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The Synthesis and Structural Characterisation of a Series of Hydrophobic Piperidones and Bispidones

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A series of dipyridin-2-yl-substituted piperidones with alkyl chains of variable length [$CH_3(CH_2)_n$–], n = 0, 5, 11, 17, have been synthesised. The piperidones are all crystalline materials and exist in the solid state as the enol tautomers, which are stabilised by hydrogen bonding. The hydrogen bonding accounts for the crystallinity of these materials, despite the presence of long alkyl chains, and extensive hydrophobic regions are observed in the extended structures of some of these molecules. A series of twelve bispidones have been synthesised from their piperidone precursors by a condensation reaction with *N*,*N*-disubstituted diamines, $H_2N(CH_2)_2$-NR_2 (R = Me, Et, *i*Pr). Solid-state structures have been obtained for three of these bispidones, all of which display a double-chair conformation. The structures show a high degree of preorganisation for metal coordination, and hence are suitable candidates for coordination complexes, where these bispidones are capable of acting as pentadenate ligands.

Introduction

Substituted diazabicyclo[3.3.1]nonanes (known as bispidones) are an important category of multidentate ligands which are currently the subject of considerable interest. Bispidone ligands feature a very rigid bicyclic backbone,[1–3] adopting either a chair-boat or a double-chair conformation.[1–3] This inherent feature has led to their utilisation in both medicinal and coordination chemistry. The rigidity of the bispidone backbone is important to medicinal chemists studying the affinity of the molecule to opioid receptors.[4–6] Even subtle changes in the substituents on the bispidone ring can result in a complete loss of affinity. Bispidones have also received attention in coordination chemistry, because replacement of the skeletal carbon atoms at the 3- and 7-positions by groups containing possible donor atoms such as nitrogen can result in the bispidone becoming a tetra-, penta-or hexadentate ligand, depending on the substituents attached to the heteroatoms at these positions (Figure 1).

Comba and co-workers have studied the complexation of a number of 2,4-bis(2-pyridinyl)-substituted 9-oxo-3,7-diazabicyclo[3.3.1]nonanedicarboxylates to a wide range of metal centres.[7–22] They have shown that the rigid nature of the backbone allows preorganisation of the coordination sphere around the metal centre, resulting in the formation of highly stable metal complexes.[7,14] Structural studies of these complexes have shown that the bicyclic backbone prefers to form a double-chair conformation, with the intramolecular distances between the two bicyclic nitrogen atoms consistently observed to fall in a small range, 2.90–2.98 Å.[14] The stability offered by metal complexes of substituted bispidone ligands has led to their utilization in stabilising peroxo species. This stability is conferred by the rigid preorganised tetradentate N_4 donor set offered by these types of bispidone ligands. Oxidation of (bispidone)copper(I) complexes with O_2 leads to the formation of (peroxido)dicopper(II) complexes,[9,10,12] whilst (bispidone)iron(III) complexes react with H_2O_2 in methanol to form (peroxido)iron(III) complexes,[13,17] which are capable of acting as catalysts in the epoxidation and dihydroxylation of olefins.[20] Other uses of bispidone complexes include the use of copper(II) complexes as efficient catalysts for catechol oxidase activity,[11] and for the aziridination of styrene.[15]

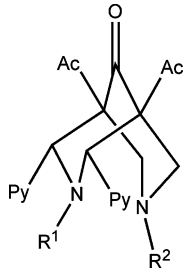

Figure 1. Double-chair conformation of bispidones showing nitrogen atoms at the 3- and 7-position on the bicyclic backbone.

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Whilst much is known about the structures of their coordination compounds, relatively little research has been conducted regarding the ligands themselves. Crystal structures of a number of bispidone ligands have been reported (27 hits for non-complexed bispidones in a search of the Cambridge Structural Database).[23] The bicyclic bispidones tend to adopt either a double-chair or a chair-boat conformation, with studies showing that systems where the two ring nitrogen atoms are markedly pyramidal tend to adopt chair-boat conformations, whilst the double-chair conformation is preferred for systems with planar nitrogen atoms.[24] All examples containing diester substituents as shown in Figure 1 (nine reported in the CCDC database)[5–7,10,18,25] feature the bicyclic backbone with a double-chair conformation. Whilst this backbone is preorganised for metal coordination, in all the examples featuring pyridyl groups the donor atoms are located away from the metal coordination site, in contrast to the orientation of the pyridyl groups in the metal complexes. Bispidone ligands also offer the option of incorporating long alkyl chains which may be useful in tailoring the properties to make the ligands and complexes more hydrophobic. To this end we now present our findings on the synthesis of a series of piperidone compounds which incorporate alkyl chains of increasing length. We have then synthesised a series of pentadentate bispidones by utilising a series of diamines $H_2NCH_2CH_2NR_2$ (R = Me, Et, *i*Pr) in the second condensation step, and the structural features of these compounds are now presented.

Results and Discussion

Synthesis of Piperidones

A series of four piperidones (**1**, **5**, **9** and **13**) have been synthesised according to the method of Haller and Ashauer[26] by a Mannich condensation reaction of pyridine-2-carbaldehyde and dimethyl 3-oxopentanedioate with a range of four primary amines, $R'NH_2$, where R′ = alkyl chains of differing lengths [R′ = CH_3, $(CH_2)_5CH_3$, $(CH_2)_{11}CH_3$ and $(CH_2)_{17}CH_3$], as shown in Figure 2.

The four compounds were recrystallised from warm methanol to yield the colourless, crystalline materials **1**, **5**, **9** and **13**. These piperidones may exhibit a number of possible conformations (as a consequence of the ring containing potentially four chiral centres), and additionally there is the possibility of keto and enol tautomers. The NMR spectra of **1**, **5**, **9** and **13** may therefore be highly complicated, but in all four cases the number of peaks observed in the ^1H and $^{13}C\{^1H\}$ NMR spectra in $CDCl_3$ suggest that one conformation dominates in solution. It appears that the keto tautomer is favoured in $CDCl_3$ solution because a resonance is observed between δ_C = 201 and 204 ppm for all four piperidones, which is consistent with a ketone C=O group. Additionally, the $^{13}C\{^1H\}$ NMR spectra of all four compounds display only one carboxylate carbon resonance (δ_C = 168–169 ppm) and one methoxy carbon resonance (δ_C = 52–53 ppm), suggesting equivalence of the two CO_2Me groups. The NMR spectra of **1** were also run in [D_4]methanol, [D_6]acetone and [D_8]toluene, and in all cases exhibited similar features to the spectra run in $CDCl_3$.

Solid-State Structure and Conformation of 1

Crystals of **1** were grown from methanol, and found to be suitable for single-crystal X-ray diffraction. The compound crystallises in the orthorhombic space group $P2_12_12_1$ with two independent molecules in the asymmetric unit. The molecular structure of **1** is shown in Figure 3, along with selected bond lengths and angles.

The structural data shows that the molecule has crystallised as the enol tautomer, due to favourable hydrogen bonding of the enol proton to a neighbouring carboxylate C=O oxygen atom [H(3)···O(15) 1.71(7) Å, H(33)···O(45) 1.68(6) Å]. This contrasts with the spectroscopic data for the piperidones in solution, where the keto form dominates. A carbon–carbon double bond is therefore formed in the ring [C(3)–C(4) 1.349(6) Å], and as a consequence the ring is flattened at the sp^2 carbon atom, resulting in distortion from a chair conformation. The piperidone ring therefore adopts an envelope conformation, which is shown for one of the two molecules of **1** in Figure 4.

The CO_2Me groups are clearly inequivalent in the crystal structure as a consequence of the hydrogen bonding present, and the solid-state preference for the enol tautomer. The CO_2Me group involved in hydrogen bonding to the

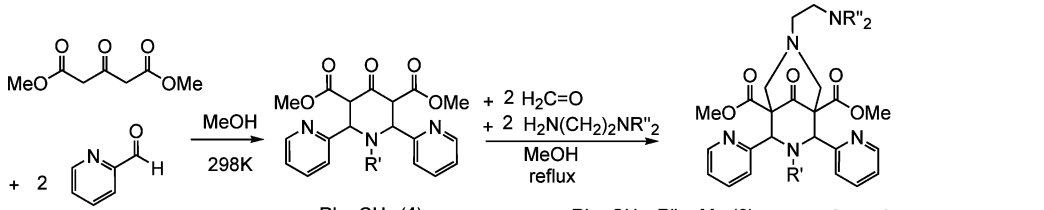

Figure 2. Reaction scheme for the formation of the intermediate piperidones **1**, **5**, **9** and **13**, and the bispidones derived from these precursors (**2**–**4**, **6**–**8**, **10**–**12** and **14**–**16**).

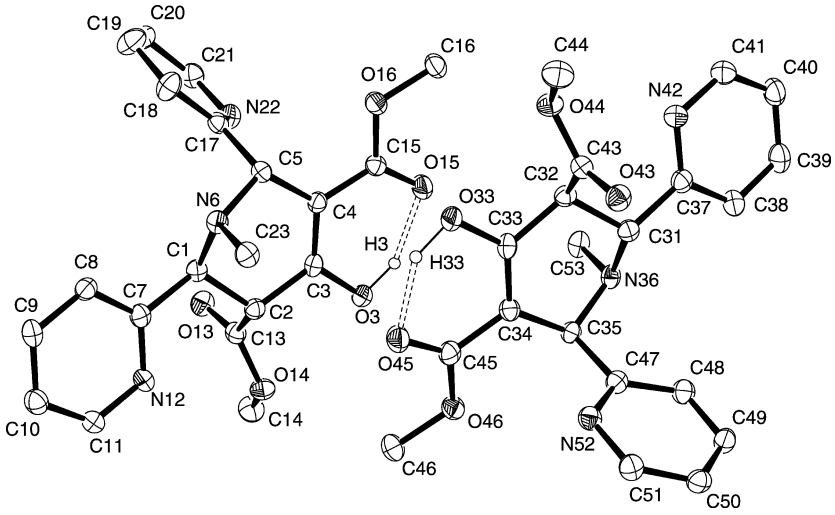

Figure 3. Molecular structure of **1**. Thermal ellipsoids are shown at the 30% probability level. Selected protons omitted for clarity. Selected bond lengths [Å] and angles [°]: Molecule 1: C(1)–C(2) 1.531(6), C(2)–C(3) 1.507(6), C(3)–C(4) 1.349(6), C(4)–C(5) 1.512(6), C(5)–N(6) 1.459(5), C(1)–N(6) 1.475(6), C(23)–N(6) 1.462(6), C(3)–O(3) 1.351(5), O(3)–H(3) 0.97(7), C(2)–C(13) 1.523(7), C(13)–O(13) 1.201(6), C(13)–O(14) 1.347(6), C(14)–O(14) 1.444(6), C(4)–C(15) 1.441(6), C(15)–O(15) 1.242(5), C(15)–O(16) 1.337(5), C(16)–O(16) 1.439(6); N(6)–C(1)–C(2) 113.4(4), C(1)–C(2)–C(3) 110.7(4), C(2)–C(3)–C(4) 123.7(4), C(3)–C(4)–C(5) 120.5(4), C(4)–C(5)–N(6) 113.2(4), C(5)–N(6)–C(1) 109.7(3), C(1)–N(6)–C(23) 113.4(4), C(5)–N(6)–C(23) 112.9(3). Molecule 2: C(31)–C(32) 1.537(6), C(32)–C(33) 1.503(6), C(33)–C(34) 1.351(6), C(34)–C(35) 1.516(6), C(35)–N(36) 1.464(6), C(31)–N(36) 1.466(6), C(53)–N(36) 1.466(6), C(33)–O(33) 1.349(5), O(33)–H(33) 1.01(6), C(32)–C(43) 1.522(7), C(43)–O(43) 1.205(6), C(43)–O(44) 1.342(6), C(44)–O(44) 1.446(6), C(34)–C(45) 1.455(6), C(45)–O(45) 1.236(6), C(45)–O(46) 1.334(6), C(46)–O(46) 1.445(6); C(31)–N(36)–C(35) 109.4(3), C(31)–N(36)–C(53) 113.7(4), C(35)–N(36)–C(53) 112.2(3), N(36)–C(31)–C(32) 112.7(4), C(31)–C(32)–C(33) 110.9(4), C(32)–C(33)–C(34) 123.5(4), C(33)–C(34)–C(35) 118.4(4), C(34)–C(35)–N(36) 112.7(3).

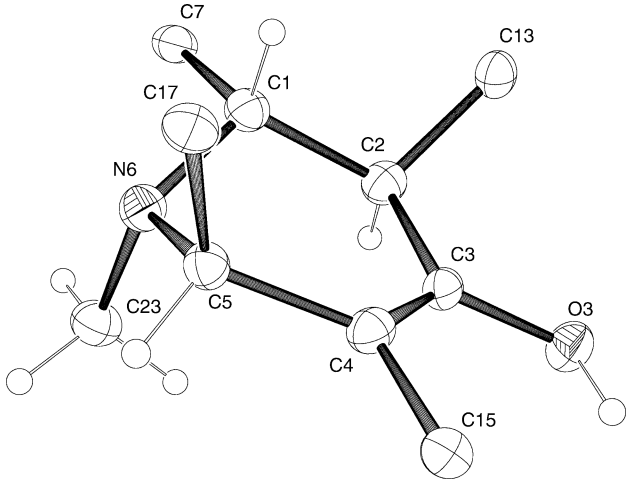

Figure 4. Conformation of the piperidone ring in **1**. C(7) and C(17) are pyridyl groups, C(13) and C(15) are CO_2Me groups.

enol proton exhibits lengthening of the C=O bond [C(15)–O(15) 1.242(5) Å, C(45)–O(45) 1.236(6) Å], compared with the C=O bonds for the CO_2Me groups not involved in hydrogen bonding [C(13)–O(13) 1.201(6) Å, C(43)–O(43) 1.205(6) Å]. The piperidone ring in **1** features three chiral centres, C(1), C(2) and C(5) as shown in Figure 4. The pyridine rings attached to C(1) and C(5) are arranged pointing away from each other, with one pyridyl group pointing up and one down, hence each chiral centre is orientated in the same fashion, either both (*R*) or both (*S*). The CO_2Me group at C(2) points up, and is adjacent to the pyridyl ring attached to C(1), which points down. This arrangement minimises steric interactions, and is presumably the energetically most favourable. The second CO_2Me group is attached to the sp^2 ring carbon atom, C(4) in Figure 4, where the potentially fourth chiral centre is removed by formation of the enol tautomer. Finally, the geometry at the ring nitrogen atom is pyramidal, with C–N–C angles varying between 109 and 113°, and thus being somewhat larger than the idealised angle of 107°.

The structure of **1** features two independent molecules which are linked by intermolecular hydrogen bonds between the C=O oxygen atom of a CO_2Me group and a methyl proton of the NMe group, [H(53b)···O(15) 2.52 Å and H(23c)···O(45) 2.42 Å], as shown in Figure 5.

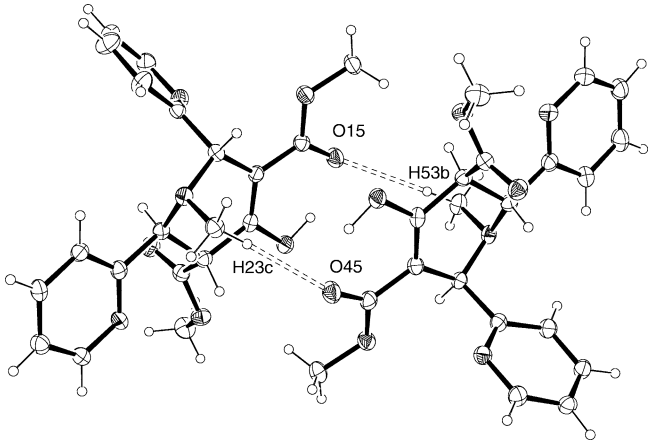

Figure 5. Intermolecular hydrogen bonding between the two independent molecules of **1**.

Synthesis and Structural Study of Bispidones 2–4

Piperidone **1** has been utilised in the synthesis of a series of bispidones by performing a second condensation with formaldehyde and a series of unsymmetrically substituted diamines, $H_2N(CH_2)_2NR''_2$, where R'' = Me (**2**), Et (**3**), and *i*Pr (**4**), as shown in Figure 2. The bispidones formed have the potential to act as pentadentate ligands, with five possible nitrogen donor atoms. The possibility of formation of an enol tautomer is removed upon bispidone formation as the protons on the two carbon atoms adjacent to the ring ketone carbon atom are removed in the condensation process. The $^{13}C\{^1H\}$ NMR spectra of **2**, **3** and **4** all therefore display a ketone carbon resonance (δ_C = 204.1 ppm). ^1H NMR spectroscopy has previously been used to provide information of the conformation of bispidones.[5] The CH protons on the ring carbon atom attached to the pyridyl rings appear at δ_H = 4.75 ppm for **2**, and δ_H = 4.80 ppm for **3** and **4**. The presence of just one peak for these protons, and the chemical shift, are consistent with observations for bispidones which display a double-chair conformation with a *cis*-sym arrangement of the pyridyl rings.[5] This suggests that in solution the bispidones **2**–**4** exhibit this conformation also.

The bispidones **2**–**4** were recrystallised from warm methanol to yield in all cases crystals suitable for X-ray diffraction. The molecular structures of **2** (orthorhombic, $P2_12_12_1$), **3** (triclinic, $P\bar{1}$) and **4** (orthorhombic, *Pbca*) are shown in Figures 6, 7 and 8, respectively, along with selected bond lengths and angles. The structure of **3** exhibits disorder with two separate sites for all the atoms in the $CH_2CH_2NEt_2$ portion of the molecule.

The three bispidone structures all show a double-chair conformation of the bicyclic ring system (as has been observed for other uncomplexed bispidone systems containing two CO_2Me groups)[5–7,10,25] and is shown for compound **2** in Figure 9. The structure shows the pyridyl rings in a *cis*-sym orientation, which confirms the solution NMR spectroscopic data. The double-chair conformation brings the two bicyclic nitrogen atoms close together in each of the three structures [N(1)···N(4) 2.938(2) Å (**2**), N(3)···N(7) 2.931(2) Å (**3**), N(3)···N(7) 2.895(2) Å (**4**)]. These close N···N distances are typical of bispidione systems, both in metal complexes, and in uncoordinated examples. The conformation of the bispidone system in **2**, **3** and **4** differs from the conformation observed for metal complexes of bispidones only in the twisting of the pyridine rings. In all three

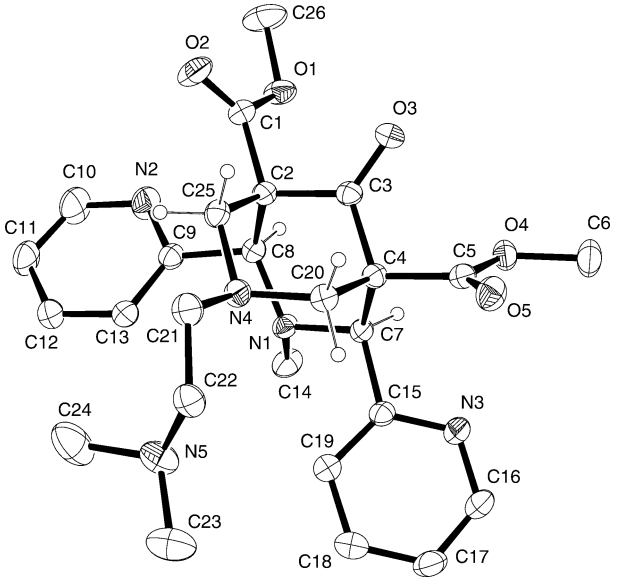

Figure 6. Molecular structure of **2**. Thermal ellipsoids are shown at the 30% probability level. Selected protons omitted for clarity. Selected bond lengths [Å] and angles [°]: C(2)–C(8) 1.564(3), C(2)–C(3) 1.516(3), C(3)–C(4) 1.520(3), C(4)–C(7) 1.563(3), C(7)–N(1) 1.465(3), C(8)–N(1) 1.472(3), C(14)–N(1) 1.470(3), C(2)–C(25) 1.542(3), C(4)–C(20) 1.546(3), C(20)–N(4) 1.458(3), C(25)–N(4) 1.459(3), C(21)–N(4) 1.468(3), C(22)–N(5) 1.445(3), C(23)–N(5) 1.460(4), C(24)–N(5) 1.457(4), C(3)–O(3) 1.203(2), C(1)–C(2) 1.531(3), C(1)–O(2) 1.201(3), C(1)–O(1) 1.328(3), C(26)–O(1) 1.449(3), C(4)–C(5) 1.522(3), C(5)–O(5) 1.207(3), C(5)–O(4) 1.330(3), C(6)–O(4) 1.441(3); N(1)–C(8)–C(2) 113.66(16), C(8)–C(2)–C(3) 110.42(17), C(2)–C(3)–C(4) 110.24(16), C(3)–C(4)–C(7) 108.83(16), C(4)–C(7)–N(1) 113.34(16), C(7)–N(1)–C(8) 116.23(16), C(7)–N(1)–C(14) 108.05(16), C(8)–N(1)–C(14) 108.38(17), C(20)–N(4)–C(21) 110.38(17), C(20)–N(4)–C(25) 110.38(16), C(21)–N(4)–C(25) 108.30(17), C(22)–N(5)–C(23) 109.3(2), C(22)–N(5)–C(24) 111.4(2), C(23)–N(5)–C(24) 109.7(2).

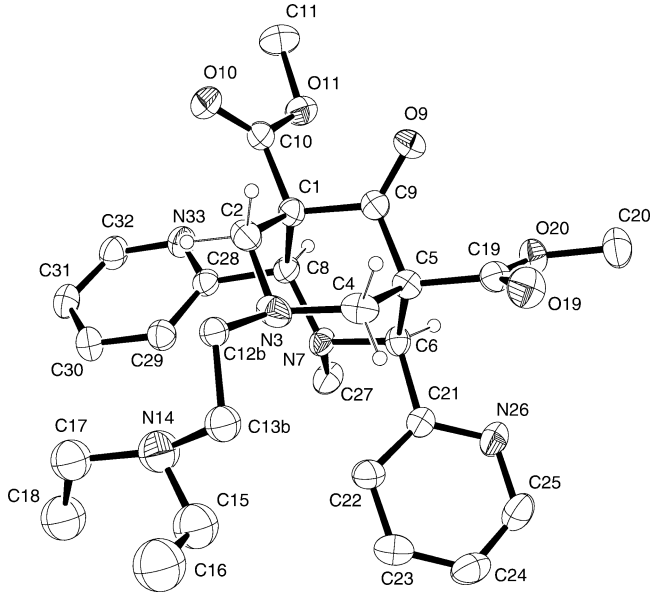

Figure 7. Molecular structure of **3**. Thermal ellipsoids are shown at the 30% probability level. Selected protons omitted for clarity. One site is shown for atoms C(12), C(13), N(14), C(15), C(16), C(17) and C(18) which are all disordered over two sites. Selected bond lengths [Å] and angles [°]: C(1)–C(2) 1.545(3), C(1)–C(9) 1.516(3), C(5)–C(9) 1.518(3), C(4)–C(5) 1.547(3), C(2)–N(3) 1.451(3), C(4)–N(3) 1.457(3), C(12b)–N(3) 1.449(4), C(1)–C(8) 1.568(3), C(5)–C(6) 1.565(3), C(6)–N(7) 1.468(2), C(8)–N(7) 1.462(3), C(27)–N(7) 1.473(3), C(9)–O(9) 1.211(3), C(1)–C(10) 1.527(3), C(10)–O(10) 1.194(3), C(10)–O(11) 1.335(3), C(11)–O(11) 1.448(4), C(5)–C(19) 1.532(3), C(19)–O(19) 1.196(2), C(19)–O(20) 1.331(2), C(20)–O(20) 1.449(3); N(3)–C(2)–C(1) 111.87(17), C(2)–C(1)–C(9) 103.96(16), C(1)–C(9)–C(5) 110.64(16), C(9)–C(5)–C(4) 104.26(16), C(2)–N(3)–C(4) 111.41(17), C(1)–C(8)–N(7) 113.87(16), C(5)–C(6)–N(7) 113.47(16), C(6)–N(7)–C(8) 116.69(15), C(6)–N(7)–C(27) 107.59(15), C(8)–N(7)–C(27) 108.32(15).

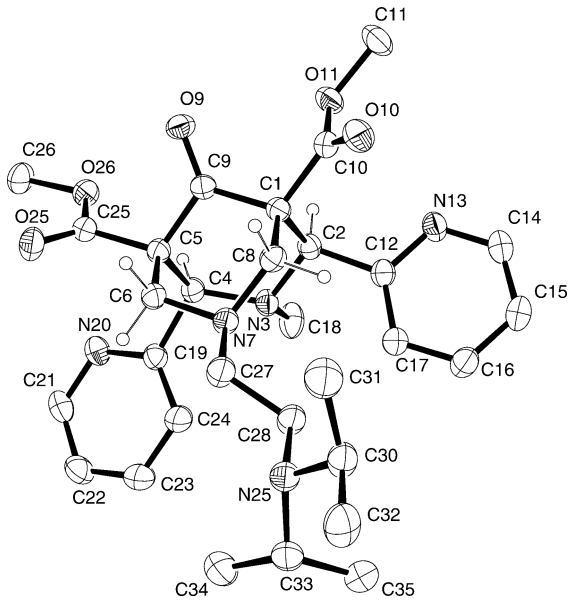

Figure 8. Molecular structure of **4**. Thermal ellipsoids are shown at the 30% probability level. Selected protons omitted for clarity. Selected bond lengths [Å] and angles [°]: C(1)–C(8) 1.545(3), C(1)–C(9) 1.519(2), C(9)–C(5) 1.519(3), C(5)–C(6) 1.542(3), C(6)–N(7) 1.459(2), C(8)–N(7) 1.454(2), C(27)–N(7) 1.467(3), C(1)–C(2) 1.566(2), C(4)–C(5) 1.564(2), C(2)–N(3) 1.460(2), C(4)–N(3) 1.470(2), C(18)–N(3) 1.466(3), C(28)–N(25) 1.478(3), C(30)–N(25) 1.482(3), C(33)–N(25) 1.481(3), C(9)–O(9) 1.208(2), C(1)–C(10) 1.534(3), C(10)–O(10) 1.202(2), C(10)–O(11) 1.329(2), C(11)–O(11) 1.444(4), C(5)–C(25) 1.530(2), C(25)–O(25) 1.200(2), C(25)–O(26) 1.332(2), C(26)–O(26) 1.446(3); C(5)–C(6)–N(7) 111.03(16), C(6)–C(5)–C(9) 105.04(15), C(5)–C(9)–C(1) 110.32(14), C(9)–C(1)–C(8) 106.33(14), C(1)–C(8)–N(7) 112.10(14), C(6)–N(7)–C(8) 110.10(14), C(6)–N(7)–C(27) 110.30(15), C(8)–N(7)–C(27) 111.07(15), C(1)–C(2)–N(3) 113.16(14), C(5)–C(4)–N(3) 114.08(14), C(2)–N(3)–C(4) 117.11(14), C(2)–N(3)–C(18) 108.70(17), C(4)–N(3)–C(18) 108.08(16), C(28)–N(25)–C(30) 110.79(16), C(30)–N(25)–C(33) 111.58(17), C(30)–N(25)–C(33) 114.81(16).

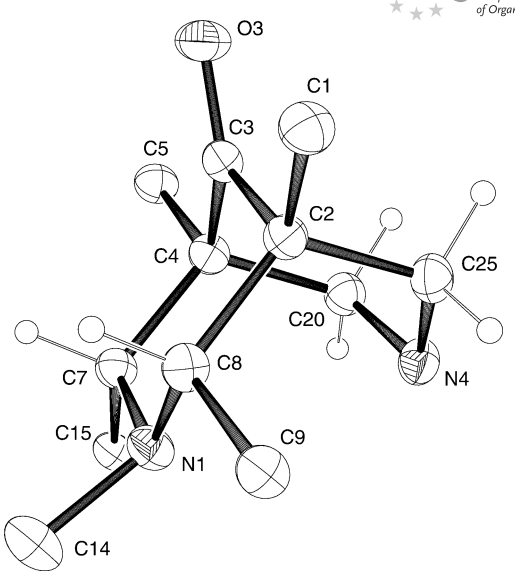

Figure 9. Double-chair conformation adopted by the bispidone backbone in compound **2**. C(9) and C(15) are pyridyl groups. N(1) is the N–CH_3 nitrogen atom, whilst N(4) is bound to the pendant diamine arm.

structures the pyridyl rings are rotated such that the nitrogen atoms are pointing away from the bicyclic ring nitrogen atoms, whilst in metal complexes the pyridyl rings rotate by 180°, and thus a pocket is created whereby the ligand can coordinate to the metal atom through all four nitrogen atoms.[7–22] The pyridine rings in **2**, **3** and **4** thus exhibit opposite chirality, in contrast to the situation observed for the piperidone **1**. This arrangement is not as energetically favourable in terms of sterics, but the energy gained by the formation of the stable bicyclic nonanone skeleton overcomes this.

Formation of the bicyclic ring system prevents tautomerism to the enol form, and this is supported by a comparison of the C=O ketone bond lengths in the three compounds [C(3)–O(3) 1.203(2) Å (**2**), C(9)–O(9) 1.211(3) Å (**3**), C(9)–O(9) 1.208(2) Å (**4**)], all being consistent with C=O double bonds. The C–C bond lengths of the bicyclic rings vary between 1.516(3) and 1.564(3) Å for **2**, 1.516(3) and 1.568(2) Å for **3**, and 1.519(2) and 1.566(2) Å for **4**. The C–N bonds to the bicyclic ring nitrogen atoms are consistent with C–N bonds to sp^3-hybridised carbon atoms [C–N 1.458(3)–1.472(3) Å (**2**), 1.449(4)–1.473(3) Å (**3**), 1.454(2)–1.470(2) Å (**4**)]. The angles around the bicyclic ring nitrogen atoms again confirm a pyramidal geometry, consistent with the presence of the nitrogen lone pair. In the case of the nitrogen atom bound to the pendant diamine arm the three C–N–C angles are all nearly equal, and often close to the idealised 107°, e.g. for atom N(4) in **2**, where the three C–N–C angles are 110.38(17)°, 110.38(16)° and 108.30(16)°. In contrast, the N–CH_3 nitrogen atom in each of the three bispidones show some distortion from regular pyramidal geometry, with the C_{ring}–N–C_{ring} angle being larger than the other two, e.g. for atom N(1) in **2**, the C_{ring}–N–C_{ring} angle is 116.23(16)°, whilst the other two C–N–C angles are 108.05(16)° and 108.38(17)°. This observation is consistently observed for **3** and **4** also, and reflects the larger steric hindrance at the N–CH_3 centre from the two pyridyl rings bound to the adjacent carbon atoms.

Solid-State Conformations of Long-Chain Piperidones

With the successful formation of a series of pentadendate bispidones from the piperidone **1**, we therefore turned our attention to the piperidones which feature longer alkyl chains. The three long-chain piperidones **5**, **9** and **13** were all treated with the same series of diamines $H_2N(CH_2)_2$-NR''_2, where R'' = Me (**6**, **10** and **14**), Et (**7**, **11** and **15**), and *i*Pr (**8**, **12** and **16**), as shown in Figure 2. These bispidones were all synthesised by the same method utilised for **2**–**4**. All of the nine bispidones formed from these long-chain piperidones exist as viscous brown oils, which did not solidify upon attempts to recrystallise. These bispidones exhibit similar NMR spectroscopic features as **2**, **3** and **4**, and in view of the long alkyl chains present, it is not surprising that these materials are oils. The NMR spectra of the long-

chain bispidones are consistent with **2**, **3** and **4**, and it seems likely that these also adopt a double-chair conformation with a *cis*-sym arrangement of the pyridyl groups.

We were able to grow crystals of the parent piperidones, **5** (monoclinic, $P2_1/n$), **9** (monoclinic, $P2_1/c$) and **13** (monoclinic, $C2/c$), all of which, despite those with long alkyl chains (a C_{18} chain in the case of **13**), were formed as crystalline solids upon recrystallisation from warm methanol. The structures of the three long-chain piperidones are shown in Figures 10, 11 and 12, along with selected bond lengths and angles.

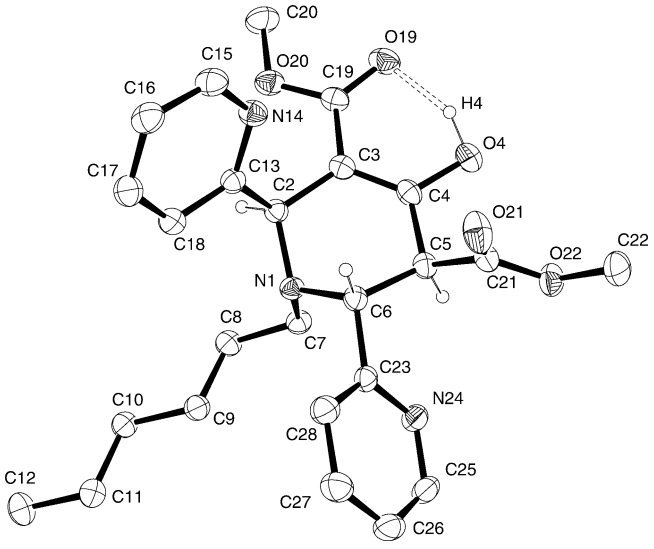

Figure 10. Molecular structure of **5**. Thermal ellipsoids are shown at the 30% probability level. Selected protons omitted for clarity. Selected bond lengths [Å] and angles [°]: C(2)–C(3) 1.521(3), C(3)–C(4) 1.351(3), C(4)–C(5) 1.494(3), C(5)–C(6) 1.536(3), C(2)–N(1) 1.469(3), C(6)–N(1) 1.469(3), C(7)–N(1) 1.475(3), C(4)–O(4) 1.351(2), O(4)–H(4) 0.96(4), C(3)–C(19) 1.451(3), C(19)–O(19) 1.234(3), C(19)–O(20) 1.331(3), C(20)–O(20) 1.439(3), C(5)–C(21) 1.517(3), C(21)–O(21) 1.195(3), C(21)–O(22) 1.324(3), C(22)–O(22) 1.449(4); N(1)–C(2)–C(3) 112.80(17), C(2)–C(3)–C(4) 121.1(2), C(3)–C(4)–C(5) 123.19(18), C(4)–C(5)–C(6) 110.28(17), C(5)–C(6)–N(1) 112.46(18), C(2)–N(1)–C(6) 109.35(16), C(2)–N(1)–C(7) 111.50(17), C(6)–N(1)–C(7) 115.26(18).

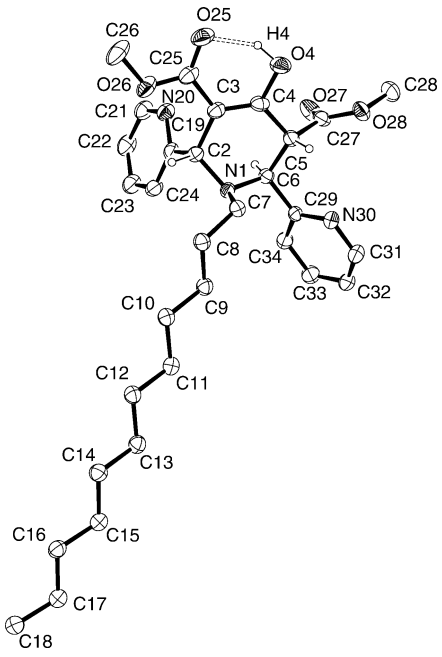

Figure 11. Molecular structure of **9**. Thermal ellipsoids are shown at the 30% probability level. Selected protons omitted for clarity. Selected bond lengths [Å] and angles [°]: C(2)–C(3) 1.528(4), C(3)–C(4) 1.335(4), C(4)–C(5) 1.503(4), C(5)–C(6) 1.527(4), C(2)–N(1) 1.469(3), C(6)–N(1) 1.475(3), C(7)–N(1) 1.474(4), C(4)–O(4) 1.351(3), O(4)–H(4) 0.94(4), C(3)–C(25) 1.451(4), C(25)–O(25) 1.235(4), C(25)–O(26) 1.335(4), C(26)–O(26) 1.454(4), C(5)–C(27) 1.514(4), C(27)–O(27) 1.199(4), C(27)–O(28) 1.315(3), C(28)–O(28) 1.454(5); N(1)–C(2)–C(3) 112.7(2), C(2)–C(3)–C(4) 121.3(2), C(3)–C(4)–C(5) 123.3(2), C(4)–C(5)–C(6) 110.5(2), C(5)–C(6)–N(1) 113.0(2), C(2)–N(1)–C(6) 109.8(2), C(2)–N(1)–C(7) 111.4(2), C(6)–N(1)–C(7) 114.4(2).

The three piperidones exist as the enol tautomers, as observed for **1**, with O–H···C=O hydrogen bonding, [O(19)···H(4) 0.96(4) Å (**5**), O(25)···H(4) 0.94(4) Å (**9**), O(33)···H(4) 0.97(4) Å (**13**)]. Presumably, this hydrogen bonding accounts for the crystalline nature of **5**, **9** and **13**, despite the long alkyl chains. This same effect was not observed for the bispidones generated from these compounds, as they are

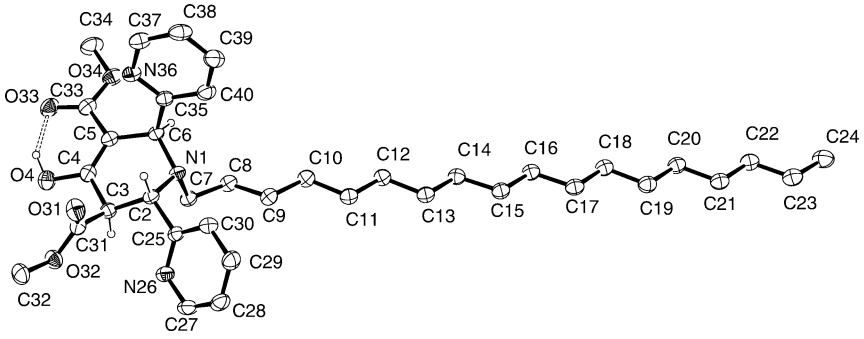

Figure 12. Molecular structure of **13**. Thermal ellipsoids are shown at the 30% probability level. Selected protons omitted for clarity. Selected bond lengths [Å] and angles [°]: C(2)–C(3) 1.525(4), C(3)–C(4) 1.510(4), C(4)–C(5) 1.341(4), C(5)–C(6) 1.516(4), C(2)–N(1) 1.470(3), C(6)–N(1) 1.471(3), C(7)–N(1) 1.479(4), C(4)–O(4) 1.351(3), O(4)–H(4) 0.97(4), C(3)–C(31) 1.517(4), C(31)–O(31) 1.203(4), C(31)–O(32) 1.326(3), C(32)–O(32) 1.445(4), C(5)–C(33) 1.459(4), C(33)–O(33) 1.228(3), C(33)–O(34) 1.334(3), C(34)–O(34) 1.453(4); N(1)–C(2)–C(3) 112.6(2), C(2)–C(3)–C(4) 109.7(2), C(3)–C(4)–C(5) 123.0(3), C(4)–C(5)–C(6) 121.4(2), C(5)–C(6)–N(1) 113.5(2), C(2)–N(1)–C(6) 109.7(2), C(2)–N(1)–C(7) 114.0(2), C(6)–N(1)–C(7) 111.98(19).

unable to convert to the enol, and thus offer no hydrogen-bonding options. The piperidone rings in all three compounds form the same envelope conformation observed for **1** and exhibit similar features with respect to the orientation of the pyridyl and acetyl groups.

In contrast to **1**, the extended structures of **5**, **9** and **13** do not show the formation of loosely linked pairs of molecules through intermolecular hydrogen bonding between the C=O oxygen atom of a CO_2Me group and a proton of the N–R group. This is likely to be a consequence of the longer alkyl chains present on this nitrogen atom in these three compounds, which contrasts with **1** where there is only an *N*-methyl group. The alkyl chains kink at the NCH_2 carbon atom so that the chain is orientated *gauche* to the nitrogen atom in the piperidone ring, with the chains then running in a regular fashion. This kink appears to direct the hydrophobic region away from the bulk of the molecule. The presence of the longer chain results in greater steric demand, and influences the extended structures of these compounds to varying degrees, through a tendency for the formation of fatty hydrophobic regions within the crystal packing. This aggregation of the long alkyl chains is different in the three molecules.

In **5** the molecules pack with weak intermolecular hydrogen bonding between the CO_2Me groups and protons on the pyridyl rings [O(21)···H(28) 2.45(3) Å, O(19)···H(25) 2.58(3) Å], as shown in Figure 13, and there appears to be no strong tendency for formation of hydrophobic regions.

In contrast, the extended structure of **9** shows a combination of the same intermolecular hydrogen bonding observed for **5**, between the CO_2Me groups and pyridyl protons, [O(25)···H(31) 2.61(3) Å, O(27)···H(34) 2.39(3) Å], and short H···H contacts between the C_{12} alkyl chains [H(8b)···H(12b) 2.21(4) Å], and therefore the crystal packing shows the formation of hydrophobic regions, see Figure 14.

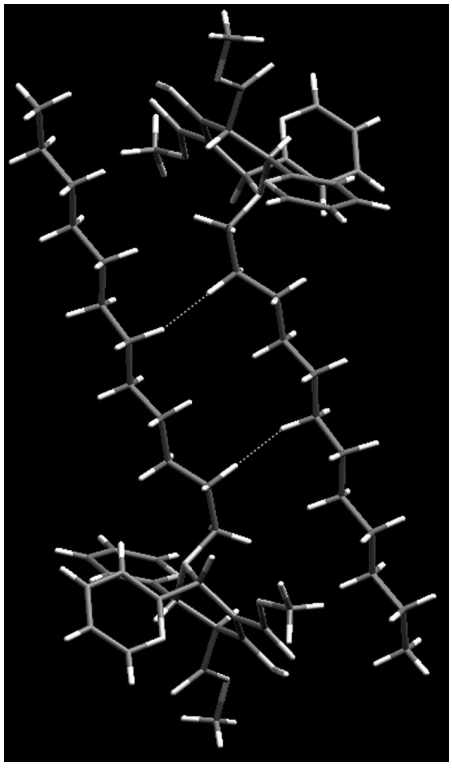

Figure 14. Extended structure of **9** showing aggregation of the hydrophobic regions.

The structure of **13** shows similar features with hydrogen bonding [O(33)···H(27) 2.63(3) Å, O(31)···H(30) 2.36(3) Å], and extensive aggregation of the C_{18} chains, although the shortest H···H contacts [H(8a)···H(24a) 2.38(4) Å, H(8b)···H(16b) 2.39(4) Å] are only just below the sum of the van der Waals radius for two hydrogen atoms. The extended structure, however, shows distinct formation of hydrophobic regions, as depicted in Figure 15.

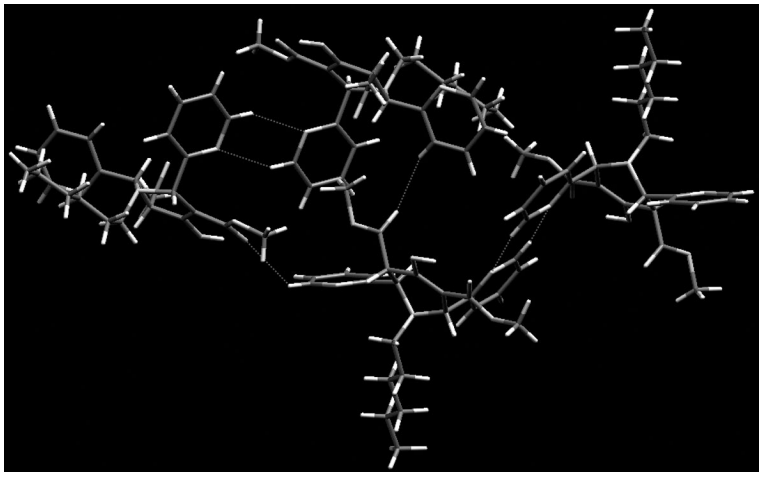

Figure 13. Extended structure of **5** showing intermolecular hydrogen bonding.

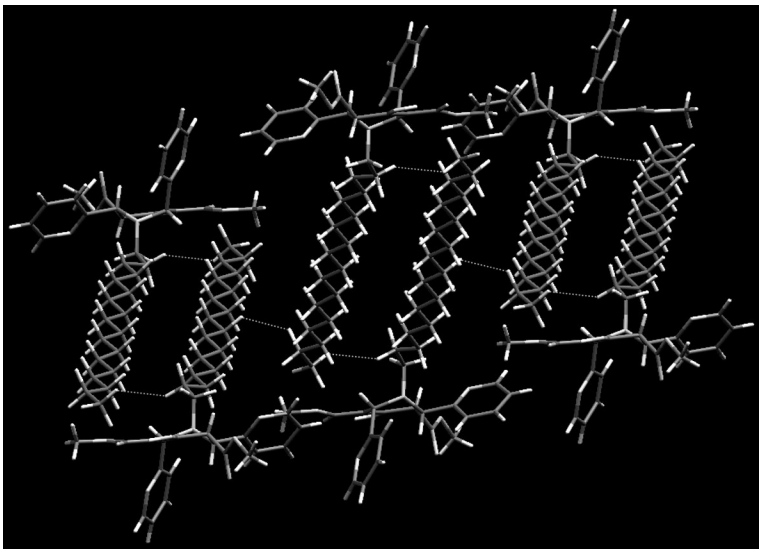

Figure 15. Extended structure of **13** showing aggregation of the hydrophobic regions.

Conclusions

This research has resulted in the successful synthesis of a series of four piperidones incorporating alkyl chains of varying length and their use in the formation of a series of bispidones capable of acting as pentadentate ligands. The piperidones all exist as the enol tautomer in the solid state, stabilised by hydrogen bonding, although NMR spectroscopic studies show that the keto tautomer is preferred in solution, indicating that formation of the enol tautomer is a solid-state phenomenon. Interestingly, the piperidones have chiral centres with matching geometry to stabilise the molecule energetically, but in the crystal structures of bispidones **2**–**4** this chirality is seen to be reversed, with pyridine rings and acetyl groups arranged with opposing chirality. This should be less favourable energetically; however, the energy gained by the formation of the rigid bicyclic backbone appears to negate this. Extensive hydrophobic regions are seen in the crystal structures of the longer-alkyl-chain piperidones **9** and **13**, with the long alkyl chains aggregating together in the extended structures. The ease of the synthesis of the bispidones and scope for future work makes these molecules important for chemists working in various fields.

Experimental Section

General Considerations: All reagents were purchased from Aldrich (methanol and Et_2O from BDH) and were used as supplied without further purification. ^1H and $^{13}C\{^1H\}$ NMR spectra were obtained with a Bruker DPX400 machine operating at 399.9 and 100.6 MHz, respectively. Peak positions for ^1H and $^{13}C\{^1H\}$ NMR spectroscopic data are quoted in ppm relative to external TMS using the high-frequency positive convention throughout. All spectra were recorded at 300 K. Mass spectra were recorded in positive-ion mode with a QTof Micromass spectrometer and a Waters 2790 separation module, using water/acetonitrile (1:1) (with 0.1% w/w formic acid) as the solvent. Melting points were recorded with a Bibby SMP10 melting point apparatus, and elemental analyses were carried out by the University of Manchester Chemistry Department's microanalytical service.

Crystallographic Details: Details of the structural analysis for compounds **1**, **2**, **3**, **4**, **5**, **9** and **13** are summarised in Tables 1 and Table 2. Diffraction data for all compounds were recorded with a Nonius κ-CCD four-circle diffractometer at 150(2) K (**1**, **5**, **9**, **13**) or 200(2) K (**2**, **3** and **4**). Graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å) was used in all cases. The structural data for all the compounds was solved by direct methods (SHELXS97) and refined by full-matrix least squares against F^2 using all data (SHELXL97).[27] Absorption corrections were carried out with the multiscan method and were applied with the SORTAV program.[28] Compound **3** features disorder of the $CH_2CH_2NEt_2$ portion of the molecule with two sites for atoms C(12), C(13), N(14), C(15), C(16), C(17) and C(18). Non-hydrogen atoms were refined with anisotropic thermal parameters. Treatment of the hydrogen atoms varied. All hydrogen atoms in **4**, **5**, **9** and **13** were refined isotropically, whilst the hydrogen atoms in **2** were all allowed for as riding atoms. In **1** the enol protons (H3/H33) and the piperidone ring protons (H1, H2, H5, H31, H32 and H35) were refined isotropically, whilst all others were allowed for as riding atoms. In **3** all hydrogen atoms were refined isotropically, except those in the disordered $N(CH_2)_2NEt_2$ portion of the molecule where they were allowed for as riding atoms. Thermal ellipsoid plots were generated using ORTEP-3 for Windows,[29] whilst other figures were generated using the Mercury program.[30] CCDC-653185, -653186, -653187, -653188, -653189, -653190 and -653191 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/data_request/cif.

General Procedures for Preparation of Piperidone Precursors 1, 5, 9 and 13: Pyridine-2-carbaldehyde (0.1 mol, 9.51 mL) and the relevant primary amine (0.05 mol) were dissolved in methanol (100 mL), with gentle heating if necessary. The solution was cooled in an ice bath and dimethyl 3-oxopentanedioate (0.05 mol, 7.35 mL) was added dropwise over 2 h, keeping the temperature at 0 °C. The methanol was removed to leave a red-brown viscous oil.

Table 1. Crystallographic data for compounds **1**, **2** and **3**.

Compound	**1**	**2**	**3**
Empirical formula	$C_{20}H_{21}N_3O_5$	$C_{26}H_{33}N_5O_5$	$C_{28}H_{37}N_5O_5$
Formula mass	383.40	495.31	523.63
Colour, habit	colourless, plate	colourless, prism	colourless, prism
Crystal system	orthorhombic	orthorhombic	triclinic
Space group	$P2_12_12_1$ (no. 19)	$P2_12_12_1$ (no. 19)	$P\bar{1}$ (no. 2)
Crystal size	$0.25\times0.20\times0.10$ mm	$0.30\times0.30\times0.30$ mm	$0.25\times0.20\times0.10$ mm
Unit-cell dimensions	a = 10.17220(10) Å	a = 9.6249(2) Å	a = 10.4490(3) Å, α = 99.581(2)°
	b = 10.3637(2) Å	b = 13.8495(3) Å	b = 11.2000(3) Å, β = 95.843(2)°
	c = 35.0599(5) Å	c = 19.6524(6) Å	c = 13.1080(4) Å, γ = 111.540(2)°
Volume	3696.07(10) Å^3	2619.67(11) Å^3	1384.60(7) Å^3
T	150(2) K	200(2) K	200(2) K
Z	8	4	2
$D_{calcd.}$	1.378 Mg/m^3	1.256 Mg/m^3	1.256 Mg/m^3
λ	0.71073 Å	0.71073 Å	0.71073 Å
μ (Mo-K_α)	0.101 mm^{-1}	0.089 mm^{-1}	0.087 mm^{-1}
F(000)	1616	1056	560
θ range	3.04–26.54°	2.94–28.27°	3.38–25.50°
No. of reflections	4220 (4220 unique)	18829 (6193 unique)	7218 (5138 unique)
$R1/wR2$	0.0593/0.1339	0.0517/0.1201	0.0765/0.2079
$R1/wR2$ (all data)	0.0868/0.1569	0.0686/0.1301	0.1139/0.2461
Largest diff. peak/hole	0.291/–0.276 e Å^{-3}	0.229/–0.283 e Å^{-3}	0.655/–0.431 e Å^{-3}

Table 2. Crystallographic data for compounds **4**, **5**, **9** and **13**.

Compound	**4**	**5**	**9**	**13**
Empirical formula	$C_{30}H_{41}N_5O_5$	$C_{25}H_{31}N_3O_5$	$C_{31}H_{43}N_3O_5$	$C_{37}H_{55}N_3O_5$
Formula mass	551.68	453.53	537.68	621.84
Colour, habit	colourless, prism	colourless, plate	colourless, plate	colourless, plate
Crystal system	orthorhombic	monoclinic	monoclinic	monoclinic
Space group	*Pbca* (no. 61)	$P2_1/n$ (no. 14)	$P2_1/c$ (no. 14)	$C2/c$ (no. 15)
Crystal size	$0.25\times0.20\times0.15$ mm	$0.30\times0.15\times0.06$ mm	$0.30\times0.12\times0.05$ mm	$0.25\times0.15\times0.07$ mm
Unit-cell dimensions	a = 19.2470(3) Å	a = 13.8840(3) Å	a = 17.9256(6) Å	a = 40.1386(8) Å
	b = 15.2110(2) Å	b = 9.2114(2) Å, β = 108.7690(10)°	b = 9.1539(3) Å, β = 113.904(10)°	b = 9.5080(2) Å, β = 114.7550(10)°
	c = 20.1970(3) Å	c = 19.9954(6) Å	c = 20.1966(7) Å	c = 20.5812(6) Å
Volume	5913.00(15) Å^3	2421.25(10) Å^3	3029.78(18) Å^3	7132.8(3) Å^3
T	200(2) K	150(2) K	150(2) K	150(2) K
Z	8	4	4	8
$D_{calcd.}$	1.239 Mg/m^3	1.244 Mg/m^3	1.179 Mg/m^3	1.158 Mg/m^3
λ	0.71073 Å	0.71073 Å	0.71073 Å	0.71073 Å
μ (Mo-K_α)	0.085 mm^{-1}	0.087 mm^{-1}	0.080 mm^{-1}	0.076 mm^{-1}
F(000)	2368	968	1160	2704
θ range	3.22–27.48°	3.09–27.56°	2.94–26.40°	2.94–26.80°
No. of reflections	12845 (6763 unique)	19445 (5499 unique)	26226 (6179 unique)	55407 (7567 unique)
$R1/wR2$	0.0563/0.1504	0.0618/0.1474	0.0619/0.1427	0.0665/0.1280
$R1/wR2$ (all data)	0.0955/0.1811	0.1128/0.1885	0.1370/0.1854	0.1273/0.1509
Largest diff. peak/hole	0.318/–0.230 e Å^{-3}	0.412/–0.343 e Å^{-3}	0.243/– 0.235 e Å^{-3}	0.199/– 0.182 e Å^{-3}

The piperidone was extracted from this using diethyl ether and then filtered under reduced pressure. Upon recrystallisation from warm methanol the products were obtained as light pink powders with yields typically 70–90%. The numbering of the carbon atoms in the NMR assignments of the piperidones is shown in Figure 16.

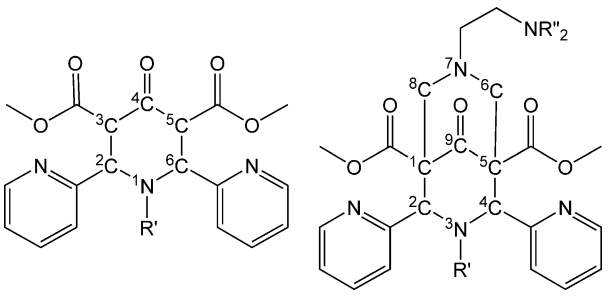

Figure 16. Numbering scheme for NMR spectroscopic data.

Dimethyl 1-Methyl-4-oxo-2,6-dipyridin-2-yl-3,5-dicarboxylate (1): Light pink powder, yield 15.53 g (81%), melting point 121–123 °C. $C_{20}H_{21}N_3O_5$ (383.40): calcd. C 62.7, H 5.5, N 11.0; found C 62.5, H 5.4, N 10.9. ^{1}H NMR ($CDCl_3$): δ = 1.80 (s, 3 H, NCH_3), 3.60 (s, 6 H, OCH_3), 4.30 (d, 2 H, $C^{3/5}H$), 4.70 (s, 2 H, $C^{2/6}H$), 7.25–8.60 (m, 8 H, H^{py}) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 45.6 (R′), 52.9 (OCH_3), 65.4 ($C^{3/5}$), 70.4 ($C^{2/6}$), 123.4, 124.5, 136.8, 149.6 (C^{py}), 158.6 ($C^{py\text{-}i}$), 169.0 (COO), 204.0 (C^4) ppm. TOF MS ES+: calcd. for $C_{20}H_{21}N_3O_5$ $[M]^+$ 383.40, found 383.1.

Dimethyl 1-Hexyl-4-oxo-2,6-dipyridin-2-yl-3,5-dicarboxylate (5): Light pink powder, yield 16.33 g (72%), melting point 108–110 °C. $C_{25}H_{31}N_3O_5$ (453.53): calcd. C 66.2, H 6.9, N 9.3; found C 66.4, H 6.8, N 8.9. ^{1}H NMR ($CDCl_3$): δ = 0.80 (t, 3 H, R′ CH_3), 1.00–

2.40 (m, 10 H, R′ CH_2), 3.60 (s, 6 H, OCH_3), 4.20 (d, 2 H, $C^{3/5}H$), 4.95 (s, 2 H, $C^{2/6}H$), 7.10–8.60 (m, 8 H, H^{py}) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 14.4 (R′ CH_3), 23.0, 26.9, 28.9, 31.8, 44.6 (R′ CH_2), 52.9 (OCH_3), 61.4 ($C^{3/5}$), 68.2 ($C^{2/6}$), 123.3, 125.5, 136.6, 149.2 (C^{py}), 159.0 ($C^{py\text{-}i}$), 168.0 (COO), 201.3 (C^4) ppm. TOF MS ES+: calcd. for $C_{25}H_{31}N_3O_5$ $[M]^+$ 453.53, found 454.0.

Dimethyl 1-Dodecyl-4-oxo-2,6-dipyridin-2-yl-3,5-dicarboxylate (9): Light pink powder, yield 18.97 g (84%), melting point 93–95 °C. $C_{31}H_{43}N_3O_5$ (537.69): calcd. C 69.3, H 8.1, N 7.8; found C 69.2, H 8.1, N 7.8. ^1H NMR ($CDCl_3$): δ = 0.80 (t, 3 H, R′ CH_3), 1.00–2.40 (m, 22 H, R′ CH_2), 3.60 (s, 6 H, OCH_3), 4.20 (d, 2 H, $C^{3/5}H$), 4.90 (s, 2 H, $C^{2/6}H$), 7.00–8.60 (m, 8 H, H^{py}) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 14.5 (R′ CH_3), 23.1, 27.2, 28.3, 30.0, 32.3, 47.5 (R′ CH_2), 52.9 (OCH_3), 61.5 ($C^{3/5}$), 68.7 ($C^{2/6}$), 122.6, 123.8, 136.5, 149.2 (C^{py}), 159.0 ($C^{py\text{-}i}$), 168.0 (COO), 202.7 (C^4) ppm. TOF MS ES+: calcd. for $C_{31}H_{43}N_3O_5$ $[M]^+$ 537.69, found 537.9.

Dimethyl 1-Octadecyl-4-oxo-2,6-dipyridin-2-yl-3,5-dicarboxylate (13): Light pink powder, yield 27.67 g (89%), melting point 89–90 °C. $C_{37}H_{55}N_3O_5$ (621.85): calcd. C 71.5, H 8.9, N 6.8; found C 71.7, H 8.8, N 6.7. ^1H NMR ($CDCl_3$): δ = 0.80 (t, 3 H, R′ CH_3), 1.00–2.40 (m, 34 H, R′ CH_2), 3.50 (s, 6 H, OCH_3), 4.10 (d, 2 H, $C^{3/5}H$), 4.90 (s, 2 H, $C^{2/6}H$), 7.00–8.55 (m, 8 H, H^{py}) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 14.5 (R′ CH_3), 23.1, 27.3, 29.0, 29.7, 30.0, 32.3, 47.6 (R′ CH_2), 52.9 (OCH_3), 61.5 ($C^{3/5}$), 64.2 ($C^{2/6}$), 122.3, 123.8, 136.6, 149.2 (C^{py}), 159.0 ($C^{py\text{-}i}$), 168.0 (COO), 203.9 (C^4) ppm. TOF MS ES+: calcd. for $C_{37}H_{55}N_3O_5$ $[M]^+$ 621.85, found 622.1.

General Procedure for the Preparation of Bispidone Ligands: The relevant piperidone (0.01 mol) was dissolved in methanol (50 mL) under reflux. To this solution was added formaldehyde (0.02 mol, 3.13 mL, 37% w/w aqueous solution) and the relevant diamine (0.01 mol), and the solution was left refluxing for 30 min and then cooled to room temperature. The methanol was removed in a rotary evaporator (60 °C), with the products ranging from dark red to dark brown viscous oils. The products were extracted using diethyl ether. Bispidones **2**–**4** were recrystallised from warm methanol as light brown powders, whilst the others remained as oils. The numbering of the carbon atoms in the NMR assignments of the bispidones is shown in Figure 16.

Dimethyl 7-[2-(Dimethylamino)ethyl]-3-methyl-9-oxo-2,4-dipyridin-2-yl-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarboxylate (2): Light brown powder, yield 3.37 g (68%), melting point 114 °C. $C_{26}H_{33}N_5O_5$ (495.57): calcd. C 63.0, H 6.7, N 14.1; found C 63.1, H 6.7, N 14.0. ^1H NMR ($CDCl_3$): δ = 2.05 (s, 3 H, NCH_3), 2.30 [s, 6 H, $N(CH_3)_2$], 2.45 (s, 4 H, $C^{6/8}H$), 2.60 (d, 2 H, $N^7CH_2CH_2N$), 3.10 (d, 2 H, $N^7CH_2CH_2N$), 3.85 (s, 6 H, OCH_3), 4.75 (s, 2 H, $C^{2/4}H$), 7.20–8.55 (m, 8 H, H^{py}) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 43.7 (R′), 46.2 [$N(CH_3)_2$], 53.0 (OCH_3), 55.5 ($N^7CH_2CH_2N$), 57.1 ($N^7CH_2CH_2N$), 59.6 ($C^{6/8}$), 62.6 ($C^{1/5}$), 74.1 ($C^{2/4}$), 123.4, 124.3, 136.8, 149.6 (C^{py}), 159.2 ($C^{py\text{-}i}$), 169.1 (COO), 204.1 (C^9) ppm. TOF MS ES+: calcd. for $C_{26}H_{33}N_5O_5$ $[M]^+$ 495.57, found 495.8.

Dimethyl 7-[2-(Diethylamino)ethyl]-3-methyl-9-oxo-2,4-dipyridin-2-yl-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarboxylate (3): Light brown powder, yield 3.67 g (70%), melting point 151 °C. $C_{28}H_{37}N_5O_5$ (523.62): calcd. C 64.2, H 7.1, N 13.4; found C 64.6, H 7.5, N 13.2. ^1H NMR ($CDCl_3$): δ = 1.10 (t, 6 H, NCH_2CH_3), 2.10 (s, 3 H, NCH_3), 2.30 (s, 4 H, $C^{6/8}H$), 2.50 (t, 2 H, $N^7CH_2CH_2N$), 2.65 (quart, 4 H, NCH_2CH_3), 3.00 (t, 2 H, $N^7CH_2CH_2N$), 3.90 (s, 6 H, OCH_3), 4.80 (s, 2 H, $C^{2/4}H$), 7.25–8.55 (m, 8 H, H^{py}) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 11.7 [$N(CH_2CH_3)_2$], 43.6 (R′), 47.5 [$N(CH_2CH_3)_2$], 50.5 ($N^7CH_2CH_2N$), 52.9 (OCH_3), 54.9 ($N^7CH_2CH_2N$), 59.4 ($C^{6/8}$), 62.7 ($C^{1/5}$), 74.0 ($C^{2/4}$), 123.4, 124.1, 136.7, 149.7 (C^{py}), 159.1 ($C^{py\text{-}i}$), 169.1 (COO), 204.1 (C^9) ppm. TOF MS ES+: calcd. for $C_{28}H_{37}N_5O_5$ $[M]^+$ 523.62, found 523.4.

Dimethyl 7-[2-(Diisopropylamino)ethyl]-3-methyl-9-oxo-2,4-dipyridin-2-yl-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarboxylate (4): Light brown powder, yield 3.42 g (62%), melting point 153 °C. $C_{30}H_{41}N_5O_5$ (551.68): calcd. C 65.3, H 7.5, N 12.7; found C 65.8, H 7.8, N 12.4. ^1H NMR ($CDCl_3$): δ = 1.00 {s, 12 H, $N[CH(CH_3)_2]_2$}, 2.10 (s, 3 H, NCH_3), 2.30 (s, 4 H, $C^{6/8}H$), 2.40 (t, 2 H, $N^7CH_2CH_2N$), 2.60 {sept, 2 H, $N[CH(CH_3)_2]_2$}, 3.00 (t, 2 H, $N^7CH_2CH_2N$), 3.90 (s, 6 H, OCH_3), 4.80 (s, 2 H, $C^{2/4}H$), 7.25–8.55 (m, 8 H, H^{py}) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 21.2 [$NCH(CH_3)_2$], 43.7 (R′), 49.4 [$NCH(CH_3)_2$], 52.9 (OCH_3), 59.6 ($C^{6/8}$), 61.2 ($N^7CH_2CH_2N$), 62.6 ($C^{1/5}$), 66.2 ($N^7CH_2CH_2N$), 73.9 ($C^{2/4}$), 123.4, 123.9, 136.5, 149.7 (C^{py}), 159.3 ($C^{py\text{-}i}$), 169.0 (COO), 204.1 (C^9) ppm. TOF MS ES+: calcd. for $C_{30}H_{41}N_5O_5$ $[M]^+$ 551.68, found 551.9.

Dimethyl 7-[2-(Dimethylamino)ethyl]-3-hexyl-9-oxo-2,4-dipyridin-2-yl-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarboxylate (6): Brown oil, yield 2.94 g (52%). $C_{31}H_{43}N_5O_5$ (565.70): calcd. C 65.8, H 7.7, N 12.4; found C 66.0, H 8.1, N 11.9. ^1H NMR ($CDCl_3$): δ = 0.50 (t, 3 H, R′ CH_3), 0.80–2.20 (m, 10 H, R′ CH_2), 2.25 (m, 6 H, NMe_2), 2.45 (s, 4 H, $C^{6/8}H$), 2.60 (d, 2 H, $N^7CH_2CH_2N$), 2.90 (d, 2 H, $N^7CH_2CH_2N$), 3.65 (s, 6 H, OCH_3), 5.00 (s, 2 H, $C^{2/4}H$), 6.95–8.65 (m, 8 H, H^{py}) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 14.3 (R′ CH_3), 21.2, 22.8, 27.1, 29.0, 32.0 (R′ CH_2), 45.9 [$N(CH_3)_2$], 52.8 (OCH_3), 55.1 ($N^7CH_2CH_2N$), 56.8 ($N^7CH_2CH_2N$), 58.2 ($C^{6/8}$), 62.4 ($C^{1/5}$), 69.8 ($C^{2/4}$), 121.8, 124.6, 136.3, 148.8 (C^{py}), 159.2 ($C^{py\text{-}i}$), 169.1 (COO), 204.1 (C^9) ppm. TOF MS ES+: calcd. for $C_{31}H_{43}N_5O_5$ $[M]^+$ 565.70, found 565.70.

Dimethyl 7-[2-(Diethylamino)ethyl]-3-hexyl-9-oxo-2,4-dipyridin-2-yl-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarboxylate (7): Brown oil, yield 3.44 g (58%). $C_{33}H_{47}N_5O_5$ (593.76): calcd. C 66.8, H 8.0, N 11.8; found C 66.9, H 7.8, N 11.6. ^1H NMR ($CDCl_3$): δ = 0.40 (t, 3 H, R′ CH_3), 0.60–1.00 (m, 10 H, R′ CH_2), 1.15 (t, 6 H, NCH_2CH_3), 2.20 (s, 4 H, $C^{6/8}H$), 2.45 (t, 2 H, $N^7CH_2CH_2N$), 2.70 (m, 4 H, NCH_2CH_3), 2.90 (m, 2 H, $N^7CH_2CH_2N$), 3.70 (s, 6 H, OCH_3), 5.05 (s, 2 H, $C^{2/4}H$), 6.90–8.70 (m, 8 H, H^{py}) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 11.2 [$N(CH_2CH_3)_2$], 14.2 (R′ CH_3), 21.3, 22.8, 27.2, 29.0, 32.0 (R′ CH_2), 47.3 [$N(CH_2CH_3)_2$], 50.4 ($N^7CH_2CH_2N$), 52.8 (OCH_3), 55.0 ($N^7CH_2CH_2N$), 59.5 ($C^{6/8}$), 62.6 ($C^{1/5}$), 69.7 ($C^{2/4}$), 123.3, 124.4, 136.3, 149.4 (C^{py}), 159.1 ($C^{py\text{-}i}$), 169.2 (COO), 203.9 (C^9) ppm. TOF MS ES+: calcd. for $C_{33}H_{47}N_5O_5$ $[M]^+$ 593.76, found 593.76.

Dimethyl 7-[2-(Diisopropylamino)ethyl]-3-hexyl-9-oxo-2,4-dipyridin-2-yl-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarboxylate (8): Brown oil, yield 4.10 g (66%). $C_{35}H_{51}N_5O_5$ (621.81): calcd. C 67.6, H 8.3, N 11.3; found C 67.4, H 8.6, N 11.1. ^1H NMR ($CDCl_3$): δ = 0.55 (t, 3 H, R′ CH_3), 0.70–1.15 (m, 10 H, R′ CH_2), 1.20 {m, 12 H, $N[CH(CH_3)_2]_2$}, 2.25 (s, 4 H, $C^{6/8}H$), 2.35 (t, 2 H, $N^7CH_2CH_2N$), 2.65 {m, 2 H, $N[CH(CH_3)_2]_2$}, 2.90 (m, 2 H, $N^7CH_2CH_2N$), 3.70 (s, 6 H, OCH_3), 5.10 (s, 2 H, $C^{2/4}H$), 7.05–8.75 (m, 8 H, H^{py}) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 14.2 [$NCH(CH_3)_2$], 14.4 (R′ CH_3), 20.9, 22.9, 27.1, 29.0, 32.0, 43.1 (R′ CH_2), 49.4 [$NCH(CH_3)_2$], 52.9 (OCH_3), 59.7 ($C^{6/8}$), 62.5 ($N^7CH_2CH_2N$), 65.2 ($C^{1/5}$), 69.6 ($N^7CH_2CH_2N$), 77.3 ($C^{2/4}$), 123.3, 124.3, 136.6, 149.5 (C^{py}), 159.2 ($C^{py\text{-}i}$), 169.2 (COO), 204.1 (C^9) ppm. TOF MS ES+: calcd. for $C_{35}H_{51}N_5O_5$ $[M]^+$ 621.81, found 621.81.

Dimethyl 7-[2-(Dimethylamino)ethyl]-3-dodecyl-9-oxo-2,4-dipyridin-2-yl-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarboxylate (10): Brown oil, yield 3.31 g (51%). $C_{37}H_{55}N_5O_5$ (649.86): calcd. C 68.4, H 8.5, N 10.8; found C 68.7, H 8.8, N 10.5. ^1H NMR ($CDCl_3$): δ = 0.60 (t, 3 H, R′ CH_3), 0.80–1.90 (m, 22 H, R′ CH_2), 2.15 (m, 6 H,

NMe$_2$), 2.30 (s, 4 H, C$^{6/8}$H), 2.50 (d, 2 H, N^{7}CH$_2$CH_2N), 2.90 (d, 2 H, N^{7}CH_2CH$_2$N), 3.70 (s, 6 H, OCH$_3$), 5.05 (s, 2 H, C$^{2/4}$H), 6.95–8.70 (m, 8 H, H^{py}) ppm. ^{13}C{^{1}H} NMR (CDCl$_3$): δ = 14.4 (R′ CH$_3$), 21.2, 22.9, 27.6, 29.0, 29.9, 32.2 (R′ CH$_2$), 45.9 [N(CH$_3$)$_2$], 52.8 (OCH$_3$), 55.0 (N^{7}CH$_2$CH$_2$N), 56.8 (N^{7}CH$_2$CH$_2$N), 58.1 (C$^{6/8}$), 62.4 (C$^{1/5}$), 69.8 (C$^{2/4}$), 121.9, 124.5, 136.6, 149.4 (C^{py}), 159.1 (C$^{py\text{-}i}$), 169.1 (COO), 203.9 (C^9) ppm. TOF MS ES+: calcd. for C$_{37}$H$_{55}$N$_5$O$_5$ [M]$^+$ 649.86, found 649.86.

Dimethyl 7-[2-(Diethylamino)ethyl]-3-dodecyl-9-oxo-2,4-dipyridin-2-yl-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarboxylate (11): Brown oil, yield 3.86 g (57%). C$_{39}$H$_{59}$N$_5$O$_5$ (677.92): calcd. C 69.1, H 8.8, N 10.3; found C 69.3, H 9.1, N 9.9. ^{1}H NMR (CDCl$_3$): δ = 0.60 (t, 3 H, R′ CH$_3$), 0.80–1.40 (m, 22 H, R′ CH$_2$), 1.60 (t, 6 H, NCH$_2$CH_3), 2.25 (s, 4 H, C$^{6/8}$H), 2.50 (t, 2 H, N^{7}CH$_2$CH_2N), 2.80 (m, 4 H, NCH_2CH$_3$), 2.95 (t, 2 H, N^{7}CH_2CH$_2$N), 3.75 (s, 6 H, OCH$_3$), 5.15 (s, 2 H, C$^{2/4}$H), 7.05–8.80 (m, 8 H, H^{py}) ppm. ^{13}C{^{1}H} NMR (CDCl$_3$): δ = 17.4 [N(CH$_2$CH_3)$_2$], 17.6 (R′ CH$_3$), 27.8, 29.3, 34.0, 35.4, 36.2, 38.5 (R′ CH$_2$), 53.6 [N(CH_2CH$_3$)$_2$], 56.9 (N^{7}CH$_2$CH_2N), 58.9 (OCH$_3$), 60.2 (N^{7}CH_2CH$_2$N), 61.2 (C$^{6/8}$), 68.9 (C$^{1/5}$), 76.1 (C$^{2/4}$), 127.8, 129.5, 142.6, 155.8 (C^{py}), 165.9 (C$^{py\text{-}i}$), 175.4 (COO), 210.2 (C^9) ppm. TOF MS ES+: calcd. for C$_{39}$H$_{59}$N$_5$O$_5$ [M]$^+$ 677.92, found 677.92.

Dimethyl 7-[2-(Diisopropylamino)ethyl]-3-dodecyl-9-oxo-2,4-dipyridin-2-yl-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarboxylate (12): Brown oil, yield 3.67 g (52%). C$_{41}$H$_{63}$N$_5$O$_5$ (705.97): calcd. C 69.8, H 9.0, N 9.9; found C 69.8, H 9.1, N 9.8. ^{1}H NMR (CDCl$_3$): δ = 0.60 (t, 3 H, R′ CH$_3$), 0.70–1.05 (m, 22 H, R′ CH$_2$), 1.15 {d, 12 H, N[CH(CH_3)$_2$]$_2$}, 2.20 (m, 4 H, C$^{6/8}$H), 2.40 (m, 2 H, N^{7}CH$_2$CH_2N), 2.65 {sept, 2 H, N[CH(CH$_3$)$_2$]$_2$}, 2.90 (m, 2 H, N^{7}CH_2CH$_2$N), 3.70 (s, 6 H, OCH$_3$), 5.05 (s, 2 H, C$^{2/4}$H), 7.00–8.50 (m, 8 H, H^{py}) ppm. ^{13}C{^{1}H} NMR (CDCl$_3$): δ = 14.4 [NCH(CH_3)$_2$], 14.6 (R′ CH$_3$), 20.9, 23.0, 27.8, 29.7, 32.2, 43.1 (R′ CH$_2$), 49.3 [NCH(CH$_3$)$_2$], 53.2 (OCH$_3$), 57.8 (C$^{6/8}$), 59.7 (N^{7}CH$_2$CH_2N), 62.6 (C$^{1/5}$), 65.2 (N^{7}CH_2CH$_2$N), 69.6 (C$^{2/4}$), 123.2, 124.9, 136.1, 149.5 (C^{py}), 159.5 (C$^{py\text{-}i}$), 169.2 (COO), 204.1 (C^9) ppm. TOF MS ES+: calcd. for C$_{41}$H$_{63}$N$_5$O$_5$ [M]$^+$ 705.97, found 705.97.

Dimethyl 7-[2-(Dimethylamino)ethyl]-3-octadecyl-9-oxo-2,4-dipyridin-2-yl-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarboxylate (14): Brown oil, yield 4.62 g (63%). C$_{43}$H$_{67}$N$_5$O$_5$ (734.02): calcd. C 70.4, H 9.2, N 9.5; found C 70.2, H 9.4, N 9.5. ^{1}H NMR (CDCl$_3$): δ = 0.50 (t, 3 H, R′ CH$_3$), 0.70–1.80 (m, 34 H, R′ CH$_2$), 2.10 (m, 6 H, NMe$_2$), 2.20 (s, 4 H, C$^{6/8}$H), 2.40 (d, 2 H, N^{7}CH$_2$CH_2N), 2.80 (d, 2 H, N^{7}CH_2CH$_2$N), 3.60 (s, 6 H, OCH$_3$), 4.95 (s, 2 H, C$^{2/4}$H), 6.90–8.60 (m, 8 H, H^{py}) ppm. ^{13}C{^{1}H} NMR (CDCl$_3$): δ = 14.3 (R′ CH$_3$), 15.5, 21.1, 22.9, 27.4, 29.5, 29.9, 32.1 (R′ CH$_2$), 45.9 [N(CH$_3$)$_2$], 52.6 (OCH$_3$), 55.3 (N^{7}CH$_2$CH$_2$N), 56.8 (N^{7}CH$_2$CH$_2$N), 59.5 (C$^{6/8}$), 62.5 (C$^{1/5}$), 69.7 (C$^{2/4}$), 123.1, 124.5, 136.7, 149.3 (C^{py}), 159.1 (C$^{py\text{-}i}$), 169.0 (COO), 203.8 (C^9) ppm. TOF MS ES+: calcd. for C$_{43}$H$_{67}$N$_5$O$_5$ [M]$^+$ 734.02, found 734.02.

Dimethyl 7-[2-(Diethylamino)ethyl]-3-octadecyl-9-oxo-2,4-dipyridin-2-yl-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarboxylate (15): Brown oil, yield 3.73 g (49%). C$_{45}$H$_{71}$N$_5$O$_5$ (762.08): calcd. C 70.9, H 9.4, N 9.2; found C 70.6, H 9.7, N 8.8. ^{1}H NMR (CDCl$_3$): δ = 0.60 (t, 3 H, R′ CH$_3$), 0.80–1.30 (m, 34 H, R′ CH$_2$), 1.40 (t, 6 H, NCH$_2$CH_3), 2.25 (s, 4 H, C$^{6/8}$H), 2.50 (m, 2 H, N^{7}CH$_2$CH_2N), 2.75 (m, 4 H, NCH_2CH$_3$), 2.95 (m, 2 H, N^{7}CH_2CH$_2$N), 3.40 (s, 6 H, OCH$_3$), 5.10 (s, 2 H, C$^{2/4}$H), 7.05–8.75 (m, 8 H, H^{py}) ppm. ^{13}C{^{1}H} NMR (CDCl$_3$): δ = 11.0 [N(CH$_2$CH_3)$_2$], 14.3 (R′ CH$_3$), 21.3, 23.0, 27.7, 29.0, 30.0, 32.2 (R′ CH$_2$), 47.2 [N(CH_2CH$_3$)$_2$], 50.6 (N^{7}CH$_2$CH_2N), 52.9 (OCH$_3$), 55.0 (N^{7}CH_2CH$_2$N), 59.5 (C$^{6/8}$), 62.7 (C$^{1/5}$), 69.7 (C$^{2/4}$), 123.3, 124.5, 136.9, 149.5 (C^{py}), 159.5 (C$^{py\text{-}i}$), 169.2 (COO), 203.9 (C^9) ppm. TOF MS ES+: calcd. for C$_{45}$H$_{71}$N$_5$O$_5$ [M]$^+$ 762.08, found 762.5.

Dimethyl 7-[2-(Diisopropylamino)ethyl]-3-octadecyl-9-oxo-2,4-dipyridin-2-yl-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarboxylate (16): Brown oil, yield 4.03 g (51%). C$_{47}$H$_{75}$N$_5$O$_5$ (790.13): calcd. C 71.4, H 9.6, N 8.9; found C 71.1, H 9.8, N 9.0. ^{1}H NMR (CDCl$_3$): δ = 0.80 {d, 12 H, N[CH(CH_3)$_2$]$_2$}, 0.90 (t, 3 H, R′ CH$_3$), 1.00–1.35 (m, 34 H, R′ CH$_2$), 2.15 (s, 4 H, C$^{6/8}$H), 2.50 (m, 2 H, N^{7}CH$_2$CH_2N), 2.70 {m, 2 H, N[CH(CH$_3$)$_2$]$_2$}, 2.95 (m, 2 H, N^{7}CH_2CH$_2$N), 3.80 (s, 6 H, OCH$_3$), 5.15 (s, 2 H, C$^{2/4}$H), 7.05–8.55 (m, 8 H, H^{py}) ppm. ^{13}C{^{1}H} NMR (CDCl$_3$): δ = 14.3 [NCH(CH_3)$_2$], 14.5 (R′ CH$_3$), 21.0, 23.0, 27.5, 29.1, 30.0, 31.3, 43.6 (R′ CH$_2$), 49.9 [NCH(CH$_3$)$_2$], 52.9 (OCH$_3$), 59.4 (C$^{6/8}$), 62.6 (N^{7}CH$_2$CH_2N), 65.2 (C$^{1/5}$), 67.6 (N^{7}CH$_2$CH$_2$N), 69.7 (C$^{2/4}$), 123.2, 124.3, 136.2, 149.5 (C^{py}), 159.5 (C$^{py\text{-}i}$), 169.3 (COO), 204.2 (C^9) ppm. TOF MS ES+: calcd. for C$_{47}$H$_{75}$N$_5$O$_5$ [M]$^+$ 790.13, found 790.13.

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