An Efficient and Facile Synthesis of Functionalized Indole-3-yl Pyrazole Derivatives Starting from 3-Cyanoacetylindole

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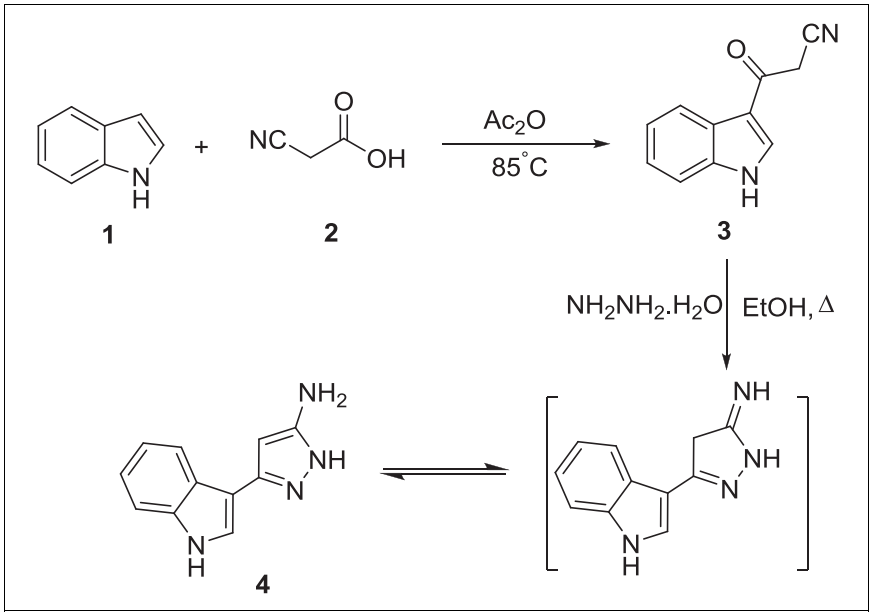

The versatile hitherto reported 3-(1H-indol-3-yl)-1H-pyrazol-5-amine (**4**) was synthesized by the reaction of 3-cyanoacetylindole (**3**) with hydrazine hydrate in refluxing ethanol and used as a key intermediate for the synthesis of novel pyrazolo[1,5-*a*]pyrimidines *via* its reactions with appropriate 1,3-biselectrophilic reagents or through three-component condensations with triethyl orthoformate and compounds possessing an activated methylene group. Besides, the applicability and synthetic potency of (**4**) to attain polyfunctionally substituted imidazo[1,2-*b*]pyrazole, pyrazolo[1,5-*a*][1,3]diazepine and pyrazolo[1,5-*c*][1,3,5]thiadiazine derivatives of an expected pharmaceutical interest have been investigated. The mechanistic aspects for the formation of the newly synthesized compounds are discussed.

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INTRODUCTION

Indole nucleus was considered as an important heterocyclic compound in nature and used in commercial drug development [1–4]. The essential amino acid, tryptophan, and metabolites thereof, for example tryptamine and serotonin, all contain the indole skeleton and participate in vital biological processes [5]. On the other hand, 3-substituted indole has exhibited various pharmacological activities as anticancer, antitumor [6], analgesic, and antipyretic activities [7,8]. It is also a versatile synthon that can act as a common intermediate for the synthesis of a wide variety of natural products [9,10]. We have recently reviewed the methods of preparation and the chemical reactivity of 3-cyanoacetylindole as building block for the synthesis of polyfunctionalized 3-substituted indole derivatives with pharmacological interest [11]. As a consequence of our recent work aimed at synthesis of new heterocyclic systems with remarkable biological importance [12–15], it was planned to present an efficient regioselective synthesis of some novel biologically active heterocycles such as pyrazolo[1,5-*a*]pyrimidines, imidazo[1,2-*b*] pyrazoles, pyrazolo[1,5-*a*][1,3]diazepine and pyrazolo [1,5-*c*][1,3,5]thiadiazine bearing indole ring system, which have not been reported hitherto. The results of screening of their biological activity will be reported in due course.

RESULTS AND DISCUSSION

Chemistry. The key precursor, 3-cyanoacetylindole (**3**) was prepared in excellent yield by short heating of

indole in acetic anhydride at 85°C with cyanoacetic acid as cyanoacetylating agent [16]. Treatment of (**3**) with excess of 85% hydrazine hydrate in refluxing ethanol afforded the corresponding aminopyrazole derivative (**4**) [17] (Scheme 1).

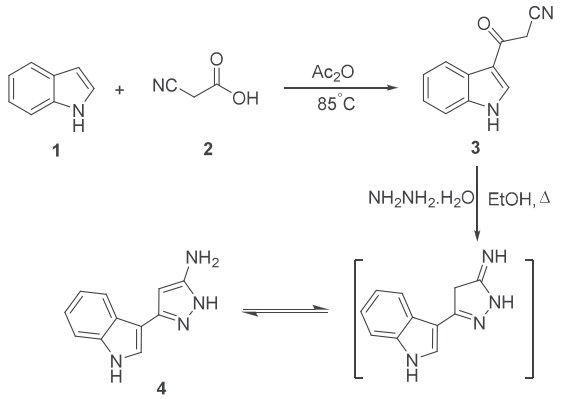
3(5)-Aminopyrazoles are versatile reagents and have been extensively used as building blocks in the synthesis of several polysubstituted pyrazolo[1,5-*a*]pyrimidines of potential biological activity [18–20] *via* cyclocondensation with some reagents having 1,3-dielectrophilic centers [21–24]. In this context, we initially investigated the reactivity of compound (**4**) towards different reactive azo compounds having 1,3-dielectrophilic centers to attain pyrazolo[1,5-*a*]pyrimidines linked directly to indole moiety of potential pharmaceutical interest. Thus, the reaction of (**4**) with 2-(phenyldiazenyl) malononitrile [25] in ethanol containing a catalytic amount of pyridine under reflux yielded 2-(1*H*-indol-3-yl)-6-(phenyldiazenyl)pyrazolo[1,5-*a*] pyrimidine-5,7-diamine (**5**) in good yield. The plausible mechanism for the formation of compound (**5**) could be attributed to the nucleophilic addition of the exocyclic amino group of (**4**) on nitrile function of 2-(phenyldiazenyl)malononitrile to yield the acyclic intermediate which underwent *in situ* intramolecular cyclization *via* the nucleophilic addition of the ring nitrogen atom to the other nitrile function to afford the target molecule. The structure of compound (**5**) was established on the basis of elemental analysis and spectral data. The IR spectrum exhibited absorption bands at 3422–3280, 3222, and 1563 cm^{-1} corresponding to two NH_2, NH, and N=N functions, respectively. The ^{1}H-NMR spectrum (DMSO-d_6) revealed two broad singlet signals at δ 11.54 and 8.80 ppm assignable to indole-NH and NH_2 protons, respectively, sharp singlet signal at δ 6.95 ppm because of pyrazole-CH, in addition to a multiplet signals at δ 8.68–7.11 ppm region owing to aromatic protons. The mass spectrum revealed molecular ion peak at $m/z = 368$ (M^+, 17.1) with relative abundance corresponding to the molecular formula $C_{20}H_{16}N_8$ (Scheme 2).

In a similar manner, cyclocondensation of compound (**4**) with either ethyl 2-cyano-2-(phenyldiazenyl)acetate or 3-(phenyldiazenyl)pentane-2,4-dione [25] under the same experimental conditions produced in each case a single product, as examined by TLC. The reaction products can be formulated as pyrazolo[1,5-*a*]pyrimidine derivatives (**6**) and (**7**), respectively, evidence for assigned structures being provided by elemental analysis and spectroscopic data (see Experimental). It is worth to mention that the regioselectivity for the formation of compounds (**6**) and (**7**) is in line with the reported results of the reaction of aminopyrazoles with 1,3-dielectrophilic centers [25] (Scheme 2).

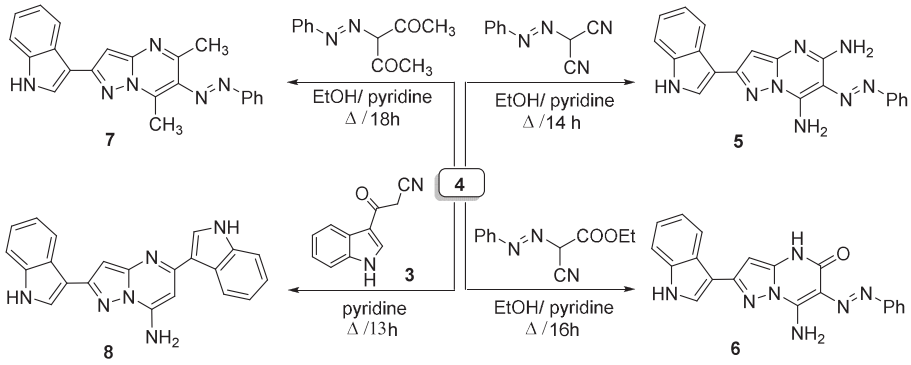
On the other hand, we have also studied the regioselectivity of the reaction of the aminopyrazole (**4**) with 3-cyanoacetylindole (**3**) as a possible synthetic route to attain pyrazolo [1,5-*a*]pyrimidine. Thus, the reaction of aminopyrazole (**4**) with 3-cyanoacetylindole (**3**) in refluxing pyridine afforded only one regioisomeric product that was identified as 2,5-di(1*H*-indol-3-yl)pyrazolo[1,5-*a*]pyrimidin-7-amine (**8**). Although one may argue that the reaction of (**4**) with 3-cyanoacetylindole (**3**) may lead to the other regioisomer, the regioselectivity of such reactions is well established [25,26]. The formation of compound (**8**) is believed to proceed *via* initial attacks of the exocyclic amino group of (**4**) on the keto group of 3-cyanoacetylindole (**3**), followed by elimination of water, and subsequent cyclization by the nucleophilic addition of the endocyclic imino group to the nitrile function. The spectral data of the isolated product were in complete agreement with the structure of (**8**) (see Experimental).

Shifting to Scheme 3, the foregoing results prompted us to investigate the applicability and synthetic potency of the condensation of aminopyrazole (**4**) with triethyl orthoformate and compounds possessing an activated methylene group to develop a facile and convenient route *via* one-pot synthesis to pyrazolo[1,5-*a*]pyrimidine derivatives. We first examined three-component condensations of aminopyrazole (**4**) with triethyl orthoformate and ethyl cyanoacetate. So, heating an equimolar mixture of (**4**) and ethyl cyanoacetate in boiling triethyl orthoformate afforded the pyrazolo[1,5-*a*]pyrimidine derivative (**9**). The formation of compound (**9**) was believed to take place through the formation of the ethoxymethylidene derivative at the activated methylene group of ethyl cyanoacetate. The subsequent reaction with the exocyclic amino group in aminopyrazole (**4**) is accompanied by loss of an ethanol molecule, followed by cyclization through the nucleophilic addition of the endocyclic imino group to the nitrile function. The structure of the latter product (**9**) was supported on the basis of elemental analysis and spectral data (see Experimental). The scope of the present method was further explored to include cyclic dicarbonyl compounds possessing an activated methylene group. Thus the reaction of aminopyrazole (**4**) with 5,5-dimethylcyclohexane-1,3-dione (dimedone) and triethyl orthoformate afforded a single product that was identified as 2-(1*H*-indol-3-yl)-8,8-dimethyl-8,9-dihydropyrazolo[1,5-*a*]quinazolin-6

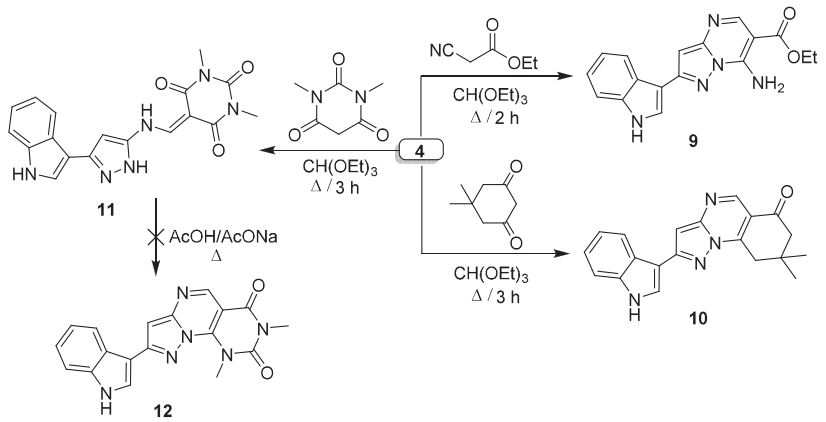
Scheme 1. Synthesis of 3-(1H-indol-3-yl)-1H-pyrazol-5-amine (**4**).



Scheme 2. Synthesis of pyrazolo[1,5-*a*]pyrimidine derivatives (**5–8**).



Scheme 3. Condensation of (**4**) with triethyl orthoformate and compounds possessing an activated methylene group.



(7*H*)-one (**10**), based on elemental analysis and spectral data. Surprisingly, treatment of (**4**) with 1,3-dimethylb arbituric acid in refluxing triethyl orthoformate afforded the corresponding linear condensation product (**11**). All attempts at cyclization of this acyclic product to obtain pyrazolo[1,5-*a*]pyrimidine derivative (**12**) were unsuccessful.

Finally, in view of the growing biological importance of imidazo[1,2-*b*]pyrazole derivatives [27,28], it was of interest to turn our attention to study the regioselectivity of the cyclization reactions of the aminopyrazole (**4**) with chloroacetyl chloride and phenacyl bromide with the aim of preparing functionalized imidazo[1,2-*b*]pyrazoles. So, the reaction of (**4**) with each of chloroacetyl chloride in dioxane or phenacyl bromide in glacial acetic acid under reflux yielded the corresponding imidazo[1,2-*b*]pyrazole derivatives (**13**) and (**14**), respectively. Although the endocyclic imino group in (**4**) is the most nucleophilic center [29–31], it is the most sterically hindered site [32]. The formation of the target compounds (**13**) and (**14**) was illustrated through elimination of two HCl molecules in case of compound (**13**) and elimination of HBr molecule followed by cyclization through elimination of a water molecule in case of compound (**14**). Moreover, cyclocondensation of (**4**) with diethyl oxalate in glacial acetic acid at reflux afforded the corresponding imidazo[1,2-*b*]pyrazole derivative (**15**), through elimination of two ethanol molecules (Scheme 4).

On the other hand, the behavior of aminopyrazole (**4**) towards succinyl dichloride was also investigated as a possible synthetic route to attain pyrazolo[1,5-*a*][1,3] diazepine derivative. Thus, the corresponding pyrazolo [1,5-*a*][1,3]diazepine (**16**) could be synthesized from the reaction of (**4**) with succinyl dichloride in refluxing dioxane. The reaction of compound (**4**) with an equimolar amount of phenyl isothiocyanate in ethanol catalyzed by piperidine gave the non-isolable adduct (**17**), which subsequently reacted with formaldehyde to give only one regioisomeric product (as examined by TLC) that was identified as pyrazolo[1,5-*c*][1,3,5]thiadiazine (**18**) rather than pyrazolo[1,5-*a*][1,3,5]triazine (**19**). The pyrazolo [1,5-*c*][1,3,5]thiadiazine (**18**) was considered most likely based on its spectroscopic data. The IR spectrum showed no absorption band characteristic to C=S group and the presence of absorption bands at 3224 and 3185 cm^{-1} because of two NH functions. The ^{1}H-NMR spectrum (DMSO-d_6) displayed a sharp singlet signal at δ 5.55 ppm assignable to methylene protons of thiadiazine ring, two broad singlet signals at δ 10.14 and 11.42 ppm owing to two NH protons, besides the other expected

signals. The mass spectrum showed a molecular ion peak at $m/z = 346$ ($M^+ + 1$), which agrees with a molecular formula $C_{19}H_{15}N_5S$. The formation of (**18**) rather than (**19**) may be attributed to the higher nucleophilicity of a thiol group in compared with secondary amino group.

In conclusion, the results of the present study indicate that 3-(1H-indol-3-yl)-1H-pyrazol-5-amine (**4**), synthesized by the reaction of 3-cyanoacetylindole (**3**) with hydrazine hydrate in refluxing ethanol, is useful precursor for the facile and convenient synthesis of polyfunctionally substituted heterocycles (e.g. pyrazolo[1,5-*a*]pyrimidines, imidazo[1,2-*b*]pyrazoles, pyrazolo[1,5-*a*][1,3]diazepine and pyrazolo[1,5-*c*][1,3,5]thiadiazine) bearing indole moiety. The compounds prepared are expected to be of pharmacological interest.

EXPERIMENTAL

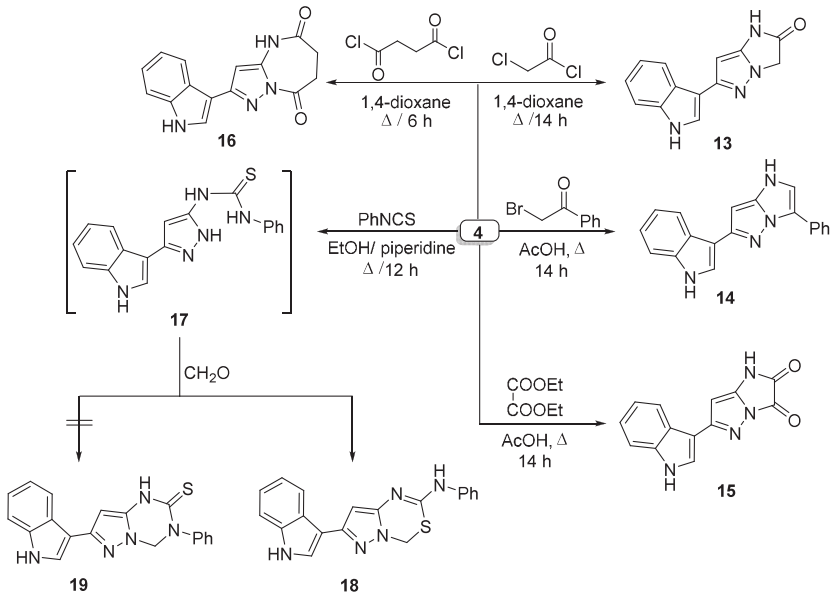
General. All melting points were determined on an electrothermal Gallenkamp apparatus (Germany). The IR spectra were measured on a Mattson 5000 FTIR Spectrometer (USA) in potassium bromide discs. The ^{1}H-NMR spectra were recorded in DMSO-d_6 on a Bruker WP spectrometer (USA) (300 MHz) and the chemical shifts δ downfield from TMS as an internal standard. The mass spectra were recorded on Finnegan MAT 212 instrument (USA), and the ionizing voltage was 70 eV, at the Faculty of Science, Cairo University. Elemental analyses were carried out by the Micro-analytical unit of Faculty of Science, Cairo University, Giza, Egypt. All reactions were followed by TLC (Silica gel, aluminum sheets 60 F254, Merck). 3-Cyanoacetylindole (**3**) and 3-(1H-indol-3-yl)-1H-pyrazol-5-amine (**4**) were prepared according to literatures procedures [16,17].

General procedure for the synthesis of pyrazolo[1,5-a] pyrimidine derivatives (5–7). A mixture of aminopyrazole (**4**) (1.98 g, 0.01 mol) and the appropriate 1,3-dielectrophilic reagents namely; 2-(phenyldiazenyl)malononitrile, ethyl 2-cyano-2-(phenyldiazenyl)acetate, or 3-(phenyldiazenyl)pentane-2,4-dione (0.01 mol) in ethanol (20 mL) containing a catalytic amount of pyridine (0.5 mL) was refluxed for 14–18 h. The reaction mixture was left to cool and poured into ice-cold water. The precipitated solid was filtered off, dried, and recrystallized from ethanol.

2-(1H-Indol-3-yl)-6-(phenyldiazenyl)pyrazolo[1,5-a]pyrimidine-5,7-diamine (5). Compound (**5**) was prepared from 2-(phenyldiazenyl)malononitrile (1.70 g, 0.01 mol) by heating for 14 h under reflux. Brown crystals; yield 79%; mp 188–190°C. IR (KBr) ν_{max}/cm^{-1}: 3422–3280 ($2NH_2$), 3222 (NH), 1634 (C=N), 1601 (C=C), 1563 (N=N). ^{1}H-NMR (DMSO-d_6) δ_{ppm}: 11.54 (s, 1H, indole-NH), 8.80 (br, 2H, NH_2), 8.68–7.11 (m, 12H, Ar—H, NH_2), 6.95 (s, 1H, pyrazole-CH). MS: (*m/z*, %): 368 (M^+, 17.1), 339 (12.4), 262 (26.8), 170 (9.5), 93 (31.4), 77 (100.0), 65 (30.7), 51 (27.9). *Anal.* Calcd. for $C_{20}H_{16}N_8$ (368.39): C, 65.21; H, 4.38; N, 30.42%. Found: C, 65.23; H, 4.40; N, 30.43%.

7-Amino-2-(1H-indol-3-yl)-6-(phenyl-diazenyl)pyrazolo[1,5-a] pyrimidin-5(4H)-one (6). Compound (**6**) was prepared from ethyl 2-cyano-2-(phenyldiazenyl)acetate (2.17 g, 0.01 mol) by heating for 16 h under reflux. Reddish brown crystals; yield 71%; mp 222–224°C. IR (KBr) ν_{max}/cm^{-1}: 3389–3310 (NH_2), 3293, 3184 (2NH), 1645 (C=O, amidic), 1623 (C=N), 1598 (C=C), 1542 (N=N). ^{1}H-NMR

Scheme 4. Synthesis of imidazo[1,2-*b*]pyrazoles (**13–15**), pyrazolo[1,5-*a*][1,3]diazepine (**16**) and pyrazolo[1,5-*c*][1,3,5]thiadiazine (**18**).



(DMSO-d_6) δ_{ppm}: 13.21 (s, 1H, NH), 11.52 (s, 1H, indole-NH), 8.02–7.13 (m, 12H, Ar—H, NH_2), 6.70 (s, 1H, pyrazole-CH). MS: (*m/z*, %): 369 (M^+, 9.2), 353 (14.5), 338 (22.7), 329 (9.9), 262 (30.2), 196 (29.1), 93 (100.0), 77 (67.0), 66 (54.5), 51 (43.2). *Anal.* Calcd. for $C_{20}H_{15}N_7O$ (369.38): C, 65.03; H, 4.09; N, 26.54%. Found: C, 65.05; H, 4.10; N, 26.57%.

2-(1H-Indol-3-yl)-5,7-dimethyl-6-(phenyldiazenyl)pyrazolo [1,5-a]pyrimidine (7). Compound (**7**) was prepared from 3-(phenyldiazenyl)pentane-2,4-dione (2.04 g, 0.01 mol) by heating for 18 h under reflux. Red crystals; yield 67%; mp 261–263°C. IR (KBr) ν_{max}/cm^{-1}: 3222 (NH), 1616 (C=N), 1600 (C=C), 1554 (N=N). ^{1}H-NMR (DMSO-d_6) δ_{ppm}: 11.62 (s, 1H, indole-NH), 8.89 (s, 1H, indole-H_2), 8.58–7.16 (m, 10H, Ar—H), 3.12 (s, 3H, CH_3), 2.79 (s, 3H, CH_3). MS: (*m/z*, %): 366 (M^+, 22.5), 262 (8.2), 233 (11.2), 204 (32.4), 92 (17.4), 79 (74.4), 52 (100.0). *Anal.* Calcd. for $C_{22}H_{18}N_6$ (366.42): C, 72.11; H, 4.95; N, 22.94%. Found: C, 72.14; H, 4.97; N, 22.96%.

Synthesis of 2,5-di(1H-indol-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine (8). An equimolar amount of (**4**) (1.98 g, 0.01 mol) and 3-cyanoacetylindole (**3**) (1.84 g, 0.01 mol) in pyridine (15 mL) was refluxed for 13 h. The reaction mixture was left to cool, poured into ice-cold water, and acidified by drops of dilute HCl. The precipitated solid was filtered off, dried, and recrystallized from ethanol. Brown crystals; yield 58%; mp 233–235°C. IR (KBr) ν_{max}/cm^{-1}: 3379–3315 (NH_2), 3254, 3235 (2NH), 1644 (C=N), 1621 (C=C). ^{1}H-NMR (DMSO-d_6) δ_{ppm}: 11.55 (s, 2H, two indole-NH), 9.25 (br, 2H, NH_2), 8.64 (s, 2H, two indole-H_2), 8.18–7.11 (m, 9H, Ar—H, pyrimidine-CH), 6.95 (s, 1H, pyrazole-CH). MS: (*m/z*, %): 364 (M^+, 16.5), 310 (31.7), 298 (22.9), 262 (59.8), 144 (100.0), 131 (14.1), 116 (43.1), 89 (41.9), 80 (39.7), 64 (42.7), 51 (19.1). *Anal.* Calcd. for $C_{22}H_{16}N_6$ (364.40): C, 72.51; H, 4.43; N, 23.06%. Found: C, 72.53; H, 4.45; N, 23.07%.

General procedure for the reaction of aminopyrazole (4) with triethyl orthoformate and active methylene compounds. A mixture of aminopyrazole derivative (**4**) (1.98 g, 0.01 mol), and active methylene compounds namely, ethyl cyanoacetate, 5,5-dimethylcyclohexane-1,3-dione or 1,3-dimethylpyri midine-2,4,6(1H,3H,5H)-trione (0.01 mol), and triethyl ortho formate (2.22 g, 0.015 mol) was heated under reflux for 2–3 h. The reaction mixture was left to cool at room temperature. The precipitated solid was washed with petroleum ether, filtered off, dried, and recrystallized from a mixture of DMF–EtOH (2:1).

Ethyl 7-amino-2-(1H-indol-3-yl)pyrazolo[1,5-a]pyrimidine-6-carboxylate (9). Compound (**9**) was prepared from ethyl cyanoacetate (1.13 g) by heating for 2 h. Brown crystals; yield 73%; mp 269–271°C. IR (KBr) ν_{max}/cm^{-1}: 3380–3303 (NH_2), 3245 (NH), 1723 (C=O, ester), 1621 (C=N), 1595 (C=C). ^{1}H-NMR (DMSO-d_6) δ_{ppm}: 11.55 (s, 1H, indole-NH), 8.58 (s, 1H, indole-H_2), 8.46 (br, 2H, NH_2), 8.10–7.13 (m, 4H, Ar—H), 7.72 (s, 1H, pyrimidine-CH), 6.92 (s, 1H, pyrazole-CH), 4.30 (q, J = 7.2, 2H, CH_2), 1.32 (t, J = 7.2, 3H, CH_3). MS: (*m/z*, %): 322 (M^++1, 17.4), 321 (M^+, 26.7), 301 (13.2), 275 (19.6), 249 (16.4), 211 (10.6), 136 (17.6), 114 (13.4), 80 (38.5), 64 (100.0), 52 (21.5). *Anal.* Calcd. for $C_{17}H_{15}N_5O_2$ (321.33): C, 63.54; H, 4.71; N, 21.79%. Found: C, 63.57; H, 4.72; N, 21.81%.

2-(1H-Indol-3-yl)-8,8-dimethyl-8,9-dihydropyrazolo[1,5-a] quinazolin-6(7H)-one (10). Compound (**10**) was prepared from 5,5-dimethylcyclohexane-1,3-dione (1.4 g) by heating for 3 h. Brown crystals; yield 51%; mp 250–252°C. IR (KBr) ν_{max}/cm^{-1}: 3283 (NH), 2980, 2963 (C–H aliph.), 1680 (C=O), 1636 (C=N), 1592 (C=C). ^{1}H-NMR (DMSO-d_6) δ_{ppm}: 11.84 (s, 1H, indole-NH), 8.43–7.21 (m, 6H, Ar—H), 7.84 (s, 1H, pyrimidine-CH), 2.69 (s, 2H, CH_2), 2.49 (s, 2H, CH_2), 1.19 (s, 6H, $2CH_3$). MS: (*m/z*, %): 331 (M^++1, 17.1), 330 (M^+, 64.5), 298 (26.1), 274 (8.8), 142 (13.7), 117 (10.3), 89 (10.7), 80 (17.9), 64 (100.0), 51 (39.3). *Anal.* Calcd. for $C_{20}H_{18}N_4O$ (330.38): C, 72.71; H, 5.49; N, 16.96%. Found: C, 72.73; H, 5.49; N, 16.98%.

5-{[(3-(1H-Indol-3-yl)-1H-pyrazol-5-yl)-amino]-methylene}-1,3-dimethyl-pyrimidine-2,4,6 (1H,3H,5H)-trione (11). Compound (**11**) was prepared from 1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (1.56 g) by heating for 3 h. Brown crystals; yield 82%; mp 294–296°C. IR (KBr) ν_{max}/cm^{-1}: 3282, 3214, 3166 (3NH), 2971, 2963 (C—H aliph.), 1684, 1665 (3C=O), 1611 (C=N), 1591 (C=C). ^{1}H-NMR (DMSO-d_6) δ_{ppm}: 12.67 (s, 1H, NH), 11.49 (s, 1H, indole-NH), 10.74 (d, 1H, NH), 8.62 (d, 1H, CH=), 7.88–7.13 (m, 5H, Ar—H), 6.67 (s, 1H, pyrazole-CH), 3.12 (s, 6H, $2CH_3$). MS: (*m/z*, %): 365 (M^++1, 24.1), 364 (M^+, 19.4), 346 (16.7), 226 (11.7), 212 (8.0), 198 (96.6), 169 (35.9), 156 (41.3), 144 (25.0), 117 (29.0), 99 (18.1), 89 (26.8), 71 (9.7), 64 (100.0), 51 (20.9). *Anal.* Calcd. for $C_{18}H_{16}N_6O_3$ (364.36): C, 59.34; H, 4.43; N, 23.07%. Found: C, 59.36; H, 4.44; N, 23.09%.

General procedure for the synthesis of imidazo[1,2-b] pyrazole derivatives (13–15). An equimolar amounts of aminopyrazole derivative (**4**) (1.98 g, 0.01 mol) and chloroacetyl chloride (0.01 mol) in 1,4-dioxane (15 mL), phenacyl bromide or diethyl oxalate (0.01 mol) in glacial acetic acid (15 mL) was refluxed for 14 h. The reaction mixture was left to cool at room temperature. The precipitated solid was filtered off, washed with ethanol, dried, and recrystallized from ethanol.

6-(1H-Indol-3-yl)-1H-imidazo[1,2-b]pyrazol-2(3H)-one (13). Compound (**13**) was prepared from chloroacetyl chloride (1.12 g). Yellow crystals; yield 78%; mp 256–258°C. IR (KBr) ν_{max}/cm^{-1}: 3328, 3259 (2NH), 1671 (CO), 1623 (C=N), 1595 (C=C). ^{1}H-NMR (DMSO-d_6) δ_{ppm}: 11.48 (s, 1H, indole-NH), 10.83 (br, 1H, NH), 7.78 (s, 1H, indole-H_2), 7.47–7.16 (m, 4H, Ar—H), 6.82 (s, 1H, pyrazole-CH), 4.27 (s, 2H, CH_2). MS: (*m/z*, %): 238 (M^+, 8.5), 225 (31.1), 213

(10.6), 198 (11.3), 185 (9.9), 141 (13.2), 115 (1.12), 80 (100.0), 64 (90.5). *Anal.* Calcd. for $C_{13}H_{10}N_4O$ (238.24): C, 65.54; H, 4.23; N, 23.52%. Found: C, 65.56; H, 4.25; N, 23.54%.

3-(3-Phenyl-1H-imidazo[1,2-b]pyrazol-6-yl)-1H-indole (14). Compound (**14**) was prepared from phenacyl bromide (1.99 g). Yellow crystals; yield 70%; mp 278–280°C. IR (KBr) ν_{max}/cm^{-1}: 3385, 3252 (2NH), 1640 (C=N), 1590 (C=C). ^{1}H-NMR (DMSO-d_6) δ_{ppm}: 11.48 (s, 1H, NH), 11.23 (s, 1H, indole-NH), 8.53–7.09 (m, 12H, Ar—H). MS: (*m/z*, %): 299 (M^++1, 10.3), 298 (M^+, 9.4), 288 (11.5), 185 (16.6), 144 (7.4), 116 (1.9), 105 (18.0), 80 (100.0), 64 (74.2). *Anal.* Calcd. for $C_{19}H_{14}N_4$ (298.34): C, 76.49; H, 4.73; N, 18.78%. Found: C, 76.51; H, 4.75; N, 18.80%.

6-(1H-Indol-3-yl)-1H-imidazo[1,2-b]pyrazole-2,3-dione (15). Compound (**15**) was prepared from diethyl oxalate (1.46 g). Yellow crystals; yield 62%; mp 253–255°C. IR (KBr) ν_{max}/cm^{-1}: 3258, 3159 (2NH), 1682, 1661 (2CO), 1632 (C=N), 1598 (C=C). ^{1}H-NMR (DMSO-d_6) δ_{ppm}: 12.74 (br, 1H, NH), 11.51 (s, 1H, indole-NH), 7.61 (s, 1H, indole-H_2), 7.42–7.06 (m, 4H, Ar—H), 7.04 (s, 1H, pyrazole-CH). MS: (*m/z*, %): 254 (M^++2, 20.18), 253 (M^++1, 8.3), 252 (M^+, 11.2), 240 (21.8), 226 (43.8), 198 (100.0), 169 (38.3), 140 (21.8), 115 (23.7), 85 (15.0), 57 (17.4). *Anal.* Calcd. for $C_{13}H_8N_4O_2$ (252.23): C, 61.90; H, 3.20; N, 22.21%. Found: C, 61.92; H, 3.22; N, 22.23%.

Synthesis of 2-(1H-indol-3-yl)-6,7-dihydro-4H-pyrazolo[1,5-a][1,3]diazepine-5,8-dione (16). To a solution of aminopyrazole derivative (**4**) (1.98 g, 0.01 mol) in 1,4-dioxane (15 mL), succinyl dichloride (1.54 g, 0.01 mol) was added dropwise with stirring at room temperature. The reaction mixture was then heated under reflux for 6 h, left to cool. The solid product that obtained was collected by filtration, washed with ethanol, dried well, and recrystallized from ethanol.

Brown crystals; yield 57%; mp 286–288°C. IR (KBr) ν_{max}/cm^{-1}: 3221, 3180 (2NH), 1697, 1644 (2CO), 1612 (C=N), 1596 (C=C). ^{1}H-NMR (DMSO-d_6) δ_{ppm}: 13.18 (s, 1H, NH), 11.49 (s, 1H, indole-NH), 7.81–7.09 (m, 5H, Ar—H), 6.51 (s, 1H, pyrazole-CH), 2.82 (s, 4H, $2CH_2$). MS: (*m/z*, %): 281 (M^+ + 1, 17.5), 280 (M^+, 38.2), 140 (8.0), 80 (53.3), 64 (100.0), 55 (15.7). *Anal.* Calcd. for $C_{15}H_{12}N_4O_2$ (280.28): C, 64.28; H, 4.32; N, 19.99%. Found: C, 64.30; H, 4.34; N, 20.02%.

Synthesis of 7-(1H-indol-3-yl)-N-phenyl-4H-pyrazolo[1,5-c][1,3,5]thiadiazin-2-amine (18). A mixture of compound (**4**) (1.98 g, 0.01 mol) and an equimolar amount of phenyl isothiocyanate (1.35 g, 0.01 mol) and formaldehyde (0.30 g, 0.01 mol) in ethanol (10 mL) containing a catalytic amount of piperidine was stirred under reflux for 12 h, then allowed to cool at room temperature and diluted with ice-cold water (30 mL). The solid product was filtered off, dried well, and recrystallized from ethanol.

Reddish brown crystals; yield 55%; mp 289–291°C. IR (KBr) ν_{max}/cm^{-1}: 3224, 3185 (2NH), 1640 (C=N), 1597 (C=C). ^{1}H-NMR (DMSO-d_6) δ_{ppm}: 11.42 (s, 1H, indole-NH), 10.14 (s, 1H, NH), 8.58–7.10 (m, 10H, Ar—H), 6.42 (s, 1H, pyrazole-CH), 5.55 (s, 2H, CH_2). MS: (*m/z*, %): 346 (M^+ + 1, 13.2), 345 (M^+, 1.3), 271 (21.29), 198 (39.9), 169 (16.1), 156 (15.5), 115 (9.9), 80 (26.8), 64 (100.0), 55 (10.3). *Anal.* Calcd. for $C_{19}H_{15}N_5S$ (345.42): C, 66.07; H, 4.38; N, 20.28%. Found: C, 66.08; H, 4.39; N, 20.30%.

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