CHAPTER 4

Synthesis of Novel fused 2-Aminopyrans and Pyranopyrimidones

In the present chapter we have reported the synthesis of bifunctional pyrano[2,3-d]pyrazolo[3,4-b]pyridine (2-Aminopyran) derivatives. The enaminonitrile derivative were utilized for synthesis of different substituted new pyrano[2,3-d]pyrazolo[3,4-b]pyridines and pyrazolo[4”,3”`:5’,6`]pyrido[3’,4’:5,6]pyrano[2,3-d]pyrimidine derivatives. All synthesized compounds were characterized by spectral and analytical methods. Chapter is divided into three sections.

Section-I. Synthesis of 3-(aryl)-4-hydroxy-1-phenyl-1H-pyrazolo[3,4-b]pyridine-6(7H)-one

Section-II. Synthesis of bifunctional pyrano[2,3-d]pyrazolo[3,4-b]pyridine derivatives

Section-III. Synthesis of Pyranopyrimidones from enaminonitrile

3.1. Introduction

Pyrano-fused heterocycles are important as antibacterial [1], antihistamines [2], antimicrobials [3], enzyme substrates [4], and alkaloids [5]. Several patents describe the synthesis and technical importance of pyrano-fused derivatives in high technology applications such as liquid crystal display devices [6], ink-jets [7], photochromic materials [8], and electroluminescent material [9]. Pyrano-fused dyes attract special attention on account of their strong fluorescence [10-13]. Wang et al. have prepared 2-amino- benzo[h]chromene and naphtha[1,2-b;6,5-b‘]dipyran derivatives from the reaction of 1-naphthol or 1,5-naph-
thalenediol with aromatic aldehydes, malononitrile or ethyl cyanoacetate catalyzed by KF-Al₂O₃ in ethanol [14]. Marco et al. have synthesized asymmetrical 3-alkoxycarbonyl-2-amino-4-aryl-4H-naphthol[1,2-b]pyrans through the Michael addition of 1-naphthol to arylidenecyanoacetates catalyzed by piperidine in toluene [15], and similarly Elnagdi, Aal and Yassin have performed the addition of dimedone to aryllidenemalononitriles catalyzed by piperidine in acetic acid to obtain benzo[b]pyran derivatives [16]. We reported the synthesis of benzochromene and benzoquinoline, derivatives by the Michael addition of 6-methoxy-1-tetralone to benzylidenemalononitrile catalyzed by piperidine in ethanol and ammonium acetate in ethanol respectively [17]. However, the development of simpler, environmentally benign, high-yielding, and clean syntheses of novel pyran derivatives is still in demand. The drive towards clean technology has also encouraged the application of solvent-free conditions in organic synthesis.

**Literature updates: 1) synthesis of 2-aminopyran derivatives.**

1) Wang et al. [18] synthesized a series of 2-aminopyran derivatives include 2-aminobenzo[h]chromene 3 and naphth[1,2-b:6,5-b']dipyrans 4 which were synthesized from arylaldehyde 1, malononitrile 2 or ethyl cyanoacetate with 1-naphthol or 1,5-naphthalenediol in refluxing ethyl alcohol catalyzed by KF-Al₂O₃.
2) Nazario Martin et. al. [19] reported the first asymmetric synthesis of 3-alkoxycarbonyl-2-amino-4-aryl-4H-naphtho[1,2-b]pyrans, by Michael addition of 1-naphthol to chirally modified arylidenecyanoacetates 6 or 7. The absolute sterochemistry at C-4 in major isomers of pyrans 8 & 9 has been assigned as S by X-ray analysis of major pyran 8.

3) M. A. Al-haiza et. al. [20] reported synthesis of 2-aminopyran derivatives 12 by condensation of 4-hydroxycoumarin 10 with α-cyano-p-bromocinnaminitrile 11a or α-carboxethoxy-p-bromocinnaminitrile 11b.

4) A. M. F. Oliveira-Campos et. al. [21] Reported the synthesis of pyrazolo[3,4-d]pyrimidine derivatives from N-aryl-5-amino-4-cyanopyrazoles 13. The reaction of 13 with amines or arylhydrazines gave only 4-substituted pyrazolo[3,4-d]pyrimidines (16, 18), resulting from cyclization followed by Dimroth rearrangement. From the reaction with
arylhydrazines, a mixture of the hydrazines and their oxidized forms, the azo products (19, 20), was obtained. This was proven by an independent synthesis starting from the corresponding 4-chloropyrazolo[3,4-d]pyrimidines 17 as starting material.


6) Tina Morwick and co-workers [23] has reported thienopyridines as class of inhibitor of IkB-kinase-β 27 from 3-amino-5-phenylthiophene-2-carboxamide 23 and formic acid.
and obtained pyrimidone 26, which on condensation with ammonia afforded compound 27.

7) V. Shah et al. and co-workers [24] has reported the synthesis and biological screening of some novel pyrazolo[3’4’:4,5]thieno[2,3-d]pyrimidin-8-ones 32 obtained by Gewald thiophene reaction. The 3-methyl-1H-pyrazol-5(4H)-one 28 on condensation with malononitrile afforded open chain compound 30, which on further cyclization reaction with elemental sulphur and catalytic amount of morpholine yielded o-aminocarbonitrile 31. This compound on further reaction with ester afforded thienopyrazolopyrimidone 32 in good yields.

8) R. B. Toche et al. and co-workers [25] has reported the synthesis and indenothienopyrimidine derivatives from 2-amino-5,6-dimethoxy-8H-indeno[2,1-b]thiophene-3-carbonitrile (33). The 2-amino-5,6-dimethoxy-8H-indeno[2,1-b]thiophene-3-carbonitrile (33) on condensation with formamide 73a or acetamide 37b or benzamide 37c or cyanoacet-
amide 37d afforded 6,7-Dimethoxy-2-substituted-9H-10-thia-1,3-diaza-indeno[1,2-a]inden-4-ylamine, (38a-d). Compound 33 reacted with formic acid furnished 6,7-Dimethoxy-9H-10-thia-1,3-diaza-indeno[1,2-a]inden-4-ol, (39) which on chlorination by refluxing in POCl₃ furnished 4-Chloro-6,7-dimethoxy-9H-10-thia-1,3-diaza-indeno[1,2-a]indenene, (40). Compound 33 on reaction with triethylorthoformate 34 furnished open chain compound 35, which on further cyclization reaction with hydrazine hydrate yielded 4-Imino-6,7-dimethoxy-4H,9H-10-thia-1,3-diaza-indeno[1,2-a]inden-3-ylamine, (36).

9) R. B. Toche et al. and co-workers [26] has reported the synthesis of thieno[2,3-d]pyrimidines from o-aminocarbonitrile 41. The o-aminocarbonitrile 41 reacted with formic acid and DMF-DMA followed by hydrazine hydrate furnished a thieno[2,3-d]pyrimidines 43 & 44 respectively.
4.2. Present Work

In the present chapter we have reported the synthesis of bifunctional pyrano[2,3-\(d\)]pyrazolo[3,4-\(b\)]pyridine (2-Aminopyran) derivatives. The enaminonitrile derivative were utilized for synthesis of different substituted new pyrano[2,3-\(d\)]pyrazolo[3,4-\(b\)]pyridines and pyrazolo[4''3';5',6']pyrido[3',4':5,6]pyrano[2,3-\(d\)]pyrimidine derivatives.

Thus, Retrosynthesis of 2-Aminopyran, pyrano[2,3-\(d\)]pyrazolo[3,4-\(b\)]pyridines and pyrazolo[4''3';5',6']pyrido[3',4':5,6]pyrano[2,3-\(d\)]pyrimidine derivatives depicted in the Scheme 1 to 5.

4.2.1. Retrosynthesis of 3-(aryl)-4-hydroxy-1-phenyl-1\(H\)-pyrazolo[3,4-\(b\)]pyridine-6(7\(H\))-One: 4-hydroxy-pyrazolo[3,4-\(b\)]pyridine 48 could be synthesized by cyclocondensation of open chain compound 47. The open chain compound 47 could be obtained by reaction of pyrazole 45 with diethyl malonate. Alternatively compound 48 could be synthesized by one-pot reaction of pyrazole 45 and diethyl malonate.

4.2.3. Retrosynthesis of Pyranopyrimidones from enaminoitrile derivative: Pyranopyrimidones 54 could be synthesized by condensation of enaminoitrile derivatives 50 with formamide. Pyranopyrimidones 52 could be obtained by reaction of compound 50 with formic acid.
4.2.4. Retrosynthesis of Pyranopyrimidones from enaminonitrile derivative: The Pyranopyrimidone 58 could be obtained by reaction of enaminonitrile derivatives 50 with DMF-DMA. The open chain compound 56 could be synthesized by reaction of 50 with triethyl orthoformate.

4.3. Results and Discussion

4.3.1. Synthesis of Ethyl 2-(3-Aryl-1-phenyl-1H-pyrazol-5-ylcarbamomyl)-acetate

47: For the synthesis of key intermediates 4-hydroxy-pyrazolo[3,4-b]pyridine we started with 5-aminopyrazole [27] and diethyl malonate.

![Reaction Scheme]

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<th>Comp. No.</th>
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<tr>
<td>47a</td>
<td>p-Cl C₆H₄</td>
</tr>
<tr>
<td>47b</td>
<td>p-Br C₆H₄</td>
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Scheme 6

Thus, the 5-aminopyrazole 45a and diethyl malonate 46 were refluxed in toluene for 10 hrs. Furnished colorless solid, which was characterized by spectral and analytical data. The ¹H-NMR spectrum (CDCl₃) of 47a showed triplet at δ 1.20 ppm (J = 6.8 Hz) for three protons of methyl group and quartet at δ 4.15 ppm (J = 6.8 Hz) for two protons of methylene group of ester. The singlet appears at δ 3.43 ppm for –CH₂ proton. The broad singlet appears at δ 9.80 ppm corresponds to –NH proton. The five aromatic protons appeared in between δ 7.23-7.55 ppm corresponded to N-phenyl ring. Two doubts of p-substituted ring are appeared at δ 7.68 and 7.76 (J = 8.4 Hz) ppm respectively. The singlet at δ 7.05 ppm for proton of pyrazole ring (Spectrum No.1, Page No. 190). The ¹³C-NMR spectrum (CDCl₃) of this solid showed peak at δ 18.1 ppm for methyl carbons and δ 59.6 ppm for the methylene carbon of the ester group. The ester carbonyl carbon appeared at δ 168.2 ppm. The amide carbonyl carbon appeared at δ 164.6 ppm. The C₇ carbon
attached to ester group was observed at $\delta$ 84.3 ppm. All six carbons of phenyl ring and six carbon of $p$-substituted ring, attached to pyrazole ring appeared between $\delta$ 119.91 - 140.58 ppm. The C$_3$ carbon of pyrazole ring observed at $\delta$ 153.6 ppm. The C$_4$ carbon of the pyrazole ring appeared at $\delta$ 96.4 ppm. On the basis of above spectral and analytical data structure 47a was assigned to this compound i.e. Ethyl-2-(4-chlorophenyl-1-phenyl-1$H$-pyrazol-5-ylcarbamoyl)-acetate an open chain compound. Analogously compound 47b was synthesized and characterized by IR, $^1$H NMR, $^{13}$C NMR and elemental analysis (Experiment No. 1, page No. 207).

![Spectrum No. 1: $^1$H NMR Spectrum of Ethyl-2-(3-chlorophenyl-1-phenyl-1$H$-pyrazol-5-ylcarbamoyl)-Acetate, 47a](image)

$\text{EtO}_2\text{CCH}_2\text{CONH}$

47a

Cl
4.3.2. Synthesis of 3-Aryl-4-hydroxy-1-phenyl-1H-pyrazolo[3,4-b]pyridine-6(7H)-one 48 from 47.

The acetate compound 47a cyclized by refluxing in diphenylether for 1 h. obtained a colorless solid. This compound was characterized by spectral and analytical data after crystallization. The $^1$H-NMR spectrum (DMSO-$d_6$) of this solid showed singlet at δ 6.02 ppm for pyridine ring proton. The five aromatic protons appeared in between δ 7.32-7.60 ppm corresponded to N-phenyl ring. Two doubts of p-substituted ring are appeared at δ 8.14 and 8.20 ($J = 8.4$ Hz) ppm respectively. The broad singlet appears at δ 11.14 ppm corresponds to –NH proton and the singlet at δ 11.68 ppm corresponds to –OH proton (Spectrum No. 2, Page No. 192). The $^{13}$C-NMR spectrum (DMSO-$d_6$) of this solid showed peak at δ 162.1 ppm for C$_4$-OH carbon and δ 164.0 ppm for C$_6$ carbonyl carbon. The C$_5$ carbon observed at δ 102.1 ppm. All six carbons of phenyl ring and six carbon of p-substituted ring, attached to pyrazole ring appeared between δ 120.2-143.5 ppm. The C$_8$ and C$_9$ carbons of pyrazole ring observed at δ 90.3 and 134.4 ppm respectively. The C$_3$ carbons of pyrazole ring observed at δ 152.3 ppm (Spectrum No. 3, Page, No. 192). The molecular ion peak at 337 [M$^+$], 339 [M+2] exactly matches to the molecular weight of

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<td>48a</td>
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<tr>
<td>48b</td>
<td>$p$-Br C$_6$H$_4$</td>
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Scheme 7
the solid. The elemental analysis agreed with molecular formula C\textsubscript{18}H\textsubscript{12}N\textsubscript{3}ClO\textsubscript{2}. On the basis of above spectral and analytical data structure 48a was assigned to this compound i.e. 3-(4-chlorophenyl)-4-hydroxy-1-phenyl-1\textit{H}-pyrazolo[3,4-\textit{b}]pyridine-6(7\textit{H})-one.

Analogously compound 48b was synthesized and characterized by IR, \textsuperscript{1}H NMR, \textsuperscript{13}C NMR and elemental analysis (Experiment No. 2, page No. 208).

Spectrum No. 2: \textsuperscript{1}H NMR Spectrum of 3-(4-chlorophenyl)-4-hydroxy-1-phenyl-1\textit{H}-pyrazolo[3,4-\textit{b}]pyridine-6(7\textit{H})-one, 48a

Spectrum No. 3: \textsuperscript{1}H NMR Spectrum of 3-(4-chlorophenyl)-4-hydroxy-1-phenyl-1\textit{H}-pyrazolo[3,4-\textit{b}]pyridine-6(7\textit{H})-one, 48a
4.3.3. Synthesis of 3-Aryl-4-hydroxy-1-phenyl-1H-pyrazolo[3,4-b]pyridine-6(7H)-one (48a,b) from 45: Alternatively compound 48 were obtained by single step.

\[
\text{45a, b} \xrightarrow{\text{CH}_2(\text{CO}_2\text{Et})_2} \text{46} \rightarrow \text{48a, b}
\]

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<tr>
<td>48a</td>
<td>p-Cl C_6H_4</td>
</tr>
<tr>
<td>48b</td>
<td>p-Br C_6H_4</td>
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Scheme 8

Thus, mixture of 5-aminopyrazol 45a and diethyl malonate 46 was refluxed in diphenyl ether for 1 h. pale yellow solid separated on cooling was characterized by spectral and analytical data and assigned structure 48a, i.e. 3-(4-chlorophenyl)-4-hydroxy-1-phenyl-1H-pyrazolo[3,4-b]pyridine-6(7H)-one. The \(^1\)H-NMR (Spectrum No. 2, Page No. 190) and \(^{13}\)C-NMR (Spectrum No. 3, Page, No. 192) spectrums in (DMSO-\(d_6\)) of 48a were explained in above reaction. Analogously compound 48b was synthesized and characterized by IR, \(^1\)H NMR, \(^{13}\)C NMR and elemental analysis (Experiment No. 3, page No. 209).

4.3.4. Synthesis of 2-amino-4,9-Aryl-5-oxo-7-phenyl-4,5,6,7-tetrahydropyran[2,3-d]pyrazolo[3,4-b]pyridine (50a-f)

Then 48 was transformed to desired 2-aminopyran derivatives 50 by heating it with 2-(4-chlorobenzylidene)-malononitrile 49a or (E)-ethyl-3-(4-chlorophenyl)-2-cyanoacrylate 49b or (E)-3-(4-chlorophenyl)-2-cyanoacrylamide 49c in ammonium acetate at 120 °C.
Thus, a mixture of 4-hydroxy-pyrazolopyridine 48a and the 2-(4-chlorobenzylidene) malononitrile 49a in ammonium acetate was thoroughly mixed at room temperature and heated for 1 hrs. at 120 °C under a short Vigreux column attached to the flask. After completion of reaction (TLC check), the reaction mixture was cooled to room temperature and slowly added to cold water (50 mL) to dissolve excess of ammonium acetate and the precipitated product was collected, washed with water, dried and recrystallized from ethanol:DMF (9:1) to give colorless solid 50a. This colorless solid showed IR bands at 3410 cm\(^{-1}\) for amide –NH, a band at 3320 cm\(^{-1}\) and 3241 cm\(^{-1}\) for –NH\(_2\), at 2212 cm\(^{-1}\) for –CN and at 1678 cm\(^{-1}\) for CONH group. The \(^1\)H-NMR (DMSO-\(d_6\)) of this solid displayed a singlet at \(\delta\) 4.55 for proton of sp\(^3\) carbon in pyran ring. It showed a broad singlet at \(\delta\) 6.80 for –NH\(_2\) protons and a singlet at \(\delta\) 12.02 for –NH proton of pyridone ring. All aromatic protons observed between \(\delta\) 7.20-8.16 ppm respectively (Spectrum No. 4, Page, No. 195). The \(^{13}\)C-NMR spectrum (DMSO-\(d_6\)) showed peak at \(\delta\) 39.1 ppm for C\(_4\).
sp³ carbon in pyran ring. The C₄-CN carbon appeared at δ 62.4 ppm and the –CN carbon appeared at δ 102.2 ppm. The C₂-NH₂ carbon appeared at δ 162.2 ppm. All six carbons of phenyl ring & six carbon of p-substituted ring, attached to pyrazole ring appeared between there respective region. The C₅ carbonyl carbon observed at δ 167.3 ppm. The C₉ carbons of pyrazole ring observed at δ 151.2 ppm (Spectrum No. 5, Page, No. 196). The molecular ion peak at 525 [M⁺], 527 [M+2], 529 [M+4] exactly matches to the molecular weight of the solid. The elemental analysis agreed with molecular formula C₂₈H₁₇N₅Cl₂O₂. On the basis of above spectral and analytical data structure 50a was assigned to this solid i.e. 2-amino-4,9-(4-chlorophenyl)-5-oxo-7-phenyl-4,5,6,7-tetrahydropyrano[2,3-d]-pyrazolo[3,4-b]pyridine-3-carbonitrile 50a. This conversion of 48a to 50a does not require any solvent and aqueous work-up of the reaction yielded product 50a. The acetate ion served as the base in this condensation reaction to give the products 50a in pure state without the need for further purification. Analogously compound 50b-f were synthesized characterized by IR, ¹H NMR, ¹³C NMR and elemental analysis (Experiment No. 4, page No. 211).

Spectrum No. 4: ¹H NMR Spectrum of 2-amino-4,9-(4-chlorophenyl)-5-oxo-7-phenyl-4,5,6,7-tetrahydropyrano[2,3-d]pyrazolo[3,4-b]pyridine-3-carbonitrile, 50a.
4.3.5. Synthesis of 1,6-Aryl-3-phenyl-6,10-dihydropyrazolo[4”,3”;5’,6’]pyrido[3’,4’:5,6]tetrahydropyran-2,3-d|pyrazolo[3,4-b]pyridine-3-carbonitrile, 50a.

The o-aminocarbonitrile 50a was treated with formic acid to annulate pyrimidine nucleus on pyrano ring.

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<th>Comp. No.</th>
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<tr>
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<td>p-Cl C₆H₄</td>
<td>p-Cl C₆H₄</td>
</tr>
<tr>
<td>52b</td>
<td>p-Br C₆H₄</td>
<td>p-Cl C₆H₄</td>
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Scheme 10
Thus, the treatment of 50a with formic acid at reflux yielded a colorless solid, it was characterized by spectroscopic and analytical methods and assigned structure 52a, i.e. 1,6-(4-chlorophenyl)-3-phenyl-6,10-diydropyrazolo[4’’,3’’;5’,6’]pyrido[3’,4’;5,6]pyranopyrimidine-5,7(3H,4H)-diones. The 1H-NMR (DMSO-d$_6$) of 52a displayed a singlet at $\delta$ 4.54 for proton of sp$^3$ carbon in pyran ring. The two doublets for $p$-substituted ring observed at $\delta$ 8.05 and 8.20 ppm ($J = 8.6$ Hz) respectively. All other aromatic protons (10H) observed between $\delta$ 7.20-7.71 ppm as a multiplate. It showed two broad singlets at $\delta$ 8.48 and 12.01 ppm for pyrimidine ring $-$NH proton & pyridone ring $-$NH proton respectively (Spectrum No. 6, Page, No. 198). The 13C-NMR spectrum (DMSO-d$_6$) of this solid showed peak at $\delta$ 39.0 ppm for C$_6$ sp$^3$ carbon in pyran ring. The C$_5$ carbonyl carbon of pyridone ring appeared at $\delta$ 162.6 ppm and C$_7$ carbonyl carbon of pyrimidine ring appeared at $\delta$ 168.1 ppm. The C$_8$ pyrimidine ring carbon appeared at $\delta$ 152.0 ppm. All six carbons of phenyl ring and six-carbon of $p$-substituted ring, attached to pyrazole ring and all other aromatic carbons appeared between there respective region. The molecular ion peak at 553 [M$^+$], 555 [M+2], 557 [M+4] exactly matches to the molecular weight of the solid. The elemental analysis agreed with molecular formula C$_{29}$H$_{17}$N$_5$Cl$_2$O$_3$. Analogously compound 52b was synthesized and characterized by IR, $^1$H NMR, $^{13}$C NMR and elemental analysis (Experiment No. 5, page No. 214).

A reaction of 50 was perform with formamide to annulat aminopyrimidine nuceus.

Spectrum No. 6: $^1$H NMR Spectrum of 1,6-(4-chlorophenyl)-3-phenyl-6,10-dihydro-pyrazolo[4'',3'':5',6']pyrido[3',4':5,6]pyrano[2,3-d]pyrimidine-5,7(3H,4H)-diones (52a).

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<th>Comp. No.</th>
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<tr>
<td>54a</td>
<td>$p$-Cl C$_6$H$_4$</td>
<td>$p$-Cl C$_6$H$_4$</td>
</tr>
<tr>
<td>54b</td>
<td>$p$-Br C$_6$H$_4$</td>
<td>$p$-Cl C$_6$H$_4$</td>
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Scheme 11
Thus, the condensation reaction of 50a with formamide in the presence of formic acid and DMF yield colorless solid which was purifide by crystalization with ethanol:DMF (9:1). The $^1$H-NMR (DMSO-$d_6$) of this solid displayed a singlet at $\delta$ 5.19 for proton of sp$^3$ carbon in pyran ring. The two doublets for $p$-substituted ring observed at $\delta$ 7.98 and 8.22 ppm ($J = 8.6$ Hz) respectively. All other aromatic protons (10H) observed between $\delta$ 7.20-7.77 ppm as a multiplate. It showed broad singlet at $\delta$ 8.52 for -NH$_2$ protons. The singlet appears at 12.06 ppm corresponds to –NH proton pyridone ring (Spectrum No. 7, Page, No. 200). The $^{13}$C-NMR spectrum (DMSO-$d_6$) of this solid showed peak at $\delta$ 38.4 ppm for C$_6$ sp$^3$ carbon in pyran ring. The C$_5$ carbonyl carbon of pyridon ring appeared at $\delta$ 162.3 ppm and C$_7$-NH$_2$ carbon of pyrimidine ring appeared at $\delta$ 164.4 ppm. The C$_8$ pyrimidine ring carbon appeared at $\delta$ 148.6 ppm. All six carbons of phenyl ring & six carbon of $p$-substituted ring, attached to pyrazole ring and all other aromatic carbons appeared between there respective region (Spectrum No. 8, Page, No. 200). The molecular ion peak at 552 [M$^+$], 554 [M+2], 556 [M+4] exactly matches to the molecular weight of the solid. The elemental analysis agreed with molecular formula C$_{29}$H$_{18}$N$_6$Cl$_2$O$_2$. On the basis of above spectral and analytical data structure 54a was assigned to this solid i.e. 7-amino-1,6-(4-chloropheny)-3-phenyl-4,6-dihydro-pyrazolo[4''',3'':5',6']pyrido[3',4':5,6]pyrano[2',3-d]pyrimidine-5(3H,4H)-one (54a). Analogously compound 54b was synth- esized and characterized by IR, $^1$H NMR, $^{13}$C NMR and elemental analysis (Experiment No. 6, page No. 216).
Spectrum No. 7: $^1$H NMR Spectrum of 7-amino-1,6-(4-chlorophenyl)-3-phenyl-4,6-dihydropyrazolo[4''',3'':5',6']pyrido[3',4':5,6]-pyrano[2,3-d]pyrimidine-5(3H,4H)-one,54a.

Spectrum No. 8: $^{13}$C NMR Spectrum of 7-amino-1,6-(4-chlorophenyl)-3-phenyl-4,6-dihydropyrazolo[4''',3'':5',6']pyrido[3',4':5,6]-pyrano[2,3-d]pyrimidine-5(3H,4H)-one,54a.
4.3.7. Synthesis of (E)-4,9-Aryl-3-cyano-2-((ethoxymethylene)amino)-7-phenyl-4,7-dihydropyrano[2,3-d]pyrazolo[3,4-b]pyridin-5-yl-acetate (56).

After successful annulation of pyrimidine nucleus on to 50, some condensation reaction of amino functionality in pyran ring of 50 was studied with triethyl orthoformate and DMF-DMA.

The reaction of 2-amino-4,9-(4-chlorophenyl)-5-oxo-7-phenyl-4,5,6,7-tetrahydropyrano[2,3-d]pyrazolo[3,4-b]pyridine-3-carbonitrile 50a with triethyl orthoformate 55 in acetic anhydride yield a colorless solid. It was characterized by spectroscopic and analytical methods and assigned structure 56a, i.e. (E)-4,9-(4-chlorophenyl)-3-cyano-2-[(ethoxymethylene)amino]-7-phenyl-4,7-dihydro-pyran[2,3-d]pyrazolo[3,4-b]pyridin-5-yl-acetate. Its IR spectrum showed bands at 2217 cm⁻¹ for -CN and 1715 cm⁻¹ for ester -C=O groups. ¹H-NMR spectrum (DMSO-d₆) of this solid showing triplet-quartet signals at δ 1.31 and 4.29 ppm respectively corresponds to ethyl group, it showed singlet at δ 2.20 for –CH₃ protons & singlet for pyran proton at δ 5.01 ppm. It showed singlet at δ 8.04 ppm corresponds to olefinic proton and broad singlet at δ 12.02 ppm for –NH proton. All other aro-

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<td>p-Cl C₆H₄</td>
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<tr>
<td>56b</td>
<td>p-Br C₆H₄</td>
<td>p-Cl C₆H₄</td>
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**Scheme 12**
matic protons appears between δ 7.30-8.11 respectively (Spectrum No. 9, Page, No. 202). The molecular ion peak at 624 [M⁺], 626 [M+2], 628 [M+4] exactly matches to the molecular weight of the solid. The elemental analysis agreed with molecular formula C₃₃H₂₃N₅Cl₂O₄. Analogously compound 56b was synthesized and characterized by IR, ¹H NMR, ¹³C NMR and elemental analysis (Experiment No. 7, page No. 217).

4.3.8. Synthesis of (E)-N’-4,9-Aryl-3-cyano-6-methyl-5-oxo-7-phenyl-4,5,6,7-tetrahydropyrano[2,3-d]pyrazolo[3,4-b]pyridin-5-yl-acetate (57)
Treatment of 50a with dimethylformamide-dimethylacetal (DMF-DMA) furnished a colorless solid which was purified by crystallization with ethanol:DMF (9:1). This colorless solid was characterized by spectroscopic and analytical methods. Its $^1$H-NMR spectrum (DMSO-$d_6$) showed three singlet at $\delta$ 2.89, 2.90 & 3.82 ppm for protons of three –CH$_3$ groups. It showed singlet for pyran proton at $\delta$ 4.75 ppm. All other aromatic protons appears between $\delta$ 7.33-8.16 ppm respectively (Spectrum No. 10, Page, No. 204). The molecular ion peak at 594[M$^+$], 596[M+2], 598[M+4] exactly matches to the molecular weight of the solid. The elemental analysis agreed with molecular formula C$_{32}$H$_{24}$N$_6$Cl$_2$-O$_2$. On the basis of above spectral and analytical data structure 58a was assigned to this compound i.e. ((E)-N'-(4,9-(4-chlorophenyl)-3-cyano-6-methyl-5-oxo-7-phenyl-4,5,6,7-tetrahydropyrano[2,3-d]pyrazolo[3,4-b]pyridin-2-yl)-N,N-dimethylformimidamide.

Analogously compound 58b was synthesized and characterized by IR, $^1$H NMR, $^{13}$C NMR and elemental analysis (Experiment No. 8, page No. 219).

<table>
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<td>58a</td>
<td>p-Cl C$_6$H$_4$</td>
<td>p-Cl C$_6$H$_4$</td>
</tr>
<tr>
<td>58b</td>
<td>p-Br C$_6$H$_4$</td>
<td>p-Cl C$_6$H$_4$</td>
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</tbody>
</table>

Scheme 13

The open chain derivatives of 56 was cyclized to pyrimidine ring on treatment with hydrazine hydrate.

<table>
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<th>Ar</th>
<th>Ar'</th>
</tr>
</thead>
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<td>p-Cl C₆H₄</td>
<td>p-Cl C₆H₄</td>
</tr>
<tr>
<td>60b</td>
<td>p-Br C₆H₄</td>
<td>p-Cl C₆H₄</td>
</tr>
</tbody>
</table>

Scheme 14
Thus, compound 56a on heating with hydrazine hydrate at reflux yielded a colorless solid. It was characterized by spectroscopic and analytical methods and assigned structure 60a, i.e. 8-amino-1,6-(4-chlorophenyl)-7-imino-4-methyl-3-phenyl-4,6-dihydropyrazolo[4’’,-3’’:5’,6’’]pyrido[3’,4’:5,6]pyrano[2,3-d]pyrimidine-5(3H)-one. Its $^1$H-NMR spectrum (DMSO-$d_6$) showed singlet at $\delta$ 2.19 for –CH$_3$ protons. It showed a broad singlet at $\delta$ 4.89 for –NH$_2$ protons. It showed singlet at $\delta$ 5.37 for proton of pyran ring. The pyrimidine proton appears at $\delta$ 7.51 ppm. All other aromatic protons appears between $\delta$ 7.19-8.14 respectively. The broad singlet appeared at $\delta$ 9.23 ppm corresponds to –NH proton (Spectrum No. 11, Page No. 206). The molecular ion peak at 609 [M$^+$], 611 [M+2], 613 [M+4] exactly matches to the molecular weight of the solid. The elemental analysis agreed with molecular formula C$_{31}$H$_{21}$N$_7$Cl$_2$O$_3$. Analogously compound 60b was synthesized and characterized by IR, $^1$H NMR, $^{13}$C NMR and elemental analysis (Experiment No. 9, page No. 220).
Conclusion

The solvent free synthesis of potentially useful bifunctional pyrano[2,3-\(d\)]pyrazolo[3,4-\(b\)]pyridine derivatives (4) have been reported. These methods include some important features, such as the solvent-free medium, the use of ammonium acetate as a green reagent, quantitative yields, short reaction times. Moreover, the experimental procedures are very easy to carry out. The enaminonitrile derivative (4a,b) were utilized for synthesis of substituted new pyrano[2,3-\(d\)]pyrazolo[3,4-\(b\)]pyridines and pyrazolo[4\(^\prime\),3\(^\prime\):5\(^\prime\),6\(^\prime\)]pyrido[3\(^\prime\),4\(^\prime\):5,6]pyrano[2,3-\(d\)]pyrimidine derivatives. All these compounds are addition to library of heterocyclic chemistry.
4.4. Experimental Section

Experiment No. 1


![Chemical Structure](image)

**Comp. No.**  | **Ar**           
----------------|------------------
**47a**         | p-Cl C₆H₄       
**47b**         | p-Br C₆H₄       

**General Procedure:** A solution of 5-aminopyrazole **45a** (2.697 g, 0.01 mol) or **45b** (3.141 g, 0.01 mol) and diethyl malonate (1.60 g, 0.01 mol) in toluene (30 mL) containing a catalytic amount of triethylamine was refluxed for 10-11 hrs. After completion of reaction (TLC check), the solvent was removed under reduced pressure to give a colorless solid. The crude solid was stirred in methanol (10 mL), collected, dried under high vacuum, and recrystallized from ethanol to give **47a** in 80 % and **47b** in 82 % yield.

**N-(3-(ethylperoxy)-prop-2-ynyloxy)-3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-5-amine (47a):** Yield 3.070 g (80%). mp: 124-125°C. IR (KBr): 3350, 3015, 1731, 1676, 1622 cm⁻¹.¹ ¹H NMR (300 MHz, CDCl₃): δ, 1.26 (t, 3H, J = 6.8 Hz, CH₃), 3.46 (s, 2H, CH₂), 4.15 (q, 2H, J = 6.8 Hz, OCH₂), 7.07 (s, 1H, Ar-H), 7.30-7.51 (m, 5H, Ar-H), 7.53 (d, J = 8.4 Hz, 2H, Ar-H), 7.75 (d, J = 8.4 Hz, 2H, Ar-H), 9.88 (s, 1H, NH) ppm. MS: m/z (%) 383 [M⁺, 100], 385 [M+2, 33]. Anal. Calcd. for C₂₀H₁₈N₃ClO₃ (383.83): C, 62.58; H, 4.73; N, 10.95. Found: C, 62.34; H, 4.48; N, 11.15.

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N-(3-((ethylperoxy)-prop-2-ynyloxy))-3-(4-bromophenyl)-1-phenyl-1H-pyrazol-5-amine (47b): Yield 3.511 g (82%). mp: 123-124°C. IR (KBr): 3350, 3015, 1731, 1676, 1622 cm\(^{-1}\). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\,1.25\) (t, 3H, \(J = 6.8\) Hz , CH\(_3\)), 3.44 (s, 2H, CH\(_2\)), 4.17 (q, 2H, \(J = 6.8\) Hz, OCH\(_2\)), 7.08 (s, 1H, Ar-H), 7.30-7.52 (m, 5H, Ar-H), 7.54 (d, \(J = 8.4\) Hz, 2H, Ar-H), 7.74 (d, \(J = 8.4\) Hz, 2H, Ar-H), 9.89 (s, 1H, NH) ppm. MS: \(m/z\) (%) 428 [M\(^+\), 100], 430[M+2, 98]. Anal. Calcd. for C\(_{20}\)H\(_{18}\)N\(_3\)BrO\(_3\) (428.28): C, 56.09; H, 4.24; N, 9.81. Found: C, 56.31; H, 4.03; N, 9.58.

Experiment No. 2

Synthesis of 3-Aryl-4-hydroxy-1-phenyl-1H-pyrazolo[3,4-b]pyridine-6(7H)-one 48 from 47.

\[
\begin{align*}
\text{EtO}_2\text{CCH}_2\text{CONH} & \quad \text{PhOPh} \\
\text{reflux 1 h.} & \\
47\text{a, b} & \quad 48\text{a, b}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>Ar</th>
</tr>
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<tr>
<td>48a</td>
<td>(p)-Cl C(_6)H(_4)</td>
</tr>
<tr>
<td>48b</td>
<td>(p)-Br C(_6)H(_4)</td>
</tr>
</tbody>
</table>

General Procedure: A solution of 47a (3.838 g, 0.01 mol) or 47b (4.282 g, 0.01 mol) and diphenyl ether (35 mL) was refluxed for 1 h. After completion of reaction (TLC check), the reaction mixture was allowed to cool at room temperature. The separated solid was stirred in diethylether (30 mL) for 1 h, collected, washed with diethylether, dried and recrystallized from ethanol:DMF (9:1) to give 48 in 86% yield.

3-(4-chlorophenyl)-4-hydroxy-1-phenyl-1H-pyrazolo[3,4-b]pyridine-6(7H)-one (48a):
Yield 2.898 g (86%). mp: 234-235°C. IR (KBr): 3419, 3312, 1681, 1619 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆): 6.04 (s, 1H, Ar-H), 7.30-7.56 (m, 5H, Ar-H), 8.09 (d, J = 8.6 Hz, 2H, Ar-H), 8.26 (d, J = 8.6 Hz, 2H, Ar-H), 11.09 (s, 1H, NH), 11.69 (s, 1H, OH). ¹³C NMR (75 MHz, DMSO-d₆): 90.1, 101.5, 121.2 (2 C’s), 125.7, 128.3 (2 C’s), 128.9 (2 C’s), 130.4 (2C’s), 131.7, 133.0, 139.2, 143.3, 152.2, 161.4, 165.5 ppm. MS: m/z (%) 337 [M⁺, 100], 339 [M+2, 33]. Anal. Calcd. for C₁₈H₁₂N₃ClO₂ (337.76): C, 64.01; H, 3.58; N, 12.44. Found: C, 64.27; H, 3.77; N, 12.30.

3-(4-bromophenyl)-4-hydroxy-1-phenyl-1H-pyrazolo[3,4-b]pyridine-6(7H)-one (48b):

Yield 3.286 g (86%). mp: 238-239°C. IR (KBr): 3419, 3312, 1681, 1619 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆): 6.06 (s, 1H, Ar-H), 7.29-7.54 (m, 5H, Ar-H), 8.07 (d, J = 8.4 Hz, 2H, Ar-H), 8.25 (d, J = 8.4 Hz, 2H, Ar-H), 11.08 (s, 1H, NH), 11.67 (s, 1H, OH). MS: m/z (%) 382 [M⁺, 100], 384 [M+2, 98]. Anal. Calcd. for C₁₈H₁₂N₃BrO₂ (382.21): C, 56.56; H, 3.16; N, 10.99. Found: C, 56.33; H, 3.38; N, 10.74.

Experiment No. 3

Syntesis of 3-Aryl-4-hydroxy-1-phenyl-1H-pyrazolo[3,4-b]pyridine-6(7H)-one (48) from 45.
**General Procedure:** A solution of 5-aminopyrazole 45a (2.697 g, 0.01 mol) or 45b (3.141 g, 0.01 mol) and diethyl malonate (1.60 g, 0.01 mol) in diphenylether (25 mL) was refluxed for 1 h. After completion of reaction (TLC check), the reaction mixture was allowed to cool at room temperature. The separated solid was stirred in diethylether (30 mL) for 1 h, collected, washed with diethylether, dried and recrystallized from ethanol: DMF (9:1) to afford 48 in 84-86% yield.

**3-(4-chlorophenyl)-4-hydroxy-1-phenyl-1H-pyrazolo[3,4-b]pyridine-6(7H)-one (48a):**
Yield 2.830 g (84%). mp: 234-235°C. IR (KBr): 3419, 3312, 1681, 1619 cm\(^{-1}\).\(^{1}\)H NMR (300 MHz, DMSO-\(d_6\)): 6.04 (s, 1H, Ar-H), 7.30-7.56 (m, 5H, Ar-H), 8.09 (d, \(J = 8.6\) Hz, 2H, Ar-H), 8.26 (d, \(J = 8.6\) Hz, 2H, Ar-H), 11.09 (s, 1H, NH), 11.69 (s, 1H, OH). \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)): 90.1, 101.5, 121.2 (2 C’s), 125.7, 128.3 (2 C’s), 128.9 (2 C’s), 130.4 (2 C’s), 131.7, 133.0, 139.2, 143.3, 152.2, 161.4, 165.5 ppm. MS: \(m/z\) (%): 337 [M\(^+\), 100], 339 [M+2, 33]. Anal. Calcd. for C\(_{18}\)H\(_{12}\)N\(_3\)ClO\(_2\): C, 64.01; H, 3.58; N, 12.44. Found: C, 64.27; H, 3.77; N, 12.30.

**3-(4-bromophenyl)-4-hydroxy-1-phenyl-1H-pyrazolo[3,4-b]pyridine-6(7H)-one (48b):**
Yield 2.903 g (86%). mp: 238-239°C. IR (KBr): 3419, 3312, 1681, 1619 cm\(^{-1}\).\(^{1}\)H NMR (300 MHz, DMSO-\(d_6\)): 6.06 (s, 1H, Ar-H), 7.29-7.54 (m, 5H, Ar-H), 8.07 (d, \(J = 8.4\) Hz, 2H, Ar-H), 8.25 (d, \(J = 8.4\) Hz, 2H, Ar-H), 11.08 (s, 1H, NH), 11.67 (s, 1H, OH). MS: \(m/z\) (%): 382 [M\(^+\), 100], 384 [M+2, 98]. Anal. Calcd. for C\(_{18}\)H\(_{12}\)N\(_3\)BrO\(_2\): C, 56.56; H, 3.16; N, 10.99. Found: C, 56.33; H, 3.38; N, 10.74.
Experiment No. 4

Synthesis of 2-amino-4,9-Aryl-5-oxo-7-phenyl-4,5,6,7-tetrahydropyano[2,3-d]pyrazolo[3,4-b]pyridine (50a-f).

General Procedure: A mixture of 4-hydroxypyrazolopyridine 48a (3.377 g, 0.01 mol) or 48b (3.822 g, 0.01 mol) and the 2-(4-chlorobenzylidene)malononitrile 49a (1.88 g, 0.01 mol) or (E)-ethyl 3-(4-chlorophenyl)-2-cyanoacrylate 49b (2.35 g, 0.01 mol) or (E)-3-(4-chlorophenyl)-2-cyanoacrylamide 49c (2.06 g, 0.01 mol) in ammonium acetate (7.70 g, 0.10 mol) was heated at 120°C for 1-1.5 hrs. under a short Vigreux column attached to the flask. After completion of reaction (TLC check), the reaction mixture was cooled to room temperature and slowly added to cold water (50 mL) to dissolve excess of ammonium acetate and the precipitated product was collected, washed with water, dried and recrystallized from ethanol:DMF (9:1) to give 50 in 74-82% yield.
2-amino-4,9-bis(4-chlorophenyl)-5-oxo-7-phenyl-4,5,6,7-tetrahydropyrano[2,3-d]-pyrazolo[3,4-b]pyridine-3-carbonitrile (50a). Yield 4.263 g (81%). mp: 241-242°C. IR (KBr): 3410, 3320, 3241, 2212, 1678, 1632 cm\(^{-1}\). \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): 4.55 (s, 1H, pyran-H), 6.80 (s, 2H, NH\(_2\)), 7.20 (d, \(J = 8.4\) Hz, 2H, Ar-H), 7.31-7.69 (m, 5H, Ar-H), 7.62 (d, \(J = 8.4\) Hz, 2H, Ar-H), 7.96 (d, \(J = 8.6\) Hz, 2H, Ar-H), 8.16 (d, \(J = 8.6\) Hz, 2H, Ar-H), 12.02 (s, 1H, NH). \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)): 41.2, 61.6, 90.2, 104.1, 117.3, 120.2 (2 C’s), 125.7, 128.3 (2 C’s), 128.8 (2 C’s), 128.9 (2 C’s), 130.4 (2 C’s), 130.5 (2 C’s), 131.3, 131.7, 133.0, 139.2, 140.3, 143.3, 152.2, 158.2, 162.5, 164.4. MS: \(m/z\) (%) 525 [M\(^+\), 100], 527 [M+2, 65], 529 [M+4, 11]. Anal. Calcd. for C\(_{28}\)H\(_{17}\)N\(_5\)Cl\(_2\)O\(_2\) (526.37): C, 63.89; H, 3.26; N, 13.30. Found: C, 63.75; H, 3.54; N, 13.22.

2-amino-4-(4-chlorophenyl)-9-(4-bromophenyl)-5-oxo-7-phenyl-4,5,6,7-tetrahydropyrano[2,3-d] pyrazolo[3,4-b]pyridine-3-carbonitrile (50b): Yield 4.680 g (82%). mp: 244-245°C. IR (KBr): 3410, 3320, 3241, 2212, 1678, 1632 cm\(^{-1}\). \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): 4.54 (s, 1H, pyran-H), 6.80 (s, NH\(_2\)), 7.21 (d, \(J = 8.4\) Hz, 2H, Ar-H), 7.30-7.69 (m, 5H, Ar-H), 7.64 (d, \(J = 8.4\) Hz, 2H, Ar-H), 7.97 (d, \(J = 8.6\) Hz, 2H, Ar-H), 8.16 (d, \(J = 8.6\) Hz, 2H, Ar-H), 12.01 (s, 1H, NH). MS: \(m/z\) (%) 570 [M\(^+\), 100], 572 [M+2, 82], 574 [M+4, 32]. Anal. Calcd. for C\(_{28}\)H\(_{17}\)N\(_5\)Cl\(_2\)BrO\(_2\) (570.82): C, 58.91; H, 3.00; N, 12.27. Found: C, 58.66; H, 2.88; N, 11.54.

Ethyl-2-amino-4,9-bis(4-chlorophenyl)-5-oxo-7-phenyl-4,5,6,7-tetrahydropyrano[2,3-d] pyrazolo[3,4-b]pyridine-3-carboxylaet (50c): Yield 4.300 g (75%). mp: 238-239°C. IR (KBr): 3435, 3387, 3259, 1732, 1681, 1630 cm\(^{-1}\). \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): 1.16 (t, 3H, \(J = 6.5\) Hz, CH\(_3\)), 4.10 (q, 2H, \(J = 6.5\) Hz, OCH\(_2\)), 4.97 (s, 1H, pyran-H), 7.22 (d, \(J = 8.4\) Hz, 2H, Ar-H), 7.31-7.69 (m, 5H, Ar-H), 7.63 (d, \(J = 8.4\) Hz, 2H, Ar-H), 8.03 (d, \(J =
8.6 Hz, 2H, Ar-H), 8.12 (d, J = 8.6 Hz, 2H, Ar-H), 12.02 (s, 1H, NH) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$): 14.2, 41.2, 61.6, 90.1, 104.0, 105.1, 120.2 (2 C’s), 125.7, 128.3 (2 C’s), 128.8 (2 C’s), 128.9 (2 C’s), 130.4 (2 C’s), 130.5 (2 C’s), 131.2, 131.7, 133.0, 139.2, 140.3, 143.3, 152.2, 158.2, 161.0, 162.4, 167.7 ppm. MS: $m/z$ (%) 572 [M$^+$, 100], 574 [M+2, 65], 576 [M+4, 11]. Anal. Calcd. for C$_{30}$H$_{22}$N$_4$Cl$_2$O$_4$ (573.43): C, 62.84; H, 3.87; N, 9.77. Found: C, 62.58; H, 3.66; N, 9.40.

**Ethyl-2-amino-4-(4-chlorophenyl)-9-(4-bromophenyl)-5-oxo-7-phenyl-4,5,6,7-tetrahydropyran[2,3-d]pyrazolo[3,4-b]pyridine-3-carboxylate (50d):** Yield 4.571 g (74%). mp: 237-238°C. IR (KBr): 3435, 3387, 3259, 1732, 1681, 1630 cm$^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$): 1.15 (t, 3H, J = 6.5 Hz, CH$_3$), 4.11 (q, 2H, J = 6.5 Hz, OCH$_2$), 4.97 (s, 1H, pyran-H), 7.24 (d, J = 8.4 Hz, 2H, Ar-H), 7.30-7.68 (m, 5H, Ar-H), 7.67 (d, J = 8.4 Hz, 2H, Ar-H), 8.06 (d, J = 8.6 Hz, 2H, Ar-H), 8.14 (d, J = 8.6 Hz, 2H, Ar-H), 12.01 (s, 1H, NH) ppm. MS: $m/z$ (%) 617 [M$^+$, 100], 619 [M+2, 80], 621 [M+4, 32]. Anal. Calcd. for C$_{30}$H$_{22}$N$_4$ClBrO$_4$ (617.88): C, 58.32; H, 3.59; N, 9.07. Found: C, 58.44; H, 3.87; N, 8.81.

**2-amino-4,9-bis(4-chlorophenyl)-5-oxo-7-phenyl-4,5,6,7-tetrahydropyran[2,3-d]pyrazolo[3,4-b]pyridine-3-carboxamide (50e):** Yield 4.191 g (77%). mp: 244-245°C. IR (KBr): 3465, 3378, 3352, 3268, 3247, 1683, 1676, 1618 cm$^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$): 4.53 (s, 1H, pyran-H), 6.80 (s, 2H, NH$_2$), 7.20 (d, J = 8.4 Hz, 2H, Ar-H), 7.30-7.69 (m, 5H, Ar-H), 7.63 (d, J = 8.4 Hz, 2H, Ar-H), 7.69 (s, 2H, NH$_2$), 7.97 (d, J = 8.6 Hz, 2H, Ar-H), 8.17 (d, J = 8.6 Hz, 2H, Ar-H), 12.01 (s, 1H, NH) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$): 41.1, 90.1, 104.6, 105.2, 120.2 (2 C’s), 125.7, 128.3 (2 C’s), 128.8 (2 C’s), 128.9 (2 C’s), 130.4 (2 C’s), 130.5 (2 C’s), 131.2, 131.7, 133.0, 139.2, 140.3, 143.3, 152.2, 158.2, 161.0, 161.7, 171.2 ppm. MS: $m/z$ (%) 543 [M$^+$, 100], 545 [M+2, 65], 547
2-amino-4-(4-chlorophenyl)-9-(4-bromophenyl)-5-oxo-7-phenyl-4,5,6,7-tetrahydro-
pyrano[2,3-d]pyrazolo[3,4-b]pyridine-3-carboxamide (50f): Yield 4.592 g (78%). mp: 241-242°C. IR (KBr): 3465, 3378, 3352, 3268, 3247, 1683, 1676, 1618 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆): 4.54 (s, 1H, pyran-H), 6.82 (s, 2H, NH₂), 7.22 (d, J = 8.4 Hz, 2H, Ar-H), 7.30-7.69 (m, 5H, Ar-H), 7.66 (d, J = 8.4 Hz, 2H, Ar-H), 7.69 (s, 2H, NH₂), 7.99 (d, J = 8.6 Hz, 2H, Ar-H), 8.16 (d, J = 8.6 Hz, 2H, Ar-H), 12.02 (s, 1H, NH) ppm. MS: m/z (%) 588 [M⁺, 100], 590 [M⁺+2, 82], 592 [M⁺+4, 32]. Anal. Calcd. for C₂₈H₁₉N₅ClBrO₃ (588.84): C, 57.11; H, 3.25; N, 11.89. Found: C, 57.33; H, 3.53; N, 12.17.

Experiment No. 5

Synthesis of 1,6-Aryl-3-phenyl-6,10-dihydropyrazolo[4''',3'''':5',6']pyrido[3',4':5,6]-
pyrano[2,3-d]pyrimidine-5,7(3H,4H)-dione (52).

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<td>p-Cl C₆H₄</td>
<td>p-Cl C₆H₄</td>
</tr>
<tr>
<td>52b</td>
<td>p-Br C₆H₄</td>
<td>p-Cl C₆H₄</td>
</tr>
</tbody>
</table>

General Procedure: A mixture of 50a (0.526 g, 0.001 mol) or 50b (0.570 g, 0.001 mol) and formic acid (20 mL) was refluxed for 6 hrs. After completion of reaction (TLC check), the reaction mixture was allowed to cool at room temperature. The separated
A colorless solid was collected by suction filtration and recrystallized from ethanol: DMF (9:1) to give 52 in 67-69% yield.

\[1,6\text{-bis(4-chlorophenyl)}-3\text{-phenyl-6,10-dihydropyrazolo[4''',3'':5',6']pyrido[3',4':5,6]}\text{-pyrano[2,3-d]pyrimidine-5,7(3H,4H)-dione (52a): Yield 0.382 g (69%). mp: 288-289^\circ C.}\]

IR (KBr): 3468, 3368, 1677, 1669, 1630 cm\(^{-1}\).\(^1\)H NMR (300 MHz, DMSO-\(d_6\)): 4.55 (s, 1H, pyran-H), 5.10 (s, 1H, pyrimidine-H), 7.20 -8.20 (m, 13H, Ar-H), 8.51 (s, 1H, pyrimidine-NH), 12.02 (s, 1H, pyridine-NH) ppm.\(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)): 41.3, 90.1, 91.8, 105.2, 120.2 (2 C’s), 125.7, 128.3 (2 C’s), 128.8 (2 C’s), 128.9 (2 C’s), 130.4 (2 C’s), 130.5 (2 C’s), 131.2, 131.7, 133.0, 139.2, 140.3, 143.3, 150.2, 152.2, 158.2, 161.1, 169.4, 176.9 ppm. MS: \(m/z\) (%) 553 [M\(^+\), 100], 555 [M+2, 65], 557 [M+4, 11].


\[1\text{-}(4\text{-chlorophenyl)}-6\text{-}(4\text{-bromophenyl)}-3\text{-phenyl-6,10-dihydropyrazolo[4''',3'':5',6']pyrano[2,3-d]pyrimidine-5,7(3H,4H)-dione (52b): Yield 0.401 g (67%). mp: 286-287^\circ C. IR (KBr): 3468, 3368, 1677, 1669, 1630 cm\(^{-1}\).\(^1\)H NMR (300 MHz, DMSO-\(d_6\)): 4.55 (s, 1H, pyran-H), 5.10 (s, 1H, pyrimidine-H), 7.20-8.20 (m, 13H, Ar-H), 8.46 (s, 1H, pyrimidine-NH), 12.02 (s, 1H, pyridine-NH) ppm. MS: \(m/z\) (%) 598 [M\(^+\), 100], 600 [M+2, 65], 602 [M+4, 32]. Anal. Calcd. for C\(_{29}\)H\(_{17}\)N\(_5\)Cl- BrO\(_3\): C, 58.16; H, 2.86; N, 11.69. Found: C, 58.39; H, 2.69; N, 11.48.
Experiment No. 6


**General Procedure:** Compound 50a (0.526 g, 0.001 mol) or 50b (0.570 g, 0.001 mol) was added to a mixture of formamide (10 mL) and dimethylformamide (15 mL). The reaction mixture was refluxed for 10-11 hrs. After completion of reaction (TLC check), the reaction mixture was allowed to cool at room temperature. The separated colorless solid was collected and recrystallized from ethanol:DMF (9:1) to afford 54 in 64-68 % yield.

7-amino-1,6-bis(4-chlorophenyl)-4-methyl-3-phenyl-4,6-dihydropyrazolo[4”,3”:5’,6’]-pyrido[3’,4’:5,6]pyrano[2,3-d]pyrimidine-5(3H)-one (54a): Yield 0.348 g (63%). mp: 287-288°C. IR (KBr): 3412, 3328, 1678, 1622 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆): 4.67 (s, 1H, pyran-H), 6.20 (s, 1H, pyrimidine-H), 7.29-8.26 (m, 13H, Ar-H), 8.91 (s, 2H, NH₂), 12.01 (s, 1H, NH) ppm. ¹³C NMR (75 MHz, DMSO-d₆): 41.2, 90.1, 106.8, 112.2, 120.2 (2 C’s), 125.7, 128.3 (2 C’s), 128.8 (2 C’s), 128.9 (2 C’s), 130.4 (2 C’s), 130.5 (2 C’s), 131.2, 131.7, 133.0, 139.3, 140.3, 143.3, 145.8, 152.1, 158.3, 161.0, 162.1, 174.4.

<table>
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<th>Comp. No.</th>
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<th>Ar’</th>
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<td>54a</td>
<td>p-Cl C₆H₄</td>
<td>p-Cl C₆H₄</td>
</tr>
<tr>
<td>54b</td>
<td>p-Br C₆H₄</td>
<td>p-Cl C₆H₄</td>
</tr>
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</table>
7-amino-1-(4-chlorophenyl)-6-(4-bromophenyl)-4-methyl-3-phenyl-4,6-dihydro-pyrazolo[4’’,3”:5’,6’]pyrido[3’,4:5,6]pyrano[2,3-d]pyrimidine-5(3H)-one (54b): Yield 4.065 g (68%). mp: 284-285°C. IR (KBr): 3412, 3328, 1678, 1622 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆): 4.66 (s, 1H, pyran-H), 6.24 (s, 1H, pyrimidine-H), 7.28 - 8.27 (m, 13H, Ar-H), 8.94 (s, 2H, NH₂), 12.01 (s, 1H, NH) ppm. MS: m/z (%) 597 [M⁺, 100], 599 [M+2, 78], 602 [M+4, 32]. Anal. Calcd. for C₂₉H₁₈N₆ClBrO₂ (597.85): C, 58.26; H, 3.03; N, 14.06. Found: C, 58.39; H, 3.30; N, 14.28.

Experiment No. 7


<table>
<thead>
<tr>
<th>Comp. No.</th>
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<td>p-Cl C₆H₄</td>
<td>p-Cl C₆H₄</td>
</tr>
<tr>
<td>56b</td>
<td>p-Br C₆H₄</td>
<td>p-Cl C₆H₄</td>
</tr>
</tbody>
</table>

General Procedure: A mixture of 50a (0.526 g, 0.001 mol) or 50b (0.570 g, 0.001 mol) and triethyl orthoformate (0.148 g, 0.001 mol) in acetic anhydride (25 mL) was refluxed for 2.5-3 hrs. (TLC check). The product was precipitated during reflux was collected after cooling. It was recrystallized from ethanol:DMF (9:1) to afford 56.
(E)-4,9-bis(4-chlorophenyl)-3-cyano-2-((ethoxymethylene)amino)-7-phenyl-4,7-dihydropyrano[2,3-d]pyrazolo[3,4-b]pyridin-5-yl-acetate (56a): Yield 0.474 g (76%). mp: 255-256°C. IR (KBr): 3012, 2971, 2217,1715,1621 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆): 1.31 (t, 3H, J = 7.5 Hz, CH₃), 2.20 (s, 3H, -CH₃), 4.29 (q, 2H, J = 7.5 Hz, OCH₂), 5.01 (s, 1H, pyran-H), 7.39-7.47 (m, 5H, Ar-H), 7.58 (d, J = 8.4 Hz, 2H, Ar-H), 7.63 (d, J = 8.4 Hz, 2H, Ar-H), 8.04 (s, 1H), 8.06 (d, J = 8.6 Hz, 2H, Ar-H), 8.11 (d,J = 8.6 Hz, 2H, Ar-H) ppm. ¹³C NMR (75 MHz, DMSO-d₆): 17.1, 20.8, 41.2, 63.3, 77.9, 81.1, 90.1, 105.0, 117.3, 120.2 (2 C’s), 125.7, 128.3 (2 C’s), 128.8 (2 C’s), 128.9 (2 C’s), 130.4 (2 C’s), 130.5 (2 C’s), 131.2, 131.6, 133.0, 139.3, 140.3, 143.4, 152.2, 155.6, 158.3, 169.8, 170.3 ppm. MS: m/z (%) 623 [M⁺, 100], 625 [M+2, 65], 627 [M+4, 11]. Anal. Calcd. for C₃₃H₂₃N₅Cl₂O₄ (624.47): C, 63.47; H, 3.71; N, 11.21. Found: C, 63.69; H, 3.53; N, 12.47.

(E)-4-(4-chlorophenyl)-9-(4-bromophenyl)-3-cyano-2-((ethoxymethylene)-amino)-7-phenyl-4,7-dihydropyrano[2,3-d]pyrazolo[3,4-b]pyridin-5-yl-acetate (56b): Yield 0.488 g (73%). mp: 258-259°C. IR (KBr): 3012, 2971, 2217,1715,1621 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆): 1.30 (t, 3H, J = 6.8 Hz, CH₃), 2.18 (s, 3H, -CH₃),4.30 (q, 2H, J = 6.8 Hz, OCH₂), 4.91 (s, 1H, pyran-H), 7.39-7.49 (m, 5H, Ar-H), 7.56 (d, J = 8.4 Hz, 2H, Ar-H), 7.64 (d, J = 8.4 Hz, 2H, Ar-H), 8.06 (s, 1H), 8.08 (d, J = 8.6 Hz, 2H, Ar-H), 8.12 (d, J = 8.6 Hz, 2H, Ar-H) ppm. MS: m/z (%) 668 [M⁺, 100], 670 [M+2, 68], 672 [M+4, 32]. Anal. Calcd. for C₃₃H₂₃N₅ClBrO₄ (668.92): C, 59.25; H, 3.47; N, 10.47. Found: C, 59.53; H, 3.19; N, 11.24.
Experiment No. 8

Synthesis of (E)-N’-4,9-Aryl-3-cyano-6-methyl-5-oxo-7-phenyl-4,5,6,7-tetrahydro-pyranono[2,3-d]pyrazolo[3,4-b]pyridin-2-yl)-N,N-dimethylformimidamide (58)

\[
\begin{align*}
\text{Comp. No.} & & \text{Ar} & & \text{Ar’} \\
58a & & p-\text{Cl C}_6\text{H}_4 & & p-\text{Cl C}_6\text{H}_4 \\
58b & & p-\text{Br C}_6\text{H}_4 & & p-\text{Cl C}_6\text{H}_4 \\
\end{align*}
\]

General Procedure: A mixture of 50a (0.526 g, 0.001 mol) or 50b (0.570 g, 0.001 mol) and DMF-DMA (0.119 g, 0.001 mol) in 1,4-dioxane (25 mL) was refluxed for 2 hrs. After completion of reaction (TLC check), the reaction mixture was allowed to cool at room temperature. The separated yellow solid was collected and recrystallized from ethanol:DMF (9:1) to give 58.

(E)-N’-4,9-bis(4-chlorophenyl)-3-cyano-6-methyl-5-oxo-7-phenyl-4,5,6,7-tetrahydro-pyranono[2,3-d]pyrazolo[3,4-b]pyridin-2-yl)-N,N-dimethylformimidamide (58a): Yield 0.422 g (71%). mp: 234-235°C. IR (KBr): 3011, 2232, 1377, 1617 cm\(^{-1}\). \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): 3.02 (s, 6H, -2CH\(_3\)), 3.82 (s, 3H, N-CH\(_3\)), 4.72 (s, 1H, pyran-H), 7.31-8.01 (m, 10H, Ar-H + olefinic-H), 8.05 (d, \(J = 8.6\) Hz, 2H, Ar-H), 8.22 (d, \(J = 8.6\) Hz, 2H, Ar-H) ppm. \(^13\)C NMR (75 MHz, DMSO-\(d_6\)): 30.8, 40.0 (2 C’s ), 41.2, 77.9, 90.2, 105.1, 117.3, 120.2 (2 C’s), 125.7, 128.3 (2 C’s), 128.8 (2 C’s), 128.9 (2 C’s), 130.4 (2 C’s), 130.5 (2 C’s), 131.2, 131.7, 133.0, 139.3, 140.3, 143.3, 152.2, 156.2, 157.3, 162.5,
170.3 ppm. MS: \textit{m/z} (\%) 594 [M\(^+\), 100], 596 [M+2, 65], 598 [M+4, 11]. Anal. Calcd. for C\(_{32}\)H\(_{24}\)N\(_6\)Cl\(_2\)O\(_2\) (595.48): C, 64.54; H, 4.06; N, 14.11. Found: C, 64.32; H, 4.27; N, 14.39.

\((E)-N’-4-(4-chlorophenyl)-9-(4-bromophenyl)-3-cyano-6-methyl-5-oxo-7-phenyl-4,5,6,7-tetrahydro-pyrazolo[2,3-d]pyrazolo[3,4-b]pyridin-2-yl)-N,N-dimethylformimidamide\) (58b): Yield 0.441 g (69\%). mp: 236-237\(^\circ\)C. IR (KBr): 3011, 2232, 1377, 1617 cm\(^{-1}\). \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): 3.04 (s, 6H, -2CH\(_3\)), 3.81 (s, 3H, N-CH\(_3\)), 4.74 (s, 1H, pyran-H), 7.31-8.06 (m, 10H, Ar-H + olefinic-H), 8.10 (d, J = 8.6 Hz, 2H, Ar-H), 8.24 (d, J = 8.6 Hz, 2H, Ar-H) ppm. MS: \textit{m/z} (\%) 639 [M\(^+\), 100], 641 [M+2, 90], 643 [M+4, 32]. Anal. Calcd. for C\(_{32}\)H\(_{24}\)N\(_6\)Cl\(_2\)O\(_2\) (639.93): C, 60.06; H, 3.78; N, 13.13. Found: C, 59.87; H, 3.97; N, 13.29.

Experiment No. 9

Synthesis of 8-amino-1,6-Aryl-7-imino-4-methyl-3-phenyl-4,6-dihydropyrazolo[4’’,3’’:5’,6’]pyrido[3’,4’:5,6]pyran[2,3-d]pyrimidine-5(3H)-one (60) from 45.

\[ \text{Comp. No.} \quad \text{Ar} \quad \text{Ar’} \]
\[ \begin{array}{ccc}
60a & p-\text{Cl C}_6\text{H}_4 & p-\text{Cl C}_6\text{H}_4 \\
60b & p-\text{Br C}_6\text{H}_4 & p-\text{Cl C}_6\text{H}_4 \\
\end{array} \]

\textbf{General Procedure}: A mixture of 56a (0.624 g, 0.001 mol) or 56b (0.668 g, 0.001 mol) and hydrazine hydrate (0.050 g, 0.001 mol) in DMF (25 mL) was refluxed for 5 hrs. After
Completion of reaction (TLC check), the reaction mixture was allowed to cool at room temperature. The separated colorless solid was collected by suction filtration and recrystallized from ethanol:DMF (9:1) to give 60a,b.

8-amino-1,6-bis(4-chlorophenyl)-7-imino-4-methyl-3-phenyl-4,6-dihydropyrazolo[4″,3″:5′,6′]pyrido[3′,4′:5,6]pyrano[2,3-d]pyrimidine-5(3H)-one (60a): Yield 0.415 g (68%). mp: 269-270°C. IR (KBr): 3381, 3306, 3205, 1647, 1616, 1210 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆): 2.19 (s, 3H, -CH₃), 4.89 (s, 2H, -NH₂), 5.37 (s, 1H, pyran-H), 7.19-7.66 (m, 10H, Ar-H), 8.03 (d, J = 8.6 Hz, 2H, Ar-H), 8.12 (d, J = 8.6 Hz, 2H, Ar-H), 9.23 (s, 1H, -NH) ppm. ¹³C NMR (300 MHz, DMSO-d₆): 18.6, 30.8, 41.2, 90.1, 93.0, 105.3, 120.2 (2 C’s), 125.7, 128.3 (2 C’s), 128.8 (2 C’s), 128.9 (2 C’s), 130.4 (2 C’s), 130.5 (2 C’s), 131.2, 131.6, 133.2, 139.2, 140.3, 143.2, 152.2, 156.0, 156.2, 158.3, 161.0, 164.1 ppm. MS: m/z (%) 609 [M⁺, 100], 611 [M+2, 66], 613 [M+4, 21]. Anal. Calcd. for C₃₁H₂₁N₇Cl₂O₃: C, 60.99; H, 3.47; N, 16.06. Found: C, 61.24; H, 3.60; N, 16.28.

8-amino-1-(4-bromophenyl)-6-(4-chlorophenyl)-7-imino-4-methyl-3-phenyl-4,6-dihydropyrazolo[4″,3″:5′,6′]pyrido[3′,4′:5,6]pyrano[2,3-d]pyrimidine-5(3H)-one (60b): Yield 0.432 g (66%). mp: 267-268°C. IR (KBr): 3380, 3308, 3207, 1649, 1618, 1215 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆): 2.18 (s, 3H, -CH₃), 4.86 (s, 2H, -NH₂), 5.35 (s, 1H, pyran-H), 7.20-7.67 (m, 10H, Ar-H), 8.02 (d, J = 8.6 Hz, 2H, Ar-H), 8.13 (d, J = 8.6 Hz, 2H, Ar-H), 9.22 (s, 1H, -NH) ppm. MS: m/z (%) 655 [M⁺, 100], 655 [M+2, 92], 657 [M+4, 18]. Anal. Calcd. for C₃₁H₂₁N₇ClBrO₃: C, 56.85; H, 3.23; N, 14.97. Found: C, 57.11; H, 3.46; N, 14.61.
REFERENCES


