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ORIGINAL PAPER

# $CeCl_3$-promoted one-pot synthesis of multisubstituted bispyrano[2,3-*c*]pyrazole derivatives

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**Abstract** A simple and efficient method was developed for the synthesis of multisubstituted bispyrano[2,3-*c*]pyrazole derivatives via one-pot reaction of β-keto esters, hydrazine (or phenylhydrazine), terephthalaldehyde, and malononitrile in the presence of $CeCl_3 \cdot 7H_2O$ (10 mol%) as a catalyst. This method provides the products in good yields after a simple workup procedure without further purification.

**Keywords** Multicomponent reaction · One-pot synthesis · $CeCl_3$-promoted · Bispyrano[2,3-c]pyrazole · Heterocycles

## Introduction

Pyrano[2,3-*c*]pyrazoles are an important class of compounds that include pharmaceuticals and biodegradable agrochemicals. Many have been previously reported in the literature as biologically important compounds with potential anticancer [1], antibacterial [2, 3], antiherpetic [4], anti-inflammatory [5, 6], and molluscicidal activity [7]. They have also been identified as promising inhibitors of human Chk1 kinase in computer-based screening and kinase inhibition assays [8, 9]. Furthermore, terephthalaldehyde is an important raw material and intermediate that is widely used for the preparation of bioactive compounds including medicinally active compounds and agrochemicals. Because of their wide range of applications, pyrano[2,3-*c*]pyrazoles are produced in large quantities. Therefore, the development of new methods for their synthesis has received considerable attention.

The combinatorial synthesis of small molecule heterocyclic libraries has emerged as a valuable tool in the search for novel lead structures. As a result, the performance of one-pot methods in the synthesis of various chemicals has recently been summarized [10–12]. Multicomponent reactions (MCRs) have attracted considerable attention because of their valuable features such as atom economy, straightforward reaction design, energy savings, and reduced waste. Highly functionalized small organic molecules and new heterocyclic compounds can be synthesized using MCRs. Multicomponent one-pot synthesis is of particular interest because of its wide applicability [13–17].

In recent decades, many synthetic approaches for the preparation of pyrano[2,3-*c*]pyrazole compounds have been reported, wherein various improvements and modifications of the reaction have been made. These methods include the two-component reaction of benzylidenemalononitrile and pyrazole-5-one catalyzed by cinchona alkaloid derivatives [18], the electrocatalyzed three-component reaction of substituted piperidin-4-ones, malononitrile, and pyrazolin-5-ones [3], as well as a simple and eco-friendly noncatalytic synthesis of both pyranopyrazoles and *N*1-phenyl-substituted pyranopyrazoles [19–23]. In addition, the four-component one-pot method is widely used for the synthesis of pyrano[2,3-*c*]pyrazole derivatives. For example, piperidine-catalyzed consecutive one-pot synthesis of trifluoromethylated spiro[indole-3,4′-pyrano[2,3-*c*]pyrazole] derivatives has been reported [24].

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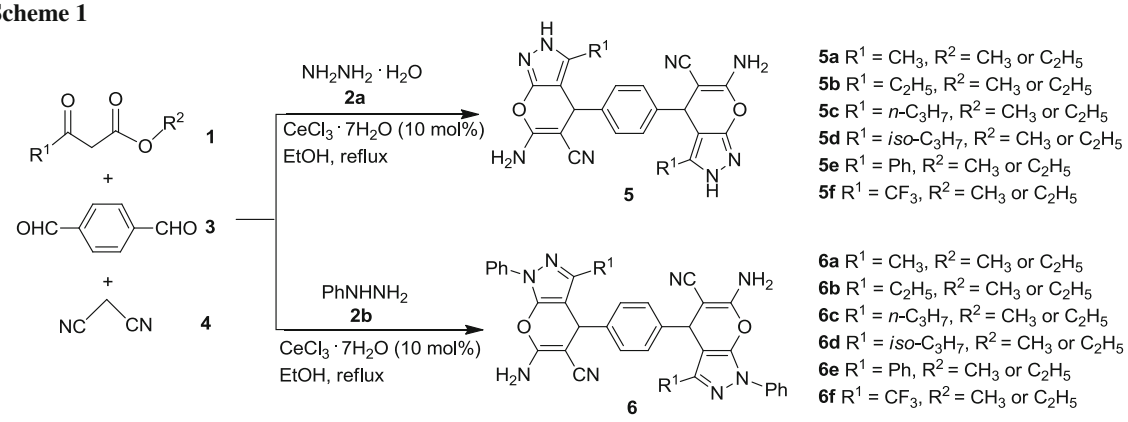
**Scheme 1**




Four-component one-pot syntheses of multisubstituted bispyrano[2,3-*c*]pyrazoles

**Table 1** Optimization of the reaction conditions and solvent screening for the synthesis of **5a** and **6a**

| Entry | Reaction conditions[a] | Solvent | Yield[b]/% | |
|---|---|---|---|---|
| | | | **5a** | **6a** |
| 1 | No catalyst, reflux, 1 h | EtOH | 5 | 8 |
| 2 | $Ce(NO_3)_2$ (10 mol%), reflux | EtOH | 60 | 62 |
| 3 | $InCl_3$ (10 mol%), reflux | EtOH | 55 | 60 |
| 4 | $ZnCl_2$ (10 mol%), reflux | EtOH | 45 | 48 |
| 5 | $CeCl_3{\cdot}7H_2O$ (10 mol%), reflux | EtOH | 76 | 75 |
| 6 | $CeCl_3{\cdot}7H_2O$ (20 mol%), reflux | EtOH | 78 | 77 |
| 7 | $CeCl_3{\cdot}7H_2O$ (10 mol%), 80 °C | No solvent | 18 | 15 |
| 8 | $CeCl_3{\cdot}7H_2O$ (10 mol%), reflux | $H_2O$ | 35 | 32 |
| 9 | $CeCl_3{\cdot}7H_2O$ (10 mol%), reflux | EtOH/$H_2O$ (1:1) | 55 | 50 |
| 10 | $CeCl_3{\cdot}7H_2O$ (10 mol%), rt, 12 h | EtOH | 20 | 15 |
| 11 | $CeCl_3{\cdot}7H_2O$ (10 mol%), reflux | DMF | 65 | 60 |
| 12 | $CeCl_3{\cdot}7H_2O$ (10 mol%), reflux | MeCN | 60 | 63 |
| 13 | $CeCl_3{\cdot}7H_2O$ (10 mol%), reflux | MeOH | 65 | 60 |
| 14 | $CeCl_3{\cdot}7H_2O$ (10 mol%), reflux | $CH_2Cl_2$ | 55 | 50 |

Product **5a** was obtained from the reaction of methyl acetoacetate (2.0 mmol), hydrazine hydrate (2.0 mmol), terephthalaldehyde (1.0 mmol), and malononitrile (2.0 mmol) in 15 $cm^3$ of solvent; product **6a** was obtained using the same conditions with phenylhydrazine (2.0 mmol) in place of hydrazine hydrate

[a] Except entries 1 and 10, reaction time of all experiments is 20 min

[b] Isolated yields

However, the systematic synthesis of multisubstituted bispyrano[2,3-*c*]pyrazoles via a one-pot reaction route has not been reported.

$CeCl_3{\cdot}7H_2O$ is a cheap, non-toxic, and "friendly" reagent [25–29], which has been utilized as an efficient Lewis acid catalyst for the three-component coupling of aldehydes, aromatic amines, and diethylphosphite to produce α-aminophosphonates [30]. A series of 1,4-dihydropyridines were efficiently synthesized by the reaction of aldehydes with ammonium acetate and ethyl acetoacetate using $CeCl_3{\cdot}7H_2O$ as a catalyst [31]. Here, we describe a facile and scalable four-component one-pot synthesis of multisubstituted bispyrano[2,3-*c*]pyrazoles in the presence of $CeCl_3{\cdot}7H_2O$ (10 mol%) as a catalyst in ethanol (Scheme 1). The products are obtained in good yield and chemical purity without further purification.

## Results and discussion

In order to determine the optimum reaction conditions for the synthesis of **5a** via the one-pot route, we initially investigated the reaction of methyl acetoacetate (**1a**), hydrazine hydrate (**2a**), terephthalaldehyde (**3**), and malononitrile (**4**) under different reaction conditions (Scheme 1). Also, we conducted the reaction of **1a**, phenylhydrazine (**2b**), **3**, and **4** for the synthesis of **6a**. The detailed results are listed in Table 1.

As shown in Table 1, when the reaction was conducted without any catalyst, products **5a** and **6a** were obtained in 5 and 8 % yield using EtOH as a solvent, respectively, and prolonged refluxing did not increase the product yield (Table 1, entry 1). Other catalysts such as $Ce(NO_3)_2$, $InCl_3$, and $ZnCl_2$ also catalyzed the reaction to give the products in low yields (Table 1, entries 2–5). However, good yields of products **5a** (76 %) and **6a** (75 %) were obtained when $CeCl_3{\cdot}7H_2O$ was used as the catalyst in refluxing EtOH (Table 1, entry 5). In addition, it is notable that the product yield did not change significantly with increased amounts of $CeCl_3{\cdot}7H_2O$ (Table 1, entry 6). In another attempt, when the reaction was carried out at room temperature, only a small amount of the product was obtained (Table 1, entry 10).

Next, the effect of the reaction solvent was evaluated. As shown in Table 1, low yields of products **5a** (55–65 %) and **6a** (50–60 %) were obtained when the mixture was refluxed in the presence of $CeCl_3{\cdot}7H_2O$ (10 mol%) as a

**Table 2** Synthesis of multisubstituted bispyrano[2,3-*c*]pyrazole derivatives **5a–5f** and **6a–6f**

| Entry | Product | $R^1$ | Reactant | Time/min; yield[a]/% | |
|---|---|---|---|---|---|
| | | | | $R^2 = CH_3$ | $R^2 = C_2H_5$ |
| 1 | **5a** | $CH_3$ | **2a** | 20/76 | 20/70 |
| 2 | **5b** | $C_2H_5$ | **2a** | 30/79 | 30/75 |
| 3 | **5c** | *n*-$C_3H_7$ | **2a** | 35/90 | 35/84 |
| 4 | **5d** | *iso*-$C_3H_7$ | **2a** | 40/81 | 40/75 |
| 5 | **5e** | Ph | **2a** | 45/75 | 45/70 |
| 6 | **5f** | $CF_3$ | **2a** | 40/85 | 40/78 |
| 7 | **6a** | $CH_3$ | **2b** | 45/75 | 45/70 |
| 8 | **6b** | $C_2H_5$ | **2b** | 50/76 | 50/70 |
| 9 | **6c** | *n*-$C_3H_7$ | **2b** | 60/72 | 60/65 |
| 10 | **6d** | *iso*-$C_3H_7$ | **2b** | 50/75 | 50/70 |
| 11 | **6e** | Ph | **2b** | 45/78 | 45/72 |
| 12 | **6f** | $CF_3$ | **2b** | 50/76 | 50/70 |

[a] Isolated yields

catalyst in different solvents such as DMF, MeCN, MeOH, and $CH_2Cl_2$ (Table 1, entries 8–11). These results revealed that using EtOH as the solvent afforded the best yields.

The optimized reaction conditions were tested for the synthesis of other multisubstituted bispyrano[2,3-*c*]pyrazole derivatives via the four-component one-pot synthesis route using $CeCl_3{\cdot}7H_2O$ (10 mol%) as a catalyst in refluxing EtOH. In all cases, products **5a–5f** and **6a–6f** were obtained in good yields (Table 2). The structures of the products were confirmed on the basis of $^1$H NMR, IR, and ESI–MS spectral analyses. The corresponding spectral data were in agreement with the proposed structures of all target compounds. Moreover, all reactions were complete within 60 min and all products could be purified by filtration of the formed precipitate and washed thoroughly with EtOH without recrystallization. Furthermore, the reaction was also investigated using other ethyl β-keto esters. As shown in Table 2, slightly lower yields of the products were afforded when ethyl acetoacetates (**1b**) were used instead of methyl acetoacetates (**1a**). Nonetheless, twelve products, **5a–5f** and **6a–6f**, were obtained under the optimized conditions mentioned above.

The $Ce^{3+}$ ions from the $CeCl_3{\cdot}7H_2O$ catalyst may have facilitated both the condensation reaction and the nucleophilic attack. A plausible reaction mechanism for the synthesis of compound **5** is shown in Scheme 2. At first, the condensation of the β-keto esters **1** with hydrazine hydrate (**2a**) forms intermediate pyrazole-5-one **A**, and the Knoevenagel condensation between terephthalic aldehyde (**3**) and malononitrile (**4**) affords intermediate **B**. Then, Michael reaction between intermediates **A** and **B** yields **C**. Subsequent intramolecular nucleophilic attack of OH onto C=N and tautomerization generated the expected target product.

## Experimental

Melting points were measured in open end capillary tubes on a Büchi B-2540 digital melting point apparatus. Infrared (IR) spectra were recorded on a Bruker EQUINOX 55 spectrophotometer as KBr pellets. $^1$H and $^{13}$C NMR spectra were obtained on a Varian INOVA-400 instrument using DMSO-$d_6$ as a solvent. Chemical shifts are given in ppm relative to TMS as an internal standard. ESI–MS spectra were determined on an HP 1100 LC–MS (ESI). HRMS (ESI) data were obtained on Micromass Q-Tof Global mass spectrometer. Silica gel (GF-254) was used for TLC. All chemical reagents were of analytical grade and used without further purification.

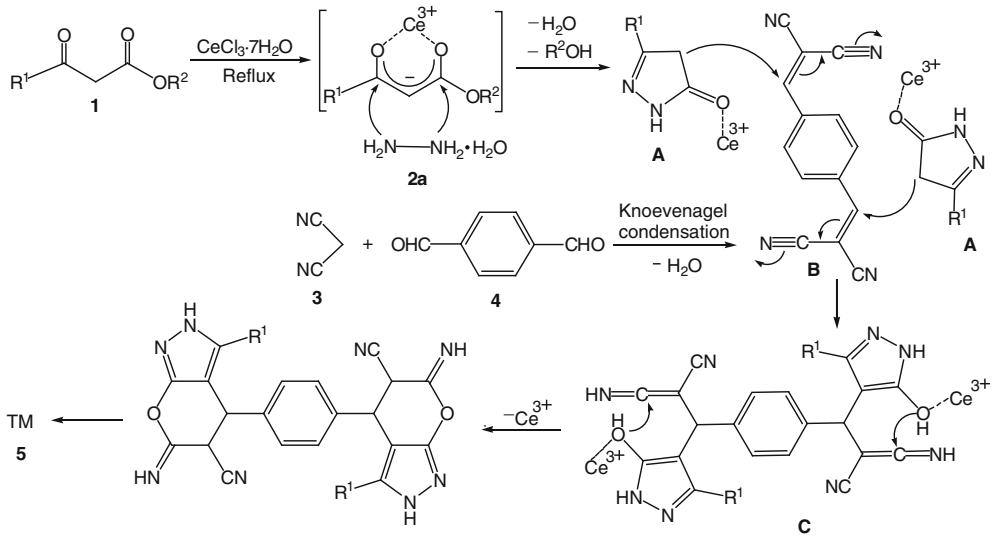
### *Synthesis of the multisubstituted bispyrano[2,3-**c**] pyrazole derivatives **5a–5f** and **6a–6f***

To a mixture of β-keto ester (**1**, 2.0 mmol) and hydrazine hydrate (85 %) or phenylhydrazine (**2**, 2.0 mmol) in 15 $cm^3$ ethanol were added terephthalaldehyde (**3**, 1.0 mmol) and malononitrile (**4**, 2.0 mmol), followed by $CeCl_3{\cdot}7H_2O$ (10 mol%). The reaction mixture was then refluxed for 20–60 min. After the reaction reached completion, the mixture was cooled and large amounts of a precipitate formed. The precipitate was filtered off and washed thoroughly with EtOH to give the desired product.

*4,4′-(1,4-Phenylene)bis(6-amino-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile)* (**5a**, $C_{22}H_{18}N_8O_2$) Light yellow crystals; yield 324 mg (76 %); m.p.: 300 °C; IR (KBr): $\bar{\nu}$ = 3,231, 3,120, 2,187, 1,641, 1,593, 1,489 $cm^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ = 1.74 (s, 6H, 2 $CH_3$), 4.57 (s, 2H, 2 CH), 6.84 (s, 4H, 2 $NH_2$), 7.11 (s, 4H, $C_6H_4$), 12.08 (s, 2H, 2 NH) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ = 9.58 (2C), 35.81 (2C), 57.04 (2C), 97.59 (2C), 120.64 (2C), 127.51 (4C), 135.47 (2C), 142.62 (2C), 154.60 (2C), 160.71 (2C) ppm; MS (ESI): *m*/*z* = 427 ($[M+H]^+$), 449 ($[M+Na]^+$); HR-MS (ESI): calcd for $C_{22}H_{18}N_8O_2$ ($[M+H]^+$) 427.1553, found 427.1556.

*4,4′-(1,4-Phenylene)bis(6-amino-3-ethyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile)* (**5b**, $C_{24}H_{22}N_8O_2$) White crystals; yield 359 mg (79 %); m.p.: >300 °C; IR (KBr): $\bar{\nu}$ = 3,479, 3,243, 3,115, 2,970, 2,195, 1,638, 1,603, 1,488 $cm^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ = 0.74 (t, 6H, 2 $CH_3$), 2.09–2.15 (m, 4H, 2 $CH_2$), 4.57 (s, 2H, 2 CH), 6.82 (s, 4H, 2 $NH_2$), 7.10 (s, 4H, $C_6H_4$), 12.10 (s, 2H, 2 NH) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ = 12.34

**Scheme 2**




A plausible one-pot reaction mechanism for the synthesis of compound **5**

(2C), 17.64 (2C), 35.90 (2C), 57.34 (2C), 96.90 (2C), 120.57 (2C), 127.51 (4C), 140.44 (2C), 143.16 (2C), 154.55 (2C), 160.50 ppm; MS (ESI): $m/z = 455$ ($[M+H]^+$), 477 ($[M+Na]^+$); HR-MS (ESI): calcd for $C_{24}H_{22}N_8O_2$ ($[M+H]^+$) 455.1866, found 455.1873.

*4,4′-(1,4-Phenylene)bis(6-amino-3-propyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile)* (**5c**, $C_{26}H_{26}N_8O_2$)
White crystals; yield 434 mg (90 %); m.p.: 238–240 °C; IR (KBr): $\overline{\nu} = 3{,}486$, 3,233, 3,111, 2,967, 2,198, 1,633, 1,594 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta = 0.59$ (t, 6H, 2 $CH_3$), 1.07–1.21 (m, 4H, 2 $CH_2$), 1.99–2.17 (m, 4H, 2 $CH_2$), 4.55 (s, 2H, 2 CH), 6.82 (s, 4H, 2 $NH_2$), 7.09 (s, 4H, $C_6H_4$), 12.09 (s, 2H, 2 NH) ppm; $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta = 13.28$ (2C), 20.83 (2C), 26.11 (2C), 36.00 (2C), 57.39 (2C), 97.23 (2C), 120.52 (2C), 127.48 (4C), 139.64 (2C), 143.12 (2C), 154.32 (2C), 160.49 (2C) ppm; MS (ESI): $m/z = 483$ ($[M+H]^+$), 505 $[M+Na]^+$; HR-MS (ESI): calcd for $C_{26}H_{26}N_8O_2$ ($[M+H]^+$) 483.2179, found 483.2166.

*4,4′-(1,4-Phenylene)bis(6-amino-3-isopropyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile)*
(**5d**, $C_{26}H_{26}N_8O_2$)
Light yellow crystals; yield 391 mg (81 %); m.p.: >300 °C; IR (KBr): $\overline{\nu} = 3{,}488$, 3,248, 3,107, 2,970, 2,877, 2,195, 1,638, 1,603 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta = 0.75$ (d, 6H, 2 $CH_3$), 1.04 (d, 6H, 2 $CH_3$), 2.49–2.52 (m, 2H, 2 CH), 4.57 (s, 2H, 2 CH), 6.79 (s, 4H, 2 $NH_2$), 7.08 (s, 4H, $C_6H_4$), 12.10 (s, 2H, 2 NH) ppm; $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta = 20.39$ (2C), 21.13 (2C), 24.91 (2C), 36.09 (2C), 57.73 (2C), 96.10 (2C), 120.52 (2C), 127.50 (4C), 143.50 (2C), 144.84 (2C), 154.62 (2C), 160.25 (2C) ppm; MS (ESI): $m/z = 483$ ($[M+H]^+$), 505 ($[M+Na]^+$); HR-MS (ESI): calcd for $C_{26}H_{26}N_8O_2$ ($[M+H]^+$) 483.2,179, found 483.2169.

*4,4′-(1,4-Phenylene)bis(6-amino-3-phenyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile)* (**5e**, $C_{32}H_{22}N_8O_2$)
Yellowish brown crystals; yield 414 mg (75 %); m.p.: >300 °C; IR (KBr): $\overline{\nu} = 3{,}251$, 3,130, 2,184, 1,641, 1,618, 1,499 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta = 4.82$ (s, 2H, 2 CH), 6.87 (s, 4H, 2 $NH_2$), 6.98–7.00 (m, 4H, $C_6H_4$), 7.13–7.25 (m, 10H, 2 $C_6H_5$) ppm; $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta = 18.40$ (2C), 36.49 (2C), 58.55 (2C), 97.30 (2C), 120.26 (2C), 126.19 (4C), 127.29 (4C), 128.45 (6C), 137.96 (2C), 143.19 (2C), 155.90 (2C), 159.95 (2C) ppm; MS (ESI): $m/z = 551$ ($[M+H]^+$), 573 ($[M+Na]^+$); HR-MS (ESI): calcd for $C_{32}H_{22}N_8O_2$ ($[M+H]^+$) 551.1866, found 551.1871.

*4,4′-(1,4-Phenylene)bis(6-amino-3-trifluoromethyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile)*
(**5f**, $C_{22}H_{12}F_6N_8O_2$)
White crystals; yield 453 mg (85 %); m.p.: >300 °C; IR (KBr): $\overline{\nu} = 3{,}245$, 3,122, 2,207, 1,639, 1,582, 1,494 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta = 0.64$ (t, 6H, 2 $CH_3$), 1.12–1.23 (m, 4H, 2 $CH_2$), 1.99–2.13 (m, 4H, 2 $CH_2$), 4.55 (s, 2H, 2 CH), 6.82 (s, 4H, 2 $NH_2$), 7.09 (s, 4H, $C_6H_4$), 12.09 (s, 2H, 2 NH) ppm; $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta = 51.05$ (2C), 73.04 (2C), 97.59 (2C), 116.52 (2C), 120.53 (q, $^1J_{CF} = 261$ Hz, 2 $CF_3$), 127.51 (4C), 137.47 (2C), 142.62 (2C), 154.20 (2C), 167.71 (2C) ppm; MS (ESI): $m/z = 535$ ($[M+H]^+$), 557 ($[M+Na]^+$); HR-MS (ESI): calcd for $C_{22}H_{12}F_6N_8O_2$ ($[M+H]^+$) 535.0987, found 535.0981.

*4,4′-(1,4-Phenylene)bis(6-amino-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile)*
(**6a**, $C_{34}H_{26}N_8O_2$)
White crystals; yield 433 mg (75 %); m.p.: 238–240 °C; IR (KBr): $\overline{\nu}$ = 3,474, 3,325, 3,260, 3,193, 2,194, 1,660, 1,595, 1,518 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ = 1.29 (s, 6H, 2 $CH_3$), 4.70 (s, 2H, 2 CH), 7.21 (s, 4H, 2 $NH_2$), 7.24–8.02 (m, 14H, $C_6H_4$ + 2 $C_6H_5$) ppm; $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ = 12.40 (2C), 51.54 (2C), 108.75 (2C), 112.28 (2C), 119.87 (2C), 126.06 (2C), 127.93 (4C), 128.64 (4C), 129.22 (4C), 137.41 (4C), 142.19 (2C), 143.67 (2C), 159.30 (2C) ppm; MS (ESI): *m/z* = 579 $[M+H]^+$; 601 ($[M+Na]^+$); HR-MS (ESI): calcd for $C_{34}H_{26}N_8O_2$ $[M+H]^+$ 579.2179, found 578.2171.

*4,4′-(1,4-Phenylene)bis(6-amino-3-ethyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile)*
(**6b**, $C_{36}H_{30}N_8O_2$)
White crystals; yield 460 mg (76 %); m.p.: 294–295 °C; IR (KBr): $\overline{\nu}$ = 3,466, 3,323, 3,192, 2,963, 2,196, 1,662, 1,594, 1,516 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ = 0.79 (t, 6H, 2 $CH_3$), 2.06–2.31 (m, 4H, 2 $CH_2$), 4.75 (s, 2H, 2 CH), 7.23 (s, 4H, 2 $NH_2$), 7.27–8.06 (m, 14H, $C_6H_4$ + 2 $C_6H_5$) ppm; $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ = 12.40 (2C), 18.69 (2C), 57.54 (2C), 107.85 (2C), 112.22 (2C), 119.76 (2C), 126.26 (2C), 127.83 (4C), 128.94 (4C), 129.32 (4C), 137.51 (4C), 143.09 (2C), 143.37 (2C), 159.69 (2C) ppm; MS (ESI): *m/z* = 607 ($[M+H]^+$), 629 ($[M+Na]^+$); HR-MS (ESI): calcd for $C_{36}H_{30}N_8O_2$ ($[M+H]^+$) 607.2492, found 607.2486.

*4,4′-(1,4-Phenylene)bis(6-amino-3-propyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile)*
(**6c**, $C_{38}H_{34}N_8O_2$)
Yellowish brown crystals; yield 456 mg (72 %); m.p.: 273–274 °C; IR (KBr): $\overline{\nu}$ = 3,466, 3,324, 3,194, 2,952, 2,193, 1,657, 1,592, 1,515 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ = 0.74 (t, 6H, 2 $CH_3$), 1.20–1.34 (m, 4H, 2 $CH_2$), 2.0–2.32 (m, 4H, 2 $CH_2$), 4.68 (s, 2H, 2 CH), 7.17 (s, 4H, 2 $NH_2$), 7.21–7.96 (m, 14H, $C_6H_4$ + 2 $C_6H_5$) ppm; $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ = 13.58 (2C), 20.56 (2C), 28.79 (2C), 36.54 (2C), 58.43 (2C), 98.15 (2C), 119.92 (2C), 126.03 (4C), 127.87 (4C), 129.20 (4C), 137.49 (4C), 142.55 (2C), 143.71 (2C), 148.96 (2C), 159.10 (2C) ppm; MS (ESI): *m/z* = 635 ($[M+H]^+$), 657 ($[M+Na]^+$); HR-MS (ESI): calcd for $C_{38}H_{34}N_8O_2$ ($[M+H]^+$) 635.2,805, found 634.2817.

*4,4′-(1,4-Phenylene)bis(6-amino-3-isopropyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile)*
(**6d**, $C_{38}H_{34}N_8O_2$)
White crystals; yield 475 mg (75 %); m.p.: >300 °C; IR (KBr): $\overline{\nu}$ = 3,462, 3,325, 3,192, 2,964, 2,197, 1,663, 1,594, 1,514 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ = 0.82 (d, 6H, 2 $CH_3$), 0.99 (d, 6H, 2 $CH_3$), 1.97–2.41 (m, 2H, 2 CH), 4.70 (s, 2H, 2 CH), 7.07 (s, 4H, 2 $NH_2$), 7.07–7.96 (m, 14H, $C_6H_4$ + 2 $C_6H_5$) ppm; $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ = 20.25 (2C), 21.39 (2C), 26.72 (2C), 36.34 (2C), 59.22 (2C), 97.31 (2C), 119.50 (2C), 120.10 (4C), 127.85 (4C), 129.12 (4C), 137.63 (4C), 142.86 (2C), 143.94 (2C), 153.81 (2C), 158.93 (2C) ppm; MS (ESI): *m/z* = 635 ($[M+H]^+$), 657 ($[M+Na]^+$); HR-MS (ESI): calcd for $C_{38}H_{34}N_8O_2$ ($[M+H]^+$) 635.2805, found 634.2815.

*4,4′-(1,4-Phenylene)bis(6-amino-1,3-diphenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile)* (**6e**, $C_{44}H_{30}N_8O_2$)
Yellowish brown crystals; yield 547 mg (78 %); m.p.: 260–261 °C; IR (KBr): $\overline{\nu}$ = 3,459, 3,320, 3,201, 3,059, 2,192, 1,653, 1,591, 1,511 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ = 4.62 (s, 2H, 2 CH), 6.79 (s, 4H, 2 $NH_2$), 7.05–7.97 (m, 20H, 4 $C_6H_5$), 7.08 (s, 4H, $C_6H_4$), 12.10 (s, 2H, 2 NH) ppm; $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ = 40.75 (2C), 58.22 (2C), 94.31 (2C), 116.50 (2C), 121.83 (4C), 127.45 (2C), 127.89 (4C), 128.15 (2C), 128.55 (4C), 129.12 (4C), 131.18 (2C), 132.63 (4C), 140.16 (4C), 149.94 (2C), 154.81 (2C), 160.93 (2C) ppm; MS (ESI): *m/z* = 703 ($[M+H]^+$), 725 ($[M+Na]^+$); HR-MS (ESI): calcd for $C_{44}H_{30}N_8O_2$ ($[M+H]^+$) 703.2492, found 702.2482.

*4,4′-(1,4-Phenylene)bis(6-amino-3-trifluoromethyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile)*
(**6f**, $C_{34}H_{20}F_6N_8O_2$)
Yellow crystals; yield 521 mg (76 %); m.p.: 259–261 °C; IR (KBr): $\overline{\nu}$ = 3,498, 3,248, 3,130, 2,986, 2,898, 2,190, 1,625, 1,602 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ = 6.74–7.21(m, 10H, 2 $C_6H_5$), 7.65 (s, 4H, $C_6H_5$), 7.86 (s, 2H, $NH_2$), 10.40 (s, 2H, 2 NH) ppm; $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ = 44.41 (2C), 58.54 (2C), 98.75 (2C), 116.28 (2C), 121.87 (4C), 122.67 (q, $^1J_{CF}$ = 265 Hz, 2 $CF_3$), 126.06 (4C), 127.93 (4C), 129.04 (2C), 132.51 (4C), 140.15 (4C), 159.30 (2C) ppm; MS (ESI): *m/z* = 687 ($[M+H]^+$), 709 ($[M+Na]^+$); HR-MS (ESI): calcd for $C_{34}H_{20}F_6N_8O_2$ ($[M+H]^+$) 687.1613, found 686.1605.

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