CHAPTER 3

Synthesis of New Dipyrazolo[3,4-b:3’,4’-f][1,8]Naphthyridines and fused pyrazolo[4’,3’:5,6]pyrido[1,2-a]pyrimidines from 6-Amino-pyrazolo[3,4-b]pyridine

In the present chapter we have reported the syntheses of dipyrazolo[3,4-b:3’,4’-f][1,8]-naphthyridines and pyrazolo[4’,3’:5,6]pyrido[1,2-a]pyrimidines. The synthesis was achieved by a multistep route in which novel synthone pyrazolo[3,4-b]pyridine-6-amine was achieved by Horner–Wadsworth–Emmons (HWE) reaction sequence. Further the new dipyrazolo[3,4-b:3’,4’-f][1,8]naphthyridines have been achieved successfully by Gould Jacobs reaction between pyrazolo[3,4-b]pyridine-6-amine and diethylethoxymethylenemalonate. The fused pyrazolo[4’,3’:5,6]pyrido[1,2-a]pyrimidine derivatives are synthesized by reaction of pyrazolo[3,4-b]pyridine-6-amine (4) and α-acetyl-γ-butyrolactone. Chapter is divided in to three sections.


Section-II. Synthesis of new dipyrazolo[3,4-b:3’,4’-f][1,8]naphthyridines derivatives from pyrazolo[3,4-b]pyridine-6-amine and diethylethoxymethylenemalonate.

3.1. Introduction

Pyrazolo-annulated heterocycles have demonstrated a wide spectrum of biological and pharmacological activities [1-7]. We have extensively studied major classes of pyrazolo-annulated heterocycles which include pyrazolo[3,4-b]pyridines, pyrazolo[3,4-b][1,8]naphthyridine, dipyrrozolo[3,4-b:3’,4’-f][1,8]naphthyridines and pyrazolo[4’,3’:5,6]pyrido-[1,2-a]pyrimidines. Herein we used pyrazolo[3,4-b]pyridine-6-amine as precursor for synthesis of pyrazolo-annulated heterocycles. Pyrazolo[3,4-b]pyridines are promising candidates in organic synthesis due to their significant medicinal activities [8-13]. Pyrazolonaphthyridines are also important in field of medicinal chemistry [14]. Pyrazolopyr-ridopyrimidines have attracted considerable interest because their derivatives display a wide range of pharmacological activities, e.g., anticonvulsant agents [15], anti-malarial agents [16], anti-inflammatory agents and central nervous system depressants [17]. They also act as antiproliferative agents [18] and have other physiological application. They are colorants, spectrochemical absorption agents [19], heat/moisture resistant agents, thermal transfer printing agents [20] and photographic couplers [21]. Pyrazolo fused pyrimidines display anti-trypanosomal or antischistosomal activities [22, 23] and some derivatives show potential activity against respiratory diseases [24]. These interesting biological properties have considerably stimulated the search for new and efficient procedures of wide generality for building this ring system [24, 25]. Compounds with these ring systems can also be used as scaffolds in the dyestuff industry [26]. Such fused pyrimidines are known to exhibit promising antiviral [27], antibacterial [28], anti-AIDS [29], and antinociceptive [30] activities. Fused pyrimidines are selective inhibitors for multidrug resistance (MDR) [31]. The relevance of fused pyrimidines as antiplatelet and antithro-
mbotic drugs [32] has been firmly established by clinical trial. Thus, further exploration of pyrimidines chemistry appears to be worthwhile.

**Literature updates: for the synthesis of pyrazolo[3,4-b:3',4'-f][1,8]naphthyridines, dipyrazolopyridines and pyrazolopyridopyrimidine derivatives**

1) *Alice Bernardino et al* [33] reported the synthesis of anti-HSV-1 3H-benzo[b]pyrazolo[3,4-h][1,6]naphthyridine derivatives 4 and 5. The pyrazolo[3,4-b]pyridine-5-carboxylates 1 on fusion with aniline led to product 2 in good yield. However, better results were obtained when reactions were carried out in DMF. Subsequently, compound 2 was hydrolyzed to the corresponding acid 3 in 88-90% yield and then cyclized to corresponding tetracyclic heteroaromatic systems 4 and 5 in good yield. The benzo[b]pyrazolo[3,4-h][1,6]naphthyridine derivatives 4 and 5 showed good fluorescence properties.

![Chemical Reaction](image)

2) *Neal J. Green et al.* [34] Reported the synthesis of dipyrazolo[3,4-b:3',4'-d]pyridin-3-ones from pyrazolo[3,4-b]pyridines. The ethyl 4-chloro-6-(3-trifluoromethyl)phenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate 6 and 4-fluorophenylhydrazine reflux in ethanol and acetic acid furnished dipyrazolo[3,4-b:3',4'-d]pyridin-3-ones 7. Study the bin-
ding to the Immune Regulatory Protein B7.1 and initial in vitro structure activity relationships of a series of these compounds.

3) M. V. Vovk et al. [35] reported the synthesis of dipyrazolo[3,4-b:4,3-e]pyridines from pyrazolo[3,4-b]pyridines. Compound 8 synthesized from 5-acetylamino-3-methyl-1-phenylpyrazole by the Vilsmeier-Haack formylation method [36] which was used as starting material for the synthesis of dipyrazolo-pyridines 12. Another route described was by the reaction of 8 with hydrazine hydrate and the cyclization in ethanol at reflux temperature yielded dipyrazolopyridines 14.

\[ \text{6} \xrightarrow{\text{EtOH, reflux, 2) AcOH, reflux}} \text{7} \]
\[ \text{R = H, Ph, Bn} \]

\[ \text{Me} \quad \text{Ph} \quad \text{O} \quad \text{H} \]
\[ \text{N3} \quad \text{NaN3} \quad \text{DMSO} \]
\[ \text{N} \quad \text{N} \quad \text{N} \quad \text{Me} \quad \text{Ph} \]
\[ \text{Ar} = \text{Ph, b Ar = 4-Cl-C6H4, c Ar = 4-MeC6H4, d Ar = 3-OMeC6H4, e Ar = 4-MeOC6H4, f Ar = 3,4-Me2C6H4} \]
4) M. A. Khan et al. [37] and recently M. N. Jachak et al. [38] has reported the synthesis of dipyrazolopyridine derivatives starting with pyrazolo[3,4-b]pyridines 15. The reaction of chloroester 15 with phenyl hydrazine an open chain derivative was formed which on treatment with acetic acid leads to the dipyrazolopyridine 16.

![Chemical Structure](image)

R = Me, p-Cl C₆H₄, p-Br C₆H₄
R₁ = H, R₂ = C₆H₅


![Chemical Structure](image)

<table>
<thead>
<tr>
<th>20</th>
<th>Ar</th>
<th>R</th>
<th>20</th>
<th>Ar</th>
<th>R</th>
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<tbody>
<tr>
<td>a</td>
<td>4-Cl C₆H₄</td>
<td>CH₂C₆H₅</td>
<td>h</td>
<td>4-Br C₆H₄</td>
<td>3-Cl C₆H₄</td>
</tr>
<tr>
<td>b</td>
<td>4-Cl C₆H₄</td>
<td>C₆H₅</td>
<td>i</td>
<td>4-Br C₆H₄</td>
<td>4-Cl C₆H₄</td>
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<tr>
<td>c</td>
<td>4-Cl C₆H₄</td>
<td>3-Cl C₆H₄</td>
<td>j</td>
<td>4-Br C₆H₄</td>
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<tr>
<td>d</td>
<td>4-Cl C₆H₄</td>
<td>4-Cl C₆H₄</td>
<td>k</td>
<td>4-Br C₆H₄</td>
<td>2-Me C₆H₄</td>
</tr>
<tr>
<td>e</td>
<td>4-Cl C₆H₄</td>
<td>4-Br C₆H₄</td>
<td>l</td>
<td>4-Br C₆H₄</td>
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<tr>
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<td>4-Cl C₆H₄</td>
<td>2-Me C₆H₄</td>
<td>m</td>
<td>4-Me C₆H₄</td>
<td>CH₂C₆H₅</td>
</tr>
<tr>
<td>g</td>
<td>4-Cl C₆H₄</td>
<td>4-Me C₆H₄</td>
<td>n</td>
<td>4-Me C₆H₄</td>
<td>C₆H₅</td>
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</table>

The synthesis of pyrazolo[3,4-b]pyridines 19 were achieved from reactive starting materials, 5-aminopyrazoles 17 and α-acetyl-γ-butyrolactone 18. The compound 19 on reaction with substituted anilines give pyrazolo[3,4-b]pyrrolo[2,3-d]pyridine 20 in good yield.
d. It was observed that the substituent at C₄-positions showed considerable increase in emission wavelength, as the π-electron donating effect of amino group increases.


![Chemical structure of compounds 21 and 22]


![Chemical structure of compounds 23, 24, and 25]

7) Jaime Portilla et. al. [41] reported a synthesis of fused pyrazolo[1,5-a]pyrimidines by reaction of 5-amino-1H-pyrazoloes and β dicarbonyl compounds containing five membered rings. The 5-amino-1H-pyrazoloes 26 on fusion with alkoxymethylene-β-dicarbonyl compounds 27 & 29 and cyclic β-triketones 31 & 33 furnished fused pyrazolo [1,5-a]pyrimidines 28, 30, 32, & 34 respectively.
Synthesis of cyclopentapyrazolo[1,5-α]pyrimidines 36, 38 & 39 on reaction of 26 with 35, 37 and 39 respectively.
8) R. B. Toche et. al. [42] reported synthesis of fused pyrimidines from amines and cyclic \( \beta \)-formylesters. The reaction of 2-aminobenzoimidazole 41 with sodium salt of lactone 42 furnished benzimidazolo[3,2-\( a \)]pyrimidin-4(1\( H \))-one 44, which on chlorinated with POCl\(_3\) furnished 45.

9) R. B. Toche et. al. [43] reported the synthesis of benzohetero[3, 2-\( a \)]pyrimidines using cyclic \( \beta \)-keto lactone as a building block and 2-aminopyrazole. 2-Aminoheterocycles 46 were condensed with \( \alpha \)-acetyl-\( \gamma \)-butyrolactone 47 either by refluxing in toluene / PTSA or by heating in ammonium acetate to obtain the target compounds. The compounds 48 or 50 were reacted with sodium ethoxide in ethanol gave 49 having 2-hydroxy ethyl side chain. Both compounds 48 or 49 on refluxing with POCl\(_3\) gave 52 having 2-chloroethyl side chain. The compound 52 having 2-chloroethyl side chain reacts with different nucleophiles to yield 53 and 54 on reaction with sodium azide and sodium ethoxide respectively.
10) M. N. Jachak et al. [44] reported the effect of donor-acceptor chromophores on photophysical properties of synthesized pyrazolo-pyrrlo-pyrimidines (PPP) 58. The 5-amino-1H-pyrazole-4-carbonitrile 55 on reaction with α-acetyl-γ-butyrolactone 56 furnished compound 57, which on reaction with substituted aniline afforded pyrazolo-pyrrlopyrimidines 58 (a-l) in good yield.
3.2. Present Work

In the present chapter we have reported the syntheses of dipyrazolo[3,4-\textit{b}:3',4'-\textit{f}][1,8]-naphthyridines and pyrazolo[4',3':5,6]pyrido[1,2-\textit{a}]pyrimidines. We have synthesized a new synthone 6-Amine-pyrazolo[3,4-\textit{b}]pyridine by \textit{Horner–Wadsworth–Emmons} (\textit{HWE}) reaction sequence. Further the new dipyrazolo[3,4-\textit{b}:3',4'-\textit{f}][1,8]naphthyridines have obtained by \textit{Gould Jacobs} reaction between pyrazolo[3,4-\textit{b}]pyridine-6-amine and diethylethoxymethylenemalonate. The fused pyrazolo[4',3':5,6]pyrido[1,2-\textit{a}]pyrimidine derivatives was synthesized by reaction of pyrazolo[3,4-\textit{b}]pyridine-6-amine and \alpha-acetyl-\gamma-butyrolactone.

Retrosynthesis of 6-Amine-pyrazolo[3,4-\textit{b}]pyridine, dipyrazolo[3,4-\textit{b}:3',4'-\textit{f}][1,8]naphthyridines and pyrazolo[4',3':5,6]pyrido[1,2-\textit{a}]pyrimidine is depicted in scheme 1 to 4.

**3.2.1. Retrosynthesis of 6-Amino-pyrazolo[3,4-\textit{b}]pyridine:**

The 6-Amino-pyrazolo[3,4-\textit{b}]pyridine 62 could be obtained by Wittig reaction of diethyl cyanomethylphosphonate with 59.

<table>
<thead>
<tr>
<th>\textit{R}</th>
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<tbody>
<tr>
<td>\textit{a}</td>
<td>4-\textit{OCH}_2\textit{C}_6\textit{H}_4</td>
</tr>
<tr>
<td>\textit{b}</td>
<td>4-\textit{CH}_3\textit{C}_6\textit{H}_4</td>
</tr>
<tr>
<td>\textit{c}</td>
<td>4-\textit{FC}_6\textit{H}_4</td>
</tr>
<tr>
<td>\textit{d}</td>
<td>3-\textit{BrC}_6\textit{H}_4</td>
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<tr>
<td>\textit{e}</td>
<td>4-\textit{BrC}_6\textit{H}_4</td>
</tr>
<tr>
<td>\textit{f}</td>
<td>\textit{C}_6\textit{H}_5</td>
</tr>
</tbody>
</table>
The Amino-pyrazolo[3,4-b]pyridine 62 could be obtained from 61 by thermal isomerization and cyclization of 61.

3.2.2. Retrosynthesis of Ethyl-5-chloro-3-(4-aryl)-1-phenyl-1H-pyrazolo[3,4-b][1,8]-naphthyridine-6-carboxylate: The compounds 65 could be synthesized by cyclocondensation of open chain derivative 64. Compound 64 could be obtained by Gould Jacobs reaction between pyrazolo[3,4-b]pyridine-6-amine 62 and diethylethoxymethylenemalonate 63.
3.2.2. Retrosynthesis of new dipyrazolo[3,4-b:3’,4’-f][1,8]naphthyridine derivatives from Ethyl-5-chloro-3-(4-aryl)-1-phenyl-1H-pyrazolo[3,4-b][1,8]naphthyridine-6-carboxylate: The dipyrazolonephthyridine derivatives 66 could be synthesized by annulation of pyrazol nucleus on chloro-ester functionality in compound 65 using hydrazines.

![Scheme 3 diagram](image)

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>Ar</th>
<th>R</th>
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<tbody>
<tr>
<td>66a</td>
<td>p-Cl C₆H₄</td>
<td>H</td>
</tr>
<tr>
<td>66b</td>
<td>p-Br C₆H₄</td>
<td>H</td>
</tr>
<tr>
<td>66c</td>
<td>p-Cl C₆H₄</td>
<td>C₆H₅</td>
</tr>
<tr>
<td>66d</td>
<td>p-Br C₆H₄</td>
<td>C₆H₅</td>
</tr>
</tbody>
</table>

3.2.3 Retrosynthesis of pyrazolo[4’,3’:5,6]pyrido[1,2-a]pyrimidine derivatives:

Compound 71 could be synthesized by S_N² displacement reactions of chlorine atom in compound 69 with p-chloroaniline. Compound 70 could be obtained by azidation of compound 69 with NaN₃. The fused pyrazolo[4’,3’:5,6]pyrido[1,2-a]pyrimidine derivative 69 could be synthesized by cyclocondensation of open chain compound 68.

The open chain compound 68 could be obtained by reaction of α-acetyl-γ-butyrolactone 67 and 6-amine-pyrazolo[3,4-b]pyridine 62.
Scheme 4

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>Ar</th>
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<tbody>
<tr>
<td>71a</td>
<td>p-Cl C₆H₄</td>
</tr>
<tr>
<td>71b</td>
<td>p-Br C₆H₄</td>
</tr>
</tbody>
</table>
3.3. Results and Discussion

3.3.1. Synthesis of (2E)-3-(5-amino-3-(4-aryl)-1-phenyl-1H-pyrazol-4-yl)-acrylonitriles and 3-(4-aryl)-1-phenyl-1H-pyrazolo[3,4-b]pyridin-6-amine

Olefination of aldehydes and ketones is very important in organic synthesis. Wittig reactions represent a highly effective and general method of alkene formation from carbonyl derivatives [45, 46] but their low stereoselectivity for allylic and benzylic ylides, the difficult removal of byproduct phosphine oxide, and poor reactivity with hindered ketones have all encouraged the use of alternative protocols. So we exclusively used HWE reaction for synthesis of novel precursor 62 using aldehyde 59. The phosphonates used here are significantly more reactive than classical Wittig stabilized ylides and as such react with ketones and aldehydes. Another advantage of the HWE reaction over the classic Wittig reaction is that the phosphorus byproducts are water-soluble and hence readily separated from the desired product.

The synthesis and wide use of 5-amino-3-(4-aryl)-1-phenyl-1H-pyrazole-4-carbaldehyde 59 in building organic moieties has been reported by us previously [47-49]. In this chapter we report the modified Wittig reaction i.e. Horner–Wadsworth–Emmons (HWE) reaction of diethyl cyanomethylphosphonate 60 with 5-amino-3-(4-subst.-phenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde 59.

\[
\text{Ar} \quad \text{N} \quad \text{NH}_2 \quad \text{Ph} \quad \text{O} \quad \text{H} \quad \text{59a-b} + \quad \text{NC} \quad \text{P} \quad \text{OEt} \quad \text{H} \quad \text{CN} \quad \text{59a-b} \quad \text{60} \quad \text{t} \quad \text{OEt} \quad \text{NaOMe} \quad \text{toluene, R.T, 3 hrs.} \quad \text{61a-b} \quad \text{Not isolated} \quad \text{62a-b}
\]
The reaction was carried out at room temperature in presence of sodium methoxide in dry toluene and furnished a mixture of two compounds after work up. These were separated by column chromatography using toluene as an eluant. Two compounds 61 and 62 were characterized by spectroscopic and analytical methods. The IR spectra of compound 61a showed –CN stretching at 2225 cm\(^{-1}\), -NH\(_2\) stretching at 3360 cm\(^{-1}\) and 3169 cm\(^{-1}\) and olefinic (C=C) at 1630 cm\(^{-1}\). The \(^1\)H-NMR spectrum of 61a in CDCl\(_3\) showed a broad singlet at 4.80 ppm for –NH\(_2\) protons, two doublets for olefinic protons appear at 6.48 and 8.10 ppm with trans coupling (\(J = 16\) Hz). All aromatic protons are appered in their respective region (Spectrum No. 1, Page No. 139).

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>Ar</th>
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<tbody>
<tr>
<td>62a</td>
<td>p-Cl C(_6)H(_4)</td>
</tr>
<tr>
<td>62b</td>
<td>p-Br C(_6)H(_4)</td>
</tr>
</tbody>
</table>

Spectrum No. 1: \(^1\)H NMR Spectrum of of (2E)-3-(5-amino-3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-acrylonitriles, 61a.
Analogously compound 62a was characterized by IR, $^1$H NMR, $^{13}$C NMR and elemental analysis (Experiment No. 1, page No. 159). Compounds 62a showed absence of –CN stretching frequency in IR spectra. It showed only -NH$_2$ stretching at 3380 cm$^{-1}$ and 3154 cm$^{-1}$ and aromatic (C=C) at 1622 cm$^{-1}$. The $^1$H-NMR spectrum of 62a in DMSO-$d_6$ showed a sharp singlet at 6.77 ppm for –NH$_2$ protons, two doublets for two protons of pyridine ring appear at δ 6.59 and 8.16 ppm with $J = 9.00$ Hz (Spectrum No. 2, Page, No. 141). The $^{13}$C-NMR spectrum (DMSO-$d_6$) of 62a showed peak at δ 160.0 for C$_6$–NH$_2$ carbon. The C$_3$ carbon of pyrazole ring observed at δ 143.7 ppm. The C$_4$ and C$_5$ carbons was observed at δ 133.9 and 106.1 respectively. The C$_8$ and C$_9$ carbons was observed at δ 107.9 and 152.2 respectively. All six carbons of phenyl ring and six carbon of p-substituted benzene ring, attached to pyrazole ring appeared between δ 119.91-140.58 (Spectrum No. 3, Page, No. 141). The molecular ion peak at 320 [M$^+$], 322 [M+2] is exactly matches to the molecular weight of the solid. The elemental analysis was in agreement with molecular formula C$_{18}$H$_{13}$N$_4$Cl of 62a. On the basis of this spectroscopic data we confirm that 61a is E isomer while 62a is a cyclized pyrazolo-[3,4-b]pyridin-6-amine. This cyclization proceeds through a Z isomer (not isolable), which is immediately converted into cyclized pyrazolo[3,4-b]pyridin-6-amine 62. Analogously compound 61b and 62b was synthesized and characterized by IR, $^1$H NMR, $^{13}$C NMR and elemental analysis (Experiment No. 1, page No. 159). So this reaction gave olification of –CHO group, yielded E and Z isomers. However Z isomer underworth cyclization in situ to yield compound 62.
Spectrum No. 2: $^1$H NMR Spectrum of 3-(4-chlorophenyl)-1-phenyl-$1H$-pyrazolo-[3,4-$b$]pyridine-6-amine, 62a.

Spectrum No. 3: $^{13}$C NMR Spectrum of 3-(4-chlorophenyl)-1-phenyl-$1H$-pyrazolo-[3,4-$b$]pyridine-6-amine, 62a.
3.3.2. Synthesis of 3-(4-aryl)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-6-amime from compounds 61.

After assignment of $E$ isomer, it gets transformed in to novel synthone 6-amino-pyrazolo[3,4-b]pyridine by thermal isomerization. Compound 3 was cyclized by heating it with catalytic amount of anhydrous ZnCl$_2$ without any solvent. This cyclization may be proceeding through thermal isomerization of $E$ isomer [50, 51].

![Scheme 6](image)

<table>
<thead>
<tr>
<th>Comp. No.</th>
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<tbody>
<tr>
<td>62a,</td>
<td>$p$-Cl C$_6$H$_4$</td>
</tr>
<tr>
<td>62b</td>
<td>$p$-Br C$_6$H$_4$</td>
</tr>
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</table>

A mixture of ($E$)-3-(5-amino-3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-acrylonitrile 61a and anhydrous ZnCl$_2$ was heated without solvent at 250°C for 2 hrs. (TLC check, toluene). After cooled down to room temperature, 50 mL water and 20 mL ethyl acetate was added. The solution was extracted three times by ethyl acetate and ethyl acetate layer were combined and dried over anhydrous sodium sulphate. Solvent was removed under reduced pressure to give a yellow solid. The crude solid was stirred in methanol, filtered, dried under high vacuum, and recrystallized from ethanol:DMF (4:1) to give C in good yield. This compound characterized by IR, $^1$H and $^{13}$C NMR, MASS and elementel analysis (Spectrum No. 2 & 3, Page No. 141). The spectral data of this compounds exactly match with 62a. Hence compounds C is pyrazolo[3,4-b]pyridine-6-
amine i.e. 62a. Analogously compound 62b was synthesized and characterized by IR, ¹H NMR, ¹³C NMR and elemental analysis (Experiment No. 2, page No. 161).

### 3.3.3. Synthesis of Diethyl-2-[3-(4-aryl)-1-phenyl-1H-pyrazolo[3,4-b]pyridin-6-yl-amino)methylene]-malonate 64a-b

Further, we studied the Gould Jacobs reaction between 62 and diethyl ethoxymethylene-malonate 63.

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>Comp. No.</th>
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<tbody>
<tr>
<td>64a</td>
<td>p-Cl C₆H₄</td>
</tr>
<tr>
<td>64b</td>
<td>p-Br C₆H₄</td>
</tr>
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</table>

Thus, the mixture of pyrazolo[3,4-b]pyridin-6-amine 62a and diethyl ethoxymethylene-malonate 63 refluxed in ethanol for 10 hrs. furnished a colorless solid (Experiment No. 3, page No. 162). The colorless solid was characterized by spectral and analytical data. The IR spectrum of this solid showed absorption bands at 1727 cm⁻¹ for carbonyl of the ester group. The ¹H-NMR spectrum (CDCl₃) of this solid showed triplet at δ 1.35 ppm (J = 6.8 Hz) for six protons of methyl group and quartet at δ 4.24 ppm (J = 6.8 Hz) for four protons of methylene group of ester functionality. Two doublets of pyridine ring protons are appeared at δ 6.75 and 8.18 (J = 8.4 Hz) ppm respectively. The two doublets of –NH and adjacent protone of methylenemalonate appered at δ 9.20 and 11.19 ppm respectively. The five aromatic protons appeared in between δ 7.36-7.60 ppm correspo-
nded to N-phenyl ring. Two doublets of p-substituted ring are appered at δ 7.95 and 8.18 (J = 8.6 Hz) ppm (Spectrum No. 4, Page No. 145). The $^{13}$C-NMR spectrum showed peak at δ 14.8 and 58.6 ppm for two carbons of methyl group and two carbons of methylene group respectively. Olefinic carbon attached to two ester functionality appears at δ 94.0 ppm, while another olefinic carbon showed peak at 154.9 ppm. All other signals appears in there respective regions (Spectrum No. 5, Page No. 145). The molecular ion peak at 491 [M$^+$], 493 [M+2] is exactly matches to the molecular weight of the solid. The elemental analysis was in agreement with molecular formula C$_{26}$H$_{23}$N$_4$O$_4$Cl of 64a. On the basis of above spectral and analytical data structure 64a was assigned to this compound i.e. Diethyl-2-[3-(4-chlorophenyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridin-6-amino)-methylene]malonate. Analogously compound 64b was synthesized and characterized by IR, $^1$H NMR, $^{13}$C NMR and elemental analysis (Experiment No. 3, page No. 163).
Spectrum No. 4: $^1$H NMR Spectrum of Diethyl 2-[3-(4-aryl)-1-phenyl-1H-pyrazolo-[3,4-b]pyridin-6-yl- amino)methylene]-malonate, 64a

Spectrum No. 5: $^{13}$C NMR Spectrum of Diethyl 2-[3-(4-aryl)-1-phenyl-1H-pyrazolo-[3,4-b]pyridin-6-yl- amino)methylene]-malonate, 64a
3.3.4. Synthesis of Ethyl 5-chloro-3-(4-aryl)-1-phenyl-1H-pyrazolo[3,4-b][1,8]naphthyridine-6-carboxylate (65a-b).

The intermediates 64 were cyclized by heating under reflux in phosphorous oxychloride to give ethyl 5-chloro-3-(4-aryl)-1-phenyl-1H-pyrazolo[3,4-b][1,8]naphthyridine-6-carboxylates 65 in 74-76% yield (Experiment No. 4, page No. 164). The structure of 65 was established by spectral and analytical data. The \(^1\)H-NMR of compound 65a in DMSO-\(d_6\) showed resonance as a triplet at 1.24 ppm for methyl protons, quartet at 4.18 ppm for methylene protons, two singlets were observed at 8.17 and 8.59 ppm for pyridine ring proton and naphthyridin ring proton respectively (Spectrum No. 6, Page No. 147). The \(^{13}\)C-NMR spectrum (DMSO-\(d_6\) of 65a showed peak at \(\delta\) 18.1 ppm for methyl carbons and \(\delta\) 55.9 ppm for the methylene carbon of the ester group. The C\(_5\)-Cl carbon observed at \(\delta\) 138.7 ppm. The C\(_6\) carbon attached to ester group was observed at \(\delta\) 125.5 ppm. The ester carbonyl carbon appeared at \(\delta\) 162.1 ppm. The C\(_3\) carbon of pyrazole ring observed at \(\delta\) 148.6 ppm. The C\(_7\) carbon of the naphthyridin ring appeared at \(\delta\) 151.42 ppm. All six carbons of phenyl ring and six carbon of \(p\)-substituted benzene ring, attached to pyrazole ring appeared between \(\delta\) 119.9-140.6 ppm. The molecular ion
peak at 462 [M⁺], 464 [M+2], 466 [M+4] is exactly matches to the molecular weight of the solid. The elemental analysis was in agreement with molecular formula C₂₄H₁₆N₄O₂-Cl₂ of 65a. i.e. Ethyl 5-chloro-3-(4-chlorophenyl)-1-phenyl-1H-pyrazolo[3,4-b][1,8]naphthyridine-6-carboxylate. Analogously compound 65b was synthesized and characterized by IR, ¹H NMR, ¹³C NMR and elemental analysis (Experiment No. 4, page No. 164).
3.3.5. Synthesis of 9-(4-aryl)-1,7-diphenyl-1,2-dihydodipyrazolo[3,4-b:3’,4’-f]-[1,8]naphthyridin-3(7H)-one (66a-d)

Thus, to annulate pyrazole nucleus on chloro-ester functionality we performed reaction of compound 65a and hydrazine hydrate or phenyl hydrazine in xylene containing a catalytic amount of triethylamine at reflux temperature for 3-4 hrs. yielded a colorless solid in 65% yield. The $^1$H-NMR of compound 66a in DMSO-$d_6$ showed two singlets at $\delta$ 7.72 and 8.38 ppm for two –NH protons respectively. The singlet of pyridine ring proton appears at $\delta$ 8.61 ppm and singlet of naphthyridine ring proton appears at $\delta$ 8.84 ppm respectively. The two doublets were observed at $\delta$ 8.22 and 8.70 ppm ($J = 8.4$ Hz) for four protons of $p$-substituted benzene ring. Five protons of phenyl ring attach to pyrazole observed between $\delta$ 7.36-7.64 ppm (Spectrum No. 7, Page No. 149). The $^{13}$C-NMR spectrum (DMSO-$d_6$) of this solid showed peak for the C$_5$ carbon at $\delta$ 159.1 ppm. The C$_6$ carbon attached to ester group was observed at $\delta$ 117.9 ppm. The carbonyl carbon appeared at $\delta$ 169.0 ppm. The C$_3$ carbon of pyrazole ring observed at $\delta$ 146.4 ppm. The C$_7$ carbon of the naphthyridin ring appeared at $\delta$ 153.9 ppm. All six carbons

<table>
<thead>
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<tr>
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<td>$p$-Cl C$_6$H$_4$</td>
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</tr>
<tr>
<td>66b</td>
<td>$p$-Br C$_6$H$_4$</td>
<td>H</td>
</tr>
<tr>
<td>66c</td>
<td>$p$-Cl C$_6$H$_4$</td>
<td>C$_6$H$_5$</td>
</tr>
<tr>
<td>66d</td>
<td>$p$-Br C$_6$H$_4$</td>
<td>C$_6$H$_5$</td>
</tr>
</tbody>
</table>

Scheme 9
of phenyl ring & six carbon of \( p \)-substituted benzene ring, attached to pyrazole ring appeared between 120.0-132.8 ppm (Spectrum No. 8, Page, No. 150). The molecular ion peak at 412 [M\(^+\)], 414 [M+2] exactly matches to the molecular weight of the solid. The elemental analysis was in agreement with molecular formula \( \text{C}_{22}\text{H}_{13}\text{N}_{6}\text{OCl} \). On the basis of above spectral and analytical data structure \( \textit{66a} \) was assigned to this compound i.e. 9-(4-chlorophenyl)-1,7-diphenyl-1,2-dihydropyrazolo[3,4-\( b \):3',4'-\( f \)][1,8]naphthyridin-3(\( 7H \))one. Analogously compound \( \textit{65b} \) was reacted with hydrazine hydrate or phenyl hydrazine to synthesized \( \textit{66b} \). Compound \( \textit{66b} \) was characterized by IR, \(^1\text{H NMR} \), \(^{13}\text{C NMR} \) and elemental analysis (Experiment No. 5, page No. 166).

Spectrum No. 7: \(^1\text{H NMR Spectrum of 9-(4-chlorophenyl)-1,7-diphenyl-1,2-dihydropyrazolo[3,4-\( b \):3',4'-\( f \)][1,8]naphthyridin-3(\( 7H \))\-one, 66a}
3.3.6. **Synthesis of** (3Z)-3-(1-(3-(4-aryl)-1-phenyl-1H-pyrazolo[3,4-b]-pyridine-6-ylamino)-ethylidene)-dihydrofuran-2(3H)-ones (68a-b).

![Scheme 10](image)

<table>
<thead>
<tr>
<th>Comp. No.</th>
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<tbody>
<tr>
<td>68a</td>
<td>p-Cl C₆H₄</td>
</tr>
<tr>
<td>68b</td>
<td>p-Br C₆H₄</td>
</tr>
</tbody>
</table>

The reaction of pyrazolo[3,4-b]pyridin-6-amin 62a with α-acetyl-γ-butyrolactone 67 in toluene, in the presence of p-toluenesulfonic acid at 120 °C furnished intermediate (3Z)-3-(1-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-6-ylamino)ethylidene)-dihydrofuran-2(3H)-ones 68a in 71% yield. The strong acid p-toluenesulfonic acid selectively protonates keto carbonyl in preference to lactone carbonyl and the subsequent
attack of amino moiety gave dihydrofuranone 68a. The intermediate 68a was characterized by spectral and analytical data. The IR of 68a showed lactone carbonyl (C=O) stretching at 1689 cm\(^{-1}\), -NH at 3340 cm\(^{-1}\). The lowering of lactone carbonyl was due to intramolecular H-bonding between -CO and -NH, which also supports the Z-configuration of furanone intermediate 68a. The \(^1\)H-NMR spectrum of 68a in CDCl\(_3\) showed singlet at 2.64 ppm for methyl protons, two triplets for CH\(_2\)CH\(_2\)O of lacton ring was observed at 2.98 and 4.39 ppm (\(J = 7.5\) Hz). The down field -NH resonance showed sharp singlet at \(\delta 10.96\) (D\(_2\)O exchangeable). All other aromatic protons were observed in the respective region (Spectrum No. 9, Page No. 151). The molecular ion peak at 430[M\(^+\)], 432 [M+2] is exactly matches to the molecular weight of the solid. The elemental analysis was in agreement with molecular formula C\(_{24}\)H\(_{19}\)N\(_4\)O\(_2\)Cl of 68a. Analogously compound 68b was synthesized and characterized by IR, \(^1\)H NMR, \(^{13}\)C NMR and elemental analysis (Experiment No. 6, page No. 168).

![Spectrum No. 10: \(^1\)H NMR Spectrum of (3Z)-3-(1-(3-(4-aryl)-1-phenyl-1H-pyrazolo-[3,4-b]-pyridine-6-yl-amino)-ethyldene)-dihydrofuran-2(3H)-ones, 68a.](image)
3.3.7. Synthesis of 8-(2-chloroethyl)-3-(4-aryl)-7-methyl-1-phenyl-1H-pyrazolo[3,4-b]pyrido[1,5-a]pyrimidine (69a-b).

Intermediate dihydrofuranones 68a was heated under reflux in POCl₃ and furnished compound pale yellow solid in 72% yield. The pale yellow solid was characterized by spectral and analytical data. The ¹H-NMR spectrum of 69a in DMSO-­-_d₆ showed singlet at δ 2.41 ppm for methyl protons, two triplets at δ 2.79 and 3.54 ppm (J = 7.2 Hz) were assignable to chloroethyl side chain -CH₂CH₂Cl. It shows two doublets at δ 7.18 and 8.26 ppm with coupling constant J= 8.4 Hz for two protons of pyridine ring. Two doublets for p-substituted ring protones observed at δ 7.65 and 7.98 ppm respectively. All other aromatic protones appears in there respective region (Spectrum No. 10, Page, No. 153). The ¹³C-NMR spectrum (DMSO-d₆) of this solid showed peak at δ 20.9 ppm for –CH₃ carbon. The carbons of chloroethyl side chain appears at δ 24.8 and 41.9 ppm respectively. The C₆ carbon appears at δ 160.5 ppm. The C₇ carbon attached to methyl group was observed at δ 149.8 ppm. The C₉ carbonyl carbon appeared at δ 159.0 ppm. The C₃ carbon of pyrazole ring observed at δ 146.2 ppm. The C₇ carbon of the naphthyridin ring appeared at δ 153.9 ppm. All other carbons of phenyl ring and six carbon of p-
substituted benzene ring, attached to pyrazole ring appeared between there respective region (Spectrum No. 11, Page, No. 154). The molecular ion peak at 448 [M⁺], 450 [M+2], 452 [M+4] is exactly matches to the molecular weight of the solid. The elemental analysis was in agreement with molecular formula C₂₅H₁₈N₄OCl₂ of 69a. On the basis of above spectral and analytical data structure 69a was assigned to this pale yellow solid i.e. (2-chloroethyl)-3-(4-aryl)-7-methyl-1-phenyl-1H-pyrazolo[4',3':5,6]-pyrido[1,2-a] pyrimidin-9-ones. Its precursor (3Z)-3-(1-(3-(4-aryl)-1-phenyl-1H-pyrazolo[3,4-b]pyridin-6-amino)ethylidene)dihydrofuran-2(3H)-ones 69a was evidencing that the cyclization proceeds with the butyrolactone ring opening as the last step after the initial condensation between the exocyclic amino group in 62 and the carbonyl group in α-acetyl-γ-butyrolactone 67. Analogously compound 69b was synthesized and characterized by IR, ¹H NMR, ¹³C NMR and elemental analysis (Experiment No. 7, page No. 169).
3.3.8. Synthesis of 8-(2-Azidoethyl)-3-(4-aryl)-7-methyl-1-phenyl-1H-pyrazolo[4',3':5,6]pyrido[1,2-a]pyrimidin-9-ones, 69a

Thus, the (2-chloroethyl)-3-(4-chlorophenyl)-7-methyl-1-phenyl-1H-pyrazolo[4',3':5,6]-pyrido[1,2-a]pyrimidin-9-ones, 69a haveing chloroethyl side chain which haveing a replacebal chlorine atom. The $S_N^2$ displacement of chlorine in 69a with sodium azide in DMF at 30°C furnished azido compound8-(2-Azidoethyl)-3-(4-chlorophenyl)-7-methyl-
1-phenyl-1H-pyrazolo[4',3':5,6]pyrido[1,2-a]pyrimidin-9(1H)-one (70a) in 64 % yield. This compound 70a was characterized by spectroscopic and analytical methods and assigned i.e. 8-(2-Azidoethyl)-3-(4-chlorophenyl)-7-methyl-1-phenyl-1H-pyrazolo[4',3':5,6]pyrido[1,2-a]pyrimidin-9(1H)-one. The IR spectra of 70a showed stretching frequency at 2120 cm\(^{-1}\) for –N\(_3\). The \(^1\)H-NMR spectrum of 70a in DMSO-\(d_6\) showed singlet at \(\delta\) 2.41 ppm for methyl protons, two triplets at \(\delta\) 2.79 and 3.54 ppm (\(J = 7.2\) Hz) were assignable to chloroethyl side chain –CH\(_2\)CH\(_2\)Cl. It shows two doublets at \(\delta\) 7.18 and 8.26 ppm with coupling constant \(J = 8.4\) Hz for two protons of pyridine ring. Two doublets for \(p\)-substituted ring protones observed at \(\delta\) 7.65 and 7.98 ppm respectively. All other aromatic protones appears in there respective region. (Spectrum No. 12, Page, No. 155). The molecular ion peak at 455 [M\(^+\)], 557 [M+2] is exactly matches to the molecular weight of the solid. The elemental analysis was in agreement with molecular formula \(C_{24}H_{18}N_7OCl\) of 70a. Analogously compound 70b was synthesized and characterized by IR, \(^1\)H NMR, \(^{13}\)C NMR and elemental analysis (Experiment No. 8, page No. 171).
3.3.9. Synthesis of 8-[2-(4-Chlorophenylamino)-ethyl]-3-(4-aryl)-7-methyl-1-phenyl
-1H-pyrazolo[4',3':5,6]pyrido[1,2-a]pyrimidin-9(1H)-one (71a-b).

Thus, the (2-chloroethyl)-3-(4-aryl)-7-methyl-1-phenyl-1H-pyrazolo[4',3':5,6]pyrido-
[1,2-a]pyrimidin-9-ones, 69a was neat heated with excess p-chloroaniline at 110°C gave
8-[2-(4-Chlorophenylamino)-ethyl]-3-(4-chlorophenyl)-7-methyl-1-phenyl-1H-pyrazolo
-[4',3':5,6]pyrido[1,2-a]pyrimidin-9(1H)-one 71a in 60 % yield. The structure of 71a
was established by spectral and analytical data. The $^1$H-NMR of compound 71a in
DMSO-$d_6$ showed singlet at $\delta$ 2.41 ppm for methyl protons, two triplets at $\delta$ 2.82 and
3.86 ppm ($J = 7.2$ Hz) for side chain protons of -CH$_2$CH$_2$-. It shows two doublets at $\delta$
6.81 and 8.40 ppm for two protons of pyridine ring with coupling constant $J = 8.2$ Hz.
The doublets for p-aniline ring was appear at $\delta$ 7.41 and 7.78 ppm while, two doublets
at $\delta$ 8.09 and 8.19 ppm corresponds to proyones of p-chloro-substituted benzene ring
on pyrazole. The broad singlet for –NH proton appear at $\delta$ 11.50 ppm. The resonance of
phenyl ring protons was observed in their respective region (Spectrum No. 13, Page,
No. 157). The molecular ion peak at 539 [M$^+$], 541 [M+2], 543 [M+4] exactly matches
to the molecular weight of the solid (Spectrum No. 14, Page No. 157). The elemental

<table>
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</tr>
<tr>
<td>71b</td>
<td>$p$-Br C$_6$H$_4$</td>
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</tbody>
</table>

Scheme 13
analysis was in agreement with molecular formula \( \text{C}_{30}\text{H}_{23}\text{N}_5\text{OCl}_2 \) of 71a. Analogously compound 71b was synthesized and characterized by IR, \(^1\text{H} \text{ NMR}, \ ^{13}\text{C} \text{ NMR} \) and elemental analysis (Experiment No. 9, page No. 173).
Conclusion

The methodology reported in this chapter is useful for synthesis of novel dipyrazolo-[3,4-b:3',4'-f][1,8]naphthyridine and pyrazolo[4',3':5,6]pyrido[1,2-a]pyrimidine derivatives from novel synthone pyrazolo[3,4-b]pyridin-6-amines 62, which was synthesized by Horner–Wadsworth–Emmons (HWE) reaction. The use of α-acetyl-γ-butyrolactone in the reaction with pyrazolo[3,4-b]pyridin-6-amines served to establish the proposed reaction pathway, due to the isolation of an intermediate 68, which indicates that the reaction starts with a condensation between the exocyclic amino group and the carbonyl moiety with higher enolic contribution. All synthesized pyrazolo-annulated heterocycles are new addition in the library of heterocyclic compounds and are may be potential biologically active heterocycles.
3.4. Experimental Section

Experiment No. 1

Synthesis \((2E)-3-(5\text{-amino}-3-(4\text{-aryl})-1\text{-phenyl}-1H\text{-pyrazol}-4\text{-yl})\text{-acrylonitriles} \) (61) and \(3-(4\text{-aryl})-1\text{-phenyl}-1H\text{-pyrazolo}[3,4-b]pyridin-6\text{-amine} \) (62).

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>Ar</th>
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<tbody>
<tr>
<td>61a, 62a</td>
<td>(p\text{-Cl} \text{C}_6\text{H}_4)</td>
</tr>
<tr>
<td>61a, 62b</td>
<td>(p\text{-Br} \text{C}_6\text{H}_4)</td>
</tr>
</tbody>
</table>

**General Procedure:** To a stirred solution of diethyl cyanomethylphosphonate 60 (0.01 mol, 1.61 ml) in anhydrous toluene (25 ml) was added excess of sodium methanolate, obtained from sodium (0.23 g) dissolved in methanol (10 ml) and stirring was continued for 15 min. The corresponding 5-amino-3-(4-aryl)-1-phenyl-1H-pyrazole-4-carbaldehyde 59a (2.977 g, 0.01 mol) or 59b (3.421 g, 0.01 mol) was added and the reaction mixture was stirred at room temperature for 3 hrs. The progress of the reaction was monitored by TLC till the aldehyde was consumed. After completion of reaction, the solvent was evaporated in vacuo and residue was stirred in water (50 ml) for 12 hrs. (the phosphorus byproducts are water-soluble and hence the desired product was readily separated). The obtained solid was filtered, washed with water, and dried, to afford a mixture of compound 61 and 62. The mixture was separated by column chromatography (silica gel) using toluene as the eluant to afford 61 as a white solid and 62 as a yellow
solid, with respect to total (75%) yield. Both the compounds were crystalized from ethanol solvent.

**(2E)-3-(5-Amino-3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-but-2-enenitrile (61a)**

Yellow solid; (1.51 g, 48 %); mp: 72-73 °C; IR (KBr):3360, 3169, 2225, 1630 cm⁻¹, ¹H NMR (300 MHz, CDCl₃): δ = 5.02 (s, b, 2H, -NH₂), 6.48 (d, J = 8.4 Hz, 1H), 7.28-7.54 (m, 5H, Ar-H), 7.89 (d, J = 8.6 Hz, 2H, Ar-H), 8.10 (d, J = 8.4 Hz, 1H), 8.22 (d, J = 8.6 Hz, 2H, Ar-H) ppm; ¹³C NMR (75 MHz, CDCl₃): δ = 106.1, 107.2, 117.0, 120.3 (2 C), 125.1, 128.2 (2 C), 128.8 (2 C), 131.1(2 C), 131.6, 132.8, 139.5, 142.2, 151.6, 159.6 ppm. Anal. Calcd. for C₁₈H₁₃ClN₄ (320.78): C, 67.40; H, 4.08; N, 17.47. Found: C, 67.60; H, 4.19; N, 17.73.

**(2E)-3-(5-Amino-3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)-but-2-enenitrile (61b)**

Yellow solid; (1.72 g, 47 %); mp: 73-74 °C; IR (KBr):3363, 3164, 2226, 1629 cm⁻¹, ¹H NMR (300 MHz, CDCl₃): δ = 5.31 (s, 2H, -NH₂), 6.49 (d, J = 8.4 Hz, 1H), 7.29-7.55 (m, 5H, Ar-H), 7.89 (d, J = 8.6 Hz, 2H, Ar-H), 8.11 (d, J = 8.4 Hz, 1H), 8.23 (d, J = 8.6 Hz, 2H, Ar-H) ppm. Anal. Calcd. for C₁₈H₁₃BrN₄(365.24): C, 59.19; H, 3.59; N, 15.34. Found: C, 59.26; H, 3.69; N, 15.48.

**3-(4-Chlorophenyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridin-6-amine (62a)**: Yellow solid; (0.890 g, 28 %); mp: 156-157 °C; IR (KBr):3380, 3154, 2922, 1622, 1598 cm⁻¹, ¹H NMR (300 MHz, DMSO-δ₆): δ= 6.59 (d, J = 9.0 Hz, 1H, Ar-H), 6.77 (s, 2H, -NH₂), 7.27-7.54 (m, 5H, Ar-H), 8.03 (d, J = 8.4 Hz, 2H, Ar-H), 8.16 (d, J = 9.0 Hz, 1H, Ar-H), 8.34 (d, J = 8.4 Hz, 2H, Ar-H) ppm; ¹³C NMR (75 MHz, DMSO-δ₆): δ = 106.2, 107.2, 120.3, 122.8, 125.1, 126.6, 128.2, 128.4, 128.7, 128.8, 129.0, 131.1, 131.6, 132.9, 139.5, 142.2, 151.6, 159.6 ppm; EIMS: m/z (%) 320 (M+, 100), 322(M+2, 33). Anal.
Calcd. for C\textsubscript{18}H\textsubscript{13}ClN\textsubscript{4}(320.78): C, 67.40; H, 4.08; N, 17.47. Found: C, 67.49; H, 4.21; N, 17.53.

3-(4-Bromophenyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridin-6-amine (62b): Yellow solid; (1.01 g, 27 %); mp: 158-159 °C; IR (KBr):3379, 3152, 2923, 1624, 1597 cm\(^{-1}\), \(^1\)H NMR (300 MHz, DMSO-\textit{d}_6):\(\delta = 6.58\) (d, \(J = 9.0\) Hz, 1H, Ar-H), 6.78 (s, 2H, -NH\textsubscript{2}), 7.27-7.55 (m, 5H, Ar-H), 8.04 (d, \(J = 8.4\) Hz, 2H, Ar-H), 8.16 (d, \(J = 9.0\) Hz, 1H, Ar-H), 8.34 (d, \(J = 8.4\) Hz, 2H, Ar-H) ppm; EIMS: \(m/z\) (%): 364 (M+, 100), 366 (M+2, 98). Anal. Calcd. for C\textsubscript{18}H\textsubscript{13}BrN\textsubscript{4} (365.24): C, 59.19; H, 3.59; N, 15.34. Found: C, 59.32; H, 3.67; N, 15.56.

Experiment No. 2

Synthesis of 3-(4-aryl)-1-phenyl-1H-pyrazolo[3,4-b]pyridin-6-amine 62 from 61 upon heating it in ZnCl\(_2\) (Lewis acid).

![Diagram](attachment://diagram.png)

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</tr>
<tr>
<td>62b</td>
<td>(p)-Br C\textsubscript{6}H\textsubscript{4}</td>
</tr>
</tbody>
</table>

**General Procedure:** A mixture of (E)-3-(5-amino-3-(4-aryl)-1-phenyl-1H-pyrazol-4-yl)-acrylonitrile 61a (3.207 g, 0.01 mol) or 61b (3.652 g, 0.01 mol) and anhydrous ZnCl\(_2\) (0.02 mol, 2.72 g) was heated without solvent at 250°C for 2 hrs. (TLC check, toluene). After cooled down to room temperature, 50 ml of water and 25 ml of ethyl
acetate were added. The solution was extracted three times by ethyl acetate (25 ml X 3) and organic layers were combined and dried over anhydrous sodium sulphate. Solvent was removed under reduced pressure to give a yellow solid. The crude solid was stirred in methanol, filtered, dried under high vacuum, and recrystallized from ethanol:DMF (4:1) gave 62.

3-(4-Chlorophenyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridin-6-amine (62a): Yellow solid; (2.27 g, 71 %); mp: 154-155 °C; IR (KBr): 3380, 3154, 2922, 1622, 1598 cm⁻¹, ¹H NMR (300 MHz, DMSO-d₆): δ = 6.59 (d, J = 9.0 Hz, 1H, Ar-H), 6.77 (s, 2H, -NH₂), 7.27-7.54 (m, 5H, Ar-H), 8.03 (d, J = 8.4 Hz, 2H, Ar-H), 8.16 (d, J = 9.0 Hz, 1H, Ar-H), 8.34 (d, J = 8.4 Hz, 2H, Ar-H) ppm; ¹³C NMR (75 MHz, DMSO-d₆): δ = 106.2, 107.2, 120.3, 122.8, 125.1, 126.6, 128.2, 128.4, 128.7, 128.8, 129.0, 131.1, 131.6, 132.9, 139.5, 142.2, 151.6, 159.6 ppm; EIMS: m/z (%) 320(M+, 100), 322 (M+2, 33). Anal. Calcd. for C₁₈H₁₃ClN₄ (320.78): C, 67.40; H, 4.08; N, 17.47. Found: C, 67.49; H, 4.21; N, 17.53.

3-(4-Bromophenyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridin-6-amine (62b): Yellow solid; (2.51 g, 69 %); mp: 157-158 °C; IR (KBr): 3379, 3152, 2923, 1624, 1597 cm⁻¹, ¹H NMR (300 MHz, DMSO-d₆): δ = 6.58 (d, J = 9.0 Hz, 1H, Ar-H), 6.78 (s, 2H, -NH₂), 7.27-7.55 (m, 5H, Ar-H), 8.04 (d, J = 8.4 Hz, 2H, Ar-H), 8.16 (d, J = 9.0 Hz, 1H, Ar-H), 8.34 (d, J = 8.4 Hz, 2H, Ar-H) ppm; EIMS: m/z (%) 364 (M+, 100), 366 (M+2, 98). Anal. Calcd. for C₁₈H₁₃BrN₄ (365.24): C, 59.19; H, 3.59; N, 15.34. Found: C, 59.32; H, 3.67; N, 15.56.
Experiment No. 3

Synthesis of Diethyl 2-[3-(4-aryl)-1-phenyl-1H-pyrazolo[3,4-b]pyridin-6-ylamino)methylene]-malonate (64a,b).

General Procedure: A solution of 3-(4-aryl)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-6-amime 62a (3.207 g, 0.01 mol) or 62b (3.652 g, 0.01 mol) and diethyl ethoxymethylene-malonate 63 (0.01 mol, 2.00 ml) in absolute ethanol (35 ml) was reflux for 10-12 hrs. (TLC check, toluene). The white solid formed on cooling was filtered by suction, recry-stslized from ethanol to afford 64 in good yields.

**Diethyl-2-[3-(4-chlorophenyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridin-6-yl-amino)-methylene]malonate (64a):** Colorless needles; (3.80 g, 77%); mp: 192-193°C; IR:(KBr): 3410, 1726, 1632, 1616, 1600 cm\(^{-1}\), \(^1\)H NMR (300 MHz, CDCl\(_3\)): δ = 1.38 (m, 6H, 2xCH\(_3\)), 4.34 (m, 4H, 2xCH\(_2\)), 6.71 (d, J = 9.0 Hz, 1H, Ar-H), 7.27-7.54 (m, 5H, Ar-H), 7.87 (d, J = 8.4 Hz, 2H, Ar-H), 8.15 (d, J = 9.0 Hz, 1H, Ar-H), 8.28 (d, J = 8.4 Hz, 2H, Ar-H), 9.19 (d, J = 12.5 Hz, 1H, C\(_7\)-H), 11.22 (d, J = 12.5 Hz, 1H, -NH) ppm; \(^13\)C NMR (75 MHz, CDCl\(_3\)): δ = 14.8 (2 C), 58.6 (2C), 94.0, 110.1, 114.9, 121.8 (2 C), 126.3, 129.1 (2 C), 129.3 (2 C), 130.4 (2 C), 131.1, 134.2, 136.5, 138.4, 145.7, 150.6, 154.9, 158.7, 165.0 (2 C) ppm; EIMS: \(m/z\) (%): 491 (M+, 100), 493 (M+2, 33). Anal. Calcd.
for C$_{26}$H$_{23}$ClN$_4$O$_4$(490.95): C, 63.61; H, 4.72; N, 11.41. Found: C, 63.76; H, 4.93; N, 11.58.

**Diethyl-2-[3-(4-bromophenyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridin-6-yl-amino)-methylene]malonate (64b):** Colorless needles; (4.22 g, 78%); mp: 189-190 °C; IR: (KBr): 3411, 1728, 1634, 1619, 1605 cm$^{-1}$, $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 1.39 (m, 6H, 2xCH$_3$), 4.36 (m, 4H, 2xCH$_2$), 6.72 (d, $J$ = 9.0 Hz, 1H, Ar-H), 7.28-7.56 (m, 5H, Ar-H), 7.87 (d, $J$ = 8.4 Hz, 2H, Ar-H), 8.16 (d, $J$ = 9.0 Hz, 1H, Ar-H), 8.28 (d, $J$ = 8.4 Hz, 2H, Ar-H), 9.19 (d, $J$ = 12.5 Hz, 1H, C$_7$-H), 11.23 (d, $J$ = 12.6 Hz, 1H, -NH) ppm; EIMS: m/z (%): 535 (M+, 100), 537 (M+2, 98). Anal. Calcd. for C$_{26}$H$_{23}$BrN$_4$O$_4$ (535.40): C, 58.33; H, 4.33; N, 10.46. Found: C, 58.41; H, 4.46; N, 11.36.

**Experiment No. 4**

**Synthesis of Ethyl-5-chloro-3-(4-subst.-phenyl)-1-phenyl-1H-pyrazolo[3,4-b][1,8]-naphthyridine-6-carboxylate (65a,b).**

![Diagram of the reaction](image)

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>Ar</th>
</tr>
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<tbody>
<tr>
<td>65a</td>
<td>$p$-Cl C$_6$H$_4$</td>
</tr>
<tr>
<td>65b</td>
<td>$p$-Br C$_6$H$_4$</td>
</tr>
</tbody>
</table>

**General Procedure:** The solution of diethyl-2-[(3-(4-aryl)-1-phenyl-1H-pyrazolo[3,4-b]pyridin-6-ylamino)-methylene]-malonate 64a (4.909 g, 0.01 mol) or 64b (5.354 g, 0.01 mol) in phosphorousoxychloride (30 ml) was heated to reflux for 4 hrs. After completion of reaction, excess POCl$_3$ was evaporated in vacuo. The yellow colored residue
obtained was poured into ice water and solution was neutralized with solid sodium carbonate. The separated solid product was collected by suction filtration, washed with cold water, dried and recrystallized from ethanol:DMF (9:1) to afford 65 in good yield.

**Ethyl-5-chloro-3-(4-chlorophenyl)-1-phenyl-1H-pyrazolo[3,4-b][1,8]naphthyridine-6-carboxylate (65a):** Yellow prisms; (3.46 g, 74%); mp: 233-234 °C; IR: (KBr): 2930, 1722, 1627, 1590 cm\(^{-1}\), \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta = 1.25\) (t, \(J = 6.9\) Hz, 3H, CH\(_3\)), 4.17 (q, \(J = 7.5\) Hz, 2H, -OCH\(_2\)), 7.31-7.55 (m, 5H, Ar-H), 8.15 (s, 1H, Ar-H), 8.29 (d, \(J = 8.6\) Hz, 2H, Ar-H), 8.53 (s, 1H, Ar-H), 8.88 (d, \(J = 8.6\) Hz, 2H, Ar-H) ppm; \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta = 14.8, 58.7, 114.9, 121.8\) (2 C), 122.7, 125.3, 126.3, 129.1 (2 C), 129.3 (2 C), 130.4 (2 C), 131.1, 134.2, 136.1, 139.1, 140.7, 145.9, 150.8, 152.1, 154.1, 168.9 ppm; EIMS: \(m/z\) (%): 463 (M+, 100), 465 (M+2, 64), 467 (M+4, 26). Anal. Calcd. for C\(_{24}\)H\(_{16}\)Cl\(_2\)N\(_4\)O\(_2\) (463.33): C, 62.22; H, 3.48; N, 12.09. Found: C, 62.10; H, 4.37; N, 12.15.

**Ethyl-5-chloro-3-(4-bromophenyl)-1-phenyl-1H-pyrazolo[3,4-b][1,8]naphthyridine-6-carboxylate (65b):** Yellow prisms; (3.88 g, 76%); mp: 238-239 °C; IR: (KBr): 2932, 1726, 1629, 1592 cm\(^{-1}\), \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta = 1.24\) (t, \(J = 6.9\) Hz, 3H, CH\(_3\)), 4.16 (q, \(J = 7.5\) Hz, 2H, -OCH\(_2\)), 7.32-7.55 (m, 5H, Ar-H), 8.16 (s, 1H, Ar-H), 8.29 (d, \(J = 8.6\) Hz, 2H, Ar-H), 8.54 (s, 1H, Ar-H), 8.89 (d, \(J = 8.6\) Hz, 2H, Ar-H) ppm; EIMS: \(m/z\) (%): 507 (M+, 100), 509 (M+2, 77), 511 (M+4, 24). Anal. Calcd. for C\(_{24}\)H\(_{16}\)BrClN\(_4\)O\(_2\) (507.78): C, 56.77; H, 3.18; N, 11.03. Found: C, 56.89; H, 3.30; N, 11.16.
Experiment No. 5

Synthesis of 9-(4-aryl)-1,7-diphenyl-1,7-dihydripyrazolo[3,4-b:3’,4’-f][1,8]naphthyridin-3(2H)-one (66a,d)

General Procedure: A solution of ethyl 5-chloro-3-(4-aryl)-1-phenyl-1H-pyrazolo[3,4-b][1,8]naphthyridine-6-carboxylate 65a (4.633 g, 0.01 mol) or 65b (5.077 g, 0.01 mol) and phenylhydrazine (0.01 mol, 0.985 ml) or hydrazine hydrate (0.01 mol, 0.480 ml) in xylene (35 ml) containing a catalytic amount of triethylamine was heated under reflux for 3-4 hrs. (TLC check, toluene: ethyl acetate 4:1). The excess solvent was removed under reduced pressure. The solid obtained was stirred in methanol (20 ml), filtered, dried, and recrystallized from ethanol/DMF (8:2) to afford 66 in good yield.

9-(4-Chlorophenyl)-7-phenyl-1,7-dihydripyrazolo[3,4-b:3’,4’-f][1,8]naphthyridin-3(2H)-one (66a): Yellow prisms; (2.73 g, 66%); mp: 303-304 °C; IR: (KBr): 3416, 3358, 1663, 1625, 1617 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ = 7.47-7.65 (m, 5H, Ar-H), 8.21 (s, 1H, Ar-H), 8.30 (d, J = 8.4 Hz, 2H, Ar-H), 8.35 (s, 1H, Ar-H), 8.45 (s, 1H, -NH), 8.78 (d, J = 8.4 Hz, 2H, Ar-H), 9.13(s, 1H, -NH) ppm; ¹³C NMR (75 MHz, DMSO-d₆): δ = 107.2, 111.4, 113.9, 122.0 (2 C), 126.4, 128.0 (2 C), 128.9 (2 C), 131.0
(2 C), 131.5, 132.8, 138.6, 144.9, 148.2, 151.6, 153.1, 159.5, 168.9 ppm; EIMS: m/z (%): 412 (M+, 100), 414 (M+2, 33). Anal. Calcd. for C_{22}H_{13}ClN_{6}O (412.84): C, 64.01; H, 3.17; N, 20.36. Found: C, 64.11; H, 3.24; N, 20.39.

9-(4-Bromophenyl)-7-phenyl-1,7-dihydrodipyrazolo[3,4-b:3',4'-f][1,8]naphthyridin-3(2H)-one (66b): Yellow prisms; (3.00 g, 65%); mp-298-299 °C; IR: (KBr): 3416, 3359, 1666, 1626, 1616 cm\(^{-1}\), \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta = 7.48-7.66\) (m, 5H, Ar-H), 8.20 (s, 1H, Ar-H), 8.31 (d, J = 8.4 Hz, 2H, Ar-H), 8.34 (s, 1H, Ar-H), 8.46 (s, 1H, -NH), 8.79 (d, J = 8.4 Hz, 2H, Ar-H), 9.12 (s, 1H, -NH) ppm; EIMS: m/z (%): 457 (M+, 100), 459 (M+2, 98). Anal. Calcd. for C_{22}H_{13}BrN_{6}O (457.29): C, 57.78; H, 2.87; N, 18.38. Found: C, 57.90; H, 2.99; N, 18.44.

9-(4-Chlorophenyl)-1,7-diphenyl-1,7-dihydrodipyrazolo[3,4-b:3',4'-f][1,8]naphthyridin-3(2H)-one (66c): Yellow prisms; (3.24 g, 66%); mp: 297-298 °C; IR: (KBr): 3360, 1667, 1620, 1612 cm\(^{-1}\), \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta = 7.27-7.56\) (m, 10H, Ar-H), 8.19 (s, 1H, Ar-H), 8.30 (d, J = 8.4 Hz, 2H, Ar-H), 8.37 (s, 1H, Ar-H), 8.47 (s, 1H, -NH), 8.78 (d, J = 8.4 Hz, 2H, Ar-H) ppm; \(^1^3\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta = 107.2, 111.4, 113.4(2\ C), 113.9, 119.3, 122.0\ (2\ C), 126.4, 128.0\ (2\ C), 129.9\ (2\ C), 129.3\ (2\ C), 131.0\ (2\ C), 131.5, 132.8, 138.6, 139.3, 144.9, 145.6, 148.2, 151.6, 153.1, 159.5, 168.9 ppm; EIMS: m/z (%): 488 (M+, 100), 490 (M+2, 33). Anal. Calcd. for C_{28}H_{17}Cl-N_{6}O(488.94): C, 68.78; H, 3.50; N, 17.19. Found: C, 68.90; H, 3.67; N, 17.33.

9-(4-Bromophenyl)-1,7-diphenyl-1,7-dihydrodipyrazolo[3,4-b:3',4'-f][1,8]naphthyridin-3(2H)-one (66d): Yellow prisms; (3.61 g, 67%); mp: 295-296 °C; IR: (KBr): 3362, 1669, 1621, 1614 cm\(^{-1}\), \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta = 7.29-7.56\) (m, 10H, Ar-H), 8.20 (s, 1H, Ar-H), 8.31 (d, J = 8.4 Hz, 2H, Ar-H), 8.36 (s, 1H, Ar-H), 8.48 (s, 1H, -
NH), 8.77 (d, J = 8.4 Hz, 2H, Ar-H) ppm; EIMS: m/z (%): 533(M+, 100), 535 (M+2, 98). Anal. Calcd. for C_{28}H_{17}BrN_{6}O (533.39): C, 63.05; H, 3.21; N, 15.76. Found: C, 63.15; H, 3.37; N, 15.92.

Experiment No. 6

Synthesis of (3Z)-3-(1-(3-(4-aryl)-1-phenyl-1H-pyrazolo[3,4-b]pyridin-6-ylamino)-ethylidene)-dihydrofuran-2(3H)-one (68a,b).

![Diagram of synthesis process]

<table>
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<th>Comp. No.</th>
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</tr>
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<tbody>
<tr>
<td>68a</td>
<td>p-Cl C_{6}H_{4}</td>
</tr>
<tr>
<td>68b</td>
<td>p-Br C_{6}H_{4}</td>
</tr>
</tbody>
</table>

General Procedure: A solution of 3-(4-aryl)-1-phenyl-1H-pyrazolo[3,4-b]pyridin-6-amine 62a (3.207 g, 0.01 mol) or 62b (3.652 g, 0.01 mol), α-acetyl-γ-butyrolactone 67 (0.01 mol, 1.076 ml) and catalytic amount (0.020 g) of p-TsOH in toluene (35 ml) was heated to reflux for 48 hrs. Azeotropic water separation was done using Dean Stark apparatus to monitor the reaction by collecting equivalent amount of water. The solvent was evaporated in vacuo and the red colored oily residue obtained was poured into methanol (25 ml). The solid separated was collected by suction filtration, dried and recrystallized from ethanol to furnish 68 in good yields.

(3Z)-3-(1-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridin-6-yl-amino)-ethylidene)-dihydrofuran-2(3H)-one (68a): Yellow prisms; (3.06 g, 71%); mp: 204-205 °C;
IR (KBr): 3340, 1735, 1689, 1602, 1210 cm\(^{-1}\), \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta = 2.64\) (s, 3H, CH\(_3\)), 2.98 (t, \(J = 7.5\) Hz, 2H, -CH\(_2\)CH\(_2\)O), 4.39 (t, \(J = 7.5\) Hz, 2H, -CH\(_2\)CH\(_2\)O), 6.70 (d, \(J = 8.4\) Hz, 1H, Ar-H), 7.26-7.52 (m, 5H, Ar-H), 7.91 (d, \(J = 8.6\) Hz, 2H, Ar-H), 8.13 (d, \(J = 8.4\) Hz, 1H, Ar-H), 8.18 (d, \(J = 8.6\) Hz, 2H, Ar-H), 10.96 (s, 1H, -NH) ppm; \(^1^3\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta = 19.3, 28.5, 69.4, 104.2, 114.8, 116.9, 121.3\) (2 C), 126.3, 128.6 (2C), 129.4 (4 C), 131.2, 134.2, 136.4, 145.9, 149.2, 152.6, 158.3, 170.2 ppm; EIMS: \(m/z\) (%): 430 (M+, 100), 432 (M+2, 33). Anal. Calcd. for C\(_{24}\)H\(_{19}\)ClN\(_4\)O\(_2\) (430.90): C, 66.90; H, 4.44; N, 13.00. Found: C, 66.68; H, 4.27; N, 12.88.

(3Z)-3-(1-(3-(4-bromophenyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridin-6-yl-amino)-ethyl-idene)-dihydrofuran-2(3H)-one (68b): Yellow prisms; (3.40 g, 71%); mp: 206-208 °C; IR (KBr): 3342, 1737, 1629, 1606, 1213 cm\(^{-1}\), \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta = 2.65\) (s, 3H, CH\(_3\)), 2.98 (t, \(J = 7.5\) Hz, 2H, -CH\(_2\)CH\(_2\)O), 4.38 (t, \(J = 7.5\) Hz, 2H, -CH\(_2\)CH\(_2\)O), 6.72 (d, \(J = 8.4\) Hz, 1H, Ar-H), 7.24-7.51 (m, 5H, Ar-H), 7.92 (d, \(J = 8.6\) Hz, 2H, Ar-H), 8.14 (d, \(J = 8.4\) Hz, 1H, Ar-H), 8.19 (d, \(J = 8.6\) Hz, 2H, Ar-H), 10.95 (s, 1H, -NH) ppm; EIMS: \(m/z\) (%): 475 (M+, 100), 477 (M+2, 98). Anal. Calcd. for C\(_{24}\)H\(_{19}\)BrN\(_4\)O\(_2\) (475.35): C, 60.64; H, 4.03; N, 11.79. Found: C, 60.91; H, 4.23; N, 12.08.

Experiment No. 7

Synthesis of 8-(2-chloroethyl)-3-(4-aryl)-7-methyl-1-phenyl-1H-pyrazolo[4',3':5,6]-pyrido[1,2-a]pyrimidin-9(1H)-one (69a,b).
General Procedure: A solution of (3Z)-3-(1-(3-(4-aryl)-1-phenyl-1H-pyrazolo[3,4-b]-pyridin-6-ylamino)-ethylidene)-dihydrofuran-2(3H)-one 68a (4.308 g, 0.01 mol) or 68b (4.753 g, 0.01 mol) in phosphorus oxychloride (30 ml) was heated to reflux for 2 hrs. After completion of the reaction, excess POCl₃ was evaporated in vacuo. The red colored residue obtained was poured into ice water and solution was neutralized with solid sodium carbonate. The separated solid product was collected by suction filtration. The crude product was recrystallized from ethanol:DMF (9:1) to furnish compound 69 in good yields.

8-(2-Chloroethyl)-3-(4-chlorophenyl)-7-methyl-1-phenyl-1H-pyrazolo-[4',3':5,6]pyrido[1,2-a]pyrimidin-9(1H)-one (69a): Yellow prisms; (3.59 g, 73%); mp: 229-230 °C; IR: (KBr): 1676, 1616, 1592 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ = 2.41 (s, 3H, CH₃), 2.79 (t, J = 7.2 Hz, 2H, -CH₂CH₂Cl), 3.53 (t, J = 7.2 Hz, 2H, -CH₂CH₂Cl), 7.15 (d, J = 8.4 Hz, 1H, Ar-H), 7.39-7.45 (m, 5H, Ar-H), 7.60 (d, J = 8.6 Hz, 2H, Ar-H), 7.96 (d, J = 8.6 Hz, 2H, Ar-H), 8.26 (d, J = 8.4 Hz, 1H, Ar-H) ppm; ¹³C NMR (75 MHz, DMSO-d₆): δ = 21.6, 29.3, 40.2, 110.6, 113.7, 120.4 (2C), 122.7, 127.3, 128.4 (2C), 129.0, 129.1, 129.8 (4C), 130.0, 133.8, 135.8, 142.6, 144.2, 148.9, 158.0, 160.2 ppm; EIMS: 448 (M+, 100), 450 (M+2, 64), 452 (M+4, 27). Anal. Calcd. for C₂₅H₁₉N₃Cl₂O (448.36): C, 66.97; H, 4.27; N, 9.37. Found: C, 66.78; H, 4.55; N, 9.61.

8-(2-Chloroethyl)-3-(4-bromophenyl)-7-methyl-1-phenyl-1H-pyrazolo-[4',3':5,6]pyrido[1,2-a]pyrimidin-9(1H)-one (69b): Yellow prisms; (3.56 g, 72%); mp: 231-321°C; IR: (KBr): 1676, 1617, 1593 cm⁻¹, ¹H NMR (300 MHz, DMSO-d₆): δ = 2.41 (s, 3H,
CH\textsubscript{3}), 2.79 (t, J = 7.2 Hz, 2H, -CH\textsubscript{2}CH\textsubscript{2}Cl), 3.53 (t, J = 7.2 Hz, 2H, -CH\textsubscript{2}CH\textsubscript{2}Cl), 7.15 (d, J = 8.4 Hz, 1H, Ar-H), 7.39-7.45 (m, 5H, Ar-H), 7.60 (d, J = 8.6 Hz, 2H, Ar-H), 7.96 (d, J = 8.6 Hz, 2H, Ar-H), 8.26 (d, J = 8.4 Hz, 1H, Ar-H) ppm; EIMS: m/z (%) 493 (M+, 100), 495 (M+2, 77), 497 (M+4, 27).

Anal. Calcd. for C\textsubscript{25}H\textsubscript{19}BrClN\textsubscript{3}O (492.81): C, 60.93; H, 3.89; N, 8.53. Found: C, 61.18; H, 4.11; N, 8.85.

Experiment No. 8

Synthesis of 8-(2-Azidoethyl)-3-(4-aryl)-7-methyl-1-phenyl-1H-pyrazolo[4',3':5,6]-pyrido[1,2-a]pyrimidin-9(1H)-one (70a,b).

\[
\begin{align*}
\text{Comp. No.} & \quad \text{Ar} \\
70a & \quad p-\text{Cl C}_6\text{H}_4 \\
70b & \quad p-\text{Br C}_6\text{H}_4
\end{align*}
\]

General Procedure: A mixture of 8-(2-Chloroethyl)-3-(4-aryl)-7-methyl-1-phenyl-1H-pyrazolo[4',3':5,6]pyrido[1,2-a]pyrimidin-9(1H)-one 69a (0.448 g, 0.001 mol) or 69b (0.492 g, 0.001 mol) and sodium azide (0.0015 mol, 0.0975 g) was stirred in DMF (25 ml) at room temperature for 8-9 hrs. The progress of reaction was monitored by TLC. After completion of reaction the reaction mixture was slowly added over ice cold water (50 ml). The obtained solid was filtered by suction and recrystallized from ethanol/DMF (9:1) to furnish compound 70 in good yields.
8-(2-Azidoethyl)-3-(4-chlorophenyl)-7-methyl-1-phenyl-1H-pyrazolo[4',3':5,6]-pyrido[1,2-a]pyrimidin-9(1H)-one (70a): Yellow prisms; (0.294 g, 64%); mp: 247-248 °C; IR: (KBr): 2120, 1670, 1620, 1600 cm\(^{-1}\), \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta = 2.44\) (s, 3H, CH\(_3\)), 2.80 (t, \(J = 7.2\) Hz, 2H, -CH\(_2\)CH\(_2\)N\(_3\)), 3.55 (t, \(J = 7.2\) Hz, 2H, -CH\(_2\)CH\(_2\)N\(_3\)), 7.14 (d, \(J = 8.4\) Hz, 1H, Ar-H), 7.40-7.59 (m, 5H, Ar-H), 7.61 (d, \(J = 8.6\) Hz, 2H, Ar-H), 7.95 (d, \(J = 8.6\) Hz, 2H, Ar-H), 8.27 (d, \(J = 8.4\) Hz, 1H, Ar-H) ppm; \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta = 21.6, 29.3, 47.1, 110.6, 113.7, 120.4\) (2C), 122.7, 127.3, 128.4 (2C), 129.0, 129.1, 129.8 (4C), 130.0, 133.8, 135.8, 142.6, 144.2, 148.9, 158.0, 160.2 ppm; EIMS: \(m/z\) (%): 455 (M\(^+\), 100), 457 (M+2, 33). Anal. Calcd. for C\(_{25}\)H\(_{19}\)ClN\(_6\)O (454.92): C, 66.01; H, 4.21; N, 18.47. Found: C, 66.32; H, 4.58; N, 18.74.

8-(2-Azidoethyl)-3-(4-bromophenyl)-7-methyl-1-phenyl-1H-pyrazolo[4',3':5,6]-pyrido[1,2-a]pyrimidin-9(1H)-one (70b): Yellow prisms; (0.326 g, 65%); mp: 248-249 °C; IR: (KBr): 2122, 1671, 1622, 1602 cm\(^{-1}\), \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta = 2.44\) (s, 3H, CH\(_3\)), 2.80 (t, \(J = 7.2\) Hz, 2H, -CH\(_2\)CH\(_2\)N\(_3\)), 3.55 (t, \(J = 7.2\) Hz, 2H, -CH\(_2\)CH\(_2\)N\(_3\)), 7.14 (d, \(J = 8.4\) Hz, 1H, Ar-H), 7.40-7.59 (m, 5H, Ar-H), 7.61 (d, \(J = 8.6\) Hz, 2H, Ar-H), 7.95 (d, \(J = 8.6\) Hz, 2H, Ar-H), 8.27 (d, \(J = 8.4\) Hz, 1H, Ar-H) ppm; EIMS: \(m/z\) (%): 499 (M\(^+\), 100), 501 (M+2, 98). Anal. Calcd. for C\(_{25}\)H\(_{19}\)BrN\(_6\)O (499.37): C, 60.13; H, 3.84; N, 16.83. Found: C, 60.39; H, 4.12; N, 17.09.
Experiment No. 9

Synthesis of 8-[2-(4-Chlorophenylamino)-ethyl]-3-(4-aryl)-7-methyl-1-phenyl-1H-pyrazolo[4',3':5,6]pyrido[1,2-a]pyrimidin-9(1H)-one (71a,b).

General Procedure: A mixture of 8-(2-Chloroethyl)-3-(4-aryl)-7-methyl-1-phenyl-1H-pyrazolo[4',3':5,6]pyrido[1,2-a]pyrimidin-9(1H)-one 69a (0.448 g, 0.001 mol) or 69b (0.492 g, 0.01 mol) and p-chloroaniline (0.001 mol, 0.128 g) was heated to 180°C for 30-35 min. After completion of reaction (TLC check) the reaction mixture was cooled to room temperature, methanol (25 ml) was added, and resulting solid formed was collected by suction filtration, dried and recrystallized from ethanol/DMF (9:1) to furnish compound 71 in 60-61% yield.

8-[2-(4-Chlorophenylamino)-ethyl]-3-(4-chlorophenyl)-7-methyl-1-phenyl-1H-pyrazolo[4',3':5,6]pyrido[1,2-a]pyrimidin-9(1H)-one (71a): Yellow prisms; (0.330 g, 61%); mp: 261-262 °C; IR: (KBr): 3400, 1676, 1620, 1608 cm\(^{-1}\); \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta = 2.42\) (s, 3H, CH\(_3\)), 2.82 (t, \(J = 7.2\) Hz, 2H, -CH\(_2\)CH\(_2\)NH-Ar), 3.86 (t, \(J = 7.2\) Hz, 2H, -CH\(_2\)CH\(_2\)NH-Ar), 6.91 (d, \(J = 8.2\) Hz, 1H, Ar-H), 7.35-7.59 (m, 5H, Ar-H), 7.60 (d, \(J = 8.4\) Hz, 2H, Ar-H), 7.75 (d, \(J = 8.6\) Hz, 2H, Ar-H), 8.07 (d, \(J = 8.6\) Hz, 2H, Ar-H),
8.17 (d, $J = 8.4$ Hz, 2H, Ar-H), 8.20 (d, $J = 8.2$ Hz, 1H, Ar-H), 11.50 (s, 1H, NH) ppm;

$^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta = 21.6$, 29.3, 42.6, 110.6, 114.7 (2C), 120.4 (2C), 122.4, 122.7, 127.3, 128.4 (2C), 129.0, 129.3, 129.7 (2C), 129.9 (4C), 130.0, 133.8, 135.8, 142.6, 144.2, 145.9, 148.9, 158.0, 160.2 ppm; EIMS: $m/z$ (%): 539 (M+, 100), 541 (M+2, 69), 543 (M+4, 34). Anal. Calcd. for C$_{30}$H$_{23}$Cl$_2$N$_5$O (540.46): C, 66.67; H, 4.29; N, 12.96. Found: C, 66.96; H, 4.19; N, 12.81.

$8$-[2-(4-Chlorophenylamino)-ethyl]-3-(4-bromophenyl)-7-methyl-1-phenyl-1H-pyrazolo[4',3':5,6]pyrido[1,2-a]pyrimidin-9(1H)-one (71b): Yellow prisms; (0.354 g, 60%); mp: 263-264 °C; IR: (KBr): 3402, 1675, 1621, 1607 cm$^{-1}$, $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta = 2.42$ (s, 3H, CH$_3$), 2.82 (t, $J = 7.2$ Hz, 2H, -CH$_2$CH$_2$NH-Ar), 3.86 (t, $J = 7.2$ Hz, 2H, -CH$_2$CH$_2$NH-Ar), 6.91 (d, $J = 8.2$ Hz, 1H, Ar-H), 7.35-7.59 (m, 5H, Ar-H), 7.60 (d, $J = 8.4$ Hz, 2H, Ar-H), 7.75 (d, $J = 8.6$ Hz, 2H, Ar-H), 8.07 (d, $J = 8.6$ Hz, 2H, Ar-H), 8.17 (d, $J = 8.4$ Hz, 2H, Ar-H), 8.20 (d, $J = 8.2$ Hz, 1H, Ar-H), 11.50 (s, 1H, NH) ppm; EIMS: $m/z$ (%): 585 (M+, 100), 583 (M+2, 97), 586 (M+4, 41). Anal. Calcd. for C$_{30}$H$_{23}$-BrClN$_5$O (584.91): C, 61.61; H, 3.96; N, 11.97. Found: C, 61.86; H, 4.19; N, 12.21.
REFERENCES


