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

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The synthesis of novel 1,2,4,5-tetrasubstituted imidazoles was carried out in a single molecular motif using niobia supported heteropoly tungstate as a mild and efficient reusable catalyst. The condensation of 3-aryl-1-phenyl-1*H*-pyrazole-4-carbaldehyde, aromatic amine, benzil, ammonium acetate and heteropoly tungstate supported on niobia was achieved under both 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 (microwave radiation). All the obtained compounds were characterized by means of spectral data and elemental analysis. 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.

Keywords: 1,2,4,5-Tetrasubstituted imidazoles, Tungstophosphoric acid, Microwave irradiation, Antibacterial agents.

INTRODUCTION

1,2,4,5-Tetrasubstituted imidazoles are fascinating and natural organic compounds,which has 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 [1,2]. Many inhibitors of p38 Kinase [3], angiotensin II receptor antagonists such as eprosartan [4], anticoagulants such as trifenagrel (2,4,5-triaryl substituted imidazole) [5] and anti-fungals such as miconazole have the imidazole moiety. Substituted imidazoles possessing antiallergic activity and analgesic activity have also been reported [6,7]. 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. Several publications on compounds having imidazole and pyrazole scaffold acting as antimicrobial and antifungal agents are available [8-10]. Due to their widespread biological and pharmaceutical importance, we aimed to synthesize tetrasubstituted imidazoles. In this study, we also reported the molecular docking studies of reported compounds against GlcN6P synthase to rationalize their experimental activity.

Literature has a number of reports on the synthetic protocols of imidazoles [11,12]. But a few protocols to synthesize 1,2,4,5-tetrasubstituted imidazoles by multi-component coupling. Tetrasubstituted imidazoles can be directly synthesize by cycloaddition of diketones, heteroaryl aldehydes, ammonium acetate and amines in glacial acetic acid. Solid catalysts such as montimorrillonite K10, montimorillonite KSF, *etc*. under microwave irradiation were also utilized [13-21].

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 palladium tetraamine (PdTA) can be used as multi-component reactions [22-24].

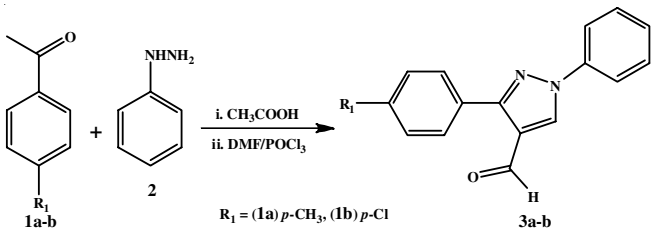
We now report niobia-supported heteropoly tungstate as a heterogeneous catalyst for synthesis of tetrasubstituted imidazoles in solvent-free conditions under traditional and non-traditional methods. These molecules were further evaluated for their antibacterial activity and molecular docking simulations were also performed using Glc N6P synthase crystal structure.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The purity of the compounds was checked routinely by the silica gel F_{254} (Merck). Microwave reactions were carried out in the Milestone MultiSYNTH microwave system. IR spectra were recorded on Shimadzu FTIR-8400s spectrophotometer. ^1H & ^{13}C NMR spectra were recorded on Avance 400 MHz and 100 MHz spectrometers, respectively, Mass spectra were recorded on Shimadzu mass spectrometer. Elemental analysis was determined by using Thermo Finnigan CHNS analyzer.

Preparation of niobia (Nb_2O_5) supported 12-Tungstophosphoric acid (TPA) catalyst: Nb_2O_5 supported TPA catalyst was prepared by impregnation method. The required quantity of TPA was dissolved in methanol (4 mL methanol was used per gram of solid support) and added to support. Methanol was removed on a rota evaporator. Solid obtained was dried at 120 ºC for overnight and finally calcined in air at 300 °C for 2 h. TPA/Nb_2O_5 catalyst was characterized by FT-infrared (FT-IR), X-ray diffraction (XRD) to know the presence of Keggin ion structure of TPA after impregnation on support. The acidity of the catalyst was measured by the temperature programmed desorption of ammonia (TPD) method.

Synthesis of 1-phenyl-3-(aryl)-1*H*-pyrazole-4-carbaldehydes (3a-b): Substituted acetophenones **(1a-b)** (7.4 mmol) and phenyl hydrazine **(2)** (8.8 mmol) taken in a 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 base. Mixture of Schiff base (4.0 mmol) and $POCl_3$ (10 mmol) in DMF (26 mmol) was stirred overnight at room temperature. Pale yellow solid crude reaction mixture poured in cold water, which was recrystallized in MeOH to obtain pure 1-phenyl-3-(aryl)-1*H*-pyrazole-4-carbaldehydes **(3a-b)** (**Scheme-I**).

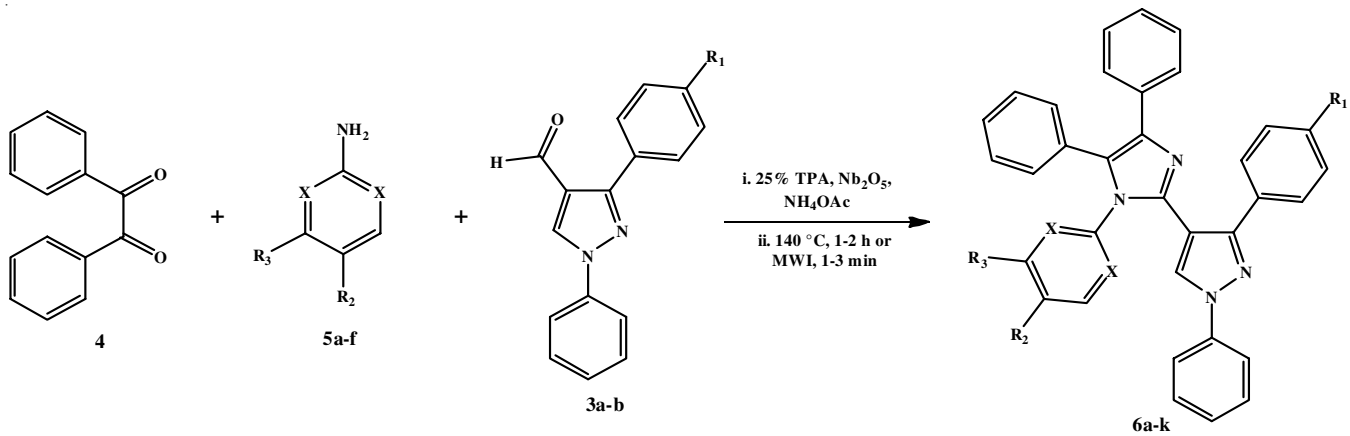


Scheme-I: Synthesis of 1-phenyl-3-(aryl)-1*H*-pyrazole-4-carbaldehydes (**3a-b**)

Synthesis of tetrasubstituted imidazoles (6a-k)

Conventional method: A mixture benzil (**4**, 4.76 mmol), 1-phenyl-3-(aryl)-1*H*-pyrazole-4-carbaldehyde (**3a-b**, 5 mmol), aromatic anilines (**5a-f**, 5.6 mmol) in methylene dichloride (3 mL) and ammonium acetate (361 mg, 4.7mmol) was taken in a round flask and 0.1 mol% of niobia supported heteropolyacid tungstate catalyst charged. The resultant dry residue was heated on the oil bath at 140 ºC for 1.5-2.0 h. Reaction mixture was cooled to room temperature and mixed thoroughly with acetone (2 × 10 mL). Under reduced pressure reaction mixture was filtered to separate the catalyst and the solvent. Crude reaction mixture was washed with diethyl ether and then the etheral layer was removed under reduced pressure resulted in the formation of crystals of 1-(aryl)-4,5-diphenyl-2-(1-phenyl-3-aryl-1*H*-pyrazol-4-yl)-1*H*-imidazole (**6a-k**) and then finally recrystallized from acetone-water (15:1, v/v) (**Scheme-II**).

Microwave Method: A mixture of 1-phenyl-3-(aryl)-1*H*-pyrazole-4-carbaldehyde (**3a-b**, 1.47 g, 5 mmol), benzil (**4**, 4.76 mmol), aromatic anilines (**5a-f**, 5.6 mmol) and ammonium acetate (4.7 mmol) taken in a quartz tube subjected to microwave irradiation for 1.0-3.0 min in Milestone MultiSYNTH microwave



Scheme-II: Synthesis of tetrasubstituted imidazoles (**6a-k**) by multicomponent reaction (MCR)

system. Reaction mixture cooled to room temperature, followed by the addition of acetone (2 × 10 mL), stirred for 5 min and finally filtered to separate the catalyst. The obtained crude product washed with diethyl ether thoroughly, then the resulted crystals were recrystallized using acetone-water (15:1, v/v) and dried to obtain pure crystals of 1-(aryl)-4,5-diphenyl-2-(1-phenyl-3-(aryl)-1*H*-pyrazol-4-yl)-1*H*-imidazole-(1,2,4,5-tetrasubstituted imidazoles) (**6a-k**) (**Scheme-II**).

The optimization and recycling data of catalyst employed for the synthesis of compound **6a** is mentioned in Tables 1 and 2, respectively. The melting point, reaction time and percent yield of the synthesized compounds **6a-k** are presented in Table-3.

TABLE-1
OPTIMIZATION STUDIES OF CATALYST EMPLOYED FOR THE SYNTHESIS 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
RECYCLING OF THE CATALYST FOR THE SYNTHESIS 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

1-(4-Bromophenyl)-4,5-diphenyl-2-(1-phenyl-3-*p*-tolyl-1*H*-pyrazol-4-yl)-1*H*-imidazole (6a): IR (KBr, ν_{max}, cm^{-1}): 3062, 2928, 1596, 1535, 1442, 1216, 692. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.70 (s, 1H, C-H), 6.09-7.12 (m, 23H, Ar-H), 2.34 (s, 3H, CH_3). ^{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: $[M+H]^+$ *m/z* = 607 (87%). Analysis calcd. (found) % for $C_{37}H_{27}N_4Br$: C, 73.26 (73.43); H, 4.45 (4.51); N, 9.24 (9.46).

1-(4-Chlorophenyl)-4,5-diphenyl-2-(1-phenyl-3-*p*-tolyl-1*H*-pyrazol-4-yl)-1*H*-imidazole (6b): IR (KBr, ν_{max}, cm^{-1}): 3062, 2930, 1597, 1535, 1442, 1412, 1216, 1092. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.35 (s, 1H, C-H), 6.42-7.98 (m, 23H, Ar-H), 2.34 (s, 3H, CH_3). MS: $[M+H]^+$ *m/z* =563. Analysis calcd. (found) % for $C_{37}H_{27}N_4Cl$: C, 79.00 (79.10); H, 4.80 (4.88), N, 9.96 (10.19).

1-(4-Nitrophenyl)-4,5-diphenyl-2-(1-phenyl-3-*p*-tolyl-1*H*-pyrazol-4-yl)-1*H*-imidazole (6c): IR (KBr, ν_{max}, cm^{-1}): 3220, 2361, 1772, 1684, 1633, 1599, 1540, 1506, 1472, 1300, 1250, 842, 754, 697. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.62 (s, 1H, C-H), 6.60-8.20 (m, 23H, Ar-H), 2.13 (s, 3H, CH_3). ^{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: $[M]^+$ *m/z* =573. Analysis calcd. (found) % for $C_{37}H_{27}N_5O_2$: C, 76.15 (76.22); H, 4.63 (4.80); N, 12.00 (12.19).

1-(4-Methoxyphenyl)-4,5-diphenyl-2-(1-phenyl-3-*p*-tolyl-1*H*-pyrazol-4-yl)-1*H*-imidazole (6d): IR (KBr, ν_{max}, cm^{-1}): 3111, 3036, 2989, 2936, 1597, 1552, 1462, 1379, 1336, 1254, 1032. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.67 (s, 1H, C-H), 6.60-7.84 (m, 23H, Ar-H), 3.60 (s, 3H, OCH_3), 2.32 (s, 3H, CH_3). MS: $[M+H]^+$ *m/z* =559. Analysis calcd. (found) % for $C_{38}H_{30}ON_4$: C, 81.72 (81.82); H, 5.37 (5.45); N, 10.03 (10.25).

2-[4,5-Diphenyl-2-(1-phenyl-3-*p*-tolyl-1*H*-pyrazol-4-yl)-1*H*-imidazol-1-yl]-4-pyridin-3-yl-pyrimidine (6e): IR (KBr, ν_{max}, cm^{-1}): 2928, 2881, 1597, 1560, 1462, 1245, 751, 702. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.60 (s, 1H, C-H), 6.50-8.35 (m, 25H, Ar-H), 2.30 (s, 3H, CH_3). MS: $[M]^+$ *m/z* = 607. Analysis calcd. (found) % for $C_{40}H_{29}N_7$ (%): C, 79.06 (78.82); H, 4.81 (4.75); N, 16.13 (16.15).

1-(4-Bromophenyl)-2-(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-4,5-diphenyl-1*H*-imidazole (6f): IR (KBr, ν_{max}, cm^{-1}): 2924, 2883, 1599, 1548, 1462, 1255, 1094, 706, 693. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1H, C-H), 6.92-7.43 (m, 23H, Ar-H). ^{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:

TABLE-3
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	**6a**	CH_3	Br	H	C	166	1.5	94	1.5	97
2	**6b**	CH_3	Cl	H	C	172	2.0	92	3.0	96
3	**6c**	CH_3	NO_2	H	C	225	2.0	90	2.0	91
4	**6d**	CH_3	OMe	H	C	155	1.5	89	2.5	92
5	**6e**	CH_3	H	Py	N	267	1.0	91	1.5	95
6	**6f**	Cl	Br	H	C	228	1.5	90	1.0	94
7	**6g**	Cl	Cl	H	C	210	2.0	91	1.0	93
8	**6h**	Cl	F	H	C	185	1.0	90	1.0	96
9	**6i**	Cl	NO_2	H	C	235	2.0	90	2.0	92
10	**6j**	Cl	OMe	H	C	165	1.5	91	1.5	94
11	**6k**	Cl	H	Py	N	243	1.5	85	1.5	90

$[M+H]^+$ *m/z* = 627. Analysis calcd. (found) % for $C_{36}H_{24}N_4BrCl$ (%): C, 69.00 (69.18); H, 3.83 (3.95); N, 8.94 (9.02).

1-(4-Chlorophenyl)-2-(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-4,5-diphenyl-1*H*-imidazole (6g): IR (KBr, ν_{max}, cm^{-1}): 3057, 2363, 1772, 1684, 1596, 1505, 1212, 1093, 1012, 960, 762, 734. ^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: $[M+H]^+$ *m/z* = 583. Analysis calcd. (found) % for $C_{36}H_{24}N_4Cl_2$ (%): C, 74.22 (74.35); H, 4.12 (4.21); N, 9.62 (9.68).

(1-(4-Fluorophenyl)-2-(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-4,5-diphenyl-1*H*-imidazole (6h): IR (KBr, ν_{max}, cm^{-1}): 3060, 2990, 2879, 1766, 1742, 1684, 1619, 1595, 1535, 1498, 1447, 1339, 1214, 1185, 1152, 1093, 1012, 960, 836. ^1H NMR (400 MHz, DMSO-d_6): δ 8.49 (s, 1H, C-H), 6.75-8.01 (m, 23H, Ar-H). MS: $[M]^+$ *m/z* = 566. Analysis calcd. (found) % for $C_{36}H_{24}N_4ClF$ (%): C, 76.25 (76.05); H, 4.27 (4.03); N, 9.88 (9.52).

1-(4-Nitrophenyl)-2-(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-4,5-diphenyl-1*H*-imidazole (6i): IR (KBr, ν_{max}, cm^{-1}): 2992, 2880, 1598, 1573, 1460, 1425, 1560, 1305, 1274, 1140, 1098, 1015. ^1H NMR (400 MHz, DMSO-d_6): δ 8.50 (s, 1H, C-H), 7.20-8.10 (m, 23H, Ar-H). MS: $[M]^+$ *m/z* = 593. Analysis calcd. (found) % for $C_{36}H_{24}N_5O_2Cl$ (%): C, 72.78 (72.64); H, 4.07 (4.15); N, 11.79 (11.95).

1-(4-Methoxyphenyl)-2-(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-4,5-diphenyl-1*H*-imidazole (6j): IR (KBr, ν_{max}, cm^{-1}): 2987, 2860, 1595, 1511, 1474, 1453, 1420, 1303, 1274, 1156, 1099. ^1H NMR (400 MHz, DMSO-d_6): δ 8.52 (s, 1H, C-H), 6.80-8.20 (m, 23H, Ar-H), 3.76 (s, 3H, OCH_3). MS: $[M+H]^+$ *m/z* = 579. Analysis calcd. (found) % for $C_{37}H_{27}N_4OCl$ (%): C, 76.74 (76.85); H, 4.70 (4.74); N, 9.67 (9.65).

2-(2-(3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-4,5-diphenyl-1*H*-imidazol-1-yl)-4-(pyridin-3-yl)pyrimidine (6k): IR (KBr, ν_{max}, cm^{-1}): 3060, 1772, 1684, 1590, 1542, 1506, 1453, 1396, 1340, 1217, 1093,1012, 961. ^1H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 8.75 (s, 1H, C-H), 6.85-7.82 (m, 25H, Ar-H). MS: $[M+H]^+$ *m/z* = 628. Analysis calcd. (found) % for $C_{39}H_{26}N_7Cl$ (%): C, 74.57 (74.72); H, 4.17 (4.22); N, 15.61 (15.65).

Antibacterial activity: All the compounds were screened for their antibacterial activity [25] against bacterial strains such as *Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (ATCC 29737), *Escherichia coli* (ATCC 10536) and *Proteus mirabilis* (ATCC 25933) using ampicillin as standard drug. The testing against bacteria was carried out by employing the paper disc method measuring the inhibition zone in millimetres.

The synthesized compounds were dissolved in DMF (AR grade) and Whatman No. 40 filter paper discs were soaked in different concentrations obtained in the range of 50-200 μg/mL. The sterile nutrient agar used as a culture medium, cooled to 50 ºC. 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 ºC. The diameter of inhibition zone (in millimetres) was measured.

***in silico* Molecular docking studies:** The docking studies of most potent molecules were performed using the Schrödinger software suite (Maestro, version 9.2) [26]. The synthesized 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) [27] for docking study were taken from the protein data bank. The protein was prepared by giving preliminary treatment like adding hydrogen, adding missing residues, refining the loop with prime and finally minimized by using OPLS2005 force field. Grids for molecular docking were generated with bound co-crystallized ligand. Compounds were docked using Glide in extra-precision mode [28], with up to three poses saved per molecule.

RESULTS AND DISCUSSION

Characterization of the prepared catalyst

FTIR studies: The FT-IR spectrum of the catalyst (Fig. 1) mainly exhibited bands at 1081, 981, 887 and 799 cm^{-1}, which are related to 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.

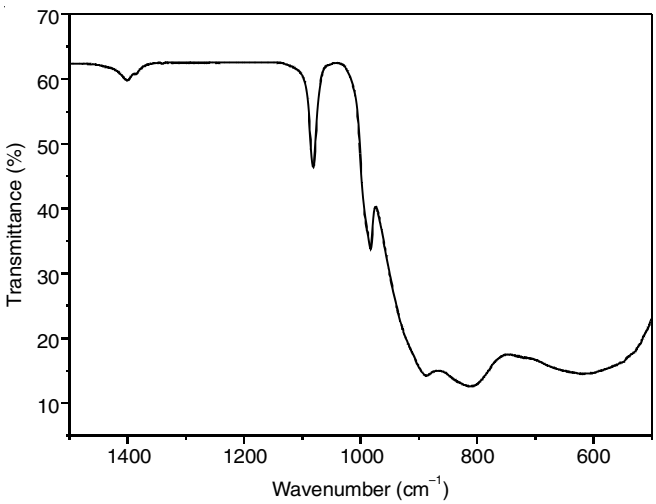


Fig. 1. FT-IR spectra of niobia supported TPA catalyst

XRD studies: The XRD patterns (Fig. 2) 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 are complement with the FT-IR results.

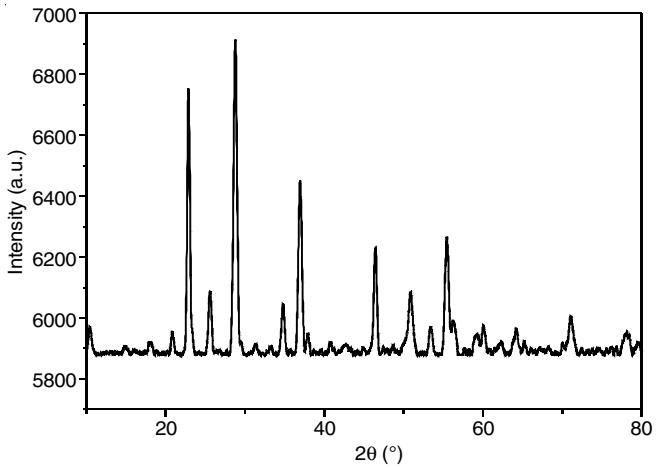


Fig. 2. XRD patterns of niobia supported TPA catalyst

Desorption of ammonia: The NH_3-TPD profiles of niobia supported TPA catalysts are shown in Fig. 3. Niobia showed a broad desorption peak between 180 and 280 ºC. The TPD spectrum of the catalyst showed a low-temperature desorption peak at 250-300 ºC and two high-temperature desorption peaks in the range of 560-680 ºC. 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.

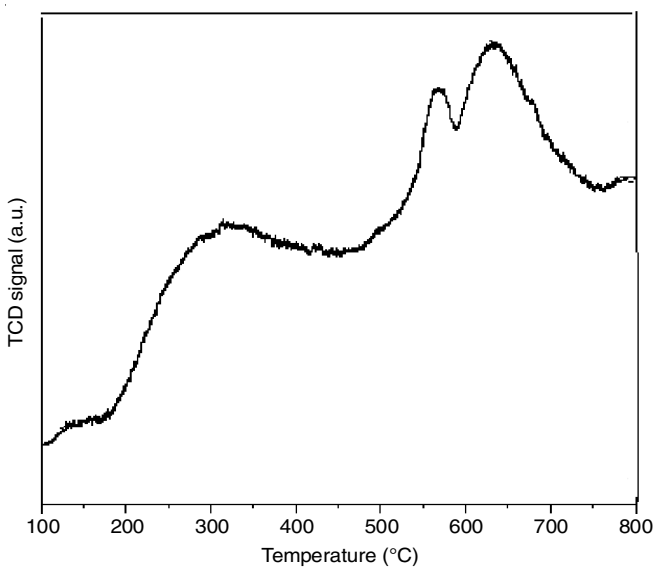


Fig. 3. NH_3-TPD profiles of niobia supported TPA catalyst

Chemistry: A simple procedure implemented for the 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 was placed in a microwave oven or oil bath (at 140 ºC). 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 elucidation of the synthesized imidazoles (**6a-k**) were performed by IR, ^1H & ^{13}C NMR and mass spectrometry (LC-MS). The multi-component reaction (MCR) of benzil, heterocyclic aldehydes, aryl amine and ammonium acetate under microwave irradiation and in the absence of catalytic activity consequently resulted in a lesser yield (20%).

Antibacterial studies: Antibacterial activity data given in Table-4. Among the compounds screened, **6f** and **6i** exhibited good antibacterial activity at 200 µg/disc against all three strains except *B. subtilis*. Compounds **6a**, **6c**, **6d** and **6h** showed moderate antibacterial activity and **6b**, **6e**, **6j**, **6g** and **6k** did not show antibacterial activity against *E. coli*. With *P. mirabilis*, compound **6c** exhibited maximum activity at 100 and 200 µg/disc. With the same strain, compounds **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, compounds **6a**, **6c**, **6e**, **6g** and **6k** exhibited moderate activity, but **6d**, **6f**, **6i** and **6j** did not show antibacterial activity. Compounds **6a**, **6c**, **6f** and **6i** showed maximum activity at 200 µg/disc, compounds **6b**, **6e**, **6g**, **6h** and **6j** exhibited moderate activity, but compounds **6d** and **6k** were found to be inactive with *S. aureus*.

Molecular docking studies: Docking studies revealed a good binding modes of compounds with the active site of protein.

TABLE-4
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

Large binding pocket of glucosamine-6-phosphate synthase was well occupied by the synthesized molecules (Fig. 4).

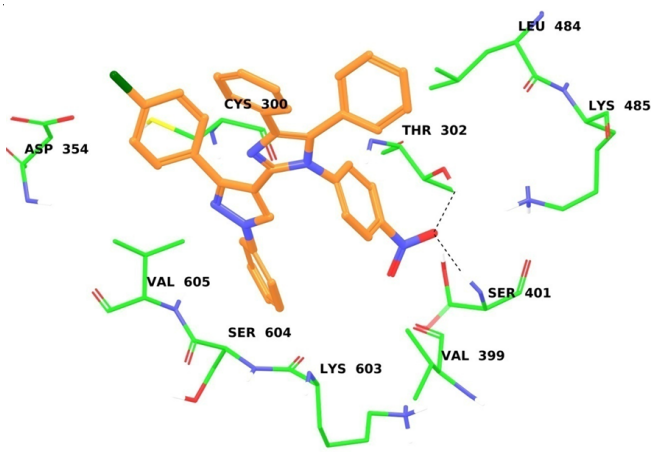


Fig. 4. Binding mode and interactions of 6i with GlcN6P synthase protein

As shown in Fig. 5, 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 are involved in hydrophobic interactions with surface hydrophobic residues, *i.e.* Leu 484, Leu 601 and Val 605.

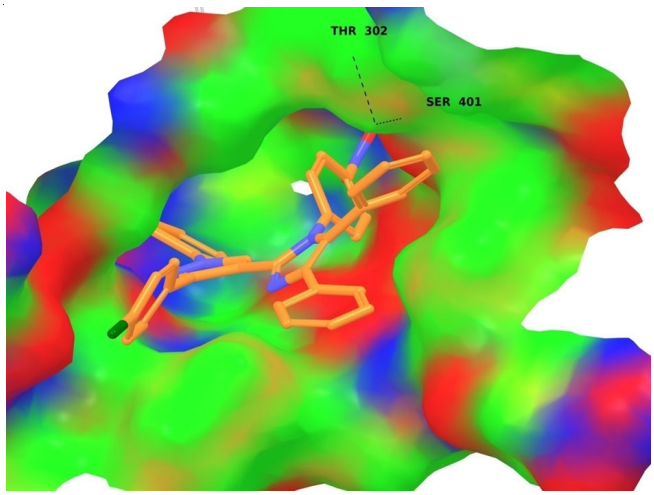


Fig. 5. Binding orientation of **6i** at the active site binding pocket of protein

Conclusion

In this study, noteworthy features of a novel catalyst and environmentally benign improvements for the efficient and single four-component condensation synthesis of 1,2,4,5-tetra-substituted imidazoles are reported. Solvents free and reusable solid catalyst was employed with a simple set-up and work-up. High yields and short reaction times make this synthetic route eco-friendly. Niobia-supported heteropoly tungstate catalyst was prepared by retaining the Keggin structure of 12-tungsto-phosphoric acid (TPA). The catalyst selectively yields desired imidazoles when different substituted heteroaromatic aldehydes were used. The catalyst was active even under solvent-free conditions. The catalyst is very easy to handle, thermally stable and active upon reuse. The synthesized heterocycles **6a-k** possess imidazole and pyrazole ring systems and thus may provide a new path for the synthesis of some biodynamic specialty materials. All the synthesized compounds were further evaluated for their antibacterial activity using ampicillin as standard drug. Among the synthesized compounds, **6f** and **6i** exhibited maximum antibacterial activity. Molecular docking studies were also performed to rationalize antibacterial activity of the synthesized compounds.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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