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Convenient syntheses of pyrazolo[3,4-*b*]pyridin-6-ones using either microwave or ultrasound irradiation

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ABSTRACT

An efficient synthesis of 12 pyrazolo[3,4-*b*]pyridin-6-one derivatives was achieved using either microwave or ultrasound irradiation, resulting in yields of 40–60% and 60–95%, respectively. Under our conditions, these reactions occurred with notably reduced reaction times as compared to literature reports involving traditional heating. Furthermore, these reactions were highly regioselective and produced only one pyrazolo[3,4-*b*]pyridin-6-one isomer, whose identity was confirmed by NOESY spectroscopy.

Pyrazolo[3,4-*b*]pyridin-6-ones are a promising class of heterocyclic compounds and have been shown to be inhibitors of cyclin-dependent protein kinase-2 (cdk-2), cyclin-dependent protein kinase-5 (cdk-5), and phosphatidylinositol 3-kinase (PI3-K).[1,2] Thus, these compounds have potential in the treatment of several diseases, including bipolar disorder, diabetes, dementia, Alzheimer's disease, schizophrenia, depression, and cancer.[2]

The synthesis of pyrazolo[3,4-*b*]pyridin-6-ones was first reported by Hoehn three decades ago. These compounds were synthesized by condensing ethylidene malonic acid diethyl ester and 1-ethyl-5-amino-methylpyrazole in refluxing dimethylformamide and water for 94 h and resulted in a 53% yield.[3] Later, Quiroga et al. synthesized dihydropyrazolo[3,4-*b*]pyridin-6-ones by refluxing equimolar amounts of aminopyrazole and the appropriate Meldrum's acid benzylidene derivative in nitrobenzene for 30 min, resulting in yields ranging from 42% to 72%.[4]

More recently, *N*-aminopyrazolo[4,3-*c*]pyridin-4-ones and *N*-aminopyrazolo[3,4-*c*]pyridin-4-ones were prepared by Vasilevsky et al. from *vic*-acetylenyl/hydrazido pyrazoles using the methyl esters of acetylenyl-pyrazole carboxylic acids and hydrazine hydrate. A cyclization reaction occurs upon heating the mixture to reflux in butanol for 1–12 h and typically results in an 80% yield.[5,6]

Urban et al. prepared pyrazolo[3,4-*c*]pyridin-7-ones by treating 3-methoxy-pyridinone with cyclopentylhydrazine dihydrochloride in THF at 95 °C for 12 h, which produced the desired product in 68% yield. At nearly the same time, Mshvidobadze et al. reported another interesting synthetic route to these compounds that relied upon a heterocyclization reaction of *vic*-acetylenylpyrazol-hydroxamic acids. These reactions were carried out in DMF using copper(I) salts as a catalyst. These reactions afforded 5-hydroxypyrazolo[4,3-*c*]pyridin-6-ones and pyrazolo[4,3-*c*]pyridin-4-ones in 50% and 90% yield, respectively, after a 12 h reaction time.[7]

Recently, Dress et al. obtained pyrazolo[3,4-*b*]pyridin-6-ones in 30–75% yield using condensation reactions that involved refluxing aminopyrazole with the appropriate aldehyde and dimedone derivatives in ethanol for 6–8 h.[1] In addition, Martínez-Teipel et al. developed a new synthetic route to this class of compound involving an intermolecular cyclization of 2-methoxy-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitriles with substituted hydrazines. Refluxing these materials between 3 and 48 h gave pyrazolo[3,4-*b*]pyridin-6-ones in 37–92% yield.[8]

Despite of the importance of the pyrazolo[3,4-*b*]pyridin-6-one motif, there are still relatively few literature reports describing the synthesis of these molecules, and those reports that do exist generally employ synthetic methods that require long reaction times. Thus, in this work we describe a new and efficient synthesis of pyrazolo[3,4-*b*]pyridin-6-ones (**6a–l**). Of the 12 target structures, nine are new compounds that we synthesized using intermolecular cyclization reactions under solvent-free microwave conditions and ultrasound irradiation conditions.

Our synthetic approach (Scheme 1) begins with substituted cinnamic acids (**1a–c**), which were obtained from high yielding (83–87%) Doebner–Knoevenagel condensation reactions between the appropriate benzaldehydes and malonic acid in the presence of pyridine and piperidine, as previously described.[9] In the next step, a solution of **1a–c** and concentrated sulfuric acid in methanol was heated to reflux for 12 h, furnishing the corresponding esters (**2a–c**) in 90–93% yield, as reported in the literature.[10,11]

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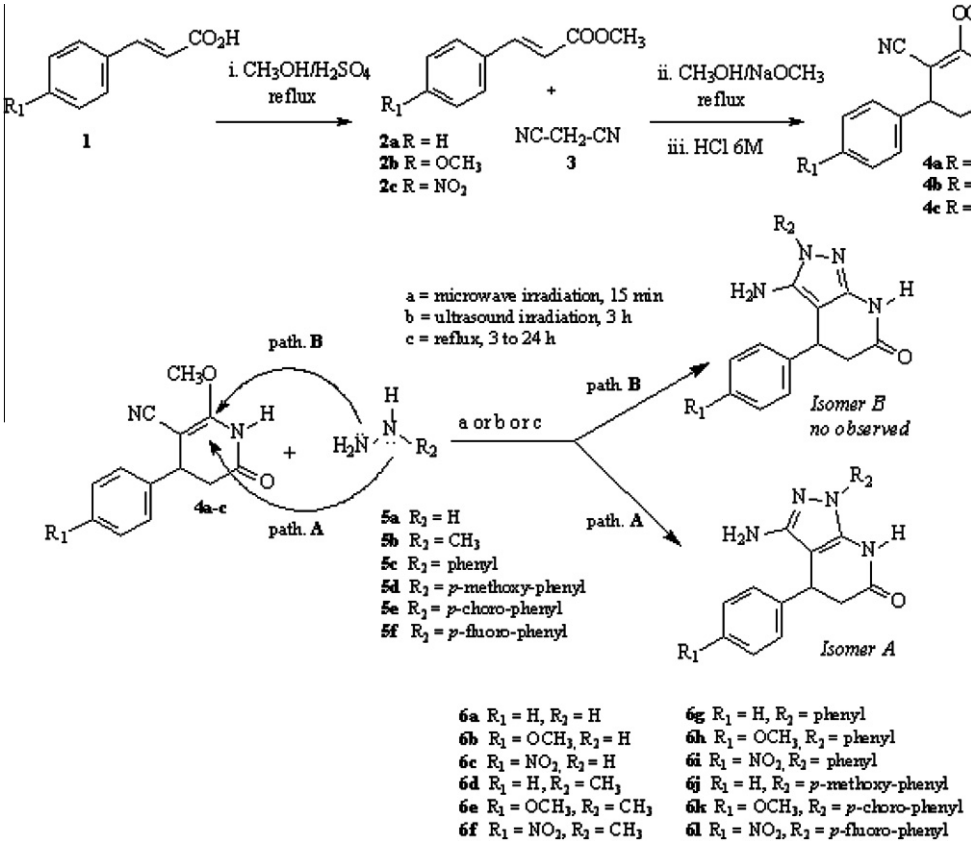

Scheme 1.

Next, the 2-methoxy-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitrile intermediates (**4a–c**) were prepared from α,β-unsaturated esters (**2a–c**) and malononitrile (**3**) in a NaOMe/MeOH solution that was heated at reflux for 4 h. This mixture was then evaporated to dryness in vacuo, and the resulting residue was dissolved in a minimum amount of water and cooled in an ice bath. The pH was then carefully adjusted to pH 8–9 with a 6 M HCl solution to prevent the rupture of the lactam group. Even so, compounds **4a–c** were only obtained in 25–60% yield, which is in accord with previous literature data.[8,12]

The target compounds, the pyrazolo[3,4-*b*]pyridin-6-ones **6a–l**, were obtained both by the conventional method, which involves refluxing in methanol, and by alternative methods, which involve either microwave or ultrasound irradiation. In all cases, we began with intermediates **4a–c** and the appropriately substituted hydrazines **5a–f**. The pyrazolo-pyridinones were obtained in moderate to good yields (50–85%) using the conventional methanol reflux method[8] (see Table 1).

To find the best microwave irradiation time, the reaction of compounds **5b** and **4b** was used as a model and was monitored by TLC and GC–MS. The results of these analyses indicated that 15 min was the optimal reaction total time. In the solvent-free microwave irradiation conditions, the maximum continuous irradiation time was established to be 3 min and was followed by a 2 min cooling period between irradiations. This method was designed to avoid overheating of the reactants, as unmodified domestic microwave ovens lack the special attributes of commercial reactors in terms of temperature control.[13,14] Using this microwave method, compounds **6a–l** were obtained in moderate yield (50–65%, see Table 1), however, it presented low yields when compared to the conventional methodology (50–85%), but in notable time conditions from 12 to 96 times faster than conventional method.

Table 1
Reaction times and yields obtained for compounds **6a–l** using the conventional methodology, microwave irradiation, and ultrasound irradiation

Compound	Conventional		Microwave		Ultrasound	
	Yield (%)	Time (h)	Yield (%)	Time (h)	Yield (%)	Time (h)
6a	50	4	55	0.25	95	3
6b	55	4	55	0.25	90	3
6c	55	4	65	0.25	80	3
6d	54	3	55	0.25	75	3
6e	85	3	50	0.25	70	3
6f	78	3	60	0.25	70	3
6g	60	24	50	0.25	[a]	[a]
6h	50	24	50	0.25	[a]	[a]
6i	60	24	55	0.25	[a]	[a]
6j	30	24	40	0.25	[a]	[a]
6k	40	24	60	0.25	[a]	[a]
6l	43	24	55	0.25	[a]	[a]

[a] No product observed.

Compounds **6j–l** were obtained using intermediates **4a–c** and a hydrazine hydrochloride.[15] After conventional treatment with NaOMe and refluxing methanol for 24 h, the desired products were obtained in low yields (30–43%). However, when these derivatives were prepared using solvent-free microwave irradiation conditions, we observed a slight increase in the yields (40–60%, see Table 1).

The ultrasound irradiation conditions were carried out in a simple way: compounds **5b** and **4b** were submitted to an ultrasound bath as a solution in ethanol at room temperature. Reaction progress was monitored by TLC and GC–MS. After 30 min, the temperature of the reaction mixture increased to 30–35 °C, and a yield of

approximately 20% was detected. We also observed that at reaction times of more than 3 h, no significant change in the yield occurred. This method led to excellent results in the synthesis of compounds **6a–f** (70–95% yield). However, compounds **6g–l** were not observed under the ultrasound conditions. Taken together, these results show this methodology to be compatible with hydrazine moieties. All three of the methodologies mentioned were ineffective when the hydrazine in the reaction contained one or more nitro moieties on the aromatic ring.

The reaction could develop into isomer A (pathway A) or B (pathway B); however, the reaction was selective and afforded only the isomer A (Scheme 1), independently of the applied methodology.

We were able to differentiate between the possible product isomers and confirm the structures of compounds **6d–l** using NOESY spectroscopy. For example, isomers **6h** and **6h′** would represent N-1 and N-2 atoms with different substituents. Our spectrum showed a strong correlation between NH-7 with H-2″, which indicates their

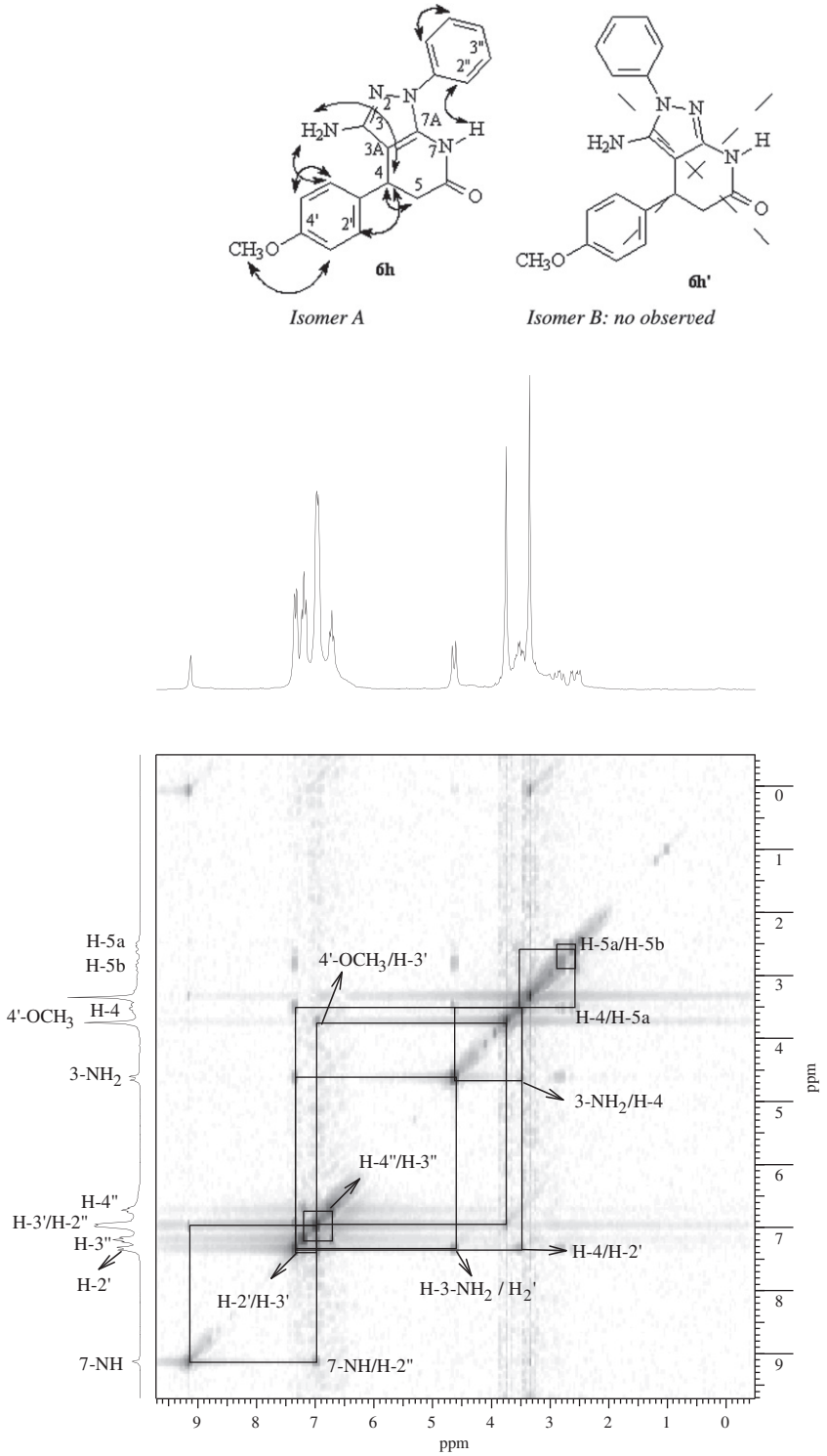

Figure 1. Possible isomers **6h** and **6h′** and the observed NOESY spectrum used to differentiate them.

spatial proximity. Furthermore, no NOE correlation was observed between the H-2″ and NH_2-3 amine hydrogen's (Fig. 1). These data were sufficient to reject the presence of isomer **6h′**.

Based on these observations, the reaction was highly regioselective and produced only the pyrazolo[3,4-*b*]pyridin-6-one isomer. All compounds were fully characterized by routine spectroscopic methods, including IR, ^{1}H and ^{13}C NMR, and MS.[16]

In conclusion, we have demonstrated a very simple and highly efficient method to prepare pyrazolo[3,4-*b*]pyridin-6-ones under either microwave or ultrasound irradiation conditions, which have shorter reaction times than those previously reported.

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16. *General procedure for the synthesis of 2-methoxy-6-oxo-1,4,5,6-tetrahydro-pyridine-3-carbonitriles* (**4a**–**c**)[8]: A solution of the α,β-unsaturated ester (**2a**–**c**) (170 mmol) in methanol (30 mL) was added dropwise to 30 mL of a 5.67 M sodium methoxide solution. Following this, malononitrile (90 mmol) was added dropwise as a solution in methanol (30 mL). This mixture was heated to reflux for 4 h and, after cooling, was concentrated in vacuo. The resulting residue was dissolved in the minimum amount of water required, cooled in an ice bath, and carefully neutralized to pH 8–9 with a 6 M HCl solution. The precipitate was filtered, washed with ice water, and extracted into CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with water, dried over $MgSO_4$ and concentrated to give the intermediates **4a**–**c**. 2-Methoxy-4-phenyl-6-oxo-1,4,5,6-tetrahydro-pyridine-3-carbonitriles (**4a**): orange solid, mp 141–142 °C (lit.[8] 143–144 °C); IR (KBr, cm^{-1}): 3426, 3106, 2958, 2207, 1697, 1643, 1336, 1287; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 10.76 (s, 1H), 7.37 (dd, *J* = 2, 10 Hz, 2H), 7.30 (dd, *J* = 2, 6 Hz, 2H), 7.23 (dd, *J* = 2, 6, 10 Hz, 2H), 3.95 (s, 3H), 3.89 (dd, *J* = 6, 8 Hz, 1H), 2.94 (dd, *J* = 6, 12 Hz, 1H), 2.56 (dd, *J* = 6, 16 Hz, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 169.8, 160.7, 141.2, 128.9, 127.4, 126.8, 118.4, 68.0, 58.9, 38.4, 36.7; MS *m/z* (% rel.) 228 ($M^{+\cdot}$ 100), 185 (60), 151 (40), 103 (20), 77 (24), 51 (20). 2-Methoxy-4-*p*-methoxy-phenyl-6-oxo-1,4,5,6-tetrahydro-pyridine-3-carbonitriles (**4b**): orange solid, mp 173–175 °C (lit.[8] 174–176 °C); IR (KBr, cm^{-1}) 3443, 3095, 2959, 2197, 1691, 1691, 1626, 1363, 1294; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.13 (d, *J* = 8 Hz, 2H), 6.89 (d, *J* = 8 Hz, 2H), 3.93 (s, 3H), 3.80 (t, *J* = 6, 8 Hz, 1H), 3.71 (s, 3H), 2.87 (dd, *J* = 6, 16 Hz, 1H), 2.49 (dd, *J* = 6, 16 Hz, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 169.9, 160.5, 158.5, 132.9, 127.9, 118.5, 114.2, 68.4, 58.8, 55.1, 38.6, 36.0; MS *m/z* (% rel.) 258 ($M^{+\cdot}$ 100), 243 (27), 227 (40), 215 (73), 77 (7). 2-Methoxy-4-*p*-nitro-phenyl-6-oxo-1,4,5,6-tetrahydro-pyridine-3-carbonitriles (**4c**): orange solid, mp 213–215 (lit.[8] 215); IR (KBr, cm^{-1}) 3428, 3093, 2950, 2193, 1696, 1627, 1554, 1297; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 10.91 (s, 1H), 8.25 (d, *J* = 8 Hz, 2H), 7.56 (d, *J* = 8 Hz, 2H), 4.15 (t, *J* = 6, 14 Hz, 1H), 3.00 (dd, *J* = 6, 16 Hz, 1H), 2.60 (dd, *J* = 6 Hz, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 169.4, 161.2, 148.9, 146.9, 128.4, 124.4, 123.4, 118.1, 66.7, 58.9, 37.8, 36.5; MS *m/z* (% rel.) 273($M^{+\cdot}$ 100), 256 (25), 232 (50), 151 (30), 63 (10). General procedure for pyrazolo[3,4-*b*]pyridin-6-ones (**6a**–**l**) synthesis: *Conventional methodology*:[8,15] The hydrazine (**5a**–**f**) solution (120 mmol) and **4a**–**c** (60 mmol) were refluxed for the time indicated in Table 1. The solvent was concentrated in vacuo, and a small amount of methanol was added. The mixture was then sonicated and the resulting solid was filtered to afford the corresponding pyrazolo[3,4-*b*]pyridin-6-ones **6a**–**l**. *Microwave irradiation*: A mixture of **4a**–**c** (0.60 mmol) and the hydrazine **5a**–**e** (0.60 mmol) was placed in the center of a microwave oven (Consul Pratice-Brastemp S.A/Model MU31AO, a domestic oven, 2450 MHz). The reaction mixture was irradiated in 3 min intervals; each followed a 2 min cooling interval. The total irradiation times are indicated in Table 1. Reaction progress was monitored by TLC (EtOAc/hexane, 7:3). After irradiation, the reaction mixture was washed with water (40 mL), and the product was extracted with $CHCl_3$ (4 × 15 mL). The material produced by this method did not require subsequent purification. *Ultrasound irradiation*: A solution of **4a**–**c** (0.60 mmol) and the hydrazine **5a**–**b** (0.60 mmol) in ethanol was ultrasound irradiated for 3 h (Ultra Cleaner 700-UNIQUE—55 kHz). Reaction progress was monitored by TLC (EtOAc/hexane, 7:3). The work-up was performed using the procedure described above for the microwave irradiation method and gave pyrazolo-[3,4-*b*]pyridin-6-ones **6a**–**l**. Compounds **6k**–**l** were obtained after the addition of NaOMe (20 mmol). 3-Amino-4-phenyl-1,4,5,7-tetrahydropyrazolo-[3,4-*b*]pyridin-6-one (**6a**): yellow solid; mp 257–259 °C (lit.[8] 261–262 °C); IR (KBr, cm^{-1}) 3345, 2879, 2927, 2838, 1656, 1614, 1492, 1452, ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.34 (m, *J* = 6, 10 Hz, 5H), 4.59 (s, 1H), 4.49 (s, 1H), 3.47 (dd, *J* = 6, 12 Hz, 1H), 2.80 (dd, *J* = 4, 12 Hz, 1H), 2.52 (dd, *J* = 4, 12 Hz, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 168.6, 144.7, 140.0, 138.6, 128.9, 127.6, 83.6, 37.4, 37.1. 3-Amino-4-*p*-methoxy-phenyl-1,4,5,7-tetrahydropyrazolo[3,4-*b*]pyridin-6-one (**6b**): yellow solid; mp 274–275 °C (lit.[8] 270–272 °C); IR (KBr, cm^{-1}) 3357, 2971, 2881, 2840, 1666, 1612, 1517, 1450; ^{1}H NMR (DMSO-d_6, 50 MHz) δ 7.29 (d, 8 Hz, 2H), 6.92 (d, 8 Hz, 2H), 4.26 (s, 1H), 4.40 (s, 1H), 3.73 (s, 3H), 2.76 (dd, *J* = 6, 12 Hz, 1H), 2.56 (d, *J* = 6 Hz, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 168.6, 158.7, 148.7, 143.9, 131.9, 128.6, 113.8, 86.1, 55.1, 38.4, 37.6. 3-Amino-4-*p*-nitro-phenyl-1,4,5,7-tetrahydropyrazolo[3,4-*b*]pyridin-6-one (**6c**): yellow solid; mp >300 °C (lit.[8] >300 °C); IR (KBr, cm^{-1}) 3403, 2983, 2929, 2840, 1658, 1631, 1513, 1452; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 10.81 (s, 1H), 10.17 (s, 1H), 8.16 (d, *J* = 8 Hz, 2H), 7.39 (d, *J* = 8 Hz, 2H), 5.00 (s, 2H), 4.25 (d, *J* = 6 Hz, 1H), 2.94 (dd, *J* = 8, 16 Hz, 1H), 2.74 (dd, *J* = 4, 16 Hz, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 169.6, 153.2, 146.5, 145.5, 128.5, 124.1, 84.8, 39.4, 36.7. 3-Amino-1-methyl-4-phenyl-1,4,5,7-tetrahydropyrazolo[3,4-*b*]pyridin-6-one (**6d**): yellow oil; IR (KBr, cm^{-1}) 3347, 2971, 2929, 2827, 1666, 1612, 1492, 1452, 1351; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 10.08 (s, 1H), 7.24 (m, *J* = 8 Hz, 5H), 7.11 (dd, *J* = 4 and 6 Hz, 2H), 5.07 (s, 1H), 4.05 (dd, *J* = 8 and 10 Hz, 1H), 3.35 (s, 3H), 2.83 (dd, *J* = 8 and 18 Hz, 1H), 2.49 (m, *J* = 2 Hz, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 170.1, 146.7, 144.7, 143.2, 128.7, 126.9, 126.6, 86.3, 40.5, 34.1, 33.0; Calcd' for $C_{13}H_{14}N_4O$: C, 64.45; H, 5.82; N, 23.13. Found: C, 64.41; H, 5.88; N, 23.18. 3-Amino-1-methyl-4-*p*-methoxy-phenyl-1,4,5,7-tetrahydropyrazolo[3,4-*b*]-pyridin-6-one (**6e**): yellow solid; mp 187–189 °C; IR (KBr, cm^{-1}) 3237, 2977, 2929, 2838, 1675, 1612, 1511, 1452, 1344; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 10.02 (s, 1H), 7.02 (d, *J* = 8 Hz, 2H), 6.80 (d, *J* = 8 Hz, 2H), 5.01 (s, 1H), 3.98 (dd, *J* = 8 Hz, 1H), 3.67 (s, 3H), 2.78 (dd, *J* = 4 and 16 Hz, 1H), 2.38 (dd, *J* = 4 and 16 Hz, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 169.8, 157.8, 146.6, 142.9, 136.5, 127.8, 113.9, 86.5, 55.1, 40.7, 33.9, 32.2; Calcd' for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.72; H, 5.89; N, 20.62. 3-Amino-1-methyl-4-*p*-nitro-phenyl-1,4,5,7-tetrahydropyrazolo[3,4-*b*]pyridin-6-one (**6f**): orange solid; mp >300 °C; IR (KBr, cm^{-1}) 3365, 2971, 2883, 1673, 1604, 1517, 1465, 1351; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 10.18 (s, 1H), 8.14 (d, *J* = 8 Hz, 2H), 7.36 (d, *J* = 8 Hz, 2H), 5.24 (s, 1H), 3.41 (s, 3H), 2.93 (dd, *J* = 8 and 16 Hz, 1H), 2.46 (dd, *J* = 2 Hz, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 169.1, 152.7, 146.5, 146.2, 128.1, 124.1, 123.4, 84.7, 39.8, 34.0, 32.9; Calcd' for $C_{13}H_{13}N_5O_3$: C, 54.35; H, 4.56; N, 24.38. Found: C, 54.39; H, 4.42; N, 24.43. Amino-1-phenyl-4-phenyl-1,4,5,7-tetrahydropyrazolo[3,4-*b*]pyridin-6-one (**6g**): white solid; mp 211–212 °C; IR (KBr, cm^{-1}) 3353, 2881, 2931, 1681, 1602, 1500; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 9.13 (s, 1H), 7.40 (m, *J* = 4 and 8 Hz, 5H), 7.17 (d, *J* = 6 Hz, 2H), 6.97 (d, *J* = 8 Hz, 2H), 6.72 (t, *J* = 6 and 8 Hz, 1H), 4.68 (s, 1H), 3.60 (m, *J* = 8 Hz, 1H), 2.87 (dd, *J* = 8 and 18 Hz, 1H), 2.63 (dd, *J* = 6 and 18 Hz, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 168.7, 145.7, 144.3, 139.7, 132.3, 129.1, 128.9, 128.6, 127.8, 122.1, 118.8, 111.7, 38.1, 37.4; Calcd' for $C_{18}H_{16}N_4O$: C, 71.04; H, 5.30; N, 18.41. Found: C, 70.98; H, 5.28; N, 18.47. Amino-1-phenyl-4-*p*-methoxy-phenyl-1,4,5,7-tetrahydropyrazolo[3,4-*b*]pyridin-6-one (**6h**): yellow solid; mp 208–210 °C; IR (KBr, cm^{-1}) 3345, 2958, 2931, 2879, 2838, 1683, 1600, 1515, 1349; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 9.12 (s, 1H), 7.34 (d, *J* = 8 Hz, 2H), 7.19 (d, *J* = 6 Hz, 2H), 6.97 (d, *J* = 8 Hz, 4H), 6.72 (t, *J* = 6 Hz, 1H), 4.61 (s, 1H), 3.75 (s, 3H), 3.55 (m, *J* = 8 Hz, 1H), 2.89 (dd, *J* = 6 and 18 Hz, 1H), 2.55 (d, *J* = 18 Hz, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 168.9, 158.8, 146.2, 131.7, 129.2, 128.7, 118.9, 117.2, 114.3, 111.8, 55.2, 38.8, 37.9; Calcd' for $C_{19}H_{18}N_4O_2$: C, 68.25; H, 5.43; N, 16.76. Found: C, 68.32; H, 5.42; N, 16.82. Amino-1-phenyl-4-*p*-nitro-phenyl-1,4,5,7-tetrahydropyrazolo[3,4-*b*]pyridin-6-one (**6i**): yellow solid; mp 234–235 °C; IR (KBr, cm^{-1}) 3345, 2925, 2879, 2854, 1691, 1598, 1517; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 9.17 (s, 1H), 8.29 (d, *J* = 8 Hz, 2H), 7.73 (d, *J* = 8 Hz, 2H), 6.97 (d, *J* = 10 Hz, 2H), 6.73 (t, *J* = 8 Hz, 1H), 4.80 (s, 1H), 3.87 (m, *J* = 8 Hz, 1H), 2.92 (dd, *J* = 6 and 18 Hz, 1H), 2.69 (m, *J* = 8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 168.2, 147.3, 147.2, 145.6, 138.2, 129.1, 128.1, 124.1, 116.8, 118.9, 111.8, 37.9, 36.94; Calcd' for $C_{18}H_{15}N_5O_3$: C, 61.89; H, 4.33; N, 20.05. Found: C, 61.82; H, 4.29; N, 20.09. Amino-1-*p*-methoxy-phenyl-4-*p*-methoxy-phenyl-1,4,5,7-tetrahydropyrazolo[3,4-*b*]pyridin-6-ne (**6j**): yellow oil; IR (KBr, cm^{-1}) 3425, 2956, 2933, 2834, 1675, 1608, 1511, 1461, 1351; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 9.3 (s, 1H), 7.44 (d, *J* = 10 Hz, 2H), 7.23 (d, *J* = 8 Hz, 2H), 6.98 (d,

J = 10 Hz, 2H), 6.88 (d, *J* = 10 Hz, 2H), 4.48 (s, 1H), 4.19 (dd, *J* = 8 Hz, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 2.85 (dd, *J* = 8 Hz, 1H), 2.61 (dd, *J* = 10 and 12 Hz, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 170.6, 159.8, 159.2, 145.1, 140.8, 135.6, 129.4, 129.1, 125.9, 124.5, 115.4, 115.2, 114.9, 56.0, 55.8, 42.3, 35.8; Calcd' for $C_{20}H_{20}N_4O_3$: C, 65.92; H, 5.53; N, 15.38. Found: C, 65.88; H, 5.49; N, 15.42. Amino-1-*p*-chloro-phenyl-4-*p*-methoxy-phenyl-1,4,5,7-tetrahydropyrazolo[3,4-*b*]pyridin-6-one (**6k**): pink solid; mp 226–228 °C; IR (KBr, cm^{-1}) 3349, 2996, 2931, 2875, 2836, 1681, 1630, 1517, 1463, 1349; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 8.59 (s, 1H), 7.40 (d, *J* = 8 Hz, 2H), 7.22 (d, *J* = 8 Hz, 2H), 7.09 (d, *J* = 8 Hz, 2H), 6.97 (d, *J* = 8 Hz, 2H), 4.44 (s, 1H), 3.80 (s, 3H), 3.63 (m, *J* = 6 Hz, 1H), 3.01 (dd, *J* = 6 and 14 Hz, 1H), 2.93 (dd, *J* = 16 Hz, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 168.8, 158.8, 144.6, 144.6, 131.6, 129.5, 128.9, 128.6, 122.0, 114.2, 113.2, 55.1, 37.8, 37.0; Calcd' for $C_{19}H_{17}ClN_4O_2$: C, 61.87; H, 4.65; N, 15.19. Found: C, 61.93; H, 4.61; N, 15.23. Amino-1-*p*-fluoro-phenyl-4-*p*-methoxy-phenyl-1,4,5,7-tetrahydropyrazolo[3,4-*b*]pyridin-6-one (**6l**): pink solid; mp 222–224 °C; IR (KBr, cm^{-1}) 3342, 2971, 2919, 2840, 1689, 1614, 1506, 1467, 1344; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 9.08 (s, 1H), 7.33 (d, *J* = 8 Hz, 2H), 7.07 (d, *J* = 8 Hz, 2H), 6.98 (d, *J* = 6 Hz, 2H), 6.93 (d, *J* = 8 Hz, 2H), 4.59 (s, 1H), 3.51 (dd, *J* = 6 Hz, 1H), 2.85 (dd, *J* = 4 and 18 Hz, 1H), 2.58 (dd, *J* = 2 Hz, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 168.8, 158.8, 153.5, 142.4, 131.6, 128.6, 117.1, 115.8, 115.4, 114.2, 112.8, 112.7, 55.1, 37.8, 37.3; Calcd' for $C_{19}H_{17}FN_4O_2$: C, 64.76; H, 4.86; N, 15.90. Found: C, 64.71; H, 4.82; N, 15.94.