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Article

Synthesis, Biological Evaluation, and Docking Studies of 1,2,4,5-Tetrasubstituted Imidazole Derivatives as Antibacterial Agents: Use of Niobia Supported Heteropoly Tungstate as an Efficient Reusable Catalyst

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ABSTRACT

The preparation of new 1,2,4,5-tetrasubstituted imidazoles was carried out in a single molecular motif using niobia supported heteropoly tungstate as an effective catalyst. The efficient condensation of benzil, 3-aryl-1-phenyl-1*H*-pyrazole-4-carbaldehyde, aromatic amine, and ammonium acetate was achieved using heteropoly tungstate supported on niobia under both the conventional and non-conventional conditions. The employed protocol provides significant advantages, as it exhibits a remarkable catalytic activity on recovery, excellent yields, and excellent reaction efficacy within short reaction times between 1–2 h (conventional) and 1–3 min (MWI). The structures of all the synthesized products were established by means of spectral and elemental analysis data. They were also screened for their antibacterial activity. To predict the binding mode of compounds with glutamine-fructose-6-phosphate transaminase (GlcN6P synthase), docking studies were performed.

Key words: 1,2,4,5-Tetrasubstituted imidazoles, Single molecular motif, Niobia, tungstophosphoric acid, Microwave irradiation, Antibacterial agents.

1. INTRODUCTION

1,2,4,5-Tetrasubstituted imidazoles as natural and fascinating organic compounds have attracted the attention of researchers for their important role in multi-component reactions (MCRs) and making possible an environmentally benign synthesis, using heteropoly acids (HPAs). This leads to their significant role in the development of combinatorial libraries and structure–activity relationship in the optimization phase of drug discovery. Imidazole, being as an important synthon, is involved in pioneering many biochemical reactions of biological systems [1]. Many inhibitors of p38 Kinase [2], angiotensin II receptor antagonists such as Eprosartan [3], *anticoagulants* such as Trifenagrel [4] (2, 4, 5-triaryl substituted imidazole), and antifungals such as Miconazole have the imidazole moiety (Figure 1). Substituted imidazoles possessing anti-allergic activity and analgesic activity have also been reported [5,6]. Transaminase or aminotransferases are a class of enzymes that catalyze the reaction between an amino acid and a α-keto acid. Glutamine-fructose-6-phosphate transaminase has been proposed as a target chemotherapy. In literature, publications on compounds having imidazole and pyrazole scaffold acting as antimicrobial and antifungal agents are available [7]. Due to their widespread biological and pharmaceutical importance, we aimed at synthesizing tetra-substituted imidazoles. In this study, we also reported the molecular docking studies of reported compounds against GlcN6P synthase to rationalize their experimental activity.

The literature has a number of reports on the synthetic protocols of imidazoles [8]. However, a very few protocols to synthesis 1,2,4,5-tetrasubstituted imidazole derivative by multi-component coupling. Tetrasubstituted imidazoles can be directly synthesized by cycloaddition of diketones, amines, heteroaryl aldehydes, and ammonium acetate in glacial acetic acid. Solid catalysts montimorrillonite K10 and montimorrillonite KSF under microwave irradiation used [9].

Various synthetic protocols also suffer from disadvantages such as diaphanous hazards, ravage reaction conditions, expensive acid catalysts, longer reaction times, complex isolation, and hectic recovery process. As a result, the synthetic procedure lacks generality, in addition to generating product still containing the catalyst, which cannot be easily recovered and disposed off. This suggests a wide scope for developing subsequent route to synthesize imidazole substitutes. Development of a clean, environmentally benign synthetic approach by employing non-sophisticated, high-yielding, and reusable catalyst is imperative for organic transformations. We proposed for the first time the novel, recyclable heterogeneous catalyst, like PDTA, can be used as multi-component reactions [10].

We now report niobia-supported heteropoly tungstate as a heterogeneous catalyst toward an easy synthesis of tetrasubstituted imidazoles in solvent-free conditions under traditional and non-traditional methods. These molecules were further evaluated for their antibacterial activity, and molecular docking simulations were also performed using GlcN6P synthase crystal structure.

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2. EXPERIMENTAL SECTION

2.1. General

Melting points of compounds were detected using open capillaries which are uncorrected. TLC (silica gel F254 – Merck) was used for checking the purity of all the products. Microwave reactor – Milestone MultiSYNTH has been employed for the conduct of all the microwave reactions. Shimadzu FTIR-8400s IR spectrometer was used to recorded the FT-IR spectra. ^{1}H-NMR and ^{13}C-NMR spectra were obtained using Advance 400/100 MHz spectrometers, Mass spectra were recorded using Shimadzu Mass-spectrometer. Thermo Finnigan CHNS analyzer was employed for the elemental characterization of the products.

2.2. Preparation of Nb_2O_5 Supported TPA Catalyst

Nb_2O_5 supported TPA catalyst was prepared using impregnation method. Required amount of TPA was dissolved in 4 mL of CH_3OH (per gram solid support), and the resultant solution was added to the support. CH_3OH was evaporated on a rotary evaporator. The solid obtained was dried for overnight at 120 °C, which was calcined at 300 °C in air for 2 h. TPA/Nb_2O_5 catalyst was characterized by FT-IR, powder XRD to establish the Keggin ion structure of TPA after impregnation on support. The acidity of the catalyst was measured using temperature-programmed desorption (TPD) of ammonia method.

2.3. Synthesis of Compounds 3a-b

Synthesis of Schiff's base is represented in Scheme 1. The substituted acetophenones **(1a-b)** (7.4 mmol) and phenyl hydrazine **(2)** (8.8 mmol) taken in round bottom flask and stirred slowly by adding 3-5 mL glacial acetic acid. A pale yellow solid compound thus formed was discharged and refluxed for 10–15 min by adding MeOH (10 mL). Thus, obtained crude reaction mass was filtered and washed with petroleum ether to obtained pure crystals of Schiff's base. Mixture of Schiff's base (4.0 mmol) and $POCl_3$ (10 mmol) in DMF (26 mmol) stirred at room temperature (rt) for overnight. Pale yellow solid crude reaction mixture poured in cold water, which was recrystallised in MeOH to obtain pure substituted pyrazole-4-carbaldehyde derivatives, **3a-b**.

2.4. Procedure for the Preparation of Tetrasubstituted Imidazoles (6a-k)

2.4.1. Conventional method: Synthesis of imidazole derivatives, 6a-k

Benzil **4** (4.76 mmol), substituted pyrazole-4-carbaldehyde (**3a-b**) (5 mmol), aromatic amine (**5a-f)** (5.6 mmol) in methylene dichloride (3 mL), and ammonium acetate (361 mg, 4.7 mmol) were added to round flask consisting 0.1 mol% of niobia supported heteropolyacid tungstate catalyst charged. The resultant dry suspension was heated under conventional method (oil bath) at 140°C for 1.5–2.0 h. The reaction mixture was cooled to rt and mixed thoroughly with acetone (2x10 mL) and filtered the resultant mixture for the separation of the catalyst. Crude reaction mixture washed thoroughly with Et_2O and ether layer was evaporated to result imidazole derivatives, **6a-k** as crystalline substances.

2.4.2. Microwave method: Synthesis of imidazole derivatives (6a-k)

Pyrazole-4-carbaldehyde derivative (**3a-b**) (1.47 g, 5 mmol), benzil **4** (4.76 mmol), ammonium acetate (4.7 mmol), and aromatic amine (**5a-f**) (5.6 mmol) were added to a quartz microwave vial and irradiated with microwaves for 1.0–3.0 min. Reaction mixture was cooled to rt, added acetone (2x10 mL) stirred for 5 min, and filtered for the separation of catalyst. The obtained crude product washed with diethyl ether, the resulted crystals recrystallized using 15:1 (v/v) acetone-water and dried to obtained pure crystals of imidazoles, **6a-k**. The optimization and recycling data of catalyst employed for the synthesis of **6a** is mentioned in Tables 1 and 2, respectively.

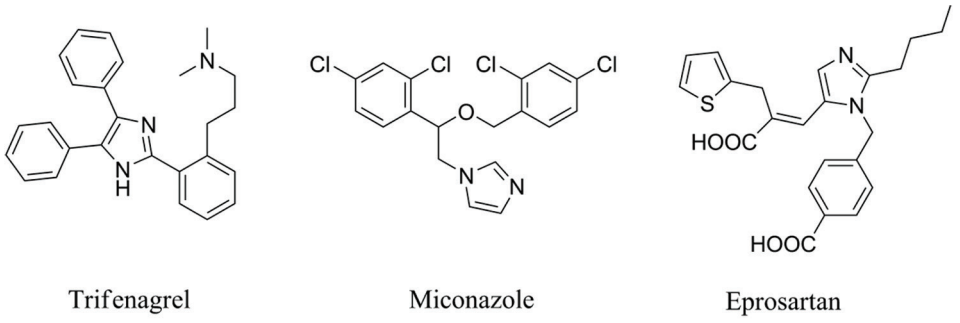
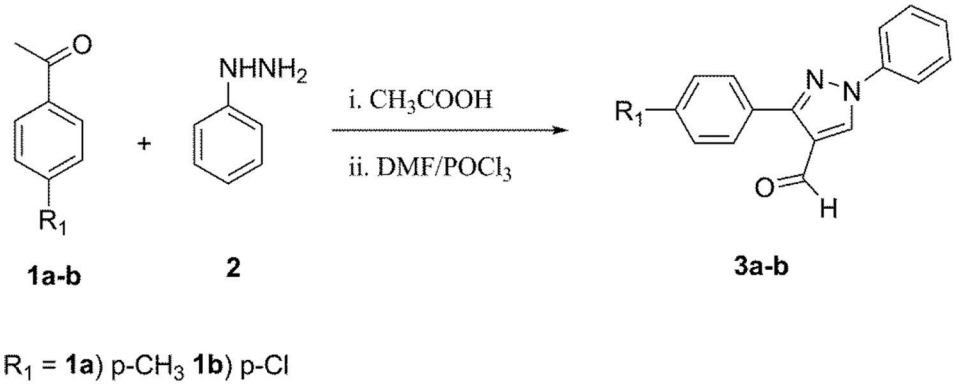


Figure 1: Imidazole moiety-based drug candidates.



Scheme 1: Synthesis of 1-phenyl-3-(aryl)-1*H*-pyrazole-4-carbaldehyde derivatives, **3a-b**.

Table 1: Screening studies of catalyst employed for the preparation of **6a.**

Entry	Catalyst (mol%)	Time (h)	Yield (%)
1	25% TPA Nb_2O_5 (0.01)	1.5	80
2	25% TPA Nb_2O_5 (0.05)	1.5	75
3	25% TPA Nb_2O_5 (0.10)	1.5	97
4	25% TPA Nb_2O_5 (0.15)	2.5	95

Table 2: Recyclability study of catalyst for the preparation of **6a.**

Entry	Recycle No.	Yield (%)
0	0	97
1	1	94
2	2	95
3	3	93
4	4	91
5	5	90
6	6	87
7	7	89

3. RESULTS AND DISCUSSION

3.1. Chemistry

The FT-IR spectrum of the catalyst (supplementary information, Figure S1) mainly exhibited bands at 1081, 981, 887, and 799 cm^{-1} corresponds to the stretching vibrations of P-O_a (O_a – oxygen atoms bound to three W atoms and to P), W-O_t (O_t – terminal oxygen atom), W-O_b-W (O_b – corner-sharing bridging oxygen atom) and W-O_c-W (O_c – edge-sharing bridging oxygen atom), respectively. The FT-IR data suggest the retention of Keggin structure during the impregnation of heteropoly acid on niobia. The XRD patterns (supplementary information, Figure S2) of the catalyst are predominantly related to the supporting niobia. However, relatively less intense peaks related to Keggin ion of TPA are also observed. The low intensity of TPA patterns suggests that it is highly dispersed on niobia. The XRD results indicate the presence of intact Keggin ion after the impregnation on the support. These findings complement the FT-IR results.

The NH_3-TPD analysis of the niobia-supported TPA catalysts showed in supplementary information (Figure S3). Niobia displayed a wide desorption peak at 180–280°C. The TPD spectrum of the catalyst displayed a low-temperature desorption peak at 250–300°C and two high-temperature desorption peaks at 560–680 °C. The high-temperature desorption peak points to the presence of strong acidic sites. This suggests that the presence of TPA on niobia generates strong acidic sites.

A simple procedure implemented for synthesis of tetrasubstituted imidazoles includes second generation heteropolyacid catalyst, 25% TPA Nb_2O_5, added to ammonium acetate–dichloromethane solution of benzil, heterocyclic aldehydes, and aromatic amines. After the solvent evaporates, the resulting solid residue is placed in microwave oven/oil bath (140°C). The four-component system involved benzil (**4**) and aromatic amines (**5a-f**) as starting materials with heterocyclic aldehydes (**3a-b**) being very provocative electron-withdrawing/-donating groups (halide/methyl). Ammonium acetate has been used as nitrogen source for formation of imidazole ring and reaction proceeds smoothly with high yields, which signifies the generality of this synthetic protocol. The structural elucidations of imidazoles (**6a-k**) were performed using ^{1}H-NMR, ^{13}C-NMR, IR, mass spectrometry (LCMS), and melting point. The multi-component reaction (MCR) of benzil, heterocyclic aldehydes, ammonium acetate, and aryl amine under microwave irradiations in the absence of catalyst resulted in a lesser yield (20%).

3.2. Antibacterial Activity

All the imidazole derivatives are screened for antibacterial activity [11] using bacterial strains; *B. subtilis* (ATCC-6633), *S. aureus* (ATCC-29737), *E. coli* (ATCC-10536), and *P. mirabilis* (ATCC-25933) employing ampicillin as a standard. The tests against bacteria were conducted using the paper disc method by measuring inhibition zone in millimeters.

DMF was used to dissolve the samples and Whatman (No. 40) filter paper discs are soaked in varying concentrations of samples from 200 µg/mL to 50 µg/mL. Sterile nutrient agar was used as culture medium was cooled to 50 °C. Actively growing agar slant culture suspension of bacteria swab inoculated separately on these solidified agar plates. Sterile filter paper discs (6 mm diameter) prepared from standard Whatman No. 1 filter papers were dipped in the test solution of different concentrations and after drying the discs, they were introduced on to the above inoculated agar plates containing bacterial strains. The plates with test compound discs were incubated for 24 h at 37°C. The diameter of inhibition zone (in mm) was measured.

3.3. In Silico Molecular Docking Studies

The docking studies of most potent molecules were performed using the Schrodinger software suite (Maestro, version 9.2) [12]. The compounds were sketched in 3D format using build panel and prepared for docking using LigPrep application. The protein coordinates of glucosamine-6-phosphate synthase (PDB ID: 2VF5) [13] for docking study were taken from protein data bank. The protein was prepared by giving preliminary treatment such as adding hydrogen, adding missing residues, refining the loop with prime, and finally minimized using OPLS2005 force field. Grids for molecular docking were generated with bound cocrystallized ligand. Compounds were docked using Glide in extra-precision mode [14], with up to three poses saved per molecule.

3.4. Antibacterial Studies

Antibacterial activity data given in Table 3.

Among the imidazoles screened, **6f** and **6i** exhibited good antibacterial property at 200 µg/disc against all three strains except *B. subtilis*. Imadazoles **6a**, **6c**, **6d,** and **6h** showed moderate antibacterial activity, while **6b**, **6e**, **6j**, **6g,** and **6k** did not show antibacterial activity to *E. coli*. With *P. mirabilis*, **6c** exhibited maximum activity at 100 and 200 µg/disc. With the same strain, imidazoles **6e, 6f, 6g,** and **6j** exhibited moderate activity, whereas **6a, 6b, 6d, 6h, 6i,** and **6k** did not show antibacterial activity. Whereas *B. subtilis*, compounds **6b** and **6h** showed maximum activity at 200 µg/disc, imidazoles **6a, 6c, 6e, 6g,** and **6k** exhibited moderate activity, but **6d, 6f, 6i,** and **6j** did not show antibacterial activity. Imidazoles **6a, 6c, 6f,** and **6i** showed maximum activity at 200 µg/disc, imidazoles **6b, 6e, 6g 6h,** and **6j** exhibited moderate activity, but **6d** and **6k** were found to be inactive with *S. aureus*. These results are shown in Table 3.

3.5. Molecular Docking Studies

Docking studies reveal good binding modes of imidazole derivatives with active site of protein. Large binding pocket of glucosamine-6-phosphate synthase was well occupied by the synthesized molecules (Figure 2).

As shown in Figure 3, in molecule 6i, the nitro group displays two hydrogen bond interactions with hydroxyl and amino groups of Thr 302 and Ser 401, respectively. The phenyl rings of all molecules

Table 3: Bacteriostatic activity of 1-aryl-4,5-diphenyl-2-(1-phenyl-3-aryl-1*H*-pyrazol-4-yl)-1*H*-imidazoles. (**6a-k**).

Entry	*E. coli*			*P. mirabilis*			*B. subtilis*			*S. aureus*		
	200	100	MIC	200	100	MIC	200	100	MIC	200	100	MIC
Ampicillin	11	10	-	11	11	-	11	10	-	11	11	-
6a	11	5	75	-	-	>200	10	6	75	12	7	75
6b	-	-	>200	-	-	>200	12	7	50	10	5	75
6c	9	-	150	12	7	75	9	5	100	12	6	75
6d	10	6	75	-	-	>200	-	-	>200	-	-	>200
6e	-	-	>200	9	6	75	11	6	75	10	5	75
6f	12	6	75	11	6	75	-	-	>200	12	5	75
6g	-	-	>200	10	5	75	10	5	75	9	7	75
6h	10	5	75	-	-	>200	12	7	75	10	5	75
6i	12	7	75	9	-	>100	-	-	>200	11	6	75
6j	-	-	>200	10	6	75	-	-	>200	9	7	75
6k	-	-	>200	-	-	>200	11	5	75	-	-	>200

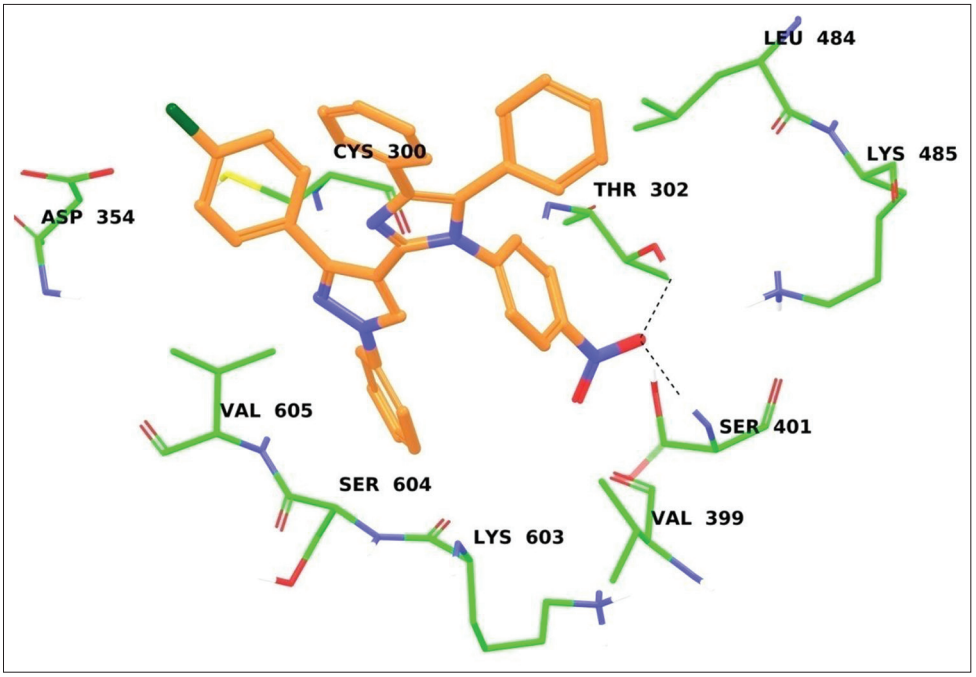


Figure 2: Binding mode and interactions of **6i** with GlcN6P synthase protein.

are involved in hydrophobic interactions with surface hydrophobic residues, that is, Leu 484, Leu 601 and Val 605.

Similarly, novel heterocycles **6b-k** were prepared using the conventional heating as well as microwave irradiations following the procedure employed above (Scheme 2). All the compounds are analyzed by elemental and spectral data. The melting point, reaction time, and percent yield of compounds **6a-k** is presented in Table 4.

*3.5.1. Compound **6a***

IR (KBr): 3062, 2928, 1596, 1535, 1442, 1216, 692 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 7.70 (s, 1H), 6.09-7.12 (m, 23H), 2.34 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$+DMSO-d_6): δ 26.1, 116.4, 123.4, 126.2, 131.5, 131.8, 132.1, 133.0, 133.5, 133.7, 134.3, 134.9, 135.7, 136.1, 139.1, 139.7, 142.6, 144.3, 145.2, 156.2. MS: m/z = 607 (M+H) (87%). Anal. Calcd. for $C_{37}H_{27}BrN_4$ (%): C, 73.26; H, 4.45; N, 9.24. Found (%): C, 73.43; H, 4.51; N, 9.46.

*3.5.2. Compound **6b***

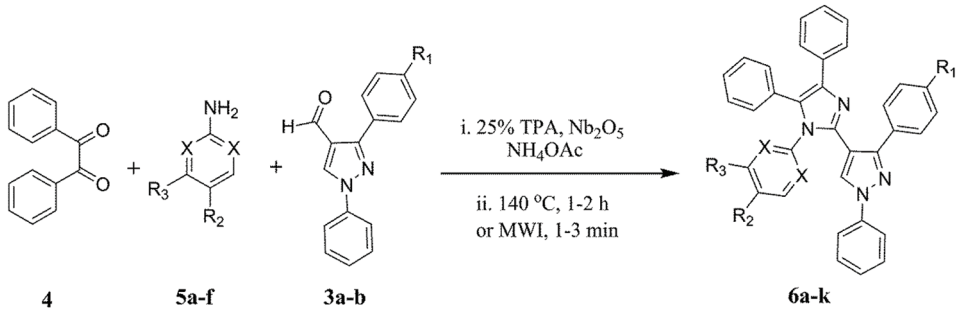
IR (KBr): 3062, 2930, 1597, 1535, 1442, 1412, 1216, 1092 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.35 (s, 1H), 6.42-7.98 (m, 23H), 2.34 (s, 3H). MS: m/z = 563 (M+H). Anal. Calcd. for $C_{37}H_{27}ClN_4$ (%): C, 79.00; H, 4.80, N, 9.96. Found (%): C, 79.10; H, 4.88; N, 10.19.

*3.5.3. Compound **6c***

IR (KBr): 3220, 2361, 1772, 1684, 1633, 1599, 1540, 1506, 1472, 1300, 1250, 842, 754, 697 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.62 (s, 1H), 6.60-8.20 (m, 23H), 2.13 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$+DMSO-d_6): δ 24.2, 112.4, 112.7, 117.7, 118.3, 126.4, 126.5, 127.1, 128.6, 129.7, 135.6, 137.6, 140.9, 142.4, 144.1, 145.8, 148.2. MS: m/z = 573 $[M]^+$. Anal. Calcd. for $C_{37}H_{27}O_2N_5$ (%): C, 76.15; H, 4.63; N, 12.00. Found (%): C, 76.22; H, 4.80; N, 12.19.

Table 4: Physical and analytical data for 25% TPA Nb_2O_5 catalyzed synthesis of 1-aryl-4,5-diphenyl-2-(1-phenyl-3-aryl-1*H*-pyrazol-4-yl)-1*H*-imidazoles (**6a-k**).

Entry	Products	R^1	R^2	R^3	X	M.P. (°C)	Conventional		Microwave	
							Time (h) (140°C)	Yield (%)	Time (min) (MWI)	Yield (%)
1.	**6 a**	CH_3	Br	H	C	166	1.5	94	1.5	97
2.	**6 b**	CH_3	Cl	H	C	172	2.0	92	3.0	96
3.	**6 c**	CH_3	NO_2	H	C	225	2.0	90	2.0	91
4.	**6 d**	CH_3	OMe	H	C	155	1.5	89	2.5	92
5.	**6 e**	CH_3	H	Py	N	267	1.0	91	1.5	95
6.	**6 f**	Cl	Br	H	C	228	1.5	90	1.0	94
7.	**6 g**	Cl	Cl	H	C	210	2.0	91	1.0	93
8.	**6 h**	Cl	F	H	C	185	1.0	90	1.0	96
9.	**6 i**	Cl	NO_2	H	C	235	2.0	90	2.0	92
10.	**6 j**	Cl	OMe	H	C	165	1.5	91	1.5	94
11.	**6 k**	Cl	H	Py	N	243	1.5	85	1.5	90



Scheme 2: Preparation of tetrasubstituted imidazoles (**6a-k**) by MCR.

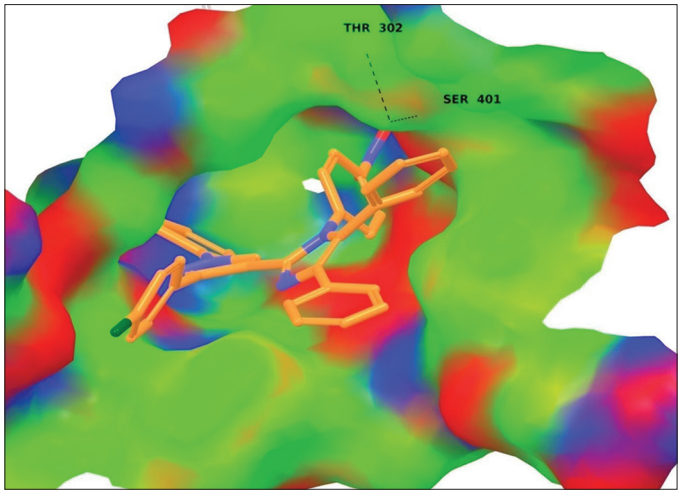


Figure 3: Binding orientation of **6i** at the active site binding pocket of protein.

*3.5.4. Compound **6d***

IR (KBr): 3111, 3036, 2989, 2936, 1597, 1552, 1462, 1379, 1336, 1254, 1032 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.67 (s, 1H), 6.60-7.84 (m, 23H), 3.60 (s, 3H), 2.32 (s, 3H). MS: m/z = 559 (M+H). Anal. Calcd. for $C_{38}H_{30}ON_4$ (%): C, 81.72; H, 5.37; N, 10.03. Found (%): C, 81.82; H, 5.45; N, 10.25.

*3.5.5. Compound **6e***

IR (KBr): 2928, 2881, 1597, 1560, 1462, 1245, 751, 702 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.60 (s, 1H), 6.50-8.35 (m, 25H), 2.30 (s, 3H). MS: m/z = 607 $[M]^+$. Anal. Calcd. for $C_{40}H_{29}N_7$ (%): C, 79.06; H, 4.81; N, 16.13. Found (%): C, 78.82; H, 4.75; N, 16.15.

*3.5.6. Compound **6f***

IR (KBr): 2924, 2883, 1599, 1548, 1462, 1255, 1094, 706, 693 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1H), 6.92-7.43(m, 23H). ^{13}C-NMR (100 MHz, $CDCl_3$+DMSO-d_6): δ 118.9, 119.5, 123.2, 126.8, 127.1, 127.5, 127.9, 128.2, 128.7, 129.0, 129.6, 130.2, 130.8, 131.6, 132.1, 133.0, 133.5, 134.3, 134.9, 135.7, 136.1, 139.1, 139.7, 142.6, 144.3, 145.2. MS: m/z = 627 (M+H). Anal. Calcd. for $C_{36}H_{24}BrClN_4$ (%): C, 69.00; H, 3.83; N, 8.94. Found (%): C, 69.18; H, 3.95; N, 9.02.

*3.5.7. Compound **6g***

IR (KBr): 3057, 2363, 1772, 1684, 1596, 1505, 1212, 1093, 1012, 960, 762, 734 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.53 (s, 1H, C-H), 6.90-8.0 (m, 23H, Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$+DMSO-d_6): δ 111.7, 118.6, 119.2, 120.0, 122.9, 126.9, 126.6, 126.8, 127.2, 127.5, 128.4, 128.9, 129.6, 129.9, 130.3, 130.6, 131.2, 133.2, 133.8, 134.6, 137.3 139.1, 139.9, 144.6, 145.2. MS: m/z = 583 (M+H). Anal. Calcd. for $C_{36}H_{24}Cl_2N_4$ (%): C, 74.22; H, 4.12; N, 9.62. Found (%): C, 74.35; H, 4.21; N, 9.68.

*3.5.8. Compound **6h***

IR (KBr): 3060, 2990, 2879, 1766, 1742, 1684, 1619, 1595, 1535, 1498, 1447, 1339, 1214, 1185, 1152, 1093, 1012, 960, 836 cm^{-1}. ^1H

NMR (400 MHz, DMSO-d_6): δ 8.49 (s, 1H), 6.75-8.01 (m, 23H). MS: m/z = 566 $[M]^+$. Anal. Calcd. for $C_{36}H_{24}ClFN_4$ (%): C, 76.25; H, 4.27; N, 9.88. Found (%): C, 76.05; H, 4.03; N, 9.52.

3.5.9. Compound ***6i***

IR (KBr): 2992, 2880, 1598, 1573, 1460, 1425, 1560, 1305, 1274, 1140, 1098, 1015 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.50 (s, 1H), 7.20-8.10 (m, 23H). MS: m/z = 593 $[M]^+$. Anal. Calcd. for $C_{36}H_{24}ClN_5O_2$ (%): C, 72.78; H, 4.07; N, 11.79. Found (%): C, 72.64; H, 4.15; N, 11.95.

3.5.10. Compound ***6j***

IR (KBr): 2987, 2860, 1595, 1511, 1474, 1453, 1420, 1303, 1274, 1156, 1099 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.52 (s, 1H), 6.80-8.20 (m, 23H), 3.76 (s, 3H). MS: m/z = 579 (M+H). Anal. Calcd. for $C_{37}H_{27}ClN_4O$ (%): C, 76.74; H, 4.70; N, 9.67. Found (%): C, 76.85; H, 4.74; N, 9.65.

3.5.11. Compound ***6k***

IR (KBr): 3060, 1772, 1684, 1590, 1542, 1506, 1453, 1396, 1340, 1217, 1093,1012, 961 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 8.75 (s, 1H), 6.85-7.82 (m, 25H). MS: m/z = 628 (M+H). Anal. Calcd. for $C_{39}H_{26}ClN_7$ (%): C, 74.57; H, 4.17; N, 15.61. Found (%): C, 74.72; H, 4.22; N, 15.65

4. CONCLUSION

In this paper, noteworthy features of a novel catalyst and environmentally benign improvements for the single and effective four-component condensation toward the easy preparation of 1,2,4,5-tetrasubstituted imidazole derivatives. Solvents free and reusable solid catalyst are employed enabling simple experimental and work-up procedures. Excellent yields of imidazole derivatives in short reaction time make this synthetic route eco-friendly. Niobia-supported heteropoly tungstate catalyst is prepared by retaining the Keggin structure of TPA. The catalyst selectively yields desired imidazoles when different substituted hetero aromatic aldehydes are used. The catalyst is active even under solvent-free situation. The catalyst is very easy to handle, thermally stable, and active on reuse. The synthesized novel heterocycles, **6a-k** which possess imidazole and pyrazole ring systems and thus may provide a new avenue for the preparation of some bio-dynamic specialty materials. All the prepared imidazole derivatives were further tested for the antibacterial activity using Ampicillin as standard compound. Among the tested compounds, **6f** and **6i** exhibited maximum antibacterial activity. Molecular docking studies performed to rationalize antibacterial property of synthesized imidazole derivatives.

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ELECTRONIC SUPPLEMENTARY INFORMATION

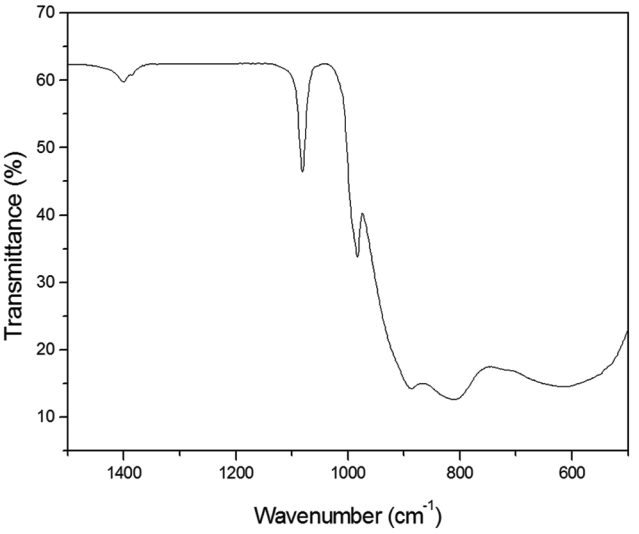

Figure S1: FT-IR spectra of the catalyst is presented.

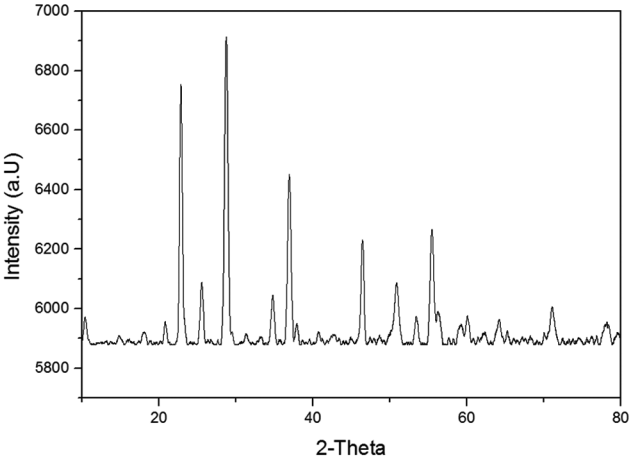

Figure S2: XRD patterns of catalyst.

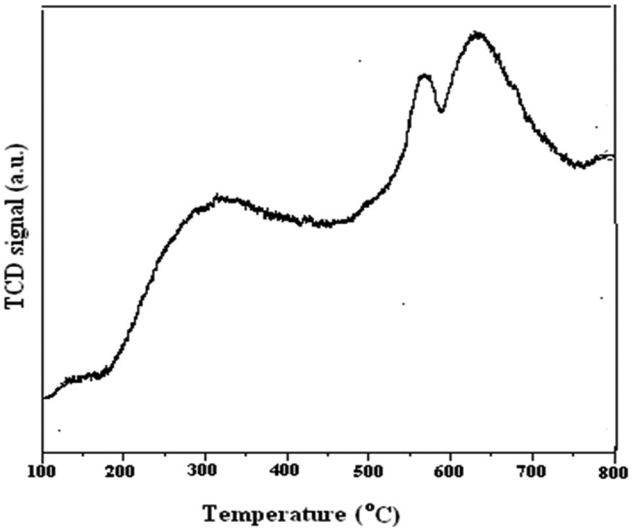

Figure S3: NH3-TPD profiles of the niobia supported TPA catalysts.