minimum inhibitory concentration (MIC) of 250 μg against *S. aureus*. Surprisingly, no other compound exhibited an antibacterial activity.

All the synthesized compounds were evaluated for their possible antimycobacterial activity toward a strain of *M. tuberculosis* $H_{37}Rv$ sensitive to isoniazid. Middlebrook (MB) 7H10 agar medium was used for testing antitubercular activity. The MIC determination was performed from 1 to 50 μg/mL concentrations. But, no compound exhibited MIC below 50 μg/mL concentration including the tetraaryl imidazoles containing isoniazid moiety (**2**, **3**, and **4**).

Anticancer activity of the synthesized compounds was evaluated by determining the percentage growth inhibition of DLA (Dalton's lymphoma ascites) cells by tryphan blue dye exclusion technique. Compounds **2**, **9**, and **13** showed good anticancer activity with CTC_{50} (cytotoxic concentration) at 190.26, 438.50, and 94.63 μg/mL, respectively. The synthesized tetraaryl imidazoles and their CTC_{50} values are as shown in Table 1.

In conclusion, we have developed a microwave assisted, convenient, efficient, and environmentally benign protocol for the syntheses of biologically active tetraaryl imidazoles. The present microwave method was found to be better than conventional method in terms of reaction time, yield, and relatively simple method to perform parallel syntheses. Thus, this methodology becomes an efficient strategy for the rapid syntheses of tetraaryl imidazoles, selectively. From the point of biological interest, compound **13** was found to be the candidate compound to investigate further for its anticancer activity.

EXPERIMENTAL

The laboratory grade chemicals and reagents were used to synthesize all the reported compounds. The melting points were determined in open capillaries. Temperatures are expressed in °C and are uncorrected. The IR spectra of compounds were recorded on Perkin-Elmer infrared–283 FTIR spectrometer by KBr pellet technique and are expressed in cm^{-1}. ^1H NMR spectra were recorded on Bruker DRX-300 (300 MHZ, FT-NMR) spectrophotometer using TMS as an internal standard, $CDCl_3$, or DMSO-d_6 as a solvent. The chemical shifts are expressed in δ ppm and following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartlet; and m, multiplet. Mass spectrum was obtained using LC-MS (Schimadzu-2010AT) under atmospheric pressure chemical ionization technique (APCI) 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 the products on precoated aluminum plates using 10% methanol in chloroform or 20% ethyl acetate in pet ether as a mobile phase.

Procedure for the preparation of benzil (1). Crude benzoin (10 g, 0.048 mole) and 15 g of sodium nitrite were transferred to a 250-mL round bottom flask containing 40 mL of glacial acetic acid. The reaction mixture was refluxed using an air condenser for about 50 min (till the evolution of white gaseous vapors ceases). Then the reaction mixture was cooled and poured into a beaker containing 100 mL of ice-cold water. The mixture was stirred well until the oil separates completely as a yellow solid. The crude benzil was collected by filtration, washed thoroughly with water, and recrystallized from ethanol. The reaction was monitored through TLC. Yellow crystals (97%); mp 95°C, IR (cm^{-1}, KBr): 3047 (Ar C—H), 1707 (C=O), 1601 (C=C).

General procedure for the preparation of Schiff's bases

Conventional method. Equimolar amounts (0.01 mole) of aromatic amine and aromatic aldehyde were transferred to a 250-mL flat bottom flask containing 15 mL of glacial acetic acid to serve as a solvent, then refluxed with stirring for about 6 h. After completion of the reaction, the reaction mixture was allowed to cool to give a corresponding product. The reactions were monitored through TLC. The completed reactions were taken directly for the preparation tetraaryl imidazoles.

Microwave method. This reaction was carried out in a parallel synthetic way as shown in Scheme 1. Equimolar amounts (0.01 mole) of aromatic amine and aromatic aldehyde were transferred to a clean and dry mortar containing 2 g of activated silica gel, triturate to become a uniform mixture. The reaction mixture was then transferred to a 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 8 min. Intermittent cooling was done after every 60 s of microwave irradiation. During intermittent cooling, the reaction mixtures were thoroughly mixed using a glass rod. The reactions were monitored through TLC. The completed reactions were taken directly for the preparation of tetraaryl imidazoles without any work up.

General procedures for the preparation of tetraaryl imidazoles (2-13)

Conventional method. Benzil (0.01 mole) was transferred along with excess of ammonium acetate (0.1 mole) into a flask containing the Schiff's base (0.01 mole) obtained in the previous 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. When

complete, the reaction mixture was poured into 250 mL of water to remove ammonium acetate and acetic acid and the product was collected by filtration dried in a hot air oven. The crude product was washed with 2 × 10 mL of toluene to remove traces of any unreacted benzil; further purification by was by recrystallized using ethyl acetate.

Microwave method. This reaction was carried out in a parallel synthetic way as shown in Scheme 1. Benzil (0.01 mole) was transferred along with excess of ammonium acetate (0.1 mole) into a dry mortar containing the Schiff's base (0.01 mole) obtained in the previous microwave procedure. Triturate to become a uniform mixture. The reaction mixture was then transferred to 100 mL beaker. Likewise, 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 14–23 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 reactions were completed. 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 along with silica gel was washed with 2 × 10 mL of toluene to remove traces of any unreacted benzil, 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 physical, analytical, and spectral data of final compounds are given in the following text.

N-*[2-(3-Nitrophenyl)-4,5-diphenylimidazol-1-yl]-pyridamide (2).* Pale yellow crystals; mp 45°C; IR (cm^{-1}, KBr): 3250 (NH), 3032 (Ar C-H), 1654 (C=O), 1621 (C=C), 1595 (C=N), 1528 (NO), 1368 (NO), 1275 (C—N); ^{1}H NMR (δ ppm): 7.25-7.82 (m, 17H, ArH), 8.5 (s, 1H, ArH), 8.82 (bs, 1H, NH); MS (m/z): found 461.80, calcd 462 $(M+H)^+$. 311.05, 326.9, 342.0, 385.10. Anal. Calcd for $C_{27}H_{19}N_2O_3$: C, 70.27; H, 4.14; N, 15.18. Found: C, 70.20; H, 4.20; N, 15.30.

N-*[2-(2-Hydroxyphenyl)-4,5-diphenylimidazol-1-yl]-pyridamide (3).* Yellow crystals; mp 48°C; IR (cm^{-1}, KBr): 3401 (OH), 3260 (NH), 3052 (Ar C—H), 1669 (C=O), 1623 (C=C), 1595 (C=N), 1255 (C=O), 1132 (C=N); ^{1}H NMR (δ ppm): 6.81-8.49 (m, 18H, ArH), 8.80 (bs, 1H, NH), 8.91 (bs, 1H, OH); MS (m/z): found 432.95, calcd 433 $(M+H)^+$. 266.0, 312.95, 352.10. Anal. Calcd for $C_{27}H_{20}N_4O_2$: C, 74.99; H, 4.66; N, 12.95. Found: C, 74.91; H, 4.52; N, 12.81.

N-*[2-(4-Chlorophenyl)-4,5-diphenylimidazol-1-yl]-pyridamide (4).* Pale yellow crystals; mp 190°C; IR (cm^{-1}, KBr): 3245 (NH), 3057 (Ar C—H), 1601 (C=O), 1618 (C=C), 1501 (C=N), 1132 (C—N), 694 (C—Cl); ^{1}H NMR (δ ppm): 7.25-7.94 (m, 18H, ArH), 8.77 (bs, 1H, NH); MS (m/z): found 449.15, calcd 449 $(M-H)^-$. 110.95, 329.30. Anal. Calcd for $C_{27}H_{19}N_4OCl$: C, 71.92; H, 4.25; N, 12.42. Found: C, 72.27; H, 4.23; N, 12.36.

4-[2-(4-Methoxyphenyl)-4,5-diphenylimidazole-1-yl]-benzenesulphonamide (5). White amorphous solid; mp 222°C; IR (cm^{-1}, KBr): 3357 (NH), 3003 (Ar C—H), 1620 (C—C), 1612 (SO), 1578 (C—N), 1327 (SO, asym. Stre), 1291 (C—O), 1251 (C—N), 1143 (SO, sym. Stre), 1071 (C—S); ^{1}H NMR (δ ppm): 3.80 (s, 3H, CH_3), 6.71 (d, 2H, NH_2), 7.28-7.88 (m, 18H, ArH); MS (m/z): found 481.95, calcd, 482 $(M+H)^+$. 327.0, 329.10. Anal. Calcd for $C_{28}H_{23}N_3O_3S$: C, 69.84; H, 4.81; N, 8.73. Found: C, 69.49; H, 4.70; N, 8.54.

4-[2-(4-Chlorophenyl)-4,5-diphenylimidazole-1-yl]-benzenesulphonamide (6). Cream colored crystals; mp 280°C; IR (cm^{-1}, KBr): 3358 (NH), 3026 (Ar C—H), 1654 (C=C), 1560 (C=C), 1485 (C=N), 1324 (SO, asym. stre), 1203 (C—N), 1139 (SO, sym. stre), 1014 (C—S), 697 (C—Cl); ^{1}H NMR (δ ppm): 6.78 (s, 2H, NH_2), 7.29-7.85 (m, 18H, ArH); MS (m/z): found 485.85, calcd, 486 $(M+H)^+$. 327.0, 297.1, 330.0, 333.0, 373.0, 469.95. Anal. Calcd for $C_{28}H_{23}N_3O_3S$: C, 66.73; H, 4.15; N, 8.65. Found: C, 66.57; H, 4.37; N, 8.77.

4-[2-(3-Nitrophenyl)-4,5-diphenylimidazole-1-yl]-benzenesulphonamide (7). Yellow amorphous solid; mp 305°C; IR (cm^{-1}, KBr): 3400 (NH), 3056 (Ar C—H), 1598 (C=C), 1522 (NO, asym. stre), 1479 (C=N), 1348 (NO, sym. stre), 1328 (SO, asym. Stre), 1252 (C—N), 1132 (SO, sym. Stre), 1025 (C—S); ^{1}H NMR (δ ppm): 6.82 (s, 2H, NH_2), 7.25-7.81 (m, 18H, ArH); MS (m/z): found 496.90, calcd 497 $(M+H)^+$. 297.05, 342.05, 344.0, 465.0. Anal. Calcd for $C_{27}H_{20}N_4O_4S$: C, 65.31; H, 4.06; N, 11.28. Found: C, 65.1; H, 4.14; N, 11.42.

4-[2-(4-Dimethylaminophenyl)-4,5-diphenylimidazole-1-yl]-benzenesulphonamide (8). Bright yellow amorphous solid; mp 200°C; IR (cm^{-1}, KBr): 3326 (NH), 3050 (Ar C—H), 2928 (Ali C—H), 1634 (C=C), 1576 (C=N), 1328(SO, asym. Stre), 1229 (C—N), 1128 (SO, sym. Stre), 1063 (C—S); ^{1}H NMR (δ ppm): 1.56 (s, 6H, CH_3), 6.68 (s, 2H, NH_2), 6.9-7.75 (m, 18H, ArH); MS (m/z): found 494.95, calcd 495 $(M+H)^+$. 149.9, 340.05. Anal. Calcd for $C_{29}H_{26}N_4O_2S$: C, 70.42; H, 5.30; N, 11.33. Found: C, 70.35; H, 5.25; N, 11.12.

4-[2-(2-Hydroxyphenyl)-4,5-diphenylimidazole-1-yl]-benzenesulphonamide (9). White crystals; mp 203°C; IR (cm^{-1}, KBr): 3218 (OH), 3064 (Ar C—H), 1666 (C=C), 1540 (C=N), 1325 (asym. stre), 1262 (C—N), 1133 (SO, sym. Stre), 1025 (C—S); ^{1}H NMR (δ ppm): 6.57 (bs, 2H, NH_2), 6.89-7.66 (m, 18H, ArH), 7.92 (bd, 1H, OH); MS (m/z): found 467.85, calcd 468 $(M+H)^+$. 313.05. Anal. Calcd for $C_{27}H_{21}N_3O_3S$: C, 69.36; H, 4.53; N, 8.99. Found: C, 69.42; H, 4.39; N, 8.78.

4-[2-(*p*-Dimethylaminophenyl)-4,5-diphenylimidazole-1-yl]-benzoic acid (10). Yellow amorphous solid; mp 250°C; IR (cm^{-1}, KBr): 3410 (OH), 3058 (Ar C—H), 2879 (Ali C—H), 1717 (C=O), 1360 (C=N), 1228 (C=O), 1198 (C=N); ^{1}H NMR (δ ppm): 3.06 [s, 6H, $(CH_3)_2$], 6.72-7.8 (m, 18H, ArH); 12.94(bs, 1H, COOH) MS (m/z): found 460.0 calcd, 460 $(M+H)^+$. 340.05, 444.95, 427.90. Anal. Calcd for $C_{30}H_{25}N_3O_2$: C, 78.41; H, 5.48; N, 9.14. Found: C, 78.55; H, 5.37; N, 9.30.

4-[2-(4-Chlorophenyl)-4,5-diphenylimidazole-1-yl]-benzoic acid (11). White crystals; mp 272°C; IR (cm^{-1}, KBr): 3390 (OH), 3058 (Ar C—H), 2852 (Ali C—H), 1709 (C=O), 1654 (C=C), 1485 (C=N), 1292 (C—O), 1248 (C—N); ^{1}H NMR (δ ppm): 7.32-7.87 (m, 18H, ArH); 13.01(bs, 1H, COOH) MS (m/z): found 450.90, calcd 451$(M+H)^+$. 313.0. Anal. Calcd for $C_{28}H_{19}N_2O_2Cl$: C, 74.58; H, 4.25; N, 6.21 Found: C, 74.51; H, 4.10; N, 6.02.

4-[2-(4-Methoxyphenyl)-4,5-diphenylimidazole-1-yl]-benzoic acid (12). White crystals; mp 255°C; IR (cm^{-1}, KBr): 3398 (OH), 3042 (Ar C—H), 2958 (Ali C—H), 1710 (C=O), 1667 (C=C), 1493 (C=N), 1292 (C—O), 1248 (C—N); ^{1}H NMR (δ ppm): 3.78 (s, 3H, OCH_3), 6.80-7.84 (m, 18H, ArH),

12.98 (bs, 1H, COOH) MS (m/z): found 446.8, calcd 447 $(M+H)^+$. 313.0. Anal. Calcd for $C_{29}H_{22}N_2O_3$: C, 78.01; H, 4.97; N, 6.27 Found: C, 78.06; H, 4.79; N, 6.24.

4-[2-(2-Hydroxyphenyl)-4,5-diphenylimidazole-1-yl]-benzoic acid (13). White crystals; mp 235°C; IR (cm^{-1}, KBr): 3374 (OH), 3060 (Ar C—H), 1716 (C=O), 1653 (C=C), 1262 (C—O), 1202 (C—N); ^1H NMR (δ ppm): 6.8-8.1 (m, 18H, ArH), 13.04 (bs, 1H, COOH); MS (m/z): found 432.95, calcd 433 $(M+H)^+$. 313.0. Anal. Calcd for $C_{28}H_{20}N_2O_3$: C, 77.76; H, 4.66; N, 6.48 Found: C, 77.45; H, 4.36; N, 6.16.

Antibacterial activity screening procedure. All the synthesized compounds were screened for their antibacterial activity against two-gram positive bacteria such as *B. subtilis* and *S. aureus* and two gram negative bacteria *E. coli* and *K. pneumoniae* according to the standard procedure [26,27]. The primary screen was carried out using the agar disc-diffusion method using Muller-Hinton agar medium. Sterile filter paper discs (8 mm diameter) were moistened with test compound solution in DMSO of specific concentration 500 μg/disc were carefully placed on agar culture plates that had been previously inoculated separately with bacteria. The plates were incubated at 37°C and inhibition of growth was measured after 24 h. The minimal inhibitory concentration (MIC) for the compound 13 against *S. aureus* was carried out using the microdilution susceptibility method in Muller-Hinton Broth by two-fold dilution method and it was found to be 250 μg/mL. Streptomycin was used as a standard drug (MIC $<$ 18 μg against all the bacteria).

Antimycobacterial activity screening procedure. 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 [28]. 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 50 μg/mL concentrations. Isoniazid (INH) was used as a standard drug (MIC, 21 μg/mL).

Anticancer activity screening procedure. Anticancer activities [29–33] of the synthesized compounds were assessed by determining the percentage inhibition of DLA (Dalton's lymphoma ascite) cells by tryphan blue dye exclusion technique according to the standard procedure [33]. 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 tetraaryl imidazoles and their CTC_{50} values are as shown in Table 1. Cyclophospamide was used as standard drug (CTC_{50}, 12 μg/mL).

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