Conformational control of HCl co-transport: imidazole functionalised isophtalamide vs. 2,6-dicarboxamidopyridine

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Synthesis of methyl 6-((1-methyl-1H-imidazol-2-yl)methylcarbamoyl)pyridine-2-carboxylate:

6-(Methoxycarbonyl)pyridine-2-carboxylic acid (1.60 g, 8.8 mmol, 1.0 equiv.) was activated by reaction with thionyl chloride (30.00 mL, 439.0 mmol, 50 equiv.) at 90°C. The solution was heated at reflux for 30 minutes, then the thionyl chloride removed under vacuum. The solid was dissolved in dry dichloromethane, triethylamine (2.45 mL, 17.5 mmol, 2.0 equiv.) and (1-methyl-1H-imidazol-2-yl)methanamine (1.170 g, 10.6 mmol, 1.2 equiv.) were added to the solution. The reaction mixture was stirred at room temperature for 12 hours. After hydrolysis the solution was washed with water. The organic phase was dried over MgSO_{4}, and concentrated. The residue was purified by column chromatography on silica using a mixture CH_{2}Cl_{2}/MeOH (93/7) to give 1.56 g (65% yield) of methyl 6-((1-methyl-1H-imidazol-2-yl)methylcarbamoyl)pyridine-2-carboxylate as a white powder.

Supplementary Material (ESI) for Chemical Communications
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**1H NMR (CDCl$_3$, 400 MHz) :** $\delta = 0.93$ (3H, t, $J = 7.2$ Hz), 1.30-1.40 (2H, m), 1.64-1.54 (2H, m), 2.58 (2H, d, $J = 8.0$ Hz), 3.63 (3H, s), 4.71 (2H, d, $J = 5.6$ Hz), 6.76 (1H, s), 6.87 (1H, s), 7.13 (2H, d, $J = 8.0$ Hz), 7.44 (2H, d, $J = 8.0$ Hz), 8.03 (1H, t, $J = 8.0$ Hz), 8.35 (1H, d, $J = 8.0$ Hz), 8.41 (1H, d, $J = 8.0$ Hz), 9.87-9.89 (2H, m).

**13C NMR (CDCl$_3$, 100 MHz):** $\delta = 13.9$, 22.3, 32.8, 33.6, 35.1, 35.5, 120.7, 121.9, 125.0, 125.2, 127.0, 128.6, 134.9, 139.0, 139.4, 144.9, 148.5, 149.2, 161.2, 163.5. IR $\nu_{\text{max}} = 3312$, 2931, 1682, 1544, 747 cm$^{-1}$.

**Analysis:** Calcd for C$_{22}$H$_{25}$N$_5$O$_2$: C, 67.50; H, 6.44; N, 17.89; O, 8.17. Found C, 67.43; H, 6.53; N, 17.87.

**Synthesis of N$^1$-(4-butylphenyl)-N$^3$-(2-mercaptothiazolide)-isophthalamide:**

N$^1$,N$^3$-Bis(2-mercaptothiazolides)-isophthalamide (500 mg, 1.4 mmol, 1.0 equiv.) was dissolved in 10mL of dry CH$_2$Cl$_2$ and then 4-butylaniline (214 μL, 1.4 mmol, 1.0 equiv.) was added to the solution. The reaction mixture was stirred 3 days at room temperature. The solution was washed with 1M NaOH aqueous solution (3x10 mL). The organic phase was dried over MgSO$_4$, and concentrated. The residue was purified by column chromatography using a mixture CH$_2$Cl$_2$/AcOEt (98/2) on silica to give 110 mg (20% yield) of N$^1$-(4-butylphenyl)-N$^3$-(2-mercaptothiazolide)-isophthalamide as a yellow powder.

**1H NMR (CDCl$_3$, 300 MHz) :** $\delta = 0.93$ (3H, t, $J = 7.5$ Hz), 1.30-1.42 (2H, m), 1.55-1.65 (2H, m), 2.60 (2H, t, $J = 7.8$ Hz), 3.50 (2H, t, $J = 7.2$ Hz), 4.57 (2H, t, $J = 7.2$ Hz), 7.18 (2H, d, $J = 8.4$ Hz), 7.50-7.54 (3H, m), 7.81-7.86 (2H, m), 8.01 (1H, d, $J = 8.1$Hz), 8.15 (1H, s). **13C NMR (CDCl$_3$, 75 MHz):** $\delta = 13.0$, 22.3, 29.7, 33.6, 35.1, 56.5, 120.4, 127.9, 128.9, 129.0, 131.1, 132.4, 134.2, 135.2, 135.4, 139.6, 164.5, 170.4, 202.3. IR $\nu_{\text{max}} = 3330$, 3099, 2927, 1663, 1519, 1531, 643 cm$^{-1}$.

**Analysis:** Calcd for C$_{21}$H$_{22}$N$_2$O$_2$S$_2$: C, 63.29; H, 5.56; N, 7.03; O, 8.03; S, 16.09. Found C, 63.42; H, 5.72; N, 7.09.

**Synthesis of compound N$^1$-(4-butylphenyl)-N$^3$-((1-methyl-1H-imidazol-2-yl)methyl)isophthalamide 4:**

N$^1$-(4-Butylphenyl)-N$^3$-(2-mercaptothiazolide)-isophthalamide (100 mg, 2.5 mmol, 1.0 equiv.) was dissolved in 10mL of dry CH$_2$Cl$_2$ then (1-methyl-1H-imidazol-2-yl)methanamine (56 mg, 5.0 mmol, 2.0 equiv.) was added to the solution. The reaction mixture was stirred 3 days at room temperature. The solution was washed with 1M NaOH aqueous solution (3x10 mL). The organic phase was dried over MgSO$_4$, and concentrated. The residue was purified by column chromatography using a mixture CH$_2$Cl$_2$/AcOEt (93/7) on silica to give 90 mg (92% yield) of N$^1$-(4-butylphenyl)-N$^3$-((1-methyl-1H-imidazol-2-yl)methyl)isophthalamide 4 as a white powder.

**1H NMR (CDCl$_3$, 300 MHz) :** $\delta = 0.95$ (3H, t, $J = 7.5$ Hz), 1.34-1.41 (2H, m), 1.59-1.64 (2H, m), 2.61 (2H, d, $J = 7.5$ Hz), 3.51 (3H, s), 4.53 (2H, d, $J = 5.1$ Hz), 6.51 (1H, s), 6.90 (1H, s), 7.12-7.17 (3H, m), 7.54 (2H, d, $J = 7.4$ Hz), 7.68 (1H, d, $J = 7.5$ Hz), 7.76 (1H, d, $J = 7.5$ Hz), 8.12 (1H, s), 8.66 (1H, s), 10.98 (1H, br). **13C NMR (CDCl$_3$, 75 MHz):** $\delta = 13.9, 22.2, 32.8, 33.8, 35.1, 36.0, 120.8, 121.6, 124.1, 126.2, 128.4, 128.8, 130.5, 131.2, 132.5, 136.3, 136.34, 138.7, 145.8, 166.4, 167.3. IR $\nu_{\text{max}} = 3248$, 2925, 2850, 1667, 1531, 1531, 1322, 702 cm$^{-1}$.

**Analysis:** Calcd for C$_{23}$H$_{26}$N$_4$O$_2$: C, 70.75; H, 6.71; N, 14.34; O, 8.19. Found C, 70.40; H, 6.75; N, 14.25.
Synthesis of compound $\text{N}_2\text{N}_6$-bis(4-butylphenyl)pyridine-2,6-dicarboxamide 5:

Isophthaloyl dichloride (1.00 g, 4.9 mmol, 1.0 equiv.) was dissolved in 50 mL of dry THF, triethylamine (2.73 mL, 19.6 mmol, 4.0 equiv.) and 4-butylaniline (2.31 mL, 14.7 mmol, 3.0 equiv.) were added to the solution. The reaction mixture was stirred at room temperature for 12 hours and the solution subsequently was washed with water. The organic phase was dried over MgSO$_4$, and concentrated. The residue was purified by column chromatography using a mixture CH$_2$Cl$_2$/MeOH (96/4) to give 1.610 mg (77% yield) of compound 3 as a white powder. $^1$H NMR (CDCl$_3$, 300 MHz): δ = 0.94 (6H, t, $J$ = 7.2 Hz); 1.31-1.43 (4H, m), 1.56-1.66 (4H, m); 2.62 (4H; $J$ = 7.5 Hz), 7.20 (4H, d, $J$ = 7.4 Hz), 7.64 (4H, d, $J$ = 7.4 Hz), 8.10 (1H, t, $J$ = 7.5 Hz), 8.47 (2H, d, $J$ = 7.5 Hz), 9.48 (s, 2H). $^{13}$C NMR (CDCl$_3$, 75 MHz): δ = 13.9, 22.2, 33.6, 35.1, 120.2, 125.4, 129.1, 134.7, 139.5, 139.8, 149.1, 161.0. IR $\nu_{\text{max}}$ = 3299, 2927, 2856, 1661, 1522, 827 cm$^{-1}$. Anal: Calcd for C$_{27}$H$_{31}$N$_3$O$_2$: C, 75.5; H, 7.27; N, 9.78; O, 7.45. Found C, 75.55; H, 7.34; N, 9.80.

NMR spectra

Figure S 1: $^1$H NMR spectra of compound 3
Figure S 2: $^{13}$C NMR spectra of compound 3

Figure S 3: $^1$H NMR spectra of compound 4
Figure S 4 \(^{13}\)C NMR spectra of compound 4

Figure S 5 \(^1\)H NMR spectra of compound 5
Figure S 6 $^{13}$C NMR spectra of compound 5
Binding studies:

![Figure S 7: Fit plot of NMR titration of compound 2 vs TBACl in DMSO-d$_6$](image)

Calculations by WinEQNMR Version 1.20 by Michael J. Hynes
Program run at 15:38:10 on 01/29/2007

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Reaction: M + L = ML
FILE: TEST11.FIT
IDEAL DATA: K1 = 63.091; DELTA M = 20.0; DELTA ML = 120.0
File prepared by M. J. Hynes, October 22 2000

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RFACTOR = 0.0126 PERCENT
Figure S 8: plot of NMR titration of compound 2$\cdot$HPF$_6$ vs TBACl in DMSO-$d_6$

Calculations by WinEQNMR Version 1.20 by Michael J. Hynes
Program run at 15:44:29 on 01/29/2007

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Figure S9: Fit plot of NMR titration of compound 3 vs TBACl in DMSO-$d_6$.

Calculations by WinEQNMR Version 1.20 by Michael J. Hynes
Program run at 17:39:09 on 02/13/2007

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IDEAL DATA: K1 = 63.091; DELTA M = 20.0; DELTA ML = 120.0
File prepared by M. J. Hynes, October 22 2000

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Figure S 10: plot of NMR titration of compound 3•HF6 vs TBACl in DMSO-d6

Calculations by WinEQNMR Version 1.20 by Michael J. Hynes
Program run at 14:57:26 on 01/29/2007

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File prepared by M. J. Hynes, October 22 2000

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Figure S 11: Fit plot of NMR titration of compound 4 vs TBACl in DMSO-\(d_6\)

Calculations by WinEQNMR Version 1.20 by Michael J. Hynes
Program run at 18:46:36 on 01/31/2007

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File prepared by M. J. Hynes, October 22 2000

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\(\text{RFACTOR} = 0.0151\) PERCENT
**Figure S 12:** plot of NMR titration of compound 4•HPF$_6$ vs TBACl in DMSO-$d_6$

Calculations by WinEQNMR Version 1.20 by Michael J. Hynes
Program run at 18:40:48 on 01/31/2007

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**Reaction:** M + L = ML

**FILE:** TEST11.FIT

**FILE DATA:** K1 = 63.091; DELTA M = 20.0; DELTA ML = 120.0

File prepared by M. J. Hynes, October 22 2000

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**RESIDUALS SQUARED = 4.60E-05**

**RFACCTOR = 0.0150 PERCENT**
Figure S 13: Fit plot of NMR titration of compound 5 vs TBACl in DMSO-\textit{d}_6.

Calculations by WinEQNMR Version 1.20 by Michael J. Hynes
Program run at 18:24:01 on 01/31/2007

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File prepared by M. J. Hynes, October 22 2000

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Figure S 14: plot of NMR titration of compound 5•HPF₆ vs TBACl in DMSO-d₆

Calculations by WinEQNMR Version 1.20 by Michael J. Hynes
Program run at 10:44:47 on 02/13/2007

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File prepared by M. J. Hynes, October 22 2000

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