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DOTTADs – readily made novel metal ligands with multivariant functionality – trans-DOTTADs and semi-DOTTADs

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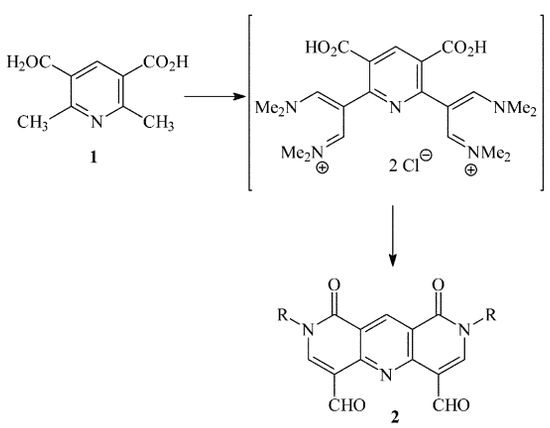
Two new ligand systems related to the previously described DOTTADs have been generated in a simple one step reaction. The first, trans-DOTTADs, were formed by Vilsmeier formylation (followed by cyclisation and *N*-demethylation) of 2,6-dimethyl-3,5-pyrazine-dicarboxylic acid, to give the novel bis-pyridinopyrazine dialdehyde ligands. The corresponding pyrazine diester, reacted similarly to an intermediate iminium ion stage, which gave trans-DOTTAD imines on work-up with amines. The treatment of Hantzsch ester with two equivalents of benzaldehyde gave 7-phenyl-2-(2-phenylethenyl)-7,8-dihydropyrano[4,3-*b*]pyridin-5-one-3-carboxylic acid. This product underwent similar cyclisation with Vilsmeier reagents to give, for example, 6-methyl-2-(2-phenylethenyl)-8-(phenylhydroxymethyl)-6*H*-[1,6]naphthyridin-5-one-3-carboxylic acid, an example of a semi-DOTTAD.

Introduction

Recently we described[1] a new double cyclisation whereby 2,6-dimethylpyridine-3,5-dicarboxylic acid **1** ('Hantzsch acid') in which the methyl groups are 'activated', reacted with a Vilsmeier reagent in a multi-step but one-pot process to form a DOTTAD **2** (1,8-*dio*xo-1,2,7,8-*t*etrahydro-2,7,10-*tri*aza-anthracene-4,5-*di*carbaldehydes). The reaction involved di-formylation at each of the two methyl groups followed by bis-intramolecular acylation at the introduced nitrogens and subsequent demethylation and hydrolysis to generate a new tricyclic dialdehyde, the DOTTAD **2**. We have shown this reaction is quite general and is a highly efficient and versatile route to useful ligands for group I and II metal ions and some transition metals (Scheme 1)[1].



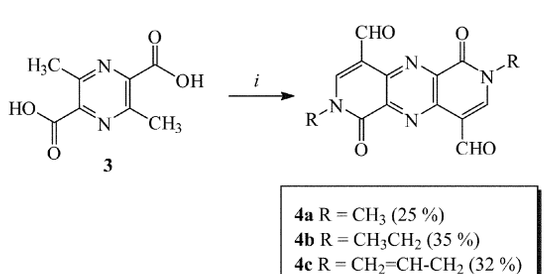
Scheme 1

In this paper we describe two related multifunctional heterocycles which show similar chelating properties; (a) the derivatives of 1,5-dioxo-1,2,5,6-tetrahydro-2,5,7,10-tetraaza-anthracene-4,9-dicarbaldehyde which by analogy we refer to as 'trans-DOTTADs' (**4** and **6**) and (b) 6-alkyl-2-(2-phenyl-ethenyl)-8-(phenylhydroxymethyl)-*6H*-[1,6]naphthyridin-5-one-3-carboxylic acids, which for simplicity we refer to as 'semi-DOTTADs' (**11**), highlighting the structural relationship to the above mentioned DOTTAD ligands.

Results and discussion

The reaction of 2,5-dimethylpyrazine-3,6-dicarboxylic acid (3) and its diethyl ester (5) with Vilsmeier reagents – synthesis of trans-DOTTADs

The reaction of 2,5-dimethyl-3,6-dicarboxypyrazine[2] (**3**) with different Vilsmeier reagents was conducted with preformed reagents, derived from the corresponding dialkylformamides using $POCl_3$ as a solvent. After 12 hours at 80 °C, the usual aqueous work-up caused no precipitation, in contrast to the formation of the very insoluble DOTTADs (**2**). However, continuous extraction of the aqueous solution with chloroform yielded the expected trans-DOTTAD products (**4a**–**c**) in low yields (Scheme 2).



4a R = CH_3 (25 %)
4b R = CH_3CH_2 (35 %)
4c R = CH_2=CH-CH_2 (32 %)

Scheme 2 *Reagents and conditions*: i. $POCl_3$, R_2NCHO, 80 °C.

Better results were achieved using diethyl 2,5-dimethyl-pyrazine-3,6-dicarboxylate (**5**). The diester **5** was added to a dimethylformamide–$POCl_3$ mixture and heated, the progress of the reaction being monitored by ^{1}H-NMR spectroscopy. After 12 hours at 80 °C, when no more starting material was observed and indications of iminium salt formation seen in the NMR spectrum (see previous papers[1]), the reaction mixture was worked up as usual. On addition of ammonium hydroxide to the resulting stable aqueous solution of the iminium salt intermediate (*cf.* Scheme 1), the parent dialdehyde (**4d**) was isolated in poor yield by continuous extraction, probably due to its high water-solubility. However when this iminium salt solution was stirred with a large excess of a primary amine, a tan coloured precipitate appeared, which after recrystallization

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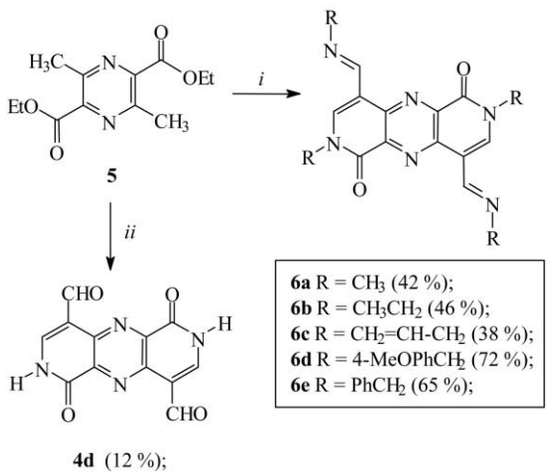
proved to be the diimines **6a**–**e** of the dialdehydes **4**, some in good yield (Scheme 3). One of these imines **6a** was quantitatively converted into the corresponding trans-DOTTAD aldehyde **4a** by brief stirring with cold aqueous hydrochloric acid and THF.

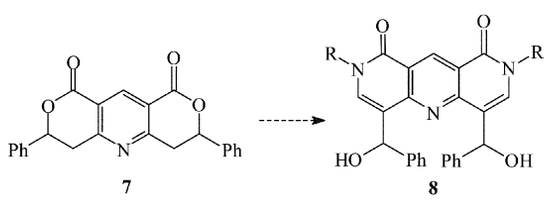


Scheme 3 *Reagents and conditions*: i. (a) $POCl_3$, DMF, 80 °C; (b) H_2O; (c) RNH_2; ii. (a) $POCl_3$, DMF, 80 °C; (b) H_2O; (c) NH_4OH.

A curious feature of the rather insoluble trans-DOTTADs **4a**,**b** compared to the more soluble **4c** was the 2.7 ppm upfield shift of the CHO protons of the former (~8.1 ppm) compared to the latter (and normal aldehydes). We attribute this to the partial, and reversible hydration of these aldehydes in warm DMSO-d_6. A similar but smaller effect is noted with the imine **6a** compared to **6b**.

Reaction of 2,6-dimethylpyridine-3,5-dicarboxylic acid ester (1) with benzaldehydes – synthesis of semi-DOTTADs

In the next series of experiment we intended to examine the reaction of the bis-pyranopyridine **7** which was described by Plieninger *et al.*[3] in 1958 and which seemed a promising candidate for the effective synthesis of new DOTTAD-type ligands, such as **8** (Scheme 4). It should be noted that the ligand action of DOTTAD aldehydes is probably due to involvement of the hydrated aldehyde, as evidenced by our preliminary examination of isolated sodium complexes. Plieninger claimed to have generated these derivatives by treatment of the ester **1** with benzaldehyde.[3]



Scheme 4

The authors were uncertain about the structure of the condensation product of diethyl 2,6-dimethylpyridine-3,5-dicarboxylate (**1**) and benzaldehyde: the compound did not dissolve in cold sodium carbonate solution which suggested the dilactone structure (**7**). However, they were able to prepare its monohydrazide which suggested at least one free carboxylic acid function. The only available spectral information, the UV-spectrum, was uninformative. Repeating the reaction gave a nicely crystalline product as described in their paper which proved to be the monolactone (**9**) on the basis of its NMR, IR and mass spectra. Other aromatic aldehydes behaved differently in this reaction: the 2-bromo- and 4-chlorobenzaldehyde gave the dicarboxylic acids **10a** and **10b** while in the other cases (*p*-methoxybenzaldehyde, piperonal, 4-nitrobenzaldehyde) we observed the formation of a complex mixture of products.

The reaction of 7-phenyl-2-(2-phenylethenyl)-7,8-dihydropyrano[4,3-*b*]pyridin-5-one-3-carboxylic acid (**9**) with different Vilsmeier reagents (preformed from the corresponding dialkylformamides using $POCl_3$ as a solvent) after the usual work-up gave the expected 'semi-DOTTADs' **11** in acceptable yields (Scheme 5).

Experimental

Melting points were determined on a Gallenkamp apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 240C or Carlo Erba 1106 Elemental Analyser. IR spectra were recorded on a Perkin-Elmer 1600 series FTIR or Unicam research series FTIR spectrophotometer using sodium chloride plates. ^{1}H NMR spectra were acquired on a Jeol GSX 270 FT NMR at 270 MHz. Coupling constants are given in Hz and all chemical shifts are relative to an internal standard of tetramethylsilane. ^{13}C NMR spectra were obtained on a Jeol GFX 270 FT NMR (68 MHz) spectrometer. The poor solubility of several of the compounds required elevated temperatures and use of DMSO-d_6 as solvent. Low resolution electron impact mass spectra were obtained on a Trio 2000 VG. High resolution spectra were obtained on a VG ZAB-E spectrometer (EPSRC Mass Spectrometry Service Centre, Swansea). Thin layer chromatography was performed on Merck silica gel $60F_{254}$. All solvents were purified according to standard procedures. The 2,5-dimethylpyrazine-3,6-dicarboxylic acid and its ester **3** were prepared by the method of Albertson *et al.*,[2] and the Hantzsch pyridine **1** was prepared by the method of Böcker and Guengerich.[4]

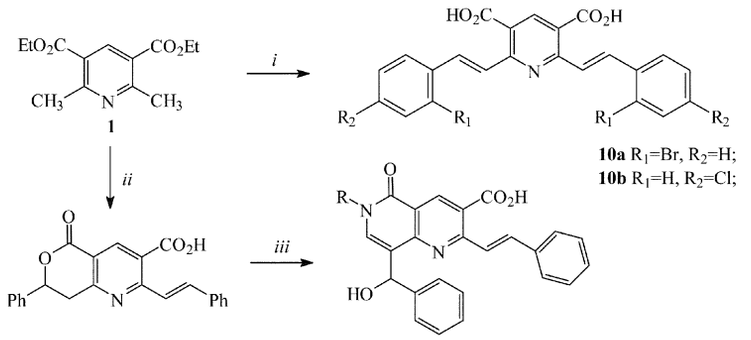
Synthesis of trans-DOTTADs from 2,5-dimethylpyrazine-3,6-dicarboxylic acid

General procedure. $POCl_3$ (9.3 mL) was added dropwise to *N*-formyldialkylamine (40 mmol) with efficient stirring and external ice cooling. To this solution was added the 2,5-dimethylpyrazine-3,6-dicarboxylic acid (10 mmol) and after one minute stirring the mixture was heated at 80–85 °C for 12 h during which it became red. Most of the $POCl_3$ was removed *in vacuo* and ice–water added, followed by concentrated NH_4OH or the required amine until basic. The deep brown solution was continuously extracted with chloroform. The organic phase was dried with magnesium sulfate and evaporated to yield the products below.

2,6-Dimethyl-1,5-dioxo-1,2,5,6-tetrahydro-2,5,7,10-tetraaza-anthracene-4,9-dicarbaldehyde (4a). Yield, 25%; pale brown powder, mp 263 °C; ν_{max} KBr/cm^{-1} 3409, 3249, 1697, 1664, 1614, 1434, 1409, 1326, 1166; δ_H (270 MHz, DMSO-d_6, 50 °C): 8.10 (s, 2H, CHO), 7.75 (s, 2H, CH=), 2.69 (s, 6H, NCH_3); δ_C (68 MHz, DMSO-d_6, 50 °C): 167.0, 155.7, 148.5, 145.1, 128.7, 111.6, 21.8 (Found: 298.0714, $C_{14}H_{10}N_4O_4$ requires 298.0702).

2,6-Diethyl-1,5-dioxo-1,2,5,6-tetrahydro-2,5,7,10-tetraaza-anthracene-4,9-dicarbaldehyde (4b). Yield, 35%; pale brown powder, mp > 250 °C; ν_{max} KBr/cm^{-1} 3411, 1696, 1662, 1614, 1437, 1411, 1322, 1106; δ_H (270 MHz, DMSO-d_6, 50 °C): 8.12 (s, 2H, CHO), 7.72 (s, 2H, CH=), 4.12 (q, 4H, *J* 7.3 Hz, CH_2), 1.35 (t, 6H, CH_3); δ_C (68 MHz, DMSO-d_6, 50 °C): 167.2, 155.5, 148.8, 145.2, 128.7, 111.3, 44.4, 14.0 (Found: 326.1019, $C_{16}H_{14}N_4O_4$ requires 326.1015).

2,6-Diallyl-1,5-dioxo-1,2,5,6-tetrahydro-2,5,7,10-tetraaza-anthracene-4,9-dicarbaldehyde (4c). Yield, 32%; brown powder, mp > 250 °C; ν_{max} KBr/cm^{-1} 1682, 1669, 1594, 1508, 1348, 1321, 1283, 1238, 1166; δ_H (270 MHz, DMSO-d_6, 50 °C): 10.85 (s, 2H,



Scheme 5 *Reagents and conditions*: i. ArCHO, 160 °C; ii. PhCHO, 160 °C; iii. (a) $POCl_3$, DMF, 80 °C; (b) H_2O; (c) RNH_2.

CH=O), 8.27 (s, 2H, CH=), 5.93 (m, 1H, allyl), 5.38 (m, 2H, allyl), 4.72 (m, 2H, allyl); δ_C (68 MHz, DMSO-d_6,100 °C): 186.4, 159.3, 145.6, 142.7, 137.5, 132.1, 118.5, 112.5, 51.0; *m*/*z* (EI): 350 (M^+, 25), 322 (base peak), 281 (6), 91 (10), 69 (22) (Found: 350.1006, $C_{18}H_{14}N_4O_4$ requires 350.1015).

Synthesis of trans-DOTTADs from diethyl 2,5-dimethylpyrazine-3,6-dicarboxylate

General procedure. $POCl_3$ (9.3 mL) was added dropwise to dimethylformamide (40 mmol) with efficient stirring and external ice cooling. To this solution was added diethyl 2,5-dimethylpyrazine-3,6-dicarboxylate (10 mmol) and after one minute stirring the mixture was heated at 80–85 °C for 12 h during which it became red. Most of the $POCl_3$ was removed *in vacuo* and ice–water added, followed by the required amine until basic. After 30 min stirring the tan coloured precipitate was filtered, washed well with water, dried and recrystallised with the exception of **6a** where the deep brown solution was continuously extracted with chloroform. The organic phase was dried and evaporated to yield the corresponding product (**6a**).

1,5-Dioxo-1,2,5,6-tetrahydro-2,5,7,10-tetraazaanthracene-4,9-dicarbaldehyde (4d). Yield, 12%; pale brown powder, mp > 290 °C; ν_{max} KBr/cm^{-1} 3187, 1702, 1681, 1596, 1508, 1311, 1280, 1143, 1056; δ_H (270 MHz, DMSO-d_6, 100 °C): 10.63 (s, 2H, CH=O), 8.15 (s, 2H, CH=); δ_C (68 MHz, DMSO-d_6): 186.3, 159.7, 146.1, 139.4, 138.0, 112.1; *m*/*z* (EI): 272 (MH_2^+, 96), 270 (M^+, 25), 242 (base peak), 231 (31), 220 (72), 214 (15), 171 (16), 132 (32), 70 (27) (Found: 270.0396, $C_{12}H_6N_4O_4$ requires 270.0389).

2,6-Dimethyl-4,9-bis(methyliminomethylenyl)-1,5-dioxo-1,2,5,6-tetrahydro-2,5,7,10-tetraazaanthracene (6a). Yield, 42%; orange crystals (from ethyl acetate), mp 211–212 °C (decomp.); ν_{max} KBr/cm^{-1} 3060, 1662, 1606, 1509, 1326, 1184; δ_H (270 MHz, DMSO-d_6, 100 °C): 8.57 (s, 2H, N=CH), 7.89 (s, 2H), 3.20 (s, 6H, CH_3), 3.04 (s, 6H, CH_3); δ_C (68 MHz, DMSO-d_6,100 °C): 159.3, 154.7, 143.1, 137.0, 128.3, 111.2, 46.8, 36.4; *m*/*z* (EI): 324 (M^+,base peak), 309 (42), 294 (13), 282 (7), 268 (6), 250 (42); (Found: 324.1336, $C_{16}H_{16}N_6O_2$ requires 324.1335).

2,6-Diethyl-4,9-bis(ethyliminomethylenyl)-1,5-dioxo-1,2,5,6-tetrahydro-2,5,7,10-tetraazaanthracene (6b). Yield, 46%; orange crystals (from ethyl acetate), mp 226 °C (decomp.); ν_{max} KBr/cm^{-1} 3496, 3365, 2965, 1664, 1641, 1610, 1334; δ_H (270 MHz, DMSO-d_6, 100 °C): 9.47 (s, 2H, N=CH), 8.77 (s, 2H), 4.59 (q, 4H, *J* 7.3 Hz, CH_2CH_3), 4.08 (q, 4H, *J* 7.3 Hz, CH_2CH_3), 1.79 (t, 6H, *J* 7.3 Hz, CH_2CH_3), 1.70 (t, 6H, *J* 7.3 Hz, CH_2CH_3); δ_C (68 MHz, DMSO-d_6,100 °C): 158.8, 152.7, 145.1, 137.4, 135.3, 111.6, 54.3, 44.1, 15.6, 13.4; *m*/*z* (EI): 380 (M^+, base peak), 373 (10), 366 (7), 351 (17), 334 (22), 324 (13), 316 (19), 287 (13), 242 (12), 213 (13), 58 (47) (Found: 380.1944, $C_{20}H_{24}N_6O_2$ requires 380.1961).

2,6-Diallyl-4,9-bis(allyliminomethylenyl)-1,5-dioxo-1,2,5,6-tetrahydro-2,5,7,10-tetraazaanthracene (6c). Yield, 38%; yellow crystals (from ethyl acetate), mp 212 °C (decomp.); ν_{max} KBr/cm^{-1} 3458, 3421, 1677, 1643, 1604, 1338; δ_H (270 MHz, DMSO-d_6): 9.07 (s, 2H, N=CH), 8.41 (s, 2H), 6.12–5.98 (m, 4H, allyl-H), 5.31–5.12 (m, 8H, allyl-H), 4.79 (d, 4H, *J* 5.3 Hz, allyl-H), 4.29 (d, 4H, *J* 5.9 Hz); δ_C (68 MHz, DMSO-d_6,100 °C): 158.9, 154.4, 145.2, 137.6, 136.1, 135.7, 132.3, 118.0, 115.4, 111.6, 62.2, 50.5; *m*/*z* (EI): 428 (M^+, base peak), 387 (44), 346 (53), 334 (14), 319 (13), 305 (17), 293 (7), 278 (6), 220 (6), 56 (21) (Found: 428.1961, $C_{24}H_{24}N_6O_2$ requires 428.1954).

2,6-Bis(4-methoxyphenylmethyl)-4,9-bis(4-methoxyphenylmethyliminomethylenyl)-1,5-dioxo-1,2,5,6-tetrahydro-2,5,7,10-tetraazaanthracene (6d). Yield, 72%; yellow crystals (from ethyl acetate), mp 255 °C (decomp.); ν_{max} KBr/cm^{-1} 3548, 3473, 3413, 2996, 2940, 2892, 2836, 1670, 1639, 1608, 1513, 1297, 1232, 1174, 1029, 989, 827; δ_H (270 MHz, DMSO-d_6, 100 °C): 9.19 (s, 2H, N=CH), 8.49 (s, 2H), 7.39 (d, 4H, *J* 8.0 Hz, Ar), 7.30 (d, 4H, *J* 8.0 Hz, Ar), 6.93 (d, 8H, *J* 8.0 Hz, Ar), 5.32 (s, 4H, CH_2), 4.79 (s, 4H, CH_2), 3.78 (s, 6H, OCH_3), 3.77 (s, 6H, OCH_3); δ_C (68 MHz, DMSO-d_6,100 °C): 158.8, 154.0, 145.3, 137.7, 131.3, 129.0, 128.6, 128.1, 113.9, 113.6, 111.8, 63.2, 54.8, 51.0; *m*/*z* (EI): 748 (M^+, 55), 729 (22), 679 (77), 629 (43), 579 (43), 552 (32), 529 (41), 479 (37), 430 (37), 368 (50), 317 (90), 121 (100) (Found: 748.3001, $C_{44}H_{40}N_6O_6$ requires 748.3009).

2,6-Dibenzyl-4,9-bis(benzyliminomethylenyl)-1,5-dioxo-1,2,5,6-tetrahydro-2,5,7,10-tetraazaanthracene (6e). Yield, 65%; yellow crystals (from ethyl acetate), mp 242 °C (decomp.); ν_{max} KBr/cm^{-1} 3548, 3469, 3411, 1670, 1641, 1606, 1494, 1355, 1336, 732, 694; δ_H (270 MHz, DMSO-d_6, 100 °C): 9.20 (s, 2H, N=CH), 8.53 (s, 2H), 7.44–7.23 (m, 20H, Ph), 5.39 (s, 2H, CH_2Ph), 4.84 (s, 2H, CH_2Ph); δ_C (68 MHz, DMSO-d_6,100 °C): 159.3, 154.5, 145.4, 139.3, 136.2, 128.2, 127.9, 127.5, 126.4, 111.9, 63.9, 51.6; *m*/*z* (EI): 628 (M^+, 0.62), 539 (0.12), 440 (0.68), 349 (0.27), 275 (0.32), 195 (22), 91 (base peak) (Found: 628.2587, $C_{40}H_{32}N_6O_2$ requires 628.2559).

Synthesis of semi-DOTTADs

7-Phenyl-2-(2-phenylethenyl)-7,8-dihydropyrano[4,3-*b*]pyridin-5-one-3-carboxylic acid (9). Diethyl 2,6-dimethylpyridine-3,5-dicarboxylate (**1**) (2.37 g, 10 mmol) and benzaldehyde (6.0 ml, 5.74 g, 54 mmol) was heated without solvent at 160–80 °C for 2 h. After cooling the precipitated crystals were washed with ethanol and recrystallised from acetic acid. The *title product* (2.89 g, 78%) was obtained as a white powder, mp 268–269 °C (lit.[3] mp 269 °C); ν_{max} KBr/cm^{-1} 3554, 3473, 3413,

1725, 1695, 1631, 1585, 1573, 1560, 1438, 1205; δ_H (270 MHz, DMSO-d_6, 50 °C): 8.64 (s, 1H, H-4), 8.19 (d, 1H, *J* 15.8 Hz, CH=), 8.01 (d, 1H, *J* 15.8 Hz, CH=), 7.64 (d, 2H, *J* 7.3 Hz, Ph–H), 7.55 (d, 2H, *J* 7.3 Hz, Ph–H), 7.45 (m, 6H, Ph–H), 5.90 (dd, 1H, *J* 3.3 and 11.5 Hz, H-7), 3.64 (dd, 1H, *J* 11.5 and 17.2 Hz, H-8), 3.44 (dd, 1H, *J* 3.3 and 17.2 Hz, H_2-8); δ_C (68 MHz, DMSO-d_6): 167.0, 164.0, 161.1, 158.0, 140.3, 138.8, 138.6, 136.3, 129.8, 129.4 (2×CH), 129.0 (2×CH), 128.2, 128.0 (2×CH), 126.8 (2×CH), 124.8, 124.7, 118.9, 78.8, 37.6; *m*/*z* (EI): 371 (M^+, base peak), 326 (22), 280 (9), 265 (13), 237 (44), 191 (20), 69 (37) (Found: 371.1141, $C_{23}H_{17}NO_4$ requires 371.1157).

2,6-Bis[2-(2-bromophenyl)ethenyl]pyridine-3,5-dicarboxylic acid (10a). Prepared from 2-bromobenzaldehyde and **1** as above. Yield, 85%; white powder, mp 290–291 °C (Found: C, 52.1; H, 2.7; N, 2.7; $C_{23}H_{15}NO_4Br_2$ requires C, 52.20; H, 2.86; N, 2.65%); ν_{max} KBr/cm^{-1} 2857, 2625, 1680, 1619, 1568, 1516, 1465, 1431, 1276, 1262, 1211, 1104, 1021; δ_H (250 MHz, DMSO-d_6): 11.25 (br s, 2H, CO_2H), 8.68 (s, 1H, H-4), 8.45 (d, 2H, *J* 15.5 Hz, CH=), 8.22 (d, 2H, *J* 15.5 Hz, CH=), 7.79 (d, 2H, *J* 7.6 Hz, Ar–H), 7.64 (d, 2H, *J* 7.6 Hz, Ar–H), 7.42 (t, 2H, *J* 7.6 Hz, Ar–H), 7.25 (t, 2H, *J* 7.6 Hz, Ar–H); δ_C (68 MHz, DMSO-d_6): 166.0, 154.8, 142.4, 135.6, 134.7, 133.2, 130.7, 128.4, 127.6, 127.5, 124.7, 123.5.

2,6-Bis[2-(4-chlorophenyl)ethenyl]pyridine-3,5-dicarboxylic acid (10b). Prepared from 4-chlorobenzaldehyde and **1** as above. Yield, 80%; yellow powder, mp 288 °C (Found: C, 62.7; H, 3.5; N, 3.1; $C_{23}H_{15}NO_4Cl_2$ requires C, 62.74; H, 3.43; N, 3.18%); ν_{max} KBr/cm^{-1} 2980, 2349, 1683, 1621, 1561, 1520, 1490, 1406, 1302, 1288, 1093; δ_H (250 MHz, DMSO-d_6): 11.45 (br s, 2H, CO_2H), 8.62 (s, 1H, H-4), 8.17 (d, 2H, *J* 15.6 Hz, CH=), 8.03 (d, 2H, *J* 15.6 Hz, CH=), 7.61 (d, 4H, *J* 8.2 Hz, Ar–H), 7.41 (d, 4H, *J* 8.2 Hz, Ar–H); δ_C (68 MHz, DMSO-d_6): 166.9, 155.4, 142.5, 135.8, 135.3, 133.6, 129.4, 128.9, 125.5, 122.4.

6-Alkyl-2-(2-phenylethenyl)-8-(phenylhydroxymethyl)-6*H*-[1,6]naphthyridin-5-one-3-carboxylic acids (11)

General procedure. $POCl_3$ (9.3 mL) was added dropwise to an *N*-formyldialkylamine (40 mmol) with efficient stirring and external ice cooling. To this solution was added in one lot the 7-phenyl-2-(2-phenylethenyl)-7,8-dihydropyrano[4,3-*b*]pyridin-5-one-3-carboxylic acid (10 mmol) and after one minute stirring the mixture was heated at 80–85 °C for 12 h during which it become red. Most of the $POCl_3$ was removed *in vacuo* and ice–water added, followed by required amine until basic. After 30 min stirring the tan coloured precipitate was filtered, washed well with water, dried and recrystallised.

6-Methyl-2-(2-phenylethenyl)-8-(phenylhydroxymethyl)-6*H*-[1,6]naphthyridin-5-one-3-carboxylic acid (11a). Yield, 57%; brown powder (from acetonitrile), mp 230 °C; ν_{max} KBr/cm^{-1} 3423, 1637, 1602, 1569, 1220; δ_H (270 MHz, DMSO-d_6): 8.90 (s, 1H, CO_2H), 8.20 (s, 1H, OH), 7.77 (m, 3H), 7.65 (m, 3H), 7.55–7.39 (m, 5H), 7.29 (t, 1H, *J* 7.4 Hz), 6.37 (s, 1H), 3.63 (s, 3H, Me); δ_C (68 MHz, DMSO-d_6): 167.0, 160.9, 157.0, 155.6, 151.9, 145.1, 139.2, 137.5, 136.2, 129.6 (2× CH), 129.1, 128.1 (2×), 127.6, 127.5 (2 × CH), 127.2 (2 × CH), 127.0, 125.2, 120.1, 118.2, 68.4, 39.1; *m*/*z* (EI): 412 (M^+, 22), 410 (98), 396 (46), 381 (base peak), 371 (25), 306 (20), 275 (18), 105 (42) (Found: 412.1422, $C_{25}H_{20}N_2O_4$ requires 412.1423).

6-Ethyl-2-(2-phenylethenyl)-8-(phenylhydroxymethyl)-6*H*-[1,6]naphthyridin-5-one-3-carboxylic acid (11b). Yield, 51%; brown powder (from acetonitrile), mp 220 °C; ν_{max} KBr/cm^{-1} 3548, 3471, 3413, 1778, 1698, 1619, 1567, 1504, 1236, 1199; δ_H (270 MHz, DMSO-d_6): 8.98 (s, 1H, CO_2H), 8.65 (s, 1H, OH), 8.22 (m, 3H), 7.98 (m, 3H), 7.91–7.67 (m, 6H), 6.43 (s, 1H), 4.11 (q, 2H, *J* 7.1 Hz, CH_2), 1.25 (t, 3H, *J* 7.1 Hz, Me); δ_C (68 MHz, DMSO-d_6): 166.9, 160.3, 160.1, 155.6, 151.8, 145.1, 139.3, 137.3, 136.3, 129.3 (2× CH), 129.2, 129.0 (2×CH), 128.1, 127.8 (2 × CH), 127.5 (2 × CH), 127.1, 124.8, 120.5, 118.2, 68.9, 43.7, 14.3; *m*/*z* (EI): 426 (M^+, 15), 424 (22), 410 (27), 371 (base peak), 326 (41), 265 (98), 237 (29), 159 (40) (Found: 426.1564, $C_{26}H_{22}N_2O_4$ requires 426.1579).

6-Allyl-2-(2-phenylethenyl)-8-(phenylhydroxymethyl)-6*H*-[1,6]naphthyridin-5-one-3-carboxylic acid (11c). Yield, 62%; brown powder (from acetonitrile), mp 167 °C; ν_{max} KBr/cm^{-1} 3421, 2989, 1724, 1687, 1623, 1567, 1519, 1270, 1216; δ_H (250 MHz, DMSO-d_6): 9.03 (s, 1H, CO_2H), 8.75 (s, 1H, OH), 8.25–7.85 (m, 6H), 7.75–7.66 (m, 6H), 6.47 (s, 1H), 6.10–5.92 (m, 1H, allyl CH), 5.47–5.37 (m, 2H, CH_2=), 4.76–4.38 (m, 2H, CH_2); δ_C (63 MHz, DMSO-d_6): 167.2, 160.2, 160.0, 155.6, 152.3, 145.6, 139.0, 137.8, 137.3, 129.4 (2 × CH), 129.2, 129.1 (2 × CH), 128.0, 127.8 (2 × CH), 127.2 (2 × CH), 127.0, 125.1, 120.6, 118.9, 118.8, 114.0, 72.1, 51.5; *m*/*z* (EI): 438 (M^+, 1) 372 (25), 357 (25), 195 (15), 125 (70), 69 (base peak) (Found: 438.1569, $C_{27}H_{22}N_2O_4$ requires 438.1579).

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