A Convenient Synthesis of New Pyrazolo[4,3-*d*]pyrimidines and Their Fused Heterocycles

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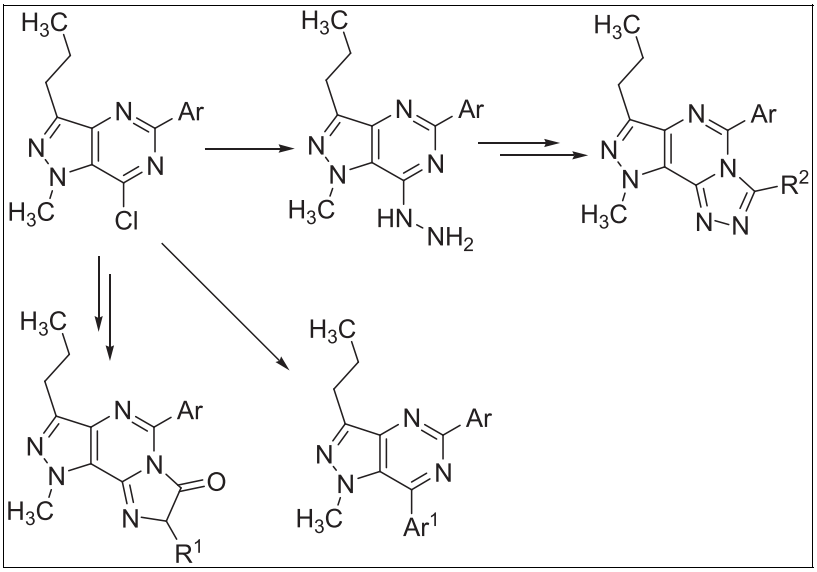

A series of some fused heterocycles originated from pyrazolopyrimidines were synthesized using 4-amino1-methyl-3-propyl-1*H*-pyrazole-5-carboxamide as a starting material. The nucleophilic substitution reactions with different amino acids followed by cyclization and *Suzuki–Miyaura* cross-coupling reactions with different aryl boronic acids of 7-chloro-5-(4-chlorophenyl)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-*d*] pyrimidine were performed. Also, the oxidative cyclization reactions of 1-(5-(4-chlorophenyl)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-7-yl)hydrazine with different aldehydes in the presence of diacetoxy iodobenzene are described. All the synthesized compounds were characterized by analytical and spectroscopic methods.

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INTRODUCTION

Analogous to sildenafil [1], 1*H*-pyrazolo[4,3-*d*]pyrimidines are a class of potent and selective second generation phosphodiesterase 5 (PDE-5) inhibitors [2]. In recent years, pyrazolopyrimidine-fused heterocycles are known to function as central nervous system depressants [3], neuroleptic agents [4], tuberculostatic [5], and adenosine receptors [6,7]. Some pyrazolopyrimidines act as antimicrobial, antifungal [8,9], and bronchodilatory agents [10]. Beside these, pyrazolopyrimidine derivatives show interesting pharmacological properties such as cyclic-dependent kinase inhibitors [11,12], antiproliferative agents [13], corticotropin-releasing factor antagonists [14], and antiviral agents [15]. Tomcufick et al. reported the application of pyrazolopyrimidines as antipyretic and analgesic agents [16]. There are few reports on the synthesis and chemistry of these compounds in literature [17–23]. The pyrazolo [4,3-*d*]pyrimidine ring system is one of them that has not received much attention, and very little is known about synthesis and chemical properties of these compounds [1,2,10–14].

Not only pyrazolopyrimidines but also their fused heterocycles such as pyrazolo-triazolo-pyrimidine and imidazo-pyrazolo-pyrimidine derivatives attract chemists owing to their impressive pharmacological properties [8,24]. The pyrazolo-triazolo-pyrimidine nucleus represented an attractive key intermediate for obtaining adenosine receptor antagonists [25–29]. Russo et al. reported anti-inflammatory activity of pyrazolo-triazolo-pyrimidines [30]. However, the literature survey reveals that the syntheses of these compounds have been very little explored [31–36].

Prompted with these findings, and our ongoing project to synthesize such nitrogen-containing heterocycles [37–40], efforts have been taken to develop the convenient synthetic

approaches for the synthesis of some new pyrazolo[4,3-*d*] pyrimidines and their fused heterocycles that might be of pharmacological importance.

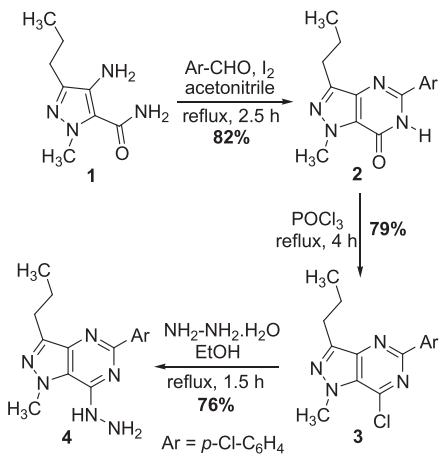
Previously, we have reported the synthesis of thieno [2,3-*d*]pyrimidine and indeno[2,1-*b*]thienopyrimidine derivatives through the cyclo-condensation reaction of 5-aminothiophene-4-carboxamide and 2-aminoindeno thiophene-3-carboxamide, respectively [41,42]. In continuation of this work and in the course of program directed toward the synthesis of novel pyrazolo[4,3-*d*]pyrimidine derivatives, we choose 4-amino-1-methyl-3-propyl-1*H*-pyrazole-5-carboxamide **1** as a substrate. Compound **1** was synthesized by literature procedure [43]. The regioselective condensation reaction of *p*-chlorobenzaldehyde with *o*-amino carboxamide **1** in the presence of acetonitrile and slight excess of molecular iodine furnished pyrazolopyrimidine **2** in quantitative yield (82%) [44]. The chlorination of compound **2** with phosphorus oxychloride yielded 7-chloro-pyrazolo pyrimidine **3** in 79% yield, which is used as precursor for further annulation reactions. The reaction of compound **3** with hydrazine hydrate in ethanol at reflux temperature underwent S_NAr displacement to give hydrazine derivative **4** in 76% yield, which is also used as a vital precursor for further heteroannulation reactions (Scheme 1).

The structural assignment of new compounds **3** and **4** is based upon spectroscopic and analytical data. For example, the ^{1}H nmr spectrum of **3** did not show the –NH signal of the precursor **2** at $\delta = 11.78$ ppm. The ^{1}H nmr spectrum of **4** showed $-NH_2$ and –NH signals at $\delta = 4.86$ and 8.78 ppm, respectively, whereas the IR spectrum showed $-NH_2$ and –NH absorption bands at 3372, 3330 and 3271 cm^{-1}.

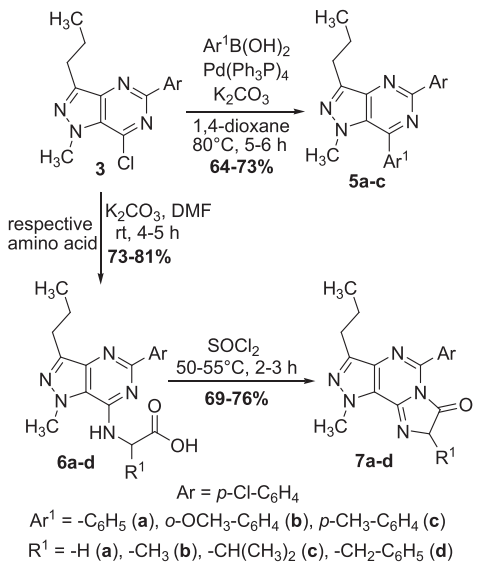
In an attempt to synthesize C-aryl derivatives of pyrazolo[4,3-*d*]pyrimidine, we tried *Suzuki–Miyaura* cross-coupling reaction of **3** with different aryl boronic acids [45–50]. Although aryl chlorides are generally unreactive toward the oxidative addition of palladium without the use of specialized and expensive ligands, the reaction of pyrazolopyrimidine **3** with aryl boronic acid occurred smoothly using tetrakis(triphenylphosphine)palladium as a heterogeneous catalyst. The regioselectivity for this coupling reaction on pyrazolo pyrimidine **3** was found to be in favor of chloropyrimidine. The electron-deficient nature of pyrimidine ring due to the inductive effect of nitrogen atoms induces a partially positive charge on the carbon atoms. Consequently, oxidative addition of chloropyrimidine to Pd(0) takes place more readily than chlorobenzene. Hence, treatment of 7-chloro-5-(4-chlorophenyl)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-*d*] pyrimidine **3** with different aryl boronic acids by using tetrakis(triphenylphosphine)palladium as a heterogeneous catalyst and K_2CO_3 as a base in an 1,4-dioxane leads to the formation of 5-(7-aryl-4-chlorophenyl)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidines **5** in excellent yields (64–73%; Scheme 2). The structural assignment of new compounds **5a–c** is based upon spectroscopic and microanalytical data. For example, the ^{1}H nmr spectrum of **5b** showed $-OCH_3$ signal at $\delta = 3.76$ ppm, and the MS showed a molecular ion peak at $m/z = 392$ (M^+) corresponding to the molecular formula $C_{22}H_{21}ClN_4O$.

The pyrazolopyrimidine **3** having reactive chloro atom at C-7 position on pyrimidine ring was further utilized for the study of their nucleophilic substitution reaction with various amino acids. Generally, the amino acids are very rarely used for nucleophilic substitution reaction because of their zwitterionic nature. The nucleophilicity of amino acid is improved by the use of two equivalents of potassium carbonate in order to free the amino group. Thus, the treatment of pyrazolo[4,3-*d*]pyrimidine **3** with various amino acids in dimethyl formamide, using K_2CO_3 as a base, under stirring at room temperature gave

Scheme 1



Scheme 2



2-((5-(4-chlorophenyl)-1-methyl-3-propyl-1*H*-pyrazolo [4,3-*d*]pyrimidin-7-yl)amino) acids **6a–d** in good yields (73–81%; Scheme 2). The structural assignment of new compounds **6a–d** is based upon spectroscopic and analytical data. For instance, the ^{1}H nmr spectrum of **6a** showed signals at $\delta = 7.34$ and 12.56 ppm corresponding to protons of –NH and –OH groups, respectively, and the IR spectrum showed characteristic –NH, –OH and –CO absorption bands at 3407, 2967 and 1721 cm^{-1}, respectively.

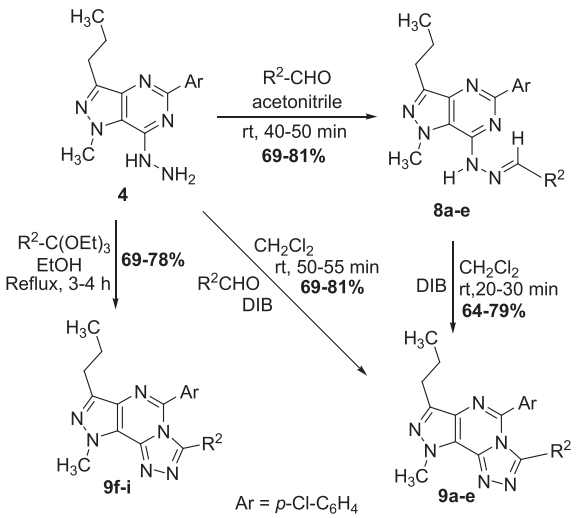
The open chain amino acid-linked pyrazolopyrimidines **6** formed were further employed for the synthesis of imidazolo-fused pyrazolopyrimidine derivatives **7a–d**. The annulations of imidazole ring were performed by cyclization of open chain amino acids on ring nitrogen atom of pyrimidine ring. The cyclization reactions were achieved by using Lewis acid $SOCl_2$ at controlled temperature. Thus, the treatment of **6a–d** with $SOCl_2$ under stirring at 50–55°C for 2–3 h afforded 5-(8-alkyl-4-chlorophenyl)-1-methyl-3-propyl-1*H*-imidazo[1,2-*c*]pyrazolo[3,4-*e*]pyrimidin-7(8*H*)-one **7a–d** in good yields (69–76%; Scheme 2). The new compounds **7a–d** were characterized by spectroscopic and analytical data. For instance, the ^{1}H nmr spectrum of **7a** did not show the –NH and –OH signals of the precursor **6a** at $\delta = 7.34$ and 12.56 ppm, and the IR spectrum showed characteristic –CO absorption band at 1734 cm^{-1}.

After a successful synthesis of imidazo-pyrazolopyrimidines **7**, targeting toward the synthesis of triazolo-fused pyrazolopyrimidines, another precursor **4** having reactive hydrazine functionality was utilized. The annulations of triazole ring were performed by the intramolecular oxidative cyclization reactions. Initially, the hydrazine **4** was converted to their imino hydrazone of aldehyde **8**, by condensation reaction with different aldehydes. Thus, the reaction of **4** with various aldehydes in acetonitrile under stirring at room temperature for 40–50 min afforded 2-alkylidene-1-(5-(4-chlorophenyl) -1-methyl-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-7-yl)hydrazines **8a–e** in good yields (69–81%; Scheme 3). The structural assignment of new compounds **8a–e** is based upon spectroscopic and analytical data. For example, the ^{1}H nmr spectrum of **8a** showed signals at $\delta = 7.96$ and 10.29 ppm corresponding to olefinic and –NH proton, respectively, and the IR spectrum showed characteristic –NH absorption band at 3302 cm^{-1}. Now, by considering the literature survey, in view of our ongoing program on the synthesis of triazolo-fused pyrazolopyrimidine derivatives via oxidative cyclization of 2-alkylidene-1-(5-(4-chlorophenyl)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-7-yl)hydrazines **8a–e**, organohypervalent iodine reagent is used [51–53]. Herein, we explored the oxidation of imino hydrazone **8** with diacetoxy iodobenzene (DIB). The high reactivity, commercial availability, easy workup, and high stability in different solvents make the use of DIB as an efficient oxidant [54]. We wish to report that the oxidation of compound **8** with DIB in dichloromethane leads to a facile intramolecular heterocyclization providing a convenient route to the synthesis of 7-alkyl pyrazolo-triazolo-pyrimidines **9a–e**. The general procedure involves the addition of 1.2 equivalent DIB at room temperature to a stirred solution of **8** in dichloromethane. The reaction is completed very smoothly within 20–30 min, when its initially pale yellow color turned to violet because of the overwhelming tendency of iodobenzene for reductive elimination. Washing the reaction mixture with 10% aqueous bicarbonate solution and removing the solvent by distillation gave the desired tricyclic 5-(7-alkyl-4-chlorophenyl)-1-methyl-3-propyl-1*H*-pyrazolo[3,4-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines **9a–e** in 64–79% yields (Scheme 3).

Alternatively, compounds **9a–e** could be synthesized from **4** without isolation of **8**, in which hydrazine **4** subsequently underwent condensation with aldehydes and oxidative cyclization with DIB to give target compounds **9a–e** in 69–81% yields (Scheme 3). The general procedure involves the fractionwise addition of 1.2 equivalent of DIB, to the solution of compound **4** and respective aldehyde in dichloromethane under stirring at room temperature for 50–55 min. The structural assignment of new compounds **9a–e** is based upon spectroscopic and microanalytical data. For example, the ^{1}H nmr spectrum of **9a** did not show the olefinic and –NH signals of the precursor **8a** at $\delta = 7.96$ and 10.29 ppm. The MS showed a molecular ion peak at $m/z = 368$ (M^+) corresponding to the molecular formula $C_{19}H_{21}ClN_6$.

Alternatively, the annulation of triazole ring on hydrazine **4** was also studied by using various triethyl orthoesters

Scheme 3



R^2 = -CH(CH$_3$)$_2$ (**a**), *p*-Cl-C$_6$H$_4$(**b**), *p*-Br-C$_6$H$_4$(**c**), *p*-OCH$_3$-C$_6$H$_4$ (**d**), m,*p*- di-OCH$_3$-C$_6$H$_3$ (**e**), -H (**f**), -CH$_3$ (**g**), -CH$_2$-CH$_3$ (**h**), -C$_6$H$_5$ (**i**)

such as triethyl orthoformate, triethyl orthoacetate, triethyl orthopropionate, and triethyl orthobenzoate to give other pyrazolo-triazolo-pyrimidine derivatives. Thus, the treatment of compound **4** with various triethyl orthoester in ethanol under reflux for 3–4 h subsequently underwent cyclo-condensation reactions to furnish desired 5-(7-alkyl-4-chlorophenyl)-1-methyl-3-propyl-1*H*-pyrazolo[3,4-*e*][1,2,4] triazolo[4,3-*c*]pyrimidine derivatives **9f-i** in excellent yields (69–78%; Scheme 3). The structural assignment of new compounds **9f–i** is based upon spectroscopic and analytical data. For instance, the ^{1}H nmr spectrum of **9f** did not show the $-NH_2$ and –NH signals of the precursor **4** at $\delta = 4.86$ and 8.78 ppm, respectively, but instead showed a sharp signal at $\delta = 8.97$ ppm belonging to triazole ring, indicating the formation of the tricyclic **9f**. The IR spectrum was devoid of the $-NH_2$ and –NH absorption bands at 3372, 3330 and 3271 cm^{-1} of the precursor.

CONCLUSION

We have successfully utilized 7-chloro-5-(4-chloro phenyl)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidine **3** and 1-(5-(4-chlorophenyl)-1-methyl-3-propyl-1*H*-pyrazolo [4,3-*d*]pyrimidin-7-yl)hydrazine **4** for the synthesis of novel pyrazolopyrimidine derivatives. The nucleophilic substitution reactions with different amino acids and *Suzuki–Miyaura* cross-coupling reactions with different aryl boronic acids of **3** were performed successfully under mild reaction condition. We established a robust and efficient route for construction of pyrazolo[3,4-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine by oxidative cyclization using DIB. Also, we described the efficient synthesis of pyrazolo-triazolo-pyrimidines **9f–i** through cyclo-condensation of hydrazine **4** with different triethylorthoesters. The reactions reported herein represent novel pyrazolo[4,3-*d*]pyrimidine derivatives and their fused heterocycles, with high yields, simple workup, clean products, and may be a valuable addition to a library of heterocyclic chemistry.

EXPERIMENTAL

General. Unless otherwise stated, materials were obtained from commercial suppliers and were used without further purification. Starting material 4-amino-1-methyl-3-propyl-1*H*-pyrazole-5-carboxamide **1** was prepared as previously reported procedure [37]. All reactions were monitored by thin layer chromatography (TLC) on 0.25-mm silica gel 60 F_{254} plates (Merck, Darmstadt, Germany) using UV light (254 and 366 nm) for detection. Compounds were purified on Biotage flash master personal plus flash chromatography system using Biotage silica gel cartridges (25 g). Melting points were determined on a Barnstead Electrothermal melting point apparatus (Nashik, India), Mod. No. IA-9200 in open capillary tubes, and are uncorrected. The ^{1}H nmr (300 MHz) and ^{13}C nmr (75 MHz) spectra were measured on a Varian XL-300 spectrometer (Pune, India), and ^{1}H nmr (400 MHz) spectra were measured on Bruker spectrometer (Mumbai, India) using tetramethylsilane as the internal standard. The solvent for nmr spectra was DMSO-d_6 unless otherwise stated. Chemical shifts are reported as δ values (ppm) relative to tetramethylsilane. The IR spectra were recorded using a Shimadzu IR-408 instrument (Nashik, India) as potassium bromide discs. Mass spectra were recorded on Shimadzu GC-MS QP 2010A mass spectrometer (Mumbai, India) with an ionization potential of 70 eV. Elemental analyses were carried out on a Thermo Finnigan at SAIF-IIT Bombay. The obtained products were moisture and oxygen stable at ambient temperature. All reagents were purchased from Merck (Mumbai, India), sd-fine Chemicals Ltd. (Mumbai, India) and Sigma Aldrich (New Delhi, India) and used without further purification.

***5-(4-Chlorophenyl)-1-methyl-3-propyl-1H*-pyrazolo[4,3-*d*] pyrimidin-7(6*H*)-one (2)**. To a clear solution of 4-amino-1-me thyl-3-propyl-1*H*-pyrazole-5-carboxamide **1** (0.182 g, 1.0 mmole) and 4-chlorobenzaldehyde (0.140 g, 1.0 mmole) in acetonitrile (15 mL), iodine (0.304 g, 1.2 mmole) was added fractionwise under stirring at room temperature. The reaction mass was then heated under reflux for 2.5 h, and the reaction progress was monitored by TLC (CH_2Cl_2/methanol 9:1). After completion of reaction, the solvent was removed *in vacuo* and the residue treated with water, stirred, filtered, and washed with 10% sodium thiosulphate solution to remove excess iodine. The obtained solid was dried under vacuum at 60°C to give product **2** (0.248 g, 82%) as a colorless solid, which was purified by flash chromatography (silica gel, CH_2Cl_2 as eluent). mp 237–239°C; lit. [44] [mp 239°C]; IR: 3291 (NH), 3163, 2922, 2812, 1654 (C = O), 1485, 1338, 1007 cm^{-1}; ^{1}H nmr (400 MHz, DMSO-d_6): δ 0.88 (t, $J = 8.0$ Hz, 3H, CH_3), 1.66 (m, 2H, CH_2), 2.69 (t, $J = 8.0$ Hz, 2H, CH_2), 4.07 (s, 3H, N–CH_3), 7.23 (d, $J = 12.0$ Hz, 2H, Ar–H), 7.92 (d, $J = 12.0$ Hz, 2H, Ar–H), 11.78 (bs, 1H, NH); ^{13}C nmr (75 MHz, DMSO-d_6): δ 13.9, 21.8, 27.7, 38.5, 122.3, 127.3, 127.9 (2C's), 129.2 (2C's), 132.1, 133.4, 145.4, 152.7, 162.3; MS (70 eV): *m/z* (%) = 302 (M^+, 71%), 304 (M + 2, 22%). *Anal*. Calcd for $C_{15}H_{15}ClN_4O$ (302.76): C, 59.51; H, 4.99; N, 18.51; Found: C, 59.83; H, 5.17; N, 18.25.

***7-Chloro-5-(4-chlorophenyl)-1-methyl-3-propyl-1H*-pyrazolo [4,3-*d*]pyrimidine (3)**. A solution of 5-(4-chlorophenyl)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-one **2** (0.302 g, 1.0 mmole) in phosphorous oxychloride (10 mL) was heated under reflux for 4 h, and the reaction progress was monitored by TLC (CH_2Cl_2/methanol 9:1). After completion of reaction, the solvent was removed *in vacuo* and the residue treated with water, stirred, filtered, and dried under vacuum at 60°C to give product **3** (0.253 g, 79%) as a colorless solid, which was purified by flash chromatography (silica gel, CH_2Cl_2/methanol 9:1 as eluent). mp 128–130°C; IR: 3112, 2983, 2927, 2812, 1627, 1492, 1336, 1091 cm^{-1}; ^{1}H nmr (300 MHz, DMSO-d_6): δ 0.99 (t, $J = 7.4$ Hz, 3H, CH_3), 1.87 (m, 2H, CH_2), 2.99 (t, $J = 7.4$ Hz, 2H, CH_2), 4.29 (s, 3H, N–CH_3), 7.61 (d, $J = 8.6$ Hz, 2H, Ar–H), 8.38 (d, $J = 8.6$ Hz, 2H, Ar–H); ^{13}C nmr (75 MHz, DMSO-d_6): δ 13.8, 21.4, 27.3, 38.8, 121.8, 128.7 (3C's), 129.3 (2C's), 131.7, 134.5, 146.3, 154.8, 159.7; MS (70 eV): *m/z* (%) = 320 (M^+, 63%), 322 (M + 2, 40%), 324 (M + 4, 7%). *Anal*. Calcd for $C_{15}H_{14}Cl_2N_4$ (321.20): C, 56.09; H, 4.39; N, 17.44; found: C, 56.48; H, 4.22; N, 17.70.

***1-(5-(4-Chlorophenyl)-1-methyl-3-propyl-1H*-pyrazolo[4,3-*d*]pyrimidin-7-yl) hydrazine (4)**. A clear solution of 7-chloro-5-(4-chlorophenyl)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidine **3** (0.321 g, 1.0 mmole) and hydrazine hydrate (0.075 mL, 1.5 mmole) in ethanol (15 mL) was heated under reflux for 1.5 h, and the reaction progress was monitored by TLC (CH_2Cl_2/methanol 9:1). After completion of reaction, the solvent was removed *in vacuo* and the residue treated with

methanol, stirred, filtered, and dried under vacuum at 60°C to give product **4** (0.240 g, 76%) as a yellow solid, which was purified by flash chromatography (silica gel, CH_2Cl_2/methanol 9:1 as eluent). mp 219–221°C; IR: 3372 (NH_2), 3330 (NH_2), 3271 (NH), 3010, 2912, 1530, 1412, 1080 cm^{-1}; ^1H nmr (300 MHz, DMSO-d_6): δ 0.96 (t, J = 7.4 Hz, 3H, CH_3), 1.80 (m, 2H, CH_2), 2.84 (t, J = 7.4 Hz, 2H, CH_2), 4.16 (s, 3H, N–CH_3), 4.86 (bs, 2H, –NH_2) 7.52 (d, J = 8.6 Hz, 2H, Ar–H), 8.46 (d, J = 8.6 Hz, 2H, Ar–H), 8.78 (bs, 1H, NH); ^{13}C nmr (75 MHz, DMSO-d_6): δ 13.9, 22.1, 27.5, 38.9, 122.1, 128.3, 128.4 (2C's), 129.2 (2C's), 131.9, 134.6, 146.5, 155.1, 162.4; MS (70 eV): m/z (%) = 316 (M^+, 74%), 318 (M + 2, 23%). *Anal*. Calcd for $C_{15}H_{17}ClN_6$ (316.79): C, 56.87; H, 5.41; N, 26.53; found: C, 57.15; H, 5.81; N, 26.32.

***General procedure for synthesis of 5-(7-aryl-4-chlorophenyl)-1-methyl-3-propyl-1H*-pyrazolo[4,3-*d*]pyrimidines 5a–c**. To a clear solution of 7-chloro-5-(4-chlorophenyl)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidine **3** (0.321 g, 1.0 mmole) and respective aryl boronic acid (1.2 mmole) in 1,4 dioxane (20 mL), tetrakistriphenylphosphine palladium [$Pd(Ph_3P)_4$] (0.058 g, 0.05 mmole) and anhydrous K_2CO_3 (0.276 g, 2.0 mmol) were added subsequently under stirring at room temperature. The reaction mixture was then stirred at 80°C for 5–6 h, and the reaction progress was monitored by TLC (hexane/ethyl acetate 9:1). After completion of reaction, the solvent was removed *in vacuo* and the residue treated with water, extracted with ethyl acetate (3 × 25 mL); organic layer was dried with Na_2SO_4 and concentrated *in vacuo*. The obtained solid was dried under vacuum at 60°C to give products **5a–c** in 64–73% yield, which was purified by flash chromatography (silica gel, hexane/ethyl acetate 9:1 as eluent).

***5-(4-Chlorophenyl)-1-methyl-7-phenyl-3-propyl-1H*-pyrazolo[4,3-*d*] pyrimidine (5a)**. This compound was synthesized by using phenylboronic acid (0.146 g, 1.2 mmole); white amorphous solid; yield 0.257 g (71%); mp 112–114°C; IR: 3021, 2983, 2971, 1563, 1491, 1068, 1012 cm^{-1}; ^1H nmr (300 MHz, DMSO-d_6): δ 1.01 (t, J = 7.4 Hz, 3H, CH_3), 1.86 (m, 2H, CH_2), 3.03 (t, J = 7.4 Hz, 2H, CH_2), 3.79 (s, 3H, N–CH_3), 7.59 (d, J = 8.7 Hz, 2H, Ar–H), 7.65 (m, 3H, Ar–H), 7.87 (dd, J = 3.0 and 6.0 Hz, 2H, Ar–H), 8.48 (d, J = 8.7 Hz, 2H, Ar–H); ^{13}C nmr (75 MHz, DMSO-d_6): δ 13.8, 21.2, 27.2, 37.1, 121.0, 127.6 (2C's), 128.7 (2C's), 128.9 (2C's), 129.1 (2C's), 129.4 (2C's), 134.2, 135.3, 143.5, 144.8, 151.1, 156.5; MS (70 eV): m/z (%) = 362 (M^+, 57%), 364 (M + 2, 19%). *Anal*. Calcd for $C_{21}H_{19}ClN_4$ (362.86): C, 69.51; H, 5.26; N, 15.44; found: C, 69.27; H, 5.61; N, 15.60.

***5-(4-Chlorophenyl)-7-(2-methoxyphenyl)-1-methyl-3-propyl-1H*-pyrazolo[4,3-*d*]pyrimidine (5b)**. This compound was synthesized by using 2-methoxyphenylboronic acid (0.182 g, 1.2 mmole); colorless solid; yield 0.286 g (73%); mp 117–119°C; IR: 3196, 2952, 2835, 1238, 1120, 1051, 912 cm^{-1}; ^1H nmr (300 MHz, DMSO-d_6): δ 1.01 (t, J = 7.4 Hz, 3H, CH_3), 1.89 (m, 2H, CH_2), 3.01 (t, J = 7.4 Hz, 2H, CH_2), 3.64 (s, 3H, N–CH_3), 3.76 (s, 3H, –OCH_3), 7.23 (m, 2H, Ar–H), 7.59 (m, 4H, Ar–H), 8.44 (d, J = 8.4 Hz, 2H, Ar–H); ^{13}C nmr (75 MHz, DMSO-d_6): δ 13.9, 21.3, 27.1, 36.9, 55.3, 111.2, 120.9, 124.8, 128.4 (2C's), 129.2 (3C's), 131.0, 131.9, 134.5, 136.8, 143.7, 144.6, 150.0, 154.9, 156.7; MS (70 eV): m/z (%) = 392 (M^+, 66%), 394 (M + 2, 20%). *Anal*. Calcd for $C_{22}H_{21}ClN_4O$ (392.88): C, 67.26; H, 5.39; N, 14.26; found: C, 67.52; H, 5.25; N, 14.60.

***5-(4-Chlorophenyl)-1-methyl-3-propyl-7-p*-tolyl-1*H*-pyrazolo[4,3-*d*]pyrimidine (5c)**. This compound was synthesized by using 4-methylphenylboronic acid (0.163 g, 1.2 mmole); offwhite solid; yield 0.241 g (64%); mp 126–129°C; IR: 3116, 2964, 2923, 2879, 1516, 1432, 1311, 1039, 985 cm^{-1}; ^1H nmr (300 MHz, DMSO-d_6): δ 1.00 (t, J = 7.5 Hz, 3H, CH_3), 1.87 (m, 2H, CH_2), 2.42 (s, 3H, CH_3), 3.02 (t, J = 7.5 Hz, 2H, CH_2), 3.69 (s, 3H, N–CH_3), 7.29 (d, J = 8.0 Hz, 2H, Ar–H), 7.51 (d, J = 7.4 Hz, 2H, Ar–H), 8.13 (d, J = 8.0 Hz, 2H, Ar–H), 8.38 (d, J = 7.4 Hz, 2H, Ar–H); ^{13}C nmr (75 MHz, DMSO-d_6): δ 13.8, 21.1, 21.3, 27.2, 36.9, 121.3, 127.6 (2C's), 127.8, 128.7 (2C's), 129.1 (2C's), 129.3 (2C's), 130.9 131.2, 134.6, 136.7, 144.5, 153.1, 154.4; MS (70 eV): m/z (%) = 376 (M^+, 58%), 378 (M + 2, 17%). *Anal*. Calcd for $C_{22}H_{21}ClN_4$ (376.88): C, 70.11; H, 5.62; N, 14.87; found: C, 70.42; H, 5.39; N, 15.11.

***General procedure for synthesis of 2-((5-(4-chlorophenyl)-1-methyl-3-propyl-1H*-pyrazolo [4,3-*d*]pyrimidin-7-yl)amino) acids 6a–d**. A mixture of 7-chloro-5-(4-chlorophenyl)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidine **3** (0.321 g, 1.0 mmole), respective amino acid (1.1 mmole) and anhydrous K_2CO_3 (0.276 g, 2 mmole) in dimethyl formamide (20 mL) was stirred at room temperature for 4–5 h, and the reaction progress was monitored by TLC (CH_2Cl_2/methanol 9:1). After completion of reaction, the solvent was removed *in vacuo* and the residue treated with water, neutralized with 2*N* HCl, stirred, filtered, and dried under vacuum at 60°C to give products **6a–d** in 73–81% yield, which was purified by flash chromatography (silica gel, CH_2Cl_2/methanol 9:1 as eluent).

***2-((5-(4-Chlorophenyl)-1-methyl-3-propyl-1H*-pyrazolo [4,3-*d*]pyrimidin-7-yl)amino)acetic acid (6a)**. This compound was synthesized by using glycine (0.083 g, 1.1 mmole); colorless solid; yield 0.283 g (79%); mp 196–198°C; IR: 3407 (NH), 2967 (OH), 2956, 2576, 1721 (C = O), 1605, 1563, 1480, 1223, 1081 cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6): δ 0.95 (t, J = 7.6 Hz, 3H, CH_3), 1.82 (m, 2H, CH_2), 2.85 (t, J = 7.6 Hz, 2H, CH_2), 4.23 (s, 3H, N–CH_3), 4.51 (d, J = 7.0 Hz, 2H, CH_2), 7.34 (t, J = 7.0 Hz, 1H, NH), 7.48 (d, J = 7.4 Hz, 2H, Ar–H), 8.37 (d, J = 7.4 Hz, 2H, Ar–H), 12.56 (bs, 1H, OH); ^{13}C nmr (75 MHz, DMSO-d_6): δ 13.8, 21.7, 27.3, 38.8, 41.6, 121.7, 128.0, 128.2 (2C's), 129.3 (2C's), 132.2, 134.3, 147.4, 154.4, 159.7, 167.1; MS (70 eV): m/z (%) = 359 (M^+, 37%), 361 (M + 2, 12%). *Anal*. Calcd for $C_{17}H_{18}ClN_5O_2$ (359.81): C, 56.75; H, 5.04; N, 19.46; found: C, 57.01; H, 4.93; N, 19.77.

***2-((5-(4-Chlorophenyl)-1-methyl-3-propyl-1H*-pyrazolo[4,3-*d*]pyrimidin-7-yl)amino) propanoic acid (6b)**. This compound was synthesized by using alanine (0.098 g, 1.1 mmole); white crystalline solid; yield 0.302 g (81%); mp 218–220°C; IR: 3421 (NH), 2980 (OH), 2963, 2563, 1712 (CO), 1600, 1556, 1473, 1207 cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6): δ 0.96 (t, J = 8.0 Hz, 3H, CH_3), 1.57 (d, J = 8.0 Hz, 3H, CH_3), 1.81 (m, 2H, CH_2), 2.86 (t, J = 8.0 Hz, 2H, CH_2), 4.23 (s, 3H, N–CH_3), 4.61 (m, 1H), 7.51 (d, J = 8.4 Hz, 2H, Ar–H), 7.54 (d, J = 4.0 Hz, 1H, NH), 8.36 (d, J = 8.4 Hz, 2H, Ar–H), 12.53 (bs, 1H, OH); ^{13}C nmr (75 MHz, DMSO-d_6): δ 13.7, 16.1, 21.5, 27.6, 38.8, 47.2, 122.1, 128.1 (3C's), 129.2 (2C's), 131.9, 134.2, 147.6, 155.1, 159.5, 168.3; MS (70 eV): m/z (%) = 373 (M^+, 43%), 375 (M + 2, 15%). *Anal*. Calcd for $C_{18}H_{20}ClN_5O_2$ (373.84): C, 57.83; H, 5.39; N, 18.73; found: C, 57.55; H, 5.71; N, 18.86.

***2-((5-(4-Chlorophenyl)-1-methyl-3-propyl-1H*-pyrazolo[4,3-*d*]pyrimidin-7-yl)amino)-3-methylbutanoic acid (6c)**. This compound was synthesized by using valine (0.129 g, 1.1 mmole); offwhite crystalline solid; yield 0.293 g (73%); mp 207–209°C; IR: 3393 (NH), 2990 (OH), 2912, 2563, 1709 (CO), 1618, 1488, 1225 cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6): δ 0.95 (t, J = 7.4 Hz, 3H, CH_3), 1.09 (m, 6H, 2 × CH_3), 1.80 (m, 2H, CH_2), 2.39 (m,

1H), 2.86 (t, $J = 7.4$ Hz, 2H, CH_2), 4.25 (s, 3H, N–CH_3), 4.40 (t, $J = 7.2$ Hz, 1H), 7.15 (d, $J = 7.2$ Hz, 1H, –NH), 7.52 (d, $J = 8.7$ Hz, 2H, Ar–H), 8.39 (d, $J = 8.7$ Hz, 2H, Ar–H), 12.75 (bs, 1H, OH); ^{13}C nmr (75 MHz, DMSO-d_6): δ 13.7, 16.4 (2C's), 21.6, 27.2, 27.7, 38.9, 66.3, 121.6, 127.9, 128.2 (2C's), 129.1 (2C's), 131.6, 134.5, 148.1, 154.8, 160.0, 168.4; MS (70 eV): *m/z* (%) = 401 (M^+, 32%), 403 (M + 2, 9%). *Anal.* Calcd for $C_{20}H_{24}ClN_5O_2$ (401.89): C, 59.77; H, 6.02; N, 17.43; found: C, 60.02; H, 6.18; N, 17.11.

***2-((5-(4-Chlorophenyl)-1-methyl-3-propyl-1H*-pyrazolo[4,3-*d*]pyrimidin-7-yl)amino)-3-phenylpropanoic acid (6d)**. This compound was synthesized by using phenyl alanine (0.182 g, 1.1 mmole); colorless solid; yield 0.346 g (77%); mp 188–190°C; IR: 3417 (NH), 2967 (OH), 2824, 1723 (CO), 1614, 1565, 1253, 1087 cm^{-1}; ^{1}H nmr (400 MHz, DMSO-d_6): δ 0.94 (t, $J = 7.5$ Hz, 3H, CH_3), 1.80 (m, 2H, CH_2), 2.84 (t, $J = 7.5$ Hz, 2H, CH_2), 2.34 (d, $J = 8.0$ Hz, 2H, CH_2), 4.13 (s, 3H, N–CH_3), 4.82 (q, $J = 8.0$ Hz, 1H), 7.18 (d, $J = 8.0$ Hz, 1H, NH), 7.19–7.37 (m, 5H Ar–H), 7.50 (d, $J = 8.0$ Hz, 2H, Ar–H), 8.35 (d, $J = 8.0$ Hz, 2H, Ar–H), 12.63 (bs, 1H, OH); ^{13}C nmr (75 MHz, DMSO-d_6): δ 13.8, 21.8, 27.7, 32.6, 38.8, 56.3, 121.2, 127.1, 127.4 (2C's), 128.0 (3C's), 128.2 (2C's), 129.2 (2C's), 131.4, 133.8, 137.5, 147.8, 155.9, 160.0, 169.3; MS (70 eV): *m/z* (%) = 449 (M^+, 41%), 451 (M + 2, 14%). *Anal.* Calcd for $C_{24}H_{24}ClN_5O_2$ (449.93): C, 64.07; H, 5.38; N, 15.57; found: C, 64.28; H, 5.31; N, 15.35.

***General procedure for synthesis of 5-(8-alkyl-4-chlorophenyl)-1-methyl-3-propyl-1H*-imidazo[1,2-*c*]pyrazolo[3,4-*e*]pyrimidin-7(8*H*)-ones 7a–d**. A solution of respective compounds **6a–d** (1.0 mmole) in thionyl chloride (10 mL) was stirred at 50–55°C for 2–3 h, and the reaction progress was monitored by TLC (hexane/ethyl acetate 9:1). After completion of the reaction, solvent was removed *in vacuo* and the residue treated with water, stirred, filtered, and dried under vacuum at 60°C to give products **7a–d** in 69–76% yield, which was purified by flash chromatography (silica gel, hexane/ethyl acetate 9:1 as eluent).

***5-(4-Chlorophenyl)-1-methyl-3-propyl-1H*-imidazo[1,2-*c*]pyrazolo[3,4-*e*]pyrimidin-7(8*H*)-one (7a)**. Pale brown solid; yield 0.242 g (71%); mp 177–179°C; IR: 2993, 2975, 2916, 1734 (CO), 1686, 1522, 1299, 1167, 1004, 986 cm^{-1}; ^{1}H nmr (300 MHz, DMSO-d_6): δ 0.97 (t, $J = 7.5$ Hz, 3H, CH_3), 1.79 (m, 2H, CH_2), 2.82 (t, $J = 7.5$ Hz, 2H, CH_2), 4.28 (s, 3H, N–CH_3), 4.59 (s, 2H, CH_2), 7.47 (d, $J = 8.0$ Hz, 2H, Ar–H), 8.21 (d, $J = 8.0$ Hz, 2H, Ar–H); ^{13}C nmr (75 MHz, DMSO-d_6): δ 13.9, 21.8, 27.5, 38.2, 46.1, 121.4, 127.1, 127.4 (2C's), 128.3 (2C's), 132.0, 134.3, 147.9, 154.1, 159.3, 167.7; MS (70 eV): *m/z* (%) = 341 (M^+, 55%), 343 (M + 2, 17%). *Anal.* Calcd for $C_{17}H_{16}ClN_5O$ (341.79): C, 59.74; H, 4.72; N, 20.49; found: C, 60.09; H, 4.46; N, 20.66.

***5-(4-Chlorophenyl)-1,8-dimethyl-3-propyl-1H*-imidazo[1,2-*c*]pyrazolo[3,4-*e*]pyrimidin-7(8*H*)-one (7b)**. Faint brown solid; yield 0.245 g (69%); mp 182–184°C; IR: 3117, 2980, 2916, 1746 (CO), 1680, 1531, 1304, 1020 cm^{-1}; ^{1}H nmr (300 MHz, DMSO-d_6): δ 0.98 (t, $J = 7.2$ Hz, 3H, CH_3), 1.43 (d, $J = 7.0$ Hz, 3H, CH_3), 1.62 (m, 2H, CH_2), 2.79 (t, $J = 7.2$ Hz, 2H, CH_2), 4.21 (s, 3H, N–CH_3), 4.52 (q, $J = 7.0$ Hz, 1H), 7.46 (d, $J = 8.0$ Hz, 2H, Ar–H), 8.18 (d, $J = 8.0$ Hz, 2H, Ar–H); ^{13}C nmr (75 MHz, DMSO-d_6): δ 13.9, 16.8, 21.7, 27.5, 38.4, 53.3, 121.2, 127.2 (3C's), 128.4 (2C's), 131.9, 134.0, 147.7, 154.3, 158.9, 169.1; MS (70 eV): *m/z* (%) = 355 (M^+, 48%), 357 (M + 2, 17%). *Anal.* Calcd for $C_{18}H_{18}ClN_5O$ (355.82): C, 60.76; H, 5.10; N, 19.68; found: C, 61.00; H, 5.33; N, 19.33.

***5-(4-Chlorophenyl)-8-isopropyl-1-methyl-3-propyl-1H*-imidazo[1,2-*c*]pyrazolo[3,4-*e*]pyrimidin-7(8*H*)-one (7c)**. Offwhite amorphous solid; yield 0.288 g (75%); Mp 166–168°C; IR: 3134, 3057, 2956, 2819, 1741 (–CO), 1689, 1564, 1287, 1107 cm^{-1}; ^{1}H nmr (300 MHz, DMSO-d_6): δ 0.96 (t, $J = 7.5$ Hz, 3H, CH_3), 1.12 (m, 6H, 2 × CH_3), 1.82 (m, 2H, CH_2), 2.38 (m, 1H), 2.85 (t, $J = 7.5$ Hz, 2H, CH_2), 4.19 (s, 3H, N–CH_3), 4.43 (d, $J = 7.0$ Hz, 1H), 7.53 (d, $J = 7.5$ Hz, 2H, Ar–H), 8.35 (d, $J = 7.5$ Hz, 2H, Ar–H); ^{13}C nmr (75 MHz, DMSO-d_6): δ 13.8, 16.6 (2C's), 21.7, 27.3, 31.3, 38.3, 66.7, 121.4, 127.1, 127.3 (2C's), 128.3 (2C's), 131.6, 134.2, 147.9, 154.7, 159.8, 168.6; MS (70 eV): *m/z* (%) = 383 (M^+, 36%), 385 (M + 2, 11%). *Anal.* Calcd for $C_{20}H_{22}ClN_5O$ (383.87): C, 62.58; H, 5.78; N, 18.24; found: C, 62.77; H, 5.51; N, 18.46.

***5-(4-Chlorophenyl)-8-benzyl-1-methyl-3-propyl-1H*-imidazo[1,2-*c*]pyrazolo[3,4-*e*]pyrimidin-7(8*H*)-one (7d)**. Faint brown crystalline solid; yield 0.328 g (76%); mp 171–173°C; IR: 3224, 3137, 3042, 2912, 1749 (CO), 1698, 1510, 1218, 1016 cm^{-1}; ^{1}H nmr (300 MHz, DMSO-d_6): δ 0.96 (t, $J = 7.5$ Hz, 3H, CH_3), 1.81 (m, 2H, CH_2), 2.86 (t, $J = 7.5$ Hz, 2H, CH_2), 3.31 (d, $J = 7.2$ Hz, 2H, CH_2), 4.22 (s, 3H, N–CH_3), 4.73 (t, $J = 7.2$ Hz, 1H), 7.22–7.39 (m, 5H, Ar–H), 7.47 (d, $J = 8.0$ Hz, 2H, Ar–H), 8.41 (d, $J = 8.0$ Hz, 2H, Ar–H); ^{13}C nmr (75 MHz, DMSO-d_6): δ 13.9, 21.7, 27.4, 34.5, 38.4, 61.1, 121.7, 127.2, 127.4 (2C's), 128.0, 128.1 (2C's), 128.3 (2C's), 129.1 (2C's), 131.6, 134.0, 137.4, 147.4, 156.1, 159.8, 169.1; MS (70 eV): *m/z* (%) = 431 (M^+, 61%), 433 (M + 2, 19%). *Anal.* Calcd for $C_{24}H_{22}ClN_5O$ (431.92): C, 66.74; H, 5.13; N, 16.21; found: C, 66.80; H, 4.87; N, 16.52.

***General procedure for synthesis of 2-alkylidene-1-(5-(4-chlorophenyl)-1-methyl-3-propyl-1H*-pyrazolo[4,3-*d*]pyrimidin-7-yl)hydrazines 8a–e**. A solution of 1-(5-(4-chlorophenyl)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-7-yl)hydrazine **4** (0.316 g, 1.0 mmole) and respective aldehyde (1.0 mmole) in acetonitrile (15 mL) was stirred at room temperature for 40–50 min, and the reaction progress was monitored by TLC (CH_2Cl_2/methanol 9:1). After completion of the reaction, solvent was removed *in vacuo* and the residue treated with hexane, stirred, filtered, and dried under vacuum at 60°C to give products **8a–e** in 69–81% yield, which was purified by flash chromatography (silica gel, CH_2Cl_2/methanol 9:1 as eluent).

***2-(2-Methylpropylidene)-1-(5-(4-chlorophenyl)-1-methyl-3-propyl-1H*-pyrazolo[4,3-*d*]pyrimidin-7-yl)hydrazine (8a)**. This compound was synthesized by using isobutyraldehyde (0.092 mL, 1.0 mmole); yellow solid; yield 0.288 g (78%); mp 163–165°C; IR: 3302 (NH), 3184, 3145, 2921, 1560, 1304, 1022 cm^{-1}; ^{1}H nmr (300 MHz, DMSO-d_6): δ 0.98 (t, $J = 7.4$ Hz, 3H, CH_3), 1.02 (m, 6H, 2 × CH_3), 1.84 (m, 2H, CH_2), 2.11 (m, 1H), 2.87 (t, $J = 7.4$ Hz, 2H, CH_2), 4.29 (s, 3H, N–CH_3), 7.49 (d, $J = 7.2$ Hz, 2H, Ar–H), 7.88 (d, $J = 7.2$ Hz, 2H, Ar–H), 7.96 (d, $J = 5.5$ Hz, 1H, olefinic-H), 10.29 (bs, 1H, NH); ^{13}C nmr (75 MHz, DMSO-d_6): δ 13.8, 18.3 (2C's), 21.9, 27.1, 31.4, 38.9, 122.7, 126.8, 127.5 (2C's), 128.8 (2C's), 132.8, 136.4, 144.3, 149.3, 151.2, 153.1; MS (70 eV): *m/z* (%) = 370 (M^+, 43%), 371 (M + 2, 15%). *Anal.* Calcd for $C_{19}H_{23}ClN_6$ (370.88): C, 61.53; H, 6.25; N, 22.66; found: C, 61.26; H, 6.53; N, 22.87.

***2-(4-Chlorobenzylidene)-1-(5-(4-chlorophenyl)-1-methyl-3-propyl-1H*-pyrazolo[4,3-*d*]pyrimidin-7-yl)hydrazine (8b)**. This compound was synthesized by using 4-chlorobenzaldehyde (0.141 g, 1.0 mmole); yellow amorphous solid; yield 0.302 g (69%); mp 175–177°C; IR: 3403 (NH), 3197, 3161, 2982, 1552, 1318, 1109, 1022 cm^{-1}; ^{1}H nmr (300 MHz, $CDCl_3$): $\delta = 1.03$ (t,

J = 7.2 Hz, 3H, CH_3), 1.86 (m, 2H, CH_2), 2.88 (t, J = 7.2 Hz, 2H, CH_2), 4.31 (s, 3H, N–CH_3), 7.43 (d, J = 8.1 Hz, 2H, Ar–H), 7.53 (d, J = 8.1 Hz, 2H, Ar–H), 7.72 (d, J = 8.1 Hz, 2H, Ar–H), 7.92 (d, J = 8.1 Hz, 2H, Ar–H), 8.51 (s, 1H, olefinic-H), 10.39 (bs, 1H, NH); ^{13}C nmr (75 MHz, $CDCl_3$): δ 13.9, 22.1, 27.2, 38.6, 122.4, 127.1, 127.8 (2C's), 128.0 (2C's), 129.2, 129.5, 131.1 (2C's), 131.8 (2C's), 134,3, 134.7, 142.0, 142.3, 146.6, 148.2; MS (70 eV): m/z (%) = 438 (M^+, 35%), 440 (M + 2, 24%), 442 (M + 4, 4%). *Anal*. Calcd for $C_{22}H_{20}Cl_2N_6$ (439.34): C, 60.14; H, 4.59; N, 19.13; found: C, 60.45; H, 4.47; N, 19.37.

***2-(4-Bromobenzylidene)-1-(5-(4-chlorophenyl)-1-methyl-3-propyl-1H*-pyrazolo[4,3-*d*]pyrimidin-7-yl)hydrazine (8c)**. This compound was synthesized by using 4-bromobenzaldehyde (0.184 g, 1.0 mmole); pale yellow solid; yield 0.358 g (74%); mp 170–172°C; IR: 3419 (−NH), 3201, 3154, 2975, 1563, 1485, 1322, 1097, 1004, 973 cm^{-1}; ^{1}H nmr (300 MHz, $CDCl_3$): δ 1.02 (t, J = 7.5 Hz, 3H, CH_3), 1.85 (m, 2H, CH_2), 2.90 (t, J = 7.5 Hz, 2H, CH_2), 4.28 (s, 3H, N-CH_3), 7.42 (d, J = 8.0 Hz, 2H, Ar–H), 7.54 (d, J = 8.0 Hz, 2H, Ar–H), 7.71 (d, J = 8.0 Hz, 2H, Ar–H), 7.90 (d, J = 8.0 Hz, 2H, Ar–H), 8.49 (s, 1H, olefinic-H), 10.37 (bs, 1H, NH); ^{13}C nmr (75 MHz, $CDCl_3$): δ 13.8, 22.1, 27.3, 38.8, 121.9, 127.2, 127.8 (2C's), 128.1 (2C's), 129.3, 129.6, 130.9 (2C's), 131.7 (2C's), 134.2, 134.8, 142.2, 142.3, 146.9, 149.5; MS (70 eV): m/z (%) = 482 (M^+, 41%), 484 (M + 2, 56%), 486 (M + 4, 12%). *Anal*. Calcd for $C_{22}H_{20}BrClN_6$ (483.79): C, 54.62; H, 4.17; N, 17.37; found: C, 54.79; H, 4.52; N, 17.25.

***2-(4-Methoxybenzylidene)-1-(5-(4-chlorophenyl)-1-methyl-3-propyl-1H*-pyrazolo[4,3-*d*]pyrimidin-7-yl)hydrazine (8d)**. This compound was synthesized by using 4-methoxybenzaldehyde (0.137 g, 1.0 mmole); yellow crystalline solid; yield 0.334 g (77%); mp 167–169°C; IR: 3411 (NH), 3176, 3054, 2926, 1561, 1242, 1035, 1005 cm^{-1}; ^{1}H nmr (300 MHz, $CDCl_3$): δ 1.03 (t, J = 7.2 Hz, 3H, CH_3), 1.85 (m, 2H, CH_2), 2.87 (t, J = 7.2 Hz, 2H, CH_2), 3.88 (s, 3H, OCH_3), 4.30 (s, 3H, N–CH_3), 6.98 (d, J = 8.7 Hz, 2H, Ar–H), 7.52 (d, J = 8.4 Hz, 2H, Ar–H), 7.74 (d, J = 8.7 Hz, 2H, Ar–H), 7.92 (d, J = 8.4 Hz, 2H, Ar–H), 8.49 (s, 1H, olefinic-H), 10.42 (bs, 1H, NH); ^{13}C nmr (75 MHz, $CDCl_3$): δ 14.0, 22.3, 27.6, 38.9, 55.3, 114.2 (2C's), 122.7, 127.4 (3C's), 129.2 (2C's), 129.3 (2C's), 131.9, 134.7, 136.8, 144.2, 146.1, 146.5, 155.2, 161.5; MS (70 eV): m/z (%) = 434 (M^+, 57%), 436 (M + 2, 20%). *Anal*. Calcd for $C_{23}H_{23}ClN_6O$ (434.92): C, 63.52; H, 5.33; N, 19.32; found: C, 63.74; H, 5.14; N, 19.61.

***2-(3,4-Dimethoxybenzylidene)-1-(5-(4-chlorophenyl)-1-methyl-3-propyl-1H*-pyrazolo[4,3-*d*]pyrimidin-7-yl)hydrazine (8e)**. This compound was synthesized by using 3,4-dimethoxybenzaldehyde (0.167 g, 1.0 mmole); yellow solid; yield 0.376 g (81%); mp 160–162°C; IR: 3393 (NH), 3042, 2994, 2891, 1552, 1508, 1241, 1257, 1034, 1003 cm^{-1}; ^{1}H nmr (300 MHz, $CDCl_3$): δ 1.03 (t, J = 7.2 Hz, 3H, CH_3), 1.86 (m, 2H, CH_2), 2.87 (t, J = 7.2 Hz, 2H, CH_2), 3.95 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 4.31 (s, 3H, N–CH_3), 6.94 (d, J = 8.1 Hz, 1H, Ar–H), 7.28 (d, J = 8.1 Hz, 1H, Ar–H), 7.42 (s, 1H Ar–H), 7.49 (d, J = 8.5 Hz, 2H, Ar–H), 7.93 (d, J = 8.5 Hz, 2H, Ar–H), 8.48 (s, 1H, olefinic-H), 10.46 (bs, 1H, NH); ^{13}C nmr (75 MHz, $CDCl_3$): δ 13.6, 21.2, 27.5, 38.9, 55.4, 55.7, 113.2, 114.6, 120.2, 121.8, 123.1, 127.3 (2C's), 130.3, 131.0 (2C's), 131.9, 135.1, 142.2, 142.4, 145.7, 147.5, 148.3, 150.6; MS (70 eV): m/z (%) = 464 (M^+, 52%), 466 (M + 2, 16%). *Anal*. Calcd for $C_{24}H_{25}ClN_6O_2$ (464.95): C, 62.00; H, 5.42; N, 18.08; found: C, 62.27; H, 5.20; N, 18.31.

General procedure for synthesis of 5-(7-alkyl-4-chlorophenyl)-1-methyl-3-propyl-1*H*-pyrazolo[3,4-*e*][1,2,4]triazolo[4,3-*c*] pyrimidines 9a–e. *By Method (ii)*: A solution of respective compound **8** (1.0 mmole) and DIB (0.385 g, 1.2 mmole) in dichloromethane (20 mL) was stirred at room temperature for 20–30 min, and the reaction progress was monitored by TLC (hexane/ethyl acetate 9:1). After completion of reaction, the reaction mixture was washed with 10% sodium bicarbonate solution and dried over Na_2SO_4, solvent was removed *in vacuo*, and the obtained residue was treated with hexane, filtered, and dried under vacuum at 60°C to give products **9a–e** in 64–79% yield, which was purified by flash chromatography (silica gel, hexane/ethyl acetate 9:1 as eluent).

By Method (iii): To a clear solution of **4** (0.316 g, 1.0 mmole) and respective aldehyde (1.0 mmole) in dichloromethane (20 mL), diacetoxy iodobenzene (0.385 g, 1.2 mmole) was added fractionwise under stirring at room temperature. The reaction mixture was stirred further for 50–55°C, and the reaction progress was monitored by TLC (hexane/ethyl acetate 9:1). After completion of reaction, the reaction mixture was washed with 10% sodium bicarbonate solution and dried over Na_2SO_4, solvent was removed *in vacuo*, and the obtained residue was treated with hexane, filtered and dried under vacuum at 60°C to give products **9a–e** in 69–81% yield, which was purified by flash chromatography (silica gel, hexane/ethyl acetate 9:1 as eluent).

***5-(4-Chlorophenyl)-1-methyl-7-(1-methylethyl)-3-propyl-1H*-pyrazolo[3,4-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine (9a)**. Colorless solid; yield 0.250 g, 68% (Method ii), 0.264 g, 72% (Method iii); mp 169–171°C; IR: 3143, 3023, 2937, 2875, 1667, 1498, 1234, 1056, 1003 cm^{-1}; ^{1}H nmr (300 MHz, $CDCl_3$): δ 1.00 (t, J = 8.1 Hz, 3H, CH_3), 1.13 (m, 6H, 2 × CH_3) 1.83 (m, 2H, CH_2), 2.41 (m, 1H), 2.84 (t, J = 8.1 Hz, 2H, CH_2), 4.33 (s, 3H, N–CH_3), 7.13 (d, J = 7.2 Hz, 2H, Ar–H), 7.32 (d, J = 7.2 Hz, 2H, Ar–H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 14.0, 19.1 (2C's), 21.7, 27.3, 29.2, 39.2, 122.4, 128.1, 128.3 (2C's), 131.2 (2C's), 132.4, 134.5, 141.2, 143.5, 144.1, 146.3; MS (70 eV): m/z (%) = 368 (M^+, 34%), 370 (M + 2, 12%). *Anal*. Calcd for $C_{19}H_{21}ClN_6$ (368.86): C, 61.87; H, 5.74; N, 22.78; found: C, 61.69; H, 6.00; N, 22.42.

***5-(4-Chlorophenyl)-1-methyl-7-(4-chlorophenyl)-3-propyl-1H*-pyrazolo[3,4-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine (9b)**. White amorphous solid; yield 0.345 g, 79% (Method ii), 0.353 g, 81% (Method iii); mp 171–173°C; IR: 3076, 2958, 2935, 2869, 1647, 1492, 1311, 1089, 1012 cm^{-1}; ^{1}H nmr (300 MHz, $CDCl_3$): δ 1.03 (t, J = 7.5 Hz, 3H, CH_3), 1.88 (m, 2H, CH_2), 3.00 (t, J = 7.5 Hz, 2H, CH_2), 4.51 (s, 3H, N–CH_3), 7.05–7.26 (m, 8H, Ar–H); ^{13}C nmr (75 MHz, DMSO-d_6): δ 13.7, 21.6, 27.1, 38.4, 121.0, 126.5, 127.2 (2C's), 127.4 (3C's), 129.6, 130.9 (2C's), 131.4 (2C's), 134.1, 134.5, 141.6, 142.2, 146.3, 147.0; MS (70 eV): m/z (%) = 436 (M^+, 47%), 438 (M + 2, 31%), 440 (M + 4, 6%). *Anal*. Calcd for $C_{22}H_{18}Cl_2N_6$ (437.32): C, 60.42; H, 4.15; N, 19.22; found: C, 60.69; H, 4.11; N, 19.31.

***5-(4-Chlorophenyl)-1-methyl-7-(4-bromophenyl)-3-propyl-1H*-pyrazolo[3,4-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine (9c)**. Offwhite solid; yield 0.341 g, 71% (Method ii), 0.355 g, 74% (Method iii); mp 166–168°C; IR: 3095, 2971, 2934, 2852, 1639, 1511, 1483, 1298, 1060, 1002 cm^{-1}; ^{1}H nmr (300 MHz, $CDCl_3$): δ 1.02 (t, J = 7.2 Hz, 3H, CH_3), 1.86 (m, 2H, CH_2), 2.97 (t, J = 7.2 Hz, 2H, CH_2), 4.52 (s, 3H, N–CH_3), 6.99–7.35 (m, 8H, Ar–H); ^{13}C nmr (75 MHz, DMSO-d_6): δ 13.7, 21.7, 27.2, 38.4, 121.1, 126.7, 127.1 (2C's), 127.3 (3C's), 129.5, 130.9

(2C's), 131.3 (2C's), 134.2, 134.5, 146.8, 142.1, 146.1, 147.2; MS (70 eV): *m/z* (%) = 480 (M^+, 59%), 482 (M + 2, 78%), 484 (M + 4, 17%). *Anal*. Calcd for $C_{22}H_{18}BrClN_6$ (481.78): C, 54.85; H, 3.77; N, 17.44; found: C, 54.68; H, 4.10; N, 17.62.

***5-(4-Chlorophenyl)-1-methyl-7-(4-methoxyphenyl)-3-propyl-1H*-pyrazolo[3,4-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine (9d)**. White crystalline solid; yield 0.277 g, 64% (Method ii), 0.298 g, 69% (Method iii); mp 172–174°C; IR: 3034, 2963, 2927, 2876, 1658, 1481, 1452, 1238, 1061 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$): δ 1.02 (t, J = 7.2 Hz, 3H, CH_3), 1.85 (m, 2H, CH_2), 2.98 (t, J = 7.2 Hz, 2H, CH_2), 3.81 (s, 3H, OCH_3), 4.41 (s, 3H, N–CH_3), 6.74 (d, J = 8.0 Hz, 2H, Ar–H), 6.92 (d, J = 8.0 Hz, 2H, Ar–H), 7.23 (d, J = 7.5 Hz, 2H, Ar–H), 7.49 (d, J = 7.5 Hz, 2H, Ar–H); ^{13}C nmr (75 MHz, DMSO-d_6): δ 13.9, 22.1, 27.4, 38.8, 55.2, 115.3 (2C's), 121.9, 127.1, 127.3 (2C's), 129.1 (2C's), 129.3 (2C's), 131.7, 134.5, 137.1, 145.1, 146.6, 146.7, 156.1, 160.8; MS (70 eV): *m/z* (%) = 432 (M^+, 62%), 434 (M + 2, 22%). *Anal*. Calcd for $C_{23}H_{21}ClN_6O$ (432.91): C, 63.81; H, 4.89; N, 19.41; found: C, 64.06; H, 4.76; N, 19.63.

***5-(4-Chlorophenyl)-1-methyl-7-(3,4-dimethoxyphenyl)-3-propyl-1H*-pyrazolo[3,4-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine (9e)**. Colorless solid; yield 0.332 g, 72% (Method ii), 0.328 g, 71% (Method iii); mp 182–184°C; IR: 3052, 2956, 2929, 2867, 1645, 1527, 1488, 1315, 1261, 1026 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$): δ 1.04 (t, J = 7.5 Hz, 3H, CH_3), 1.89 (m, 2H, CH_2), 3.01 (t, J = 7.5 Hz, 2H, CH_2), 3.79 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.52 (s, 3H, N–CH_3), 6.55 (m, 2H, Ar–H), 6.80 (s, 1H, Ar–H), 7.10 (d, J = 8.7 Hz, 2H, Ar–H), 7.20 (d, J = 8.7 Hz, 2H, Ar–H); ^{13}C nmr (75 MHz, DMSO-d_6): δ 13.8, 21.7, 27.2, 38.5, 55.2, 55.8, 111.1, 113.5, 119.8, 121.1, 122.8, 127.0 (2C's), 129.5, 130.8 (2C's), 131.8, 134.2, 141.9, 142.0, 146.3, 147.6, 148.0, 149.7; MS (70 eV): *m/z* (%) = 462 (M^+, 54%), 464 (M + 2, 17%). *Anal*. Calcd for $C_{24}H_{23}ClN_6O_2$ (462.93): C, 62.27; H, 5.01; N, 18.15; found: C, 62.60; H, 5.09; N, 18.36.

***General procedure for synthesis of 5-(7-alkyl-4-chlorophenyl)-1-methyl-3-propyl-1H*-pyrazolo[3,4-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines 9f–i**. A solution of 1-(5-(4-chlorophenyl)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-7-yl) hydrazine **4** (0.317 g, 1.0 mmole) and respective triethylorthoester (1.2 mmole) in ethanol (20 mL) was heated under reflux temperature for 3–4 h, and the reaction progress was monitored by TLC (hexane/ethyl acetate 9:1). After completion of the reaction, solvent was removed *in vacuo*, and the obtained residue was treated with hexane, filtered, and dried under vacuum at 60°C to give products **9f–i** in 69–78% yield, which was purified by flash chromatography (silica gel, hexane/ethyl acetate 9:1 as eluent).

***5-(4-Chlorophenyl)-1-methyl-3-propyl-1H*-pyrazolo[3,4-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine (9f)**. This compound was synthesized by using triethyl orthoformate (0.20 mL, 1.2 mmole); pale yellow solid; yield 0.231 g (71%); mp 211–213°C; IR: 3114, 2958, 2927, 1797, 1652, 1492, 1336, 1007 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$): δ 1.03 (t, J = 7.5 Hz, 3H, CH_3), 1.88 (m, 2H, CH_2), 3.00 (t, J = 7.5 Hz, 2H, CH_2), 4.48 (s, 3H, N–CH_3), 7.62 (d, J = 8.4 Hz, 2H, Ar–H), 7.82 (d, J = 8.4 Hz, 2H, Ar–H), 8.97 (s, 1H, olefinic-H); ^{13}C nmr (75 MHz, DMSO-d_6): δ 14.1, 22.5, 27.5, 38.9, 121.1, 128.7 (2C's), 129.9, 132.1 (2C''s), 132.6, 135.5, 142.4, 142.5, 145.6, 146.5; MS (70 eV): *m/z* (%) = 326 (M^+, 29%), 328 (M + 2, 9%). *Anal*. Calcd for $C_{16}H_{15}ClN_6$ (326.78): C, 58.81; H, 4.63; N, 25.72; found: C, 59.08; H, 4.44; N, 26.00.

***5-(4-Chlorophenyl)-1,7-dimethyl-3-propyl-1H*-pyrazolo[3,4-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine (9g)**. This compound was synthesized by using triethyl orthoacetate (0.22 mL, 1.2 mmole); faint yellow solid; yield 0.258 g (76%); mp 198–200°C; IR: 3087, 3049, 2958, 2929, 2869, 1650, 1500, 1390, 1317, 1091 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$): δ 1.00 (t, J = 6.9 Hz, 3H, CH_3), 1.84 (m, 2H, CH_2), 2.19 (s, 3H, CH_3), 2.96 (t, J = 6.9 Hz, 2H, CH_2), 4.45 (s, 3H, N–CH_3), 7.54 (m, 4H, Ar–H); ^{13}C nmr (75 MHz, DMSO-d_6): δ 14.2, 14.5, 22.2, 27.6, 38.8, 121.3, 128.6 (2C's), 129.5, 131.9 (2C's), 132.7, 135.6, 142.0, 142.2, 145.6, 146.6; MS (70 eV): *m/z* (%) = 340 (M^+, 38%), 342 (M + 2, 12%). *Anal*. Calcd for $C_{17}H_{17}ClN_6$ (340.81): C, 59.91; H, 5.03; N, 24.66; found: C, 60.14; H, 5.35; N, 24.44.

***5-(4-Chlorophenyl)-7-ethyl-1-methyl-3-propyl-1H*-pyrazolo[3,4-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine (9h)**. This compound was synthesized by using triethyl orthopropionate (0.25 mL, 1.2 mmole); white amorphous solid; yield 0.244 g (69%); mp 182–184°C; IR: 3108, 3057, 2966, 2917, 2871, 1646, 1518, 1401, 1326, 1053 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$): δ 1.02 (t, J = 7.2 Hz, 3H, CH_3), 1.36 (t, J = 6.9 Hz, 3H, CH_3), 1.85 (m, 2H, CH_2), 2.43 (q, J = 6.9 Hz, 2H, CH_2), 2.94 (t, J = 7.2 Hz, 2H, CH_2), 4.46 (s, 3H, N–CH_3), 7.58(d, J = 8.0 Hz, 2H, Ar–H), 7.81 (d, J = 8.0 Hz, 2H, Ar–H); ^{13}C nmr (75 MHz, DMSO-d_6): δ 13.9, 14.2, 21.8, 23.1, 27.4, 38.7, 122.4, 127.9 (2C's), 129.2, 131.4 (2C's), 132.1, 136.2, 142.6, 143.2, 145.8, 147.4; MS (70 eV): *m/z* (%) = 354 (M^+, 61%), 356 (M + 2, 19%). *Anal*. Calcd for $C_{18}H_{19}ClN_6$ (354.84): C, 60.93; H, 5.40; N, 23.68; found: C, 60.72; H, 5.70; N, 23.54.

***5-(4-Chlorophenyl)-7-phenyl-1-methyl-3-propyl-1H*-pyrazolo[3,4-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine (9i)**. This compound was synthesized by using triethyl orthobenzoate (0.27 mL, 1.2 mmole); offwhite solid; yield 0.314 g (78%); mp 174–176°C; IR: 3188, 3087, 2947, 2918, 2893, 1667, 1534, 1399, 1338, 1009 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ 1.04 (t, J = 7.4 Hz, 3H, CH_3), 1.90 (m, 2H, CH_2), 3.01 (t, J = 7.4 Hz, 2H, CH_2), 4.53 (s, 3H, N–CH_3), 7.01–7.07 (m, 2H, Ar–H), 7.11–7.18 (m, 6H, Ar–H), 7.29–7.35 (m, 1H, Ar–H); ^{13}C nmr (75 MHz, DMSO-d_6): δ 13.9, 21.8, 27.7, 39.2, 122.0, 127.3 (2C's), 127.5 (4C's), 128.2 (2C's), 129.1 (2C's), 129.6, 132.5, 133.3, 139.7, 142.0, 146.1, 149.9; MS (70 eV): *m/z* (%) = 402 (M^+, 54%), 404 (M + 2, 19%). *Anal*. Calcd for $C_{22}H_{19}ClN_6$ (402.88): C, 65.59; H, 4.75; N, 20.86; found: C, 65.87; H, 4.71; N, 20.98.

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