ChemInform Abstract: One-Pot Synthesis and Antiproliferative Evaluation of Pyrazolo[3,4-d]pyrimidine Derivatives.

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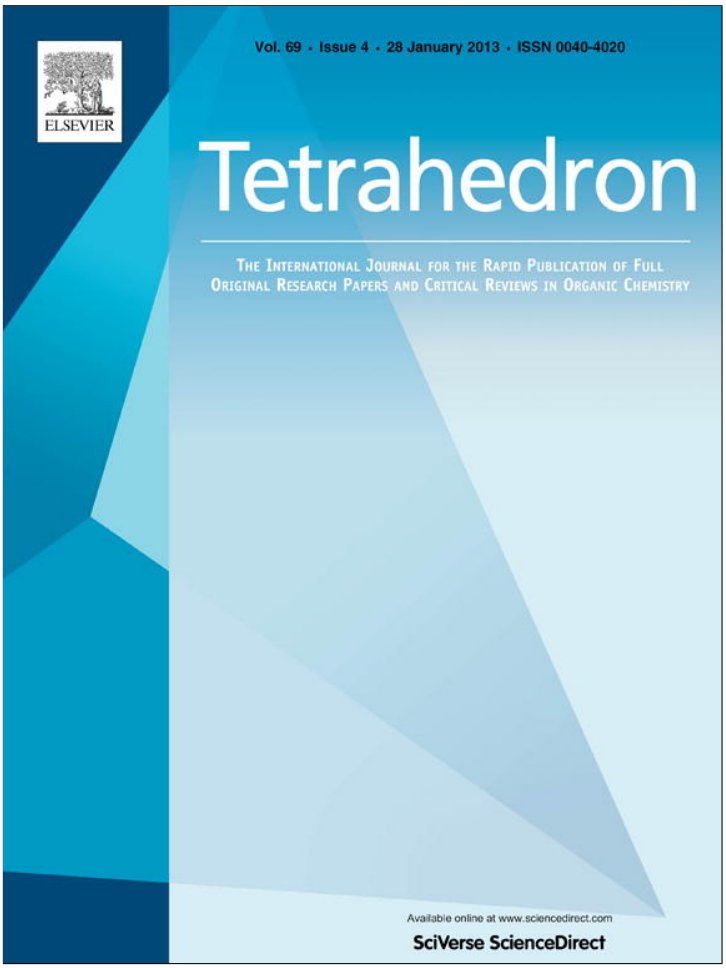

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Selective synthesis of pyrazolo[3,4-*d*]pyrimidine, *N*-(1*H*-pyrazol-5-yl) formamide, or *N*-(1*H*-pyrazol-5-yl)formamidine derivatives from *N*-1-substituted-5-aminopyrazoles with new Vilsmeier-type reagents

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ABSTRACT

Various halomethyleniminium salts as novel Vilsmeier agents were synthesized from formamide or *N*-methylformamide with $POCl_3$. Treatment of *N*-1-substituted-aminopyrazoles including *N*-1-phenyl-5-aminopyrazoles, *N*-1-(2-pyridinyl)-5-aminopyrazoles, and *N*-1-(2-quinolinyl)-5-aminopyrazoles with these agents gave the corresponding pyrazolo[3,4-*d*]pyrimidine, *N*-(1*H*-pyrazol-5-yl)formamide, or *N*-(1*H*-pyrazol-5-yl)formamidine. The reaction was different from the traditional Vilsmeier-type reaction and the plausible reactive pathways were proposed for the unexpected result.

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., $POCl_3$, PBr_3, $(COCl)_2$ or $SOCl_2$) 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 reagents[7] were enthusiastically developed to explore the new skeleton, extend the construction, or improve the yields.

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 ($POCl_3$). 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*-(1*H*-pyrazol-5-yl)formamide, and *N*-(1*H*-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-aryl-5-aminopyrazoles **1** were treated with classical Vilsmeier reagent (DMF+$POCl_3$) under the microwave-

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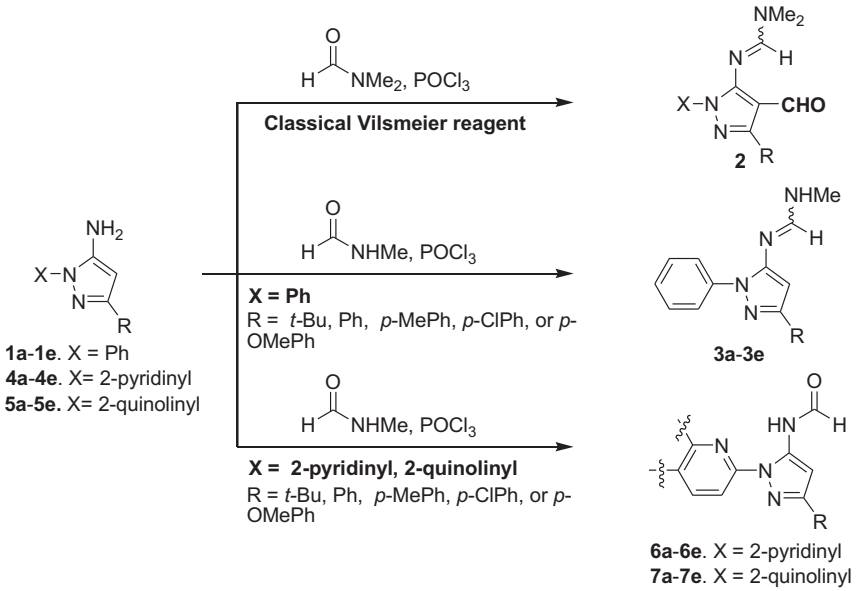
assisted[21,22] or normal heating reaction.[23,24] The Vilsmeier formylated amidines **2** were formed as the major products (see Scheme 1), which was introduced with a formyl group at the C-4 position on pyrazoyl ring with *N*-(1*H*-pyrazol-5-yl)formamidines **3** as the minor product.[6c,21,25]



Scheme 1.

By employing the newly developed Vilsmeier reagent, which was synthesized by using *N*-methylformamide in the presence of phosphorous oxychloride $POCl_3$, 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-(1*H*-Pyrazol-5-yl) formamidines (**3a**–**e**)	
S.M.	C3-R	No.	Yield (%)
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+$POCl_3$) 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 δ 8.48 ppm for $-C^1H{=}O$ in ^1H NMR. In ^{13}C NMR spectrum, compound **6e** possessed characterization absorptions at δ 157.1 ppm for carbonyl carbon $-^{13}CH{=}O$. The IR absorptions of **6e** showed peaks at 1697 cm^{-1} for stretching of the –NHCH=O amide group. The ORTEP drawing of compound **6e** was shown in Fig. 1. Following our

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 $POCl_3$

Pyrazoles (**4a**–**e** and **5a**–**e**)			Products	
			N-(1*H*-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

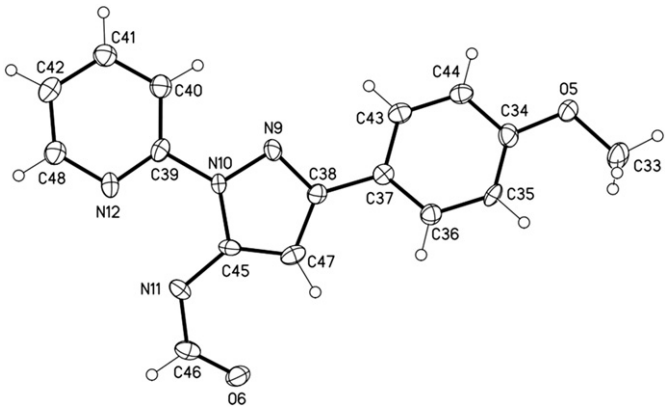


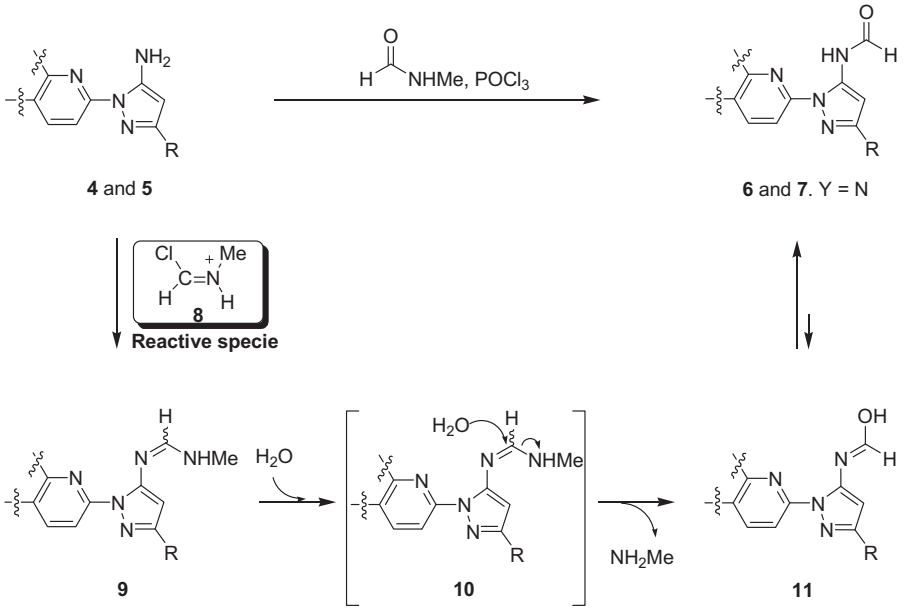
Fig. 1. The ORTEP diagram of *N*-(1-(2-pyridinyl)-3-(4-methoxyphenyl)-1*H*-pyrazol-5-yl)formamide **6e**.

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*-(1*H*-pyrazol-5-yl)formamides **6a**–**e** and **7a**–**e**. Firstly, *N*-methylformamide was fast reacted with phosphorous oxychloride $POCl_3$ 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*-(1*H*-pyrazol-5-yl)formamidine intermediate **9** (see Scheme 2). After aqueous workup, nucleophile H_2O 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 ^{13}C NMR spectrum, compound **12b** possessed characterization absorptions at δ 155.0 ppm for pyrimidine carbon N=^{13}CH–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**,

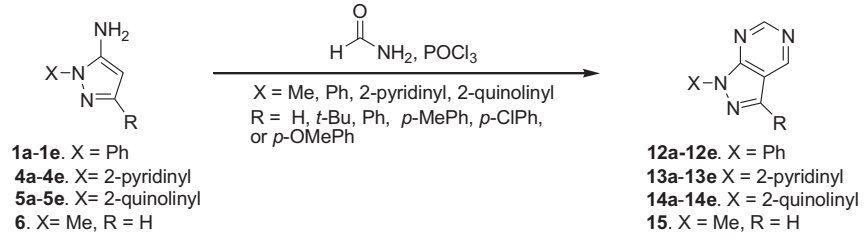


Scheme 2.

Consequently, we explored another modified halomethyleniminium salts by means of formamide in the presence of phosphorous oxychloride $POCl_3$ 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 $POCl_3$ 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]

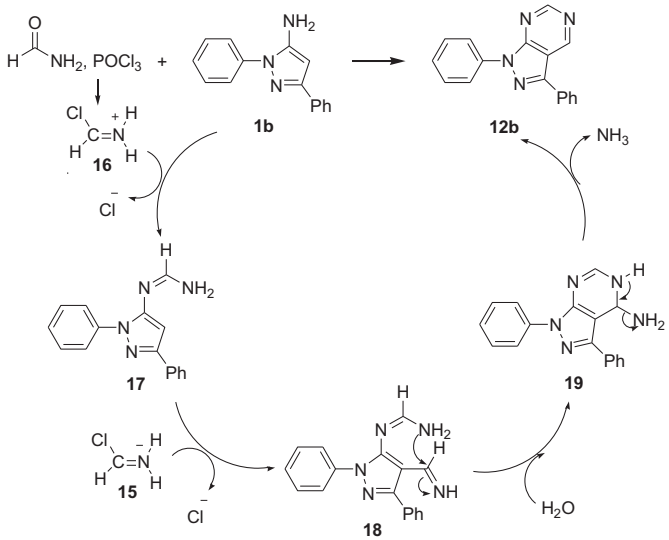
The plausible mechanism for the unexpected Vilsmeier heterocyclization reaction is shown in Scheme 4 to account for the design of our approach. Formamide was reacted with $POCl_3$ coupling agent to form the Vilsmeier reactive specie **16**.[26] In the model study, reaction of 5-aminopyrazole **1b** with **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



1a-1e. X = Ph
4a-4e. X= 2-pyridinyl
5a-5e. X= 2-quinolinyl
6. X= Me, R = H

12a-12e. X = Ph
13a-13e X = 2-pyridinyl
14a-14e. X = 2-quinolinyl
15. X = Me, R = H

Scheme 3.



Scheme 4.

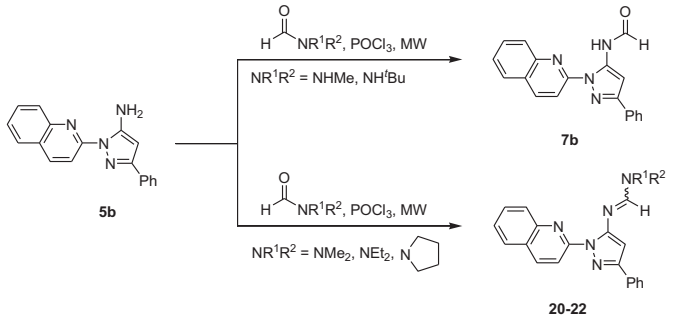
Table 3
Reactions *N*-1-phenyl-5-aminopyrazoles **1a**–**e**, *N*-1-(2-pyridinyl)-5-aminopyrazoles **4a**–**e**, *N*-1-(2-quinolinyl)-5-aminopyrazoles **5a**–**e**, and 1-methyl-1*H*-pyrazol-5-amine **6** with formamide in the presence of $POCl_3$

Pyrazoles (**1a**–**e**, **4a**–**e**, **5a**–**e** and **6**)			Products	
			Pyrazolo[3,4-*d*] 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	H	**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)-3-phenylpyrazole (**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 $POCl_3$ 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*-pyrazol-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**



Scheme 5.

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

3. Conclusion

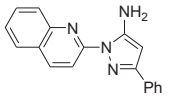
Various Vilsmeier agents were synthesized by using formamide or *N*-methylformamide in the presence of phosphorous oxychloride $POCl_3$. The *N*-1-substituted-aminopyrazoles, including *N*-1-phenyl-5-aminopyrazoles, *N*-1-(2-pyridinyl)-5-aminopyrazoles, and *N*-1-(2-quinolinyl)-5-aminopyrazoles, were 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 Vilsmeier-type reaction. Furthermore, the plausible reactive mechanisms were proposed to describe the unexpected result.

4. Experimental section

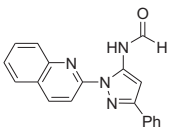
4.1. General procedure

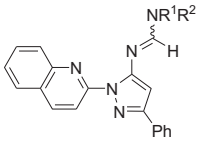
All chemicals were reagent grade and used as purchased. All reactions were carried out under nitrogen atmosphere and monitored by TLC analysis. Flash column chromatography was carried out on silica gel (230–400 mesh). Commercially available reagents were used without further purification unless otherwise 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*-toluoylacetonitrile 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 $CDCl_3$ as solvent. Carbon-13 NMR spectra were obtained on a Bruker (50 or 100 MHz) spectrometer by used of $CDCl_3$ as solvent. Carbon-13 chemical shifts are referenced to the center of the $CDCl_3$ 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^1R^2





Substrates	R^1	R^2	Formamide (**7b**) Products	Yield (%)	Formamidines (**20**–**22**) Products	Yield (%)
5b	H	Me	**7b**	90	—[a]	—[a]
5b	H	*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*-(1*H*-pyrazol-5-yl)formamidines 3a–e

The reliable procedure involved the treatment of *N*-1-phenyl-5-aminopyrazoles (**1a**–**e**, 1.0 equiv) with catalytic amount of $POCl_3$ (~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 $MgSO_4$, 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; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.32 (s, 9H, $CH_3\times3$), 2.92 (s, 3H, CH_3), 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); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.8 (CH_3), 30.4 ($CH_3\times3$), 32.4 (CH_3), 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 $C_{15}H_{20}N_4$; 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-1H-pyrazol-5-yl)-N-methyl-methanimidamide (**3b**).* Mp (purified by column chromatography on silica gel) 157–158 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.90–2.92 (m, 3H, CH_3), 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); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.7 (CH_3), 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 $C_{17}H_{16}N_4$; 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)-1H-pyrazol-5-yl)-N-methyl-methanimidamide (**3c**).* Mp (purified by column chromatography on silica gel) 182–183 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.21–2.36 (m, 3H, CH_3), 2.82–2.95 (m, 3H, CH_3), 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); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.3 (CH_3), 27.8 (CH_3), 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 $C_{18}H_{18}N_4$; 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-methyl-methanimidamide (**3d**).* Mp (purified by column chromatography on silica gel) 179–180 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.95–3.03 (m, 3H, CH_3), 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); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.9 (CH_3), 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 $C_{17}H_{15}ClN_4$; 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)-1H-pyrazol-5-yl)-N-methyl-methanimidamide (**3e**).* Mp (purified by column chromatography on silica gel) 160–161 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.87–2.89 (m, 3H, CH_3), 3.82 (s, 3H, OCH_3), 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); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.7 (CH_3), 55.3 (OCH_3), 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 $C_{18}H_{18}N_4O$; 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 $POCl_3$ (~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 $MgSO_4$, 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-1H-pyrazol-5-yl)-formamide (**6a**).* Mp (purified by column chromatography on silica gel) 210–212 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.33 (s, 9H, $CH_3\times3$), 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.0 ($CH_3\times3$), 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 $C_{13}H_{16}N_4O$; 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-1H-pyrazol-5-yl)-formamide (**6b**).* Mp (purified by column chromatography on silica gel) 117–118 °C; ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR (50 MHz, $CDCl_3$) 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 $C_{15}H_{12}N_4O$; 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)-1H-pyrazol-5-yl)-formamide (**6c**).* Mp (purified by column chromatography on silica gel) 123–124 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.37 (s, 3H, CH_3), 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); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.3 (CH_3), 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 $C_{16}H_{14}N_4O$; 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)-1H-pyrazol-5-yl)-formamide (**6d**).* Mp (purified by column chromatography on silica gel) 158–159 °C; ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR (50 MHz, $CDCl_3$) 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 $C_{15}H_{11}ClN_4O$; 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)-1H-pyrazol-5-yl)-formamide (**6e**).* Mp (purified by column chromatography on silica gel) 144–145 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.84 (s, 3H, OCH_3), 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.3 (OCH_3), 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 $C_{16}H_{14}N_4O_2$; 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; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.46 (s, 9H, $CH_3\times3$), 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, $CDCl_3$) δ 29.7, 30.0 ($CH_3\times3$), 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 $C_{17}H_{18}N_4O$; 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; ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR (50 MHz, $CDCl_3$) 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 $C_{19}H_{14}N_4O$; 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; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.39 (s, 3H, CH_3), 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); ^{13}C NMR (50 MHz, $CDCl_3$) 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 $C_{20}H_{16}N_4O$; 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; ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR (50 MHz, $CDCl_3$) 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 $C_{19}H_{13}ClN_4O$; 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-5-yl)-formamide (**7e**).* Mp (purified by column chromatography on silica gel) 144–145 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.84 (s, 3H, OCH_3), 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.3 (OCH_3), 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 $C_{20}H_{16}N_4O_2$; 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[3,4-*d*]pyrimidine products 12a–e, 13a–e, and 14a–e

The reliable procedure involved the treatment of *N*-1-phenyl-5-aminopyrazoles, *N*-1-phenyl-5-aminopyrazoles (**1a-e**, 1.0 equiv),

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 $POCl_3$ (~3 equiv) with formamide (2 mL) in CH_2Cl_2 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 $MgSO_4$, 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; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.55 (s, 9H, 3×CH_3), 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{15}H_{16}N_4$ ($M+H^+$) 253.1375, found 253.1377. Anal. Calcd for $C_{15}H_{16}N_4$; 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). ^{1}H NMR ($CDCl_3$, 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). ^{13}C NMR (125 MHz, $CDCl_3$): 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 $C_{17}H_{12}N_4$: 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-1H-pyrazolo[3,4-d]pyrimidine (**12c**).* Mp (purified by column chromatography on silica gel) 139–140 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.43 (s, 3H, CH_3), 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4 (CH_3), 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 $C_{18}H_{14}N_4$ ($M+H^+$) 287.1218, found 287.1216. Anal. Calcd for $C_{18}H_{14}N_4$; 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-1H-pyrazolo[3,4-d]pyrimidine (**12d**).* Mp (purified by column chromatography on silica gel) 196–197 °C; ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{17}H_{11}ClN_4$ ($M+H^+$) 307.0672, found 307.0671. Anal. Calcd for $C_{17}H_{11}ClN_4$; 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-1H-pyrazolo[3,4-d]pyrimidine (**12e**).* Mp (purified by column chromatography on silica gel) 175–176 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.87 (s, 3H, CH_3), 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.4 (CH_3), 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 $C_{18}H_{14}1N_4O$ ($M+H^+$) 303.1168, found 303.1169. Anal. Calcd for $C_{18}H_{14}1N_4O$; 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**).* ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.50 (s, 9H, CH_3), 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{14}H_{15}N_5$; 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; ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{16}H_{11}N_5$; 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; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.42 (s, 1H, CH_3), 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{17}H_{13}N_5$; 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; ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{16}H_{10}ClN_5$; 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 ($CDCl_3$, 500 MHz) δ 3.84 (s, 1H, CH_3), 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); ^{13}C 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 $C_{17}H_{13}N_5O$; 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 ($CDCl_3$, 500 MHz) δ 1.58 (s, 3H, CH_3), 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{18}H_{17}N_5$; 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 ($CDCl_3$, 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{20}H_{13}N_5$; 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 ($CDCl_3$, 500 MHz) δ 2.42 (s, 3H, CH_3), 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{21}H_{15}N_5$; 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 ($CDCl_3$, 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{20}H_{12}ClN_5$; 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 ($CDCl_3$, 500 MHz) δ 3.86 (s, 3H, CH_3), 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{21}H_{15}N_5O$; 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 ($CDCl_3$, 500 MHz) δ 4.12 (s, 3H, CH_3), 8.11 (s, 1H), 9.00 (s, 1H), 9.15 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_6H_6N_4$; 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-5-aminopyrazoles, *N*-1-(2-quinolinyl)-5-aminopyrazoles (**5b**, 1.0 equiv) with catalytic amount of $POCl_3$ (~3 equiv) with *N,N*-dimethylformamide (DMF), *N,N*-diethylformamide (DEF), or 1-pyrrolidinecarboxaldehyde (2 mL) in CH_2Cl_2 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 $MgSO_4$, 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 ($CDCl_3$, 200 MHz) δ 2.96 (s, 6H, CH_3×2), 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); ^{13}C NMR (50 MHz, $CDCl_3$) δ 34.5 (CH_3), 40.3 (CH_3), 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 $C_{21}H_{19}N_5$; 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 ($CDCl_3$, 500 MHz) δ 1.08–1.11 (m, 3H, CH_3), 1.08–1.11 (m, 3H, CH_3), 3.21–3.25 (m, 2H, CH_2), 3.44–3.48 (m, 2H, CH_2), 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.5 (CH_3), 12.7 (CH_3), 40.0 (CH_2), 41.7 (CH_2), 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 $C_{23}H_{23}N_5$; 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; ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR (50 MHz, $CDCl_3$) 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 $C_{23}H_{21}N_5$; 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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