New Synthesis and Reactions of Ethyl 5-amino-4-cyano-1-phenyl-1*H*-pyrazole-3-carboxylate

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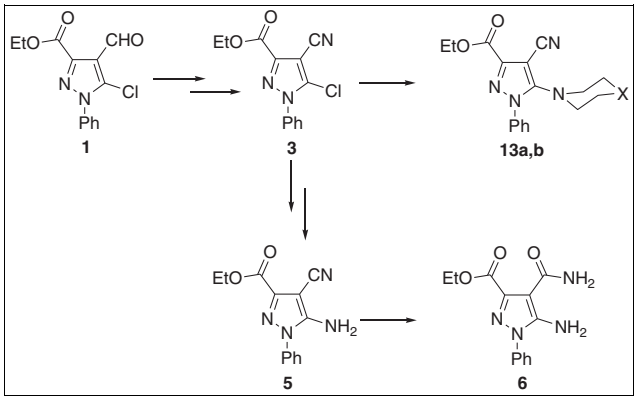


Synthesis of ethyl 5-amino-4-cyano-1-phenyl-1*H*-pyrazole-3-carboxylate **5** has been achieved via abnormal Beckmann rearrangement of *o*-chloroaldehyde **1**. Reaction of *o*-aminocarbonitrile **5** with concentrated H_2SO_4 furnished expected *o*-aminocarboxamide pyrazole **6**. Key intermediates *o*-aminocarbonitrile **5** and *o*-aminocarboxamide **6** were successfully utilized for the synthesis of pyrazolopyrimidine derivatives. The replacement of Cl in *o*-chlorocarbonitrile **3** with secondary amine furnished new synthon **13**, which was further used for the synthesis of polysubstituted heterocycles. The obtained new products were well characterized by IR, ^{1}H and ^{13}C NMR, and mass spectra.

INTRODUCTION

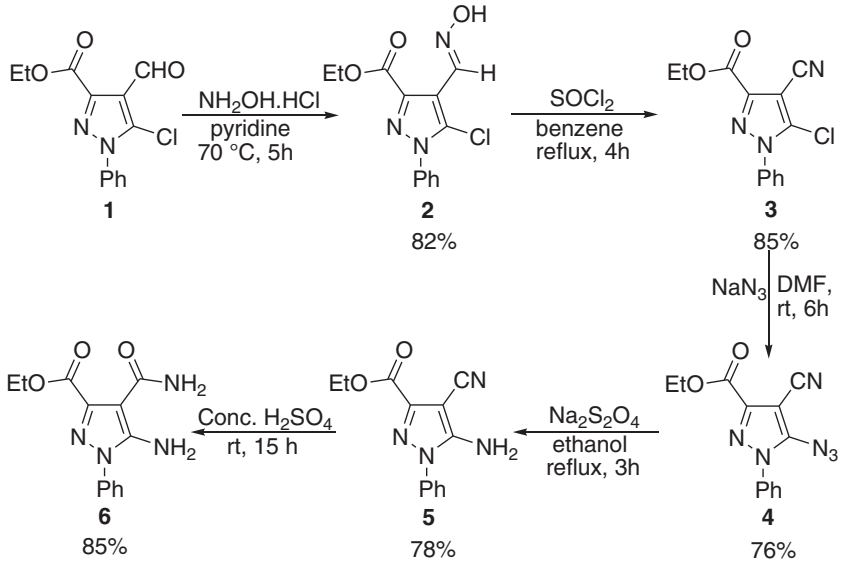
In recent years, pyrazolopyrimidines and related fused heterocycles have been identified as bioactive molecules, were known to function as central nervous system depressants, neuroleptic agents, and as tuberculostatic [1–3]. Pyrazolo[3,4-*d*]pyrimidines were identified as a general class of adenosine receptors [4]. Several conformational analogous of pyrazole-3-carboxamide derivatives have been recently described as cannabinoid receptor-1 antagonists [5]. Pyrazole and pyrimidine derivatives incorporating benzothiazole moiety showed very good antimicrobial activity [6]. The remarkable applications of these compounds have not only prompted many chemists to synthesize these derivatives but also become an active research area of continuing interest.

In literature, the synthesis of ethyl 5-amino-4-cyano-1-phenyl-1*H*-pyrazole-3-carboxylate **5** by the reaction of potassium salt of 2-cyano-4-ethoxy-4-oxobut-2-en-2-olate with phenylhydrazine in ethanol is relatively expensive [7]. The same compound has also been synthesized by treating aryldiazonium salt with ethyl-2-chloroacetoacetate to furnish ethyl 2-chloro-2-phenylhydrazonoacetate that was further condensed with malononitrile [7–9]. However, both established methods were suffered from disadvantages of low yield, tedious workup, and requirement of low temperature below −5°C for the latter method. In continuation of our recent work aiming at the synthesis of various new pyrazole derivatives [10–13], we report a new method for the synthesis of ethyl 5-amino-4-cyano-1-phenyl-1*H*-pyrazole-3-carboxylate **5** and novel pyrazolopyrimidine, *N*-alkylated pyrazolo[3,4-*d*]pyridazin-7-one, and 3-(hydrazinylcarbonyl) pyrazole-4-carboxamide derivatives, which have been tested for their antimicrobial activity.

RESULTS AND DISCUSSION

The required *o*-chloroaldeyde **1** was prepared according to reported method in 78% yield [13], which was further treated with hydroxylamine hydrochloride in pyridine to furnish oxime **2**. The abnormal Beckmann rearrangement is a convenient method for the conversion of oxime to carbonitrile, hence used for the synthesis of ethyl 5-chloro-4-cyano-1-phenyl-1*H*-pyrazole-3-carboxylate **3** (Scheme 1). Accordingly, oxime **2** was treated with thionyl chloride in dry benzene to yield carbonitrile **3** in 85% yield. The nucleophilic C_5-Cl substitution by azide furnished azido derivative **4** in 76% yield. The nucleophilic substitution on aromatic pyrazole ring was made possible because of strong

Scheme 1



electron-withdrawing nitrile at C_4 position. Compound **4** on reduction with sodium dithionite gave target molecule ethyl 5-amino-4-cyano-1-phenyl-1*H*-pyrazole-3-carboxylate **5** in 78% yield, higher than in earlier reported procedures [7–9] and also economical as this process does not require expensive 18-crown-6 or 2-chloroacetoacetate.

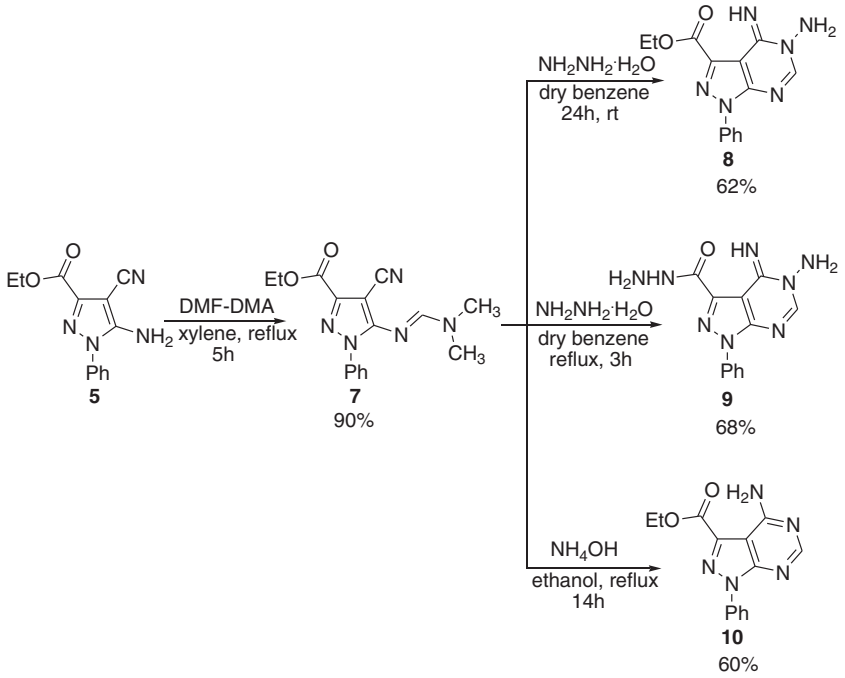
The carbonitrile on reaction with acid yielded carboxylic acid or carboxamide depending upon the reaction conditions [14]. Reaction of carbonitrile **5** with concentrated (conc.) H_2SO_4 at room temperature afforded carboxamide **6**, which is our vital precursor. It was observed that during the course of reaction, the ester group is not hydrolyzed to carboxylic acid. The active *o*-aminocarbonitrile **5** and *o*-aminocarboxamide **6** moieties have found wide applications in the synthesis of annulated heterocyclic ring systems [14–16] and hence were successfully utilized for synthesis of pyrazolopyrimidine derivatives in good yields.

In continuation of our work, an intermediate **5** was condensed with *N*,*N*-dimethylformamide dimethylacetal in *p*-xylene at reflux temperature to yield amidine **7**, which was further utilized for the synthesis of pyrazolo[3,4-*d*] pyrimidines **8–10.** The chemoselective reaction of **7** with hydrazine hydrate at room temperature in dry benzene furnished pyrazolo[3,4-*d*]pyrimidine-3-carboxylate **8** whereas at reflux temperature furnished hydrazine derivative **9** in 62 and 68% yields, respectively. Compound **7** with ammonium hydroxide solution in ethanol led the formation of ethyl 4-amino-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-3-carboxylate **10** at reflux temperature (Scheme 2). The structures of **8–10** were established on the basis of spectral data and by elemental analysis. For instance, IR spectrum of **8** and **10** showed absorption band at 1710 and 1715 cm^{-1}, respectively, for ester carbonyl group. However, in IR spectrum of **9**, absorption band was observed at 1610 cm^{-1} for amide group. In the ^1H NMR spectrum of **8** in DMSO-d_6, two broad singlets were observed at 4.88 and 10.51 δ corresponding to two NH_2 and one NH protons, respectively. However, ^1H NMR spectrum of **9** in DMSO-d_6 showed two broad singlets at 4.78 and 4.91 δ corresponding to four NH_2 protons and another two singlets at 9.40 and 10.11 δ corresponding to two NH protons. The ^1H NMR spectrum of **10** in DMSO-d_6 showed triplet and quartet at 1.42 and 4.46 δ, respectively, for ethoxy protons and one broad singlet at 5.60 δ corresponding to two NH_2 protons. Furthermore, ^{13}C NMR and elemental analysis data of these compounds were in agreement with the proposed structure.

The regioselective reaction of aldehydes with *o*-aminocarboxamide **6** in acetonitrile and slight excess of iodine furnished pyrazolo[3,4-*d*]pyrimidines **11a–c** in 60–68% yield, whereas the same reaction in *n*-butanol and catalytic amount of piperidine afforded tetrahydropyrimidines **12a–c** in 58–62% yield (Scheme 3). It was clearly observed that mild Lewis acid and oxidant [17], that is, iodine play important role in C═N bond formation in pyrazolo[3,4-*d*] pyrimidines **11a–c**.

The novel intermediate ethyl 5-chloro-4-cyano-1-phenyl-1*H*-pyrazole-3-carboxylate **3** was used for the synthesis of new pyrazolo[3,4-*d*]pyridazin-7-one and pyrazole-4-carboxamide derivatives **13–17** (Scheme 4). The nucleophilic substitution reactions were performed on *o*-chlorocarbonitrile **3** using cyclic secondary amines as nucleophiles. Thus, reaction of **3** with secondary amines at reflux temperature furnished pyrazole derivatives **13a,b** in quantitative yield. Compounds **13a,b** were treated with conc. H_2SO_4 at room temperature and afforded carboxamide derivatives **14a,b**. However, the reaction of **14a,b** with hydrazine hydrate proved to be difficult at low temperature, which might be because C_4-carboxamide of pyrazole blocks the attack of

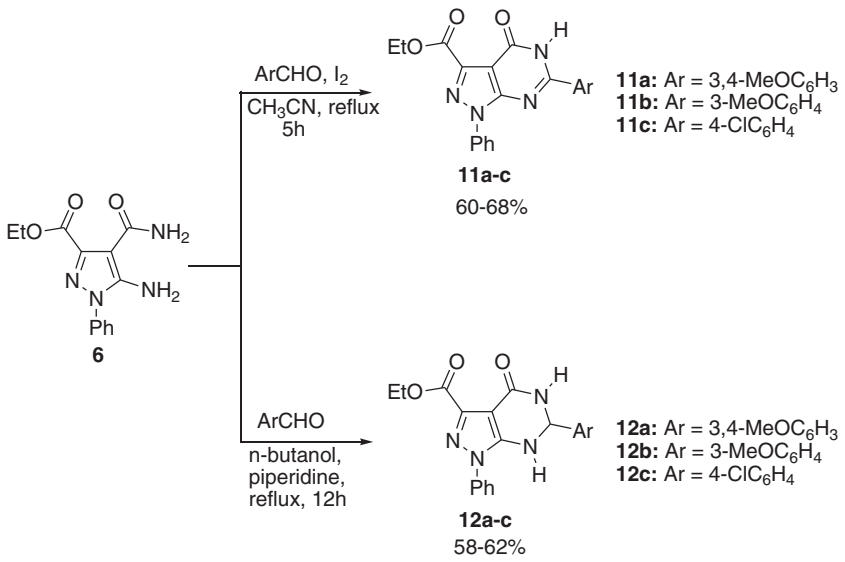
Scheme 2



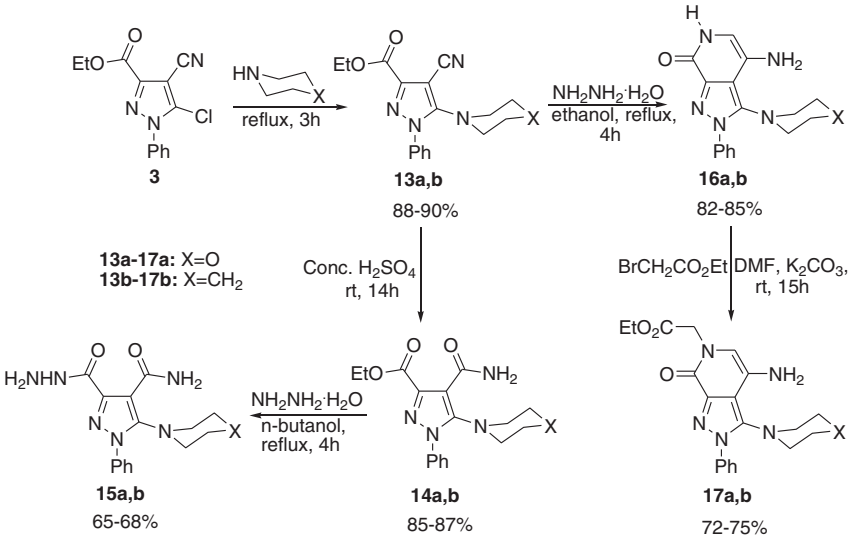
weakly nucleophilic hydrazine hydrate on ester functionality due to hydrogen bonding. Hence, we perform this reaction in high-boiling solvent *n*-butanol at reflux temperature to yield 3-(hydrazinylcarbonyl)-pyrazole-4-carboxamide **15a,b** in 65–68% yield.

Compounds **13a,b** containing nitrile and ester functionality at ortho position were utilized for the synthesis of novel pyrazolo[3,4-*d*]pyridazin-7-one **16a,b**. The reaction of **13a, b** with hydrazine hydrate in ethanol at reflux temperature yielded pyrazolo[3,4-*d*]pyridazin-7-one **16a,b** in 82–85% yield. N-alkylation of compounds **16a,b** with ethyl bromoacetate in DMF at 20–25°C with stoichiometric amount of potassium carbonate selectively occurred at secondary amide NH instead of amine NH_2 and gave **17a,b** in 72–75% yield without any O-substituted and/or O,N-disubstituted products. It might be due to amide–enaminol tautomerism. IR, ^{1}H NMR, MS, and elemental analysis were used to deduce the structures of **16** and **17**. For example, ^{1}H NMR spectrum of **16a** in DMSO-d_6 contained broad singlets at 5.38 and 11.17 δ corresponding to two NH_2 and one NH

Scheme 3



Scheme 4



protons. However, ^{1}H NMR of **17a** in DMSO-d_6 showed triplet and quartet at 1.20 and 4.14 δ, respectively, for ethoxy protons and one broad singlet at 5.60 δ corresponding to two NH_2 protons, but singlet corresponding to amide NH disappeared. Furthermore, elemental analysis data of these compounds was in agreement with the proposed structure.

Antimicrobial activity. The antibacterial activities of the synthesized compounds **8**, **9**, **10**, **11a–c**, **12a–c**, **15a,b**, and **17a,b** were determined by the well-diffusion method [18]. In this work, *Escherichia coli* (ATCC-25922), *Pseudomonas aeruginosa* (ATCC 27853), and *Staphylococcus aureus* (ATCC 25923) were used to investigate the antibacterial activities by using gentamycin and nystatin as standards. The investigation of antibacterial screening data revealed that these compounds did not show significant bacterial inhibition even at higher concentration, that is, 1 mg ml^{-1}.

CONCLUSION

A simple and convenient method for the synthesis of ethyl 5-amino-4-cyano-1-phenyl-1*H*-pyrazole-3-carboxylate **5** with improved yield was developed. A new class of pyrazolo[3,4-*d*]pyrimidines, tetrahydropyrimidines, pyrazolo[3,4-*d*]pyridazin-7-one, and 3-(hydrazinylcarbonyl)-pyrazole-4-carboxamide was obtained in good yield from *o*-aminopyrazolecarbonitrile **5** and *o*-aminopyrazolecarbonitrile **6** with simple workup and clean products.

EXPERIMENTAL

General remarks. Melting points were determined on a Gallenkamp melting point apparatus (Nashik, India) in an open capillary tube and are uncorrected. The ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Varian XL-300 spectrometer (Pune, India). Chemical shifts were reported in ppm relative to TMS, and multiplicities are given as s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). Infrared spectra were recorded as KBr pellets on a Shimadzu FTIR-408 spectrophotometer (Nashik, India). Mass spectra were recorded on a Shimadzu LC-MS: EI QP 2010A mass spectrometer (Mumbai, India) with an ionization potential of 70 eV. Elemental analyses were performed on ThermoQuest Flash 1112 Series EA analyzer (Mumbai, India). Reactions were monitored by TLC, carried out on 0.2-mm silica gel 60 F_{254} (Merck, Mumbai, India) plates using UV light (254 and 366 nm) for detection, and compounds were purified by column chromatography by using silica gel of 5–20 μm (Merck, 60–120 mesh). Column dimension is 39 × 2 cm, and elution volume used is about 200–400 mL for each product where necessary. Common reagent-grade chemicals are either commercially available and were used without further purification or were prepared by standard literature procedures.

Ethyl 5-chloro-4-formyl-1-phenyl-1*H*-pyrazole-3-carboxylate (1). White solid, yield 78%, mp 135–136°C (lit. mp 135°C [12]).

Ethyl 5-chloro-4-[(*E*)-(hydroxyimino) methyl]-1-phenyl-1*H*-pyrazole-3-carboxylate (2). A mixture of ethyl 5-chloro-4-formyl-pyrazole-3-carboxylate **1** (0.27 g, 1.0 mmol) and hydroxyl amine hydrochloride (0.69 g, 1.0 mmol) dissolved in pyridine (5 mL) was heated with stirring at 70–75°C for 5 h (TLC check, chloroform : methanol, 9:1). The solution was cooled, poured into cold water, and neutralized with dilute hydrochloric acid. The solid obtained was isolated by filtration under vacuum, and using column chromatography eluting with chloroform : methanol (9:1) gave **2** as pale yellow solid, yield 82%, 0.23 g, mp 125–126°C; IR (KBr) ν_{max} 1625 (C═N), 1735 (C═O), 2940 (C-H aliph.), 3560 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.43 (t, J = 6.9 Hz, 3H), 4.46 (q, J = 6.9 Hz, 2H, OCH_2), 7.54 (m, 5H, Ar-H), 7.51 (s, 1H, CH), 8.72 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 14.2, 61.7, 114.0, 125.7, 127.3, 129.1, 129.4, 129.6, 137.0, 141.8, 161.3; MS *m/z* (%): 293 (M^+, 100%), 295 (M + 2, 33%); *Anal.* Calcd. for $C_{13}H_{12}ClN_3O_3$: C, 53.16; H, 4.12; N, 14.31. Found: C, 53.30; H, 4.20; N, 14.38.

Ethyl 5-chloro-4-cyano-1-phenyl-1*H*-pyrazole-3-carboxylate (3). A solution of oxime **2** (0.29 g, 1.0 mmol) and thionyl chloride (0.15 mL, 2.0 mmol) in dry benzene (20 mL) was reflux

for 4 h (TLC check, chloroform : methanol, 9:1). The excess solvent was removed under reduced pressure. The solid obtained was filtered, washed with cold methanol and recrystallized from ethanol to afford compound **3** as white solid, yield 85%, 0.23 g, mp 125–126°C; IR (KBr) ν_{max} 1602 (C═C), 1732 (C═O), 2239 (C≡N) 2916 (C═H) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (t, $J = 6.9$ Hz, 3H, CH_3), 4.52 (q, $J = 6.9$ Hz, 2H, CH_2), 7.56 (m, 5H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 13.6, 61.9, 95.5, 109.9, 124.9, 129.1, 129.9, 134.8, 135.9, 144.1, 158.4; MS *m/z* (%): 275 (M^+, 100%), 277 (M + 2, 33%); *Anal*. Calcd. for $C_{13}H_{10}ClN_3O_2$: C, 56.64; H, 3.66; N, 15.24. Found: C, 56.79; H, 3.61; N, 15.41.

Ethyl 5-azido-4-cyano-1-phenyl-1*H*-pyrazole-3-carboxylate (4). To the vigorously stirred solution of compound **3** (0.27 g, 1.0 mmol) dissolved in DMF (5 mL), sodium azide (0.078 g, 1.2 mmol) was slowly added for 10 min. The reaction mixture was stirred at room temperature for 6 h (TLC check, chloroform : methanol, 9:1). The solution was then poured into cold water; the solid obtained was filtered off and recrystallized from ethanol to give compound **4** as pale green solid, yield 76%, 0.21 g, mp 70°C; IR (KBr) ν_{max} 1593 (C═C), 1740 (C═O), 2133 (N_3), 2227 (C≡N), 2929 (C-H aliph.) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (t, $J = 6.6$ Hz, 3H, CH_3), 4.52 (q, $J = 6.6$ Hz, 2H, CH_2), 7.51 (m, 5H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 13.9, 62.2, 85.7, 110.2, 124.2, 125.1, 129.3, 136.2, 142.0, 144.0, 159.1; MS *m/z* (%): 305 (M + Na, 100%); *Anal*. Calcd. for $C_{13}H_{10}N_6O_2$: C, 55.32; H, 3.57; N, 29.77. Found: C, 55.25; H, 3.60; N, 29.74.

Ethyl 5-amino-4-cyano-1-phenyl-1*H*-pyrazole-3-carboxylate (5). A solution of **4** (0.28 g, 1.0 mmol) and sodium dithionite (0.2 g, 1.2 mmol) in ethanol (10 mL) was refluxed for 3 h (TLC check, chloroform : methanol, 9:1). The reaction mixture was concentrated and cooled, and residue was poured into cold water. The solid obtained was filtered off and recrystallized from ethanol to give compound **5** as white solid, yield 78%, 0.19 g, mp 158–159°C (Lit. mp 157–161°C [7,8]); IR (KBr) ν_{max} 1706 (C═O), 2217 (C≡N), 3222, 3306 (NH_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (t, $J = 7.2$ Hz, 3H, CH_3), 4.43 (q, $J = 7.2$ Hz, 2H, CH_2), 4.96 (s, 2H, NH_2), 7.49 (m, 5H, Ar-H); MS *m/z* (%): 257 (M + 1, 30%), 279 (M + 23, 100%); *Anal*. Calcd for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72; N, 21.86. Found: C, 61.01; H, 4.66; N, 21.72.

Ethyl 5-amino-4-carbamoyl-1-phenyl-1*H*-pyrazole-3-carboxylate (6). Compound **5** (0.25 g, 1.0 mmol) was stirred in conc. H_2SO_4 (8 mL) at room temperature for 15 h (TLC check, chloroform : methanol, 9:1). The reaction mass was then added to crushed ice (150 mL) and neutralized with saturated $NaHCO_3$ (20 mL). The crude solid separated was filtered, washed with water, dried, and recrystallized from ethanol to give compound **6** as white solid, yield 85%, 0.23 g, mp 170–171°C; IR (KBr) ν_{max} 1613 (C═C arom.), 1670 (C═O, amide), 1725 (C═O, ester), 3310, 3440, 3210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (t, $J = 6.7$ Hz, 3H, CH_3), 4.49 (q, $J = 6.7$ Hz, 2H, CH_2), 7.58 (m, 5H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 14.1, 62.2, 96.4, 124.7, 128.9, 129.6, 136.6, 139.2, 151.6, 164.2, 166.1; MS *m/z* (%): 275 (M + 1, 100%); *Anal*. Calcd for $C_{13}H_{14}N_4O_3$: C, 56.93; H, 5.14; N, 20.43. Found: C, 56.88; H, 5.10; N, 20.48.

Ethyl 4-cyano-5-((*E*)-formamido)-1-phenyl-1*H*-pyrazole-3-carboxylate (7). Compound **5** (0.25 g, 1.0 mmol) and DMF-DMA (0.13 mL, 1.0 mmol) in dry *p*-xylene (10 mL) was refluxed for 5 h (TLC check, chloroform : methanol, 9:1). The excess solvent was removed under reduced pressure. The solid obtained was stirred in hexane (20 mL) for 1 h. The solid that formed was filtered, washed with cold methanol, and dried. The crude product was recrystallized from toluene to give **7** as white solid, yield 90%, 0.27 g, mp 137–138°C; IR (KBr) ν_{max} 1600 (C═C, arom.), 1622 (C═N), 1722 (C═O), 2228 (C≡N), 2929 (C-H), 2932 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.42 (t, $J = 7.2$ Hz, 3H, CH_3), 3.01 (s, 3H, NCH_3), 3.13 (s, 3H, NCH_3), 4.46 (q, $J = 7.2$ Hz, 2H, CH_2), 7.34–7.74 (m, 5H, Ar-H), 8.35 (s, 1H, N═C-H); ^{13}C NMR ($CDCl_3$) δ 13.6, 61.8, 40.6, 79.5, 114.9, 124.3, 127.6, 128.3, 138.0, 138.5, 142.9, 155.6, 160.7; MS *m/z* (%): 312 (M + 1, 100%); *Anal*. Calcd for $C_{16}H_{17}N_5O_2$: C, 61.72; H, 5.50; N, 22.49. Found: C, 61.66; H, 5.47; N, 22.54.

Ethyl 5-amino-4-imino-1-phenyl-4,5-dihydro-1*H*-pyrazolo [3,4-*d*]pyrimidine-3-carboxylate (8). A mixture of **7** (0.31 g, 1.0 mmol) and hydrazine hydrate (0.05 mL, 1.0 mmol) in dry benzene (15 mL) was stirred at room temperature for 24 h (TLC check, chloroform : methanol, 8:2). The obtained solid was collected by filtration under vacuum, washed with hexane, dried, and recrystallized from ethanol-DMF (7:3) to give compound **9** as white solid, yield 62%, 0.18 g, mp 299–300°C; IR (KBr) ν_{max} 1600 (C═C), 1710 (C═O), 2925 (CH aliph.), 3306, 3420 (NH_2), 3470 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.42 (t, $J = 6.9$ Hz, 3H, CH_3), 4.46 (q, $J = 6.9$ Hz, 2H, CH_2), 4.88 (s, 2H, NH_2), 7.39–7.5 (m, 5H, Ar-H), 8.39 (s, 1H, Ar-H), 10.51 (brs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 13.9, 61.4, 118.2, 124.3, 127.6, 128.3, 138.0, 140.9, 145.1, 158.9, 163.2, 163.9; MS *m/z* (%): 298 (M^+, 100%); *Anal*. Calcd for $C_{14}H_{14}N_6O_2$: C, 56.37; H, 4.73; N, 28.17. Found: C, 56.45; H, 4.82; N, 28.11.

5-Amino-4-imino-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*] pyrimidine-3-carbohydrazide (9). A mixture of **7** (0.31 g, 1.0 mmol) and hydrazine hydrate (0.05 mL, 1.0 mmol) in dry benzene (15 mL) was refluxed for 3 h (TLC check, chloroform : methanol, 8:2). The reaction mixture was cooled to room temperature, and obtained solid was collected by filtration under vacuum, washed with hexane, dried, and recrystallized from ethanol-DMF (6:4) to give compound **9** as white solid, yield 68%, 0.19 g, mp 314–315°C; IR (KBr) ν_{max} 1604 (C═C, arom.), 1610 (C═O, amide), 3278, 3335, 3465 (NH_2/NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.78 (s, 2H, NH_2), 4.91 (s, 2H, NH_2), 7.40–7.57 (m, 5H, Ar-H), 8.42 (s, 1H, Ar-H), 9.40 (s, 1H, NH), 10.11 (brs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 112.1, 124.3, 127.6, 128.3, 138.0, 141.8, 142.7, 145.1, 161.2, 163.1, 163.9; MS *m/z* (%): 285 (M + 1, 100%); *Anal*. Calcd for $C_{12}H_{12}N_8O$: C, 50.70; H, 4.25; N, 39.42 Found: C, 50.48; H, 4.32; N, 39.29.

Ethyl 4-amino-1-phenyl-1*H*-pyrazolo [3, 4-*d*] pyrimidine-3-carboxylate (10). A solution of compound **7** (0.31 g, 1.0 mmol) and ammonium hydroxide (8 mL, excess) in ethanol (15 mL) was refluxed for 14 h (TLC check, chloroform : methanol, 8:2). The solution was cooled to room temperature, and obtained solid was collected by filtration under vacuum, washed with ethanol, and dried to afford analytically pure compound **8** as white crystalline solid, yield 60%, 0.17 g, mp 250°C; IR (KBr) ν_{max} 1604 (C═C, arom.), 1715 (C═O), 2920, 3430, 3370 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.42 (t, $J = 6.9$ Hz, 3H, CH_3), 4.46 (q, $J = 6.9$ Hz, 2H, CH_2), 5.60 (s, 2H, NH_2), 7.46–7.65 (m, 5H, Ar-H), 8.42 (s, 1H, CH); ^{13}C NMR (DMSO-d_6) δ 13.6, 61.9, 104.3, 124.9, 129.1, 129.9, 135.8, 142.9, 148.1, 154.9, 155.5, 161.1; MS *m/z* (%): 284 (M + 1, 100%); *Anal*. Calcd for $C_{14}H_{13}N_5O_2$: C, 59.36; H, 4.63; N, 24.72. Found: C, 59.42; H, 4.55; N, 24.71.

General procedure for the synthesis of compounds 11a–c. To a mixture of compound **6** (0.27 g, 1.0 mmol) and aromatic aldehydes (1.0 mmol), namely, 3,4-dimethoxybenzaldehyde,

3-methoxybenzaldehyde, and 4-chlorobenzaldehyde in dry acetonitrile (15 mL), iodine (0.27 g, 1.1 mmol) was added. The mixture was refluxed for 5–6 h (TLC check, chloroform : methanol, 8:2). The reaction mixture was cooled to room temperature. An aqueous solution of sodium thiosulphate (5%, 15 mL) was added, and resulted solid was filtered off, washed with water, and dried. The crude product was recrystallized from ethanol : DMF (8:2) to give **11a–c**.

Ethyl 4, 5-dihydro-6-(3,4-dimethoxyphenyl)-4-oxo-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine-3-carboxylate (11a). White solid, yield 68%, 0.29 g, mp 280–281°C; IR (KBr) ν_{max} 1612 (C═C arom.), 1666 (C═O), 1718 (C═O), 2925 (C-H, aliph.), 3480, 3460 (NH) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.35 (t, $J = 6$ Hz, 3H, CH_3), 3.83 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.48 (q, $J = 6$ Hz, 2H, CH_2), 7.11 (d, $J = 9$ Hz, 1H, Ar-H), 7.46 (t, $J = 9$ Hz, 1H, Ar-H). 7.61 (m, 2H, Ar-H), 7.80 (s, 1H, Ar-H), 7.85 (m, 1H, Ar-H), 8.09 (d, $J = 9$ Hz, 2H, Ar-H), 12.54 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 13.6, 55.6, 61.7, 112.4, 112.9, 115.5, 118.3, 120.2, 121.4, 124.9, 129.1, 129.9, 134.8, 142.1, 144.0, 148.1, 148.6, 160.1, 160.9, 161.2; MS *m/z* (%): 421 (M + 1, 100%); *Anal*. Calcd for $C_{22}H_{20}N_4O_5$: C, 62.85; H, 4.79; N, 13.33. Found: C, 62.91; H, 4.66; N, 13.44.

Ethyl 4,5-dihydro-6-(3-methoxyphenyl)-4-oxo-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine-3-carboxylate (11b). White solid, yield 65%, 0.25 g, mp 265–266°C; IR (KBr) ν_{max} 1612 (C═C arom.), 1665 (C═O), 1718 (C═O), 2925 (C-H, aliph.), 3480, 3460 (NH) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.43 (t, $J = 6.9$ Hz, 3H), 3.85 (s, 3H, OCH_3), 4.46 (q, $J = 6.9$ Hz, 2H, OCH_2), 7.19 (d, $J = 7.8$ Hz, 1H, Ar-H), 7.51 (t, $J = 7.8$ Hz, 2H, Ar-H), 7.63 (t, $J = 7.8$ Hz, 2H, Ar-H), 7.77 (t, $J = 8.1$ Hz, 2H, Ar-H), 7.11 (d, $J = 8.1$ Hz, 2H, Ar-H), 13.20 (s, 1H, NH). MS *m/z* (%): 391 (M + 1, 100%); *Anal*. Calcd for $C_{21}H_{18}N_4O_4$: C, 64.61; H, 4.65; N, 14.35. Found: C, 64.44; H, 4.70; N, 14.28.

Ethyl 6-(4-chlorophenyl)-4,5-dihydro-4-oxo-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine-3-carboxylate (11c). White solid, yield 68%, 0.26 g, mp 301–302°C; IR (KBr) ν_{max} 1612 (C═C arom.), 1668 (C═O), 1720 (C═O), 2926 (C-H, aliph.), 3480, 3460 (N-H) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.44 (t, $J = 6.9$ Hz, 3H), 4.46 (q, $J = 6.9$ Hz, 2H, OCH_2), 7.32–7.62 (m, 5H, Ar-H), 7.63–7.65 (m, 4H, Ar-H), 12.89 (s, 1H, NH); MS *m/z* (%): 395 (M^+, 100%), 397 (M + 2, 33%); *Anal*. Calcd for $C_{22}H_{22}N_4O_5$: C, 60.84; H, 3.83; N, 14.19. Found: C, 62.48; H, 3.77; N, 13.98.

General procedure for the synthesis of compounds 12a–c. To a mixture of compound **6** (0.27 g, 1.0 mmol) and aromatic aldehydes (1.0 mmol), namely, 3,4-dimethoxybenzaldehyde, 3-methoxybenzaldehyde, and 4-chlorobenzaldehyde in *n*-butanol (10 mL) with catalytic amount of piperidine was refluxed in oil bath with stirring for 10–12 h (TLC check, chloroform : methanol, 8:2). The reaction mixture was cooled and poured into crushed ice (30 mL). The residue obtained was filtered, washed with cold ethanol, and recrystallized from ethanol-DMF (8:2) to give **12a–c**.

Ethyl 4,5,6,7-tetrahydro-6-(3,4-dimethoxyphenyl)-4-oxo-1-phenyl-1H-pyrazolo[3,4-d] pyrimidine-3-carboxylate (12a). White solid, yield 58%, 0.24 g, mp 319–320°C; IR (KBr) ν_{max} 1600 (C═C, arom.), 1672 (C═O), 2930 (C-H), 3455, 3472 (N-H) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.44 (t, $J = 7.2$ Hz, 3H, CH_3), 4.46 (q, $J = 7.2$ Hz, 2H, OCH_2), 5.82 (s, 1H, CH), 7.15–7.70 (m, 5H, Ar-H), 7.73–7.86 (m, 3H, Ar-H), 8.4 (bs, 1H, NH), 9.78 (bs, 1H, NH); MS *m/z* (%): 422 (M^+, 100%); *Anal*. Calcd for $C_{22}H_{22}N_4O_5$: C, 62.55; H, 5.25; N, 13.26. Found: C, 62.61; H, 5.23; N, 13.32.

Ethyl-4,5,6,7-tetrahydro-6-(3-methoxyphenyl)-4-oxo-1-phenyl-1H-pyrazolo[3,4-d]pyrimidi-ne-3-carboxylate (12b). White solid, yield 60%, 0.23 g, mp 336–337°C; IR (KBr) ν_{max} 1600 (C═C, arom.), 1675 (C═O), 2934 (C-H), 3455, 3472 (N-H) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.44 (t, $J = 7.2$ Hz, 3H, CH_3), 4.46 (q, $J = 7.2$ Hz, 2H, OCH_2), 5.85 (s, 1H, CH), 7.15–7.70 (m, 5H, Ar-H), 7.73–7.86 (m, 4H, Ar-H), 8.50 (bs, 1H, NH), 10.21 (bs, 1H, NH); Mass *m/z*: 392 (M^+, 100%); *Anal*. Calcd for $C_{21}H_{20}N_4O_4$: C, 64.28; H, 5.14; N, 14.28. Found: C, 64.15; H, 5.23; N, 14.30.

Ethyl 6-(4-chlorophenyl)-4,5,6,7-tetrahydro-4-oxo-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine-3-carboxylate (12c). White solid, yield 62%, 0.24 g, mp 345–346°C; IR (KBr) ν_{max} 1600 (C═C arom.), 1673 (C═O), 2932 (C-H), 3455, 3472 (N-H) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.44 (t, $J = 7.2$ Hz, 3H, CH_3), 4.46 (q, $J = 7.2$ Hz, 2H, OCH_2), 5.86 (s, 1H, CH), 7.15–7.62 (m, 5H, Ar-H), 7.63–7.80 (m, 3H, Ar-H), 8.50 (bs, 1H, NH), 10.53 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 14.1, 62.2, 70.3, 109.3, 124.7, 128.9, 129.0, 129.6, 131.2, 133.1, 136.6, 139.1, 142.9, 149.4, 158.6, 162.5; MS *m/z* (%): 397 (M^+, 100%), 399 (M + 2, 33%); *Anal*. Calcd for $C_{20}H_{17}ClN_4O_3$: C, 60.53; H, 4.32; N, 14.12. Found: C, 60.47; H, 4.41; N, 14.08.

General procedure for the synthesis of compounds 13a,b. A solution of compound **3** (0.27 g, 1.0 mmol) and secondary amines (10 mL), namely, morpholine and piperidine was refluxed for 3 h (TLC check, chloroform : methanol, 9:1). The reaction mixture after cooling was poured into cold water, and precipitate that separated was filtered off and recrystallized from ethanol to give **13a,b**.

Ethyl 4-cyano-5-morpholino-1-phenyl-1H-pyrazole-3-carboxylate (13a). White solid, yield 88%, 0.28 g, mp 143–144°C; IR (KBr) ν_{max} 1719 (C═O), 2223 (C≡N), 2920, 2930 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.45 (t, $J = 7.2$ Hz, 3H, CH_3), 3.13 (m, 4H, $2 \times CH_2$), 3.54 (m, 4H, $2 \times CH_2$), 4.52 (q, $J = 7.2$ Hz, 2H, CH_2), 7.56–7.71 (m, 5H, Ar-H). ^{13}C NMR ($CDCl_3$) δ 13.9, 61.8, 49.9, 66.6, 83.2, 113.4, 123.8, 129.9, 129.5, 138.1, 147.8, 153.7, 159.7; MS *m/z* (%): 326 (M^+, 100%); *Anal*. Calcd for $C_{17}H_{18}N_4O_3$: C, 62.57; H, 5.56; N, 17.17. Found: C, 62.63; H, 5.48; N, 17.20.

Ethyl 4-cyano-1-phenyl-5-(piperidin-1-yl)-1H-pyrazole-3-carboxylate (13b). White solid, yield 90%, 0.29 g, mp 132°C; IR (KBr) ν_{max} 1722 (C═O), 2221 (C≡N), 2920, 2932 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.18–1.39 (m, 6H, $3 \times CH_2$), 1.46 (t, $J = 6.9$ Hz, 3H, CH_3), 3.05 (m, 4H, $2 \times NCH_2$), 4.52 (q, $J = 6.9$ Hz, 2H, CH_2), 7.56–7.66 (m, 5H, Ar-H); MS *m/z* (%): 324 (M^+, 100%); *Anal*. Calcd for $C_{18}H_{20}N_4O_2$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.58; H, 6.31; N, 17.12.

General procedure for the synthesis of compounds 14a,b. Compound **13a,b** (1.0 mmol) was stirred in conc. H_2SO_4 (10 mL) at room temperature for 14 h (TLC check, chloroform : methanol, 9:1). The reaction mass was then added to crushed ice (150 mL) and neutralized with saturated $NaHCO_3$ (40 mL). The crude product separated was filtered, washed with water, and recrystallized from acetonitrile to give **14a,b**.

Ethyl 4-carbamoyl-5-(morpholin-4-yl)-1-phenyl-1H-pyrazole-3-carboxylate (14a). White solid, yield 85%, 0.29 g, mp 220°C; IR (KBr) ν_{max} 1665 (C═O, amide), 1735 (C═O, ester), 2942 (C-H), 3338, 3468 (NH_2); ^1H NMR ($CDCl_3$): δ 1.46 (t, $J = 6.9$ Hz, 3H, CH_3), 3.14 (m, 4H, $2 \times CH_2$), 3.55 (m, 4H, $2 \times CH_2$), 4.52 (q, $J = 6.9$ Hz, 2H, CH_2), 7.1 (brs, 2H, NH_2), 7.48–7.68 (m, 5H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 13.9, 61.8, 49.9, 66.5, 83.2, 123.8, 129.9, 129.5, 138.1, 147.8, 149.9,

160.9, 166.2; MS *m/z* (%): 344 (M^+, 100%); *Anal*. Calcd for $C_{17}H_{20}N_4O_4$: C, 59.29; H, 5.85; N, 16.27. Found: C, 59.33; H, 5.82; N, 16.40.

Ethyl 4-carbamoyl-1-phenyl-5-(piperidin-1-yl)-1H-pyrazole-3-carboxylate (14b). White solid, yield 87%, 0.29 g, mp 225°C; IR (KBr) ν_{max} 1662 (C═O, amide), 1736 (C═O, ester), 2942, 3335, 3463 (NH_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.17–1.39 (m, 6H, 3 × CH_2), 1.46 (t, J = 6.9 Hz, 3H, CH_3), 3.05 (m, 4H, 2 × NCH_2), 4.52 (q, J = 6.9 Hz, 2H, CH_2), 6.89 (brs, 2H, NH_2), 7.56–7.66 (m, 5H, Ar-H); MS *m/z* (%): 342 (M^+, 100%); *Anal*. Calcd for $C_{18}H_{22}N_4O_3$: C, 63.14; H, 6.48; N, 16.36. Found: C, 63.17; H, 6.50; N, 16.28.

General procedure for the synthesis of compounds 15a,b. An equimolar mixture of compound **14a,b** (1.0 mmol) and hydrazine hydrate (1.0 mmol) in *n*-butanol (10 mL) was heated under reflux for 4 h (TLC check, chloroform : methanol, 8:2). The mixture was then cooled to room temperature, and the obtained crude solid was collected by filtration under vacuum, washed with ethanol (25 mL), and recrystallized from ethanol-DMF (8:2) to give compounds **15a,b**.

4-Carbamoyl-5-morpholino-1-phenyl-1H-pyrazole-3-carbohydrazide (15a). White solid, yield 68%, 0.22 g, mp 308–309°C; IR (KBr) ν_{max} 1210 (C-O), 1610 (C═O, amide), 1615 (C═C), 1661 (C═O, amide), 3278, 3335, 3450 (NH/NH_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.14 (m, 4H, 2 × NCH_2), 3.54 (m, 4H, 2 × CH_2), 4.82 (s, 2H, NH_2), 6.80 (s, 2H, NH_2), 9.62 (brs, 1H, NH), 7.48–7.68 (m, 5H, Ar-H); ^{13}C NMR (DMSO-d_6) δ 49.5, 66.0, 110.4, 125.0, 128.3, 129.0, 138.4, 143.6, 149.5, 162.7, 163.5; MS *m/z* (%): 330 (M^+, 100%); *Anal*. Calcd for $C_{15}H_{18}N_6O_3$: C, 54.54; H, 5.49; N, 25.44. Found: C, 54.43; H, 5.56; N, 25.51.

4-Carbamoyl-1-phenyl-5-(piperidin-1-yl)-1H-pyrazole-3-carbohydrazide (15b). White solid, yield 65%, 0.21 g, mp 298–300°C; IR (KBr) ν_{max} 1610 (C═O, amide), 1615 (C═C), 1660 (C═O, amide), 3278, 3335, 3450 (NH/NH_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.17–1.39 (m, 6H, 3 × CH_2), 3.05 (m, 4H, 2 × NCH_2), 5.09 (s, 2H, NH_2), 6.92 (s, 2H, NH_2), 9.43 (s, 1H, NH), 7.56–7.66 (m, 5H, Ar-H); MS *m/z* (%): 328 (M^+, 100%); *Anal*. Calcd for $C_{16}H_{20}N_6O_2$: C, 58.52; H, 6.14; N, 25.59. Found: C, 58.61; H, 6.09; N, 25.64.

General procedure for the synthesis of compounds 16a,b. A mixture of compound **13** (0.31 g, 1.0 mmol) and hydrazine hydrate (0.05 mL, 1.0 mmol) in ethanol (10 mL) was refluxed 4 h (TLC check, chloroform : methanol, 8:2). The reaction mixture after cooling was poured into cold water. The solid separated was filtered off and recrystallized from ethanol-DMF (80:20) to give **16a,b**.

***4-Amino-3-morpholino-2-phenyl-2H-pyrazolo[3,4-c]pyridin-7(6H)*-one (16a)**. White solid, yield 75%, 0.23 g, mp 325–326°C; IR (KBr) ν_{max} 1210 (C-O), 1668 (C═O, amide), 3400, 3468, 3312 (NH/NH_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.92 (m, 4H, 2 × CH_2), 3.57 (m, 4H, 2 × CH_2), 5.38 (s, 2H, NH_2), 7.61 (m, 5H, Ar-H), 11.17 (s, 1H, NH); MS *m/z* (%): 313 (M + 1, 100%); *Anal*. Calcd for $C_{15}H_{16}N_6O_2$: C, 57.68; H, 5.16; N, 26.91. Found: C, 57.72; H, 5.05; N, 26.89.

***4-Amino-2-phenyl-3-(piperidin-1-yl)-2H-pyrazolo [3,4-d] pyridazin-7(6H)*-one (16b)**. White solid, yield 78%, 0.24 g, mp 315–317°C; IR (KBr) 1670 (C═O), 3400, 3468, 3312 (NH/NH_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.17–1.39 (m, 6H, 3 × CH_2), 3.05 (m, 4H, 2 × NCH_2), 5.37 (s, 2H, NH_2), 7.61 (m, 5H, Ar-H), 11.20 (s, 1H, NH); MS *m/z* (%): 310 (M^+, 100%); *Anal*. Calcd for $C_{16}H_{18}N_6O$: C, 61.92; H, 5.85; N, 27.08. Found: C, 61.88; H, 5.78; N, 27.19.

General procedure for the synthesis of compounds 17a,b. A solution of compound **16a,b** (1.0 mmol) and ethyl 2-bromoacetate (1.0 mmol) in 9 mL DMF containing K_2CO_3 (0.13 g, 1.0 mmol) was stirred at room temperature for 15–16 h (TLC check, chloroform : methanol, 9:1). Resulting reaction mixture was poured into cold water and neutralized with dil. HCl. The separated solid was filtered, washed with cold water, dried under vacuum, and recrystallized from ethanol-DMF (85:15) and afforded white amorphous solid compound **17a,b**.

Ethyl 2-(4-amino-3-morpholino-7-oxo-2-phenyl-2H-pyrazolo [3,4-d]pyridazin-6(7H)-yl) acetate (17a). White solid, yield 72%, 0.28 g, mp 321–323°C; IR (KBr) ν_{max} 1220 (C-O), 1662 (C═O amide), 1695 (C═O, ester), 2932 (C-H), 3320, 3410 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.20 (t, J = 7.2 Hz, 3H, CH_3), 2.95 (m, 4H, 2 × CH_2), 3.58 (m, 4H, 2 × CH_2), 4.14 (q, J = 7.2 Hz, 2H, OCH_2), 4.65(s, 2H, CH_2), 5.60 (s, 2H, NH_2), 7.59–7.63 (m, 5H, Ar-H); MS *m/z* (%): 399 (M + 1, 100); *Anal*. Calcd for $C_{19}H_{22}N_6O_4$: C, 57.28; H, 5.57; N, 21.09. Found: C, 57.68; H, 5.42; N, 21.88.

***Ethyl 2-(4-amino-7-oxo-2-phenyl-3-(piperidin-1-yl)-2H-*pyrazolo[3,4-*d*]pyridazin-6(7*H*)-yl)acetate (17b)**. White solid, yield 75%, 0.29 g, mp 338–339°C; IR (KBr) ν_{max} 1665 (C═O, amide), 1692 (C═O, ester), 2932 (C-H), 3320, 3410 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.17–1.39 (m, 9H, 3 × CH_2, CH_3), 3.05 (m, 4H, 2 × NCH_2), 3.58 (m, 4H, 2 × CH_2), 4.14 (q, 2H, OCH_2), 4.64(s, 2H, CH_2), 5.60 (s, 2H, NH_2), 7.59–7.63 (m, 5H, Ar-H); MS *m/z* (%): 396 (M + 1, 100%); *Anal*. Calcd for $C_{20}H_{24}N_6O_3$: C, 60.59; H, 6.10; N, 21.20. Found: C, 60.41; H, 5.96; N, 21.32.

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