CHAPTER 2

Acid-Promoted Multi-Component Synthesis of Imidazolyl-Pyrazole Derivatives Using Microwave Irradiation
Chapter-2

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2.1 Introduction:

Imidazole is an aromatic heterocycle classified as an alkaloid having 5-membered planar ring, which is soluble in water and other polar solvents. It exists in two tautomeric forms, 1H-imidazole and 3H-imidazole, because the hydrogen atom can be positioned on either of the two nitrogen atoms. Imidazole is a highly polar compound, as evident by a calculated dipole of 3.61D, and is entirely soluble in polar solvent water. The compound is classified as aromatic due to the presence of 6π-electrons, consisting of a pair of electrons from the protonated nitrogen atom and one from each four atoms of the ring.

![Imidazole](image)

Imidazole is amphoteric as, it can behave as both an acid and as a base. As an acid, the pKa of imidazole is 14.4, being less acidic than carboxylic acids, phenols, and imides, but slightly more acidic than alcohols. The acidic proton is positioned on N-1. As a base, the pKa of the conjugate acid is approximately 7, making imidazole approximately sixty times more basic than pyridine. The basic position is N-3. Protonation gives the imidazolium cation, which is symmetrical.
2.2 Pharmaceutical importance of imidazoles:

Imidazole is present in many biologically important building-blocks, such as histidine, and the related hormone histamine. When imidazole fused with a pyrimidine nucleus, it forms purine, which is the most widely occurring nitrogen-containing heterocycle in nature.\(^1\) The most persistent is the amino acid histidine which contains imidazole nucleolus. Histidine is present in various proteins and enzymes and plays an essential part in the structure and binding functions of hemoglobin. Literature survey revealed that imidazole and its derivative are reported to have various activity like analgesic, anti-inflammatory activity\(^2,3,4\), cardiovascular activity\(^5,6\), anti-neoplastic activity\(^7\), anti-fungal activity\(^8\), enzyme inhibition activity\(^9\), anthelmintic activity\(^10\), anti-filarial agent, anti-viral activity and anti-ulcer activity.

Many drugs contain an imidazole such as Metronidazole (antibacterial), Midazolam (CNS depressant), Dacarbanine (anti-neoplastic) and antifungal drugs\(^{11}\) such as Ketoconazole, Miconazole and Clotrimazole are listed below (Figure 2.1).

![Chemical structures of Metronidazole, Midazolam, Ketoconazole, Dacarbanine, Miconazole and Clotrimazole]
Baroniya and coworkers worked on synthesis of imidazoles derivatives (1). They reported that cancer is the second leading cause of death world-wide after heart disease. A number of novel drugs have been discovered for the treatment of cancer. At present, imidazole plays an important part in the development of new drug for treatment of cancer. Imidazole derivatives have significant application in cancer treatment and an important agent used in medicinal chemistry. Despite of this the majority of patient diagnosed with their major malignancies will die because of disease and therefore, there is a need for few new agents with novel mechanism of action. Though much effect has been focused on the development of novel tyrosine-kinase inhibitors and antibiotics directed at signal transduction, exploration of new compound directly against traditional target of DNA and tubulin preserve to be important\textsuperscript{12}.

$$\text{R} = 4\text{-Cl}$$
$$R_1 = 3,4,5-(\text{MeO})_3$$

\textbf{(1)}

Figure 2.2

Al-soud and coworkers synthesized imidazole derivatives and were tested for their in vitro anti-HIV-1 (strain IIIb) and HIV-2 (strain ROD) activity in human T-lymphocyte (MT-4) cells using the MT-4/MTT assay. The results were summarized, in which the data for Efavirenz and Capravirine (2) were included for comparison\textsuperscript{13}.

$$\text{H}_2\text{NCO}$$

\textbf{(2)}
Bhatnagar and coworkers synthesized a series of 1-benzyl-3-(imidazol-1-ylmethyl) indole derivatives (3) under mild reaction conditions and tested for their antifungal activity. All the compounds were evaluated 'in vitro' against two human fungal pathogens, *Candida albicans* (CA980001) and *Aspergillus fumigatus* (AF980003); amphotericin B, fluconazole and itraconazole were used as references. Seven out of 27 compounds exerted significant antifungal activity against *C. albicans*.

![Chemical structure](image1.png)

**Figure 2.3**

Chena and coworkers synthesized novel hybrid compounds of 2-phenyl-3-alkylbenzofuran (4) and imidazole (5) and evaluated in vitro activity against a panel of human tumor cell lines. The results suggested that the 2-ethyl-imidazole derivatives and substitution of the imidazolyl-3-position with a 2-bromobenzyl or naphthylacetyl groups, were vital for modulating inhibitory activity.

![Chemical structures](image2.png)

**Figure 2.4**

Seerdan and coworkers reported the synthesis and structure–activity relationships of novel 4-(4'-fluorophenyl) imidazole derivatives (6) as
selective p38α, MAPK, CK1δ and JAK2 inhibitors with improved water solubility. Microwave-assisted MCRs afforded 4-fluorophenyl-2,5-disubstituted imidazoles whereas, carboxylate and phosphonate groups were introduced via ‘click’ reactions\textsuperscript{16}.

![p38α, MAPK](6)

Figure 2.6

2.3 Synthetic aspect:

Imidazole was first synthesized by Heinrich Debus in 1858, but various imidazole derivatives (9) had been synthesized later on, as shown below, glyoxal (7) and formaldehyde (8) in ammonia was used to form imidazole\textsuperscript{17} (Figure 2.7).

![imidazole synthesis](7) + ![imidazole synthesis](8) → ![imidazole synthesis](9)

Figure 2.7

A milder reagent barium manganate was used to convert imidazolines to imidazoles in the presence of sulphur. Imidazolines were obtained from 1,2 ehnediamine (10) and alkynitriles (11) on reaction with BaMnO\textsubscript{4} to yield 2-substituted imidazoles (12)\textsuperscript{18} (Figure 2.8).

![imidazole synthesis](10) + ![imidazole synthesis](11) → ![imidazole synthesis](12)

Figure 2.8
Wallach et al. reported that when N,N-dimethyloxamide (13) is reacted with phosphorus pentachloride, a chlorine containing compound (14) is obtained, which on reduction with hydroiodic acid gave N-methyl imidazole (15). Under the same condition N,N-diethylxamnide can be converted to a chlorine compound, which on reduction gives 1-ethyl-2-methyl imidazole\textsuperscript{19,20,21,22} (Figure 2.9).

\[
\text{O} \quad \text{NHCH}_2\text{R} \quad + \quad \text{PCl}_5 \quad \rightarrow \quad \text{Cl} \quad \text{N} \quad \text{N} \quad \text{R} \quad \rightarrow \quad \text{N} \quad \text{N} \quad \text{R} \\
(13) \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad 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Kruetzberger found that condensation of 1,2-hydrazine dicarboxamidine (22) with benzoin derivatives (23) in alkali media yields symmetrically substituted azoimidazoles (24) after spontaneous oxidation of the bis-imidazol hydrazine. Reductive cleavage of the azo group by hydrogenolysis gives two mole equivalents of the 2-aminoimidazole (25). This methodology is useful but limited to the preparation of 4,5-diaryl substituted 2-aminoimidazoles (Figure 2.12).

Lancini and Lazzari reported synthesis of 2- amino imidazole derivatives (28) by condensation of α-aminoketones, including the use of N-alkylamines (26) and cyanamide (27). They were the first to observe the severe pH dependence condensation. At very low pH the cyanamide is quickly converted to urea. At high pH, dimerization of the aminoketone to the piperazine competes with cyanamide condensation. Having established the optimum pH of the reaction to be ~4.5, these conditions are now routinely adopted (Figure 2.13).
Mixture of aldehyde (29) and aminonitrile (30) were condensed under suitable reaction condition to give substituted imidazole (31)²⁸ (Figure 2.14).

\[
R^\text{CN} + R_1^\text{NH}_2 \quad \rightarrow \quad \text{imidazole} \quad + \quad \text{H}_2\text{O}
\]

(29)   (30)       (31)

Figure 2.14

Zhao and coworkers reported an efficient and a quick microwave-assisted synthesis of benzimidazole and trisubstituted imidazole derivatives (34). The benzimidazoles were obtained as a result of the condensation of 1,2-phenylenediamine (32) with carboxylic acids and acetoacetic ester (33) without catalyst²⁹ (Figure 2.15).

\[
\text{PhNH}_2 + R_1^\text{CO}_2 \quad \rightarrow \quad \text{benzimidazole}
\]

(32)   (33)       (34)

Figure 2.15

Pathan et al. reported the reaction of alkyl cyanide (35) with ethylenediamine (36) in the presence of CS₂ to give 2-substituted 2-imidazolines (37) under microwave irradiation. The yields of product obtained using the method was significantly high and the reaction time was reduced³⁰ (Figure 2.16).

\[
R^\text{CN} + \text{H}_2\text{N}\text{(CH}_2\text{NH}_2 \quad \rightarrow \quad \text{imidazolines} \quad \text{CS}_2 \quad \text{MW}
\]

(35)   (36)       (37)

Figure 2.16

Ermolat and coworkers synthesized mono and disubstituted-2-amino-1H imidazoles (39) via microwave assisted hydrazinolysis of substituted imidazo [1,2-a]pyrimidines (38). This method avoids strong acidic conditions and is
superior to the conventional cyclocondensation of a halo ketones with N-acetyl guanidine\textsuperscript{31} (Figure 2.17).

\begin{equation}
\begin{array}{c}
\text{R} = \text{Ph, Br-Ph} \\
\end{array}
\end{equation}

Figure 2.17

Bharadwaj and coworkers performed the condensation of different oxazolones (1a-f) (40) with 5-(4-nitrophenyl)-1,3,4-thiadiazol-2-amine (41) under microwave oven. The structures of the synthesized compounds (42), 3a-3j were confirmed on the basis of spectral and elemental analysis. The synthesized compounds were found in better yield than in conventional methods and also screened for 'in vitro' antimicrobial study\textsuperscript{32} (Figure 2.18).

\begin{equation}
\begin{array}{c}
\text{R} \\
\end{array}
\end{equation}

Figure 2.18

Safari and coworkers reported synthesis of 2,4,5-trisubstituted imidazoles (46) by a three-component, one-pot condensation of benzil (43), aryl aldehydes (45) and ammonium acetate (44) in good yields under solvent-free conditions using microwave irradiation and (NH\textsubscript{4})\textsubscript{6}Mo\textsubscript{7}O\textsubscript{24}·4H\textsubscript{2}O was used as an efficient catalyst for an improved and rapid conversion. The reactions in conventional heating conditions were compared with the microwave-assisted reactions\textsuperscript{33} (Figure 2.19).

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Nalage and coworkers described an efficient and green method for the synthesis of 2,4,6-triaryl-1H imidazole (49) in PEG by condensing benzil (47) and 3-methoxy-4-hydroxy benzaldehyde (48) under microwave irradiation in excellent yield. Polyethylene glycol is non toxic, reusable; inexpensive and easily available green solvent \(^{34}\) (Figure 2.20).

Kawashita and coworkers synthesized a variety of heteroaromatic 2-substituted imidazoles (51) by oxidative aromatization of 2-substituted imidazolines (50) using the activated carbon and molecular oxygen system\(^ {35}\) (Figure 2.21).

Ermolat’ev and coworkers reported an efficient microwave-assisted one-pot two-step method for the construction of disubstituted 2-amino-1H-imidazoles (54). This process involves the sequential formation of 2,3-
dihydro-2-hydroxyimidazo[1,2-α]pyrimidinium salts from readily available 2-aminopyrimidines (52) and α-bromoketones (53), followed by cleavage of the pyridine ring with hydrazine (Figure 2.22).

![Figure 2.22](image)

Ermolat’ev and coworkers also reported a microwave-assisted, one-pot, two-step protocol for construction of polysubstituted 2-aminimidazoles (57). This process involves the sequential formation of imidazo[1,2-α]pyrimidinium salts from readily available 2-aminopyrimidines (55) and alpha-bromocarbonyl compounds (56), followed by opening of the pyridine ring with hydrazine (Figure 2.23).

![Figure 2.23](image)

Soh and coworkers reported a microwave-assisted protocol for the construction of di and monosubstituted 2-aminimidazoles. The two-step reaction involves the synthesis of N-(1Himidazol-2-yl)acetamides (59) from readily available alpha-haloketones (58) and N-acetylguanidine, followed by deacetylation. Significant rate enhancement was observed for both steps of the protocol and the overall reaction time was shortened to 20 min compared to 48 h of the conventional procedures. A representative set of di- and monosubstituted 2-aminimidazoles were prepared using commercially available parallel reactors (Figure 2.24).
Sparks and coworkers synthesized 2,4,5-triaryl-imidazoles (62) directly from the keto-oxime (60) and aldehyde (61) in moderate to good yields via cyclization to the N-hydroxyimidazole and an unprecedented ‘in situ’ thermal reduction of the N-O bond upon microwave irradiation at 200°C for 20 min\textsuperscript{39} (Figure 2.25).

Kandasamy Rajaguru and coworkers reported highly substituted imidazole derivatives (66) from various α-azido chalcones (63), aryl aldehydes (64) and anilines (65) using erbium triflate as a catalyst resulted in excellent yield of the desired imidazoles\textsuperscript{40} (Figure 2.26).

Chung-Yu Chen and coworkers reported an expedient and metal-free synthetic route for the construction of tri- and tetrasubstituted imidazole
derivatives (70) from alkyne (67), aromatic aldehyde (68) and aniline derivative (69) via acid promoted multicomponent reaction. The smoothly proceeded reaction produced a wide range of functionalities of the imidazole derivatives with good to excellent yields \(^{41}\) (Figure 2.27).

![Figure 2.27](image)

Zhong-Jian Cai and coworkers constructed novel substituted imidazoles (73) in one step under mild conditions using CuI/BF\(_3\)Et\(_2\)O/O\(_2\)-mediated reaction by utilizing ketones (71) and benzylamines (72)\(^{47}\) (Figure 2.28).

![Figure 2.28](image)

Katrin Illgen and coworkers synthesized 1H-imidazol-4-yl-pyridines (77) from a novel three-component, one-pot condensation of aldehydes (75), o-picolyamines (74), and isocyanides (76)\(^{13}\) (Figure 2.29).

![Figure 2.29](image)

Scott E. Wolkenberg and coworkers synthesized 2,4,5-trisubstituted imidazoles (80) via a simple, high-yielding and microwave irradiation from 1,2-diketones (78) and aldehydes (79) in the presence of NH\(_4\)OAc. Short
synthesis of lepidiline B and trifenaqrel was illustrated by the utility of the approach\(^{44}\) (Figure 2.30).

\[
\begin{array}{c}
\text{O} \quad \text{O} \\
\text{R}_2 \quad \text{R}_3 \\
\text{N} \quad \text{H} \\
\text{R}_1 \quad \text{R}_2 \quad \text{R}_3
\end{array}
\]

\[
\begin{array}{c}
\text{NH}_2\text{OAc (10 eq.)} \\
\text{AcOH} \\
180 \degree \text{C, MW} \\
5 \text{ min}
\end{array}
\]

\[\quad \Rightarrow \quad \]

Figure 2.30

Richard B and coworkers synthesized 2,4,5-triaryl-imidazoles (83) directly from the keto-oxime (81) and aldehyde (82) in moderate to good yields via cyclization to the N-hydroxyimidazole and an unprecedented \textit{in situ} thermal reduction of the N–O bond via microwave irradiation at 200\degreeC for 20 min\(^{45}\) (Figure 2.31).

\[
\begin{array}{c}
\text{R}_1 \quad \text{R}_2 \\
\text{N} \quad \text{OH} \\
\text{R}_3
\end{array}
\]

\[
\begin{array}{c}
\text{R}_1 \quad \text{R}_2 \\
\text{N} \quad \text{H} \\
\text{R}_3
\end{array}
\]

\[
\begin{array}{c}
\text{NH}_2\text{OAc} \\
\text{AcOH, MW} \\
200 \degree \text{C, 20 min}
\end{array}
\]

Figure 2.31

Shan Li and coworkers synthesized 2-fluoroalkyl imidazole derivatives (85) and 2-fluoro keto imidazole derivatives (86) catalyzed by gold(I), propargyl amidines (84) underwent a 5-exo-digcyclization to afford 2-fluoroalkyl-5-methyl imidazoles\(^{46}\) (Figure 2.32).

\[
\begin{array}{c}
\text{R}_1 \quad \text{N} \\
\text{Ar} \\
\text{R}_2
\end{array}
\]

\[
\begin{array}{c}
\text{N} \\
\text{Ar}
\end{array}
\]

\[
\begin{array}{c}
\text{R}_1 \quad \text{N} \\
\text{Ar}
\end{array}
\]

\[
\begin{array}{c}
\text{[Ph}_3\text{PAu}^+] \\
\text{MeCN, 60 \degree C}
\end{array}
\]

\[
\begin{array}{c}
\text{N} \\
\text{Ar}
\end{array}
\]

\[
\begin{array}{c}
\text{[Ph}_3\text{PAu}^+] \\
\text{NIS/K}_2\text{CO}_3 \\
\text{acetone, rt}
\end{array}
\]

Figure 2.32

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Hu et al. synthesized 1,2,4,5-tetra substituted imidazoles (89) using a highly efficient and convenient method from readily accessible 2-azido acrylates (87) and nitrones (88) under mild conditions without the assistance of any metal, acid, or base (Figure 2.33).

\[
\begin{align*}
    \text{R}_1 & \quad \text{R}_2 \\
    \text{N}_3 & \quad \text{O}^+ \text{R}_4 \\
(87) & \quad + \quad (88) \\
\text{MgSO}_4, \text{DCE} & \quad 66^\circ \text{C}, 48h \\
\rightarrow & \quad \text{R}_3 \quad \text{R}_4 \\
(89) &
\end{align*}
\]

Figure 2.33

Petit and coworkers reported peptidomimetics based on the imidazole scaffold (91) from amino acid esters (90) using an efficient and rapid sequence consisting of two subsequent one-pot procedures and applied to various amino acids (Figure 2.34).

\[
\begin{align*}
    \text{MeOCOC}_\text{R}_1 & \quad \text{NH}_2 \\
(90) & \quad \rightarrow \quad \text{two one-pot procedures} \\
& \quad \text{PG} \quad \text{SCH}_3 \\
(91) &
\end{align*}
\]

Figure 2.34

Benjamin Pooi and coworkers reported synthesis of 1,4-diaryl-1H-imidazoles (94) from isocyanide derivatives (93) via NHC and copper-catalyzed isocyanide insertion (92) into alcohol to form an N-arylformimidate intermediate and subsequent base promoted cycloaddition with benzyl isocyanide derivatives. The cooperation between two processes through the deprotonation of benzyl isocyanide was achieved by KOtBu (Figure 2.35).
Jiang and coworkers reported concise and efficient six-component and four-component domino approaches to anti-1,2-diarylethylbenzamides (96) and highly substituted 2-(2'-azaaryl)imidazoles derivatives (95) under solvent-free and microwave-irradiation conditions. The reactions showed broad scope of substrates in which a lot of common commercial aromatic aldehydes and heteroaryl nitriles were used. The synthesis was finished within short periods (15-34 min) with good to excellent yields and stereoselectivity that avoided tedious workup and isolations\textsuperscript{50}(Figure 2.36).

Subhendu Maity and coworkers synthesized 2,3-diaryl-6,7-dihydro-5H-pyrrrolo[1,2-a]imidazoles (99) in moderate yields by using microwave irradiation of a solid mixture of aryl 1,2-diketones (97), L-proline (98), and ammonium acetate (excess) for 15 min. This one-pot three-component
reaction produced pyrroloimidazoles through the intramolecular cyclization of 1,2-diimine intermediates derived from the condensation of aryl 1,2-diketones, L-proline and ammonia in 1:1:1 molar proportion\(^{51}\) (Figure 2.37).

\[
\begin{align*}
\text{Ar}_1\text{C}(\text{Ar}_1)\text{C} & \quad \text{R} \quad \text{NH}_2\text{OAc} \\
(97) & \quad \text{NH}_3\text{OH} \quad \text{OH} \\
& \quad \text{MW, 15 min} \\
\text{Ar}_1\text{N} & \quad \text{R} \\
(99) & \quad \text{R}
\end{align*}
\]

Figure 2.37

Narayana Murthy and coworkers synthesized highly substituted imidazoles (104) through the condensation of aldehyde (100), ammonium acetate (101), aromatic amine (102) and 1,2-dicarbonyl compound (103) via multicomponent condensation strategy using DABCO as mild and efficient catalyst\(^{52}\) (Figure 2.38).

\[
\begin{align*}
\text{CHO} & \quad \text{NH}_3\text{OAc} \\
(100) & \quad \text{NH}_2 \\
+ & \quad \text{PhCO} \quad \text{PhCO} \\
(101) & \quad (102) \\
& \quad \text{DABCO} \\
& \quad \text{1-BuOH, 60-85 °C} \\
\text{N} & \quad \text{N} \\
(104) & \quad (104)
\end{align*}
\]

Figure 2.38

Sivakumar and coworkers synthesized 2,4,5-trisubstituted imidazoles (108) from aromatic aldehyde (105), ammonium acetate (106), and benzil (107) using Cu(II) nitrate impregnated zeolite. Condensation in the presence of supported reagents through operational simplicity, inexpensive reagents, high yield of products, and the use of non-toxic reagents makes this synthetic protocol, an attractive one\(^{53}\) (Figure 2.39).

\[
\begin{align*}
\text{CHO} & \quad \text{NH}_3\text{OAc} \\
(105) & \quad \text{PhCO} \quad \text{PhCO} \\
+ & \quad \text{Ph} \\
(106) & \quad (107) \\
& \quad \text{Cu(NO}_3)_2 \quad \text{Z} \\
& \quad \text{Z} \\
\text{N} & \quad \text{N} \\
(108) & \quad (108)
\end{align*}
\]

Figure 2.39
David Ma Gee and coworkers synthesized 2-alkyl and 2-aryl-4,5-diphenyl-1H-imidazoles (112) using highly efficient one-pot reactions of benzil or benzoin (111), ammonium acetate (110), and aliphatic or aromatic aldehydes (109) in the presence of 1-methylimidazolium trifluoroacetate ([Hmim]TFA) in water under mild and green conditions. By conducting the reactions in water, the obtained solid products were isolated simply by filtration\(^\text{34}\) (Figure 2.40).

\[
R-\text{CHO} + 2\text{NH}_4\text{OAc} + \text{Ph} \overset{[\text{Hmim}]\text{TFA} (10 \text{ mol\%})}{\text{water, } 80^\circ\text{C}} \rightarrow \text{Ph} \overset{\text{N}}{\text{N}} \overset{\text{Ph}}{\text{N}} \overset{\text{R}}{\text{N}}
\]

Figure 2.40

81
2.4 Aim of current work:

Multi-substituted imidazoles, an important class of pharmaceutical compounds, exhibit a wide spectrum of biological activities such as nitric-oxide synthase inhibition, anti-inflammatory, anti-parasitic, antifungal, antidepressant, antitubercular, anticancer and antiviral activities. Some of these compounds could also be used as organic optical materials in many fields, for example as signaling, fluorescent biosensory chemosensory materials, molecular switches and organic light emitting diodes (OLEDs). They can also be useful in asymmetric organic synthesis and polymer and material science.

Therefore, preparation of substituted imidazoles has attracted considerable attention in recent years and numerous methods for their synthesis have been reported. Some of these methods are associated with one or more disadvantages such as using expensive reagents, long reaction time, tedious work-up procedures and generation of large amount of toxic waste. So, to minimize the disadvantages, microwave irradiation approach could be used to synthesize imidazole derivative in good yields.

2.5 Chemistry/ Result & Discussion:

\[ \text{(1)} R_1 = H, Cl \\
R_1 = \text{CH}_3, \text{Ar} \]
Initial experiments demonstrated that our microwave-assisted approach could be used to accelerate the synthesis of imidazoles in yields comparable to those of conventional heating methods. Benzil (2) (1.0 mmol) was condensed with pyrazole aldehyde (1) (1.0 mmol) (where \(R_1 = \text{Ph}, R_2 = \text{H}\)) in the presence of ammonium acetate (3) (5.0 mmol) at different reaction conditions as described in optimization table (Table 1.). Initially, different polar and non polar solvents were tried and polar solvent resulted in good yields as compared to that of non polar. Beside this, temperature play important role, by increasing temperature it was observed that at higher temperature reaction was progressed smoothly with good yields.

**Table 1: Optimization of the reaction conditions**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp °C</th>
<th>Time min</th>
<th>Yieldb %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH</td>
<td>70</td>
<td>20</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>EtOH</td>
<td>80</td>
<td>20</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>70</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>MeCN</td>
<td>80</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>Dioxane</td>
<td>110</td>
<td>20</td>
<td>44</td>
</tr>
<tr>
<td>6</td>
<td>Toluene</td>
<td>110</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
<td>gla. CH₃COOH</td>
<td>110</td>
<td>20</td>
<td>66</td>
</tr>
<tr>
<td>8</td>
<td>DMF</td>
<td>150</td>
<td>20</td>
<td>58</td>
</tr>
<tr>
<td>9</td>
<td>MeOH:CH₃COOH</td>
<td>140</td>
<td>20</td>
<td>72</td>
</tr>
<tr>
<td>10</td>
<td>EtOH:CH₃COOH</td>
<td>140</td>
<td>20</td>
<td>78</td>
</tr>
<tr>
<td>11</td>
<td>dioxane:CH₃COOH</td>
<td>140</td>
<td>20</td>
<td>74</td>
</tr>
</tbody>
</table>

*a Pyrazole-4-carboxaldehyde: benzil : ammonium acetate (1:1:0.5:0)
bYields of isolated pure products.

Then combination of different polar solvents were tried which resulted in the high yield (entry 10, Table 1). As starting materials were consumed during the course of reaction and the obtained product is
insoluble in the solvent system used for the reaction, the purification could be achieved by simple filtration and washing with cold ethanol. These conditions proved to be general for the reacting aldehydes, as shown in Table 2. Aldehydes bearing either electron-withdrawing or electron-donating groups (Table 2.) can be used for synthesis of triaryl substituted imidazole derivatives which can produce moderate to good yields. The structures were established on the basis of their elemental analysis, Mass, IR, $^1$H NMR and $^{13}$C NMR spectral data.

Table 2: Synthesis of imidazole derivatives.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>$R_1$</th>
<th>Time min</th>
<th>Yield %</th>
<th>mp °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>BHB-A-1</td>
<td>H</td>
<td>Ph</td>
<td>20</td>
<td>78</td>
<td>238</td>
</tr>
<tr>
<td>BHB-A-2</td>
<td>H</td>
<td>4-F-C$_6$H$_5$</td>
<td>20</td>
<td>86</td>
<td>242</td>
</tr>
<tr>
<td>BHB-A-3</td>
<td>H</td>
<td>4-Br-C$_6$H$_5$</td>
<td>20</td>
<td>82</td>
<td>226</td>
</tr>
<tr>
<td>BHB-A-4</td>
<td>Cl</td>
<td>CH$_3$</td>
<td>25</td>
<td>80</td>
<td>196</td>
</tr>
<tr>
<td>BHB-A-5</td>
<td>H</td>
<td>4-OH-C$_6$H$_5$</td>
<td>30</td>
<td>76</td>
<td>222</td>
</tr>
<tr>
<td>BHB-A-6</td>
<td>H</td>
<td>4-CH$_3$-C$_6$H$_5$</td>
<td>30</td>
<td>78</td>
<td>208</td>
</tr>
<tr>
<td>BHB-A-7</td>
<td>H</td>
<td>4-Cl-C$_6$H$_5$</td>
<td>25</td>
<td>82</td>
<td>232</td>
</tr>
<tr>
<td>BHB-A-8</td>
<td>H</td>
<td>4-NO$_2$-C$_6$H$_5$</td>
<td>20</td>
<td>88</td>
<td>242</td>
</tr>
<tr>
<td>BHB-A-9</td>
<td>H</td>
<td>3-NO$_2$-C$_6$H$_5$</td>
<td>25</td>
<td>80</td>
<td>248</td>
</tr>
<tr>
<td>BHB-A-10</td>
<td>H</td>
<td>2-NO$_2$-C$_6$H$_5$</td>
<td>20</td>
<td>85</td>
<td>256</td>
</tr>
<tr>
<td>BHB-A-11</td>
<td>H</td>
<td>2-OCH$_3$-C$_6$H$_5$</td>
<td>30</td>
<td>74</td>
<td>224</td>
</tr>
<tr>
<td>BHB-C-12</td>
<td>H</td>
<td>3-OH-C$_6$H$_5$</td>
<td>30</td>
<td>72</td>
<td>258</td>
</tr>
</tbody>
</table>

All reactions were performed under microwave irradiation using $1.0$ mmol of (1), $1.1$ mmol of (2), $5.0$ mmol of (3) and $5$ ml of (EtOH: gla AcOH, 1:1) at $140$ °C temperature.
2.6 Plausible reaction mechanism:

In the presence of acid, carbcation is generated on the carbonyl carbon of pyrazole-4-carboxaldehyde, which was attacked by NH₃ followed by elimination of water molecule to give intermediate (2a). Nucleophilic attack of generated intermediate (2a, imine) to the carbonyl carbon of benzil followed by elimination of water molecule gave intermediate (2b) (enol form). Further nucleophilic attack by NH₃ and removal of water molecule followed by cyclization and aromatization respectively gave desired imidazole (4).
2.7 Experimental section:

2.7.1 Preparation of acetophenone phenyl hydrazones derivatives (Step - 1):

Appropriately substituted acetophenone or ethylacetoacetate (0.1 mol) was dissolved in 50 ml of ethanol into 250 ml single necked RBF. Phenyl hydrazine (0.1 mol) was added to above flask along with 3-4 drops of glacial acetic acid. The reaction mixture was refluxed for 3-6 hours. Progress and the completion of reaction were checked by TLC using hexane: ethyl acetate (4: 6) as mobile phase. After the completion of the reaction, the reaction mixture was kept to room temperature for 1 hour and the solid crystalline product was filtered, washed with cold ethanol and dried to give substituted acetophenone hydrazone in good yield which was used without further purification in the next step.

2.7.2 Preparation of Pyrazole aldehydes derivatives (Step - 2):
Dimethylformamide (0.032 mol) was transferred into 25 ml flat bottom flask. Phosphorous oxychloride (0.032 mol) was added drop wise to above flask under stirring at 0-5 °C. After completion of the addition, the reaction mixture was stirred at this temperature for 10-15 min. freshly prepared acetophenone hydrazones (0.015 mol) or 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one was added to above mixture and the content was heated at 80°C on oil bath for 6-9 hours. The progress and the completion of reaction were checked by TLC using toluene: ethylacetate (6: 4) as mobile phase. After consumption of starting material, the reaction mixture was cooled to room temperature and poured onto crushed ice. The separated solid was filtered off and it was washed with cold methanol, dried at 65 °C and recrystallized from the mixture of DMF-Methanol to give the pure product.

2.7.3 General Procedure for the preparation of imidazolyl pyrazole derivatives (step-3):

Pyrazole aldehyde (1.0 mmol), benzil (1.0 mmol) and ammonium acetate (5.0 mmol) in 5 ml ethanol-acetic acid (1:1) were charged in 10 ml microwave vial and it was irradiated at 140 °C for 20 to 30 minutes. Completion of the reaction was checked by TLC using hexane: ethyl acetate (8:2) and the obtained solid was filtered and washed with cold ethanol to give pure product.
2.8 Conclusion:

In conclusion, a one-pot microwave assisted multi-component reaction for the synthesis of triaryl imidazole derivatives bearing pyrazole group in presence of EtOH:AcOH in good to excellent yields was developed. This method involves mild reaction conditions, easy work-up, cleaner reaction profiles, and isolation of final product by simple filtration. The newly synthesized compounds were characterized by IR, Mass, $^1$H NMR, $^{13}$C NMR spectroscopy and elemental analysis.
2.9 Spectral Characterization:

<table>
<thead>
<tr>
<th>BHB-A-1</th>
<th>4-(4,5-diphenyl-1H-imidazol-2-yl)-1,3-diphenyl-1H-pyrazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mol. Formula</td>
<td>C₃₀H₂₂N₄</td>
</tr>
<tr>
<td>M.P.</td>
<td>238 °C</td>
</tr>
<tr>
<td>Mol. wt.</td>
<td>438.52</td>
</tr>
<tr>
<td>Ele. Analysis</td>
<td>C</td>
</tr>
<tr>
<td>Cal</td>
<td>82.17</td>
</tr>
<tr>
<td>Obs</td>
<td>82.15</td>
</tr>
</tbody>
</table>

${}^1\text{H NMR} \delta \text{ ppm}$

(400 MHz, DMSO) $\delta$ 12.50 (s, 1H), 8.99 (s, 1H), 8.09 (d, $J = 7.2$ Hz, 2H), 7.95 (d, $J = 7.8$ Hz, 2H), 7.63 – 7.51 (m, 4H), 7.43 (ddd, $J = 30.8$, 13.1, 6.9 Hz, 9H), 7.31 (t, $J = 7.5$ Hz, 2H), 7.22 (t, $J = 7.3$ Hz, 1H).

${}^{13}\text{C NMR} \delta \text{ ppm}$

(100 MHz, DMSO) $\delta$ 157.24, 154.82, 144.22, 139.97, 138.82, 133.56, 131.49, 130.85, 129.70, 129.14, 129.11, 128.72, 128.54, 128.51, 128.03, 127.93, 127.89, 127.73, 126.17, 119.95, 113.63.

FT-IR $\nu_{\text{max}} \text{ cm}^{-1}$

3450, 3010, 2950, 1665, 1590, 1520, 1500, 1440, 1365, 1220, 1120, 1062, 960, 940, 910, 862, 800, 760, 750, 725, 690, 680.

<table>
<thead>
<tr>
<th>BHB-A-2</th>
<th>4-(4,5-diphenyl-1H-imidazol-2-yl)-3-(4-fluorophenyl)-1-phenyl-1H-pyrazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mol. Formula</td>
<td>C₃₀H₂₁FN₄</td>
</tr>
<tr>
<td>M.P.</td>
<td>242 °C</td>
</tr>
<tr>
<td>Mol. wt.</td>
<td>456.51</td>
</tr>
<tr>
<td>Ele. Analysis</td>
<td>C</td>
</tr>
<tr>
<td>Cal</td>
<td>78.93</td>
</tr>
<tr>
<td>Obs</td>
<td>78.94</td>
</tr>
</tbody>
</table>

${}^1\text{H NMR} \delta \text{ ppm}$

(400 MHz, DMSO) $\delta$ 12.53 (s, 1H), 9.01 (s, 1H), 8.21 (s, 2H), 7.94 (d, $J = 7.4$ Hz, 2H), 7.64 – 7.53 (m, 4H), 7.49 (s, 2H), 7.40 (ddd, $J = 18.5$, 10.4 Hz, 4H), 7.31 (s, 4H), 7.23 (d, $J = 6.3$ Hz, 1H).

${}^{13}\text{C NMR} \delta \text{ ppm}$

(100 MHz, DMSO) $\delta$ 163.32, 160.88, 148.89, 139.35, 139.03, 136.29, 135.08, 131.00, 130.42, 130.34, 129.66, 129.30, 129.01, 128.63, 128.15, 128.01, 127.62, 127.20, 126.83, 126.70, 126.36, 118.29, 114.88, 114.67, 112.69.

FT-IR $\nu_{\text{max}} \text{ cm}^{-1}$

3342, 3057, 2968, 1598, 1548, 1502, 1442, 1373, 1301, 1222, 1157, 1109, 1070, 1028, 997, 960, 908, 835, 754, 734.
### BHB-A-3

<table>
<thead>
<tr>
<th><strong>Mol. Formula</strong></th>
<th>C₂₀H₂₂BrN₄</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M.P.</strong></td>
<td>226 °C</td>
</tr>
<tr>
<td><strong>Mol. wt.</strong></td>
<td>516.04</td>
</tr>
<tr>
<td><strong>Ele. Analysis</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Cal</strong></td>
<td>69.64</td>
</tr>
<tr>
<td><strong>Obs</strong></td>
<td>69.62</td>
</tr>
</tbody>
</table>

**¹H NMR δ ppm**

(400 MHz, DMSO) δ 12.52 (s, 1H), 9.01 (s, 1H), 8.15 (d, J = 8.3 Hz, 2H), 7.94 (d, J = 7.9 Hz, 2H), 7.67 (d, J = 8.3 Hz, 2H), 7.58 (dd, J = 14.2, 7.3 Hz, 4H), 7.50 (d, J = 7.2 Hz, 2H), 7.47 – 7.36 (m, 4H), 7.32 (t, J = 7.4 Hz, 2H), 7.23 (t, J = 7.0 Hz, 1H).

**¹³C NMR δ ppm**

(100 MHz, DMSO) δ 148.68, 139.30, 139.05, 136.43, 135.12, 131.84, 131.05, 130.97, 130.31, 129.75, 129.55, 128.71, 128.23, 128.09, 127.7, 127.33, 126.93, 126.89, 126.45, 121.62, 118.42, 112.94.

**FT—IR νmax cm⁻¹**

3342, 3049, 2968, 1595, 1500, 1548, 1500, 1444, 1371, 1301, 1219, 1157, 1107, 1070, 1028, 960, 908, 831, 752, 732.

### BHB-A-4

<table>
<thead>
<tr>
<th><strong>Mol. Formula</strong></th>
<th>C₂₅H₁₉ClN₄</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M.P.</strong></td>
<td>196 °C</td>
</tr>
<tr>
<td><strong>Mol. wt.</strong></td>
<td>410.9</td>
</tr>
<tr>
<td><strong>Ele. Analysis</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Cal</strong></td>
<td>73.08</td>
</tr>
<tr>
<td><strong>Obs</strong></td>
<td>73.04</td>
</tr>
</tbody>
</table>

**¹H NMR δ ppm**

(400 MHz, DMSO) δ 12.44 (s, 1H), 7.61 (t, J = 7.4 Hz, 4H), 7.53 (dd, J = 24.3, 7.4 Hz, 6H), 7.44 (t, J = 7.4 Hz, 2H), 7.37 (d, J = 7.2 Hz, 1H), 7.31 (t, J = 7.5 Hz, 2H), 7.22 (t, J = 7.2 Hz, 1H), 2.47 (s, 3H).

**¹³C NMR δ ppm**

(100 MHz, DMSO) δ 148.56, 137.71, 137.59, 136.92, 135.10, 130.98, 129.30, 128.66, 128.56, 128.24, 128.17, 127.67, 127.59, 127.07, 126.48, 125.39, 125.01, 110.87, 13.23.

**FT—IR νmax cm⁻¹**

3340, 3126, 3028, 2978, 1597, 1542, 1508, 1446, 1374, 1222, 1159, 1107, 1073, 1028, 958, 905, 832, 754, 732.
<table>
<thead>
<tr>
<th>BHB-A-5</th>
<th>4-(4,5-diphenyl-1H-imidazol-2-yl)-1-phenyl-1H-pyrazol-3-yl)phenol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mol. Formula</td>
<td>$C_{30}H_{22}N_4O$</td>
</tr>
<tr>
<td>M.P.</td>
<td>222 °C</td>
</tr>
<tr>
<td>Mol. wt.</td>
<td>454.52</td>
</tr>
<tr>
<td>Ele. Analysis</td>
<td>C</td>
</tr>
<tr>
<td>Cal</td>
<td>79.27</td>
</tr>
<tr>
<td>Obs</td>
<td>79.24</td>
</tr>
<tr>
<td>$^1H$ NMR δ ppm</td>
<td>(400 MHz, DMSO) δ 12.54 (s, 2H), 8.96 (s, 3H), 7.95 (t, $J = 7.1$ Hz, 12H), 7.56 (dd, $J = 15.6$, 7.6 Hz, 19H), 7.37 (d, $J = 7.1$ Hz, 15H), 7.30 (s, 8H), 6.86 (d, $J = 8.4$ Hz, 6H).</td>
</tr>
<tr>
<td>$^{13}C$ NMR δ ppm</td>
<td>(100 MHz, DMSO) δ 157.64, 150.20, 139.75, 139.20, 129.69, 129.60, 129.27, 128.47, 127.52, 127.47, 126.47, 123.43, 118.15, 114.80, 112.16, 30.66.</td>
</tr>
<tr>
<td>FT—IR $v_{\text{max}}$ cm$^{-1}$</td>
<td>3520, 3448, 3016, 2957, 1658, 1592, 1519, 1506, 1438, 1368, 1218, 1125, 1062, 966, 942, 912, 864, 806, 766, 750, 726, 692, 682.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BHB-A-6</th>
<th>4-(4,5-diphenyl-1H-imidazol-2-yl)-1-phenyl-3-(p-tolyl)-1H-pyrazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mol. Formula</td>
<td>$C_{31}H_{24}N_4$</td>
</tr>
<tr>
<td>M.P.</td>
<td>208 °C</td>
</tr>
<tr>
<td>Mol. wt.</td>
<td>452.55</td>
</tr>
<tr>
<td>Ele. Analysis</td>
<td>C</td>
</tr>
<tr>
<td>Cal</td>
<td>82.27</td>
</tr>
<tr>
<td>Obs</td>
<td>82.26</td>
</tr>
<tr>
<td>$^1H$ NMR δ ppm</td>
<td>(400 MHz, DMSO) δ 12.51 (s, 1H), 8.98 (s, 1H), 8.02 (d, $J = 7.9$ Hz, 2H), 7.95 (d, $J = 7.9$ Hz, 2H), 7.58 (t, $J = 7.7$ Hz, 4H), 7.49 (d, $J = 7.3$ Hz, 2H), 7.44 (t, $J = 7.5$ Hz, 2H), 7.38 (t, $J = 7.4$ Hz, 2H), 7.32 (t, $J = 7.6$ Hz, 2H), 7.24 (dd, $J = 18.3$, 7.6 Hz, 3H), 2.35 (s, 3H).</td>
</tr>
<tr>
<td>$^{13}C$ NMR δ ppm</td>
<td>(100 MHz, DMSO) δ 149.93, 139.59, 139.17, 137.54, 136.39, 135.24, 131.09, 129.76, 129.72, 129.46, 128.71, 128.61, 128.22, 128.06, 128.03, 127.64, 127.21, 126.94, 126.63, 126.43, 118.27, 112.74, 20.87.</td>
</tr>
<tr>
<td>FT—IR $v_{\text{max}}$ cm$^{-1}$</td>
<td>3342, 3120, 3028, 2978, 1595, 1509, 1438, 1374, 1304, 1217, 1157, 1103, 1067, 1032, 964, 834, 753, 692.</td>
</tr>
</tbody>
</table>
### BHB-A-7
**3-(4-chlorophenyl)-4-(4,5-diphenyl-1H-imidazol-2-yl)-1-phenyl-1H-pyrazole**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mol. Formula</td>
<td>C$<em>{30}$H$</em>{21}$ClN$_4$</td>
</tr>
<tr>
<td>M. P.</td>
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<td>Mol. wt.</td>
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<td>Ele. Analysis</td>
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<td>Cal</td>
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<tr>
<td>Obs</td>
<td>76.16</td>
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**$^1$H NMR δ ppm**

(400 MHz, DMSO) δ 12.56 (s, 1H), 9.03 (s, 1H), 8.22 (d, J = 8.5 Hz, 2H), 7.95 (d, J = 7.9 Hz, 2H), 7.63 – 7.53 (m, 6H), 7.50 (d, J = 7.3 Hz, 2H), 7.45 (t, J = 7.5 Hz, 2H), 7.43 – 7.35 (m, 2H), 7.32 (t, J = 7.5 Hz, 2H), 7.23 (t, J = 7.3 Hz, 1H).

**$^{13}$C NMR δ ppm**

(100 MHz, DMSO) δ 148.62, 139.31, 139.03, 136.39, 135.09, 132.93, 131.45, 131.02, 130.02, 129.76, 129.53, 128.73, 128.25, 128.08, 127.72, 127.32, 126.91, 126.47, 118.39, 112.92.

**FT—IR $\nu_{max}$ cm$^{-1}$**

3340, 3126, 3059, 2978, 1597, 1548, 1502, 1442, 1371, 1219, 1157, 1109, 1070, 1026, 960, 904, 831, 752, 734.

### BHB-A-8
**4-(4,5-diphenyl-1H-imidazol-2-yl)-3-(4-nitrophenyl)-1-phenyl-1H-pyrazole**

<table>
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<td>Mol. wt.</td>
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<td>Ele. Analysis</td>
<td>C</td>
</tr>
<tr>
<td>Cal</td>
<td>74.52</td>
</tr>
<tr>
<td>Obs</td>
<td>74.51</td>
</tr>
</tbody>
</table>

**$^1$H NMR δ ppm**

(400 MHz, DMSO) δ 12.63 (s, 1H), 9.10 (s, 1H), 8.53 (d, J = 8.7 Hz, 2H), 8.35 (d, J = 8.7 Hz, 2H), 7.97 (d, J = 7.9 Hz, 2H), 7.60 (dd, J = 16.9, 8.3 Hz, 4H), 7.52 (d, J = 7.2 Hz, 2H), 7.49 – 7.42 (m, 3H), 7.42 – 7.37 (m, 1H), 7.33 (t, J = 7.4 Hz, 2H), 7.24 (t, J = 7.0 Hz, 1H).

**$^{13}$C NMR δ ppm**

(100 MHz, DMSO) δ 147.52, 146.92, 139.11, 138.99, 138.87, 136.49, 134.98, 130.94, 129.89, 129.82, 129.25, 128.75, 128.28, 128.11, 127.80, 127.52, 127.25, 126.95, 126.53, 123.31, 118.59, 113.65.

**FT—IR $\nu_{max}$ cm$^{-1}$**

3342, 3055, 2968, 1595, 1500, 1444, 1371, 1301, 1219, 1157, 1107, 1070, 1028, 960, 831, 754, 690.
### BHB-A-9

<table>
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<tr>
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<tr>
<td>Obs</td>
<td>74.50</td>
</tr>
<tr>
<td>$^1$H NMR δ ppm</td>
<td>(400 MHz, DMSO) δ 12.64 (s, 1H), 9.48 (s, 1H), 9.12 (s, 1H), 8.66 (d, J = 7.7 Hz, 1H), 8.29 (d, J = 7.5 Hz, 1H), 7.97 (d, J = 7.9 Hz, 2H), 7.78 (t, J = 8.0 Hz, 1H), 7.63 (dd, J = 14.5, 7.5 Hz, 4H), 7.54 (d, J = 7.3 Hz, 2H), 7.50 – 7.39 (m, 4H), 7.32 (t, J = 7.4 Hz, 2H), 7.24 (t, J = 7.1 Hz, 1H).</td>
</tr>
<tr>
<td>$^{13}$C NMR δ ppm</td>
<td>(100 MHz, DMSO) δ 147.70, 147.42, 139.16, 138.88, 136.38, 134.93, 134.57, 134.17, 130.98, 129.81, 129.55, 129.52, 128.75, 128.16, 127.82, 127.47, 127.14, 126.90, 126.50, 123.36, 122.98, 118.53, 113.20.</td>
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<tr>
<td>FT–IR $\nu_{\text{max}}$ cm$^{-1}$</td>
<td>3342, 3055, 2968, 1595, 1500, 1444, 1371, 1301, 1219, 1157, 1107, 1070, 1028, 960, 831, 754, 690.</td>
</tr>
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### BHB-A-10

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</tr>
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<td>Cal</td>
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<tr>
<td>Obs</td>
<td>74.24</td>
</tr>
<tr>
<td>$^1$H NMR δ ppm</td>
<td>(400 MHz, DMSO) δ 12.66 (s, 1H), 9.34 (s, 1H), 8.26 (s, 1H), 7.87 (dd, J = 7.5, 1.4 Hz, 1H), 7.78 (td, J = 7.5, 1.4 Hz, 1H), 7.64 – 7.59 (m, 5H), 7.58 (dd, J = 7.4, 1.2 Hz, 2H), 7.52 (t, J = 7.4 Hz, 2H), 7.45 (dt, J = 4.6, 1.8 Hz, 1H), 7.40 (td, J = 7.4, 1.9 Hz, 4H), 7.34 – 7.29 (m, 2H).</td>
</tr>
<tr>
<td>$^{13}$C NMR δ ppm</td>
<td>(100 MHz, DMSO) δ 148.66, 147.36, 139.33, 138.72, 136.32, 134.80, 134.40, 134.12, 129.98, 129.70, 129.56, 129.50, 128.79, 128.24, 127.88, 127.32, 127.08, 126.94, 126.58, 123.28, 122.88, 118.34, 112.66.</td>
</tr>
<tr>
<td>FT–IR $\nu_{\text{max}}$ cm$^{-1}$</td>
<td>3342, 3034, 2977, 1598, 1516, 1436, 1374, 1309, 1224, 1162, 1118, 1070, 1024, 962, 838, 760, 696.</td>
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**BHB-A-11** | 4-(4,5-diphenyl-1H-imidazol-2-yl)-3-(2-methoxyphenyl)-1-phenyl-1H-pyrazole

<table>
<thead>
<tr>
<th>Mol. Formula</th>
<th>C\textsubscript{32}H\textsubscript{24}N\textsubscript{4}O</th>
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<td>Cal</td>
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<tr>
<td>Obs</td>
<td>79.43</td>
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\[^1^H\text{NMR} \delta \text{ ppm}\]

(400 MHz, DMSO) \(\delta\) 12.54 (s, 1H), 9.22 (s, 1H), 7.60 (dd, \(J = 12.6, 4.6\) Hz, 7H), 7.51 (t, \(J = 7.4\) Hz, 2H), 7.47 – 7.36 (m, 5H), 7.36 – 7.28 (m, 3H), 7.08 (m, 2H), 3.87 (s, 3H).

\[^{13}\text{C NMR} \delta \text{ ppm}\]

(100 MHz, DMSO) \(\delta\) 154.97, 153.22, 152.97, 144.22, 139.97, 138.82, 134.66, 132.62, 130.98, 129.70, 129.14, 129.12, 128.51, 128.24, 128.11, 128.03, 127.93, 127.74, 127.43, 122.06, 121.06, 119.95, 115.14, 113.42, 56.79.

FT—IR \(\nu_{\text{max}} \text{ cm}^{-1}\)

3357, 3128, 3030, 2982, 1580, 1520, 1444, 1370, 1304, 1240, 1174, 1120, 1075, 1068, 972, 840, 758, 698.

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**BHB-A-12** | 3-(4-(4,5-diphenyl-1H-imidazol-2-yl)-1-phenyl-1H-pyrazol-3-yl)phenol

<table>
<thead>
<tr>
<th>Mol. Formula</th>
<th>C\textsubscript{30}H\textsubscript{22}N\textsubscript{4}O</th>
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\[^1^H\text{NMR} \delta \text{ ppm}\]

(400 MHz, DMSO) \(\delta\) 12.62 (s, 1H), 9.24 (s, 1H), 7.62 – 7.58 (m, 6H), 7.52 (t, \(J = 7.4\) Hz, 2H), 7.47 – 7.37 (m, 5H), 7.37 – 7.29 (m, 2H), 7.28 – 7.21 (m, 2H), 7.19 (d, \(J = 7.5, 1.4\) Hz, 1H), 6.94 (d, \(J = 7.5, 1.4\) Hz, 1H).

\[^{13}\text{C NMR} \delta \text{ ppm}\]

(100 MHz, DMSO) \(\delta\) 157.25, 157.05, 156.03, 144.22, 139.97, 138.82, 133.56, 132.15, 131.44, 130.85, 129.70, 129.14, 129.12, 128.51, 128.03, 127.93, 127.74, 127.43, 126.17, 121.60, 119.95, 119.28, 115.78, 111.668.

FT—IR \(\nu_{\text{max}} \text{ cm}^{-1}\)

3536, 3457, 3010, 2952, 1658, 1592, 1519, 1506, 1428, 1374, 1220, 1134, 1058, 957, 940, 918, 836, 806, 788, 752, 720, 688, 672.
$^1$H NMR spectrum of BHB-A-1

Expanded $^1$H NMR spectrum of BHB-A-1
$^1$H NMR spectrum of BHB-A-2

Expanded $^1$H NMR spectrum of BHB-A-2
$^{13}$C NMR spectrum of BHB-A-2

Expanded $^{13}$C NMR spectrum of BHB-A-2
$^1$H NMR spectrum of BHB-A-3

Expanded $^1$H NMR spectrum of BHB-A-3
$^{13}$C NMR spectrum of BHB-A-3

Expanded $^{13}$C NMR spectrum of BHB-A-3
$^1$H NMR spectrum of BHB-A-4

Expanded $^1$H NMR spectrum of BHB-A-4
$^1$H NMR spectrum of BHB-A-5

Expanded $^1$H NMR spectrum of BHB-A-5
$^1$H NMR spectrum of BHB-A-6

Expanded $^1$H NMR spectrum of BHB-A-6
$^{13}$C NMR spectrum of BHB-A-6

Expanded $^{13}$C NMR spectrum of BHB-A-6
$^1$H NMR spectrum of BHB-A-7

Expanded $^1$H NMR spectrum of BHB-A-7
$^{13}\text{C}$ NMR spectrum of BHB-A-7

Expanded $^{13}\text{C}$ NMR spectrum of BHB-A-7
$^1$H NMR spectrum of BHB-A-8

Expanded $^1$H NMR spectrum of BHB-A-8
$^{13}\text{C}$ NMR spectrum of BHB-A-8

Expanded $^{13}\text{C}$ NMR spectrum of BHB-A-8
$^1$H NMR spectrum of BHB-A-9

Expanded $^1$H NMR spectrum of BHB-A-9
$^{13}$C NMR spectrum of BHB-A-9

Expanded $^{13}$C NMR spectrum of BHB-A-9
Mass spectrum of BHB-A-1

Mass spectrum of BHB-A-3
Mass spectrum of BHB-A-5

Mass spectrum of BHB-A-7
IR spectrum of BHB-A-2

IR spectrum of BHB-A-3
IR spectrum of BHB-A-7

IR spectrum of BHB-A-8
2.10 References:

15. Wen Chena, Xiao-Yan Deng, Yan Li, Li-Juan Yang, Wei-Chao Wan, Xue-
Quan Wang, Hong-Bin Zhang, Xiao-Dong Yang, Bio. & Med. 
16. Jean-Paul Seerden, Gabriela Leusink-Ionescu, TitiaWoudenberg-
Vrenken, Bas Dros, GrietjeMolema, Jan A. Kamps, Richard Kellogg, 
17. H. Debus, Annalen der Chemie und Pharmacie., 1858, 107(2), 199-
208.
20. Wallach, Ber., 1876, 184, 33-35.
21. (a) Wallach, Ber., 1881, 14, 735; (b) Wallach, Stricker, Ber., 1880,
13, 51; (c) Wallach & Schulze, Ber., 1880, 13,1514.
775-780.
3(1), 268-282.
30. M. Y. Pathan, V. V. Paike, P. R. Pachmase, S. P. More, S. S. Ardhapure,
Pharm. Res., 2010, 2(5), 392-398
35. Y. Kawashita, M. Hayashi, Mole., 2009, 14, 3073-3093.


