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Selective synthesis of pyrazolo[3,4-*d*]pyrimidine, *N*-(1*H*-pyrazol-5-yl) formamide, or N-(1H-pyrazol-5-yl)formamidine derivatives from N-1-substituted-5-aminopyrazoles with new Vilsmeier-type reagents

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1. Introduction

Vilsmeier-type reaction has evolved into a powerful synthetic tool for building up many heterocyclic compounds.^{1–5} The classical Vilsmeier reagent involves the electrophilic substitution of an activated aromatic or heterocyclic compound with a halomethyleniminium salt, which results from the reaction between an acid agent (e.g., POCl₃, PBr₃, (COCl)₂ or SOCl₂) and an amide solvent, usually DMF.⁶ Thus, Vilsmeier reaction is usually called as Vilsmeier formylation.⁶ Due to its wide application, many of modified Vilsmeier reagents⁷ were enthusiastically developed to explore the new skeleton, extend the construction, or improve the vields.

Halomethyleniminium salt (Vilsmeier agent) was not only a formylating agent,⁶ but also as an activating reagent for carboxylic acids to give esters,⁸ amides,⁹ and acid chlorides,¹⁰ and for alcohols to give alkyl chlorides,¹¹ esters,¹² alkyl aryl sulfides,¹³ and imides.¹⁴ Herein, we report the investigation of the modified halomethyleniminium salts, which were prepared by means of formamide or N-methylformamide in the presence of phosphorous oxychloride (POCl₃). The reactivity via the modified halomethyleniminium salts with various N-1-substituted-aminopyrazoles, including N-1-phenyl-5-aminopyrazoles, N-1-(2-pyridinyl)-5-aminopyrazoles, and N-1-(2-quinolinyl)-5-aminopyrazoles were investigated. Three new Vilsmeier-type reactions to synthesize pyrazolo[3,4-d]pyrimidine, N-(1H-pyrazol-5-yl)formamide, and N-(1H-pyrazol-5-yl)formamidine derivatives were eventually developed. The plausible reactive pathways were also provided to explain our experimental result.

2. Result and discussion

Functionalized N-arylpyrazole moiety has been shown to exhibit antihyperglycemic, analgesic, anti-inflammatory, sedative, and hypnotic activities.^{15–17} More specifically, 5-alkyl/arylamino substituted pyrazoles have been exploited in the design of pharmaceuticals and agrochemical agents exhibiting a range of biological activities.^{16,18–20} In the previous published literature, the electrophilic *N*-1-arvl-5-aminopyrazoles **1** were treated with classical Vilsmeier reagent (DMF+POCl₃) under the microwave-



ABSTRACT

Various halomethyleniminium salts as novel Vilsmeier agents were synthesized from formamide or *N*-methylformamide with POCl₃. Treatment of *N*-1-substituted-aminopyrazoles including *N*-1-phenyl-5aminopyrazoles. N-1-(2-pyridinyl)-5-aminopyrazoles, and N-1-(2-quinolinyl)-5-aminopyrazoles withthese agents gave the corresponding pyrazolo[3,4-d]pyrimidine, N-(1H-pyrazol-5-yl)formamide, or N-(1Hpyrazol-5-yl)formamidine. The reaction was different from the traditional Vilsmeier-type reaction and the plausible reactive pathways were proposed for the unexpected result.

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assisted^{21,22} or normal heating reaction.^{23,24} The Vilsmeier formylated amidines **2** were formed as the major products (see Scheme 1), which was introduced with a formyl group at the C-4 position on pyrazoyl ring with *N*-(1*H*-pyrazol-5-yl)formamidines **3** as the minor product.^{6c,21,25} δ 8.48 ppm for $-C^{1}H=0$ in ¹H NMR. In ¹³C NMR spectrum, compound **6e** possessed characterization absorptions at δ 157.1 ppm for carbonyl carbon $-^{13}CH=0$. The IR absorptions of **6e** showed peaks at 1697 cm⁻¹ for stretching of the -NHCH=0 amide group. The ORTEP drawing of compound **6e** was shown in Fig. 1. Following our



Scheme 1.

By employing the newly developed Vilsmeier reagent, which was synthesized by using *N*-methylformamide in the presence of phosphorous oxychloride POCl₃, toward *N*-1-phenyl-5-aminopyrazoles **1a**–**e** at 50–60 °C with 100 W of microwave energy within 20–30 min, the unexpected *N*-(1*H*-pyrazol-5-yl)formamidine products **3a**–**e** without forming a formyl group were produced in 76–97% yields (see Scheme 1 and Table 1).

Table 1

Reaction of the N-1-phenyl-5-aminopyrazoles with N-methylformamide in the presence of POCl_3

N-1-phenyl-5- aminopyrazoles (1a–e)		Products N-(1H-Pyrazol-5-yl) formamidines (3a–e)		
1a	t-Bu	3a	76	
1b	Ph	3b	97	
1c	p-MePh	3c	88	
1d	p-ClPh	3d	91	
1e	p-OMePh	3e	94	

For further investigation of the substituent effect, we applied this newly developed Vilsmeier reagent (*N*-methylformamide+POCl₃) to *N*-1-(2-pyridinyl)-5-aminopyrazoles **4a**–**e**, and *N*-1-(2-quinolinyl)-5-aminopyrazoles **5a**–**e**, which containing Me, *tert*-butyl, *p*-Me–Ph, *p*-Cl–Ph, or *p*-OMe–Ph groups at the C-3 position of the pyrazolic ring. The unexpected *N*-(1*H*-pyrazol-5-yl)formamides **6a**–**e** and **7a**–**e** were produced in 81–88% and 82–92% yields, respectively (see Scheme 1 and Table 2). All of the *N*-(1*H*-pyrazol-5-yl) formamide products **6a**–**e** and **7a**–**7e** were fully characterized by spectroscopic methods including single-crystal X-ray diffraction study (ORTEP). For example, compound **6e** presented a peak at

Table 2

Reactions N-1-(2-pyridinyl)-5-aminopyrazoles **4a**–**e**, and N-1-(2-quinolinyl)-5-aminopyrazoles **5a**–**e** with N-methylformamide in the presence of POCl₃

Pyrazoles (4a – e and 5a – e)		Products N-(1H-Pyrazol-5-yl)formamides (6a–e and 7a–e)		
S.M.	N1-R ¹	C3-R ²	No.	Yield (%)
4a	2-Pyridinyl	t-Bu	6a	84
4b	2-Pyridinyl	Ph	6b	86
4c	2-Pyridinyl	p-MePh	6c	82
4d	2-Pyridinyl	p-ClPh	6d	88
4e	2-Pyridinyl	p-OMePh	6e	81
5a	2-Quinolinyl	t-Bu	7a	82
5b	2-Quinolinyl	Ph	7b	92
5c	2-Quinolinyl	p-MePh	7c	87
5d	2-Quinolinyl	p-ClPh	7d	91
5e	2-Quinolinyl	p-OMePh	7e	84



Fig. 1. The ORTEP diagram of *N*-(1-(2-pyridinyl)-3-(4-methoxyphenyl)-1*H*-pyrazol-5-yl)formamide **6e**.

experimental result, the yield of *N*-(1*H*-pyrazol-5-yl)formamide products seemed related to *N*-1 substituted 2-pyridinyl and 2-quinolinyl groups (see Scheme 1).

Furthermore, we proposed the plausible mechanism shown in Scheme 2, to account for the generation of N-(1H-pyrazol-5-yl)formamides **6a**—**e** and **7a**—**e**. Firstly, N-methylformamide was fast reacted with phosphorous oxychloride POCl₃ to form the reactive halomethyleniminium salts **8** (see Scheme 2).²⁶ Further, pyrazoles **6** were in situ reacted with the reactive iminium species **8** to generate the N-(1H-pyrazol-5-yl)formamidine intermediate **9** (see Scheme 2). After aqueous workup, nucleophile H₂O attacked toward intermediate **9** to form intermediate **10** and left methylamine. Finally, the active formimidic acid **11** formed and tautomerized to generate **6** or **7**. two singlet peaks at δ 9.02 ppm and 9.31 ppm for pyrimidine ring in ¹H NMR. In ¹³C NMR spectrum, compound **12b** possessed characterization absorptions at δ 155.0 ppm for pyrimidine carbon N=¹³CH-N=C, at δ 34.4 ppm for $-^{13}C(CH_3)_3$, and at 30.0 ppm for $-C(^{13}CH_3)_3$.

Furthermore, we extended this new condition toward 5-amino-1-(2-pyridinyl)-3-substituted pyrazoles **4**, 5-amino-1-(2-quinolinyl)-3-substituted pyrazoles **5**, and 1-methyl-1*H*-pyrazol-5-amine **6**, which contained the H, methyl, *tert*-butyl, Ph, *p*-Me–Ph, *p*-Cl–Ph, *p*-OMe–Ph groups at the C-3 position of pyrazolic ring. The corresponding heterocyclization products **13a–e**, **14a–e**, and **15** were obtained the in 87–96%, 87–96%, and 93% yields, respectively (see Scheme 3 and Table 3). All of pyrazolo[3,4-*d*]pyrimidines **13a–e**,



Consequently, we explored another modified halomethyleniminium salts by means of formamide in the presence of phosphorous oxychloride POCl₃ to various 5-amino-1-arylpyrazole substrates **1a**–**e** bearing various C3-substituted substituents, including Me, *t*-Bu, Ph, *p*-Me–Ph, *p*-Cl–Ph, and *p*-OMe–Ph (see Scheme 3). The experimental procedure involved the treatment of 5-amino-1-arylpyrazoles **1a**–**e** with 3.0 equiv of POCl₃ in formamide solution at 80–90 °C within 0.5–1 h. After work-up and purification by column chromatography on silica gel, we isolated the unexpected pyrazolo[3,4-*d*]pyrimidine products **12a**–**e** in good to excellent yields (>91%, see Scheme 4 and Table 3). All of pyrazolo[3,4-*d*]pyrimidines **12a**–**e** were fully characterized by spectroscopic methods. For example, compound **12b** presented **14a**–**e**, and **15** were also fully characterized by spectroscopic methods and consistent with the published data.²⁷

The plausible mechanism for the unexpected Vilsmeier heterocyclization reaction is shown in Scheme 4 to account for the design of our approach. Formamide was reacted with POCl₃ coupling agent to form the Vilsmeier reactive specie **16**.²⁶ In the model study, reaction of 5-aminopyrazole **1b** with **16** through the amidination reaction gave the azadiene **17** (see Scheme 4). In the presence of excess Vilsmeier agent, azadiene compound **17** was simultaneously reacted with secondary equivalent of oxonium specie **16** to carry out the electrophilic heteroaromatic substitution and give the corresponding imination intermediate **18**. After the hydrolysis reaction was completed and went through intermediate **19**, the

$$\begin{array}{c} \begin{array}{c} & & & \\ NH_2 \\ X-N \\ N \\ R \end{array} \end{array} \xrightarrow[R]{} R \end{array} \xrightarrow[R]{} R \\ \begin{array}{c} & & \\ H \\ \hline NH_2, POCI_3 \\ \hline X = Me, Ph, 2-pyridinyl, 2-quinolinyl \\ R = H, t-Bu, Ph, p-MePh, p-CIPh, \\ or p-OMePh \\ \end{array} \xrightarrow[R]{} \begin{array}{c} & \\ X-N \\ N \\ R \\ \hline 12a-12e. X = Ph \\ 13a-13e X = 2-pyridinyl \\ 13a-13e X = 2-pyridinyl \\ 14a-14e. X = 2-quinolinyl \\ 14a-14e. X = 2-quinolinyl \\ 15. X = Me, R = H \end{array}$$

Scheme 3.





Reactions *N*-1-phenyl-5-aminopyrazoles 1a-e, *N*-1-(2-pyridinyl)-5-aminopyrazoles 4a-e, *N*-1-(2-quinolinyl)-5-aminopyrazoles 5a-e, and 1-methyl-1*H*-pyrazol-5-amine **6** with formamide in the presence of POCl₃

Pyrazoles (1a–e, 4a–e, 5a–e and 6)			Products		
			Pyrazolo[3,4- <i>d</i>] pyrimidines (12a–e , 13a–e, 14a–e and 15)		
S.M.	N1-R ¹	C3-R ²	No.	Yield (%)	
1a	Ph	t-Bu	12a	91	
1b	Ph	Ph	12b	96	
1c	Ph	o-MePh	12c	93	
1d	Ph	p-ClPh	12d	91	
1e	Ph	p-OMePh	12e	94	
4a	2-Pyridinyl	t-Bu	13a	84	
4b	2-Pyridinyl	Ph	13b	86	
4c	2-Pyridinyl	o-MePh	13c	82	
4d	2-Pyridinyl	p-ClPh	13d	88	
4e	2-Pyridinyl	p-OMePh	13e	81	
5a	2-Quinolinyl	t-Bu	14a	82	
5b	2-Quinolinyl	Ph	14b	92	
5c	2-Quinolinyl	o-MePh	14c	87	
5d	2-Quinolinyl	p-ClPh	14d	91	
5e	2-Quinolinyl	p-OMePh	14e	84	
6	Me	Н	15	93	

intramolecular heterocyclization was accomplished to give the final product **12b**.

We are of interest to realize the reactivity of the various modified Vilsmeier reagents. Therefore, 5-amino-1-(2-quinolinyl)-3phenylpyrazole (**5a**) was selected as the model case to react with various Vilsmeier reagents, which were prepared by amides solvent such as *N-tert*-butylformamide, *N*,*N*-dimethylformamide (DMF), *N*,*N*-diethylformamide (DEF), *N*,*N*-diisopropylformamide, and piperidine-1-carbaldehyde, in the presence of phosphorous oxychloride POCl₃ under the microwave-assisted condition (see Scheme 5).

When 5-amino-1-(2-quinolinyl)-3-phenylpyrazole (**5a**) was treated toward *N*-*tert*-butylformamide, we found only *N*-(1*H*-pyr-azol-5-yl)formamide **7b** product was obtained in 89% yield (see Scheme 5 and Table 4). Furthermore, sterically hindered amides including *N*,*N*-dimethylformamide (DMF), *N*,*N*-diethylformamide (DEF), and 1-pyrrolidinecarboxaldehyde cyclic amide were used as reaction solvents, the *N*-(1*H*-pyrazol-5-yl)formamidines **20–22**



were obtained as main products in 91–95% yield and very small amount of N-(1H-pyrazol-5-yl)formamide **7b** (3.0%) was observed in DEF (see Table 4).

3. Conclusion

Various Vilsmeier agents were synthesized by using formamide or *N*-methylformamide in the presence of phosphorous oxychloride POCl₃. The *N*-1-substituted-aminopyrazoles, including *N*-1-phenyl-5-aminopyrazoles, *N*-1-(2-pyridinyl)-5-aminopyrazoles, and *N*-1-(2-quinolinyl)-5-aminopyrazoles, were reacted with the newly developed Vilsmeier agents to give the corresponding products such as pyrazolo[3,4-*d*]pyrimidine, *N*-(1*H*-pyrazol-5-yl) formamide, or *N*-(1*H*-pyrazol-5-yl)formamidine derivations. Our experimental result was different with the traditional Vilsmeiertype reaction. Furthermore, the plausible reactive mechanisms were proposed to describe the unexpected result.

4. Experimental section

4.1. General procedure

All chemicals were reagent grade and used as purchased. All reactions were carried out under nitrogen atmosphere and monitored by TLC analysis. Flash column chromatography was carried out on silica gel (230-400 mesh). Commercially available reagents were used without further purification unless otherwise noted. Dichloromethane, ethyl acetate, ethanol, hexanes, and methanol were purchased from Mallinckrodt Chemical Co. The following compounds were purchased from Acoros Chemical Co: benzoylacetonitrile, N,N-diethylformamide, formamide, N-methylformamide, pivaloylacetonitrile. 2-Hydrazinopyridine was purchased from Aldrich Chemical Co. N-tert-Butylformamide, 4-chlorobenzoylacetonitrile, 2-chloroquinoline, 4-methoxybenzoylacetonitrile, methanesulfonic acid, and *p*-toluovlacetonitrile were purchased from Alfa Chemical Co. Phosphorylchloride was purchased from FERAK Chemical Co. Purification by gravity column chromatography was carried out by use of Merck Reagents Silica Gel 60 (particle size 0.063-0.200 mm, 70-230 mesh ASTM). Infrared (IR) spectra were measured on a Bomem Michelson Series FT-IR spectrometer. The wavenumbers reported are referenced to the polystyrene 1601 cm⁻¹ absorption. Absorption intensities are recorded by the following abbreviations: s, strong; m, medium; w, weak. Proton NMR spectra were obtained on a Bruker (200 or 500 MHz) spectrometer by use of CDCl₃ as solvent. Carbon-13 NMR spectra were obtained on a Bruker (50 or 100 MHz) spectrometer by used of CDCl₃ as solvent. Carbon-13 chemical shifts are referenced to the center of the CDCl₃ triplet (δ 77.0 ppm). Multiplicities are recorded by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; J, coupling constant (Hz). Elemental analyses were carried out on a Heraeus CHN-O RAPID element analyzer.

Table 4 The results of 5-amino-1-(2-quinolinyl)-3-phenylpyrazole 5b with various modified Vilsmeier reagents

	Amide solvents HC(=O) NR ¹ R ²					
			Formamide (7b)		Formamidines (20–22)	
Substrates	$\overline{\mathbb{R}^1}$	R ²	Products	Yield (%)	Products	Yield (%)
5b	Н	Me	7b	90	a	a
5b	Н	t-Bu	7b	89	a	a
5b	Me	Me	7b	a	20	91
5b	Et	Et	7b	3	21	92
5b	Pyrrolidinyl		7b	a	22	95

^a Non-detectable.

4.2. Standard procedure for the preparation of N-(1H-pyr-azol-5-yl)formamidines 3a-e

The reliable procedure involved the treatment of *N*-1-phenyl-5aminopyrazoles (**1a**–**e**, 1.0 equiv) with catalytic amount of POCl₃ (~3 equiv) with *N*-methylformamide (2 mL) at 50–60 °C with 100 W of microwave energy within 20–30 min. When the reaction was completed, the reaction mixture was concentrated, added to saturate sodium bicarbonate (15 mL), and extracted with dichloromethane (15 mL). The organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residues were purified by column chromatography on silica gel to give the corresponding *N*-(1*H*-pyrazol-5-yl)formamidines **3a**–**e** in 76–97% yield.

4.2.1. N'-(1-Phenyl-3-tert-butyl-1H-pyrazol-5-yl)-N-methyl-methanimidamide (**3a**). Mp (purified by column chromatography on silica gel) 159–160 °C; ¹H NMR (CDCl₃, 200 MHz) δ 1.32 (s, 9H, CH₃×3), 2.92 (s, 3H, CH₃), 4.98 (s, 1H, NH), 5.71 (s, 1H, pyrazole-H), 7.15 (s, 1H, N=C-H), 7.35–7.38 (m, 2H, ArH), 7.82–7.84 (m, 3H, ArH); ¹³C NMR (50 MHz, CDCl₃) δ 27.8 (CH₃), 30.4 (CH₃×3), 32.4 (CH₃), 88.3, 123.4 (2×CH), 125.2, 128.3 (2×CH), 140.4, 151.2, 151.7, 161.8; IR (KBr) 3442 (m), 2900 (m), 1631 (m, -C=N), 1537 (m), 1500 (m), 1443 (m), 1410 (m), 1371 (m), 908 (m) cm⁻¹; EIMS *m/z* (relative intensity) 256 (95), 255 (M⁺, 15), 241 (100), 214 (40), 200 (37), 207 (9), 77 (15). Anal. Calcd for C₁₅H₂₀N₄; C: 70.28; H: 7.86; N: 21.86. Found: C: 70.31; H: 7.84; N: 21.85.

4.2.2. *N'*-(1,3-*Diphenyl*-1*H*-*pyrazol*-5-*yl*)-*N*-*methyl*-*methanimidamide* (**3b**). Mp (purified by column chromatography on silica gel) 157–158 °C; ¹H NMR (CDCl₃, 200 MHz) δ 2.90–2.92 (m, 3H, CH₃), 4.98 (s, 1H, NH), 6.14 (s, 1H, pyrazole-H), 7.19–7.43 (m, 6H, ArH), 7.83–7.94 (m, 4H, ArH), 7.87 (s, 1H, N=C-H); ¹³C NMR (50 MHz, CDCl₃) δ 27.7 (CH₃), 88.9, 123.5 (2×CH), 125.6 (2×CH), 125.8, 127.7, 128.4 (2×CH), 128.5 (2×CH), 133.9, 140.1, 150.9, 152.4, 152.6; IR (KBr) 3269 (m), 2360 (m), 1626 (m, -C=N), 1538 (m), 1501 (m), 1464 (m), 1423 (m), 1368 (m), 954 (m) cm⁻¹; EIMS *m/z* (relative intensity) 276 (100), 275 (M⁺, 5), 246 (12), 235 (28), 234 (27), 207 (9), 77 (19). Anal. Calcd for C₁₇H₁₆N₄; C: 73.89; H: 5.84; N: 20.27. Found: C: 73.93; H: 5.87; N: 20.23.

4.2.3. *N'*-(1-*Phenyl*-3-(4-*methylphenyl*)-1*H*-*pyrazol*-5-*yl*)-*N*-*methyl*-*methanimidamide* (**3c**). Mp (purified by column chromatography on silica gel) 182–183 °C; ¹H NMR (CDCl₃, 200 MHz) δ 2.21–2.36 (m, 3H, CH₃), 2.82–2.95 (m, 3H, CH₃), 4.93 (s, 1H, NH), 6.14 (s, 1H, pyrazole-H), 6.97–7.40 (m, 5H, ArH), 7.43–7.77 (m, 4H, ArH), 7.91 (s, 1H, N=C-H); ¹³C NMR (50 MHz, CDCl₃) δ 21.3 (CH₃), 27.8 (CH₃), 88.8, 123.5, 125.4 (3×CH), 128.3 (3×CH), 129.2 (3×CH), 131.0,

137.4, 150.9, 152.1, 152.3; IR (KBr) 3265 (m), 2333 (m), 1616 (m, -C= N), 1519 (m), 1489 (m), 1305 (m), 1267 (m), 1151 (m), 937 (m) cm⁻¹; EIMS *m*/*z* (relative intensity) 290 (100), 289 (M⁺, 5), 249 (28), 248 (20), 221 (5), 91 (10), 77 (10). Anal. Calcd for C₁₈H₁₈N₄; C: 74.46; H: 6.25; N: 19.30. Found: C: 74.50; H: 6.27; N: 19.33.

4.2.4. N'-(1-Phenyl-3-(4-chlorophenyl)-1H-pyrazol-5-yl)-N-methylmethanimidamide (**3d**). Mp (purified by column chromatography on silica gel) 179–180 °C; ¹H NMR (CDCl₃, 200 MHz) δ 2.95–3.03 (m, 3H, CH₃), 4.91 (s, 1H, NH), 6.14 (s, 1H, pyrazole-H), 7.20–7.44 (m, 6H, ArH), 7.73–7.93 (m, 4H, ArH), 7.70 (s, 1H, N=C-H); ¹³C NMR (50 MHz, CDCl₃) δ 27.9 (CH₃), 88.8, 123.5 (2×CH), 125.9, 126.8 (3×CH), 128.4, 128.6 (3×CH), 132.4, 133.3, 149.7, 152.1, 152.5; IR (KBr) 3427 (m), 2355 (m), 1627 (m, -C=N), 1527 (m), 1492 (m), 1442 (m), 1340 (m), 1284 (m), 948 (m) cm⁻¹; EIMS *m/z* (relative intensity) 312 (M⁺², 33), 310 (100), 309 (M⁺, 5), 270 (12), 269 (28), 268 (19), 92 (5), 77 (16). Anal. Calcd for C₁₇H₁₅ClN₄; C: 65.70; H: 4.86; N: 18.03. Found: C: 65.71; H: 4.88; N: 18.01.

4.2.5. *N*'-(1-*Phenyl*-3-(4-*methoxylphenyl*)-1*H*-*pyrazol*-5-*yl*)-*N*-*methylmethanimidamide* (**3e**). Mp (purified by column chromatography on silica gel) 160–161 °C; ¹H NMR (CDCl₃, 200 MHz) δ 2.87–2.89 (m, 3H, CH₃), 3.82 (s, 3H, OCH₃), 5.08 (s, 1H, NH), 6.04 (s, 1H, pyrazole-H), 6.90–6.91 (m, 2H, ArH), 7.22–7.25 (m, 1H, ArH), 7.35–7.43 (m, 2H, ArH), 7.75–7.80 (m, 4H, ArH), 7.89 (s, 1H, N=C-H); ¹³C NMR (50 MHz, CDCl₃) δ 27.7 (CH₃), 55.3 (OCH₃), 88.5, 113.9 (3×CH), 123.4 (2×CH), 125.6, 126.7 (3×CH), 128.3 (2×CH), 140.1, 150.7, 152.2, 159.3; IR (KBr) 3423 (m), 2351 (m), 1627 (m, -C=N), 1506 (m), 1446 (m), 1400 (m), 1336 (m), 1244 (m), 960 (m) cm⁻¹; EIMS *m/z* (relative intensity) 306 (100), 305 (M⁺), 250 (10), 132 (5), 92 (5), 91 (5), 77 (16). Anal. Calcd for C₁₈H₁₈N₄O; C: 70.57; H: 5.92; N: 18.29. Found: C: 70.59; H: 5.93; N: 18.27.

4.3. Standard procedure for the preparation of *N*-(1*H*-pyrazol-5-yl)formamides 6a–e and 7a–e

The reliable procedure involved the treatment of *N*-1-(2-pyridinyl)-5-aminopyrazoles (**4a**–**e** 1.0 equiv) or *N*-1-(2-quinolinyl)-5-aminopyrazoles (**5a**–**e**, 1.0 equiv) with catalytic amount of POCl₃ (~3 equiv) with *N*-methylformamide (2 mL) at 80–90 °C within 0.5–1 h. When the reaction was completed, the reaction mixture was concentrated, added to saturate sodium bicarbonate (15 mL), and extracted with dichloromethane (15 mL). The organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residues were purified by column chromatography on silica gel to give the corresponding *N*-(1*H*-pyrazol-5-yl)formamide products **6a**–**e** and **7a**–**e** were obtained in 81–88% yield and in 82–91% yield, respectively.

4.3.1. *N'*-(1-(2-*Pyridinyl*)-3-*tert-butyl*-1*H*-*pyrazol*-5-*yl*)-formamide (**6a**). Mp (purified by column chromatography on silica gel) 210–212 °C; ¹H NMR (CDCl₃, 500 MHz) δ 1.33 (s, 9H, CH₃×3), 6.82 (s, 1H, pyrazole-H), 7.09–7.12 (m, 1H, ArH), 7.79–7.82 (m, 1H, ArH), 8.05–8.07 (m, 1H, ArH), 8.29–8.30 (m, 1H, ArH), 8.44 (s, 1H, CHO), 12.09 (s, 1H, NH); ¹³C NMR (125 MHz, CDCl₃) δ 30.0 (CH₃×3), 30.4, 95.8, 114.1, 119.9, 138.4, 139.2, 146.0, 145.7, 156.9, 163.7; IR (KBr) 3217 (m), 2962 (m), 1695 (s, C=O), 1595 (m), 1550 (m), 1440 (m), 1398 (m), 1249 (m), 981 (m) cm⁻¹; EIMS *m/z* (relative intensity) 244, 243 (M⁺), 216 (90), 201 (100), 174 (40), 94 (13), 79 (13). Anal. Calcd for C₁₃H₁₆N₄O; C: 63.91; H: 6.60; N: 22.93. Found: C: 63.90; H: 6.62; N: 22.95.

4.3.2. *N'*-(*1*-(2-*Pyridinyl*)-3-*phenyl*-1*H*-*pyrazol*-5-*yl*)-formamide (**6b**). Mp (purified by column chromatography on silica gel) 117–118 °C; ¹H NMR (CDCl₃, 200 MHz) δ 7.13–7.20 (m, 1H, ArH), 7.29 (s, 1H, pyrazole-H), 7.34–7.47 (m, 3H, ArH), 7.81–7.94 (m, 3H, ArH), 7.81–7.82 (m, 1H, ArH), 8.33–8.36 (m, 1H, ArH), 8.50 (s, 1H, CHO), 12.10 (s, 1H, NH); ¹³C NMR (50 MHz, CDCl₃) δ 96.1, 114.2, 120.5, 126.0 (2×CH), 128.6 (3×CH), 132.5, 139.3, 139.4, 146.1, 152.5, 154.5, 157.1; IR (KBr) 2920 (m), 1695 (s, C=O), 1538 (m), 1448 (m), 1363 (m), 1244 (m), 1029 (m), 946 (m) cm⁻¹; EIMS *m/z* (relative intensity) 264 (41), 263 (M⁺, 7), 236 (100), 235 (26), 196 (41), 102 (12), 79 (12). Anal. Calcd for C₁₅H₁₂N₄O; C: 68.17; H: 4.58; N: 21.20. Found: C: 68.19; H: 4.56; N: 21.22.

4.3.3. *N'*-(*1*-(*2*-*Pyridinyl*)-3-(*4*-*methylphenyl*)-1*H*-*pyrazol*-5-*yl*)formamide (**6***c*). Mp (purified by column chromatography on silica gel) 123–124 °C; ¹H NMR (CDCl₃, 200 MHz) δ 2.37 (s, 3H, CH₃), 7.18–7.20 (m, 2H, ArH), 7.26 (s, 1H, pyrazole-H), 7.78–7.88 (m, 4H, ArH), 8.15–7.20 (m, 1H, ArH), 8.33–8.35 (m, 1H, ArH), 8.49 (s, 1H, CHO), 12.11 (s, 1H, NH); ¹³C NMR (50 MHz, CDCl₃) δ 21.3 (CH₃), 95.9, 114.1, 120.4, 125.9 (2×CH), 129.3, 129.7, 138.5, 139.2, 139.4, 146.4, 152.6, 154.5, 157.1; IR (KBr) 3439 (m), 3064 (m), 1712 (s, C=O), 1552 (m), 1456 (m), 1303 (m), 1244 (m), 1091 (m), 995 (m) cm⁻¹. Anal. Calcd for C₁₆H₁₄N₄O; C: 69.05; H: 5.07; N: 20.13. Found: C: 69.04; H: 5.09; N: 20.14.

4.3.4. *N'*-(1-(2-*Pyridinyl*)-3-(4-*chlorophenyl*)-1*H*-*pyrazol*-5-*yl*)-formamide (*6d*). Mp (purified by column chromatography on silica gel) 158–159 °C; ¹H NMR (CDCl₃, 200 MHz) δ 7.13–7.19 (m, 1H, ArH), 7.30–7.37 (m, 1H, ArH), 7.38 (s, 1H, pyrazole-H), 7.72–7.88 (m, 4H, ArH), 8.11–8.15 (m, 1H, ArH), 8.31–8.33 (m, 1H, ArH), 8.48 (s, 1H, CHO), 12.12 (s, 1H, NH); ¹³C NMR (50 MHz, CDCl₃) δ 95.9, 113.7, 119.7, 127.2 (2×CH), 128.8 (2×CH), 131.0, 134.4, 139.4, 139.5, 146.5, 151.3, 154.4, 157.1; IR (KBr) 3199 (m), 2924 (m), 1695 (s, C=O), 1591 (m), 1448 (m), 1361 (m), 1244 (m), 1128 (m), 948 (m) cm⁻¹. Anal. Calcd for C₁₅H₁₁ClN₄O; C: 60.31; H: 3.71; N: 18.76. Found: C: 60.32; H: 3.73; N: 18.74.

4.3.5. *N'*-(1-(2-*Pyridinyl*)-3-(4-*methoxylphenyl*)-1*H*-*pyrazol*-5-*yl*)formamide (**6***e*). Mp (purified by column chromatography on silica gel) 144–145 °C; ¹H NMR (CDCl₃, 500 MHz) δ 3.84 (s, 3H, OCH₃), 6.94–6.96 (m, 2H, ArH), 7.15–7.17 (m, 1H, ArH), 7.23–7.25 (m, 1H, ArH), 7.85–7.87 (m, 3H, ArH), 8.17 (s, 1H, pyrazole-H), 8.33–8.35 (m, 1H, ArH), 8.50 (s, 1H, CHO), 12.18 (s, 1H, NH); ¹³C NMR (125 MHz, CDCl₃) δ 55.3 (OCH₃), 95.7, 114.0 (2×CH), 149.1, 120.3, 125.3, 127.3 (2×CH), 139.2, 139.4, 146.1, 152.4, 154.4, 157.0, 160.1; IR (KBr) 3209 (m, NH), 2922 (m), 1697 (s, C=O), 1531 (m), 1471 (m), 1246 (m), 1174 (m), 1028 (m), 948 (m) cm⁻¹; EIMS *m/z* (relative intensity) 294 (57), 293 (M⁺, 5), 266 (100), 251 (12), 226 (37), 133 (19), 79 (11). Anal. Calcd for C₁₆H₁₄N₄O₂; C: 65.30; H: 4.79; N: 19.04. Found: C: 65.29; H: 4.80; N: 19.05.

4.3.6. N'-(1-(2-Quinolinyl)-3-tert-butyl-1H-pyrazol-5-yl)-formamide (**7a**). Mp (purified by column chromatography on silica gel) 125–126 °C; ¹H NMR (CDCl₃, 200 MHz) δ 1.46 (s, 9H, CH₃×3), 6.89 (s, 1H, pyrazole-H), 7.45–7.53 (m, 1H, ArH), 7.66–7.90 (m, 3H, ArH), 8.18–8.30 (m, 2H, ArH), 8.53 (s, 1H, CHO), 12.6 (s, 1H, NH); 13 C NMR (50 MHz, CDCl₃) δ 29.7, 30.0 (CH₃×3), 32.7, 96.3, 113.8, 125.9, 127.2, 127.9, 130.5, 138.8, 139.3, 144.9, 153.8, 156.9, 163.9; IR (KBr) 3169 (m), 2960 (m), 1699 (s, C=O), 1537 (m), 1504 (m), 1433 (m), 1375 (m), 1246 (m), 977 (m) cm⁻¹; EIMS *m*/*z* (relative intensity) 294 (33), 293 (M⁺, 10), 267 (14), 266 (79), 265 (13), 251 (74), 101 (11). Anal. Calcd for C₁₇H₁₈N₄O; C: 69.37; H: 6.16; N: 19.03. Found: C: 69.35; H: 6.18; N: 19.05.

4.3.7. *N'*-(1-(2-Quinolinyl)-3-phenyl-1H-pyrazol-5-yl)-formamide (**7b**). Mp (purified by column chromatography on silica gel) 163–164 °C; ¹H NMR (CDCl₃, 200 MHz) δ 7.36–7.58 (m, 4H, ArH), 7.35 (s, 1H, pyrazole-H), 7.70–7.93 (m, 5H, ArH), 8.27–8.43 (m, 2H, ArH), 8.60 (s, 1H, CHO), 12.06 (s, 1H, NH); ¹³C NMR (50 MHz, CDCl₃) δ 96.1, 114.2, 120.5, 126.0 (2×CH), 128.6 (3×CH), 132.5, 139.3, 139.4, 146.1, 152.5, 154.5, 157.1; IR (KBr) 3441 (m), 2063, 1645 (s, C=O), 1627 (m), 1537 (m), 1371 (m), 1242 (m), 1035 (m), 912 (m) cm⁻¹; EIMS *m/z* (relative intensity) 314 (42), 313 (M⁺, 10), 286 (100), 246 (30), 143 (11), 128 (25), 102 (15). Anal. Calcd for C₁₉H₁₄N₄O; C: 72.60; H: 4.49; N: 17.82. Found: C: 72.61; H: 4.51; N: 17.80.

4.3.8. *N'*-(1-(2-Quinolinyl)-3-(4-methylphenyl)-1H-pyrazol-5-yl)formamide (**7c**). Mp (purified by column chromatography on silica gel) 123–124 °C; ¹H NMR (CDCl₃, 200 MHz) δ 2.39 (s, 3H, CH₃), 7.22–7.32 (m, 1H, ArH), 7.52 (s, 1H, pyrazole-H), 7.53–7.57 (m, 1H, ArH), 7.74–7.95 (m, 6H, ArH), 8.26–8.42 (m, 2H, ArH), 8.60 (s, 1H, CHO), 12.12 (s, 1H, NH); ¹³C NMR (50 MHz, CDCl₃) δ 96.5, 110.0, 113.8, 126.1, 126.3 (2×CH), 127.3, 128.0, 128.7, 128.8, 130.8 (2×CH), 132.5, 139.6, 139.7, 146.1, 152.5, 154.5, 157.0; IR (KBr) 2920 (m), 2360 (m), 1689 (s, C=O), 1548 (m), 1506 (m), 1463 (m), 1408 (m), 1367 (m), 825 (m) cm⁻¹. Anal. Calcd for C₂₀H₁₆N₄O; C: 73.15; H: 4.91; N: 17.06. Found: C: 73.12; H: 4.93; N: 17.08.

4.3.9. *N'*-(1-(2-Quinolinyl)-3-(4-chlorophenyl)-1H-pyrazol-5-yl)formamide (**7d**). Mp (purified by column chromatography on silica gel) 152–153 °C; ¹H NMR (CDCl₃, 200 MHz) δ 7.32 (s, 1H, pyrazole-H), 7.37–7.43 (m, 2H, ArH), 7.51–7.58 (m, 2H, ArH), 7.71–7.85 (m, 5H, ArH), 8.27–8.39 (m, 1H, ArH), 8.59 (s, 1H, CHO), 12.70 (s, 1H, NH); ¹³C NMR (50 MHz, CDCl₃) δ 96.3, 110.0, 113.7, 126.2, 126.4, 127.3 (2×CH), 128.0, 130.8 (2×CH), 131.0, 134.6, 139.7, 139.8, 144.8, 151.6, 153.5, 157.1; IR (KBr) 2920 (m), 1695 (s, C=O), 1602 (m), 1502 (m), 1429 (m), 1367 (m), 1242 (m), 947 (m) cm⁻¹; EIMS *m/z* (relative intensity) 312 (M⁺², 14), 348 (41), 347 (M⁺, 28), 320 (100), 282,¹⁰ 280 (29), 144 (12), 143 (11). Anal. Calcd for C₁₉H₁₃ClN₄O; C: 65.43; H: 3.76; N: 16.06. Found: C: 65.44; H: 3.73; N: 16.03.

4.3.10. N'-(1-(2-Quinolinyl)-3-(4-methoxylphenyl)-1H-pyrazol-5yl)-formamide (**7e**). Mp (purified by column chromatography on silica gel) 144–145 °C; ¹H NMR (CDCl₃, 500 MHz) δ 3.84 (s, 3H, OCH₃), 6.94–6.96 (m, 2H, ArH), 7.29 (s, 1H, pyrazole-H), 7.42–7.56 (m, 1H, ArH), 7.65–8.05 (m, 6H, ArH), 8.13–8.41 (m, 2H, ArH), 8.59 (s, 1H, CHO), 12.18 (s, 1H, NH); ¹³C NMR (125 MHz, CDCl₃) δ 55.3 (OCH₃), 96.1, 113.7, 114.1 (2×CH), 125.1, 126.2, 127.3, 127.4 (2×CH), 127.9, 130.7, 139.5, 139.6, 144.9, 146.1, 152.4, 154.4, 157.0, 160.1; IR (KBr) 2920 (m), 1695 (s, C=O), 1606 (m), 1531 (m), 1431 (m), 1369 (m), 1247 (m), 948 (m) cm⁻¹; EIMS *m*/*z* (relative intensity) 344 (100), 343 (M⁺, 13), 316 (94), 301 (5), 276 (39), 129 (25), 128 (34). Anal. Calcd for C₂₀H₁₆N₄O₂; C: 69.76; H: 4.68; N: 16.27. Found: C: 69.77; H: 4.64; N: 16.25.

4.4. Standard procedure for the preparation of pyrazolo[3,4d]pyrimidine products 12a-e, 13a-e, and 14a-e

The reliable procedure involved the treatment of N-1-phenyl-5aminopyrazoles, N-1-phenyl-5-aminopyrazoles (**1a-e**, 1.0 equiv), *N*-1-(2-pyridinyl)-5-aminopyrazoles (**4a**–**e** 1.0 equiv), or *N*-1-(2quinolinyl)-5-aminopyrazoles (**5a**–**e**, 1.0 equiv) with catalytic amount of POCl₃ (~3 equiv) with formamide (2 mL) in CH₂Cl₂ solution at 80–90 °C within 0.5–1 h. When the reaction was completed, the reaction mixture was concentrated, added to saturate sodium bicarbonate (15 mL), and extracted with dichloromethane (15 mL). The organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residues were purified by column chromatography on silica gel to give the corresponding pyrazolo[3,4-*d*]pyrimidine products **12a–e**, **13a–e** or **14a–e** were obtained in 91–96%, 81–88%, or 82–91% yield, respectively.

4.4.1. 3-tert-Butyl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine (**12a**). Mp (purified by column chromatography on silica gel) 48–49 °C; ¹H NMR (CDCl₃, 500 MHz) δ 1.55 (s, 9H, 3×CH₃), 7.23–7.29 (m, 1H, ArH), 7.44–7.52 (m, 2H, ArH), 8.19–8.12 (m, 2H, ArH), 9.02 (s, 1H), 9.31 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 30.3 (3×CH), 34.4, 114.0, 121.0 (2×CH), 126.2, 129.0 (2×CH), 138.6, 152.8, 153.1, 154.8, 155.0; IR (KBr) 3049 (w), 2968 (w), 2666 (w), 1599 (m), 1578 (m), 1555 (m), 1508 (m), 1427 (m), 1366 (m), 1261 (m), 1098 (m), 961 (m), 756 (m) cm⁻¹; EIMS *m*/*z* (relative intensity) 253 (100), 252 (M⁺, 34), 244 (5), 218 (5), 195 (6), 169 (4), 142 (12), 115 (4), 91 (2), 77 (14); HRMS (ESI) calcd for C₁₅H₁₆N₄ (M+H⁺) 253.1375, found 253.1377. Anal. Calcd for C₁₅H₁₆N₄; C: 71.40; H: 6.39; N: 22.21. Found: C: 71.43; H: 6.35; N: 22.17.

4.4.2. 1,3-Diphenyl-1H-pyrazolo[3,4-d]pyrimidine (**12b**). Mp (purified by column chromatography on silica gel) 157–158 °C (hexane–EtOAc). ¹H NMR (CDCl₃, 500 MHz): δ 7.29–7.36 (1H, m), 7.41–7.48 (1H, m), 7.48–7.56 4H, m), 7.97–8.07 (2H, m), 8.25–8.35 (2H, m), 9.09 (1H, s), 9.45 (1H, s). ¹³C NMR (125 MHz, CDCl₃): δ 114.1, 121.2 (2 × C), 126.7, 127.2 (2 × C), 129.0 (2 × C), 129.1 (2 × C), 129.5, 131.4, 138.5, 144.8, 152.7, 153.2, 155.5. IR (KBr): 2364, 2331, 1589, 1498, 1417, 1369, 1219, 1093 cm⁻¹. EIMS *m*/*z* (rel int): 272 (100, M⁺). Anal. Calcd for C₁₇H₁₂N₄: C, 74.98; H, 4.44; N, 20.58. Found: C, 74.96; H, 4.45; N, 20.61.

4.4.3. 3-(4-*Methylphenyl*)-1-*phenyl*-1*H*-*pyrazolo*[3,4-*d*]*pyrimidine* (**12c**). Mp (purified by column chromatography on silica gel) 139–140 °C; ¹H NMR (CDCl₃, 500 MHz) δ 2.43 (s, 3H, CH₃), 7.32–7.42 (m, 3H, ArH), 7.51–7.61 (m, 2H, ArH), 7.86–8.02 (m, 2H, ArH), 8.24–8.38 (m, 2H, ArH), 9.11 (s, 1H), 9.47 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 21.4 (CH₃), 114.2, 121.3 (2×CH), 126.7, 127.2 (2×CH), 128.7, 129.2 (2×CH), 129.9 (2×CH), 138.5, 139.8, 145.0, 152.8, 153.3, 155.5; IR (KBr) 3030 (w), 2920 (w), 2374 (w), 2349 (w), 2313 (w), 1584 (m), 1503 (m), 1430 (m), 1368 (m), 1220 (m), 953 (m), 785 (m), 756 (m) cm⁻¹; EIMS *m/z* (relative intensity) 286 (100), 285 (M⁺, 34), 244 (5), 218 (5), 195 (6), 169 (4), 142 (12), 115 (4), 91 (2), 77 (11). HRMS (ESI) calcd for C₁₈H₁₄N₄ (M+H⁺) 287.1218, found 287.1216. Anal. Calcd for C₁₈H₁₄N₄; C: 75.50; H: 4.93; N: 19.57. Found: C: 75.49; H: 4.91; N: 19.55.

4.4.4. 3-(4-*Chlorophenyl*)-1-*phenyl*-1*H*-*pyrazolo*[3,4-*d*]*pyrimidine* (**12d**). Mp (purified by column chromatography on silica gel) 196–197 °C; ¹H NMR (CDCl₃, 500 MHz) δ 7.34–7.38 (m, 1H, ArH), 7.48–7.58 (m, 4H, ArH), 7.96–8.02 (m, 2H, ArH), 8.24–8.30 (m, 2H, ArH), 9.12 (s, 1H), 9.46 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 114.0, 121.5 (2×CH), 127.0, 128.5 (2×CH), 129.3 (2×CH), 129.5 (2×CH), 130.0, 135.7, 138.4, 143.8, 152.6, 153.3, 155.7; IR (KBr) 3043 (w), 2926 (w), 2848 (w), 1585 (m), 1555 (m), 1503 (m), 1368 (m), 1219 (m), 1093 (m), 954 (m), 831 (m), 789 (m), 745 (m) cm⁻¹; EIMS *m/z* (relative intensity) 306,⁵ 305 (M⁺, 1), 302 (100), 287 (24), 259 (8), 233 (3), 195 (7), 151 (2), 91 (5), 77 (12); HRMS (ESI) calcd for C₁₇H₁₁ClN₄ (M+H⁺) 307.0672, found 307.0671. Anal. Calcd for C₁₇H₁₁ClN₄; C: 66.56; H: 3.61; N: 18.26. Found: C: 66.53; H: 3.62; N: 18.29.

4.4.5. 3-(4-*Methoxylphenyl*)-1-*phenyl*-1*H*-*pyrazolo*[3,4-*d*]*pyrimidine* (**12e**). Mp (purified by column chromatography on silica gel) 175–176 °C; ¹H NMR (CDCl₃, 500 MHz) δ 3.87 (s, 3H, CH₃), 7.08–7.84 (m, 2H, ArH), 7.32–7.36 (m, 1H, ArH), 7.50–7.56 (m, 2H, ArH), 7.95–8.01 (m, 2H, ArH), 8.28–8.32 (m, 2H, ArH), 9.10 (s, 1H), 9.45 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 55.4 (CH₃), 114.2, 114.6 (2×CH), 121.3 (2×CH), 124.1, 126.7, 128.7 (2×CH), 129.2 (2×CH), 138.6, 144.8, 152.8, 153.2, 155.5, 160.8; IR (KBr) 3047 (w), 2924 (w), 1612 (m), 1582 (m), 1503 (m), 1431 (m), 1356 (m), 1254 (m), 1219 (m), 1092 (m), 962 (m), 835 (m), 758 (m) cm⁻¹; EIMS *m/z* (relative intensity) 302 (100), 301 (M⁺, 6), 287 (25)^{6c}, 265 (4), 259 (8), 233 (3), 195 (2), 151 (4), 91 (5), 77 (12); HRMS (ESI) calcd for C₁₈H₁₄1N₄O (M+H⁺) 303.1168, found 303.1169. Anal. Calcd for C₁₈H₁₄1N₄O; C: 71.51; H: 4.67; N: 18.53. Found: C: 75.48; H: 4.68; N: 18.50.

4.4.6. 3-*tert-Butyl-1-(pyridin-2-yl)-1H-pyrazolo*[3,4-*d*]*pyrimidine* (**13a**). ¹H NMR (CDCl₃, 500 MHz) δ 1.50 (s, 9H, CH₃), 7.15–7.19 (m, 1H, ArH), 7.77–7.81 (m, 1H, ArH), 8.05–8.07 (m, 1H, ArH), 8.60–8.62 (m, 1H, ArH), 9.07 (s, 1H), 9.28 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 29.7, 34.4, 114.2, 116.1, 121.5, 138.2, 148.8, 151.1, 152.8, 153.6, 155.7, 155.7; IR (KBr) 2970 (w), 2227 (w), 1595 (m), 1556 (m), 1498 (m), 1450 (m), 1369 (m), 1192 (m), 1112 (m), 9100 (m), 779 (m) cm⁻¹; EIMS *m/z* (relative intensity) 253,²³ 252 (M⁺, 2), 238 (100), 198 (12), 171 (2), 105 (3), 78 (31), 57 (5), 51 (7). Anal. Calcd for C₁₄H₁₅N₅; C: 66.38; H: 5.97; N: 27.65. Found: C: 66.40; H: 5.99; N: 27.63.

4.4.7. 3-Phenyl-1-(pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (**13b**). Mp (purified by column chromatography on silica gel) 206–207 °C; ¹H NMR (CDCl₃, 500 MHz) δ 7.22–7.30 (m, 1H, ArH), 7.41–7.55 (m, 3H, ArH), 7.83–7.91 (m, 1H, ArH), 7.99–8.05 (m, 2H, ArH), 8.20–8.26 (m, 1H, ArH), 8.66–8.70 (m, 1H, ArH), 9.19 (s, 1H), 9.47 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 114, 116, 122, 128 (2×CH), 129 (2×CH), 130, 131, 139, 146, 149, 151, 153, 154, 156; IR (KBr) 3049 (w), 2920 (w), 2851 (w), 2380 (w), 2349 (w), 1593 (m), 1481 (m), 1452 (m), 1368 (m), 1265 (m), 1219 (m), 1080 (m), 957 (m), 736 (m), 592 (m) cm⁻¹; EIMS *m/z* (relative intensity) 273 (100), 272 (M⁺, 17), 230 (16), 196 (10), 170 (22), 143 (27), 91 (20), 78(35), 51 (17). Anal. Calcd for C₁₆H₁₁N₅; C: 70.32; H: 4.06; N: 25.63. Found: C: 70.28; H: 4.09; N: 25.66.

4.4.8. 3-(4-Methylphenyl)-1-(pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (**13c**). Mp (purified by column chromatography on silica gel) 127–128 °C; ¹H NMR (CDCl₃, 500 MHz) δ 2.42 (s, 1H, CH₃), 7.28–7.34 (m, 3H, ArH), 7.89–7.95 (m, 3H, ArH), 8.26–8.28 (m, 1H, ArH), 8.71–8.72 (m, 1H, ArH), 9.21 (s, 1H), 9.49 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 21.4, 114.7, 116.4, 122.0, 127.5 (2×CH), 128.2, 129.8 (2×CH), 138.5, 140.1, 146.2, 149.0, 151.1, 152.9, 153.9, 156.2; IR (KBr) 2922 (W), 2853 (W), 1591 (m), 1481 (m), 1445 (m), 1366 (m), 1317 (m), 1221 (m), 1080 (m), 957 (m), 793 (m) cm⁻¹; EIMS *m/z* (relative intensity) 287 (100), 286 (M⁺, 22), 259 (7), 196 (6), 170 (18), 154 (9), 143 (21), 91 (9), 78 (32), 65 (7), 51 (10). Anal. Calcd for C₁₇H₁₃N₅; C: 71.06; H: 4.56; N: 24.37. Found: C: 71.08; H: 4.54; N: 24.39.

4.4.9. 3-(4-Chlorophenyl)-1-(pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (**13d**). Mp (purified by column chromatography on silica gel) 164–165 °C; ¹H NMR (CDCl₃, 500 MHz) δ 7.28–7.34 (m, 1H, ArH), 7.48–7.52 (m, 2H, ArH), 7.88–8.02 (m, 3H, ArH), 8.25–8.29 (m, 1H, ArH), 8.70–8.74 (m, 1H, ArH), 9.22 (s, 1H), 9.48 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 114.5, 116.5, 122.3, 128.5 (2×CH), 128.8, 129.5 (2×CH), 136.0, 138.7, 145.0, 150.9, 152.7, 153.9, 156.4; IR (KBr) 2920 (w), 2851 (w), 1587 (m), 1481 (m), 1217 (m), 1094 (m), 957 (m), 833 (m), 770 (m) cm⁻¹; EIMS m/z (relative intensity) 309 (M+2, 30), 307 (100), 306 (M⁺, 13), 279 (5), 196 (9), 174 (8), 170 (27), 143 (30), 111 (6), 78 (39), 75 (6), 51 (13). Anal. Calcd for C₁₆H₁₀ClN₅; C: 62.45; H: 3.28; N: 22.76. Found: C: 62.43; H: 3.30; N: 22.75.

4.4.10. 3-(4-Methoxyphenyl)-1-(pyridin-2-yl)-1H-pyrazolo[3,4-d] pyrimidine (**13e**). Mp (purified by column chromatography on silica gel) 167–168 °C; ¹H NMR (CDCl₃, 500 MHz) δ 3.84 (s, 1H, CH₃), 6.99–7.05 (m, 2H, ArH), 7.22–7.28 (m, 1H, ArH), 7.87–7.99 (m, 3H, ArH), 8.22–8.26 (m, 1H, ArH), 8.66–8.70 (m, 1H, ArH), 9.18 (s, 1H), 9.44 (s, 1H); ¹³C NMR (125 MHz, CDCl3) δ 55.4, 114.0 (2×CH), 114.6, 116.3, 122.0, 123.6, 129.0 (2×CH), 138.5, 146.0, 149.0, 151.1, 152.9, 153.8, 156.2, 161.0; IR (KBr) 3460 (w), 3057 (w), 2960 (w), 2924 (w), 2850 (w), 1614 (m), 1529 (m), 1367 (m), 1253 (m), 1219 (m), 1178 (m), 1080 (m) cm⁻¹. Anal. Calcd for C₁₇H₁₃N₅O; C: 67.32; H: 4.32; N: 23.09. Found: C: 67.35; H: 4.30; N: 23.11.

4.4.11. 3-tert-Butyl-1-(quinolin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (**14a**). Mp (purified by column chromatography on silica gel) 144–145 °C; ¹H NMR (CDCl₃, 500 MHz) δ 1.58 (s, 3H, CH₃), 7.49–7.53 (m, 1H, ArH), 7.70–7.72 (m, 1H, ArH), 7.80–7.82 (m, 1H, ArH), 8.18–8.20 (m, 1H, ArH), 8.29–8.31 (m, 1H, ArH), 9.18 (s, 1H), 9.38 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 29.8, 34.6, 114.6, 115.5, 126.5, 126.9, 127.4, 129.3, 130.1, 138.8, 146.9, 150.0, 152.9, 154.3, 154.7, 156.2; IR (KBr) 2964 (w), 2922 (w), 2851 (w), 1622 (m), 1600 (m), 1583 (m), 1502 (m), 1433 (m), 1367 (m), 1190 (m), 1047 (m) cm⁻¹. Anal. Calcd for C₁₈H₁₇N₅; C: 71.27; H: 5.65; N: 23.09. Found: C: 71.29; H: 5.62; N: 23.11.

4.4.12. 3-Phenyl-1-(quinolin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (**14b**). Mp (purified by column chromatography on silica gel) 194–195 °C; ¹H NMR (CDCl₃, 500 MHz) δ 7.49–7.59 (m, 4H, ArH), 7.75–7.79 (m, 1H, ArH), 7.87–7.89 (m, 1H, ArH), 8.11–8.13 (m, 2H, ArH), 8.37–8.39 (m, 1H, ArH), 8.47–8.49 (m, 1H, ArH), 9.26 (s, 1H), 9.55 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 114.9, 115.6, 126.8, 127.2, 127.5, 127.8 (2×CH), 129.2 (2×CH), 129.5, 130.4, 131.2, 139.0, 146.6, 147.0, 149.8, 153.0, 154.4, 156.4; IR (KBr) 3055 (w), 2376 (w), 2347 (w), 1582 (m), 1557 (m), 1502 (m), 1477 (m), 1409 (m), 1368 (m), 1325 (m), 1219 (m), 1090 (m), 962 (m), 825 (m), 761 (m), 694 (m) cm⁻¹; EIMS *m/z* (relative intensity) 323 (100), 295 (M⁺, 21) 246,¹⁷ 220 (29), 193 (39), 140 (12), 128 (46), 101 (18), 77 (21). Anal. Calcd for C₂₀H₁₃N₅; C: 74.29; H: 4.05; N: 21.66. Found: C: 74.31; H: 4.07; N: 21.69.

4.4.13. 3-(4-Methylphenyl)-1-(quinolin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (**14c**). Mp (purified by column chromatography on silica gel) 163–164 °C; ¹H NMR (CDCl₃, 500 MHz) δ 2.42 (s, 3H, CH₃), 7.32–7.36 (m, 2H, ArH), 7.50–7.58 (m, 1H, ArH), 7.70–7.86 (m, 2H, ArH), 7.96–8.00 (m, 2H, ArH), 8.22–8.48 (m, 3H, ArH), 9.23 (s, 1H), 9.51 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 21.4, 114.8, 115.4, 126.7, 127.0, 127.4, 127.5 (2×CH), 128.3, 129.4, 129.8 (2×CH), 130.3, 138.8, 140.1, 146.5, 146.9, 149.7, 152.9, 154.3, 156.3; IR (KBr) 3473 (m), 3048 (w), 2924 (w), 2855 (w), 1557 (m), 1504 (m), 1477 (m), 1431 (m), 1367 (m), 1325 (m), 1217 (m), 1089 (m), 1022 (m) cm⁻¹; EIMS *m/z* (relative intensity) 337 (100), 336 (21), 316 (5), 220 (17), 193 (22) 128 (31), 101, ⁹ 77.⁵ Anal. Calcd for C₂₁H₁₅N₅; C: 74.46; H: 4.48; N: 20.76. Found: C: 74.48; H: 4.50; N: 20.73.

4.4.14. 3-(4-Chlorophenyl)-1-(quinolin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (14d). Mp (purified by column chromatography on silica gel) 127–128 °C; ¹H NMR (CDCl₃, 500 MHz) δ 7.50–7.60 (m, 4H, ArH), 7.69–7.89 (m, 3H, ArH), 8.01–8.07 (m, 2H, ArH), 8.22–8.26 (m, 1H, ArH), 8.33–8.49 (m, 2H, ArH), 9.24 (s, 1H), 9.50 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 114.6, 115.5, 126.9, 127.2, 127.6, 128.9 (3×CH), 129.5 (3×CH), 130.5, 136.1, 139.1, 145.3, 147.0, 149.5, 152.8, 154.4, 156.4; IR (KBr) 3455 (m), 3051 (w), 2922 (w), 1602 (m), 1581 (m), 1554 (m), 1477 (m), 1431 (m), 1219 (m), 1089 (m) cm⁻¹; EIMS m/z (relative intensity) 359 (M+2, 34), 357 (100), 356 (M⁺, 17), 246 (13), 220 (26), 193 (36), 128 (42), 101 (15), 77 (7). Anal. Calcd for C₂₀H₁₂ClN₅; C: 67.14; H: 3.38; N: 19.57. Found: C: 67.12; H: 3.41; N: 19.57.

4.4.15. 3-(4-Methoxyphenyl)-1-(quinolin-2-yl)-1H-pyrazolo[3,4-d] pyrimidine (**14e**). Mp (purified by column chromatography on silica gel) 153–154 °C; ¹H NMR (CDCl₃, 500 MHz) δ 3.86 (s, 3H, CH₃), 7.05–7.07 (m, 2H, ArH), 7.53–7.55 (m, 1H, ArH), 7.72–7.76 (m, 1H, ArH), 7.83–7.85 (m, 1H, ArH), 8.02–8.04 (m, 2H, ArH), 8.23–8.25 (m, 1H, ArH), 8.32–8.34 (m, 1H, ArH), 8.45–8.47 (m, 1H, ArH), 9.21 (s, 1H), 9.49 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 55.5, 114.7 (2×CH), 114.9, 115.5, 123.7, 126.7, 127.1, 127.5, 129.1 (2×CH), 129.4, 130.4, 139.0, 146.4, 147.0, 149.8, 153.0, 156.3, 161.1, 167.8; IR (KBr) 2955 (w), 2924 (w), 2851 (w), 1612 (m), 1583 (m), 1530 (m), 1503 (m), 1481 (m), 1433 (m), 1251 (m), 1219 (m), 1177 (m), 1090 (m), 1030 (m) cm⁻¹; EIMS *m/z* (relative intensity) 353 (100), 352 (M⁺, 12), 338 (13), 128 (35), 102 (3), 101 (8), 77 (4), 75 (2). Anal. Calcd for C₂₁H₁₅N₅O; C: 71.38; H: 4.28; N: 19.82. Found: C: 71.39; H: 4.25; N: 19.81.

4.4.16. 1-Methyl-1H-pyrazolo[3,4-d]pyrimidine (**15**). Mp (purified by column chromatography on silica gel) 105–106 °C; ¹H NMR (CDCl₃, 500 MHz) δ 4.12 (s, 3H, CH₃), 8.11 (s, 1H), 9.00 (s, 1H), 9.15 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 33.8, 114.4132.3 (2×CH), 152.2, 155.1; IR (KBr) 3093 (w), 2924 (w), 2353 (w), 1735 (m), 1689 (m), 1558 (m), 1504 (m), 1411 (m), 1357 (m), 1249 (m), 1195 (m), 1141 (m), 1095 (m), 987 (m) cm⁻¹. Anal. Calcd for C₆H₆N₄; C: 53.72; H: 4.51; N: 41.77. Found: C: 53.71; H: 4.48; N: 41.76.

4.5. Standard procedure for the preparation of methanimidamide products 20–22

The reliable procedure involved the treatment of *N*-1-phenyl-5aminopyrazoles, *N*-1-(2-quinolinyl)-5-aminopyrazoles (**5b**, 1.0 equiv) with catalytic amount of POCl₃ (~3 equiv) with *N*,*N*-dimethylformamide (DMF), *N*,*N*-diethylformamide (DEF), or 1-pyrrolidinecarboxaldehyde (2 mL) in CH₂Cl₂ solution at 80–90 °C within 0.5–1 h. When the reaction was completed, the reaction mixture was concentrated, added to saturate sodium bicarbonate (15 mL), and extracted with dichloromethane (15 mL). The organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residues were purified by column chromatography on silica gel to give the corresponding methanimidamide products **19–21** were obtained in 91–95% yield.

4.5.1. *N'*-(1-(2-quinolinyl)-3-diphenyl-1H-pyrazol-5-yl)-N,N-dimethylmethanimidamide (**20**). Mp (purified by column chromatography on silica gel) 166–167 °C; ¹H NMR (CDCl₃, 200 MHz) δ 2.96 (s, 6H, CH₃×2), 6.19 (s, 1H, pyrazole-H), 7.28–7.49 (m, 4H, ArH), 7.62–7.69 (m, 1H, ArH), 7.74–7.80 (m, 2H, ArH), 7.91–7.95 (m, 2H, ArH), 8.09–8.16 (m, 2H, ArH), 8.13 (s, 1H, N=C-H); ¹³C NMR (50 MHz, CDCl₃) δ 34.5 (CH₃), 40.3 (CH₃), 89.5 (2×CH), 117.9 (2×CH), 126.0 (4×CH), 127.3 (2×CH), 127.9 (3×CH), 128.4 (2×CH), 129.3 (2×CH), 129.6 (2×CH), 137.3 (2×CH), 154.8 (2×CH); IR (KBr) 3045 (m), 2924 (m), 1693 (m, -C=N), 1556 (m), 1514 (m), 1317 (m), 1265 (m), 1107 (m), 948 (m) cm⁻¹; EIMS *m/z* (relative intensity) 341 (61), 340 (M⁺, 3), 326 (50), 297 (36), 237 (13), 168 (17), 128 (100). Anal. Calcd for C₂₁H₁₉N₅; C: 73.88; H: 5.61; N: 20.51. Found: C: 73.89; H: 5.63; N: 20.50.

4.5.2. N'-(1-(2-Quinolinyl)-3-diphenyl-1H-pyrazol-5-yl)-N,N-diethylmethanimidamide (**21**). Mp (purified by column chromatography on silica gel) 142–143 °C; ¹H NMR (CDCl₃, 500 MHz) δ 1.08–1.11 (m, 3H, CH₃), 1.08–1.11 (m, 3H, CH₃), 3.21–3.25 (m, 2H, CH₂), 3.44–3.48 (m, 2H, CH₂), 6.20 (s, 1H, pyrazole-H), 7.27–7.38 (m, 1 H, ArH), 7.39–7.45 (m, 2H, ArH), 7.47–7.48 (m, 1H, ArH), 7.64–7.67 (m, 1H, ArH), 7.77–8.11 (m, 7H, ArH), 7.53 (s, 1H, N=C-H); ¹³C NMR (125 MHz, CDCl₃) δ 12.5 (CH₃), 12.7 (CH₃), 40.0 (CH₂), 41.7 (CH₂), 89.5, 117.8, 125.8, 125.9, 126.7, 127.2 (2×CH), 127.8, 128.3, 129.3, 129.4, 133.7, 137.1, 147.0, 151.3, 152.3, 153.6, 154.1, 162.1; IR (KBr) 2924 (m), 2852 (m), 1701 (m, -C=N), 1602 (m), 1539 (m), 1504 (m), 1435 (m), 1265 (m), 740 (m) cm⁻¹. Anal. Calcd for C₂₃H₂₃N₅; C: 74.77; H: 6.27; N: 18.96. Found: C: 74.79; H: 6.27; N: 18.98.

4.5.3. *N'*-(1-(2-Quinolinyl)-3-diphenyl-1H-pyrazol-5-yl)-*N*-pyrrolidinmethanimidamide (**22**). Mp (purified by column chromatography on silica gel) 168–169 °C; ¹H NMR (CDCl₃, 200 MHz) δ 1.23 (m, 4H), 3.40 (m, 4H), 6.17 (s, 1H, pyrazole-H), 7.23–7.46 (m, 4H, ArH), 7.59–7.74 (m, 2H, ArH), 7.91–7.97 (m, 1H, ArH), 8.07 (s, 1H, N=C-H), 7.12–8.19 (m, 2H, ArH); ¹³C NMR (50 MHz, CDCl₃) δ 24.5 (CH), 25.2 (CH), 45.6 (CH), 48.8 (CH), 89.4, 117.9, 126.0, 126.7, 127.3 (2×CH), 127.9, 128.3, 128.7 (2×CH), 129.3, 129.5, 133.7, 137.2, 147.1, 151.3, 151.7, 152.3, 154.2; IR (KBr) 3849 (m), 3645 (m), 1693 (m, -C= N), 1556 (m), 1587 (m), 1116 (m), 1082 (m), 948 (m), 827 (m) cm⁻¹; EIMS *m/z* (relative intensity) 367 (100), 366 (M⁺, 26), 310 (23), 297 (34), 264 (11), 129 (26), 128 (70). Anal. Calcd for C₂₃H₂₁N₅; C: 75.18; H: 5.76; N: 19.06. Found: C: 75.12; H: 5.72; N: 19.02.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.11.002.

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