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Silica gel-supported tungstic acid (STA): A new, highly efficient and recyclable catalyst for the synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione carbonitriles and carboxylates under neat conditions

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ABSTRACT

1*H*-Pyrazolo[1,2-*b*]phthalazine-5,10-dione carbonitriles and carboxylates possess a broad range of applications as active compounds in the pharmacological and biological fields. We developed an efficient and ecofriendly silica gel-supported tungstic acid (STA)-catalyzed one-pot synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione carbonitriles and carboxylates by a three-component reaction of an aldehyde, a malononitrile/ethyl cyanoacetate and a phthalhydrazide under solvent-free conditions. The major advantages of the present method are experimental simplicity, use of an inexpensive and ecofriendly reusable catalyst, good yields, and short reaction times.

1. Introduction

An increasing number of studies have reported on the environmentally friendly production of fine chemicals using recyclable heterogeneous catalysts via multi-component reactions (MCRs). They are considered to be superior synthetic strategies [1–10], with highly efficient atom economy compared to other organic reactions. Their advantages in terms of one-pot multi-component reaction, reaction time, product yield, minimization of waste production, energy consumption and reproducibility have been repeatedly exploited in various efficient syntheses of heterocyclic compounds.

Due to numerous important biological activities as versatile building blocks for the synthesis of natural products and as drug molecules [11–15], the pyrazolo[1,2-*b*]phthalazine-dione and their derivatives are important targets in synthetic organic chemistry. In particular, pyrazolo[1,2-*b*]phthalazine-diones are biologically active and occur in structures of a number of anti-inflammatory, anti-allergic, analgesic antihypoxic, anticonvulsant, cardiotonic, vasorelaxant, antipyretic antihyperglycemic, anti-bacterial, and anti-viral compounds [16–18]. This core also has been utilized in diverse pharmaceutical applications, such as in anti-cancer [19] and anti-diabetes [20] agents.

So far, only a few methods have been reported for the preparation of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione carbonitriles and carboxylates [21]. However, the above-mentioned catalysts have one or more disadvantages, such as long reaction time, high reaction temperature, use of volatile and hazardous organic solvents, occurrence of side products, and they were reported in homogenous catalysts. Even though Pandurangan et al. used heterogeneous catalysts, they reported they worked in solvents, with long

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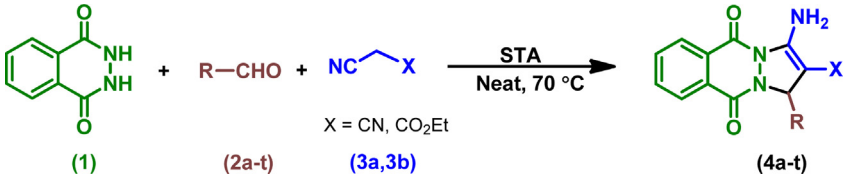


Scheme 1. Neat synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione carbonitriles and carboxylates catalyzed by STA.

reaction times [21a]. The use of homogenous catalysts has received little attention as alternatives to alleviating some of the limitations. Solid acids as heterogeneous catalysts have received tremendous attention in different areas of organic synthesis [22]. Heterogeneous solid acids are advantageous over conventional homogeneous acid catalysts as they can be easily recovered from the reaction mixture by simple filtration and can be reused after with or without activation, thereby making the process economically more viable. Among them, silica gel-supported tungstic acid (STA) is a well-known and widely used solid acid catalyst in synthetic organic chemistry. It has received considerable attention due to its non-toxicity, cost effectiveness, air and water compatibility, ease of handling, good reactivity, recyclability, experimental simplicity, remarkable ability as a green catalyst to suppress side reactions in acid-sensitive substrates and as supports for a wide variety of reactions. Despite its great importance, only a few publications are reported on its catalytic application in organic synthesis [23]. It is evident from recent literature that the solvent-free endorsed STA reactions are well known as environmentally benign methods that also usually provide improved selectively, enhanced reaction rates, cleaner products, and manipulative simplicity [23a,b].

In continuation of our efforts to develop new green methodologies and as well as our interest in applications of heterogeneous-catalyzed organic reactions [24], we reported herein STA as a new heterogeneous catalytic system for MCR. The STA catalytic activity was investigated for the one-pot synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione carbonitriles and carboxylates through a three-component condensation reaction of phthalhydrazide, aldehydes and malononitrile/ethyl cyanoacetate in solvent-free conditions at 70 °C (Scheme 1).

2. Results and discussion

For our initial investigation, the reaction of phthalhydrazide (**1**), 2,3-dihydrobenzo[*b*][1,4]dioxine-6-carbaldehyde (**2a**), and malononitril (**3a**) under neat conditions was chosen as a model reaction. At 70 °C and in the absence of catalyst, we could not isolate any desired MCR product, even after 6 h of stirring. After 10 h of stirring, a trace amount of the corresponding product was obtained (Table 1, entry 1). Next, the same set of reactions was performed in the presence of 5 mol% of PS/PTSA. Within 4 h, the corresponding title product **4a** was isolated in 40% product yield (Table 1, entry 2). The product **4a** was confirmed by usual spectroscopic techniques. Encouraged by this result, we attempted to optimize the yield of the reaction by screening the same set of reactions with various heterogeneous catalysts, such as BF_3–SiO_2, CAN–SiO_2, TiO_2–SiO_2 and STA, and the results are summarized in Table 1. Among all the screened catalysts, STA was found superior with respect to reaction time and product yield (Table 1, entry 6). Moreover, we found that the yields were obviously affected by the amount of loaded STA. When 1 mol%, 2 mol%, 5 mol% and 10 mol% of STA were used, the yields were 58, 70, 93, and 94%, respectively (Table 1, entries 6–9). Therefore, 5 mol% of STA was sufficient and no more significant improvement in the reaction rate and product yield was observed while increasing the amount of the catalyst from 5 to 10 mol% (Table 1, entry 9).

Table 1
Influence of the catalyst for the synthesis of 3-amino-1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile **4a**[a].

Entry	Catalyst (mol%)	Time (min)	Yield (%)[b]
1	Neat	600	Trace
2	PT/PTSA (5 mol%)	240	40
3	BF_3–SiO_2 (5 mol%)	170	60
4	CAN–SiO_2 (5 mol%)	110	75
5	TiO_2–SiO_2 (5 mol%)	130	66
6[c]	STA (5 mol%)	20	93, 92, 90, 89
7	STA (1 mol%)	100	58
8	STA (2 mol%)	55	70
9	STA (10 mol%)	20	94

[a] Reaction of 2,3-dihydrobenzo[*b*][1,4]dioxine-6-carbaldehyde (**2a**, 1 mmol), phthalhydrazide (**1**, 1 mmol) and malononitrile (**3a**, 1 mmol) under neat at 70 °C.
[b] Isolated yield.
[c] The catalyst was reused four times.

Table 2
Optimal reaction conditions and temperatures for different solvents in the synthesis of 3-amino-1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile **4a**[a].

Entry	Solvent	Temp (°C)	Yield (%)[b]	
			Catalyst-free conditions	STA (5 mol%)
1	Toluene	110	33.4	52.6
2	Chlorobenzene	120	32.2	48.7
3	CH_2Cl_2	75	34.1	48.4
4	CCl_4	75	30.4	45.1
5	THF	65	43.6	50.8
6	Acetonitrile	65	48.8	61.4
7	Ethanol	70	57.4	80.4
8	No solvent	70	20.5	93.0

[a] Reaction conditions: 3-dihydrobenzo[*b*][1,4]dioxine-6-carbaldehyde (**2a**, 1 mmol), phthalhydrazide (**1**, 1 mmol), and malononitrile (**3a**, 1 mmol). Reaction times: 20 min.
[b] Isolated yield.

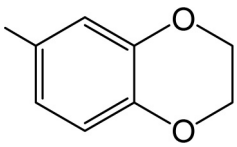
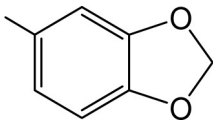
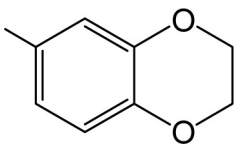
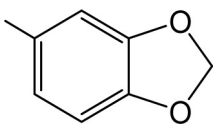
Then, we investigated the influence of various organic solvents at different reaction temperatures on the model reaction with 5 mol% of STA with and without catalyst. Among various solvents, such as toluene, THF, CH_2Cl_2, CH_3CN, and DMF, the reaction rate is very slow and resulted in lower product yields (Table 2, entries 1–6). Conducting the same reaction in ethanol improved both the reaction rate and the product yield (Table 2, entry 7). However, the better product yield was observed in solvent-free conditions (Table 2, entry 8) and could be explained by a uniform distribution of the eutectic mixture of reactants, which are in closer proximity to react. It was concluded that irrespective of the nature of solvent, even at its boiling temperature, the optimum conversion rate of the reactants was always observed, whereas under solvent-free conditions, the maximum conversion rate of the reactants was only achieved at 70 °C.

Solvent and temperature variations have also been tested on the model reaction using 5 mol% of STA in different solvents at their boiling temperatures for 20 min of reaction (Table 2, entries 1–7). Irrespective of the nature of the solvent, even at its boiling temperature, we always observed an optimum conversion rate of the products (Fig. 1), but under solvent-free conditions, the maximum conversion yield was achieved (Table 2, entry 8). The lower yields in solvent medium may be due to salvation of reaction medium.

In order to investigate the catalytic activity and the possibility of catalyst recyclability and reusability, the STA was recovered from the reaction mixture by simple filtration in hot EtOH. The separated catalyst was dried in a vacuum oven at 100 °C and was reused as such for subsequent experiments under similar reaction conditions. The results showed that the catalyst could be effectively reused for at least four consecutive cycles without much appreciable loss in its catalytic activity (Table 1, entry 6). The recyclability data demonstrate a high stability of the catalyst under the reaction conditions.

Having optimized the reaction conditions for the synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione

Table 3
STA-catalyzed multi-component synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione carbonitriles and carboxylates **4a**–**t.**

Compound	*R*	*X*	Yield (%)[a]	Time (min)	Mp (°C)	
					Found	Reported
4a		CN	93	20	261–263	
4b		CN	90	25	259–261	
4c	2-Cl–6-F–C_6H_3	CN	91	30	266–268	
4d	3,5-F–C_6H_3	CN	92	26	272–274	
4e	2-F–4-Br–C_6H_3	CN	91	28	252–254	
4f	3-F–C_6H_4	CN	93	20	263–265	264–266 [21f]
4g	3-F–4-Me-C_6H_3	CN	90	26	260–262	261–263 [21f]
4h	C_2H_5	CN	88	30	240–242	238–240 [21f]
4i	C_3H_7	CN	89	28	223–225	220–222 [21f]
4j	2-thiophene (C_4H_3S)	CN	85	32	245–247	244–246 [21f]
4k		CO_2Et	91	24	220–222	
4l		CO_2Et	88	30	211–213	
4m	2-Cl–6-F–C_6H_3	CO_2Et	88	31	217–219	
4n	3,5-F–C_6H_3	CO_2Et	90	26	246–248	
4o	2-F–4-Br–C_6H_3	CO_2Et	89	32	215–217	
4p	3-F–C_6H_4	CO_2Et	92	22	228–230	228–230 [21f]
4q	3-F–4-Me–C_6H_3	CO_2Et	90	30	220–222	222–224 [21f]
4r	C_2H_5	CO_2Et	87	35	167–169	165–167 [21f]
4s	C_3H_7	CO_2Et	89	32	151–153	150–152 [21f]
4t	2-thiophene (C_4H_3S)	CO_2Et	90	35	228–230	228–230 [21f]

[a] Isolated yield.

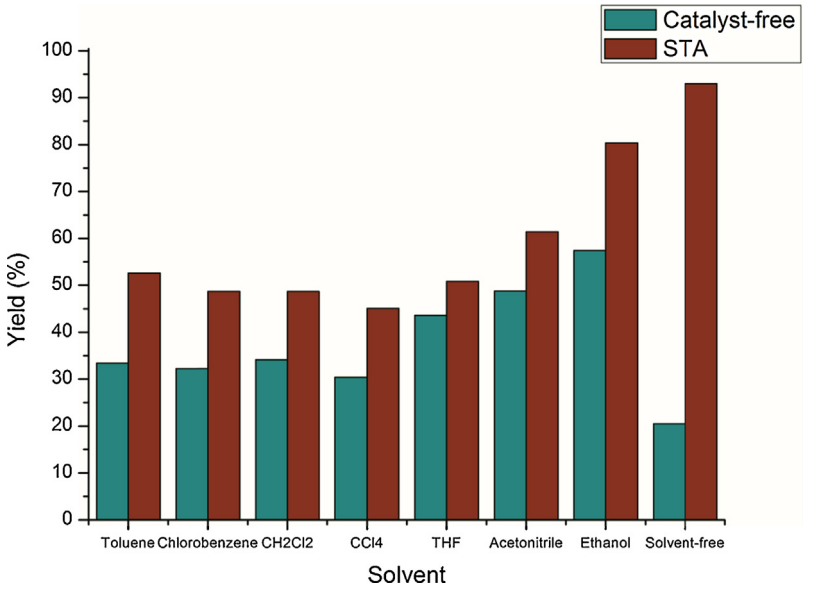
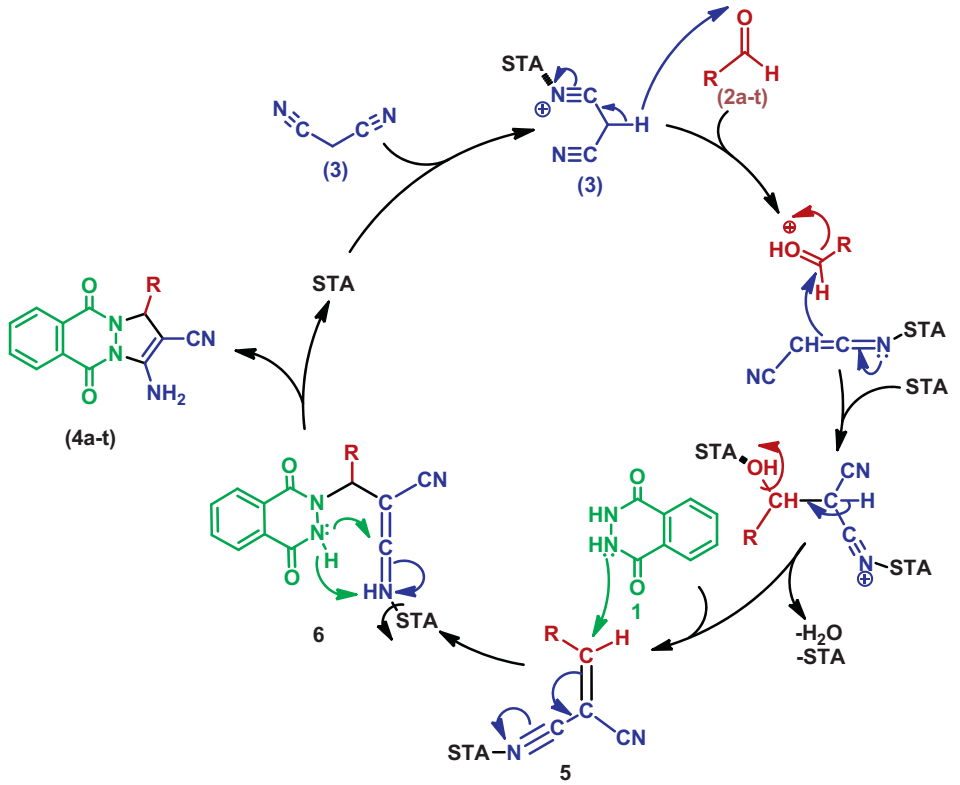


Fig. 1. (Color online.) Product yields at various solvents on model reaction.

carbonitriles and carboxylates using STA as the catalyst under solvent-free conditions, we subsequently applied the optimized reaction conditions to various aldehydes to explore the generality of the reaction system. As shown in Table 3, multi-component reactions produced excellent product yields for a wide range of aromatic aldehydes bearing both electron-donating and electron-withdrawing substituents. Non-aromatic and heteroaromatic aldehydes, however, were less reactive, producing only moderate yields (Table 3). In a similar manner to what was observed with malononitrile, ethyl cyanoacetate also participated in this multi-component reaction to afford the



Scheme 2. (Color online.) Schematic presentation of the postulated mechanistic activity of our STA catalyst.

corresponding 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione carbonitriles and carboxylates in good yields. In all cases, the pure product was isolated by simple filtration, without chromatography or a cumbersome work-up procedure. After the reaction, the catalyst can be easily separated from the product and reused without any significant decrease in its catalytic activity. All new structures were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS. Data and melting point of compounds **4f–j** and **4p–t** coincide with those of the reported ones.

The role of STA as a catalyst in the synthesis of the title compounds (**4a–t**) should be postulated as shown in Scheme 2. The multi-component reaction should be proceeding in a stepwise manner. First, the reaction occurs via a Knoevenagel condensation between the enolic form of malononitrile (**3**) and aldehyde (**2**) in the presence of acidic STA as a catalyst to form intermediate **5**. Here, the solid catalyst can facilitate active hosting sites for reactant molecules and accelerate the reaction rate. Second, intermediate **5** immediately transforms into one more intermediate, **6**, by Michael addition of 2,3-dihydrophthalazine-1,4-dione (**1**) at the conjugated C=C bond of **5**. Finally, by intramolecular concerted cyclisation of the adduct, **6** gave the title compounds (**4a–t**) in good yields.

3. Conclusion

In conclusion, we have explored the use of the heterogeneous STA catalyst as an effective and reusable catalyst for the synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione carbonitriles and carboxylates. The use of an environmentally friendly and inexpensive catalyst and solvent-free conditions, along with the reusability of the catalyst, provides a good example of a competitive alternative synthetic methodology for these compounds.

4. Experimental

4.1. General

Chemicals were purchased from Aldrich and Alfa Aesar Chemical Companies. NMR spectra were recorded in ppm in DMSO-d_6 on a Jeol JNM ECP 400 NMR instrument using TMS as an internal standard. Mass spectra were recorded on a Jeol JMS-700 mass spectrometer. All melting points were determined using open capillaries on an Electro-thermal-9100 (Japan) instrument.

4.2. General procedure for the synthesis of 3-amino-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile (4a)

A mixture of phthalhydrazide (**1**, 1 mmol, 162 mg), 2,3-dihydrobenzo[*b*][1,4]dioxine-6-carbaldehyde (**2a**, 1 mmol, 164 mg), malononitrile (**3a**, 1 mmol, 66 mg) and STA (5 mol%, 21 mg) was stirred at 70 °C under solvent-free conditions for 20 min (Table 3, entry 1). The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was dissolved in hot ethanol and the catalyst was filtered. The residue was crystallized from ethanol to afford product **4a** (93%). The catalyst was washed with diethylether, dried at 100 °C for 2 h, and reused in another reaction.

4.2.1. 3-Amino-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo-[1,2-b]phthalazine-2-carbonitrile (4a)

Yield 93%; yellow powder; mp 261–263 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.25–8.23 (m, 1H), 8.11 (s, 2H), 8.10–8.06 (m, 1H), 7.96–7.92 (m, 2H), 6.95 (d, J = 8.2 Hz, 1H), 6.82 (d, J = 9.2 Hz, 2H), 6.25 (s, 1H), 4.20 (s, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.5, 153.9, 150.5, 146.8, 135.5, 134.5, 133.7, 129.0, 128.4, 127.2, 126.6, 120.5, 117.5, 115.5, 112.8, 64.2, 59.5, 58.3. HRMS (ESI, m/z): calcd for $C_{20}H_{14}N_4O_4$ ($M+H^+$) 374.1015; found: 374.1011.

4.2.2. 3-Amino-1-(benzo[d][1,3]dioxol-5-yl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile (4b)

Yield 90%; yellow powder; mp 259–261 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.24–8.19 (m, 1H), 8.12 (s, 2H), 8.09–8.05 (m, 1H), 7.97–7.93 (m, 2H), 6.75–6.70 (m, 3H), 6.65 (s, 1H), 6.10 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.5, 153.5, 152.5, 151.4, 146.6, 144.1, 136.5, 134.6, 133.4, 129.2, 128.5, 127.0, 126.1, 118.5, 115.9, 112.5, 104.5, 59.8, 58.6. HRMS (ESI, m/z): calcd for $C_{19}H_{12}N_4O_4$ ($M+H^+$) 360.059; found: 360.059.

4.2.3. 3-Amino-1-(2-chloro-6-fluorophenyl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile (4c)

Yield 91%; yellow powder; mp 266–268 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.25–8.24 (m, 1H), 8.12 (s, 2H), 8.10–8.06 (m, 1H), 7.98–7.95 (m, 2H), 7.45 (t, J = 8.8 Hz, 1H), 7.30 (dd, J = 2.2, 12.8, Hz, 1H), 7.05 (dd, J = 2.2, 11.0, Hz, 1H), 6.09 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.4, 156.5, 153.2, 150.4, 134.7, 133.8, 129.7, 129.6, 128.4, 127.5, 126.7, 124.6, 119.7, 117.6, 111.3, 59.9, 57.5. HRMS (ESI, m/z): calcd for $C_{18}H_{10}ClFN_4O_2$ 368.0476; found: 368.0470.

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

Yield 92%; yellow powder; mp 272–274 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.28–8.26 (m, 1H), 8.08–8.06 (m, 1H), 8.05 (s, 2H), 7.88–7.86 (m, 2H), 6.95 (d, J = 7.2 Hz, 2H), 6.74–6.69 (m, 1H), 6.39 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.2, 159.6, 155.6, 154.4, 151.4, 140.3, 134.7, 133.8, 128.9, 128.1, 127.7, 117.4, 110.4, 104.6, 62.9, 60.8. HRMS (ESI, m/z): calcd for $C_{18}H_{10}F_2N_4O_2$ 352.077; found: 352.070.

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

Yield 91%; yellow powder; mp 252–234 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.27–8.24 (m, 1H), 8.12 (s, 2H), 8.11–8.07 (m, 1H), 7.96–7.93 (m, 2H), 7.34 (t, J = 8.8 Hz, 2H), 7.01 (dd, J = 2.2, 12.8, Hz, 1H), 6.30 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.5, 156.6, 153.4, 150.8, 134.7, 133.8, 130.5, 129.7, 128.6, 128.4, 127.3, 126.7, 121.4, 119.4,

115.7, 59.9, 57.5. HRMS (ESI, *m*/*z*): calcd for $C_{18}H_{10}BrFN_4O_2$411.997; found: 411.997.

*4.2.6. Ethyl 3-amino-1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carboxylate (**4k**)*

Yield 91%; yellow powder; mp 220–222 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.25–8.23 (m, 1H), 8.10 (s, 2H), 8.08–8.06 (m, 1H), 7.96–7.92 (m, 2H), 6.90 (d, J = 8.2 Hz, 1H), 6.72 (d, J = 9.2 Hz, 2H), 6.05 (s, 1H), 4.20 (s, 4H), 4.02–3.95 (m, 2H), 1.02 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.5, 155.5, 153.6, 149.5, 146.4, 135.0, 133.9, 133.0, 129.3, 128.0, 127.2, 126.8, 120.5, 118.5, 116.5, 112.9, 80.5, 60.2, 59.5, 58.2, 14.2. HRMS (ESI, *m*/*z*): calcd for $C_{22}H_{19}N_3O_6$ (M+H$^+$) 421.127; found: 421.121.

*4.2.7. Ethyl 3-amino-1-(benzo[*d*][1,3]dioxol-5-yl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carboxylate* **(4l)**

Yield 88%; yellow powder; mp 211–213 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.27–8.24 (m, 2H), 8.16 (s, 2H), 8.09–8.05 (m, 1H), 7.95–7.91 (m, 2H), 6.70–6.68 (m, 2H), 6.50 (s, 1H), 6.12 (s, 2H), 4.00–3.94 (m, 2H), 1.03 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.9, 156.2, 152.5, 151.5, 150.0, 146.4, 144.9, 135.5, 134.3, 133.0, 129.2, 128.2, 127.0, 126.8, 117.5, 116.0, 112.5, 104.5, 80.5, 60.5, 58.6, 13.9. HRMS (ESI, *m*/*z*): calcd for $C_{21}H_{17}N_3O_6$ (M+H$^+$) 407.112; found: 407.115.

*4.2.8. Ethyl 3-amino-1-(2-chloro-6-fluorophenyl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carboxylate (**4m**)*

Yield 88%; yellow powder; mp 217–219 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22–8.18 (m, 1H), 8.10 (s, 2H), 8.08–8.04 (m, 1H), 7.94–7.90 (m, 2H), 7.35 (t, J = 8.0 Hz, 1H), 7.20 (d, J = 7.8 Hz, 1H), 7.05 (dd, J = 2.2, 11.0, Hz, 1H), 6.10 (s, 1H), 3.99–3.94 (m, 2H), 1.05 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.6, 161.0, 156.5, 153.0, 150.2, 134.7, 133.8, 129.4, 129.0, 128.4, 127.5, 125.7, 124.3, 118.7, 117.6, 112.3, 81.1, 58.9, 56.5, 14.3. HRMS (ESI, *m*/*z*): calcd for $C_{20}H_{15}ClFN_3O_4$ (M + H$^+$) 415.074; found: 415.074.

*4.2.9. Ethyl 3-amino-1-(3,5-difluorophenyl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carboxylate* **(4n)**

Yield 90%; Yellow powder; mp 246–248 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.25–8.22 (m, 1H), 8.12–8.08 (m, 1H), 8.06 (s, 2H), 7.98–7.92 (m, 2H), 6.85 (d, J = 7.2 Hz, 2H), 6.70 (d, J = 7.2 Hz, 1H), 6.25 (s, 1H), 3.96–3.90 (m, 2H), 1.02 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.0, 162.2, 159.5, 156.6, 153.6, 151.3, 141.3, 135.7, 133.3, 128.9, 128.3, 127.7, 117.4, 110.4, 104.6, 80.3, 60.8, 58.4, 13.8. HRMS (ESI, *m*/*z*): calcd for $C_{20}H_{15}F_2N_3O_4$ (M + H$^+$) 399.103; found: 399.100.

*4.2.10. Ethyl 3-amino-1-(4-bromo-2-fluorophenyl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carboxylate (**4o**)*

Yield 89%; yellow powder; mp 215–217 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.27–8.24 (m, 1H), 8.10 (s, 2H), 8.09–8.06 (m, 1H), 7.96–7.93 (m, 2H), 7.30 (t, J = 8.8 Hz, 2H), 7.01 (dd, J = 2.2, 12.8, Hz, 1H), 6.23 (s, 1H), 4.00–3.94 (m, 2H), 1.03 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.9, 160.0, 156.5, 154.4, 151.8, 134.7, 133.2, 130.2, 128.2, 128.6, 128.3, 127.2, 126.9, 121.4, 118.4, 116.7, 80.5, 58.0, 56.5, 13.9. HRMS (ESI, *m*/*z*): calcd for $C_{20}H_{15}BrFN_3O_4$ 459.023 (M+H$^+$) 459.023; found: 459.023.

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