Imidazole-containing Bispidine Ligands: Synthesis, Structure and Cu(II) Complexation

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The preparation and characterization of tris-pyridyl bispidine (3,7-diazabicyclo[3.3.1]nonane) derivatives with benzimidazole and imidazole donor groups at the N-3 position of the bispidine skeleton and their copper(II) complexes are reported. The impact of the hetaryl substituents on the configurational isomerism of piperidones and their corresponding bispidones has been studied by NMR spectroscopy, revealing the exclusive appearance in the enol form for the piperidones in solution and the *trans*-configuration regarding the two pyridyl substituents, as well as the sole formation of the unsymmetric *exo-endo* isomers for the corresponding bispidones. Thus, the bispidones are preorganized ligands for building pentacoordinated complexes, confirmed by the preparation and characterization of the corresponding Cu(II) complexes. Of the di-pyridyl piperidones with benzimidazole and imidazole substituents, and of the Cu(II) complex of the benzimidazole-containing bispidone, crystals have become available for the analysis by X-ray diffraction, showing that the piperidones form the enol tautomers also in the solid state.

Key words: Piperidone, Bispidine, Copper(II), Configuration Isomerism

Introduction

The advantageous properties of numerous 3,7-diazabicyclo[3.3.1]nonane (bispidine) derivatives have attracted much attention and caused intensive research efforts in different directions. The variable number, type and position of the donor groups provide a variety of tailor-made coordination sites for metal ions with different preferences with regard to size, shape and electronic properties [1]. Bispidine ligands form very stable complexes especially with copper(II) ions [2 – 4]. The thermodynamic stability of copper(II)-bispidines is in the same range as that of copper(II) complexes with azamacrocyclic ligands. Furthermore, the bispidine skeleton opens suitable pathways to introduce biomolecules, which are important in view of the pharmaceutical targeting of such complexes. Due to these interesting features, bispidines are predestined as attractive bifunctional chelating agents for the development of target-specific copper-based radiopharmaceuticals [5 – 7]. Thus, we have shown that hexadentate ligands with pyridine units in the positions C-2, C-4, N-3, and N-7 form stable ^{64}Cu(II) complexes under mild conditions [6]. This tetrakis-pyridyl bispidine ligand adopts a double-chair conformation with *endo-endo* orientation of the pyridyl groups in the C-2/C-4 positions to give six-coordinate complexes with an efficiently encapsulated and shielded copper(II) ion. Interestingly, hexadentate bispidine ligands are quite scarce, and only bispidine-based bis(amine)tetrakis(pyridine) derivatives have been described [2, 4, 6 – 8].

Like many biologically relevant copper complexes, especially imidazole-containing derivatives appear to be promising due to their favorable complex formation and solubility characteristics [9 – 11]. Hitherto, only the synthesis and complexation properties of a tetradentate bispidine derivative with methylimidazole groups in C-2/C-4 positions have been reported [12, 13]. The Cu(II) complex of this tetradentate ligand shows square pyramidal coordination geometry completed by an additional chloro ligand. It is worth mentioning that the imidazolyl nitrogen donors form quite short bonds with the Cu(II) center

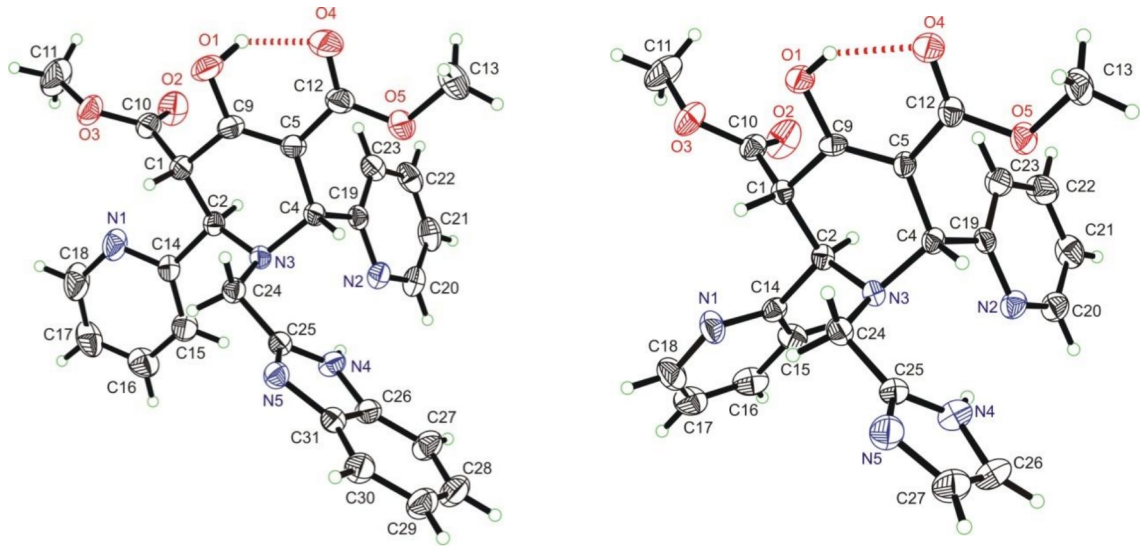


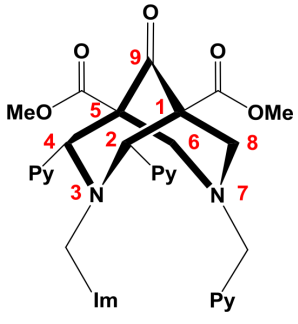
Fig. 1 (color online). ORTEP representation of **1** (left) and **2** (right) shown with 30 % probability displacement ellipsoids and the atom labeling adopted.

(1.967, 1.971 Å) pointing to strong interactions. Owing to these interesting features of complexation, we have set out to develop new bispidine derivatives with imidazole-containing donor groups.

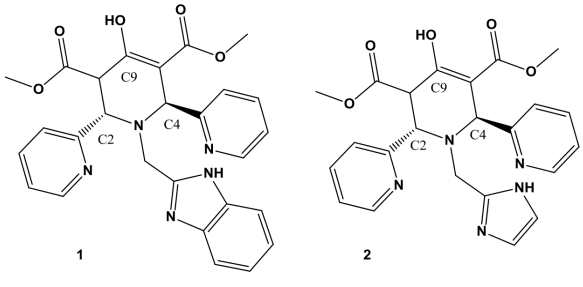
We report here the synthesis of bispidone ligands with imidazole and benzimidazole substituents in N-3 position, the X-ray structure analyses of the corresponding piperidone intermediates and of the Cu(II) complex of the benzimidazolyl bispidone ligand. In parallel, the impact of the imidazol substituents on the configurational isomerism of piperidones and their corresponding bispidones is discussed based on ^{1}H NMR spectroscopy studies.

Results and Discussion

The bispidine skeleton is assembled in two consecutive Mannich reactions, starting with piperidone formation by condensation of dimethyl 3-oxopentanedioate, pyridine-2-carbaldehyde, and (1*H*-benzimidazol-2-yl)- or (1*H*-imidazol-2-yl)methanamine. The purified piperidones **1** and **2** have been characterized in solution by NMR analysis. It was found that both compounds show only NMR signals of the unsymmetric enol form in $CDCl_3$ solution: For instance the ^{1}H NMR spectrum of **1** shows two separate singlets at δ = 3.56 and 3.76 ppm of methyl ester C*H*$_3$ groups and three separate signals of C*H* groups (C-1, C-2, C-4, the numbering in Scheme 2 and Fig. 1 is adopted from the bispidone numbering of Scheme 1 for better comparison) for the cage consisting of two doublets at δ = 4.28, 4.55 and one singlet at 4.98 ppm. The corresponding ^{13}C NMR pattern of **1** with a characteristic



Scheme 1 (color online). The hexadentate bispidone ligand with skeleton numbering.



Scheme 2. Observed *trans* isomers of **1** and **2** in their enol form (the numbering in Scheme 2 and Fig. 1 is adopted from the bispidone numbering in Scheme 1 for better comparison and does not follow the IUPAC rules).

Table 1. Crystal structure data for **1**, **2** and **3Cu**.

	1	**2**	**3Cu**
Formula	$C_{27}H_{25}N_5O_5$	$C_{23}H_{23}N_5O_5$	$C_{35}H_{33}CuN_7O_5$
M_r	499.52	449.46	695.24
Crystal size, mm^3	$0.35 \times 0.27 \times 0.08$	$0.27 \times 0.25 \times 0.16$	$0.27 \times 0.22 \times 0.18$
Crystal system	triclinic	monoclinic	monoclinic
Space group	$P\bar{1}$ (no. 2)	$P2_1/n$ (no. 14)	$P2_1/n$ (no. 14)
a, Å	8.1752(6)	10.149(6)	13.248(4)
b, Å	11.1511(8)	9.722(6)	17.973(6)
c, Å	15.8128(14)	22.416(14)	15.648(5)
α, deg	69.416(4)	90	90
β, deg	82.088(5)	95.920(11)	91.973(6)
γ, deg	69.136(3)	90	90
V, Å^3	1260.89(17)	2200(2)	3724(2)
Z	2	4	4
D_{calcd}, g cm^{-3}	1.32	1.36	1.49
μ(MoK_α), cm^{-1}	0.1	0.1	0.7
F(000), e	524	944	1732
hkl range	$-10 \le h \le 10$	$-9 \le h \le 9$	$-17 \le h \le 17$
	$-14 \le k \le 14$	$-8 \le k \le 8$	$0 \le k \le 23$
	$21 \le l \le 15$	$-20 \le l \le 15$	$0 \le l \le 20$
Refl. measd / unique / R_{int}	11177 / 5862 / 0.0366	6137 / 3386 / 0.0682	9189 / 9189 / 0.00
Param. refined	335	494	521
$R1(F)$ / $wR2(F^2)$[a] (all refl.)	0.0449 / 0.1089	0.0472 / 0.0743	0.0350 / 0.0823
GoF (F^2)[a]	0.953	0.923	1.129
$\Delta\rho_{fin}$ (max / min), e Å^{-3}	0.32 / −0.15	0.16 / −0.11	0.98 / −0.21

[a] $R1 = \Sigma\|F_o| - |F_c\|/\Sigma|F_o|$, $wR2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$, $w = [\sigma^2(F_o^2) + (AP)^2 + BP]^{-1}$, where $P = (\mathrm{Max}(F_o^2,0) + 2F_c^2)/3$ and A and B are constants adjusted by the program; GoF = $S = [\Sigma w(F_o^2 - F_c^2)^2/(n_{obs} - n_{param})]^{1/2}$, where n_{obs} is the number of data and n_{param} the number of refined parameters.

Table 2. Selected bond lengths (Å) for piperidones **1** and **2** with estimated standard deviations in parentheses.

Distances	**1**	**2**
N(3)–C(2)	1.465(15)	1.476(3)
N(3)–C(4)	1.472(16)	1.468(3)
C(1)–C(2)	1.540(18)	1.524(4)
C(4)–C(5)	1.514(19)	1.508(4)
C(1)–C(9)	1.501(19)	1.500(4)
C(5)–C(9)	1.355(19)	1.348(4)
O(1)–C(9)	1.346(17)	1.340(3)

Table 3. Selected bond lengths (Å) and angles (deg) for **3Cu** with estimated standard deviations in parentheses.

Cu–N(1)	2.3407(1)	Cu–N(3)	2.0889(1)
Cu–N(5)	1.946(16)	Cu–N(6)	1.9955(16)
Cu–N(7)	2.0363(15)	Cu–O(8)	2.729(17)
N(5)–Cu–N(6)	106.9(7)	N(5)–Cu–N(7)	156.9(6)
N(6)–Cu–N(7)	85.1(6)	N(5)–Cu–N(3)	84.0(6)
N(6)–Cu–N(3)	166.0(7)	N(7)–Cu–N(3)	87.8(6)
N(5)–Cu–N(1)	100.6(6)	N(6)–Cu–N(1)	91.5(6)
N(7)–Cu–N(1)	98.6(6)	N(3)–Cu–N(1)	77.6(6)

signal at 96.0 ppm for the sp^2-hybridized carbon atom C-9 gives evidence for the enol form. The detection of only one set of NMR signals for each compound points to the existence of only one diastereomeric form regarding the configuration at C-2 and C-4 in solution (Scheme 2). Additional diastereomers would appear as different sets of signals side by side. An X-ray crystal structure determination identified the present isomeric form as the *trans* isomer regarding the C-2/C-4 orientation. The molecular structures are displayed in Fig. 1, and crystallographic data are given in Tables 1 – 3.

Piperidone **1** crystallizes in the triclinic space group $P\bar{1}$ with two molecules in the unit cell. Due to the centrosymmetry of the space group, the compound crystallizes as a racemate. The two pyridine rings are in *trans*-position. Between the six-membered benzene ring (C26···C31) of the benzimidazole substituent and a benzene ring of the second molecule in the unit cell a π-π interaction is observed with a distance of d = 3.864 Å between the ring centroids and a dihedral angle of $\alpha = 0^\circ$ between the planes (Fig. 2).

Piperidone **2** crystallizes in the monoclinic space group $P2_1/n$ with four molecules in the unit cell. The molecule contains three asymmetric carbon atoms (C-2, C-1 and C-9). Due to the centrosymmetry of the crystals, the compound is racemic with two enantiomers of the molecule. The pyridine rings are in *trans*-position. There are no solvent molecules and no voids in the structure. In the crystal structures of both piperidones **1** and **2** an intramolecular hydrogen bond (d(O1···O4) = 2.544(19) (**1**); 2.550(4) Å (**2**)) between the carbonyl oxygen atoms of the methyl ester and the hydroxyl group clearly indicates the existence of the piperidones in the enol form in the solid state. The short bond lengths (C5–C9) of 1.355(19) Å in **1** and 1.348(4) Å in **2** are also characteristic for C–C double bonds in enols.

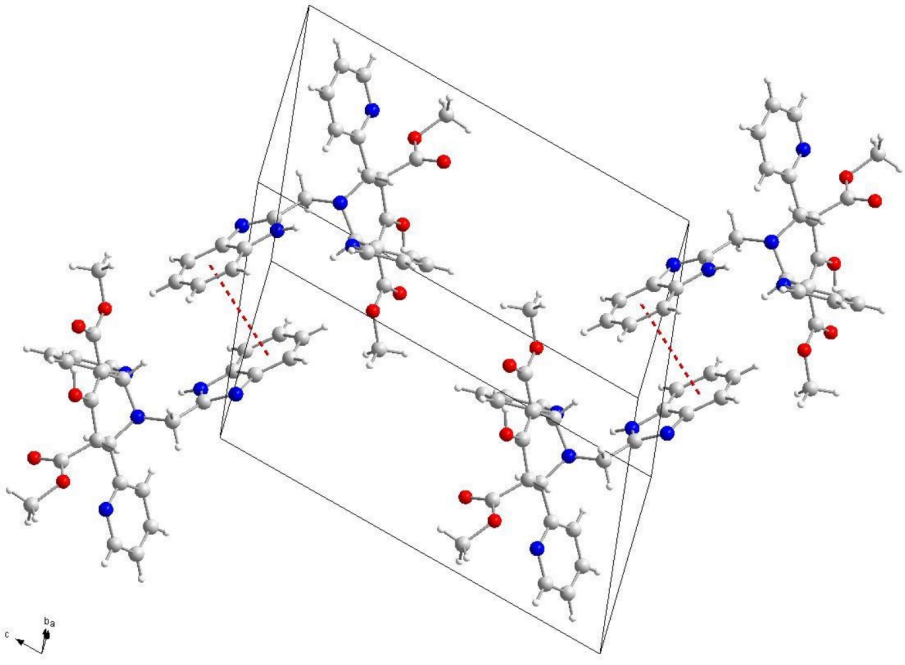
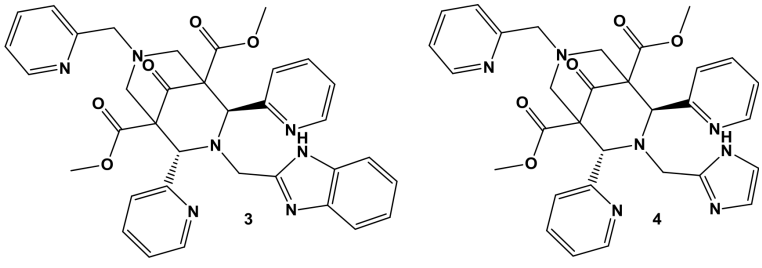


Fig. 2 (color online). Crystal structure of **1**, gray spheres represent C atoms, red spheres O atoms and blue spheres N atoms. The π-π interactions between benzimidazole units of adjacent molecules are indicated by red dotted lines (d = 3.865(2) Å, $\alpha = 0°$).

In the second step of the bispidone synthesis, the isolated piperidones **1** and **2** were reacted with formaldehyde and 2-pyridyl-methylamine to form the bicyclic bispidones **3** and **4** (Scheme 3). According to NMR spectra showing one single set of signals for each compound, the bispidones **3** and **4** were isolated exclusively as the unsymmetric *exo-endo* isomers. Evidence for this conclusion is given in the ^{1}H NMR spectrum by two different singlets for methyl ester CH_3 groups at δ = 3.37 and 3.75 ppm, by three characteristic pyridyl C*H*-N signals with the largest downfield shifts (δ = 8.18, 8.61 and 8.74 ppm) and by two singlets (δ = 4.55 and 5.53 ppm) for the two C*H* units at C-2 and C-4 position. The assignment as *exo-endo* isomers was finally confirmed by X-ray crystal structure analysis of the copper complex **3Cu**. Experiments to convert the isolated *exo-endo* into the *endo-endo* isomers by solvolysis in refluxing ethanol according to references [1, 6, 9] failed due to decomposition because of the low thermal stability of these two bispidones.

The formation of the copper(II) complexes **3Cu** and **4Cu** can be observed immediately by the appearance of blue to turquoise color after addition of copper salts to **3** or **4** in methanolic solution. Detailed information on the coordination behavior and related structural aspects are available from single-crystal X-ray data of **3Cu** (Fig. 3). In the case of the (benz)imidazol-substituted bispidone-type ligand, the isomerism assigned at positions C-2 and C-4 is reflected in the fivefold coordination of the copper ion by the ligand.

In **3Cu** the bispidone ligand **3** acts only as a pentadentate chelator since one of the dangling pyridine groups is not capable to coordinate the copper ion because of the unfavorable configuration at the carbon atom C4. Complex **3Cu** crystallizes in the



Scheme 3. Bispidones **3** and **4** are isolated exclusively as *exo-endo* isomers.

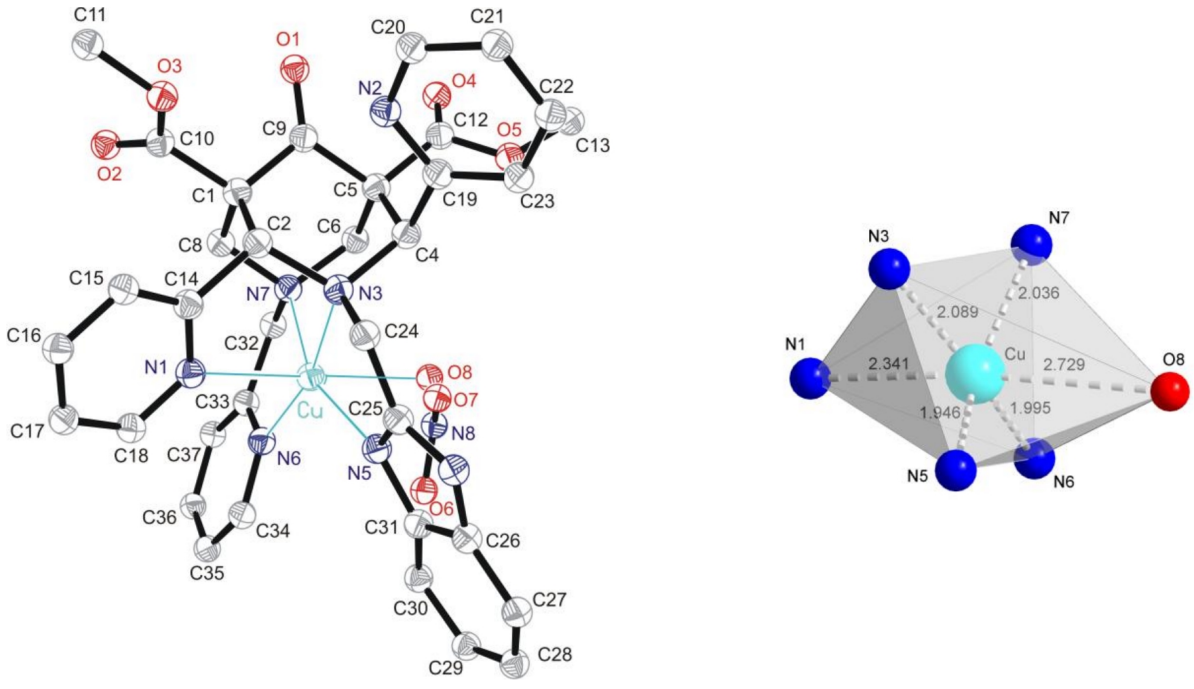


Fig. 3 (color online). ORTEP representation of the cation in **3Cu** shown with 30 % probability displacement ellipsoids and atom labeling adopted. Hydrogen atoms are omitted for clarity (left). Cu(II) coordination environment in the complex **3Cu** (right).

monoclinic space group $P2_1/n$ with four molecules in the unit cell. The coordination geometry of the Cu(II) center is distorted square-pyramidal with the nitrogen atoms N3 and N7 of the bispidine scaffold, N5 of the benzimidazole substituent, and N6 of the methylene-bridged pyridine ring spanning the square base of the pyramid around the metal ion. The nitrogen atom N1 of the pyridine ring in *endo* configuration occupies the apical position (d(Cu–N1) = 2.3407(10) Å). As expected from other bispidine complexes [9], the bond lengths between Cu(II) and the two amine nitrogen atoms of the bispidine scaffold are approximately 2 Å (d(Cu–N3) = 2.0809(10) Å and d(Cu–N7) = 2.0363(15) Å).

The bond lengths between the Cu(II) center and the other equatorial amine nitrogen atoms are in the range between d(Cu–N6) = 1.9955(16) Å and the slightly shorter distance d(Cu–N5) = 1.946(16) Å. The counterion NO_3^- completes the octahedral coordination around the copper(II) forming a longer distance of d(Cu – O8) = 2.729(17) Å. The two donor substituents (pyridine rings) at C2 and C4 are in *trans*-position. The crystal structure contains two NO_3^- anions and one water molecule in the asymmetric unit.

Conclusion

New functionalized piperidones containing benzimidazolyl (**1**) or imidazolyl (**2**) in addition to two pyridyl substituents have been synthesized and characterized by NMR and X-ray diffraction studies. Interesting similarities regarding their unsymmetric *trans* isomers and the enol forms both in solution and in crystalline state were observed. After conversion to their corresponding bispidones **3** and **4** accompanied by introduction of a third pyridyl substituent, the exclusive formation of analogous unsymmetric *exo-endo* isomers has been observed, which means that both ligands are preorganized to build pentacoordinated complexes. The bispidone Cu(II) complexes **3Cu** and **4Cu** have been prepared and characterized. The expected fivefold coordination of copper(II) by the ligand was confirmed by X-ray diffraction analysis for **3Cu**. Further experiments to introduce imidazole groups into the positions C-2 and C-4 of bispidones, and to study their impact on the configuration of this type of ligands which then might be able to act in a hexadentate fashion to coordinate the copper(II) ion are underway.

Experimental Section

General

Chemical reagents and solvents were purchased from commercial sources and used without further purification. Melting points were determined on a Mikroheiztisch Boetius apparatus by VEB Carl Zeiss Jena. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz Varian Inova spectrometer. The chemical shifts (δ, ppm) are relative to TMS or the solvent. Elemental analyses were performed on a Leco Elemental Analyzer CHNS-932. Electrospray ionization mass spectrometry (ESI-MS) was carried out using a micromass tandem quadrupole mass spectrometer (Quattro LC). Thin layer chromatography (TLC) was performed using RP-18-F_{254} TLC plates (Merck), developed in a 10 : 8 : 5 mixture chloroform/methanol/ammonia. HPLC was performed using either of two eluents (eluent A: acetonitrile, containing 0.1 % trifluoroacetic acid; eluent B: water, containing 0.1 % trifluoroacetic acid). The purity of the compounds was determined on a Knauer Smartline system, including a pump 1000, a UV detector 2500, and a manager 5000; Jupiter 4 μm C12 90 Å (Phenomenex), 250 × 4.6 mm^2, elution gradient 10 % to 70 % A in 20 min, 1 mL min^{-1}.

*Dimethyl 1-((1H-benzimidazol-2-yl)methyl)-4-hydroxy-2,6-di(pyridin-2-yl)-1,2,3,6-tetrahydropyridine-3,5-dicarboxylate (**1**)*

(1*H*-Benzimidazol-2-yl)methanaminium chloride (2.00 g) was converted into the free base with 50 mL of ammonia (25 % aq.), and subsequently extracted into 50 mL of chloroform. The solvent was removed. To a stirred solution of 334 mg (2.68 mmol) (1*H*-benzimidazol-2-yl)methanamine in 2 mL methanol, 394 μL (2.68 mmol) dimethyl 3-oxopentanedioate and 511 μL (5.35 mmol) pyridine-2-carbaldehyde dissolved in 47 μL water were added. The reaction mixture was stirred for 4 h at r. t. until a bright-brown solution occurred. The solvent was removed under reduced pressure. The residue was dissolved in dichloromethane, and the solvent was removed again. This procedure was repeated twice resulting in a yellow powder. The product was stirred for 12 h in diethyl ether. Filtration gave **1** as a colorless solid. Yield: 402 mg (30 %), m. p. 164 °C. – Anal. for $C_{27}H_{25}N_5O_5$: calcd. C 64.92, H 5.04, N 14.02; found C 64.44, H 5.25, N 13.54. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.56 (s, 3 H), 3.76 (s, 3 H), 3.83 – 4.07 (m, 2 H), 4.28 (d, ^3J = 11.6 Hz, 1 H), 4.55 (d, ^3J = 11.8 Hz, 1 H), 4.98 (s, 1 H), 7.03 (m, 1 H), 7.16 (d, ^3J = 8.0 Hz, 1 H), 7.20 (m, 2 H), 7.30 (d, ^3J = 8.0 Hz, 1 H), 7.34 (m, 1 H), 7.42 (t, ^3J = 7.6 Hz, 1 H), 7.62 (m, 2 H), 7.77 (t, ^3J = 7.6 Hz, 1 H), 8.38 (d, ^3J = 4.8 Hz, 1 H), 8.87 (d, ^3J = 4.8 Hz, 1 H). – ^{13}C NMR (101 MHz, $CDCl_3$): δ = 44.1, 46.2, 52.3, 53.0, 59.3, 61.5, 96.0, 122.3, 122.5, 122.9, 123.1, 123.2, 136.9, 137.0, 137.3, 137.4, 148.6, 148.7, 149.6, 149.7, 154.4, 157.1, 161.1, 170.1, 171.3, 172.0. – ESI-MS: m/z (%) = 500.19 (100) $[M+H]^+$. – HPLC: t_R = 13.78 min.

*Dimethyl 1-((1H-imidazol-2-yl)methyl)-4-hydroxy-2,6-di-(pyridin-2-yl)-1,2,3,6-tetrahydropyridine-3,5-dicarboxylate (**2**)*

With stirring, a solution of 329 μL (2.24 mmol) dimethyl 3-oxopentanedioate dissolved in 2 mL methanol was added to 428 μL (4.48 mmol) pyridine-2-carbaldehyd, 381 mg (2.24 mmol) (1*H*-imidazol-2-yl)methanaminium chloride [14], 47 μL water and 776 μL (5.6 mmol) triethylamine. The reaction mixture was stirred for 4 h until a milky solution had formed. Triethylammonium chloride was separated by filtration. The solvent was removed under reduced pressure. The residue was dissolved in 25 mL water and extracted thrice with 25 mL chloroform. The organic phase was dried over Na_2SO_4, and the solvent was removed *in vacuo*. The product was stirred for 12 h in diethyl ether. Filtration gave **2** as a colorless powder. Yield: 332 mg (33 %), m. p. 139 °C. – Anal. for $C_{23}H_{23}N_5O_5$: calcd. C 61.46, H 5.16, N 15.58; found C 61.12, H 5.54, N 15.64. – ^{1}H NMR (400 MHz, CD_3OD): δ = 3.56 (s, 3 H), 3.65 (s, 3 H), 3.58 – 3.74 (m, 2 H), 4.28 (d, ^3J = 11.6 Hz,1 H), 4.50 (d, ^3J = 10.4 Hz, 1 H), 4.78 (s, 1 H), 6.97 (s, 2 H), 7.16 (m, 1 H), 7.28 (d, ^3J = 8.0 Hz, 1 H), 7.32 (m, 1 H), 7.45 (d, ^3J = 8.0 Hz, 1 H,), 7.63 (t, ^3J = 8.6 Hz, 1 H), 7.80 (t, ^3J = 8.6 Hz, 1 H), 8.39 (d, ^3J = 7.6 Hz, 1 H), 8.59 (d, ^3J = 7.6 Hz, 1 H). – ^{13}C NMR (101 MHz, CD_3OD): δ = 45.0, 51.7, 59.5, 61.3, 61.5, 63.4, 97.1, 122.8, 122.9, 123.2, 123.3, 136.9, 137.0, 137.2, 137.5, 148.3, 148.4, 148.6, 157.3, 160.9, 167.8, 171.2, 171.9. – ESI-MS: m/z (%) = 450.38 (100) $[M+H]^+$. – HPLC: t_R = 11.60 min.

*Dimethyl 3-((1H-benzimidazol-2-yl)methyl)-9-oxo-2,4-di(pyridin-2-yl)-7-(pyridin-2-ylmethyl)-3,7-diazabicyclo-[3.3.1]nonane-1,5-dicarboxylate (**3**)*

To 100 mg (0.2 mmol) of **1** dissolved in 2 mL tetrahydrofuran, 25 μL (0.24 mmol) 2-picolylamine and 36 μL (0.48 mmol) formaldehyde (37 % aq.) were added. The reaction mixture was refluxed for 7 h to give a clear brown solution. After removing the solvent, the solid residue was dissolved in 10 mL of an acetonitrile/water mixture (1/4) to allow the separation of insoluble by-products. The solvent was removed *in vacuo*. The crude product was recrystallized from acetone to give **3** as a colorless solid. Yield: 55 mg (44 %), m. p. 148 °C. – Anal. for $C_{35}H_{33}N_7O_5$: calcd. C 66.55, H 5.27, N 15.52; found C 66.14, H 5.04, N 15.46. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.77 (d, ^2J = 12.4 Hz, 1 H), 3.32 (d, ^2J = 12.8 Hz, 1 H), 3.37 (s, 3 H) 3.40 (m, 2 H), 3.54 (d, ^2J = 4.0 Hz, 2 H), 3.75 (s, 3 H), 3.86 (d, ^2J = 11.2 Hz, 1 H), 4.16 (d, ^2J = 12.8 Hz, 1 H), 4.55 (s, 1 H), 5.53 (s, 1 H), 6.89 – 6.95 (m, 2 H), 7.12 – 7.15 (m, 2 H), 7.24 (m,

2 H), 7.30 – 7.36 (m, 2 H), 7.65 (t, ^3J = 4.4 Hz, 1 H), 7.69 – 7.77 (m, 2 H), 8.18 (broad, 1 H), 8.61 (d, ^3J = 4.4 Hz, 1 H), 8.74 (d, ^3J = 4 Hz, 1 H). – ^{13}C NMR (101 MHz, $CDCl_3$): δ = 47.7, 52.5, 52.7, 61.0, 63.5, 68.9, 68.9, 111.8, 119.2, 122.4, 123.2, 124.3, 135.2, 136.4, 137.4, 144.1, 148.6, 149.0, 149.4, 149.5, 150.0, 154.1, 154.6, 156.9, 157.2, 162.2, 168.3, 169.2, 201.0. – ESI-MS: m/z (%) = 632.21 (100) $[M+H]^+$. – HPLC: t_R = 9.60 min.

*Dimethyl 3-((1H-imidazol-2-yl)methyl)-9-oxo-2,4-di(pyridin-2-yl)-7-(pyridin-2-ylmethyl)-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarboxylate (**4**)*

To a solution of 200 mg (0.44 mmol) **2**, 55 μL (0.54 mmol) 2-picolylamine and 80 μL (1.07 mmol) formaldehyde (37 % aq.) were slowly added. The reaction mixture was refluxed for 7 h until a clear yellow solution had formed. After removing the solvent *in vacuo*, the crude product was recrystallized from ethyl acetate to give **4** as a colorless solid. Yield: 144 mg (56 %). – Anal. for $C_{31}H_{31}N_7O_5$: calcd. C 64.02, H 5.36, N 16.86; found C 64.44, H 5.03, N 16.36. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.80 (d, ^2J = 12.0 Hz, 1 H), 3.21 (d, ^2J = 10.8 Hz, 1 H), 3.32 (s, 2 H), 3.38 (s, 3 H), 3.52 (d, ^2J = 12.0 Hz, 1 H), 3.70 (d, ^2J = 12.8 Hz, 1 H), 3.79 (s, 3 H), 4.46 (s, 1 H), 5.40 (s, 1 H), 6.97 (m, 1 H), 7.10 (d, ^3J = 7.6 Hz, 1 H), 7.13 – 7.23 (m, 4 H), 7.25 (d, ^3J = 7.6 Hz, 1 H), 7.35 (m, 1 H), 7.55 (m, 1 H), 7.62 (t, ^2J = 5.6 Hz, 1 H), 7.71 (t, ^3J = 5.6 Hz, 1 H), 8.25 (d, ^3J = 4.0 Hz, 1 H), 8.59 (d, ^3J = 4.0 Hz, 1 H), 8.78 (d, ^3J = 4.0 Hz, 1 H). – ^{13}C NMR (101 MHz, $CDCl_3$): δ = 47.4, 52.5, 61.0, 62.6, 63.8, 65.9, 68.5, 122.4, 123.3, 128.4, 136.3, 137.4, 146.8, 148.6, 150.0, 154.9, 157.5, 168.7, 169.4, 200.5. – ESI-MS: m/z (%) = 582.28 (100) $[M+H]^+$. – HPLC: t_R = 7.67 min.

*[Dimethyl 3-((1H-benzimidazol-2-yl)methyl)-9-oxo-2,4-di(pyridin-2-yl)-7-(pyridin-2-ylmethyl)-3,7-diazabicyclo-[3.3.1]nonane-1,5-dicarboxylate]-(nitrato)copper(II) hydrate nitrate (**3Cu**)*

To 32 mg (0.05 mmol) of **3** dissolved in 2 mL methanol, 8.65 mg (0.05 mmol) $Cu(NO_3)_2$ dissolved in 1 mL methanol was added. The reaction mixture was refluxed for 5 min, and the clear blue solution was cooled to r. t. The product was precipitated by addition of 50 mL diethyl ether and filtered off. Crystals suitable for X-ray analysis were obtained by slow diffusion of diethyl ether into a solution of **3Cu** in methanol. Yield: 20.5 mg (59 %). – Anal. for $C_{35}H_{33}CuN_7O_5 2NO_3$ 2 H_2O: calcd. C 49.15, H 4.36, N 14.74; found C 49.11, H 4.25, N 14.91. – ESI-MS: m/z (%) = 693.3 (100), 695.3 (50) $[C_{35}H_{33}CuN_7O_5–H]^+$. – HPLC: t_R = 8.77 min.

*[Dimethyl 3-((1H-imidazol-2-yl)methyl)-9-oxo-2,4-di(pyridin-2-yl)-7-(pyridin-2-ylmethyl)-3,7-diazabicyclo[3.3.1]-nonane-1,5-dicarboxylate]-(nitrato)copper(II) hydrate nitrate (**4Cu**)*

To 29 mg (0.05 mmol) of **4** dissolved in 2 mL methanol, 8.65 mg (0.05 mmol) $Cu(NO_3)_2$ dissolved in 1 mL methanol was added. The reaction mixture was refluxed for 5 min, and the clear green solution was cooled to r. t. The product was precipitated by addition of 50 mL diethyl ether and filtered off. Yield: 8.4 mg (26 %). – Anal. for $C_{31}H_{31}CuN_7O_5$ $2NO_3$ H_2O: calcd. C 47.30, H 4.23, N 16.01; found C 46.95, H 4.03, N 15.86. – ESI-MS: m/z (%) = 643.2 (100), 645.2 (50) $[C_{31}H_{31}CuN_7O_5–H]^+$. – HPLC: t_R = 7.5 min.

X-Ray structure analyses

The single-crystal X-ray data collection was carried out on a Bruker AXS SMART diffractometer at r. t. (**3Cu** at 190 K) using MoK_α radiation (λ = 0.71073 Å), monochromatized by means of a graphite crystal. All data were collected at r. t. Data reductions and absorption corrections were performed with the Bruker AXS SAINT [15] and SADABS [16] packages, respectively. The structures were solved by Direct Methods and refined by full-matrix least-squares calculations using the programs SHELXS/L [17]. Anisotropic displacement parameters were employed for non-hydrogen atoms. The hydrogen atoms were treated isotropically with U_{iso} = 1.2 times the U_{eq} value of the parent atom. In case of methylene groups U_{iso} = 1.5 times the U_{eq} value was chosen. Crystal data and refinement details are summarized in Table 1.

CCDC 809601 (**1**), 809602 (**2**) and 809603 (**Cu3**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.cdc.cam.ac.uk /data_request/cif.

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