An improved procedure for the three-component synthesis of 1*H*-pyrazolo[1,2-b]phthalazine-5,10-dione derivatives using basic ionic liquid

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An efficient and green method for the synthesis of 1*H*-pyrazolo[1,2-b]phthalazine-5,10-dione derivatives has been achieved through the one-pot, three-component condensation of aromatic aldehydes, malononitrile or ethyl cyanoacetate, and phthalhydrazide in the presence of 1-butyl-3-methyl imidazolium hydroxide ([bmim]OH) as catalyst in EtOH. This reaction does not involve any hazardous organic solvent and toxic catalyst. The ionic liquid can be recovered and recycled for subsequent reactions. Moreover, this protocol has the advantages of easy work-up, short reaction time, mild reaction conditions and environmentally benign procedures compared with the reported methods.

Keywords: one-pot, three-component condensation, ionic liquid

Multicomponent reactions (MCRs) can be used to produce elaborate biologically active compounds and have become an important area of research in organic, combinatorial, and medicinal chemistry.[1–4] The MCR strategy offers significant advantages over conventional linear-type synthesis because of its flexible, convergent, and atom efficient nature.[5,6] In recent years, the synthesis of combinatorial small-molecule heterocyclic libraries has emerged as a valuable tool in the search for novel lead structures.[7–9] Thus, the success of combinatorial chemistry in the drug discovery process considerably depends on further advances in the synthesis of heterocyclic compounds using MCR methodology and environmentally benign procedures.

In the past few decades, the synthesis of new heterocyclic compounds has been a subject of great interest due to their wide applicability. Heterocyclic compounds occur widely in nature and are essential to life. Among a large variety of heterocyclic compounds, those containing a pyrazole ring are of interest because they show some pharmacological and biological activities,[10–13] and phthalazine derivatives have been reported to possess anticonvulsant,[14] cardiotonic,[15] and vasorelaxant[16] activities. In order to synthesise new biologically active compounds, our plan was to target compounds in which both ring systems were present and fused together.

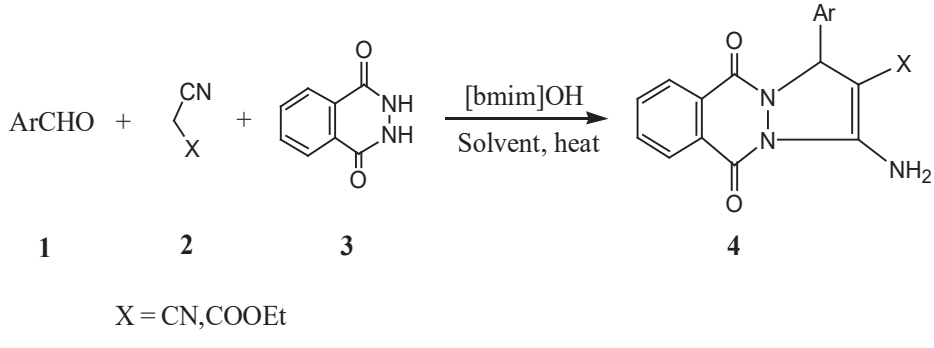
To the best of our knowledge, only a few methods are available for the synthesis of 1*H*-pyrazolo[1,2-b]phthalazine-5,10-dione derivatives,[17,18] most of which have various drawbacks. They require long reaction times, harsh reaction conditions, and use toxic and non-recyclable catalysts. It is thus desirable to develop more efficient methods for the synthesis of such heterocycles.

Our recent interest has been in the development of new synthetic methods using ionic liquids as reaction media and catalyst.[19–21] Herein, we would like to report a highly efficient, convenient, and facile method for the synthesis of 1*H*-pyrazolo[1,2-b]phthalazine-5,10-dione derivatives using an ionic liquid as the basic catalyst.

Results and discussion

We chose [bmim]OH as the ionic liquid, and our method of synthesis of 1*H*-pyrazolo[1,2-b]phthalazine-5,10-dione derivatives **4** is shown in Scheme 1. In order to optimise the conditions, we used as a simple model, the three-component reaction of benzaldehyde (**1**, Ar = Ph) (1 mmol), malononitrile (**2**, X = CN) (1 mmol) and phthalhydrazide **3** (1 mmol) in the presence of [bmim]OH (10 mol%). The reaction was carried out in six different solvents and at different temperatures and the results are shown in Table 1. Ethanol gave the best yield (entry 8) and after evaluating various temperatures (entries 6–11), 60 °C was found to be optimal. We also investigated the effect of lowering and raising the mol% of the catalyst. The yield using 5 mol% dropped to 79% and there was no improvement in the yield when 15 and 20 mol% was used. The optimum conditions were thus to heat a 1:1:1 ratio of reactants in EtOH at 60 °C in the presence of 10 mol% [bmim]OH.

Based on the optimised reaction conditions, a series of 1*H*-pyrazolo[1,2-b]phthalazine-5,10-dione derivatives were synthesised. The results, summarised in Table 2, show that the three-component reaction in the presence of 10 mol% [bmim]OH at 60 °C gave the corresponding products in moderate to very good yields. It is clear that this method can be applied to aromatic aldehydes with either electron-withdrawing groups or electron-donating groups, but those substrates bearing electron-withdrawing groups have higher reactivity (higher yields and shorter reaction time) than those bearing electron-donating groups. So, it is concluded that the electronic nature of the



Scheme 1

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Table 1 Optimisation of the reaction conditions for the [bmim]OH-catalysed synthesis of a 1-phenyl-1*H*-pyrazolo[1,2-b]phthalazine-5,10-dione derivative (**4**, Ar = Ph, X = CN) using a three-component model reaction (Scheme 1)[a]

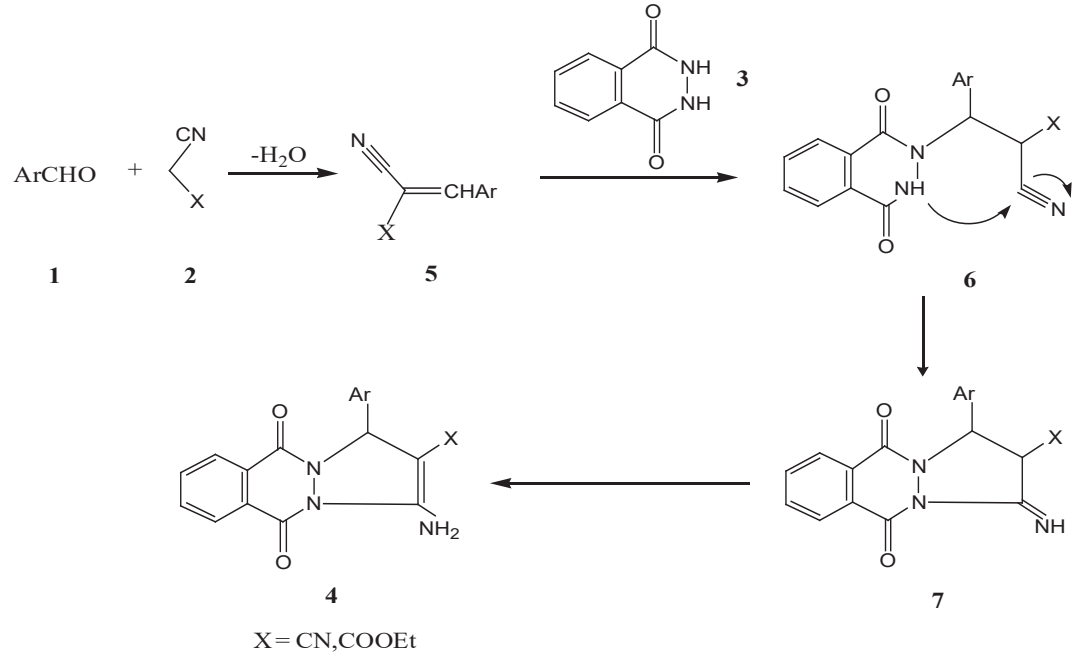
Entry	Solvent	Temperature/°C	Time/h	Yield/%[b]
1	$CHCl_3$	Reflux	8	28
2	CH_3CN	Reflux	8	75
3	DMF	Reflux	8	70
4	CH_3OH	Reflux	8	61
5	H_2O	Reflux	12	Trace
6	C_2H_5OH	80	3	85
7	C_2H_5OH	70	3	88
8	C_2H_5OH	60	1.5	93
9	C_2H_5OH	50	4	82
10	C_2H_5OH	40	4	65
11	C_2H_5OH	25	12	35

[a]Reaction conditions: a mixture of benzaldehyde (**1**, Ar = Ph) (1.0 mmol), malononitrile (**2**, X = CN) (1.0 mmol) and phthalhydrazide (**3**) (1.0 mmol) was stirred in various solvents for various times and heated at various temperatures in the presence of 10 mol%[bmim]OH (Scheme 1).
[b]Isolated yields.

Table 2 Synthesis of 1-aryl-1*H*-pyrazolo[1,2-b]phthalazine-5,10-dione derivatives **4a–l** *via* a three-component reaction using [bmim]OH as catalyst in ethanol (Scheme 1)[a]

Entry	Ar	X	Products	Time/h	Yield/%[b]
1	C_6H_5–	CN	**4a**	1.5	93
2	4-Cl–C_6H_4–	CN	**4b**	1	97
3	4-MeO–C_6H_4–	CN	**4c**	2.0	88
4	4-F–C_6H_4–	CN	**4d**	1	95
5	2-Cl–C_6H_4–	CN	**4e**	1	95
6	4-CH_3–C_6H_4–	CN	**4f**	2	86
7	3-Br–C_6H_4–	CN	**4g**	0.8	97
8	2,4-Cl_2–C_6H_3–	CN	**4h**	1	94
9	4-NO_2–C_6H_4–	CN	**4i**	0.8	98
10	4-isopropyl–C_6H_4–	CN	**4j**	1.5	90
11	4-CH_3–C_6H_4–	COOEt	**4k**	3	84
12	4-NO_2–C_6H_4–	COOEt	**4l**	2.5	90

[a]Reaction conditions: a mixture of araldehyde (**1**) (1.0 mmol), malononitrile or ethyl cyanoacetate (**2**, X = CN, COOEt) (1.0 mmol) and phthalhydrazide (**3**) (1.0 mmol) was stirred in EtOH and heated at 60 °C for various times in the presence of 10 mol%[bmim]OH (Scheme 1).
[b]Isolated yields.



Scheme 2

substituents on aldehydes has some effect on this reaction. These three-component condensation reactions also proceeded with ethyl cyanoacetate (Table 2, entries 11 and 12), but in these cases the reaction times are longer. It may be due to the lower reactivity of ethyl cyanoacetate compared to that of malononitrile. When an aliphatic aldehyde was subjected to this reaction, no product was obtained. We attribute this to the slow formation and unstable nature of the alkylidenemalonitrile formed from the aliphatic aldehydes examined. In a further study, alkylidenemalonitrile and phthalhydrazide were reacted under the same conditions, but no product was obtained. This may be due to an electronic effect. In this study, all the products were characterised by their m.p., IR, ^{1}H NMR, ^{13}C NMR, mass spectroscopy and elemental analyses.

We studied the reuse of [bmim]OH using the model reaction (Scheme 1) and found that it could be successively recovered and reused five times (93, 93, 91, 92 and 90%) without much loss in its catalytic activity.

A reasonable mechanism for the formation of the product **4** is outlined in Scheme 2. The reaction occurs *via* initial formation of intermediate **5** by the Knoevenagel addition of malononitrile or ethyl cyanoacetate **2** to the aldehyde **1** followed by loss of H_2O. Then, Michael-type addition of the phthalhydrazide **3** to **5** yields **6**, which after cyclisation and tautomerisation, affords the corresponding products **4**.

Experimental

Melting points were determined with an X-4 microscopic melting-point apparatus and are uncorrected. IR spectra were recorded on a Nexus 670 spectrometer in KBr. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker Avance-II 500 MHz spectrometer using TMS as internal standard and DMSO-d_6 as solvent. NMR spectra were obtained on a Bruker Avance-II 500 MHz spectrometer (^{1}H NMR at 500 Hz, ^{13}C NMR at 125 Hz) in DMSO-d_6 using TMS as an internal standard. Chemical shifts (δ) are given in ppm and coupling constants (*J*) in Hz.

The synthesis of this task-specific ionic liquid has been carried out from a similar method in the literature.[22] The ionic liquid was formed quantitatively and in high purity as assessed by ^{1}H NMR. All other chemicals (AR grade) were commercially available and used without further purification.

1H-pyrazolo[1,2-b]phthalazine-5,10-dione derivatives **4**

A mixture of the aromatic aldehyde **1** (1 mmol), malononitrile or ethyl cyanoacetate **2** (1 mmol), phthalhydrazide **3** (1 mmol), [bmim]OH (0.1 mmol) in EtOH (5 mL) was stirred at 60 °C for the appropriate time (monitored by thin-layer chromatography [TLC]). After completion of the reaction, the mixture was cooled to room temperature and poured into water (10 mL). The solid product was collected by filtration and recrystallised from ethanol to give the pure compound **4**. The filtrate was extracted with diethyl ether several times to remove unreacted starting materials and other organic contaminations. Then the water was evaporated under reduced pressure and dried to recover the ionic liquid for subsequent use.

*3-Amino-5,10-dihydro-5,10-dioxo-1-phenyl-1*H*-pyrazolo[1,2-b]phthalazine-2-carbonitrile* (**4a**): Yellow powder, m.p. 282–283 °C (EtOH) (lit.[18] 276–278 °C). IR ν_{max} (KBr): 3360, 3259, 2197, 1660, 1566, 1438, 1382, 1297 cm^{-1}; ^{1}H NMR: δ 6.13 (1H, s, CH), 7.32–8.27 (11H, m, ArH and NH_2); ^{13}C NMR: δ 61.4, 62.9, 116.0, 126.6, 126.7, 127.2, 128.2, 128.5, 128.6, 128.8, 133.7, 134.6, 138.4, 150.6, 153.6, 156.6; MS (EI, 70 eV) *m/z* (%): 316 (M^+, 13.9), 299 (28.1), 239 (100). Anal. calcd for $C_{18}H_{12}N_4O_2$: C, 68.35; H, 3.82; N, 17.71; found: C, 68.29; H, 3.78; N, 17.75%.

*3-Amino-1-(4-chlorophenyl)-5,10-dihydro-5,10-dioxo-1*H*-pyrazolo[1,2-b]phthalazine-2-carbonitrile* (**4b**): Yellow powder, m.p. 269–271 °C (EtOH) (lit.[18] 270–272 °C). IR ν_{max} (KBr): 3376, 3265, 2200, 1661, 1564, 1437, 1380, 1277 cm^{-1}; ^{1}H NMR: δ 6.15 (1H, s, CH), 7.42–8.27 (10H, m, ArH and NH_2); ^{13}C NMR: δ 60.9, 62.3, 115.9, 126.6, 127.2, 128.4, 128.5, 128.8, 132.8, 133.7, 134.6, 137.4, 150.7, 153.6, 156.6; MS (EI, 70 eV) *m/z* (%): 350 (M^+, 6.9), 333 (17.6), 239 (50.1), 188 (45.3), 153 (100). Anal. calcd for $C_{18}H_{11}ClN_4O_2$: C, 61.64; H, 3.16; N, 15.97; found: C, 61.55; H, 3.11; N, 15.92%.

*3-Amino-5,10-dihydro-1-(4-methoxyphenyl)-5,10-dioxo-1*H*-pyrazolo[1,2-b]phthalazine-2-carbonitrile* (**4c**): Yellow powder, m.p. 264–266 °C (EtOH). IR ν_{max} (KBr): 3369, 3264, 2193, 1660, 1566, 1438, 1380, 1276 cm^{-1}; ^{1}H NMR: δ 3.75 (3H, s, OCH_3), 6.10 (1H, s, CH), 6.91–8.26 (10H, m, ArH and NH_2); ^{13}C NMR: δ 18.5, 61.4, 62.6, 113.8, 116.1, 126.6, 127.2, 128.4, 128.7, 130.1, 133.6, 134.6, 150.5, 153.5, 156.6, 159.2; MS (EI, 70 eV) *m/z* (%): 346 (M^+, 11.2), 329 (43.9), 184 (100), 133 (35.4), 114 (62.0). Anal. calcd for $C_{19}H_{14}N_4O_3$: C, 65.89; H, 4.07; N, 16.18; found: C, 65.81; H, 4.02; N, 16.12%.

*3-Amino-1-(4-fluorophenyl)-5,10-dihydro-5,10-dioxo-1*H*-pyrazolo[1,2-b]phthalazine-2-carbonitrile* (**4d**): Yellow powder, m.p. 267–268 °C (EtOH) (lit.[17] 263–265 °C). IR ν_{max} (KBr): 3367, 3264, 2192, 1659, 1566, 1512, 1440, 1380, 1278 cm^{-1}; ^{1}H NMR: δ 6.16 (1H, s, CH), 7.18–8.27 (10H, m, ArH and NH_2); ^{13}C NMR: δ 61.1, 62.3, 115.1, 115.3, 116.0, 126.6, 127.2, 128.6, 128.8, 129.1, 129.2, 133.7, 134.6, 150.6, 153.6, 156.6, 160.9, 162.9; MS (EI, 70 eV) *m/z* (%): 334 (M^+, 16.9), 317 (45.2), 239 (100). Anal. calcd for $C_{18}H_{11}FN_4O_2$: C, 64.67; H, 3.32; N, 16.76; found: C, 64.58; H, 3.28; N, 16.69%.

*3-Amino-1-(2-chlorophenyl)-5,10-dihydro-5,10-dioxo-1*H*-pyrazolo[1,2-b]phthalazine-2-carbonitrile* (**4e**): Yellow powder, m.p. 261–262 °C (EtOH) (lit.[18] 259–262 °C). IR ν_{max} (KBr): 3375, 3245, 2205, 1662, 1564, 1471, 1380, 1279 cm^{-1}; ^{1}H NMR: δ 6.46 (1H, s, CH), 7.33–8.30 (10H, m, ArH and NH_2); ^{13}C NMR: δ 59.8, 60.6, 115.6, 126.7, 127.3, 127.8, 128.3, 128.7, 129.7, 129.9, 131.2, 133.8, 134.7, 151.1, 153.5, 156.6; MS (EI, 70 eV) *m/z* (%): 350 (M^+, 10.6), 239 (100), 188 (20.9), 153 (67.2). Anal. calcd for $C_{18}H_{11}ClN_4O_2$: C, 61.64; H, 3.16; N, 15.97; found: C, 61.56; H, 3.12; N, 15.98%.

*3-Amino-5,10-dihydro-5,10-dioxo-1-p-tolyl-1*H*-pyrazolo[1,2-b]phthalazine-2-carbonitrile* (**4f**): Yellow powder, m.p. 254–256 °C. IR ν_{max} (KBr): 3364, 3263, 2197, 1659, 1565, 1467, 1380, 1278 cm^{-1}; ^{1}H NMR: δ 2.30 (3H, s, CH_3), 6.09 (1H, s, CH), 7.16–8.26 (10H, m, ArH and NH_2); ^{13}C NMR: δ 20.7, 61.5, 62.8, 116.0, 126.6, 126.8, 127.2, 128.6, 128.7, 129.0, 133.6, 134.6, 135.3, 137.6, 150.5, 153.5, 156.6; MS (EI, 70 eV) *m/z* (%): 330 (M^+, 20.0), 313 (48.6), 239 (100), 140 (37.8). Anal. calcd for $C_{19}H_{14}N_4O_2$: C, 69.08; H, 4.27; N, 16.96; found: C, 69.01; H, 4.24; N, 16.92%.

*3-Amino-1-(3-bromophenyl)-5,10-dihydro-5,10-dioxo-1*H*-pyrazolo[1,2-b]phthalazine-2-carbonitrile* (**4g**): Yellow powder, m.p. 273–275 °C (EtOH) (lit.[17] 270–272 °C). IR ν_{max} (KBr): 3369, 3261, 2194, 1656, 1566, 1470, 1381, 1277 cm^{-1}; ^{1}H NMR: δ 6.14 (1H, s, CH), 7.32–8.27 (10H, m, ArH and NH_2); ^{13}C NMR: δ 60.8, 62.3, 115.9, 121.8, 126.0, 126.6, 127.2, 128.5, 129.0, 129.5, 130.6, 131.1, 133.7, 134.5, 141.2, 150.7, 153.7, 156.7; MS (EI, 70 eV) *m/z* (%): 394 (M^+, 2.7), 239 (27.3), 234 (32.4), 153 (100). Anal. calcd for $C_{18}H_{11}BrN_4O_2$: C, 54.70; H, 2.81; N, 14.18; found: C, 54.62; H, 2.79; N, 14.22%.

*3-Amino-1-(2,4-dichlorophenyl)-5,10-dihydro-5,10-dioxo-1*H*-pyrazolo[1,2-b]phthalazine-2-carbonitrile* (**4h**): Yellow powder, m.p. 257–258 °C (EtOH). IR ν_{max} (KBr): 3366, 3243, 2202, 1663, 1564, 1471, 1377, 1279 cm^{-1}; ^{1}H NMR: δ 6.45 (1H, s, CH), 7.41–8.29 (9H, m, ArH and NH_2); ^{13}C NMR: δ 59.3, 60.1, 115.6, 126.7, 127.4, 128.0, 128.3, 128.8, 129.1, 130.6, 132.3, 133.6, 133.9, 134.5, 134.8, 151.3, 153.6, 156.7; MS (EI, 70 eV) *m/z* (%): 384 (M^+, 9.7), 239 (100), 222 (24.8), 187 (45.5). Anal. calcd for $C_{18}H_{10}Cl_2N_4O_2$: C, 56.12; H, 2.62; N, 14.54; found: C, 56.07; H, 2.59; N, 14.59%.

*3-Amino-5,10-dihydro-1-(4-nitrophenyl)-5,10-dioxo-1*H*-pyrazolo[1,2-b]phthalazine-2-carbonitrile* (**4i**): Yellow powder, m.p. 272–274 °C (EtOH). IR ν_{max} (KBr): 3433, 3324, 2197, 1679, 1660, 1604, 1558, 1517, 1379, 1276 cm^{-1}; ^{1}H NMR: δ 6.30 (1H, s, CH), 7.80–8.29 (10H, m, ArH and NH_2); ^{13}C NMR: δ 60.4, 62.1, 115.7, 123.8, 126.7, 127.3, 128.0, 128.4, 128.9, 133.9, 134.7, 145.8, 147.4, 150.9, 153.8, 156.7; MS (EI, 70 eV) *m/z* (%): 361 (M^+, 11.1), 344 (32.5), 239 (100), 114 (22.6). Anal. calcd for $C_{18}H_{11}N_5O_4$: C, 59.84; H, 3.07; N, 19.38; found: C, 59.78; H, 3.03; N, 19.34%.

*3-Amino-5,10-dihydro-1-(4-isopropylphenyl)-5,10-dioxo-1*H*-pyrazolo[1,2-b]phthalazine-2-carbonitrile* (**4j**): Yellow powder, m.p. 277–278 °C (EtOH). IR ν_{max} (KBr): 3368, 3265, 2193, 1660, 1567, 1467, 1381, 1277 cm^{-1}; ^{1}H NMR: δ 1.18 (6H, d, J = 7.0 Hz, CH_3), 2.85–2.90 (1H, m, CH), 6.10 (1H, s, CH), 7.22–8.27 (10H, m, ArH and NH_2); ^{13}C NMR: δ 23.7, 23.8, 33.1, 61.4, 62.7, 116.1, 126.4, 126.6, 126.8, 127.2, 128.7, 133.7, 134.6, 135.7, 148.4, 150.6, 153.6, 156.6; MS (EI, 70 eV) *m/z* (%): 358 (M^+, 18.1), 341 (52.1), 239 (100), 154 (22.7). Anal. calcd for $C_{21}H_{18}N_4O_2$: C, 70.38; H, 5.06; N, 15.63; found: C, 70.30; H, 5.02; N, 15.68%.

*Ethyl 3-amino-5,10-dihydro-5,10-dioxo-1-p-tolyl-1*H*-pyrazolo[1,2-b]phthalazine-2-carboxylate* (**4k**): Yellow powder, m.p. 208–210 °C (EtOH) (lit.[18] 204–206 °C). IR ν_{max} (KBr): 3438, 3331, 1714, 1657, 1620, 1493, 1344, 1265 cm^{-1}; ^{1}H NMR: δ 1.25 (3H, t, J = 7.5 Hz, CH_3), 2.30 (3H, s, CH_3), 4.29 (2H, q, J = 7.0 Hz, OCH_2), 6.06 (1H, s, CH), 7.56–8.27 (10H, m, ArH and NH_2); ^{13}C NMR: δ 14.2, 20.5, 59.1, 62.6, 106.8, 126.8, 127.2, 128.4, 128.9, 129.1, 133.9, 134.8, 136.6, 136.9, 150.1, 153.1, 157.3, 162.8; MS (EI, 70 eV) *m/z* (%): 377 (M^+, 19.8), 286 (100), 240 (32.1), 162 (55.8). Anal. calcd for $C_{21}H_{19}N_3O_4$: C, 66. 83; H, 5.07; N, 11.13; found: C, 66.76; H, 5.02; N, 11.17%.

*Ethyl 3-amino-5,10-dihydro-1-(4-nitrophenyl)-5,10-dioxo-1*H*-pyrazolo-[1,2-b]phthalazine-2-carboxylate* (**4l**): Yellow powder, m.p. 240–242 °C (EtOH) (lit.[18] 241–243 °C). IR ν_{max} (KBr): 3426, 3223, 1722, 1657, 1614, 1494, 1348, 1265 cm^{-1}; ^{1}H NMR: δ 1.31 (3H, t, J = 7.5 Hz, CH_3), 4.34 (2H, q, J = 7.0 Hz, OCH_2), 6.19 (1H, s, CH), 7.74–8.56 (10H, m, ArH and NH_2); ^{13}C NMR: δ 13.9, 58.8, 62.5, 62.7, 106.7, 114.9, 123.1, 124.1, 125.1, 126.7, 128.7, 131.6, 132.5, 133.7, 137.3, 149.2, 152.6, 161.1; MS (EI, 70 eV) *m/z* (%): 408 (M^+, 7.8), 286 (100), 240 (28.1), 162 (72.7), 104 (74.7). Anal. calcd for $C_{20}H_{16}N_4O_6$: C, 58. 82; H, 3.95; N, 13.72; found: C, 58.76; H, 3.90; N, 13.76%.

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