Study on One-pot Biginelli-like Synthesis of Pyrazolo[3,4-*d*]pyrimidines in Bronsted Acidic Ionic Liquid Under Sonication and its Mechanism

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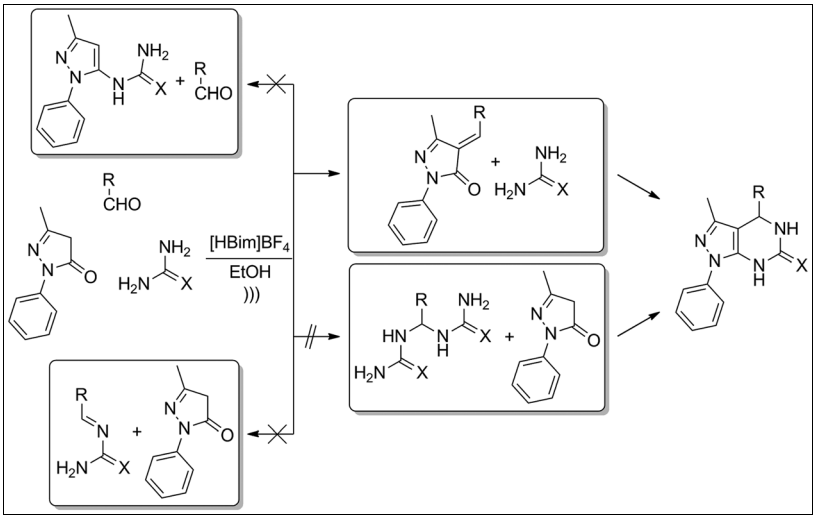

Pyrazolo[3,4-*d*]pyrimidine derivatives were synthesized using ionic liquid, 1-butylimidazolium tetrafluoroborate, under ultrasound irradiation at ambient condition without any added catalyst. Mechanistic pathway based on the catalytic role of ionic liquid has been proposed. This method offers the advantages of simple procedure, milder reaction condition, easier workup and improved yield over the conventional method. The ionic liquid could be recycled at least three times with marked retention in its activity.

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INTRODUCTION

Pyrazolo[3,4-*d*]pyrimidine derivatives exhibit various biological [1] and pharmacological [2] activities. Several methods and catalysts have been reported for the synthesis of pyrazolo[3,4-*d*]pyrimidines [3]. Besides, Biginelli reaction is one of the most familiar and widely employed multicomponent reactions because of diverse products that can be prepared in a single step just by varying reaction substrates [4]. Accordingly, few methods have been reported to synthesize pyrazolo[3,4-*d*]pyrimidines using 5 (4H)-pyrazolones [5]. However, these methods are inadequate as far as green chemistry aspects are concerned. Moreover, the multistep syntheses lack the ease of one-step procedure. Thus, literature survey come up to the need to develop a protocol, which provides better results under milder reaction conditions.

In recent years, significant progress has been made in the application of ionic liquids (ILs) in catalytic processes because of their versatile properties [6]. Thus, use of IL as reactions media may offer a convenient solution to both the solvent emission and catalytic recycling problem with high efficiency. Ultrasound irradiation has been considered as a clean protocol and increasingly been used in organic syntheses [7] because it leads to the acceleration of reactions in homogeneous or heterogeneous systems with higher yield, better selectivity and under milder conditions within shorter reaction time [8].

In continuation to our efforts to develop the non-classical and better protocols for the organic conversions [9], herein we report one-pot synthesis of pyrazolo[3,4-*d*]pyrimidines from aromatic aldehydes, 3-methyl-1-phenyl-5(4H)-pyrazolone and urea/thiourea in 1-butylimidazolium tetrafluoroborate, $[HBim]BF_4$, as the reaction medium and promoter under ultrasound irradiation at ambient condition (Scheme 1).

RESULTS AND DISCUSSION

Optimization of the reaction conditions. Owing to its intrinsic Bronsted acidic nature IL, $[HBim]BF_4$, was chosen and synthesized by the reported method [10]. Initially, 4-nitrobenzaldehyde (**1a**), 3-methyl-1-phenyl-5 (4H)-pyrazolone (**2**), and urea (**3a**) were taken as the model substrates to optimize the reaction conditions. Results are shown in Table 1. When reaction was run in neat IL (Table 1, Entry 5), Knoevenagel adduct (**4a**), as an intermediate, (*Reaction mechanism*) was precipitated

Scheme 1

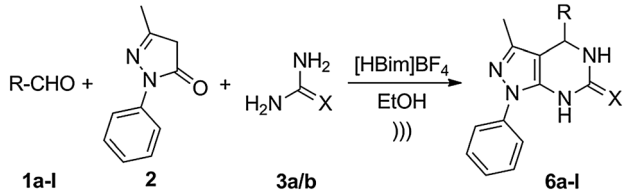


Table 1

Effect of different conditions on model reaction.[a]

Entry	Reaction condition	Time (h)	Yield (%)	
			Heat[b]	US[c]
1	Methanol	10	0	0
2	THF	10	0	0
3	MDC	10	0	0
4	Ethanol	10	0	0
5	$[HBim]BF_4$ (3 g)	5	Trace	15
6	Methanol + HCl[d]	7	32	41
7	THF + HCl[d]	7.5	30	38
8	MDC + HCl[d]	7.5	27	34
9	Ethanol + HCl[d]	6.5	41	52
10[e]	$[HBim]BF_4$ + methanol	5	49	62
11[e]	$[HBim]BF_4$ + THF	5.5	46	56
12[e]	$[HBim]BF_4$ + MDC	5.5	45	55
13[e]	$[HBim]BF_4$ + ethanol	4.5	57	70

[a]4-Nitrobenzaldehyde (0.01 mol), 3-methyl-1-phenyl-5(4H)-pyrazolone (0.011 mol) and urea (0.01 mol).
[b]Isolated yield under reflux condition.
[c]Isolated yield at ambient temperature under ultrasound irradiation.
[d]0.5 mL 11.3 N HCl.
[e]IL (3 g) + co-solvent (5 mL), without any added catalyst.

out and it was found difficult to carry forward the reaction. Therefore several solvents were attempted as co-solvent to solubilize the intermediate for further progress of the reaction. IL containing ethanol as a co-solvent under ultrasound irradiation was found to be the optimum reaction condition among all (Table 1, Entry 13).

Reaction acceleration. During optimization of the reaction procedure, we observed formation of desired product in neat IL (Table 1, Entry 5), whereas molecular solvents failed to yield the desired product without any added catalyst (Table 1, Entry 1–4). Thus, IL has not only provided the reaction medium but has also promoted the reaction. This acceleration was explained in terms of H-bonding by IL activating the reaction substrates [11]. Moreover, IL has exhibited better catalytic effect than HCl in terms of yield and time (Compare Table 1, Entries 6–9 with 10–13).

It is observed that ultrasound irradiation accelerated the reaction better than conventional method (Table 1). Under the same reaction medium, reactions under ultrasonic irradiation have led to relatively higher yields at ambient temperature, whereas comparable results are only obtained under reflux. Sonochemistry is a result of acoustic cavitation that comprises formation and collapse of microbubbles [12]. These produce high local temperature and pressure in liquids that enhance the reaction. A mechanical effect of cavitation, high pressure jetting, enhances mass transfer, which in turn may have enhanced the reaction in non-homogeneous system (Table 1, Entry 5). Ultrasonic shockwaves in reaction media induce reduction of particle size and enhance the collision chances of substrates to precede reaction smoothly.

Thus, in conventional method, change over from "heating at reflux" to "sonication at ambient temperature" has improved 11% of yield (Table 1, Entry 9). Replacement of HCl with IL has improved 16% of yield with reduction of 2 h in reaction time by conventional method (Table 1, Entries 9 and 13, Heating). A marked improvement of 29% of yield within 4.5 h was observed while changing over from "heating at reflux in EtOH + HCl" to "sonication at ambient temperature in EtOH + IL" (Table 1, Entry 9 – Heating and Entry 13 – Ultrasound). The IL, having negligible vapor pressure, as the reaction media should have changed the characteristics of cavitation and forced less volatile substrates to undergo the cavitational activation. Hence, it was the synergy of ultrasound and IL as the reaction medium considered responsible for acceleration of reaction in the present protocol.

Scope of the synthesis of pyrazolo[3,4-d]pyrimidine derivatives. The generality of this reaction was examined by employing various aromatic aldehydes (**1b–l**) and thiourea (**3b**) under optimized reaction conditions. Results are shown in Table 2. All the compounds were characterized by physical and spectroscopic methods. Results showed that nature of the substituent on aromatic aldehyde did not affect the reaction much in terms of yield. However, the reactions pertaining to aldehydes containing electron-withdrawing group were observed to be little faster than that of aldehydes containing electron-donating group.

Table 2

Synthesis of pyrazolo[3,4-d]pyrimidine derivatives in IL under sonication.

Product	R	X	Time (h)	Yield (%)[a]
6a	4-NO_2-C_6H_4-	O	4.5	70
6b	4-OH-C_6H_4-	O	5	62
6c	4-Cl-C_6H_4-	O	4.5	64
6d	C_6H_5-	O	5	58
6e	4-OCH_3-C_6H_4-	O	5	67
6f	2-NO_2-C_6H_4-	O	4.5	65
6g	3-Cl-C_6H_4-	O	4.5	66
6h	4-CH_3-C_6H_4-	O	5	70
6i	2-OH-C_6H_4-	O	5	63
6j	4-OCH_3-C_6H_4-	S	5	66
6k	C_6H_5-	S	5	59
6l	2-OH-C_6H_4-	S	5	60

[a]Isolated yield

This strategy offers the first example of ultrasound and IL promoted one-pot synthesis of pyrazolo[3,4-*d*]pyrimidine derivatives from aromatic aldehyde, pyrazolone and urea/thiourea at ambient temperature. In terms of yield, this protocol has been proved better as compared with presently available one-pot synthetic protocol furnishing 28–48% of product [5c].

Reusability of IL. The activity of recycled IL was studied on model reaction in terms of yield of desired product. The IL could be reused at least three times without much depletion in its activity. Yields of the product obtained using recycled IL in three consecutive reactions were 69, 67 and 63% against 70% using fresh IL. Slight loss in activity of IL may be ascribed to presence of trace impurities from the reaction or degradation of IL during recovery.

Reaction mechanism. The Biginelli reaction is quiet under dispute from mechanistic view point. Knoevenagel adduct (**4**), bisureid derivative (**5**), and enamine derivative (**8**) were suggested to be involved as the intermediates [13]. A mechanism based on the formation of carbenium ion in acid-catalyzed Knoevenagel reaction was also included [14]. It was also suggested to proceed via formation of an imine (**9**) or iminium ion as a key intermediate in Lewis acidic or Protic acidic media [15]. We were interested to recognize the mechanistic pathway in present protocol because the reaction medium was Bronsted acidic.

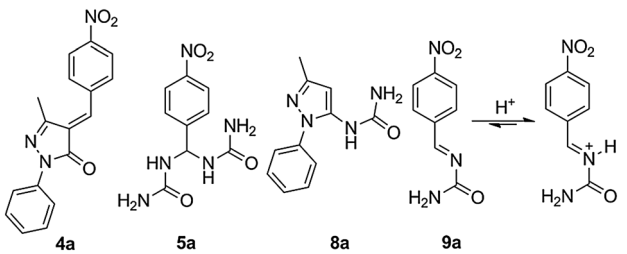


Figure 1. Possible reaction intermediates.

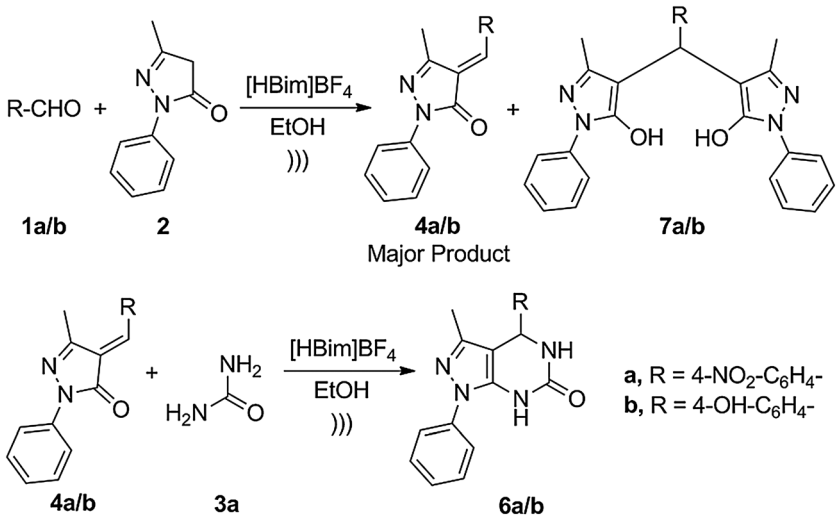
To investigate the reaction mechanism, we assumed that the model reaction might have proceeded through any of the intermediates shown in Figure 1. Following three sets of equimolar mixtures of the substrates for the model reaction were irradiated under optimum reaction condition; (**I**) 4-nitrobenzaldehyde with 3-methyl-1-phenyl-5(4H)-pyrazolone, (**II**) 4-nitrobenzaldehyde with urea, and (**III**) 3-methyl-1-phenyl-5(4H)-pyrazolone with urea.

In case of set **I**, Knoevenagel adduct (**4a**) together with bis-pyrazolone derivative (**7a**) as a Knoevenagel–Michael adduct were isolated and characterized (Scheme 2). Knoevenagel adduct (**4a**) was then treated with equimolar amount of urea under optimum reaction condition to confirm its intermediacy. This resulted in pyrazolo[3,4-*d*] pyrimidine (**6a**).

In case of set **II**, the reaction mixture turned dense from which formed intermediates could not be isolated. We assumed either compound **5a** or **9a** or both as the intermediate. Reaction mixture was further treated with pyrazolone (**2**), which resulted in the formation of Knoevenagel adduct (**4a**) and pyrazolo[3,4-*d*]pyrimidine (**6a**). This might be due to the formation of **5a** or **9a** in poor amount, leaving behind the aldehyde, which in turn has reacted with pyrazolone added afterwards in the reaction mixture.

To synthesize compound **5a**, 1:2 amounts of 4-nitrobenzaldehyde and urea were condensed in toluene containing catalytic amount of p-toluensulfonic acid for 24 h under reflux [16]. Imine (**9a**) might also be an intermediate; however, we failed to synthesize it. No reports are available on the occurrence of imine using aldehyde and urea/thiourea as the substrates. Hence, equimolar mixture

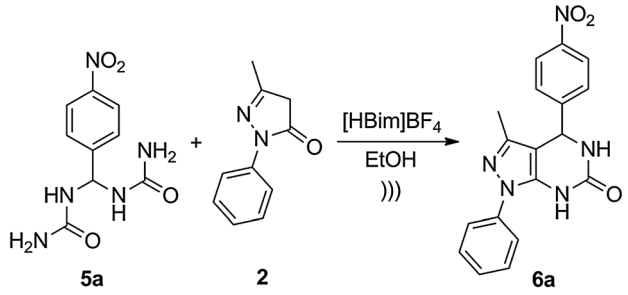
Scheme 2



of bisureid (**5a**) and pyrazolone (**2**) was irradiated under optimum reaction condition to confirm its intermediacy, which resulted in pyrazolo[3,4-*d*]pyrimidine (**6a**) (Scheme 3).

Thus, we suspected that the reaction might have proceeded through the formation of bisureid in the present method. The mass spectrum of the dense reaction mixture in set **II** also provided the useful evidence for intermediacy of bisureid (**5a**) (Supporting information).

Scheme 3



In case of set **III**, the substrates remained unchanged even after prolong time (checked by TLC). This eliminates the possibility of reaction following enamine intermediate (**8a**).

Thus, we had two intermediates (**4a** and **5a**) in hand to follow the reaction through, which caused dilemma for the precise intermediate in one-pot reaction under study. In all cases, it was observed during the course of reaction that the reaction mass gradually turned colored. This indicated that Knoevenagel condensation of aldehydes (**1a–l**) with pyrazolone (**2**) has overtaken the formation of bisureid derivatives (also checked by TLC). Reaction mixture, from one-pot model reaction after 15 min, was analyzed by mass spectrometry for verification of our claim. The mass spectrum provided evidences for Knoevenagel adduct and unreacted model substrates only (Figure 2). This suggested that the one-pot three-component reaction has proceeded through the formation of Knoevenagel adduct surpassing formation of bisureid derivatives in the present protocol.

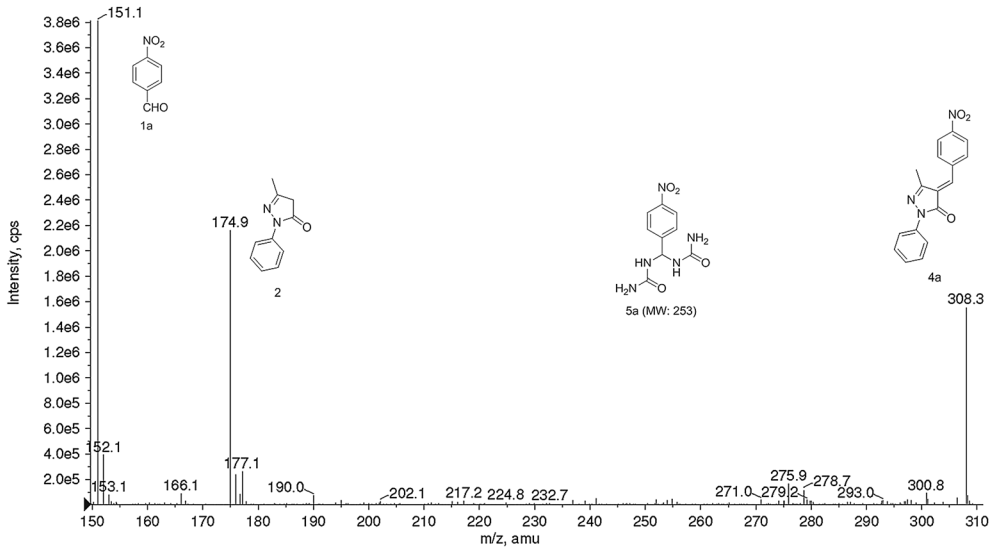
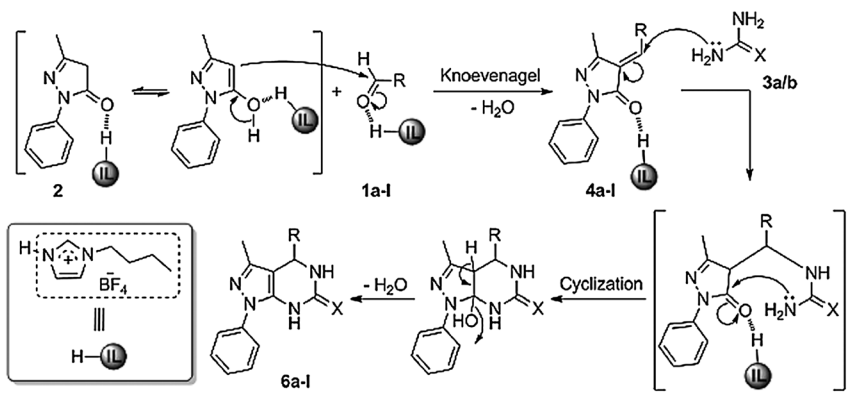


Figure 2. Mass spectrum of one-pot model reaction mixture after 15 min.

Scheme 4



Knoevenagel pathway would exhibit a step with the activation barrier [15], whereas reactions with activation barrier are accelerated with pressure [17]. So the reaction acceleration in present protocol is elucidated in terms of the "hot spot" phenomenon [12].

On the basis of these facts, mechanistic pathway has been proposed (Scheme 4). It involves initial formation of intermediate (**4a–l**) by Knoevenagel condensation of aldehydes (**1a–l**) and pyrazolone (**2**). Subsequent Michael addition of urea/thiourea (**3a/b**) followed by cyclization and dehydration gives the corresponding pyrazolo[3,4-*d*] pyrimidine derivatives (**6a–l**).

CONCLUSION

We have demonstrated an improved method for the preparation of pyrazolo[3,4-*d*]pyrimidine derivatives in $[HBim]BF_4$ without any added catalyst. Ultrasonic irradiation has shown better reaction acceleration through cavitation at ambient temperature than that of conventional method under reflux. IL has exhibited better catalytic effect than HCl in terms of yield and time. Knoevenagel adduct is suggested as the intermediate for this type of reactions in Bronsted acidic media. The method offers advantage of simple procedure, milder reaction condition, easier workup, and improved yield over conventional method.

EXPERIMENTAL

All reactions were carried out with commercially available reagents and used without further purification. 3-Methyl-1-phenyl-5(4H)-pyrazolone was synthesized by reported method [18]. Ultrasonication was performed in D-Compact ultrasonic cleaner (Trans-O-Sonic, Mumbai, Maharashtra, India) with a frequency of 50 kHz and power of 250 W. The reaction flask was suspended in the center of ultrasonic bath so as surface of the reactants remains slightly lower than the level of water in the bath. The temperature of water bath was controlled at 25–30°C. TLC was carried out on fluorescent coated aluminum plates (0.25 mm thick, silica gel 60 F254 coated, Merck KGaA, Darmstadt, Germany), and components were detected by UV light. The columns were hand-packed with silica gel 60–120 mesh. Melting points were measured in open capillaries and are uncorrected. IR spectra were recorded on Shimadzu FTIR 8401 spectrophotometer (Shimadzu Corporation, Nakagyo-ku, Kyoto, Japan) using KBr pellets and frequencies of only characteristic peaks are expressed in reciprocal centimeter. ^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 on Bruker Avance 400 MHz spectrometer (Bruker, Billerica, Massachusetts, USA). The chemical shifts are reported in δ parts per million. Mass spectral data were obtained using Applied Biosystems API 2000 spectrometer (Applied Biosystems Inc., Foster City, California, USA). Elemental analyses were performed on PerkinElmer 2400 series-II elemental analyzer (PerkinElmer Inc., Waltham, Massachusetts, USA).

Synthesis of pyrazolo[3,4-d]pyrimidine derivatives under conventional conditions. A 50 mL flask, fitted with a reflux condenser, was charged with a mixture of aldehyde (**1a–l**, 0.01 mol), 3-methyl-1-phenyl-5(4H)-pyrazolone (**2**, 0.011 mol) and urea/thiourea (**3a/b**, 0.01 mol) in absolute ethanol (30 mL) containing HCl as catalyst (0.5 mL, 11.3 N). The mixture was heated under reflux for the required time period. After completion of reaction (as indicated by TLC), the reaction mixture was cooled to room temperature and then poured into crushed ice and stirred for 15–20 min. The precipitated crude product was filtered, washed with cold ethanol, dried, and purified by column chromatography.

Synthesis of pyrazolo[3,4-d]pyrimidine derivatives in IL under ultrasound irradiation. A 50 mL flask was charged with a mixture of aldehyde (**1a–l**, 0.01 mol), 3-methyl-1-phenyl-5(4H)-pyrazolone (**2**, 0.011 mol) and urea/thiourea (**3a/b**, 0.01 mol) in IL (3 g) containing ethanol (5 mL). The reaction mixture was irradiated by ultrasound at ambient temperature for required hours. After completion of reaction (as indicated by TLC), insoluble bis-pyrazolone derivative as the side product was isolated from the reaction mixture by simple filtration in all cases. Filtrate containing the desired product was then poured into crushed ice and stirred for 15–20 min. The solid mass thus separated was collected by filtration, washed with cold ethanol, dried, and crystallized from ethanol. The aqueous filtrate was then subjected to distillation at 80°C under reduced pressure (10 mmHg) for 4 h to leave behind the IL in almost complete recovery. Thus, recycled IL was found active enough to be reused in three subsequent reactions.

3-Methyl-4-(4-nitrophenyl)-1-phenyl-4,5-dihydro-1H-pyrazolo [3,4-d]pyrimidin-6(7H)-one (6a). Solid; $C_{18}H_{15}N_5O_3$; mp 269°C; IR (KBr ν, cm^{-1}): 3253 (N–H), 3090 (Ar–H), 2850 (C–H), 1680 (C═O); ^1H NMR (400 MHz, DMSO-d_6) δ: 2.42 (s, 3H, CH_3), 5.23 (s, 1H, CH), 7.32 (t, J = 6.8 Hz, 2H, Ar–H), 7.46–7.54 (m, 5H, Ar–H), 7.70 (d, J = 7.6 Hz, 2H, Ar–H), 8.16 (s, 1H, NH), 8.38 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 11.65, 33.25, 104.64, 121.83, 123.94, 127.05, 129.11, 129.56, 133.85, 134.65, 136.56, 140.32, 146.47, 146.67 (C═O); ESI–MS (*m/z*): 350.1 (M^{+1}); Elemental *Anal*. Calcd (%) – C 61.89, H 4.33, N 20.05; Found (%) – C 61.81, H 4.32, N 20.01.

4-(4-Hydroxyphenyl)-3-methyl-1-phenyl-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6(7H)-one (6b). Solid; $C_{18}H_{16}N_4O_2$; mp 254°C; IR (KBr ν, cm^{-1}): 3401 (O–H), 3180 (N–H), 3082 (Ar–H), 2880 (C–H), 1670 (C═O); ^1H NMR (400 MHz, DMSO-d_6) δ: 2.44 (s, 3H, CH_3), 5.19 (s, 1H, CH), 7.42–7.55 (m, 9H, Ar–H), 8.01 (s, 1H, NH), 8.17 (s, 1H, NH), 9.10 (s, 1H, Ar–OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.98, 64.86, 120.79, 121.65, 125.69, 127.51, 129.95, 131.92, 133.42, 135.88, 140.21, 144.42, 148.68 (C═O), 155.12 (C–OH); ESI–MS (*m/z*): 321.2 (M^{+1}); Elemental *Anal*. Calcd (%) – C 67.49, H 5.03, N 17.49; Found (%) – C 67.41, H 5.00, N 17.41.

4-(4-Chlorophenyl)-3-methyl-1-phenyl-4,5-dihydro-1H-pyrazolo [3,4-d]pyrimidin-6(7H)-one (6c). Solid; $C_{18}H_{15}ClN_4O$; mp 235°C; IR (KBr ν, cm^{-1}): 3260 (N–H), 3088 (Ar–H), 2843 (C–H), 1678 (C═O); ^1H NMR (400 MHz, DMSO-d_6) δ: 2.48 (s, 3H, CH_3), 5.50 (s, 1H, CH), 7.24 (t, J = 7.6 Hz, 2H, Ar–H), 7.42 (d, J = 7.6 Hz, 2H, Ar–H), 7.51–7.59 (m, 5H, Ar–H), 7.95 (s, 1H, NH), 8.24 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 12.38, 50.48, 108.24, 122.47, 128.50, 129.01, 129.58, 130.47, 137.68, 138.83, 143.23, 146.24, 150.48 (C═O); ESI–MS (*m/z*): 339.3 (M^{+1}); Elemental *Anal*. Calcd (%) – C 63.81, H 4.46, N 16.54; Found (%) – C 63.74, H 4.40, N 16.59.

3-Methyl-1,4-diphenyl-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6(7H)-one (6d). Solid; $C_{18}H_{16}N_4O$; mp 165°C; IR (KBr ν, cm^{-1}): 3236 (N–H), 3060 (Ar–H), 2890 (C–H), 1681 (C═O); ^1H NMR (400 MHz, DMSO-d_6) δ: 2.44 (s, 3H, CH_3), 5.19 (s, 1H, CH),

7.11–7.48 (m, 10H, Ar–H), 8.13 (s, 1H, NH), 8.21 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.52, 40.57, 110.51, 123.33, 129.42, 131.05, 135.32, 144.61, 148.32, 158.06 (C═O); ESI–MS (*m/z*): 305.3 (M^{+1}); Elemental *Anal*. Calcd (%) – C 71.04, H 5.30, N 18.41; Found (%) – C 71.03, H 5.24, N 18.38.

4-(4-Methoxyphenyl)-3-methyl-1-phenyl-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6(7H)-one (6e). Solid; $C_{19}H_{18}N_4O_2$; mp 234°C; IR (KBr ν, cm^{-1}): 3260 (N–H), 3081 (Ar–H), 2860 (C–H), 1671 (C═O), 1118 (C–O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.45 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 5.20 (s, 1H, CH), 7.09–7.45 (m, 9H, Ar–H), 8.01 (s, 1H, NH), 8.30 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.01, 60.54, 75.62, 119.65, 124.59, 127.65, 130.89, 134.81, 136.40, 140.67, 144.78, 148.65, 155.89 (C═O), 161.32 (C–OCH_3); ESI–MS (*m/z*): 335.5 (M^{+1}); Elemental *Anal*. Calcd (%) – C 68.25, H 5.43, N 16.76; Found (%) – C 68.19, H 5.40, N 16.70.

3-Methyl-4-(2-nitrophenyl)-1-phenyl-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6(7H)-one (6f). Solid; $C_{18}H_{15}N_5O_3$; mp 182°C; IR (KBr ν, cm^{-1}): 3240 (N–H), 3074 (Ar–H), 2856 (C–H), 1675 (C═O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.44 (s, 3H, CH_3), 5.31 (s, 1H, CH), 7.01–7.49 (m, 8H, Ar–H), 7.81 (s, 1H, Ar–H), 8.42 (s, 1H, NH), 8.65 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 12.98, 41.98, 102.46, 119.65, 123.54, 125.12, 125.87, 127.99, 131.84, 136.64, 141.58, 144.42, 148.64 (C═O); ESI–MS (*m/z*): 350.2 (M^{+1}); Elemental *Anal*. Calcd (%) – C 61.89, H 4.33, N 20.05; Found (%) – C 61.83, H 4.30, N 20.00.

4-(3-Chlorophenyl)-3-methyl-1-phenyl-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6(7H)-one (6g). Solid; $C_{18}H_{15}ClN_4O$; mp 135°C; IR (KBr ν, cm^{-1}): 3255 (N–H), 3053 (Ar–H), 2858 (C–H), 1670 (C═O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.49 (s, 3H, CH_3), 5.13 (s, 1H, CH), 7.08 (d, J = 7.8 Hz, 2H, Ar–H), 7.20–7.52 (m, 7H, Ar–H), 8.20 (s, 1H, NH), 8.75 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 15.12, 51.89, 119.48, 121.09, 130.11, 132.04, 132.57, 146.76, 151.48, 160.23 (C═O); ESI–MS (*m/z*): 339.5 (M^{+1}); Elemental *Anal*. Calcd (%) – C 63.81, H 4.46, N 16.54; Found (%) – C 63.75, H 4.40, N 16.42.

3-Methyl-1-phenyl-4-(p-tolyl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6(7H)-one (6h). Solid; $C_{19}H_{18}N_4O$; mp 189°C; IR (KBr ν, cm^{-1}): 3252 (N–H), 3086 (Ar–H), 2854 (C–H), 1692 (C═O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.35 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 5.05 (s, 1H, CH), 7.10–7.20 (m, 4H, Ar–H), 7.45–7.50 (m, 5H, Ar–H) 7.98 (s, 1H, NH), 8.13 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.59, 55.09, 114.03, 123.31, 124.34, 128.27, 129.62, 130.03, 133.01, 137.11, 137.97, 142.05, 145.71, 148.34, 154.35 (C═O); ESI–MS (*m/z*): 319.4 (M^{+1}); Elemental *Anal*. Calcd (%) – C 71.68, H 5.70, N 17.60; Found (%) – C 71.60, H 5.64, N 17.50.

4-(2-Hydroxyphenyl)-3-methyl-1-phenyl-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6(7H)-one (6i). Solid; $C_{18}H_{16}N_4O_2$; mp 179°C; IR (KBr ν, cm^{-1}): 3410 (O–H), 3240 (N–H), 3070 (Ar–H), 2860 (C–H), 1695 (C═O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.43 (s, 3H, CH_3), 5.28 (s, 1H, CH), 7.51–7.65 (m, 9H, Ar–H), 8.10 (s, 1H, NH), 8.34 (s, 1H, NH), 8.95 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 12.64, 37.65, 103.62, 116.98, 120.82, 121.67, 125.35, 125.97, 127.98, 135.65, 142.32, 144.85, 150.95 (C═O), 152.51 (C–OH); ESI–MS (*m/z*): 321.3 (M^{+1}); Elemental *Anal*. Calcd (%) – C 67.49, H 5.03, N 17.49; Found (%) – C 67.42, H 5.01, N 17.43.

4-(4-Methoxyphenyl)-3-methyl-1-phenyl-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidine-6(7H)-thione (6j). Solid; $C_{19}H_{18}N_4OS$; mp 253°C; IR (KBr ν, cm^{-1}): 3252 (N–H), 3072 (Ar–H), 2875 (C–H), 1210 (C–O), 1082; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.15 (s, 3H, CH_3), 3.68 (s, 3H, OCH_3), 4.89 (s, 1H, CH), 7.11–7.39 (m, 9H, Ar–H), 8.56 (s, 1H, NH), 8.80 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.01, 50.85, 53.91, 113.95, 116.84, 124.85, 125.36, 128.98, 136.25, 139.54, 143.65, 149.84, 155.64 (C–OCH_3), 159.97 (C═S); ESI–MS (*m/z*): 351.6 (M^{+1}); Elemental *Anal*. Calcd (%) – C 65.12, H 5.18, N 15.99; Found (%) – C 65.08, H 5.10, N 15.82.

3-Methyl-1,4-diphenyl-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidine-6(7H)-thione (6k). Solid; $C_{18}H_{16}N_4S$; mp 180°C; IR (KBr ν, cm^{-1}): 3244 (N–H), 3075 (Ar–H), 2863 (C–H), 1067; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.21 (s, 3H, CH_3), 5.29 (s, 1H, CH), 7.15–7.49 (m, 10H, Ar–H), 8.50 (s, 1H, NH), 8.78 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.94, 49.87, 113.94, 124.94, 125.67, 130.84, 139.41, 143.65, 145.65, 157.31, 160.21 (C═S); ESI–MS (*m/z*): 321.5 (M^{+1}); Elemental *Anal*. Calcd (%) – C 67.47, H 5.03, N 17.49; Found (%) – C 67.41, H 5.00, N 17.43.

4-(2-Hydroxyphenyl)-3-methyl-1-phenyl-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidine-6(7H)-thione (6l). Solid; $C_{18}H_{16}N_4OS$; mp 187°C; IR (KBr ν, cm^{-1}): 3415 (O–H), 3250 (N–H), 3075 (Ar–H), 2863 (C–H), 1094; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.31 (s, 3H, CH_3), 5.35 (s, 1H, CH), 7.01–7.30 (m, 9H, Ar–H), 8.53 (s, 1H, NH), 8.77 (s, 1H, NH), 8.90 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.01, 40.98, 114.35, 119.65, 120.11, 125.51, 126.31, 126.98, 130.61, 138.94, 144.34, 147.98, 155.95 (C–OH), 161.04 (C═S); ESI–MS (*m/z*): 337.5 (M^{+1}); Elemental *Anal*. Calcd (%) – C 64.26, H 4.79, N 16.65; Found (%) – C 64.21, H 4.73, N 16.60.

4,4′-((4-nitrophenyl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (7a). Solid; $C_{27}H_{23}N_5O_4$; mp 220–222°C; IR (KBr ν, cm^{-1}): 3420 (O–H), 2960 (Ar–H), 2872 (C–H); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.34 (s, 6H, CH_3), 5.24 (s, 1H, CH), 7.32 (t, J = 7.2 Hz, 2H, Ar–H), 7.46–7.54 (m, 6H, Ar–H), 7.71 (d, J = 8 Hz, 4H, Ar–H), 8.17 (d, J = 8.8 Hz, 2H, Ar–H), 12.20 (brs, 2H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 11.59, 33.10, 104.70, 121.95, 123.90, 129.43, 136.34, 146.64, 150.05, 158.11; ESI–MS (*m/z*): 482.0 (M^{+1}); Elemental *Anal*. Calcd (%) – C 67.35, H 4.81, N 14.54; Found (%) – C 67.31, H 4.77, N 14.50.

4,4′-((4-hydroxyphenyl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (7b). Solid; $C_{27}H_{24}N_4O_3$; mp 160–162°C; IR (KBr ν, cm^{-1}): 3410 (O–H), 2955 (Ar–H), 2880 (C–H), 1691; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.45 (s, 6H, CH_3), 5.01 (s, 1H, CH), 6.72 (d, J = 8.4 Hz, 2H, Ar–H), 7.06 (d, J = 8.4 Hz, 2H, Ar–H), 7.36 (t, J = 7.6 Hz, 2H, Ar–H), 7.51 (t, J = 8 Hz, 4H, Ar–H), 7.71 (d, J = 8.4 Hz, 4H, Ar–H), 13.88 (brs, 3H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 11.24, 32.25, 105.26, 122.31, 129.60, 131.42, 135.75, 140.61, 146.51, 158.34; ESI–MS (*m/z*): 452.9 (M^{+1}); Elemental *Anal*. Calcd (%) – C 71.67, H 5.35, N 12.38; Found (%) – C 71.64, H 5.32, N 12.32.

3-Methyl-4-(4-nitrobenzylidene)-1-phenyl-1H-pyrazol-5(4H)-one (4a). Solid; $C_{17}H_{13}N_3O_3$; mp 173°C; IR (KBr ν, cm^{-1}): 3064 (Ar–H), 3033 (C–H), 1673 (C═O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.30 (s, 3H, CH_3), 6.93 (d, J = 8.8 Hz, 2H, Ar–H), 7.17 (t, d = 7.6 Hz, 1H, Ar–H), 7.40 (t, J = 8.4 Hz, 2H, Ar–H), 7.72 (s, 1H, CH), 7.90 (d, J = 7.6 Hz, 2H, Ar–H), 8.63 (d, J = 8.8, 2H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 12.62, 116.31, 117.57, 122.23, 124.18, 125.36, 128.42, 136.75, 137.81, 148.98, 150.11, 151.27, 162.62; ESI–MS (*m/z*): 308.3 (M^{+1}); Elemental *Anal*. Calcd (%) – C 66.44, H 4.26, N 13.67; Found (%) – C 66.39, H 4.22, N 13.63.

4-(4-Hydroxybenzylidene)-3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (4b). Solid; $C_{17}H_{14}N_2O_2$; mp 238°C; IR (KBr ν, cm^{-1}): 3410 (O–H), 3090 (C–H), 3052 (Ar–H), 1673 (C═O); ^{1}H NMR

(400 MHz, DMSO-d_6) δ: 2.32 (s, 3H, CH_3), 6.94 (d, J = 8.8 Hz, 2H, Ar–H), 7.18 (t, J = 7.6 Hz, 1H, Ar–H), 7.43 (t, J = 8.4 Hz, 2H, Ar–H), 7.70 (s, 1H, CH), 7.93 (d, J = 7.6 Hz, 2H, Ar–H), 8.64 (d, J = 8.8, 2H, Ar–H), 10.82 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.61, 116.31, 118.75, 123.11, 124.81, 125.36, 129.25, 137.87, 138.93, 148.98, 152.27, 162.45, 163.54; ESI–MS (*m/z*): 279.2 (M^{+1}); Elemental *Anal*. Calcd (%) – C 73.37, H 5.07, N 10.07; Found (%) – C 73.32, H 5.04, N 10.01.

1,1′-((4-Nitrophenyl)methylene)diurea (5a). 4-Nitrobenzaldehyde (**1a**, 0.03 mol), urea (**3a**, 0.06 mol), p-toluensulfonic acid (0.005 mol), and toluene (150 mL) were taken in a 250 mL flask fitted with a reflux condenser. The mixture was refluxed for 24 h. After completion of reaction, the precipitated product was filtered, washed with saturated aqueous solution of $NaHCO_3$ followed by water, dried, and characterized (Isolated yield 65%). Solid; $C_9H_{11}N_5O_4$; mp 190°C; IR (KBr ν, cm^{-1}): 3290 (N–H), 3064 (Ar–H), 2872 (C–H), 1673 (C═O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 5.80 (s, 4H, NH_2), 6.18 (t, J = 8.4 Hz, 1H, CH), 6.97 (d, J = 8 Hz, 2H, NH), 7.57 (d, J = 8.4 Hz, 2H, Ar–H), 8.21 (d, J = 8.4 Hz, 2H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 59.20, 123.74, 123.77, 146.95, 151.11, 158.17; ESI–MS (*m/z*): 254.0 (M^{+1}); Elemental *Anal*. Calcd (%) – C 42.69, H 4.38, N 27.66; Found (%) – C 42.64, H 4.32, N 27.61.

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