Supporting Information
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A Green One-Pot Synthesis of vic-Amidino (Hetero)aromatic Acids from 1,2-Dinitriles

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SUPPORTING INFORMATION

Experimental Section

1H and 13C NMR spectra copies of synthesized compounds
X-ray diffraction data for compounds 5e, 5c, 17, 20, 21a, 4

Experimental Section

Materials and Instrumentation

General: Melting points were determined on a Boetius microscope hot plate apparatus. Elemental analyses (C, H, N) were conducted using the Vario Micro Cube. Mass spectra were recorded on an Agilent 1100 LC/MSD SL instrument by chemical ionization (CI). 1H and 13C NMR spectra (in D2O or DMSO-d6, 25 °C) were measured on a Mercury Varian-400 (400 MHz for 1H, 100 MHz for 13C) and a Bruker Avance 400 (400 MHz 1H, 100 MHz for 13C) instruments with tetramethylsilane as an internal reference. A drop of conc. HCl was added to D2O solutions of compounds 5d and 5e for a better solubility. IR spectra were recorded with a Perkin–Elmer Spectrum BX FTIR Spectrometer as KBr disk. TLC analyses were carried out on silica gel coated aluminium plates (Merck) in CHCl3/MeOH, 9:1 and spots were visualized with UV light.
Starting dinitriles were synthesized by known methods: pyridine-2,3-dicarbonitrile 10, pyrazine-2,3-dicarbonitrile 12, quinoxaline-2,3-dicarbonitrile 15, 1H-imidazole-4,5-dicarbonitrile 18.

3-methoxybenzene-1,2-dicarbonitrile (7)

was prepared according to the procedure for the synthesis of 4-methoxybenzene-1,2-dicarbonitrile.5 To the solution of 3-nitrophthalonitrile 6 (3.46 g, 20 mmol) in DMF (25 mL) K2CO3 (5.52 g, 40 mmol) and MeOH (5 mL) were added. After stirring the suspension for 30 h at ambient temperature, 500 mL of distilled water were added with continued stirring. The precipitate was collected by filtration, washed with distilled water, dried and crystallized from MeOH (20 mL).

Off-white needle-shaped crystals; yield: 2.72 g (86%), mp 175-176 °C (Lit. 178-179 °C).

IR (KBr), cm⁻¹: 3394, 3090, 2228 (CN), 1588, 1540, 1480.

1H NMR (400 MHz, DMSO-d6, 25 °C): δ = 4.02 (s, 3H, OCH3), 7.56 (d, J = 7.6 Hz, 1H, HAr), 7.61 (d, J = 8.8 Hz, 1H, HAr), 7.83 (2×d, J1 = 7.6 Hz, J2 = 8.8 Hz, 1H, H5).

13C NMR (100 MHz, DMSO-d6, 25 °C): δ = 162.3, 136.5, 126.3, 118.4, 116.4, 116.0, 114.3, 103.4, 57.8.

LCMS: m/z (%) = 159 (100) [M+H]⁺.

3-morpholin-4-ylbenzene-1,2-dicarbonitrile (9)

was prepared according to7 (Method D): To the solution of 3-nitrophthalonitrile 6 (1.73 g, 10 mmol) in DMF (10 mL) was added morpholine (4.1 g, 40 mmol). The temperature was raised to 50 °C and maintained for 1.5 h. The reaction mixture was poured into ice-water, the resultant precipitate was filtered off, dried, and crystallized from MeOH (20 mL).

Maize yellow crystals; yield: 1.77 g (83 %), mp 169–170 °C (Lit. 168-170 °C).

IR (KBr), cm⁻¹: 3448, 2980, 2954, 2850, 2226 (CN), 1582, 1466, 1450.

1H NMR (400 MHz, DMSO-d6, 25 °C): δ = 3.25 (m, 4H), 3.76 (m, 4H), 7.51 (d, J = 8.8 Hz, 1H, HAr), 7.60 (d, J = 6.8 Hz, 1H, HAr), 7.76 (2×d, J1 = 8.8 Hz, J2 = 6.8 Hz, 1H, H5).

13C NMR (100 MHz, DMSO-d6, 25 °C): δ = 156.5, 135.5, 126.9, 124.8, 116.9, 116.8, 116.2, 106.5, 66.7, 51.7.

LCMS: m/z (%) = 214 (100) [M+H]⁺.
Synthesis of Amidino Acids 5a, 5c-e; General Procedure

**Method A:** To a solution of NaOH (0.4 g, 10 mmol) in aqueous MeOH (25 mL, MeOH/H₂O, 3:2) 1,2-dinitrile (10 mmol) was added and the obtained suspension was brought to reflux with stirring. The resulting clear solution was refluxed for 15-20 min before the elimination of ammonia began. Then the hot reaction mixture, if necessary, was filtered through cotton wool in order to separate the phthalocyanine impurities. The solution was left to cool at room temperature overnight during which time well firmed crystals were formed. The crystals were filtered off, washed with MeOH (10 mL) and dried in air. Acidification of the mother liquor with HOAc (≈1 mL) to neutral pH produced an additional portion of target product. Molecular ions m/z of acids 5a,e-e were not detected by LC/MS.

**Method B:** To a freshly prepared solution of MeONa obtained by dissolving sodium metal (0.23 g, 10 mmol) in MeOH (15 mL) 1,2-dinitrile (10 mmol) was added. The resulting suspension was stirred at ambient temperature until TLC showed no starting nitrile. The obtained solution or suspension was diluted with distilled water (10 mL), brought to reflux with stirring and kept under reflux for 20-25 min before the elimination of ammonia began. Then the hot reaction mixture, if necessary, was filtered through cotton wool in order to separate the phthalocyanine impurities. The solution was left to cool at room temperature overnight during which time the crystalline solid was formed. The crystals were filtered off, washed with MeOH (10 mL) and dried in air. Acidification of the mother liquor with HOAc (≈1 mL) to neutral pH produced an additional portion of target product.

**2-carbamimidoylbenzoic Acid (5a) (Method A)**

Colorless crystals of methanol solvate (appr. 1:0.7) which lost methanol on standing in air; yield 1.34 g (72%); mp 179-180 °C.

IR (KBr), cm⁻¹: 3395, 3232, 3092, 2954, 2829, 1667, 1579, 1538, 1468, 1437, 1384.

¹H NMR of methanol solvate (400 MHz, D₂O, 25 °C): δ = 3.32 (s, 2H, MeOH), 7.52 (d, J = 7.6 Hz, Jₘ = 0.8 Hz, 1H, H₃), 7.56 (dd, J₁ = 7.6 Hz, J₂ = 7.6 Hz, Jₘ = 1.2 Hz, 1H, H₄), 7.63 (dd, J₁ = 7.6 Hz, J₂ = 7.6 Hz, Jₘ = 1.2 Hz, 1H, H₅), 7.73 (d, J = 7.6 Hz, 1H, H₆).

¹H NMR (400 MHz, D₂O, 25 °C): δ = 7.72-7.80 (m, 2H, H₃+H₄), 7.85 (dd, J₁ = 7.2 Hz, J₂ = 7.2 Hz, 1H, H₅), 7.93 (d, J = 7.6 Hz, 1H, H₆).

¹³C NMR (100 MHz, D₂O, 25 °C): δ = 171.3 (COOH), 166.9 (C(NH₂)=NH), 135.2 (C₁), 129.8, 127.7, 126.7, 125.8 (C₂), 125.7.


**2-carbamimidoyl-3-methoxybenzoic Acid (5c) (Method B):**

Colorless crystals of methanol solvate (appr. 1:1); yield 1.40 g (62%); mp 190–191 °C (subl.).
IR (KBr), cm\(^{-1}\): 3388, 3069, 1686, 1615, 1579, 1522, 1466, 1432, 1377.

\(^1\)H NMR (400 MHz, D\(_2\)O, 25 °C): \(\delta = 3.33\) (s, 3H, CH\(_3\)OH), 3.89 (s, 3H, OCH\(_3\)), 7.25 (d, \(J = 8.4\) Hz, 1H, H\(_{Ar}\)), 7.36 (d, \(J = 8.0\) Hz, 1H, H\(_{Ar}\)), 7.58 (dd, \(J_1 = 8.0\) Hz, \(J_2 = 8.4\) Hz, 1H, H\(_3\)).

\(^1\)C NMR (100 MHz, D\(_2\)O, 25 °C): \(\delta = 175.2\) (COOH), 168.5 (C(NH\(_2\))=NH), 157.9, 140.3, 134.8, 123.1, 119.4, 115.8, 58.5 (CH\(_3\)O), 50.9 (CH\(_3\)OH).

Anal. Calcd for C\(_9\)H\(_{10}\)N\(_2\)O\(_3\)×CH\(_3\)OH: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.30; H, 6.31; N, 12.76.

2-carbamimidoyl-3-morpholin-4-ylbenzoic Acid (5d) (Method B)

Pale yellow crystals of methanol solvate (appr. 1:1); yield 1.71 g (61%); mp 194–195 °C (dec.).

IR (KBr), cm\(^{-1}\): 3360, 3244, 3064, 2962, 2924, 2858, 2826, 1688, 1610, 1574, 1520, 1430, 1386.

\(^1\)H NMR (400 MHz, D\(_2\)O, 25 °C): \(\delta = 3.10\) (m, 4H, H\(_{morph}\)), 3.45 (s, 4H, MeOH), 3.95 (m, 4H, H\(_{morph}\)), 7.55 (d, \(J = 7.6\) Hz, 1H, H\(_4\)), 7.60 (d, \(J = 7.6\) Hz, 1H, H\(_6\)).

\(^1\)H NMR (400 MHz, D\(_2\)O+HCl, 25 °C): \(\delta = 2.88\) (m, 4H, H\(_{morph}\)), 3.20 (s, 2H, MeOH), 3.72 (m, 4H, H\(_{morph}\)), 7.58-7.64 (m, 2H, H\(_4\), H\(_5\)), 7.82 (d, \(J = 6.4\) Hz, 1H, H\(_6\)).

\(^1\)C NMR (100 MHz, D\(_2\)O+HCl, 25 °C): \(\delta = 168.0\) (COOH), 167.0 (C(NH\(_2\))=NH), 150.6, 132.8, 129.3, 128.2, 127.7, 127.6, 66.9, 52.7, 48.8.

Anal. Calcd for C\(_{12}\)H\(_{15}\)N\(_3\)O\(_3\)×CH\(_3\)OH: C, 55.50; H, 6.81; N, 14.94. Found: C, 55.84; H, 6.78; N, 14.63.

3-carbamimidoylpyridine-2-carboxylic Acid (5e) (Method B)

Colorless crystals; yield 1.14 g (69%); mp 250–251 °C.

IR (KBr), cm\(^{-1}\): 3016, 2360, 1706, 1583, 1565, 1526, 1446, 1428, 1377.

\(^1\)H NMR (400 MHz, D\(_2\)O, 25 °C): \(\delta = 7.61\) (dd, \(J_1 = 7.6\) Hz, \(J_2 = 7.6\) Hz, 1H, H\(_5\)), 8.04 (d, \(J = 8\) Hz, \(J_M = 1.2\) Hz, 1H, H\(_4\)), 8.70 (d, \(J = 4.4\) Hz, 1H, H\(_6\)).

\(^1\)C NMR (100 MHz, D\(_2\)O, 25 °C): \(\delta = 170.3\), 169.0, 162.5, 153.6, 139.6, 133.0, 126.7.

\(^1\)H NMR (400 MHz, D\(_2\)O+HCl, 25 °C): \(\delta = 8.03-8.06\) (m, 1H, H\(_3\)), 8.49 (d, \(J = 7.2\) Hz, 1H, H\(_4\)), 8.80 (d, \(J = 4\) Hz, 1H, H\(_6\)).

\(^1\)C NMR (100 MHz, D\(_2\)O+HCl, 25 °C): \(\delta = 164.0\) (COOH), 161.7 (C(NH\(_2\))=NH), 146.6, 144.6, 143.1, 129.2, 128.2.

Anal. Calcd for C\(_7\)H\(_7\)N\(_3\)O\(_2\): C, 50.91; H, 4.27; N, 25.44. Found: C, 51.28; H, 4.34; N, 25.75.

Sodium 3-carbamoylquinoxaline-2-carboxylate Pentahydrate (17)
To freshly prepared solution of MeONa obtained by dissolving sodium metal (0.035 g, 1.5 mmol) in MeOH (7 mL) quinoxaline-2,3-dicarbonitrile 15 (0.270 g, 1.5 mmol) was added. The suspension was stirred until no starting nitrile was observed on TLC. The obtained orange solution was diluted with distilled water (3 mL), brought to reflux with stirring and kept under reflux for 10 min before the elimination of ammonia began. The solution was left to cool at room temperature overnight and acidified with AcOH (≈1 mL) to neutral reaction. After 2 days light brown crystals of 17 were filtered and dried in air.

Light brown crystals; yield: 0.106 g (24%), mp 260-261°C.

$^1$H NMR (400 MHz, DMSO-$d_6$, 25 ºC): $\delta$ = 7.76-7.85 (m, 3H, 5,8-H$_{Ar}$+NH), 7.96-8.04 (m, 2H, 6,7-H$_{Ar}$), 8.24 (br s, 1H, NH).

IR (KBr), cm$^{-1}$: 3463, 1700, 1653, 1579, 1469, 1442, 1397.

$^{13}$C NMR (100 MHz, DMSO-$d_6$, 25 ºC): $\delta$ = 170.1 (COO$^-$), 169.3 (CONH$_2$), 153.2, 147.9, 141.4, 139.8, 131.6, 130.8, 129.5, 129.3.

Anal. Calcd for C$_{10}$H$_6$N$_3$NaO$_3$$\times$5H$_2$O: C, 36.48; H, 4.90; N, 12.76. Found: C, 36.10; H, 5.07; N, 12.93.

LCMS: m/z (%) not detected.

Attempted of 1H-imidazole-4,5-dicarbonitrile (18) Hydrolysis by Method B

To freshly prepared solution of MeONa obtained by dissolving sodium metal (0.046 g, 2 mmol) in MeOH (6 mL) 1H-imidazole-4,5-dicarbonitrile 18 (0.236 g, 2 mmol) was added with stirring. The obtained clear solution was diluted with distilled water (4 mL), brought to reflux with stirring and kept under reflux for 15 min before the elimination of ammonia began. The solution was left to cool at room temperature overnight and acidified with AcOH (5 mL) to neutral reaction. After 3 days a few light beige plate crystals were isolated which were identified by X-ray diffraction as methyl ester of 4-cyano-1H-imidazol-5-carboxylic acid 20. The obtained filtrate was evaporated at room temperature. To the residual material water (5 mL) and then 1M HCl (≈2 mL) to slightly acidic pH were added. The white precipitate of 1H-imidazole-4,5-dicarboxamide 19 was filtered and dried in air.

LCMS revealed molecular ion of m/z = 155 [M+H]$^+$. 

White solid; yield: 0.268 g (87%). Mp > 300 ºC (Lit. 300 ºC$^9$).

$^1$H NMR (400 MHz, DMSO-$d_6$, 25 ºC): $\delta$ = 7.46 (br s, 1H, NH), 7.60-7.64 (m, 3H, CH+NH$_2$), 10.44 (br s, 1H, NH), 13.00 (br s, 1H, NH$_{im}$).

$^{13}$C NMR (100 MHz, DMSO-$d_6$, 25 ºC): $\delta$ = 163.2 (CONH$_2$), 160.9 (CONH$_2$), 140.2, 137.0, 136.6 (CH).

Anal. Calcd for C$_5$H$_6$N$_4$O$_2$: C, 38.96; H, 3.92; N, 36.35. Found: C, 38.43; H, 4.01; N, 36.61.
Synthesis of Amidino Acids Hydrochlorides 21a,c,e. General Procedure

Dry HCl was bubbled through the stirred suspension of powdered amidino acid (1 mmol) in dry Et₂O (5 mL) in an ice bath for 1-2 h. The solid amidino acid hydrochloride was filtered, washed with dry cold ether (33 mL) and dried.

2-carbamimidoylbenzoic Acid Hydrochloride (21a)

Colorless crystals; yield: 0.195 g (97%); mp 163–164 ºС.
IR (KBr), cm⁻¹: 3392, 3330, 3070, 2784, 2724, 2560, 1704, 1680, 1598.
¹H NMR (400 MHz, DMSO-d₆, 25 ºС): δ = 7.54 (d, J = 7.6 Hz, Jₘ= 1.6 Hz, 1H, H₃), 7.70 τa 7.74 (2×dd, J = 7.6 Hz, Jₘ= 1.6 Hz, 2H, H₄+H₅), 8.06 (d, J = 7.6 Hz, Jₘ= 1.2 Hz, 1H, H₆), 9.29 and 9.34 (2s, 2×2H, NH₂ and NH₂⁺), 13.43 (br s, OH).
¹³C NMR (100 MHz, DMSO-d₆, 25 ºС): δ = 168.6 (COOH), 166.4 (C(NH₂)=NH₂⁺), 132.9, 131.9, 131.8, 130.9, 130.2, 129.6.
Anal. Calcd for C₈H₉ClN₂O₂: C, 47.89; H, 4.52; N, 13.96. Found: C, 47.62; H, 4.60; N, 14.13.
LCMS: m/z (%) = 165 (100) [M-Cl]⁺.

2-carbamimidoyl-3-methoxybenzoic Acid Hydrochloride (21c)

Colorless crystals; yield: 0.226 g (98%); mp 158–159 ºС.
IR (KBr), cm⁻¹: 3393, 3328, 3097, 2869, 2565, 1705, 1680, 1598, 1562, 1473, 1457, 1429, 1375, 1280, 1227, 1208.
¹H NMR (400 MHz, DMSO-d₆, 25 ºС): δ = 3.87 (s, 3H, OCH₃), 7.48 (d, J = 8.0 Hz, 1H, H₆), 7.61-7.68 (m, 2H, H₄+H₅), 9.18 and 9.25 (2s, 2×2H, NH₂ τa NH₂⁺), 13.51 (br s, 1H, COOH).
¹³C NMR (100 MHz, DMSO-d₆, 25 ºС): δ = 166.2 (COOH), 165.7 (C(NH₂)=NH₂⁺), 157.0, 132.7, 131.2, 122.5, 120.8, 116.7, 57.1.
Anal. Calcd for C₉H₁₀ClN₂O₃: C, 46.87; H, 4.81; N, 12.15. Found: C, 46.58; H, 4.90; N, 12.36.
LCMS: m/z (%) = 195 (100) [M-Cl]⁺.

3-carbamimidoyl-2-pyridynecarboxylic Acid Hydrochloride (21e)

Colorless crystals; yield: 0.197 g (98%); mp 165–167 ºС (dec.).
IR, cm⁻¹: 3314, 3067, 2931, 1728, 1680, 1588, 1569, 1434, 1382.
$^1$H NMR (400 MHz, DMSO-$d_6$, 25 ºС): $\delta$ = 7.79 (dd, $J_1$ = 5.2 Hz, $J_2$ = 6.8 Hz, 1H, H$_3$), 8.11 (d, $J$ = 7.2 Hz, 1H, H$_4$), 8.86 (d, $J$ = 3.2 Hz, 1H, H$_6$), 9.43 and 9.51 (2s, 2×2H, NH$_2$ and NH$_2^+$).

$^{13}$C NMR (100 MHz, DMSO-$d_6$, 25 ºС): $\delta$ = 167.0 (COOH), 165.7 (C(NH$_2$)=NH$_2^+$), 152.0, 147.1, 138.5, 128.2, 126.8.

Anal. Calcd for C$_7$H$_8$ClN$_3$O$_2$: C, 41.70; H, 4.00; N, 20.84. Found: C, 41.39; H, 4.14; N, 21.02.

LCMS: $m/z$ (%) = 167 (100) [M-Cl]$^+$. 

**Synthesis of Amidino Acids Esters Hydrochlorides 22a,b. General Procedure**

To a suspension of 2-carbamimidoylbenzoic acid 5a (0.164 g, 1 mmol) in corresponding dry alcohol (10 mL) an excess of SOCl$_2$ (0.4 mL, 6 mmol) was added dropwise with vigorous stirring. The resulting mixture was refluxed for 1-3 h. The solvent was removed under reduced pressure, and the oily residue was treated with ether (5 mL) to give a crude ester hydrochloride which filtered off, washed with ether (2×5 mL) and dried.

**Methyl 2-carbamimidoylbenzoate Hydrochloride (22a)**

Colorless crystals; yield: 0.211 g (98%); mp 166–167 ºС.

IR, cm$^{-1}$: 3230, 3062, 1720, 1669, 1600, 1583, 1474, 1431, 1290.

$^1$H NMR (400 MHz, DMSO-$d_6$, 25 ºС): $\delta$ = 3.89 (s, 3H, OCH$_3$), 7.59 (d, $J$ = 7.2 Hz, 1H, H$_3$), 7.74 and 7.79 (2×d, $J_1$ = 7.6 Hz, $J_2$ = 7.6 Hz, 2H, H$_4$+H$_5$), 8.05 (d, $J$ = 7.2 Hz, 1H, H$_6$), 9.39 and 9.45 (2s, 2×2H, NH$_2$ and NH$_2^+$).

$^{13}$C NMR (100 MHz, DMSO-$d_6$, 25 ºС): $\delta$ = 168.2 (COOH), 165.4 (C(NH$_2$)=NH$_2^+$), 133.4, 132.1, 131.6, 130.7, 129.9, 128.9, 53.1.


LCMS: $m/z$ (%) = 179 (100) [M-Cl]$^+$. 

**Ethyl 2-carbamimidoylbenzoate Hydrochloride (22b)**

Colorless crystals; yield: 0.220 g (97%); mp 164–165 ºС.

IR, cm$^{-1}$: 3352, 3207, 3001, 1700, 1675, 1600, 1580, 1526, 1476, 1445, 1374, 1307.

$^1$H NMR (400 MHz, DMSO-$d_6$, 25 ºС): $\delta$ = 1.39 (t, $J$ = 7.2 Hz, 3H, CH$_3$), 4.34 (q, $J$ = 7.2 Hz, 2H, CH$_2$), 7.57 (d, $J$ = 7.2 Hz, $J_m$ = 1.2 Hz, 1H, H$_3$), 7.72 and 7.77 (2×d, $J_1$ = 7.6 Hz, $J_2$ = 7.6 Hz, 2×d, $J_1$ = 7.6 Hz, $J_2$ = 7.6 Hz), $J_m$ = 1.6 Hz, 2H, H$_4$+H$_5$), 8.04 (d, $J$ = 7.2, 1H, H$_6$), 9.29 and 9.42 (2s, 2×2H, NH$_2$ and NH$_2^+$).
13C NMR (100 MHz, DMSO-d$_6$, 25 °C): $\delta = 168.3$ (COOH), 165.1 (C(NH$_2$)=NH$_2$), 133.5, 132.3, 131.8, 130.9, 129.9, 129.3, 62.2, 14.5.

Anal. Calcd for C$_{10}$H$_{13}$ClN$_2$O$_2$: C, 52.52; H, 5.73; N, 12.25. Found: C, 52.28; H, 5.83; N, 12.44.

LCMS: m/z (%) = 193 (100) [M-Cl]+.

**Alternative Procedure for 22a**

Dry HCl was bubbled through the stirred suspension of powdered amidino acid 5a (0.164 g, 1 mmol) in dry MeOH (10 mL) at ambient temperature. The solution got warmed up and the crystals 5a got dissolved completely. After stirring for 1 h at ambient temperature, the methanol was removed under reduced pressure, and the oily residue was treated with ether (5 mL) to give a crude product 22a which filtered off, washed with ether (2×5 mL) and dried.

**3-amino-1H-isoindole-1-one (4)**

To a solution of methyl 2-carbamimidoylbenzoate hydrochloride 22a (0.215 g, 1 mmol) in MeOH (5 mL) was added triethylamine (1.4 mL, 1 mmol) or 10% aqueous NaHCO$_3$ (1 mL). The reaction mixture was stirred at ambient temperature until TLC showed no starting ester. The solution was then evaporated under reduced pressure to a volume of about 2 mL. After cooling to 0 °C the crystalline precipitate 4 was filtered, washed with MeOH (1 mL) and dried.

White crystalline powder; yield: 0.141 g (96%); mp 201-202 °C (Lit. 203 °C$^{10}$).

IR, cm$^{-1}$: 3262, 3054, 2966, 2754, 1722, 1672, 1612, 1594, 1536, 1463, 1440.

1H NMR (400 MHz, DMSO-d$_6$, 25 °C): $\delta = 7.64$-7.73 (m, 3H, H$_{Ar}$), 8.01 (d, $J = 5.6$ Hz, 1H, H$_{Ar}$), 9.61 and 10.37 (2 br s, 2×1H, 2NH).

13C NMR (100 MHz, DMSO-d$_6$, 25 °C): $\delta = 173.7$ (NCO), 165.3 (C(NH)=NH), 134.2, 133.2, 133.1, 132.7, 122.8, 122.3.

LCMS: m/z (%) = 147 (100) [M+H]$^+$. 

**4-aminophthalazin-1(2H)-one (24)**

To a suspension of 2-carbamimidoylbenzoic acid 5a (0.164 g, 1 mmol) in MeOH (5 mL) an excess of hydrazine hydrate (0.1 g, 2 mmol) was added. The reaction mixture was stirred at ambient temperature until complete dissolution and disappearance by TLC analysis of the starting acid 5a. The methanol was removed under reduced pressure to a volume of about 2 mL. The residue was underwent repeated addition and evaporation of MeOH portion (5 mL). After standing overnight, the mixture deposited colorless needles of 24 which filtered off, washed with hexane (2×5 mL) and dried.

Colorless needle-shaped crystals; yield 0.161 g (97%). mp 269-270 °C (Lit. 268-269 °C$^{11}$).
IR (KBr), cm\(^{-1}\): 3305, 3256, 3164, 1648, 1598.

\(^1\)H NMR (400 MHz, DMSO-\(d_6\), 25 °C): \(\delta = 5.75\) (s, 2H, NH\(_2\)), 7.74 (2×d, \(J_1 = 7.2\) Hz, \(J_2 = 7.6\) Hz, 1H, H\(_6\)), 7.81 (2×d, \(J_1 = 8.0\) Hz, \(J_2 = 7.2\) Hz, 1H, H\(_7\)), 8.01 (d, \(J = 7.6\) Hz, 1H, H\(_3\)), 8.20 (d, \(J = 7.6\) Hz, 1H, H\(_8\)), 11.38 (s, 1H, NH).

\(^13\)C NMR (100 MHz, DMSO-\(d_6\), 25 °C): \(\delta = 158.6, 146.7, 133.2, 131.7, 128.8, 126.6, 125.4, 124.4\).

LCMS: m/z (%) = 162 (100) [M+H]\(^+\).

3-(hydroxyimino)-2,3-dihydro-1\(H\)-isoindol-1-one (25)

To a solution of \(\text{NH}_2\text{OH.HCl}\) (0.084 g, 1.2 mmol) in MeOH (5 mL) was added triethylamine (1.7 mL, 1.2 ммоль) and after a short stirring acid \(5a\) (0.164 g, 1 mmol). The suspension was stirred overnight. Then the reaction mixture was evaporated under reduced pressure to a volume of about 2 mL. After cooling to ambient temperature, a precipitate of the product 25 was filtered, washed with MeOH (2×2 mL) and dried.

Colorless crystalline powder; yield 0.155 g (96%); mp 260-261 °C (dec.) (Lit. 257-258 °C\(^1\))

IR (KBr), cm\(^{-1}\): 3210, 2952, 1706, 1674.

\(^1\)H NMR (400 MHz, DMSO-\(d_6\), 25 °C): \(\delta = 7.58-7.75\) (m, 4H, H\(_4\)-H\(_7\)), 11.13 (s, 1H, NH), 11.29 (s, 1H, OH).

\(^13\)C NMR (100 MHz, DMSO-\(d_6\), 25 °C): \(\delta = 167.5\) (N\(\text{СО}\)), 145.0 (C(NH)=NOH), 134.5, 133.5, 131.0, 130.9, 123.6, 120.8.

LCMS: m/z (%) = 163 (100) [M+H]\(^+\).

2-(4,5-dihydro-1\(H\)-imidazol-2-yl)benzoic acid (26)

To a suspension of 2-carbamimidoylbenzoic acid \(5a\) (0.328 g, 2 mmol) in EtOH (10 mL) was added an excess of 70% ethylenediamine solution in water (1.5 mL, 18 mmol). This reaction mixture was refluxed until no more ammonia gas was fixed by pH paper. The obtained clear solution was evaporated under reduced pressure to a volume of about 5 mL and acidified with a few drops of 10M HCl to neutral pH with stirring. After standing for 2 h, fine colorless crystals were formed and separated by filtration, washed with EtOH (2 mL) and dried.

Colorless crystals of hydrate (1:1); yield: 0.277 g (73 %); mp 222–223 °C.

IR (KBr), cm\(^{-1}\): 3382, 3218, 3106, 2944, 2896, 2686, 1628, 1604, 1577, 1556, 1380, 1286.

\(^1\)H NMR (400 MHz, D\(_2\)O, 25 °C): \(\delta = 4.07\) (s, 4H, CH\(_2\)), 7.55 (d, \(J = 7.6\) Hz, 1H, H\(_3\)), 7.59 (2×d, \(J_1 = 7.6\) Hz, \(J_2 = 7.2\) Hz, 1H, H\(_4\)), 7.68 (2×d, \(J_1 = 7.2\) Hz, \(J_2 = 7.2\) Hz, 1H, H\(_5\)), 7.76 (d, \(J = 7.2\) Hz, 1H, H\(_6\)).

\(^13\)C NMR (100 MHz, D\(_2\)O, 25 °C): \(\delta = 173.6\) (COOH), 168.7 (C(NH)=NH), 138.0, 132.8, 130.1, 129.0, 128.4, 122.0, 45.0 (2CH\(_2\)).
Anal. Calcd for C_{10}H_{10}N_{2}O_{2}×H_{2}O: C, 57.68; H, 5.81; N, 13.45. Found: C, 58.03; H, 6.19; N, 13.80.

LCMS: m/z (%) = 191 (100) [M+H]^+.

References

$5a$, $^1H$ NMR, 400 MHz, D$_2$O
$\text{Sa (after drying), }^{13}\text{C NMR, 100 MHz, D}_2\text{O}$

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**Solvent:** D2O  
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**TE:** 302 K  
**AQ:** 1.20 sec, RD: 0.00 sec  
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$^7$, $^{13}$C NMR, 100 MHz, DMSO[D$_6$]
$5c$, $^1H$ NMR, 400 MHz, $D_2O$
$\text{MeOH}$

$5c$, $^{13}$C NMR, 100 MHz, D$_2$O

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13C OBSERVE
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O

NH

NH$_2$

OH
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Parameter file, TOPSPIN□□Version 2.1
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Parameter file, TOPSPIN □□ Version 2.1□
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![NMR spectrum image]

**Table**

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$5e, \text{ }^{13}\text{C NMR, 100 MHz, D}_2\text{O}$

$5e, \text{ }^1\text{H NMR, 400 MHz, D}_2\text{O}+\text{HCl}$
$^{13}$C NMR, 100 MHz, D$_2$O+HCl

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19, $^{13}$C NMR, 100 MHz, DMSO[D$_6$]
21a, $^1$H NMR, 400 MHz, DMSO[D$_6$]
21a, $^{13}$C NMR, 100 MHz, DMSO[$D_6$]
$21c$, $^{13}$C NMR, 100 MHz, DMSO[D$_6$]
21e, $^1$H NMR, 400 MHz, DMSO[D$_6$]
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23a, $^1$H NMR, 400 MHz, DMSO[D$_6$]

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user1_17May2006
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13C OBSERVE
$^1$H NMR, 400 MHz, DMSO[D$_6$]

**Chemical Structure**

![Chemical Structure](attachment:image.png)

**Data Table**

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$^{13}$C NMR, 100 MHz, DMSO[D$_6$]
24, $^1$H NMR, 400 MHz, DMSO[D$_6$]
$^{13}$C NMR, 100 MHz, DMSO[D$_6$]
25, $^1$H NMR, 400 MHz, DMSO[D$_6$]
$^{13}$C NMR, 100 MHz, DMSO[D$_6$]
26, $^1$H NMR, 400 MHz, D$_2$O

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$^{13}$C NMR, 100 MHz, D$_2$O
X-ray diffraction studies of compounds 5c, 5e, 17, 20, 21a, 4 were performed on an “Xcalibur 3” diffractometer (graphite-monochromated MoKα radiation (λ = 0.71073), CCD detector, ω-scans). Structure 4 was studied at both low and room temperatures. Structures were solved by direct method and refined against F² within anisotropic approximation for all non-hydrogen atoms using OLEX2 program package with SHELXS and SHELXL modules. In 5e and 21a, all H atoms were located from difference electronic maps and refined isotropically. In all other structures, all H atoms were placed in idealized positions and constrained to ride on their parent atoms with Uiso = nUeq (n=1.5 for CH₃ groups and n = 1.2 for all other H atoms), except of hydrogen atoms of NH₂ and OH groups that were refined using isotropic approximation. Structures 5e and 20 were refined as twins with twinning matrices (−1,0,0,−1,0,0,0.815,0,1) and (1,0,1,0,−1,0,0,0,−1), respectively, using HKLF 5 instruction (refined BASF parameters are 0.438(1) and 0.163(9), respectively). Crystallographic data, details of the data collection and processing, structure solution and refinement are summarized in Table S1. CCDC numbers 1509780 – 1509785 and 1509778 contain 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](http://www.ccdc.cam.ac.uk).

### Table S1. Crystallographic data, details of the data collection and processing, structure solution and refinement

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These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk](http://www.ccdc.cam.ac.uk).
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**Figure 1.** Molecular structure of 5c according to the X-ray diffraction data. Atoms are shown as 50% thermal ellipsoids
Both 5e and 5c in crystalline phase are present in zwitterionic form, with similar local structure of protonated carbamimidoyl and deprotonated carboxyl groups (more symmetrical C–NH$_2$ 1.305(2) – 1.310(2) and 1.311(2) – 1.316(2) Å, respectively, and slightly asymmetrical C–O (1.247(2) – 1.257(2) and 1.248(2) – 1.258(2) Å). Amino groups are planar or almost planar (sum of bond angles centered on amino nitrogen atoms is 358(1) – 360(1) °). Angle between carbamimidoyl and carboxyl planes is 86.2(2)° in 5c and 68.0(2)° in 5e, at the time in 5c carboxyl group is almost coplanar to aromatic cycle plane (10.89(6)°), but rotated on 48.87(9)° in 5e. However, it does not affects the C$_{aromatic}$–COO$^-$ bond lengths (1.517(2) Å in 5c and 1.520(2) Å in 5e), both are longer as compare to mean value of 1.504 Å$^{15}$ that indicates disturbance of π-conjugation. In both structures, carbamimidoyl group is rotated with respect to aromatic ring (89.65(5)° and 53.53(8)° respectively), and C$_{aromatic}$–C(NH$_2$)$_2$ bonds are similar (1.489(2) Å and 1.479(2) Å) and only little longer than mean value (1.476 Å$^{15}$).

Presence of charged substituents does not cause the bond alternation in aromatic rings, neither in 5c nor in 5e. Elongation of C(1)–C(2) bond (1.400(2) Å) as compare to other aromatic C–C bonds (1.379(2) – 1.385(2) Å) in 5e is caused by inductive effect and repulsion of neighboring substituents. In 5c, C(2)–C(7) bond 1.396(2) Å is of the similar length as compare to other endocyclic bonds (1.378(2) – 1.405(2) Å) because of the greater value of angle between carbamimidoyl and carboxyl planes (see before). At the time, in 5c the longest endocyclic bond is C(6)–C(7) 1.405(2) Å because of repulsion between carbamimidoyl and methoxy substituents.
Figure 3. Molecular structure of 21a according to the X-ray diffraction data. Atoms are shown as 50% thermal ellipsoids

Structure of 21a is similar to 5c and 5e but the presence of chlorine anion and therefore neutral state of carboxyl groups causes marked differences. The asymmetry in C–O bond lengths is strongly pronounced (1.203(2) vs 1.315(2) Å) and C_{aromatic}–COO^– bond of 1.485(2) Å is notably shorter than in 5c and 5e (see before). Carboxyl group is almost coplanar to benzene ring (20.39(1)°) and perpendicular to carbamimidoyl group (69.84(1)°). Angle between benzene ring and carbamimidoyl group is 67.74(1)° and C_{aromatic}–C(NH₂)₂ bond (1.490(2) Å) is little longer than in 5c and 5e. All amino groups are also planar, C(1)–C(2) bond of 1.395(3) Å is also the longest among the aromatic C–C bonds in 21a (1.366(3) – 1.385(3) Å).

Figure 4. Molecular structure of 17 according to the X-ray diffraction data. Atoms are shown as 50% thermal ellipsoids

Crystal structure of 17 is also molecular ionic like in 21a, however the organic molecule is not cation but anion in this case. Negative charge is localized on carboxyl group with slightly asymmetrical C–O bonds (1.243(2) and 1.255(2) Å). Carboxyl group is almost perpendicular to pyrazine plane (106.08(6)°) and C_{aromatic}–COO^– bond of 1.516(2) Å is elongated as in 5c and 5e. On the contrary, amide group is almost coplanar to aromatic ring (17.13(8)°). Angle between carboxyl and amide groups is 108.1(2)°. C(2)–C(9) bond (1.425(2) Å) is also elongated as compare to other C–C aromatic bonds in 17 (1.356(2) – 1.413(2) Å).

Amide oxygen is incorporated in coordination surrounding of Na cation. [NaO₆] coordination polyhedra includes also five oxygen atoms of crystalline water molecules, four of them are bridging forming coordination polymeric chain along (100) crystallographic direction with (Na-2µ-O-Na) regular tetragons as a basic
Coordination octahedra undergoes both equatorial and axial angular distortion (O–Na–O angles in Na–µO₄ equatorial plane vary in the range of 79.4(3) – 110.0(2)°, axial O–Na–O angle is 166.1(3)°), at the time Na–O bond are quite similar (2.357(2) – 2.471(3) Å).

**Figure 5.** Molecular structure of 20 according to the X-ray diffraction data. Atoms are shown as 50% thermal ellipsoids.

In 20, both neighboring methylcarboxyl and cyano substituents lie in the plane of aromatic ring (angles are 4.82(8)° and 0.08(2)°, respectively). Methylated carboxyl group reveals asymmetrical C–O bonds (1.201(2) and 1.330(2) Å) and short C aromatic–COO bond of 1.467(2) Å that confirms its π-conjugation with imidazole. Interestingly, OCH₃ bond is also lie in the plane of the molecule.

**Figure 6.** Molecular structure of 4 according to the X-ray diffraction data. Atoms are shown as 50% thermal ellipsoids.

In the crystalline phase, structure 4 exists as amino form. Differences between structures studied at low temperature (100K) and room temperature (298K) are negligible. All molecule is strictly planar (up to 0.05 Å), C–NH₂ bond of 1.306(3) Å is strongly shortened as compare to the mean value of 1.355 Å and C(7)–N(1) bond of 1.334(3) Å is elongated (1.314 Å) that indicated very strong conjugation in imino-amino fragment. At the time no extra conjugation is observed with carbonyl group.
Crystal structure of all compounds listed above is defined by prima facie the number of strong intramolecular hydrogen bonds involving N and O atoms of functional groups (amino, amide, carboxyl). Full list is given in Table S2. In the case of ionic or zwitterionic structures substituents those bonds are charge-assisted. In 5c, 5e, 17 and 21a, they lead to formation of three-dimensional structure in the absence of other strong specific intermolecular interaction. In 20 and 4 both molecules are strictly planar, and that is favorable for stacking interactions. Indeed, hydrogen bonding in both crystals forms primary structural motif (chains along (010) axis in 20 and layers parallel to (102) plane in 4), and stacking interaction between π-systems (Table S3) join them to planes parallel to (100) or three-dimensional structure in 20 and 4, respectively. In 20, planes are interlinked with weaker interactions like C–H…N.

Table S2. List of the most important intermolecular H-bonds in the crystals of 5e, 5c, 17, 20, 21a, 4

<table>
<thead>
<tr>
<th>Donor</th>
<th>Acceptor</th>
<th>symmetry</th>
<th>H…A’, Å</th>
<th>D–H…A’, °</th>
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<tbody>
<tr>
<td>5c</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>N1–H1B</td>
<td>O2</td>
<td>2-x,2-y,-z</td>
<td>2.172</td>
<td>142</td>
</tr>
<tr>
<td>N1–H1A</td>
<td>O1</td>
<td>2-x,1-y,-z</td>
<td>2.052</td>
<td>171</td>
</tr>
<tr>
<td>N2–H2B</td>
<td>O4</td>
<td>1-x,2-y,-z</td>
<td>2.024</td>
<td>177</td>
</tr>
<tr>
<td>N2–H2A</td>
<td>O2</td>
<td>2-x,2-y,-z</td>
<td>2.023</td>
<td>149</td>
</tr>
<tr>
<td>O4–H4A</td>
<td>O1</td>
<td>x,y,z</td>
<td>1.873</td>
<td>166</td>
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<tr>
<td>5e</td>
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<td></td>
<td></td>
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<tr>
<td>N2–H2A</td>
<td>O1</td>
<td>-x,1-y,1-z</td>
<td>1.834</td>
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<tr>
<td>N2–H2B</td>
<td>O1</td>
<td>x,1.5-y,-1/2+z</td>
<td>1.888</td>
<td>175</td>
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<tr>
<td>N3–H3A</td>
<td>O2</td>
<td>x,1.5-y,-1/2+z</td>
<td>1.976</td>
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<tr>
<td>N3–H3B</td>
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<td>1-x,1-y,1-z</td>
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<tr>
<td>17</td>
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<tr>
<td>N3–H3B</td>
<td>O2</td>
<td>x,1+y,z</td>
<td>2.018</td>
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<tr>
<td>O4–H4A</td>
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<td>x,1+y,z</td>
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<tr>
<td>O4–H4B</td>
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<td>1-x,1-y,-z</td>
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<tr>
<td>O5–H5B</td>
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<td>-x,1-y,-z</td>
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<tr>
<td>O5–H5A</td>
<td>O3</td>
<td>1-x,1-y,-z</td>
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<tr>
<td>O6A–H6A</td>
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<td>1-x,y,-z</td>
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<tr>
<td>O6A–H6AA</td>
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<td>O6B–H6B</td>
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<td>-x,2-y,-z</td>
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<tr>
<td>N2–H2</td>
<td>N1</td>
<td>1-x,1/2+y,1.5-z</td>
<td>2.086</td>
<td>157</td>
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<tr>
<td>N2–H2</td>
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<td>1-x,1/2+y,1.5-z</td>
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<tr>
<td>C6–H6A</td>
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<tr>
<td>21a</td>
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<tr>
<td>N1–H1A</td>
<td>Cl1</td>
<td>1-x,-1/2+y,1/2-z</td>
<td>2.426</td>
<td>156</td>
</tr>
<tr>
<td>N1–H1B</td>
<td>Cl1</td>
<td>x,2.5-y,1/2+z</td>
<td>2.396</td>
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Table S3. Parameters of stacking interactions in 20 and 4.

<table>
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<tr>
<th>structure</th>
<th>interplanar separation, Å</th>
<th>intercentroid distance, Å</th>
<th>plane shift, Å</th>
<th>symmetry</th>
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<tbody>
<tr>
<td>20</td>
<td>3.332</td>
<td>3.676</td>
<td>1.552</td>
<td>x,1/2-y,1/2+z</td>
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<tr>
<td>4</td>
<td>3.360</td>
<td>3.687</td>
<td>1.518</td>
<td>2-x,-y,1-z</td>
</tr>
</tbody>
</table>