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DMAP as a new efficient catalyst for the one-pot synthesis of condensed phthalazines

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Abstract: A new, convenient, and efficient method for the synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones is developed starting from phthalhydrazide, aromatic aldehydes, and malononitrile using 4-*N*,*N*-dimethylaminopyridin as catalyst. This modified route provides much higher yields and a simple work-up procedure of products. Also this methodology is of interest due to the use of ethanol as a solvent without use of any toxic metals as catalyst, thus minimizing the cost, the operational hazards, and environmental pollution.

Keywords: catalyst; DMAP; heterocycles; multicomponent reaction; phthalazine; X-ray structure determination.

1 Introduction

Numerous research programs have been devoted to the establishment of new synthetic methods and new heterocyclic combination because several biological active compounds contain a heterocyclic moiety as a fundamental subunit [1]. Bridgehead nitrogen-containing heterocycles are important targets in synthetic and medicinal chemistry due to their useful biological activities [2]. Condensed phthalazines which have two bridgehead nitrogen atoms in a fused ring system are of particular interest.

The different structures of condensed phthalazine compounds showed different biological activities. They have been reported to possess antimicrobial [3, 4], anti-inflammatory [5, 6], anticancer [7], inotropic [8], anticonvulsant [9], antihypertensive [10], cytotoxic, and antioxidant activities [11, 12]. Over time, numerous studies have been reported for the synthesis of condensed phthalazine derivatives [13–18]. Thus, the development of simple methods for the preparation of heterocycles containing phthalazine moiety is an interesting challenge in organic synthesis.

On the other hand, multicomponent reactions constitute an efficient synthetic strategy for drug design and drug discovery because of their simplicity, efficiency, and high selectivity [19]. The products are obtained in a one-pot and one step synthesis and diver skeletons can be obtained by changing the reaction components [20, 21].

Recently, several well-designed multicomponent strategies for the synthesis of condensed phthalazines such as 1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-triones and 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones have been reported by one-pot reactions of various aldehydes, activated methylene, and phthalhydrazide using different types of catalysts such as Fe_3O_4/SiO_2 nanoparticles, sodium hydrogenocarbonate, piperidine, and basic ionic liquids [22–26].

Herein we report a new efficient synthesis of structurally diverse 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones via a three-component reaction of various aromatic aldehydes **1**, malononitrile as active methylene **2** and phthalhydrazide **3**, in the presence of 4-*N*,*N*-dimethylaminopyridin (DMAP) as catalyst (Scheme 1).

2 Results and discussion

After some experimentation with respect to the molar ratio of the reactants, reaction temperature, reaction time, and possible solvents, we found optimized conditions for benzaldehyde as a representative example. The results indicate that 20% mol of DMAP with respect to

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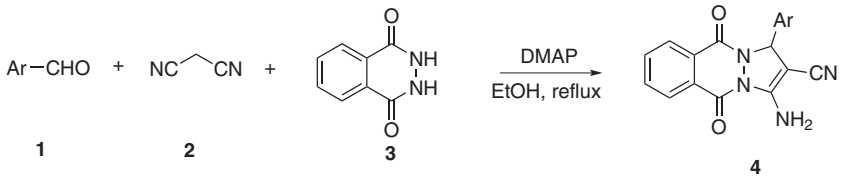


Scheme 1: DMAP catalyze the synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones.

phthalhydrazide suffices for complete conversion of the starting materials and the yield was not obviously affected with different amounts of DMAP.

Ethanol was chosen as a solvent due to some advantages, including its low cost and low toxicity. Moreover, we found that the best results were observed when the molar ratio of phthalhydrazide to malononitrile to benzaldehyde was 1:1.1:1.1.

After completion of the reaction, ethanol was removed and water was added to the reaction mixture in order to solidify the residual and dissolve the catalyst before the precipitated product is isolated by filtration. The crude product **4a** was isolated in good yield and no further purification processes were required (Table 1, Entry 1).

In order to determine the effects of substituents on the phenyl moiety, several substituted benzaldehydes were used instead of benzaldehyde under the conditions mentioned above (Table 1). In most cases, the envisaged compounds were obtained in similar yields indicating that the change in the substituent on the phenyl moiety did not affect the result of the reaction (Entries 2–9). However, the use of aromatic aldehydes possessing either strong electron-donating substituents at *para*-position, such as dimethylamino, hydroxy, or methoxy group, inhibited the reaction, and the Knoevenagel condensation compound (A) (Scheme 2) was the sole isolated product. The reason for this behavior is not clear to us.

Next, we examined a variety of heterocyclic aldehydes to establish the scope of the catalyst. As represented in Table 1 (Entries 10–12), all reactions worked well and the results were excellent in terms of yields and product purity using DMAP.

According to the literature [24, 25], aromatic aldehyde and malononitrile undergo base-catalyzed Knoevenagel condensation to obtain the intermediate (A) in the presence of DMAP [26], which reacts with phthalhydrazide via Michael addition followed by cyclization and tautomerization to afford the corresponding 1*H*-pyrazolo[1,2-*b*] phthalazine-5,10-dione derivatives (Scheme 2).

All compounds **4a–l** obtained according to this protocol were characterized and identified by their melting points, mass spectra, and NMR spectra in comparison to the analytical data reported in the literature [3, 24, 27–34]. For example, the ^{1}H NMR spectrum of **4a** shows one singlet at 7.89 ppm due to the $-NH_2$ substituent at the pyrazole ring. The signals of the aromatic protons of the phthalazine nucleus are found at 8.29 and 7.93 ppm as multiplets. The signals of the aromatic protons of the phenyl group appear between 7.47 and 7.30 ppm as multiplets. The signal attributable to the proton of the pyrazole ring is found at 6.16 ppm as singlet.

The ^{13}C NMR spectrum data in **4a** showed the signals of the two C=O carbon at 157.1 and 154.1 ppm. The carbon of the pyrazolo ring absorbs at 63.6 ppm. The signal attributable to the carbon atom of the nitrile is found at 62.5 ppm. The signals of the other aromatic carbon atom appear between 151.1 and 116.0 ppm. The MS spectrum of **4a** shows a molecular ion peak at $m/z = 317.1$.

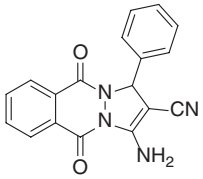
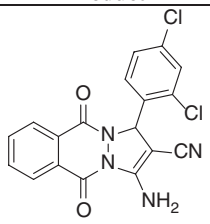
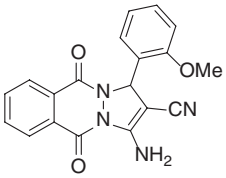
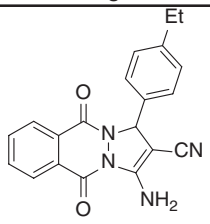
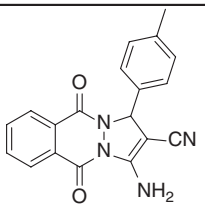
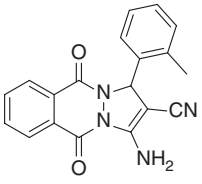
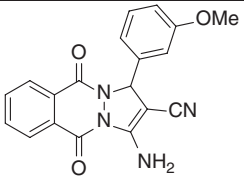
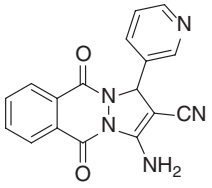
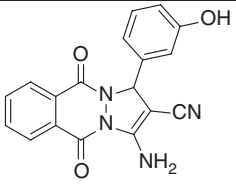
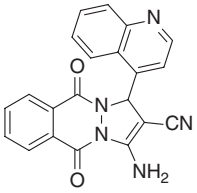
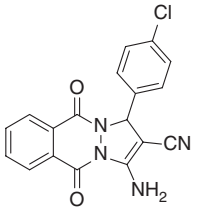
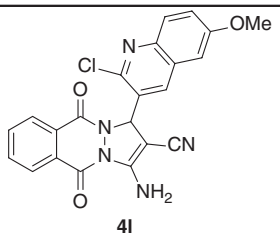
Furthermore, single crystals of **4c** suitable for X-ray diffraction were obtained from a hot acetone-dimethylformamide solution of **4c**. The structure determination verified the proposed structure (Fig. 1, Tables 2 and 3) consisting of a phthalazine ring fused to a pyrazolo moiety and one phenyl group linked to the pyrazole ring.

The fragment pyrazolo[1,2-*b*]phthalazine is essentially planar and forms a dihedral angle of 86.25(5)° with the phenyl ring. The packing of the molecules in the crystal can be described as double layers running parallel to the $(2\bar{2}0)$ plane along the crystallographic *c* axis (Fig. 2). These layers are interconnected by N–H···O and N–H···N hydrogen bond interactions (Fig. 3, Table 4). The crystal structure is also supported by one strong intermolecular Cg···Cg (π–π stacking) interaction with an inter-ring distance of 3.8109(12) Å and C–H···π interactions (Table 5). These interactions link the molecules within the layers and also link layers together thus reinforcing the cohesion of the crystal structure.

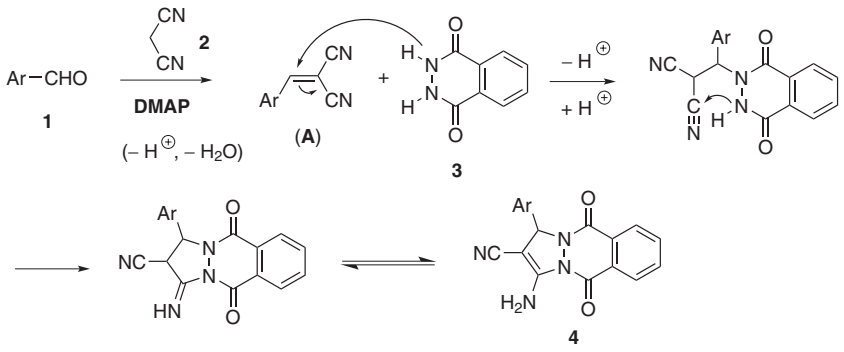
3 Conclusions

In conclusion, as demonstrated herein, the approaches developed in this work allow an efficient access to some

Table 1: Synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones **4a–l** catalyzed by DMAP.

Entry	Product	Yield (%)	Time (h)	Entry	Product	Yield (%)	Time (h)
1	 **4a**	96	1	**7**	 **4g**	97	1
2	 **4b**	97	1	**8**	 **4h**	94	2
3	 **4c**	88	2	**9**	 **4i**	95	2
4	 **4d**	97	1.5	**10**	 **4j**	92	1
5	 **4e**	92	2	**11**	 **4k**	85	0.5
6	 **4f**	94	2	**12**	 **4l**	92	1

condensed phthalazines using new appropriate catalyst, DMAP as Brønsted base catalyst. These approaches allow a diverse range of substituted 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones. In all cases, quantitative yields and pure products were obtained without the need for recrystallization or chromatographic separation.



Scheme 2: Proposed mechanism for the synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones catalyzed by DMAP.

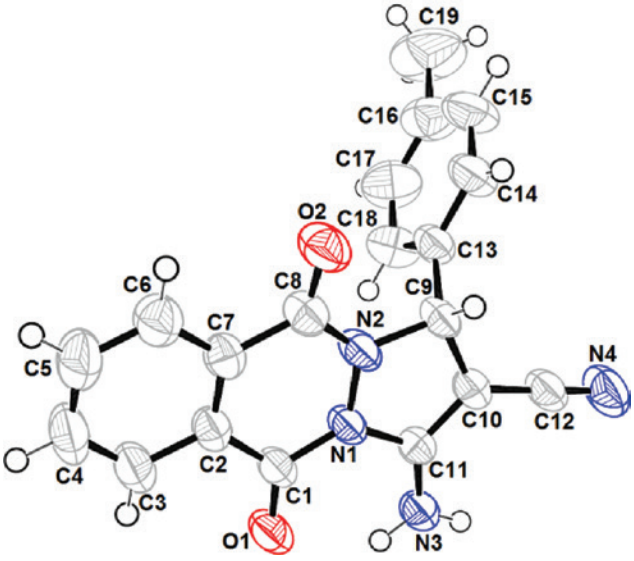


Fig. 1: ORTEP plot of the molecular structure of **4c** in the crystal and atom numbering scheme adopted (displacement ellipsoids at the 50% probability level; H atoms with arbitrary radii; blue: nitrogen, red: oxygen).

Table 2: Crystal structure data for **4c**.

Formula	$C_{19}H_{14}N_4O_2$
M_r	330.34
Cryst. size, mm³	0.11 × 0.13 × 0.16
Crystal system	Triclinic
Space group	$P\bar{1}$ (#2)
a, Å	5.5916(2)
b, Å	10.9002(4)
c, Å	14.8247(5)
α, deg	111.067(2)
β, deg	91.269(2)
γ, deg	98.131(2)
V, Å³	832.08(5)
Z	2
D_{calcd}, g cm⁻³	1.318
μ(MoK_α), cm⁻¹	0.089
F(000), *e*	344
hkl range	±6, ±12, ±17
$((\sin\theta)/\lambda)_{max}$, Å⁻¹	0.717
Refl. measured/unique/R_{int}	13 210/2821/0.0313
Param. refined	227
$R(F)/wR(F^2)$[a,b] ($I > 2\sigma(I)$)	0.0474/0.1395
$R(F)/wR(F^2)$[a,b] (all data)	0.0654/0.1595
GoF (F^2)[c]	1.045
$\Delta\rho_{fin}$(max/min), *e* Å⁻³	0.242/−0.284

[a] $R(F) = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; [b] $wR(F^2) = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$; $w = [\sigma^2(F_o^2) + (AP)^2 + BP]^{-1}$, where $P = (\text{Max}(F_o^2, 0) + 2F_c^2)/3$; [c] $\text{GoF} = S = [\Sigma w(F_o^2 - F_c^2)^2/(n_{obs} - n_{param})]^{1/2}$.

4 Experimental section

The starting materials were generally used as received (Acros, Fontenay-sous-Bois, France) without any further purification. Melting points were determined in open capillary tubes and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 300 spectrometers. Phthalhydrazide was synthesized following a literature procedure starting from phthalic anhydride [3]. Fourier transform-infrared (FT-IR) measurements were carried out by the KBr method using a Shimadzu FT/IR-8201 PC spectrophotometer. The purity of the final compound (greater than 95%) was determined by uHPLC/MS on an Agilent 1290 system (Lyon 1 University, Lyon, France) using an Agilent 1290 Infinity ZORBAX Eclipse Plus C18 column (2.1 mm × 50 mm, 1.8 µm particle size) with a gradient mobile phase of H_2O–CH_3CN (90:10, v/v) with 0.1% of formic acid to H_2O–CH_3CN (10:90, v/v) with 0.1% of formic acid at a flow rate of 0.5 mL/min, with UV monitoring at the wavelength of 254 nm with a run time of 10 min. The mass spectra were performed by direct ionization on a ThermoFinnigan MAT 95 XL apparatus.

4.1 General procedure

A mixture of aromatic aldehyde **1** (1.1 mmol), malononitrile **2** (1.1 mmol), phthalhydrazide **3** (1.0 mmol), and DMAP

Table 3: Selected bond lengths (Å) and angles (deg) for **4c** with estimated standard deviations in parentheses.

Distances	
N1–C1	1.371(2)
N1–C11	1.406(2)
N2–C8	1.354(2)
N2–C9	1.477(2)
N3–C11	1.327(2)
N4–C12	1.151(2)
O1–C1	1.224(2)
O2–C8	1.225(2)
Angles	
C1–N1–C11	128.71(14)
C8–N2–C9	124.47(14)
N2–C9–C13	112.57(14)
C10–C9–C13	114.33(14)

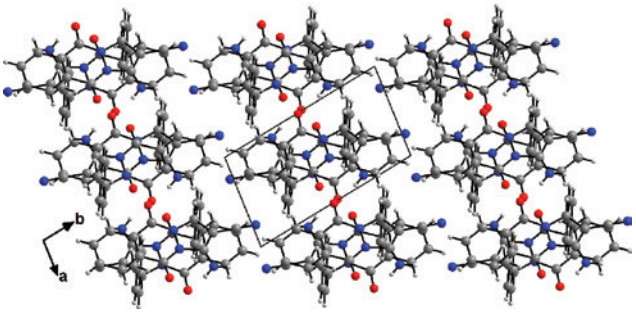


Fig. 2: A diagram of the layered crystal structure of **4c** as viewed down the crystallographic *c* axis.

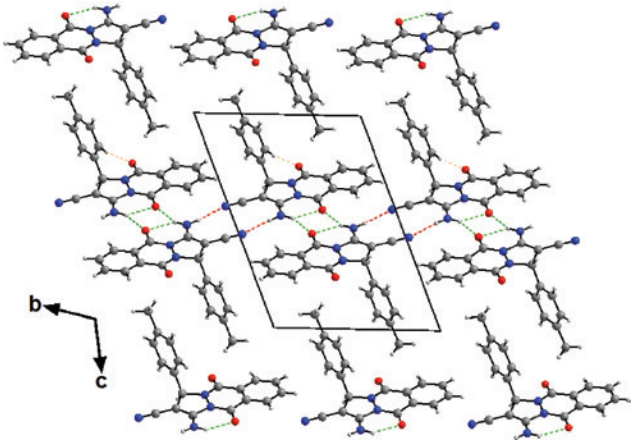


Fig. 3: N–H···O and N–H···N hydrogen bond interactions resulting in the formation of an infinite two-dimensional network of compound **4c** in the crystal (in red N–H···N and in green N–H···O).

Table 4: Hydrogen bond distances (Å) and angles (deg) for **4c**.

D–H···A	*d*(D–H)	*d*(H···A)	*d*(D–A)	D–H···A	Symmetry
N3–H3a···N4	0.86	2.2000	3.060(2)	177	2–*x*, 2–*y*, 1–*z*
N3–H3b···O1	0.86	2.1100	2.725(2)	128	*x*, *y*, *z*
N3–H3b···O1	0.86	2.2400	3.018(2)	151	2–*x*, 1–*y*, 1–*z*

(20 mol%) was placed in 10 mL of ethanol. The reaction mixture was then refluxed for appropriate time (the reaction was monitored by thin-layer chromatography; see Table 1). After completion, ethanol was evaporated under vacuum and 10 mL of water was added. The resulting solid was filtered, and washed with water and then hexane. The structures of the products were fully established on the basis of their ^{1}H NMR, ^{13}C NMR, and IR spectra as well as MS spectral analysis.

4.2 Spectral data

4.2.1 3-Amino-5,10-dioxo-1-phenyl-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (4a)

Yield 92%; yellow solid; m.p. 278–281°C (lit. 275–276°C [28, 30]). – IR (KBr): υ = 3359, 2194, 1654, 1380, 1276, 1149, 698, 582. – ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 8.29–8.26 (m, 1H, Harom), 8.13–8.11 (m, 1H, Harom), 7.99–7.93 (m, 2H, Harom), 7.89 (sL, 2H, NH$_2$), 7.47–7.30 (m, 5H, Harom), 6.16 (s, 1H, H-1) ppm. – ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 157.1 (C), 154.2 (C), 151.1 (C), 138.7 (C), 135.3 (CH), 134.1 (CH), 129.2 (C), 129.1 (C), 128.9 (CH), 128.7 (CH), 127.7 (CH), 127.2 (CH), 127.2 (CH), 116.0 (C), 63.6 (CH), 62.5 (C) ppm. – MS (ES-API): *m*/*z* = 317.1 [M + H]$^+$.

4.2.2 3-Amino-1-(2-methoxyphenyl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (4b)

Yield 97%; yellow solid; m.p. 260–263°C (lit. 259–260°C [27]). – IR (KBr): υ = 3382, 2198, 1666, 1380, 698, 497. – ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 8.31–8.28 (m, 1H, Harom), 8.12–8.09 (m, 1H, Harom), 8.03–7.97 (m, 4H, 2Harom and NH$_2$), 7.33–7.28 (m, 2H, Harom), 7.05 (d, 1H, *J* = 8.0 Hz, Harom), 6.93 (t, 1H, *J* = 7.0 Hz, Harom), 6.36 (s, 1H, H-1), 3.75 (s, 3H, OMe) ppm. – ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 157.1 (C), 156.9 (C), 153.7 (C), 151.4 (C), 135.1 (CH), 134.2 (CH), 129.8 (CH), 129.1 (C), 129.0 (C), 127.8 (CH), 127.7 (CH), 127.1 (CH), 126.3 (C), 121.1 (CH), 116.5 (C), 112.1 (CH), 61.1 (C), 59.4 (CH), 56.3 (OCH$_3$) ppm. – MS (ES-API): *m*/*z* = 347.1 [M + H]$^+$.

4.2.3 3-Amino-5,10-dioxo-1-*p*-tolyl-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (4c)

Yield 88%; yellow solid; m.p. 261–262°C (lit. 253–255°C [29]). – IR (KBr): υ = 3359, 2194, 1658, 1380, 1276, 1149, 694, 574. – ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 8.26–8.25 (m, 1H,

Table 5: Intramolecular C–H···π interaction in the crystal structure of **4c** (Å, deg).[a]

C–H···Cg	*d*(C–H)	*d*(H···Cg)	*d*(C–Cg)	C–H···Cg	Symmetry
C(18)–H(18)···Cg1 (N1 N2 C9 C10 C11)	0.93	2.69	2.978(2)	99	*x*, *y*, *z*

[a]Cg1 = center of gravity of N1-N2-C9-C10-C11.

Harom), 8.11–8.09 (m, 3H, 1Harom and NH_2), 8.00–7.96 (m, 2H, Harom), 7.35 (d, 2H, J = 7.9 Hz, Harom), 7.18 (d, 2H, J = 7.9 Hz, Harom), 6.10 (s, 1H, H-1), 2.31 (s, 3H, CH_3) ppm. – ^{13}C NMR ([D_6]DMSO, 75 MHz): δ = 157.0 (C), 154.0 (C), 151.0 (C), 138.1 (C), 135.9 (C), 135.1 (CH), 134.1 (CH), 129.5 (CH), 129.2 (C), 129.1 (C), 127.7 (CH), 127.3 (CH), 127.1 (CH), 116.5 (C), 63.3 (CH), 61.9 (C), 21.2 (CH_3) ppm. – MS (ES-API): m/z = 331.1 $[M+H]^+$.

4.2.4 3-Amino-1-(3-methoxyphenyl)-5,10-dioxo-5, 10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (4d)

Yield 95%; yellow solid; m.p. 265–269°C (lit. 264–266°C [30]). – IR (KBr): υ = 3355, 2191, 1651, 1384, 1153, 690. – ^{1}H NMR ([D_6]DMSO, 300 MHz): δ = 8.29–8.26 (m, 1H, Harom), 8.12–8.10 (m, 3H, 1Harom and NH_2), 7.99–7.95 (m, 2H, Harom), 7.30 (t, 1H, J = 8.3 Hz, Harom), 7.04–7.01 (m, 2H, Harom), 6.93–6.89 (m, 1H, Harom), 6.11 (s, 1H, H-1), 3.76 (s, 3H, OMe) ppm. – ^{13}C NMR ([D_6]DMSO, 75 MHz): δ = 159.8 (C), 157.1 (C), 154.1 (C), 151.1 (C), 140.5 (C), 135.1 (CH), 134.1(CH), 130.1 (C), 129.3 (C), 129.2 (C), 127.7 (CH), 127.1 (C), 119.2 (CH), 116.5 (C), 113.8 (CH), 113.1 (CH), 63.3 (CH), 61.8 (C), 55.6 (OCH_3) ppm. – MS (ES-API): m/z = 347.1 $[M+H]^+$.

4.2.5 3-Amino-1-(3-hydroxyphenyl)-5,10-dioxo-5, 10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (4e)

Yield 92%; yellow solid; m.p. 270–271°C (lit. 270–272°C [31, 34]). – IR (KBr): υ = 3355, 2191, 1651, 1384, 1153, 690, 563. – ^{1}H NMR ([D_6]DMSO, 300 MHz): δ = 9.48 (s, 1H, OH), 8.29–8.24 (m, 1H, Harom), 8.14–8.09 (m, 3H, 1Harom and NH_2), 8.01–7.97 (m, 2H, Harom), 7.17 (t, 1H, J = 8.2 Hz, Harom), 6.87 (d, 1H, J = 7.7 Hz, Harom), 6.73 (dd, 1H, J = 8.0 Hz, J = 1.7 Hz, Harom), 6.06 (s, 1H, H-1) ppm. – ^{13}C NMR ([D_6] DMSO, 75 MHz): δ = 157.9 (C), 157.0 (C), 154.0 (C), 151.0 (C), 140.3 (C), 135.2 (CH), 134.2 (CH), 130.0 (CH), 129.1 (C), 129.1 (CH), 127.7 (CH), 127.2 (CH), 117.7 (CH), 116.5 (C), 115.7 (CH), 113.8 (CH), 63.2 (CH), 61.7 (C) ppm. – MS (ES-API): m/z = 333.1 $[M+H]^+$.

4.2.6 3-Amino-1-(4-chlorophenyl)-5,10-dioxo-5, 10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (4f)

Yield 94%; yellow solid; m.p. 274–276°C (lit. 272–274°C [28]). – IR (KBr): υ = 3371, 2198, 1662, 1566, 1377, 1265, 1141, 833, 694, 551. – ^{1}H NMR ([D_6]DMSO, 300 MHz): δ = 8.30–8.26 (m, 1H, Harom), 8.14–8.09 (m, 3H, 1Harom and NH_2), 8.00–7.96 (m, 2H, Harom), 7.54 (d, 1H, J = 8.4 Hz, Harom), 7.44 (d, 1H, J = 8.4 Hz, Harom), 6.17 (s, 1H, H-1) ppm. – ^{13}C NMR ([D_6]DMSO, 75 MHz): δ = 157.1 (C), 154.1 (C), 151.2 (C), 137.9 (C), 136.7 (C), 135.1 (CH), 134.2 (CH), 133.3 (C), 129.3 (CH), 129.1 (C), 129.0 (CH), 127.7 (CH), 127.1 (CH), 116.4 (C), 62.7 (CH), 61.4 (C) ppm. – MS (ES-API): m/z = 351.1 $[M+H]^+$.

4.2.7 3-Amino-1-(2,4-dichlorophenyl)-5,10-dioxo-5, 10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (4g)

Yield 97%; yellow solid; m.p. 245–247°C (lit. 242–244°C [30]). – IR (KBr): υ = 3259, 2202, 1380, 1149, 698, 505. – ^{1}H NMR ([D_6]DMSO, 300 MHz): δ = 8.31–8.28 (m, 1H, Harom), 8.19 (s_L, 2H, NH_2), 8.12–8.09 (m, 1H, Harom), 8.01–7.98 (m, 2H, Harom), 7.71–7.67 (m, 2H, Harom), 7.43 (dd, 1H, J = 8.4 Hz, J = 1.9 Hz, Harom), 6.46 (s, 1H, H-1) ppm. – ^{13}C NMR ([D_6]DMSO, 75 MHz): δ = 157.1 (C), 154.1 (C), 151.7 (C), 135.2 (CH), 135.0 (C), 134.4 (CH), 134.0 (C), 132.7 (CH), 129.6 (C), 129.3 (C), 128.7 (C), 128.5 (CH), 127.8 (CH), 127.1 (CH), 116.0 (C), 60.5 (CH), 59.7 (C) ppm. – MS (ES-API): m/z = 385.0 $[M+H]^+$.

4.2.8 3-Amino-1-(4-ethylphenyl)-5,10-dioxo-5, 10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (4h)

Yield 94%; yellow solid; m.p. 275–276°C. – IR (KBr): υ = 3359, 2194, 1658, 1380, 694, 578; – ^{1}H NMR ([D_6]DMSO, 300 MHz): δ = 8.28–8.25 (m, 1H, Harom), 8.11–8.09 (m, 3H, 1Harom and NH_2), 7.98–7.96 (m, 2H, Harom), 7.37 (d, 2H, J = 7.7 Hz, Harom), 7.22 (d, 2H, J = 7.7 Hz, Harom), 6.12 (s, 1H, H-1), 2.60 (q, 2H, J = 7.4 Hz, CH_2CH_3), 1.18 (t, 3H, J = 7.5 Hz,

CH_2CH_3) ppm. – ^{13}C NMR ([D_6]DMSO, 75 MHz): – ^{13}C NMR ([D_6]DMSO, 75 MHz): δ = 157.0 (C), 154.0 (C), 151.0 (C), 144.3 (C), 136.1 (C), 135.1 (CH), 134.1 (CH), 129.2 (C), 129.1 (C), 128.3 (CH), 127.7 (CH), 127.3 (CH), 127.1 (CH), 116.6 (C), 63.3 (CH), 61.9 (C), 28.3 (CH_2), 15.9 (CH_3) ppm. – ESI-HRMS: m/z = 345.1349 (calcd. 345.1346 for $C_{20}H_{17}N_4O_2$, $[M+H]^+$).

4.2.9 3-Amino-5,10-dioxo-1-*o*-tolyl-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (4i)

Yield 95%; yellow solid; m.p. 249–250°C (lit. 248–251°C [32]). – IR (KBr): υ = 3371, 2194, 1670, 1573, 1423, 1272, 1149, 1095, 759, 694. – ^{1}H NMR ([D_6]DMSO, 300 MHz): δ = 8.31–8.26 (m, 1H, Harom), 8.11–8.07 (m, 3H, 1Harom and NH_2), 8.01–7.97 (m, 2H, Harom), 7.35 (d, 1H, J = 7.4 Hz, Harom), 7.22–7.20 (m, 3H, 1Harom), 6.34 (s, 1H, H-1), 2.47 (s, 3H, Me) ppm. – ^{13}C NMR ([D_6]DMSO, 75 MHz): δ = 157.1 (C), 153.9 (C), 151.2 (C), 136.9 (C), 135.6 (C), 135.2 (CH), 134.2 (CH), 134.0 (CH), 131.6 (CH), 130.9 (CH), 129.2 (C), 129.0 (C), 128.4 (CH), 127.8 (CH), 127.1 (CH), 116.5 (C), 61.5 (C), 60.4 (CH), 19.1 (CH_3) ppm. – MS (ES-API): m/z = 331.1 $[M+H]^+$.

4.2.10 3-Amino-5,10-dioxo-1-(pyridin-3-yl)-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (4j)

Yield 91%; yellow solid; m.p. 267–270°C (lit. 268–270°C [33]). – IR (KBr): υ = 3259, 2191, 1569, 1280, 698, 567; – ^{1}H NMR ([D_6]DMSO, 300 MHz): δ = 8.75 (d, 1H, J = 1.8 Hz, Harom), 8.55 (dd, 1H, J = 4.7 Hz, J = 1.5 Hz, Harom), 8.30–8.24 (m, 1H, Harom), 8.19 (sL, 2H, NH_2), 8.13–8.07 (m, 1H, Harom), 7.01–7.92 (m, 3H, Harom), 7.44–7.40 (m, 1H, Harom), 6.24 (s, 1H, H-1) ppm. – ^{13}C NMR ([D_6]DMSO, 75 MHz): δ = 157.2 (C), 154.2 (C), 151.4 (C), 150.0 (CH), 149.1 (CH) 135.1 (CH), 135.1 (CH), 134.4 (C), 134.2 (CH), 129.4 (C), 128.9 (C), 127.7 (CH), 127.1 (CH), 124.2 (CH), 116.4 (C), 61.3 (CH), 60.8 (C) ppm. – MS (ES-API): m/z = 318.1 $[M+H]^+$.

4.2.11 3-Amino-5,10-dioxo-1-(quinolin-4-yl)-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (4k)

Yield 84%; yellow solid; m.p. 256°C; IR (KBr): υ = 3382, 2206, 1662, 1562, 1423, 1369, 1276, 1149, 752, 694; – ^{1}H NMR ([D_6]DMSO, 300 MHz): δ = 8.87 (d, 1H, J = 4.5 Hz, Harom), 8.42–8.33 (m, 2H, Harom), 8.23 (sL, 2H, NH_2), 8.15–7.99 (m, 4H, Harom), 7.85 (t, 1H, J = 7.5 Hz, Harom), 7.75–7.7. (m, 2H, Harom), 7.05 (s, 1H, H-1) ppm; – ^{13}C NMR ([D_6]DMSO, 75 MHz): δ = 157.3 (C), 154.4 (C), 151.6 (C), 150.9 (CH), 148.0 (C), 144.6 (C), 135.5 (CH), 134.6 (CH), 130.5 (CH), 129.9 (CH), 129.2 (C), 128.5 (C), 127.9 (CH), 127.7 (CH), 127.2 (CH), 125.3 (C), 123.5 (CH), 116.1 (C), 83.5 (CH), 60.8 (C), 49.0 (CH) ppm. – ESI-HRMS: m/z = 368.1134 (calcd. 368.1142 for $C_{21}H_{14}N_5O_2$, $[M+H]^+$).

4.2.12 3-Amino-1-(2-chloro-6-methoxyquinolin-3-yl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (4l)

Yield 92%; yellow solid; m.p. 285–286°C (lit. 220–222°C [24]). – IR (KBr): υ = 3371, 2206, 1666, 1569, 1496, 1377, 1276, 1234, 1168, 1045, 833, 694. – ^{1}H NMR ([D_6]DMSO, 300 MHz): δ = 8.68 (s, 1H, Harom), 8.36–8.35 (m, 1H, Harom), 8.26 (sL, 2H, NH_2), 8.12–7.97 (m, 3H, Harom), 7.91 (d, 1H, J = 9.2 Hz, Harom), 7.48 (dd, 1H, J = 9.1 Hz, J = 2.4 Hz, Harom), 7.34 (s, 1H, Harom), 6.57 (s, 1H, H-1), 3.86 (s, 3H, OMe) ppm. – ^{13}C NMR ([D_6]DMSO, 75 MHz): δ = 158.4 (C), 157.2 (C), 154.1 (C), 153.3 (C), 151.8 (C), 143.3 (C), 135.3 (CH), 134.4 (CH), 129.5 (CH), 129.3 (C), 129.0 (C), 128.8 (C), 127.8 (CH), 127.2 (CH), 124.4 (CH), 116.1 (C), 106.0 (CH), 83.5 (C), 61.5 (CH), 56.0 (CH_3) ppm. – MS (ES-API): m/z = 432.1 $[M+H]^+$.

4.3 X-ray structure determination

Yellow crystals of compound **4c** were obtained from acetone-dimethylformamide solution. Diffraction data were collected with a Bruker Apex II CCD area detector diffractometer with graphite-monochromatized MoK_α radiation (λ = 0.71073 Å) at 298 K. Tables 2 and 3 summarize important crystal structure data and selected bond lengths and angles of **4c**, respectively.

CCDC 1476723 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

5 Supplementary information

Pictures of the NMR and mass spectra of compounds **4a–4l** are given as Supporting Information available online (DOI: 10.1515/znb-2016-0262).

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