Supplementary Material

Binary co-crystals of the active pharmaceutical ingredient 1,4-bis(4-pyridyl)-2,3-diaza-1,3-butadiene and camphoric acid

Kamal Kumar Bisht\textsuperscript{a,b}, Priyank Patel\textsuperscript{a,c}, Yadagiri Rachuri\textsuperscript{a,b}, Eringathodi Suresh*\textsuperscript{a,b}

Correspondence email: esuresh@csncri.org; sureshe123@rediffmail.com

S1. Synthesis of 1,4-bis(4-pyridyl)-2,3-diaza-1,3-butadiene (1)

Ligand 1,4-bis(4-pyridyl)-2,3-diaza-1,3-butadiene (1) was synthesized by adopting the procedure reported by Ciurtin \textit{et al.} (2001) with slight modifications. Pyridine-4-carboxaldehyde (4.4 mL, 44 mmol) and hydrazine hydrate (2.1 mL, 22 mmol) were separately dissolved in 12.5 mL of ethanol each. The resulting solutions were mixed gently and allowed to stir at room temperature for 24 h under a nitrogen atmosphere. The yellow precipitate thus obtained was collected and washed with cold ethanol/ether mixture (1:1, 10 mL) and dried in air. Yield 87\%. \textsuperscript{1}H NMR (MeOD): $d$ 7.84 (d, 4H), 8.61 (s, 2H), 8.66 (d, 4H); Melting point 176 \degree C.

S2. Synthesis of [(1)((+)-cam)] (CCP1:1)

60 mg (0.3 mmol) (+)-cam, 63 mg (0.3 mmol) (1) and 3 ml methanol were taken in a 5 ml glass vial and the mixture was dissolved by sonication. The clear yellow-coloured solution thus obtained was kept for slow evaporation and block-shaped crystals suitable for single-crystal analysis were obtained within two weeks. Yield 89\%; CHN analysis: Calculated values for C\textsubscript{22}H\textsubscript{26}N\textsubscript{4}O\textsubscript{4} (%): C = 64.37; H = 6.38; N= 13.65; O= 15.59 Observed Values (%): C= 64.33; H=6.49; N=13.92; IR Spectral Data: ($\nu_{\text{max}}$ / cm\textsuperscript{-1}) 3694 (b), 3429 (w), 2953 (s), 1700 (s), 1603 (s), 1554 (w), 1455 (w), 1407 (m), 1275 (m), 1229 (m), 1199 (w), 1010 (m), 978 (w), 947 (m), 820 (m), 459 (w); \textsuperscript{1}H nmr (DMSO-$d$\textsubscript{6}) (ppm): 8.76 (d, 4H, $J = 6$ Hz), 8.69 (s), 7.82 (d, 4H, $J = 6$ Hz), 2.74 (m, 1H), 2.35 (m, 1H), 1.95 (m, 1H), 1.74 (m, 1H), 1.72 (m, 1H), 1.37 (m, 1H), 1.20 (s, 3H), 1.14 (s, 3H), 0.77 (s, 3H); Melting point: 456 K.
S3. Synthesis of [(1)$_3$((+)-cam)$_2$] (CCP3:2)

120 mg (0.6 mmol) (+)-cam, 190 mg (0.9 mmol) (1) were separately dissolved in 5 ml methanol each and then mixed gradually with constant stirring at ambient temperature for 2 h. The clear solution thus obtained yielded plate-shaped crystals suitable for single-crystal analysis within three to four days. Yield 95%; CHN analysis: Calculated values for C$_{22}$H$_{26}$N$_4$O$_4$ (%): C = 65.23; H = 6.06; N= 16.30; O = 12.41 Observed Values (%): C= 65.28; H=6.12; N=16.32; IR Spectral Data: ($\nu_{\text{max}}$ /cm$^{-1}$) 3431 (b), 2978 (m), 1700 (s), 1693 (s), 1601 (s), 1270 (s), 1237 (s), 1209 (s), 1116 (w), 1010 (m), 508 (m), 449 (w); $^1$H nmr (DMSO-d$_6$) (ppm): 8.76 (d, 12H, $J = 6$ Hz), 8.69 (s, 12H), 7.82 (d, 12H, $J = 6$ Hz), 2.74 (m, 2H), 2.35 (m, 2H), 1.95 (m, 2H), 1.74 (m, 2H), 1.72 (m, 2H), 1.37 (m, 2H), 1.20 (s, 6H), 1.14 (s, 6H), 0.77 (s, 6H); Melting point: 434 K.

S4. Synthesis of [(1)$_3$((–)-cam)$_2$] (CCM3:2)

CCM3:2 was synthesized by adopting a similar procedure as for CCP3:2 except (–)-cam was used instead of (+)-cam. Yield 95%; CHN analysis: Calculated values for C$_{22}$H$_{26}$N$_4$O$_4$ (%): C = 65.23; H = 6.06; N= 16.30; O = 12.41 Observed Values (%): C= 65.31; H=6.12; N=16.28; IR Spectral Data: ($\nu_{\text{max}}$ /cm$^{-1}$) 3430(b), 2974(m), 1690(s), 1602(s), 1554(m), 1235(m), 1202(s), 1124(m), 1061(m), 1011(s), 683(m), 514(m), 452(w); $^1$H nmr (DMSO-d$_6$) (ppm): 8.76 (d, 12H, $J = 6$ Hz), 8.68 (s, 12H), 7.83 (d, 12H, $J = 6$ Hz), 2.74 (m, 2H), 2.35 (m, 2H), 1.95 (m, 2H), 1.74 (m, 2H), 1.72 (m, 2H), 1.36 (m, 2H), 1.21 (s, 6H), 1.14 (s, 6H), 0.76 (s, 6H); Melting point: 434 K.

S5. Synthesis of [(1)$_3$((rac)-cam)$_2$]; (CCR3:2)

CCR3:2 was synthesized by adopting similar procedure as for CCP3:2 except (rac)-cam was used instead of (+)-cam. Yield 95%; CHN analysis: Calculated values for C$_{22}$H$_{26}$N$_4$O$_4$ (%): C = 65.23; H = 6.06; N= 16.30; O = 12.41 Observed Values (%): C= 65.29; H=6.10; N=16.35; IR Spectral Data: ($\nu_{\text{max}}$ /cm$^{-1}$) 3432(b), 2969(m), 1686(m), 1601(s), 1410(m), 1374(m), 1199(s), 1119(m), 1062(m), 1012(s), 955(m), 816(m), 512(m); $^1$H nmr (DMSO-d$_6$) (ppm): 8.75 (d, 12H, $J = 6$ Hz), 8.69 (s, 12H), 7.81 (d, 12H, $J = 6$ Hz), 2.74 (m, 2H), 2.35 (m, 2H), 1.95 (m, 2H), 1.74 (m, 2H), 1.72 (m, 2H), 1.36 (m, 2H), 1.20 (s, 6H), 1.14 (s, 6H), 0.77 (s, 6H); Melting point: 466 K.
S6. pKₐ values

pKₐ values for azine (I) and camphoric acids have been calculated using online computational resources available at http://www.chemaxon.com/marvin/sketch/index.php and http://aceorganic.pearsoncmg.com/epoch-plugin/public/pKa.jsp.

S7. FTIR spectra for all co-crystals and their constituents

![FTIR spectra](image)

S8. Proton NMR spectra of CCP1:1 and CCP3:2 constituents as recorded in DMSO-d6

![Proton NMR spectra](image)
S9. Proton NMR spectra of CCM3:2 and constituents as recorded in DMSO-$d_6$.

S10. Proton NMR spectra of CCR3:2 and constituents as recorded in DMSO-$d_6$. 
S11. Simulated and experimental powder XRD patterns for all co-crystals.

S12. DSC (red) and TGA (black) plots for CCP1:1, CCP3:2, CCM3:2 and CCR3:2 in temperature range 30-500 °C. (TGA and DSC plots were obtained at a scan rate of 10 °C min⁻¹). Melting points are represented by blue dotted line and marked temperatures in each plot.
S13. Absorbance spectra of CCP1:1, CCP3:2, CCM3:2 and CCR3:2 in methanol solutions (~ $10^{-5}$ M) (a) and in water after DCM-Water extraction.

S14. (a) CD spectra of (+)- and (-)-cam in $10^{-5}$ methanolic solutions; (b) CD spectra of L1 in $10^{-5}$ methanol solution; (c), (e) addition of 1 eq. L1 in (+)- and (-)-cam in methanol solutions mask the CD characteristic of enantiopure camphoric acids turning it into noise; (d), (f) similar noisy spectra recorded for CCP3:2 and CCM3:2.