Chapter 2

Synthesis of $N$-aryl Pyrazoles via Chan-Lam Coupling Reaction And Their Antimicrobial Evaluation

2.1 Introduction

The recent development of copper(II)-promoted N-and O-arylation with boronic acid is a major breakthrough in the C-heteroatom$[X] (X = O, N, S)$ transformation. The copper mediated C-N, C-O and C-S bond formation between N-, O- or S-containing nucleophilic substrate and aryl-alkenylboronic acid to form N-arylated, O-arylated or S-arylated product is now referred as the Chan-Lam Coupling reaction. This methodology has emerged as a powerful tool for C-heteroatom$[X] (X = O, N, S)$ bond formation, and has found wide applications in organic synthesis because of the mildness of the reaction conditions, for example, room temperature, weak base, and ambient atmosphere (“open-flask chemistry”). This approach also takes advantage of the ready availability of the boronic acid and the chemistry developed in the Suzuki-Miyaura coupling arena.

$N$-Arylation of azoles was carried out by metal mediated reactions such as the Ullmann coupling, aromatic nucleophilic substitution and Pd or Cu catalyzed arylation. The copper-promoted arylation has been known for a century as the classical Ullmann$^{1-3}$ and Goldberg$^{4,6}$ coupling reaction (Figure-2.1). It necessitates the use of strongly aggressive conditions (high temperatures, extended reaction times, and strong base) and has been plagued by poor substrate scope and a capricious nature. Besides these procedures, Buchwald$^{7,8}$ and Hartwig$^{9,10}$ established the wide applicability of Pd-source in the C–N coupling reactions (Figure-2.1). Another copper mediated protocol for the C-N bond formation reaction was developed by Chan$^{11}$ and Lam$^{12,13}$ using aryl boronic acid as coupling partner (Figure-2.2). However requirement of 1-2 equivalent of Cu(OAc)$\_2$, large excess of boronic acid and long reaction time are the few limitation associated with this cross coupling reaction.
In general, there are a wide variety of protocols describing the metal-mediated arylation of amines, amides and imides, imidazoles, benzimidazoles, sulfonamides, pyrroles, lactams, sulfonyl azide, glucosamine, Sulfonediimines and Coumarines. However the Chan-Lam coupling reaction made even more attractive by the mild conditions required. Significant progress has been made in expanding the scope and the applications as well as understanding the mechanism of this reaction.
2.2 Pharmacological Profile of Various Substituted Pyrazoles

Pyrazole derivatives possessed diverse biological activities such as anti-hyperglycemic, analgesic, anti-inflammatory, antipyretic, antibacterial, and sedative-hypnotic activity, cyclooxygenase-2 (Cox-2) inhibitors, IL-1 synthesis inhibitors, protein kinase inhibitors, A3 adenosine receptor antagonists as well as useful activities in conditions like schizophrenia, hypertension, and Alzheimer's disease. In addition, they also have agrochemical properties including herbicidal and soil fungicidal activity; thus, they have been used as pesticides and insecticides. The clinically useful derivatives of pyrazole nucleus with their activity are listed as under (Figure 2.3).
Ningaiah, S. et al.\textsuperscript{29} have reported antimicrobial activity of novel pyrazole integrated oxadiazole. All the synthesized compounds screened for their in vitro antimicrobial activity. All synthesized compounds demonstrated potent to weak antimicrobial activity with MIC value 20-50 gmL\textsuperscript{-1} against bacteria and 25-55 gmL\textsuperscript{-1} against fungi (Figure-2.4).

![Figure-2.4](image)

**Figure-2.4**

Tanitame, A. et al.\textsuperscript{30} have synthesized pyrazole derivatives possesses antibacterial activity and inhibitory activity against DNA gyrase and topoisomerase IV. They have synthesized new pyrazole derivatives and found that 5-[(E)-2-(5-chloroindol-3-yl)vinyl]pyrazole (Figure-2.5) possesses potent antibacterial activity and selective inhibitory activity against bacterial topoisomerases. Many of the synthesized pyrazole derivatives were potent against clinically isolated quinolone coumarin-resistant Gram-positive strains and had minimal inhibitory concentration values against these strains equivalent to those against susceptible strains.

![Figure-2.5](image)

**Figure-2.5**

Bagley, M. C. et al.\textsuperscript{31} have synthesized substituted \textit{N}-pyrazole urea under the microwave irradiation. The reaction of substituted hydrazine and \textit{\beta}-ketoesters afforded 5-aminopyrazoles in excellent yield, which can be transformed to the corresponding \textit{N}-carbonyl derivatives by treatment with an isocyanate or chloroformate. Derivatization of 4-nitronaphth-1-ol using predominantly microwave heating methods and reaction with an \textit{N}-pyrazole carbamate provides a rapid route to the \textit{N}-pyrazole urea BIRB 796 (Figure-2.6) in high purity, as a potent and selective inhibitor of p38a
mitogen-activated protein kinase for the study of accelerated ageing in Werner syndrome cells.

![Image](image)

**Figure-2.6**

Stein, R. G. *et al.*\(^{32}\) have combined the features of the pyrazole ring, a substituted quinoline, and an "antimalarial" side chain in one molecule for antimalarial testing. The key intermediate required was a 4-chloro-1H-pyrazolo[3,4-b]quinoline (**Figure-2.7**), in which the active C\(_1\) could be replaced with suitable amines expected to impart antimalarial activity to the final products.

![Image](image)

**Figure-2.7**

In 2004, Edwards, P. J. *et al.*\(^{33}\) have synthesized numerous highly functionalized pyrazole derivatives (**Figure-2.8**) using various diketone and substituted hydrazine hydrate and screened for HIV mediated diseases. Among them such compounds were found to useful in the treatment of a variety of disorders including those in which the inhibition of reverse transcriptase is implicated. Disorders of interest include those caused by HIV and genetically related retroviruses, such as AIDS.

![Image](image)

**Figure-2.8**

Shen, *et al.*\(^{34}\) have discovered novel class of 1,3,5-pyrazoles as potent human glucagon receptor antagonists. They showed that one of the synthesized compound
(Figure-2.9) showed excellent oral pharmacodynamics efficacy in rhesus monkeys and transgenic mice by blocking glucagon-induced hyperglycemia. Extensive profiling of this compound has demonstrated that the pyrazole class of human glucagon receptor antagonists holds great potential for the treatment of T2DM.

\[ \text{Figure-2.9} \]

2.3 Synthetic Aspect

2.3.1 C-N bond formation via Chan-Lam cross coupling reaction

The advantage of copper-mediated boronic acid C(aryl)-N bond formation reaction is it’s high tolerability of a wide range of functional groups and its high success rate on a broad spectrum of substrates. In this communication Chan group demonstrated that a wide range of the NH-containing nucleophile partners including amides, amines, imides, urea, carbamates and sulfonamide, underwent stoichiometric copper-mediated C-N bond formation reaction with p-tolyl boronic acid to afford N-arylated compounds.
Lam, P. et al.\textsuperscript{12} initially studied a new aryl/heteroaryl C-N bond cross-coupling reaction \textit{via} the arylboronic acid/cupric acetate arylation of pyrazoles. This new methodology is mild, proceeds at room temperature exposed to air, and works for many heteroarenes and arylboronic acids providing good yields of \textit{N}-arylated heteroarenes (\textbf{Figure-2.10}).

\begin{equation}
\begin{array}{c}
R - \text{B(OH)}_2^- \text{OH} \\
\text{2 eq.} \\
R = \text{CF}_3, \text{CH}_3, \text{CH}_2\text{O}
\end{array}
+ \begin{array}{c}
\text{HN} - \text{N} \\
\text{1 eq.}
\end{array}
\xrightarrow{1.5 \text{ eq Cu(OAc)}_2, \text{2 eq pyridine, CH}_2\text{Cl}_2, \text{RT, air, 2 day}}
\begin{array}{c}
\text{R} \\
\text{N} - \text{N}
\end{array}
\end{equation}

\textbf{Figure-2.10}

Yu, S. and Mederski \textit{et al.}\textsuperscript{21,35} was reported that \textit{N}-arylation proceeded in good yields with pyrroles and indoles containing a chelating aldehyde, ketone or ester located in a position alpha to the NH group. Recently, Bekolo \textit{et al.}\textsuperscript{36} reported \textit{N}-arylation of electron-deficient pyrroles and indoles having no carbonyl group at the C2-position (2) was developed to give the \textit{N}-arylated indole(3) in good to excellent yields using diisopropylethylamine as the base (\textbf{Figure-2.11}). Neither triethylamine nor pyridine gave the desired product under these conditions.

\begin{equation}
\begin{array}{c}
\text{R}_1 \text{N} - \text{H} \\
\text{R}_1 = \text{H, R}_2 = \text{COMe} \\
\text{R}_1 = \text{NO}_2, \text{R}_2 = \text{H}
\end{array}
+ \begin{array}{c}
\text{ArB(OH)}_2^- \\
\text{2.5 eq}
\end{array}
\xrightarrow{\text{Cu(OAc)}_2 (2.5 \text{ eq}), \text{i-Pr}_2\text{NEt} (2.5 \text{ eq), CH}_2\text{Cl}_2, \text{r.t., 4-10 d}}
\begin{array}{c}
\text{R}_1 \text{N} - \text{H} \\
\text{R}_1 = \text{H, R}_2 = \text{COMe} \\
\text{R}_1 = \text{NO}_2, \text{R}_2 = \text{H}
\end{array}
\end{equation}

\textbf{Figure-2.11}

Lam, P. Y. S. \textit{et al.}\textsuperscript{37} was explored the cross-coupling between 3-pyridylboronic acid and benzimidazole and obtained only 22% yield. However, changing the boron reagent to the corresponding propylene glycol boronic ester resulted in a higher yield of 54% (\textbf{Figure-2.12}). The C-N cross coupling between two heteroarenes using Chan-Lam coupling reaction has been widely used, particular in pharmaceutical research for the synthesis of drug-like small molecules.
Yu, X. Q. et al.\textsuperscript{38,39} was developed an efficient and mild method for the direct \(N\)-arylation of nucleosides (10, 11) with aryloboronic acids catalyzed by copper(II) acetate hydrates. The presence of water was important. Replacing copper(II) acetate with copper(II) acetate monohydrate in the absence of molecular sieves significantly increased the yield. The mixed solvent methanol:water (4:1) was optimal. In addition, only \(N,N,N',N'\)-tetramethylethylenediamine as the base gave products (12, 13) in good yields (Figure-2.13).

Chen, S. et al.\textsuperscript{40} was carried out \(N\)-arylation of amines using phenylboronic acid could be efficiently promoted in the presence of Cu(OAc)\(_2\) and DBU as base under the microwave (MW) irradiation (Figure-2.14).
Rossi, S. A. et al. was carried out the copper-catalyzed mono alkylation of primary amides using alkylboronic acids. The key to this reaction is the discovery that the combination of a mild base (sodium trimethylsilanolate) and di-tert-butyl peroxide (DTBP) as the oxidant is uniquely effective in promoting the catalytic cross-coupling reaction of primary amides and primary boronic acids (Figure-2.15).

\[
\text{R}^+\text{NH}_2 + \text{O} \xrightarrow{\text{cat. CuBr}} \xrightarrow{\text{NaOSiMe, DTBP}} \text{R}^+\text{NH}_2
\]

**Figure-2.15**

Joshi, R. A. et al. was reported that the cross-coupling of aminopurines (5) and aminopyrimidines (7) and (8) with arylboronic acids gave N-arylated products in moderate to good yields (Figure-2.16).

\[
\begin{align*}
\text{Cl} & \quad + \text{ArB(OH)}_2 \\
\text{H}_2\text{N} & \quad \xrightarrow{\text{Cu(OAc)}_2, \text{Et}_3\text{N}, \text{DMAP, CHCl}_3, \text{air, RT, 24 h}} \text{R} \\
5 & \quad \xrightarrow{\text{same as above}} \text{R}
\end{align*}
\]

**Figure-2.16**

2.3.2 C-O and C-S bond formation via Chan-Lam coupling.

The formation of C-S bonds has received less attention. Difficulties in C-S bond formation can be attributed to the sulfur species rapidly and irreversibly deactivating the catalyst. So the efficient formation of the C-S bond is a most important aspect of organic chemistry. Many research groups have made great effort to overcome this problem in recent years, and several excellent catalytic systems that used Pd, Cu, Ni, Fe and other metals as catalysts have been found for C–S bond
formation. Xu, H-J. et al.\textsuperscript{43} was developed a general protocol to achieve the oxidative cross-coupling reactions of diverse boronic acids with thiols using a simple copper catalyst in environment-friendly solvent at room temperature (Figure-2.17).

\begin{center}
\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2_17}
\caption{Figure-2.17}
\end{figure}
\end{center}

Medda, A. et al.\textsuperscript{26} was developed a convenient protocol for the efficient synthesis of aryloxyxycoumarins by Cu-promoted C-O coupling reactions from readily available hydroxycoumarin derivatives in the presence of the catalytic system Cu(OAc)\textsubscript{2}/Et\textsubscript{3}N. By applying this condition, a series of arylboronic acids have been successfully reacted to afford the coupled products in fair to good yields (Figure-2.18).

\begin{center}
\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2_18}
\caption{Figure-2.18}
\end{figure}
\end{center}

Mondal, M. et al.\textsuperscript{44} was reported the Chan–Lam C–O cross coupling methodology for the synthesis of O-aryloxime ether at room temperature using aryl oxime and aryl boronic acids as coupling partners in the presence of different bases, solvents, and copper acetate as a catalyst (Figure-2.19).

\begin{center}
\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2_19}
\caption{Figure-2.19}
\end{figure}
\end{center}

\subsection*{2.3.3 Modification in Chan-Lam Coupling}
Collman, J. P. et al.\textsuperscript{45,46} was first introduced catalytic carbon–nitrogen coupling by using catalytic amount of [Cu(OH).TMEDA]\textsubscript{2}Cl\textsubscript{2} (10 mol%) arylboronic acids react smoothly with imidazoles (19) in dichloromethane at room temperature to give a variety of \textit{N}-arylimidazoles (20) in good to excellent yields. The reaction also
occurs in water in lower yield. $N$-Arylation of imidazole is faster than $O$-arylation of bulk water (Figure-2.20).

![Figure-2.20]

Raghuvanshi, D. et al.$^{47,48}$ have been developed viable and efficient Ni-catalyzed $N$-arylation using the reaction of arylboronic acids with amines, amides, and $N$-heterocycles under atmospheric conditions. The method is practical and offers an alternative to the corresponding Cu-mediated Chan-Lam process for the construction of the C-N bond (Figure-2.21).

![Figure-2.21]

Lakshmi Kantam, M. et al.$^{49}$ have been carried out the coupling of imides with various arylboronic acids using Cu-Al hydrotalcite in refluxing methanol with continuous bubbling of air through the mixture without employing base or ligand to afford $N$-arylated products in very good yields. Cu-Al hydrotalcite is used for four cycles successfully with minimal loss of activity (Figure-2.22).

![Figure-2.22]

Gogoi, A. et al.$^{50}$ have been reported the catalytic activity of a unique Cu-salen type complex in $N$-arylation of anilines with arylboronic acids in water. The protocol is found to be applicable for a wide range of electronically diversified arylboronic
acids and anilines with excellent yields of the isolated product. Further the scope of this protocol has been extended to the synthesis of various N-aryl imidazoles in isopropanol (Figure-2.23).

2.3.4 N-Arylation of Pyrazoles

N-Aryl derivatives of azoles are very important organic compound for an organic synthesis because of their wide range of biological activity. N-Arylation of azoles was carried out by metal mediated reactions such as the Ullmann coupling, aromatic nucleophilic substitution and Pd or Cu catalyzed arylation. Many reactions are reported for the synthesis of N-aryl pyrazoles using halides and copper catalyst.

Buchwald, S. L. et al.\(^{51}\) was reported the copper-catalyzed N-arylation of \(\pi\)-excessive nitrogen heterocycles. The coupling of either aryl iodides or aryl bromides with common nitrogen heterocycles (pyrroles, pyrazoles, indazoles, imidazoles, and triazoles) was successfully performed in good yield with catalysts derived from diamine ligands and CuI (Figure-2.24).

Tan, Z. et al.\(^{52}\) have described a new method for the expedient and facile access to BIRB796 and its N-arylated analogs in good to moderate yields. Direct cross-coupling of aryl boronic acids with urea (5) in the presence of cupric acetate and base gave the corresponding N-arylated analogs in one step (Figure-2.25). Key intermediate urea (5) was readily prepared from commercially available materials in
good yield. This method uses inexpensive reagents and readily available starting materials under mild conditions.

![Figure-2.25](image)

Figure-2.25

Kurpet, M. K. *et al.*\(^{53}\) have developed an efficient and simple method for the cross coupling of aryl boronic acids with C-nitro-NH-azoles in the presence of a catalytic amount of simple copper salts. The reaction takes place in a protic solvent containing a base, both of which are necessary for providing good yields of the products. The method represents an important supplement to the synthetic methodologies for the preparation of N-aryl-C-nitroazoles and can be successfully applied to the synthesis of a series of diverse C-nitroazoles functionalized with an aryl substituent on a ring nitrogen atom (Figure-2.26).

![Figure-2.26](image)

Figure-2.26

Janin, Y. L. *et al.*\(^{54}\) have synthesized new pyrazole derivatives. They reported selective N-arylation, by using Chan and Lam method, the C\(_4\) and C\(_5\)-arylation of some of these 3-ethoxypyrazole derivatives by using the Suzuki–Miyaura reaction, and C\(_5\)-benzylation reactions by means of the Negishi reaction (Figure-2.27).
Wang, L. *et al.* have developed SiO$_2$-NHC-Cu$^I$ catalyst as highly selective and efficient for the $N$-arylation of azoles with aryl boronic acids. The reactions were performed smoothly to generate the desired products $N$-aryl azoles in good yields under base-free and simple reaction conditions. The notable advantages of this methodology are mild conditions, short reaction times, and good yields free from any side reaction products (Figure-2.28).

*Figure-2.27*

You, J. *et al.* have described mild and highly efficient CuI-catalyzed $N$-arylation protocol for the nitrogen containing heterocycles (e.g., imidazoles, benzimidazoles, pyroles, pyrazoles, indoles, triazoles, etc.) with aryl and heteroaryl halides. This protocols can be performed easily and tolerate a number of functional groups, such as ester, nitrile, nitro, ketone, free hydroxyl, and free primary amine on the aryl halide (Figure-2.29).

*Figure-2.28*

*Figure-2.29*
2.4 Current Research Work

C-N cross-coupling between aryl and aromatic heterocycles is an important process. Many reactions for the N-arylation of azoles are reported.\textsuperscript{57-60} The advantage of the copper-mediated boronic acid carbon–nitrogen bond formation reaction is its high tolerance of a wide range of functional groups and its high success rate on a broad spectrum of substrates because of the mildness and efficiency of the reaction conditions.

In current research work a series of N-substituted pyrazoles was prepared by Chan-Lam cross coupling reaction. Initially, 5-isopropyl-3-(methylthio)-N-phenyl-1H-pyrazole-4-carboxamide was obtained by condensation of 2-(bis(methylthio)methylene)-4-methyl-3-oxo-N-phenylpentanamide with hydrazine hydrate in water at reflux temperature. These pyrazole was further reacted with different aryl boronic acids in presence of copper acetate and triethyl amine under oxygen environment. The newly synthesized N-substituted pyrazoles were purified by column chromatography and characterized by IR, Mass, \textsuperscript{1}H NMR, \textsuperscript{13}C NMR spectroscopy and elemental analysis.
2.5 Results and Discussion

Scheme 2.1 Synthesis of 3-isopropyl-5-(methylthio)-N-phenyl-1H-pyrazole-4-carboxamide

Scheme 2.2 Synthesis of N-arylpyrazoles

\[ \text{Int-3} + \text{HO-B(OH)}_2 \xrightleftharpoons{\text{Cu(OAc)}_2, \text{O}_2, \text{TEA, MDC, 18h}} \text{VK-2a-o} \]

*N-aryl* pyrazoles were synthesized by reaction of pyrazole with various aryl boronic acids and copper acetate using triethyl amine as a base in dichloromethane at room temperature for 16–22 h. The required pyrazole (**Int-1**) was prepared by condensation reaction of 2-(bis(methylthio)methylene)-4-methyl-3-oxo-N-phenylpentanamide with hydrazine hydrate in water at refluxing temperature for 3 h. All the synthesized compounds are required to purify by column chromatography using mixture of ethyl acetate and hexane.
The structures of VK-2a-o were established on the basis of their elemental analysis and spectral data (MS, IR, $^1$H NMR and $^{13}$C NMR). Some representative examples for each step are described here.

The structure of VK-2a supported by its mass (m/z 351), which agrees with its molecular formula $C_{20}H_{21}N_3OS$. $^1$H NMR spectrum shows signals at 9.49 ppm (s, 1H, -CONH), 7.68 ppm (d, J= 7.6 Hz, 2H, Ar-H), 7.57-7.47 ppm (m, 5H, Ar-H), 7.14 ppm (t, 1H, Ar-H), 3.89-3.78 (m, 1H, isopropyl -CH), 2.25 (s, 3H, -SCH$_3$), 1.37 (d, J=6.8 Hz, 6H, -(CH$_3$)$_2$).

The structure of VK-2d supported by its mass (m/z 430), which agrees with its molecular formula $C_{20}H_{20}BrN_3OS$. The $^1$H NMR spectrum shows signals at 9.40 ppm (s, 1H, -CONH), 7.67 ppm (d, J= 8.4 Hz, 2H, Ar-H), 7.64 ppm (d, J= 8.4 Hz, 2H, Ar-H), 7.45 ppm (d, J= 8.6 Hz, 2H, Ar-H), 7.14 ppm (t, 2H, Ar-H), 3.86-3.77 ppm (m, 1H, ipr-CH), 2.26 ppm (s, 3H, -SCH$_3$), 1.36 ppm (d, J= 6.8 Hz, 6H, -(CH$_3$)$_2$).

### Table 2.1 Synthesis of N-aryl pyrazoles

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Reaction Time h</th>
<th>M.W.</th>
<th>Yield %</th>
<th>mp$^o$C</th>
</tr>
</thead>
<tbody>
<tr>
<td>VK-2a</td>
<td>H</td>
<td>18</td>
<td>351</td>
<td>84</td>
<td>106</td>
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<tr>
<td>VK-2b</td>
<td>4-CN</td>
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<td>376</td>
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<td>116</td>
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<td>VK-2c</td>
<td>4-F</td>
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<td>369</td>
<td>83</td>
<td>128</td>
</tr>
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<td>4-Br</td>
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<tr>
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<td>VK-2f</td>
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<td>379</td>
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<td>385</td>
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<tr>
<td>VK-2i</td>
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<td>20</td>
<td>394</td>
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<td>17</td>
<td>381</td>
<td>66</td>
<td>108</td>
</tr>
</tbody>
</table>
Plausible Mechanism for the Formation of N-Arylpyrazole

In the proposed general mechanism for Chan-Lam coupling reaction (Figure-2.30), the arylboronic acid initially undergoes transmetalation with copper complex 1 to generate boric acid and intermediate 2, which then coordinates the NH-pyrazole substrate, forming complex 3. In the presence of dioxygen, complex 3 has been proposed to undergo oxidation, forming a expected Cu(III) intermediate 4, which undergoes reductive elimination, yielding the coupling product 5.
2.6 Antimicrobial Sensitivity Testing


In vitro effectivity of antimicrobial agents can be demonstrated by observing their capacity to inhibit bacterial growth on suitable media. The production of a zone depends on two factors namely bacterial growth and concentration of antimicrobial agent. The hole/well punch method was first used by Bennett. This diffusion method has proved more effective than many other methods. According to Lt. General Raghunath the well technique is 5-6 times more sensitive than using disk method.

Principle

When antimicrobial substance is added in agar cup (made in a medium previously inoculated with test organism) the radial diffusion of an antimicrobial agent through the agar, produces a concentration gradient. The test organism is inhibited at the minimum inhibitory concentration (MIC), giving rise to a clear zone of inhibition.

Requirements

1. Young broth culture of a standard test organism
2. Sterile Mueller Hinton Agar plate
3. Solution of antimicrobial substance
4. Cup borer
5. Alcohol etc.

Inoculum preparation

Inoculum was prepared by selecting 4-5 colonies from slope of stock culture of the indicator organism and emulsifying them in a suitable broth. The inoculated broth was incubated at 37 °C till it equals turbidity of a 0.5 McFarl and standard. This happens in 2-8 h.

Procedure
1. Inoculate test organism on the top of Mueller Hinton Agar plate with help of sterile swab. (it can be inoculated in melted agar also)
2. The swab was dipped in the inoculum and surface of plate was streaked with swab.
3. Streaking was repeated for 3 times and each time the plate was rotated at angle of 60°.
4. Sterilize the cup-borer make four cups of the diameter of 8-10 mm. at equal distance in the plate previously inoculated with seed culture.
5. The depth of well was 2.5-5.0 mm.
6. The wells have been clearly punched so the surrounding medium is not lifted when the plug was removed out.
7. The plates were incubated at 37°C for 24 h. Then the zone of inhibition measured and the size of zone cited in table.
### Antimicrobial Sensitivity Assay

<table>
<thead>
<tr>
<th>Compound</th>
<th>MIC(µg/mL)</th>
<th>Antibacterial activity</th>
<th>Antifungal activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>E.coli (MTCC 443)</td>
<td>S. typhi (MTCC 98)</td>
</tr>
<tr>
<td>VK-2a</td>
<td><strong>200</strong></td>
<td>250</td>
<td>500</td>
</tr>
<tr>
<td>VK-2b</td>
<td>250</td>
<td>200</td>
<td>500</td>
</tr>
<tr>
<td>VK-2c</td>
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2.7 Conclusion

In summary, we have synthesized a small library of \( N \)-aryl pyrazole derivatives via Chan-Lam cross coupling reaction using diverse boronicacids at room temperature using \( \text{Cu(OAc)}_2/\text{TEA} \) as a catalytic system without utilization of any ligand or additive and exposed to air to afford moderate to excellent yield. Usually in Chan-Lam coupling reaction major problem arise of low yield. In present work we reports mild and efficient protocol for \( N \)-aryl pyrazoles (VK-2a-o) with excellent yield. Structure of all the synthesized compound confirmed by spectroscopic data and elemental analysis. Additionally, all the synthesized compounds were screened for their antimicrobial activity against the selected pathogens and compared with standard drugs. The investigation of antibacterial and antifungal screening data revealed that, the compounds VK-2a, VK-2c, VK-2e, VK-2j, VK-2m and VK-2n shows very good activity against bacterial stain. VK-2e, VK-2j and VK-2n shows comparatively good activity against fungal stain.
2.8 Experimental Section

All research chemicals were purchased from Sigma-Aldrich Chemicals and used as received. Reactions were monitored by thin layer chromatography (TLC) on pre-coated silica gel GF254 plates (E-Merck Co) by using appropriate solvent systems. Melting points were determined in open capillaries and are uncorrected. Infrared (IR) spectra (KBr pellets) were recorded on a Shimadzu-FTIR-8400 spectrophotometer over frequencies ranging from 4000-400 cm\(^{-1}\). The NMR Spectra (\(^1\)H NMR & \(^13\)C NMR) were recorded on a Bruker Avance-III Spectrospin 400 MHz spectrometer using CDCl\(_3\) as solvents and TMS as an internal standard. Mass spectra were recorded on a Shimadzu GC-MS-QP-2010 spectrometer by using Electron Impact (EI) (0.7 kV) ionization source. The ion source temperature was 220 °C and interface temperature was 240 °C.

- **Synthesis of 4-methyl-3-oxo-N-phenylpentanamide (Int-1).**
  A mixture of aniline (10 mmol), methyl-4-methyl-3-oxopentanoate (10 mmol) and catalytic amount of sodium or potassium hydroxide lie (10 %) in toluene (50ml) was refluxed at 110 °C for 12-15 h. The reaction was monitored by TLC. After completion of reaction, the solvent was removed under reduce pressure and washed with water to afford pure product.

- **Synthesis of 2-(bis(methylthio)methylene)-4-methyl-3-oxo-N-phenylpentanamide (Int-2).**
  To a well stirred suspension of 4-methyl-3-oxo-N-phenylpentanamide (10 mmol) and potassium carbonate (20 mmol) in DMF (20 mL) at 0-5 °C was added CS\(_2\) (10 mmol) over a period of 30 min. After completion of the addition, the reaction mixture was stirred at 0-5 °C for 1 h. Appearance of reddish solid in the reaction medium indicated the formation of dipotassium salt. To this reaction, a solution of methyl iodide (20 mmol) was added drop wise within 15 min at 0-5 °C. The mixture was allowed to warm at room temperature and stirred for 15 h, and then poured onto crushed ice under stirring. The separated solid was washed with water and collected by filtration.

- **Synthesis of 3-isopropyl-5-(methylthio)-N-phenyl-1\(^H\)-pyrazole-4-carboxamide (Int-3).**
  To a suspension of 2-(bis(methylthio)methylene)-4-methyl-3-oxo-N-phenylpentanamide Int-2 (10 mmol) in water (25 mL), hydrazine hydrate 80% (1 mL,
20 mmol) was added and the reaction mixture was refluxed for 3 to 4 h with constant stirring. After completion of the reaction, the reaction mixture was cooled to room temperature and added cold water (50 mL). The separated solid was filtered, washed with water (2 × 50 mL), dried and crystallized from methanol to afford analytically pure products which were used for next step without further purification.

**General synthesis of N-aryl pyrazoles VK-2a-o**

Dry dichloromethane (10 V) and dry molecular sieves were taken in RBF. Pyrazole Int-3 (5 mmol), triethyl amine (20 mmol), boronic acid (6 mmol), and copper (II) acetate (6 mmol) were added to this solution. The suspension then stirred for appropriate time (Table 1) under air. The calcium chloride guard tube was used to protect the reaction from moisture. The reaction was monitored by TLC using Ethyl acetate:Hexane (3:7) as a mobile phase. The suspension was diluted with dichloromethane, filtered and washed with water and brine. The organic phase was dried (Na$_2$SO$_4$) and the solvent removed under reduced pressure. All the synthesized compound purified by column chromatography using ethyl acetate and hexane.

**Spectral data of the synthesized compounds**

3-isopropyl-5-(methylthio)-N-phenyl-1H-pyrazole-4-carboxamide (Int-3): White Solid; Yield, 88%; m.p. 136 °C; R$_f$ 0.52 (7:3 hexane-EtOAc); IR (KBr) cm$^{-1}$: 3250, 3142, 3032, 2926, 2863, 1647, 1548, 1446, 763, 748; $^1$H NMR (400 MHz, CDCl$_3$): 13.00 (s, 1H, -NH pyrazole), 9.68 (s, 1H, -CONH), 7.64 (d, $J$ = 8.0 Hz, 2H, Ar-H), 7.31 (t, 2H, Ar-H), 7.05 (t, 1H, Ar-H), 3.40-3.33 (m, 1H, ipr-CH), 2.50 (s, 3H, -SCH$_3$), 1.24 (d, $J$ = 6.8 Hz, 6H, (CH$_3$)$_2$); MS (m/z): 275 (M+); Elemental analysis: Calcd. for: C$_{14}$H$_{17}$N$_3$OS; C, 61.06; H, 6.22; N, 15.26; Found: C, 61.48; H, 6.72; N, 14.86.

3-isopropyl-5-(methylthio)-N,1-diphenyl-1H-pyrazole-4-carboxamide (VK-2a): Light brown solid; Yield, 84%; m.p. 106 °C; R$_f$ 0.43 (7:3 hexane-EtOAc); IR (KBr) cm$^{-1}$: 3228, 3131, 3064, 2970, 2863, 1641, 1596, 1443, 755, 696; $^1$H NMR (400 MHz, CDCl$_3$): 9.49 (s, 1H, -CONH), 7.68 (d, $J$ = 7.6 Hz, 2H, Ar-H), 7.57-7.47 (m, 5H, Ar-H), 7.37 (t, 2H, Ar-H), 7.14 (t, 1H, Ar-H), 3.89-3.78 (m, 1H, ipr-CH), 2.25 (s, 3H, -SCH$_3$), 1.37 (d, $J$ = 6.8 Hz, 6H, -(CH$_3$)$_2$); $^{13}$C NMR (400 MHz, CDCl$_3$): 161.86, 161.26, 139.17,
138.49, 133.41, 129.28, 129.19, 128.97, 126.50, 124.37, 120.09, 117.47, 27.58, 22.20, 20.01; MS (m/z): 351 (M+); Elemental analysis: Calcd. for: C_{20}H_{21}N_{3}OS; C, 68.35; H, 6.02; N, 11.96; Found: C, 67.87; H, 6.34; N, 12.21.

1-(4-cyanophenyl)-3-isopropyl-5-(methylthio)-N-phenyl-1H-pyrazole-4-carboxamide (VK-2b): Brown solid; Yield, 87%;
m.p. 116 °C; R\textsubscript{f} 0.52 (7:3 hexane-EtOAc); IR (KBr) cm\textsuperscript{-1}: 3288, 3135, 3064, 2958, 2866, 2222, 1648, 1444, 750, 693; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): 9.28 (s, 1H, -CONH), 7.82 (d, J=9.6 Hz, 2H, Ar-H), 7.81 (d, J=9.6 Hz, 2H, Ar-H), 7.79 (d, J=7.2 Hz, 2H, Ar-H), 7.78 (t, 2H, Ar-H), 7.76 (m, 1H, ipr-CH), 2.30 (s, 3H, -SCH\textsubscript{3}), 1.36 (d, J=6.4 Hz, 6H, -(CH\textsubscript{3})\textsubscript{2}); \textsuperscript{13}C NMR (400 MHz, CDCl\textsubscript{3}): 162.69, 160.77, 142.49, 138.16, 133.71, 133.12, 129.34, 126.52, 124.67, 120.10, 119.22, 118.21, 118.21, 27.58, 22.07, 20.26; MS (m/z): 376 (M+); Elemental analysis: Calcd. for: C_{21}H_{20}N_{4}OS; C, 67.00; H, 5.35; N, 14.88; Found: C, 67.38; H, 5.67; N, 14.42.

1-(4-fluorophenyl)-3-isopropyl-5-(methylthio)-N-phenyl-1H-pyrazole-4-carboxamide (VK-2c): Brown solid; Yield, 83%;
m.p. 128 °C; R\textsubscript{f} 0.48 (7:3 hexane-EtOAc); IR (KBr) cm\textsuperscript{-1}: 3305, 3282, 3067, 3053, 2983, 2959, 1644, 1478, 1221, 742; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): 9.43 (s, 1H, -CONH), 7.68 (d, J=7.6 Hz, 2H, Ar-H), 7.55-7.51 (m, 2H, Ar-H), 7.37 (t, 2H, Ar-H), 7.20 (t, 2H, Ar-H), 7.14 (t, 1H, Ar-H), 3.88-3.77 (m, 1H, ipr-CH), 2.25 (s, 3H, -SCH\textsubscript{3}), 1.36 (d, J=6.8 Hz, 6H, -(CH\textsubscript{3})\textsubscript{2}); \textsuperscript{13}C NMR (400 MHz, CDCl\textsubscript{3}): 163.85, 161.89, 161.09, 138.36, 135.16, 133.56, 129.26, 128.27, 124.41, 120.06, 116.24, 116.02, 27.51, 22.14, 19.96; MS (m/z): 369 (M+); Elemental analysis: Calcd. for: C_{20}H_{20}FN_{3}OS; C, 65.02; H, 5.46; N, 11.37; Found: C, 65.41; H, 5.11; N, 11.88.

1-(4-bromophenyl)-3-isopropyl-5-(methylthio)-N-phenyl-1H-pyrazole-4-carboxamide (VK-2d): Dark brown solid; Yield, 85%;
m.p. 118 °C; R\textsubscript{f} 0.52 (7:3 hexane-EtOAc); IR (KBr) cm\textsuperscript{-1}: 3295, 3270, 3128, 3062, 2959, 2866, 1645, 1494, 752, 575; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): 9.40(s, 1H, -CONH), 7.67 (d, J= 8.4 Hz, 2H, Ar-H), 7.64 (d, J= 8.4 Hz, 2H, Ar-H), 7.45 (d, J= 8.6 Hz, 2H, Ar-H), 7.37 (t, 2H, Ar-H), 7.14 (t, 1H, Ar-H),
3.86-3.77 (m, 1H, ipr-CH), 2.26 (s, 3H, -SCH$_3$), 1.36 (d, J= 6.8 Hz, 6H, -(CH$_3$)$_2$); $^{13}$C NMR (400 MHz, CDCl$_3$): 161.10, 161.00, 138.31, 138.05, 133.40, 132.31, 129.27, 127.85, 124.44, 122.76, 120.05, 117.95, 27.51, 22.10, 20.07; MS (m/z): 429 (M+); Elemental analysis: Calcd. for: C$_{20}$H$_{20}$BrN$_3$OS; C, 55.82; H, 4.68; N, 9.76; Found: C, 55.26; H, 4.24; N, 10.14.

1-(4-chlorophenyl)-3-isopropyl-5-(methylthio)-N-phenyl-1H-pyrazole-4-carboxamide (VK-2e): Light brown solid; Yield, 79%; m.p. 110 °C; R$_f$ 0.50 (7:3 hexane-EtOAc); IR (KBr) cm$^{-1}$: 3281, 3263, 3129, 3056, 2959, 2863, 1640, 1443, 1411, 833, 752, 694; $^1$H NMR (400 MHz, CDCl$_3$): 9.40(s, 1H, -CONH), 7.68 (d, J = 8.0 Hz, 2H, Ar-H), 7.52 (d, J = 8.8 Hz, 2H, Ar-H), 7.48 (d, J = 8.8 Hz, 2H, Ar-H), 7.37 (t, 2H, Ar-H), 7.14 (t, 1H, Ar-H), 3.85-3.77 (m, 1H, ipr-CH), 2.26 (s, 3H, -SCH$_3$), 1.36 (d, J = 6.8 Hz, 6H, -(CH$_3$)$_2$); $^{13}$C NMR (400 MHz, CDCl$_3$): 162.06, 161.03, 138.33, 137.56, 134.77, 133.45, 129.34, 129.27, 127.59, 124.44, 120.07, 117.91, 27.54, 22.13, 20.04; MS (m/z): 385 (M+); Elemental analysis: Calcd. for: C$_{20}$H$_{20}$ClN$_3$OS; C, 62.25; H, 5.22; N, 10.89; Found: C, 62.72; H, 5.56; N, 10.28.

1-(4-ethylphenyl)-3-isopropyl-5-(methylthio)-N-phenyl-1H-pyrazole-4-carboxamide (VK-2f): Light brown solid; Yield, 77%; m.p. 114 °C; R$_f$ 0.50 (7:3 hexane-EtOAc); IR (KBr) cm$^{-1}$: 3301, 3059, 2963, 2928, 2868, 1644, 1465, 1435, 1378, 752; $^1$H NMR (400 MHz, CDCl$_3$): 9.50 (s, 1H, -CONH), 7.69 (d, J = 7.6 Hz, 2H, Ar-H), 7.43 (d, J = 8.8 Hz, 2H, Ar-H), 7.38 (d, J = 7.6 Hz, 2H, Ar-H), 7.34 (t, 2H, Ar-H), 7.13 (t, 1H, Ar-H), 3.87-3.79 (m, 1H, ipr-CH), 2.77-2.70 (q, 2H, -CH$_2$-), 2.25 (s, 3H, -SCH$_3$), 1.37 (d, J = 7.2 Hz, 6H, -(CH$_3$)$_2$), 1.28 (t, 3H, -CH$_3$); $^{13}$C NMR (400 MHz, CDCl$_3$): 161.68, 161.29, 145.35, 138.51, 136.83, 133.33, 129.25, 128.59, 126.37, 124.29, 120.05, 117.17, 28.78, 27.55, 22.19, 20.02, 15.68; MS (m/z): 379 (M+); Elemental analysis: Calcd. for: C$_{22}$H$_{25}$N$_3$OS; C, 69.62; H, 6.64; N, 11.07; Found: C, 70.08; H, 6.48; N, 11.52.
3-isopropyl-1-(4-methoxyphenyl)-5-(methylthio)-N-phenyl-
1H-pyrazole-4-carboxamide (VK-2g): Brown solid; Yield, 73%; m.p. 120 °C; Rf 0.55 (7:3 hexane-EtOAc); IR (KBr) cm⁻¹: 3288, 3142, 2953, 2914, 1648, 1468, 763, 654; ¹H NMR (400 MHz, CDCl₃): 9.36 (s, 1H, -CONH), 7.61 (d, J = 7.6 Hz, 2H, Ar-H), 7.43-7.32 (m, 4H, Ar-H), 7.27 (t, 2H, Ar-H), 7.11 (t, 1H, Ar-H), 3.89 (s, 3H, -OCH₃), 3.78-3.67 (m, 1H, ipr-CH), 2.28 (s, 3H, -SCH₃), 1.32 (d, J = 6.8 Hz, 6H, -(CH₃)₂); ¹³C NMR (400 MHz, CDCl₃): 162.24, 161.37, 142.87, 137.54, 134.88, 133.40, 133.40, 129.29, 127.59, 121.90, 116.03, 115.81, 49.65, 27.58, 22.13, 20.05; MS (m/z): 381 (M⁺); Elemental analysis: Calcd. for: C₁₂₀.18, 118.88, 48.05, 27.52, 22.15, 21.11

1-(3-chlorophenyl)-3-isopropyl-5-(methylthio)-N-phenyl-
1H-pyrazole-4-carboxamide (VK-2h): Light brown solid; Yield, 74%; m.p. 102 °C; Rf 0.57 (7:3 hexane-EtOAc); IR (KBr) cm⁻¹: 3252, 3172, 3035, 2972, 2830, 1653, 1406, 829, 746; ¹H NMR (400 MHz, CDCl₃): 9.37 (s, 1H, -CONH), 7.54 (d, J = 7.9 Hz, 2H, Ar-H), 7.28-7.31 (m, 4H, Ar-H), 7.21 (d, J = 8.4 Hz, 2H, Ar-H), 7.11 (t, 1H, Ar-H), 3.86-3.73 (m, 1H, ipr-CH), 2.31 (s, 3H, -SCH₃), 1.32 (d, J = 6.8 Hz, 6H, -(CH₃)₂); ¹³C NMR (400 MHz, CDCl₃): 162.70, 161.36, 140.32, 139.63, 134.30, 131.47, 129.62, 122.69, 121.93, 117.86, 116.04, 115.82, 114.12, 27.59, 22.13, 20.05; MS (m/z): 385 (M⁺); Elemental analysis: Calcd. for: C₂₀H₂₀ClN₃O₅S; C, 62.25; H, 5.22; N, 10.89; Found: C, 65.92; H, 5.64; N, 10.38.

1-(3-(dimethylamino)phenyl)-3-isopropyl-5-(methylthio)-N-
phenyl-1H-pyrazole-4-carboxamide (VK-2i): Light brown solid; Yield, 67%; m.p. 128 °C; Rf 0.51 (7:3 hexane-EtOAc); IR (KBr) cm⁻¹: 3304, 3178, 2968, 2920, 1644, 1488, 776; ¹H NMR (400 MHz, CDCl₃): 9.31 (s, 1H, -CONH), 8.16-7.83 (m, 2H, Ar-H), 7.81-7.57 (m, 4H, Ar-H), 7.38 (t, 2H, Ar-H), 7.16 (t, 1H, Ar-H), 3.87-3.70 (m, 1H, ipr-CH), 3.29 (s, 6H, -N(CH₃)₂), 2.39 (s, 3H, -SCH₃), 1.37 (d, J = 4.8 Hz, 6H, -(CH₃)₂); ¹³C NMR (400 MHz, CDCl₃): 162.39, 160.78, 143.59, 138.18, 134.14, 131.45, 129.31, 126.74, 124.59, 120.66, 120.18, 118.88, 48.05, 27.52, 22.15, 21.11; MS (m/z): 394 (M⁺); Elemental analysis: Calcd. for: C₂₂H₂₆N₄O₅S; C, 66.97; H, 6.64; N, 14.20; Found: C, 66.48; H, 6.92; N, 14.58.
3-isopropyl-5-(methylthio)-N-phenyl-1-(4-(trifluoromethyl)phenyl)-1H-pyrazole-4-carboxamide (VK-2j): Light brown solid; Yield, 81%; m.p. 109 °C; Rf 0.41 (7:3 hexane-EtOAc); IR (KBr) cm⁻¹: 3300, 3283, 3267, 2969, 2929, 2872, 1663, 1496, 1247, 780, 755; ¹H NMR (400 MHz, CDCl₃): 9.27 (s, 1H, -CONH), 7.71 (d, J = 8.4 Hz, 2H, Ar-H), 7.67 (d, J = 8.8 Hz, 2H, Ar-H), 7.60 (d, J = 7.6 Hz, 2H, Ar-H), 7.30 (t, 2H, Ar-H), 7.07 (t, 1H, Ar-H), 3.79-3.70 (m, 1H, ipr-CH), 2.21 (s, 3H, -SCH₃), 1.29 (d, J = 6.8 Hz, 6H, (CH₃)₂); ¹³C NMR (400 MHz, CDCl₃): 162.43, 160.95, 141.89, 138.29, 133.60, 129.34, 127.23, 126.50, 126.39, 126.36, 124.57, 120.12, 118.59, 27.59, 22.13, 20.19; MS (m/z): 419 (M+); Elemental analysis: Calcd. for: C₂₁H₂₀F₃N₃OS; C, 60.13; H, 4.81; N, 10.02; Found: C, 60.52; H, 4.34; N, 10.44.

3-isopropyl-5-(methylthio)-N-phenyl-1-(m-tolyl)-1H-pyrazole-4-carboxamide (VK-2k): Light brown solid; Yield, 69%; m.p. 98 °C; Rf 0.48 (7:3 hexane-EtOAc); IR (KBr) cm⁻¹: 3265, 3176, 3028, 2970, 2856, 1668, 1473, 763; ¹H NMR (400 MHz, CDCl₃): 9.40 (s, 1H, -CONH), 7.60 (d, J = 8.0 Hz, 2H, Ar-H), 7.33-7.22 (m, 4H, Ar-H), 7.17 (d, J = 8.0 Hz, 2H, Ar-H), 7.04 (t, 1H, Ar-H), 3.80-3.70 (m, 1H, ipr-CH), 2.35 (s, 3H, -SCH₃), 2.16 (s, 3H, -CH₃), 1.29 (d, J = 7.2 Hz, 6H, -(CH₃)₂); ¹³C NMR (400 MHz, CDCl₃): 161.70, 161.25, 139.35, 138.47, 133.37, 129.77, 129.23, 128.85, 127.11, 124.29, 123.55, 120.03, 117.23, 27.53, 22.18, 21.54, 20.02; MS (m/z): 365 (M+); Elemental analysis: Calcd. for: C₂₁H₂₃N₃OS; C, 69.01; H, 6.34; N, 11.50; Found: C, 68.74; H, 6.68; N, 11.16.

1-(3-bromophenyl)-3-isopropyl-5-(methylthio)-N-phenyl-1H-pyrazole-4-carboxamide (VK-2l): Light brown solid; Yield, 68%; m.p. 100 °C; Rf 0.52 (7:3 hexane-EtOAc); IR (KBr) cm⁻¹: 3308, 3238, 3128, 3049, 2970, 2830, 1670, 1484, 763, 669; ¹H NMR (400 MHz, CDCl₃): 9.38 (s, 1H, -CONH), 7.63 (d, J = 8.0 Hz, 2H, Ar-H), 7.43-7.35 (m, 4H, Ar-H), 7.19 (d, J = 8.2, 2H, Ar-H), 7.07 (t, 1H, Ar-H), 3.88-3.73 (m, 1H, ipr-CH), 2.35 (s, 3H, -SCH₃), 1.28 (d, J = 6.6Hz, 6H, -(CH₃)₂); ¹³C NMR (400 MHz, CDCl₃): 162.48, 161.57, 139.28, 137.71, 133.78, 131.69, 128.62, 126.92, 124.48, 123.12.
Chapter 2

N-arylpyrazoles

120.36, 115.76, 27.59, 22.18, 20.12; MS (m/z): 430 (M+); Elemental analysis: Calcd. for: C_{20}H_{20}BrN_{3}OS; C, 55.82; H, 4.68; N, 9.76; Found: C, 55.38; H, 4.24; N, 9.42.

1-(2-fluorophenyl)-3-isopropyl-5-(methylthio)-N-phenyl-1H-pyrazole-4-carboxamide (VK-2m): Brown solid; Yield, 58%; m.p. 116°C; R_{f} 0.49 (7:3 hexane-EtOAc); IR (KBr) cm\(^{-1}\): 3265, 3192, 3108, 2986, 2852, 1654, 1448, 774, 654; MS (m/z): 369 (M+); Elemental analysis: Calcd. for: C_{20}H_{20}FN_{3}OS; C, 65.02; H, 5.46; N, 11.37; Found: C, 65.46; H, 5.16; N, 10.92.

1-(3-chloro-4-(trifluoromethyl)phenyl)-3-isopropyl-5-(methylthio)-N-phenyl-1H-pyrazole-4-carboxamide (VK-2n): Light brown solid; Yield, 62%; m.p. 124°C; R_{f} 0.52 (7:3 hexane-EtOAc); IR (KBr) cm\(^{-1}\): 3328, 3264, 3208, 2954, 2912, 2882, 1671, 1448, 1268, 748, 658; MS (m/z): 453 (M+); Elemental analysis: Calcd. for: C_{21}H_{19}ClF_{3}N_{3}OS; C, 55.57; H, 4.22; N, 9.26; Found: C, 55.12; H, 3.86; N, 10.08.

3-isopropyl-1-(3-methoxyphenyl)-5-(methylthio)-N-phenyl-1H-pyrazole-4-carboxamide (VK-2o): Light brown solid; Yield, 66%; m.p. 108°C; R_{f} 0.50 (7:3 hexane-EtOAc); IR (KBr) cm\(^{-1}\): 3288, 3142, 2953, 2914, 1648, 1468, 763, 654; MS (m/z): 381 (M+); Elemental analysis: Calcd. for: C_{21}H_{21}N_{3}O_{2}S; C, 66.12; H, 6.08; N, 11.01; Found: C, 65.88; H, 6.34; N, 10.84.
$^1$H NMR spectrum of Int-3

Expanded $^1$H NMR Spectrum of Int-3
$^1$H NMR Spectrum of VK-2a

Expanded $^1$H NMR Spectrum of VK-2a
\(^{13}\)C NMR Spectrum of VK-2a

Mass spectrum of VK-2a
Chapter 2

Heterocyclic Analogues of Medicinal Interest

IR Spectrum of VK-2a

H NMR Spectrum of VK-2d
Expanded $^1$H NMR Spectrum of VK-2d

$^{13}$C NMR Spectrum of VK-2d
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N-arylpyrazoles

Mass spectrum of VK-2d

IR Spectrum of VK-2d
$^1$H NMR Spectrum of VK-2e

Expanded $^1$H NMR Spectrum of VK-2e
$^{13}$C NMR Spectrum of VK-2e

Mass spectrum VK-2e
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N-arylpyrazoles

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IR Spectrum of VK-2e

\[ \text{IR Spectrum of VK-2e} \]

\[ \text{H NMR Spectrum of VK-2f} \]
Expanded $^1$H NMR Spectrum of VK-2f
$^{13}$C NMR Spectrum of VK-2f

Mass spectrum of VK-2f

Heterocyclic Analogues of Medicinal Interest
IR Spectrum of VK-2f
2.9 References


