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A Family of Hydrazone-Based Nucleosides for Use in Metal-Mediated Base Pairs

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Dedicated to Professor Werner Uhl on the Occasion of His 60th Birthday

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Abstract. A new family of hydrazone-based nucleosides for use in metal-mediated base pairs was devised. The artificial nucleobases are derivatives of the papy ligand (papy = pyridinecarboxaldehyde-2′-pyridylhydrazone). By replacing the pendant pyridine moiety in papy by furan and thiophene, respectively, tridentate nucleosides with N,N,N-, N,N,O- and N,N,S-donor sites were obtained. As only a few transition metal complexes with pendant furan ligands have been reported, a model nucleobase for the N,N,O-donor nucleoside was synthesized. The molecular structures of its Cu^{2+}, Ni^{2+}, and Co^{2+} complexes are reported. In all complexes, only weak *M*–O(furan) bonding is observed. The Co^{2+} complex displays a pentagonal bipyramidal coordination arrangement. In general, the structures of the metal complexes suggest that the respective nucleosides can be applied in metal-mediated base pairs.

Introduction

Mainly as a result of its superb self-assembly properties, DNA is of utmost importance not only in the field of biochemistry. In fact, numerous applications for DNA have been developed that are independent of its biological origin. Examples are its use as a breadboard for chemical reactions,[1] in asymmetric catalysis,[2] or as a scaffold for functional molecules in nanotechnology.[3] In the latter aspect, the site-specific decoration of nucleic acids with metal ions (and hence with metal-based functionality) represents another important area of research. The most prominent method for the site-specific introduction of metal ions is the formation of so-called metal-mediated base pairs. In these base pairs, the hydrogen bonds between complementary nucleosides are formally replaced by coordinative bonds. As a result, transition metal ions can be incorporated inside the double helix, aligned along the helical axis.[4] Metal-mediated base pairs can in principle be formed from entirely natural nucleosides,[5] but many more examples are known for artificial metal-mediated base pairs.[6] Most of these comprise ligands with either nitrogen donor atoms (e.g. imidazole,[4] triazole,[7] dipicolylamine,[8] 1-deazaadenine,[9] 1,3-dideazaadenine[10]), oxygen donor atoms (e.g. hydroxypyridone[11]), or combinations thereof (e.g. salen,[12] hydroxyquinoline[13]). RNA-based metal-mediated base pairs have been reported, too.[14] Only a limited number of reports exists on the use of sulfur donor atoms, namely in the S,N,S-ligand 2,6-bis(ethylthiomethyl)pyridine,[15] in the O,S-ligands mercaptopyridone and hydroxylpyridinethione,[16] and in thiopyrimidines.[17] The use of sulfur-containing ligands is particularly interesting as it potentially allows the incorporation of softer metal ions into metal-mediated base pairs. However, all metal-mediated base pairs with sulfur-containing nucleosides that have been reported to date inside a double helical context comprise silver(I) only. It is therefore highly important to study systematically the effect of a gradually increasing softness of the donor atoms within an otherwise unchanged system. We therefore set out to devise a new class of artificial tridentate ligand-based nucleosides with N,N,N-, N,N,O-, and N,N,S-donor sets to elucidate this effect.

Results and Discussion

To further explore the possible applications of nucleic acids with metal-mediated base pairs, a family of novel hydrazone-based artificial nucleosides was developed. Starting from 2-hydrazinylpyridine (**2a**), the condensation with a furan-, pyridine-, or thiophene-based aldehyde led to a variety of hydrazones with N,N,N-, N,N,O-, or N,N,S-chelating abilities (Scheme 1, *R* = H). Ligand **3a** is commonly known as papy

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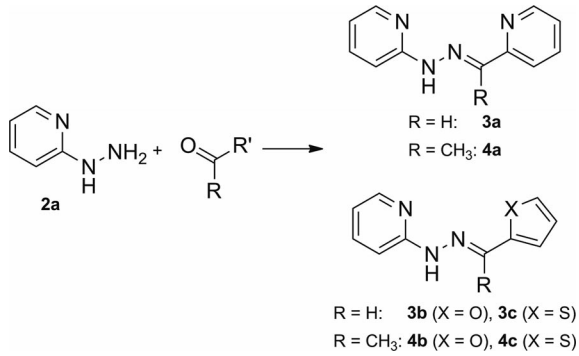
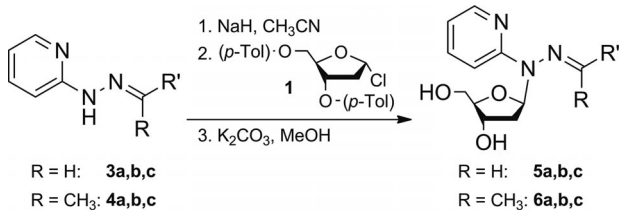
(pyridinecarboxaldehyde-2′-pyridylhydrazone). Accordingly, we have dubbed ligands **3b** and **3c** fapy (derived from furan) and tapy (derived from thiophene), respectively.



Scheme 1. Synthesis of hydrazones **3a** (papy, R' = pyridine-2-yl), **3b** (fapy, R' = furan-2-yl), and **3c** (tapy, R' = thiophene-2-yl) from 2-hydrazinylpyridine (**2a**) via condensation reaction with the respective aldehyde (R = H). Reaction with the respective methyl ketone results in hydrazones **4a**, **4b**, and **4c**.

These ligands were incorporated as artificial nucleobases into hydrazone-based nucleosides via reaction with Hoffer's chloro sugar (Scheme 2).



Scheme 2. Synthesis of hydrazone-based artificial nucleosides (**a**: R' = pyridine-2-yl; **b**: R' = furan-2-yl; **c**: R' = thiophene-2-yl).

Initial investigations revealed that the papy nucleoside with N,N,N-donor capability (**5a**) is rather unstable under aqueous conditions, showing a decomposition by 50% already within less than 5 h (Figure 1). A change to other polar solvents such as methanol slightly increased the hydrolytic stability, albeit not to a satisfactory extent.

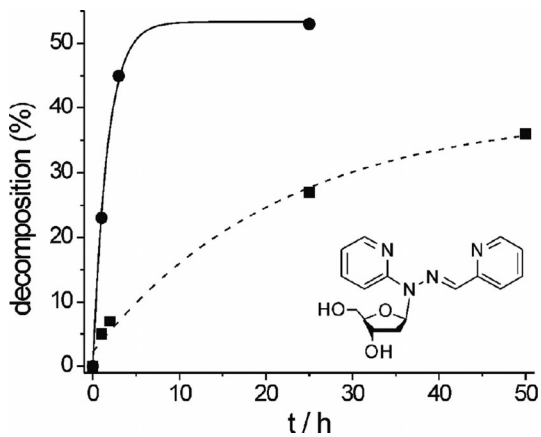
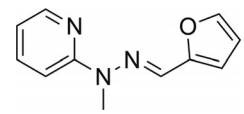


Figure 1. Decomposition of papy nucleoside **5a** in different solvents as monitored by ^{1}H NMR spectroscopy (• = D_2O; ■ = CD_3OD).

To prohibit (or at least to slow down the rate of) a nucleophilic attack of a water molecule at the imino carbon atom, a second series of hydrazone-based nucleosides was synthesized. In these nucleosides, the position at the imino carbon is sterically blocked by a methyl group (R = CH_3 in Scheme 1 and Scheme 2). This was achieved by replacing the aldehyde in the condensation reaction by the respective methyl ketone. As a result, hydrazones **4a**–**4c** and nucleosides **6a**–**6c** were obtained. These nucleosides proved to be much more hydrolytically stable: In methanol containing 15% D_2O, no decomposition was detected even after one day. This increased hydrolytic stability is important for an application in automated DNA synthesis. Hence, the methylated nucleosides represent promising building blocks for new metal-mediated base pairs.

Typically, model nucleobases are used to investigate the metal-binding behavior of nucleosides. In these model nucleobases, the sugar moiety is formally replaced by an alkyl group. As a result, the metal complexes have much simpler NMR spectra and, more importantly, they crystallize more easily. The alkylation prevents the nitrogen atom that is originally involved in the glycosidic bond to participate in any metal binding.[18a] In the natural nucleobases, this leads to N9-alkylated purine and N1-alkylated pyrimidine bases. Model nucleobases have been successfully applied in previous structural studies on metal-mediated base pairs.[18b–e]

In the presented study, we investigated the metal-binding behavior of a model nucleobase for the furan-containing nucleoside **5b** in more detail. This particular ligand was chosen because only little data are available regarding transition metal complexes of ligands with pendant furan rings.[19] The synthesis of model nucleobase **7** (Scheme 3) followed the procedure detailed in Scheme 1. However, it started from 2-(1-methylhydrazin-1-yl)pyridine (**2b**) rather than 2-hydrazinylpyridine (**2a**). The reaction of **7** with Cu^{2+}, Ni^{2+}, and Co^{2+} yielded the respective metal complexes, whose molecular structures were determined by single-crystal X-ray diffraction analyses. For an application in metal-mediated base pairs, the complexes should ideally be planar, to allow stacking interactions with neighboring nucleobases. Additional axial coordination by labile ligands is not necessarily of any disadvantage, as it indicates that weak metal–metal interactions between consecutive metal-mediated base pairs might be possible.



Scheme 3. Chemical representation of model nucleobase **7**.

Reaction of **7** with $CuCl_2$ gave [Cu(**7**)Cl_2] (**8**). Figure 2 shows the molecular structure of **8**, and Table 1 lists relevant bond lengths and angles. As can be seen, the metal complex is not planar. Cu1 is coordinated by two nitrogen atoms with bond lengths slightly below 2 Å and by two chlorido ligands with bond lengths in the order of 2.20–2.25 Å. While the Cu–N distances are in the normal range, the Cu–Cl bonds are rather short. The shorter Cu–Cl distance is found for the equa-

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Table 1. Relevant bond lengths /Å and angles /° in the molecular structures of compounds **8** and **9a**. For comparison, selected bond lengths and angles are also given for compound **10**.

Bond, angle[a)]	**8**	**9a**	**10**
M–N1p	1.9780(16)	2.0092(14)	2.0398(12)
M–N2h	1.9960(15)	2.0707(13)	2.1533(11)
M–O1f	2.8519(15)	2.7504(14)	2.7667(11)
M–Cl1[b)]	2.201(6)	2.3339(5)	–
M–Cl2	2.2542(5)	2.3378(5)	–
M–O2	–	2.0565(12)	–
N1p–*M*–N2h	79.66(6)	78.44(5)	76.16(5)
N1p–*M*–Cl1[b)]	102.99(18)	102.93(4)	–
N1p–*M*–Cl2	127.94(5)	100.58(4)	–
N1p–*M*–O2	–	93.46(5)	–
N1p–*M*–O1f	141.91(6)	146.64(5)	142.58(4)
N2h–M–Cl1	149.19(15)	173.73(4)	–
Cl1–*M*–Cl2[b)]	103.11(17)	93.361(17)	–
Cl1–*M*–O2	–	89.34(4)	–

a) **8**: *M* = Cu1, **9a**: *M* = Ni1, **10**: *M* = Co1. b) **8**: Cl1 ≡ Cl1a.

torial chlorido ligand. The furan ligand is oriented in a way that an additional weak Cu1–O1f interaction is feasible. The respective distance amounts to 2.8519(15) Å and is therefore significantly longer than a typical Cu–O bond. Previously, Cu–O bond lengths in copper complexes with pendant furan ligands have been reported up to 2.595 Å.[20] Nonetheless, by applying the van der Waals radii reported for copper (1.4 Å) and oxygen (1.52 Å),[21] a weak bonding interaction between Cu1 and O1f can be concluded for compound **8**.

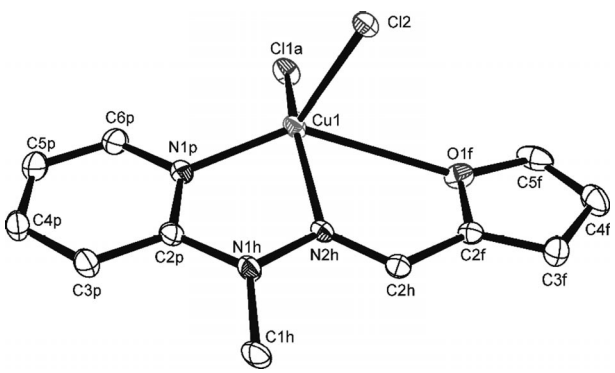


Figure 2. Molecular structure of [Cu(**7**)Cl_2] (**8**). Hydrogen atoms are omitted for clarity. Thermal ellipsoids are drawn at a 30% probability level.

Reaction of **7** with $NiCl_2 \cdot 6H_2O$ gave [Ni(**7**)Cl_2] (**9**). Recrystallization of **9** from DMSO in an atmosphere of methanol gave [Ni(**7**)Cl_2(DMSO)]·DMSO (**9a**). Figure 3 shows the molecular structure of **9a**. Relevant bond lengths and angles are listed in Table 1. In **9a**, the central nickel ion adopts a distorted octahedral coordination arrangement. The coordination sites on the axis oriented perpendicular to the tridentate ligand are occupied by one DMSO and one chlorido ligand. The DMSO ligand coordinates by its oxygen atom. As the sum of the van der Waal radii of nickel (1.63 Å) and oxygen (1.52 Å) is significantly larger than the observed Ni1–O1f distance [2.7504(14) Å], a bonding interaction between Ni1 and O1f can be concluded. Again, this bond is longer than previously reported Ni–O bonds in nickel complexes with pendant furan ligands (2.202–2.358 Å).[19] The sum of the inner angles N1p–Ni1–N2h, N2h–Ni1–O1f, O1f–Ni1–Cl1, and Cl1–Ni1–N1p amounts to 359.33(9)°, thereby indicating the planarity of the tridentate ligand in combination with Cl1.

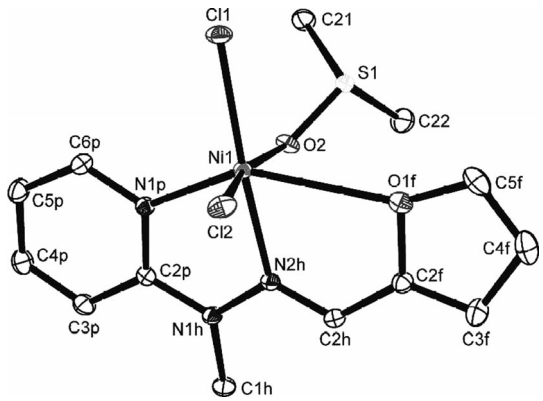


Figure 3. Molecular structure of [Ni(**7**)Cl_2(DMSO)]·DMSO (**9a**). Hydrogen atoms and the non-coordinating DMSO molecule are omitted for clarity. Thermal ellipsoids are drawn at a 30% probability level.

Reaction of **7** with $Co(NO_3)_2 \cdot 6H_2O$ gave [Co(**7**)$(NO_3)_2$-(H_2O)] (**10**). Figure 4a shows the molecular structure of **10**. Relevant bond lengths and angles are listed in Table 2. In **10**, the cobalt ion adopts an unusual pentagonal bipyramidal structure (Figure 4b). One aqua ligand and one monodentate nitrato ligand bind in the axial positions. The O3–Co1–O1a angle amounts to 154.42(4)°, indicating a non-perfect bipyramid. A bidentate nitrato ligand and the three donor sites from ligand **7** are responsible for the pentagonal coordination. The sum of the inner angles N1p–Co1–N2h, N2h–Co1–O1f, O1f–Co1–O2b, O2b–Co1–O2a, and O2a–Co1–N1p amounts to 360.3(1)°, showing the perfect planarity of the pentagonal plane. With Co–O bond lengths of 2.1433(11) Å and 2.3416(11) Å, the bidentate nitrato ligand binds in a slightly asymmetric fashion. Applying the criteria proposed by *Driessen* and co-workers,[22] the bidentate binding mode can be confirmed. The Co1–O1f distance in **10** amounts to 2.7667(11) Å. Similar to what has already been concluded for compounds **8** and **9a**, this distance suggests a weak bonding interaction.

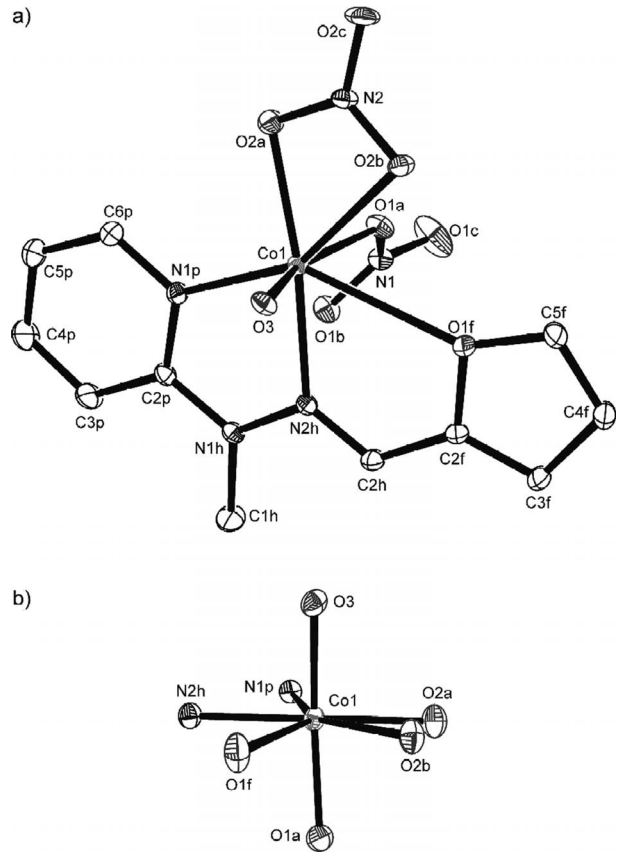


Figure 4. (a) Molecular structure of [Co(**7**)$(NO_3)_2(H_2O)$] (**10**). Hydrogen atoms are omitted for clarity. (b) Distorted pentagonal bipyramidal coordination environment of Co1. Thermal ellipsoids are drawn at a 30% probability level.

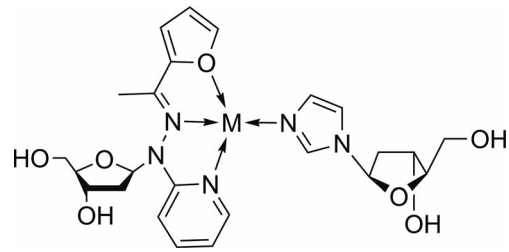
Table 2. Relevant bond lengths /Å and angles /° in the molecular structure of compound **10**.

Co1–N1p	2.0398(12)	N1p–Co1–N2h	76.16(5)
Co1–N2h	2.1533(11)	N1p–Co1–O3	96.35(4)
Co1–O1f	2.7667(11)	N1p–Co1–O1a	109.08(4)
Co1–O1a	2.0537(10)	N1p–Co1–O2a	95.46(4)
Co1–O2a	2.1433(11)	N1p–Co1–O1f	142.58(4)
Co1–O2b	2.3416(11)	O3–Co1–O1a	154.42(4)
Co1–O3	2.0653(11)	O3–Co1–O2a	93.96(4)

Conclusions

A new family of hydrazone-based nucleosides for use in metal-mediated base pairs was synthesized and characterized. Depending on the identity of the pendant heterocyclic ligand, the artificial nucleobases provide an N,N,N-, N,N,O-, or N,N,S-donor set. To be applied in the formation of metal-mediated base pairs, the tridentate hydrazone nucleoside will be placed in one strand and a monodentate nucleoside (e.g. an azole nucleoside)[23] in the complementary strand (Scheme 4).

The first-generation nucleoside **5a** showed a relatively fast decomposition in aqueous solution, rendering it inadequate for an application in metal-mediated base pairs. The second-generation nucleosides **6a**–**6c**, all carrying a methyl substituent at the imino carbon of the hydrazone moiety, were much more stable against hydrolysis. They hence represent feasible building blocks for DNA.



Scheme 4. Chemical representation of a potential metal-mediated base pair formed from nucleoside **6b** and an imidazole nucleoside.

A model nucleobase **7** was synthesized, representing the furan-containing artificial nucleoside. The molecular structures of the metal complexes of **7** with Cu^{2+} (**8**), Ni^{2+} (**9a**), and Co^{2+} (**10**) clearly indicate that the family of hydrazone-based nucleosides should be capable of forming planar metal-mediated base pairs.

The complex [Cu(**7**)Cl_2] (**8**) shows a strong distortion from planarity. Moreover, it contains the weakest M–O1f bond between the central metal atom and the furan ring. Hence, out of the three transition metals under investigation, Cu^{2+} appears to be the least favored one in terms of applicability in a metal-mediated base pair. In contrast, the octahedral complex [Ni(**7**)Cl_2(DMSO)]·DMSO (**9a**) indicates that Ni^{2+} might be a good candidate for the central metal ion in a metal-mediated base pair containing one of the hydrazone nucleosides. When incorporated into a DNA duplex, the two axial ligands (DMSO, Cl^-) could either be substituted by donor sites from within the DNA strand (a related finding has been reported previously)[24] or could be replaced by a weak axial metal–metal interaction between neighboring artificial base pairs. The same reasoning applies for the pentagonal bipyramidal [Co(**7**)$(NO_3)_2(H_2O)$] (**10**) with the axially coordinating aqua and nitrato ligands. Moreover, the pentagonal coordination environment in this complex nicely demonstrates the relatively large space available for the monodentate complementary nucleoside. In contrast to other combinations of tridentate and monodentate ligands, in which a steric clash prohibits the formation of entirely planar complexes,[8,18c] the furan-containing systems are therefore more promising in terms of their applicability in planar metal-mediated base pairs.

Experimental Section

General: The *para*-toluoyl-protected 2-deoxy-D-ribose (**1**) as well as 2-hydrazinylpyridine (**2a**) and 2-(1-methylhydrazin-1-yl)pyridine (**2b**) were synthesized according to published procedures.[25] ^1H and ^{13}C NMR spectra were recorded with Bruker Avance (I) 400 and Avance (III) 400 spectrometers with an internal standard relative to TMS (δ / ppm = 0) for measurements in $CDCl_3$. In case of using [D_6]DMSO and [D_4]methanol the residual solvent signal was used for internal standards. For a complete assignment of the nucleosides, $^1H,^1H$-ROESY, $^1H,^{13}C\{^1H\}$-HSQC, $^1H,^{13}C\{^1H\}$-HMBC and $^1H,^1H$-gCOSY experiments were performed. Mass spectra were recorded with a Bruker Reflex IV (MALDI-TOF) and with a Bruker Daltonics Micro TOF spectrometer (EI, ESI).

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Synthesis of the Hydrazones (3a, 3b, 3c): To a solution of **2a** in EtOH (40 mL) were added 0.5 equivalents of acetic acid as catalyst and one equivalent of the pyridine- (**3a**), furan- (**3b**) or thiophene-substituted (**3c**) aldehyde. The reaction mixture was stirred for 45 min at 55 °C. After reducing the reaction volume to the half, H_2O (10 mL) was added, and the yellow-orange product crystallized overnight at –26 °C. The product was filtered and dried (40 °C). **3a**: Yield 80 %. **^{1}H NMR** ($CDCl_3$): δ = 10.07 (s, 1 H, NH); 8.56 (dd, 1 H, H6**); 8.21 (dd, 1 H, H6*); 7.99 (dd, 1 H, H3**); 7.92 (s, 1 H, H3); 7.68 (ddd, 1 H, H4*); 7.62 (ddd, 1 H, H4**); 7.42 (dd, 1 H, H3*); 7.18 (ddd, 1 H, H5**); 6.81 (ddd, 1 H, H5*). **^{13}C NMR** ($CDCl_3$): δ = 156.8 (C2**); 154.4 (C2*); 149.3 (C6**); 147.3 (C6*); 139.3 (C3); 138.3(C4*); 136.2 (C4**); 122.9 (C5**); 119.7 (C3**); 116.2 (C5*); 107.7 (C3*). $C_{11}H_{10}N_4$ (198.0905): C 66.8 (calcd. 66.7); H 5.1 (calcd. 5.1); N 28.3 (calcd. 28.3) %. **MALDI-TOF-MS**: *m/z* = 198 (M^+: 198). **3b**: Yield 70 %. **^{1}H NMR** ($CDCl_3$): δ = 9.30 (s, 1 H, NH); 8.13 (dd, 1 H, H6*); 7.70 (s, 1 H, H3); 7.60 (ddd, 1 H, H4*); 7.48 (dd, 1 H, H5**); 7.36 (ddd, 1 H, H5*); 6.78 (dd, 1 H, H3*); 6.60 (dd, 1 H, H3**); 6.46 (ddd, 1 H, H4**). **^{13}C NMR** ($CDCl_3$): δ = 156.7 (C2*); 150.3 (C2**); 146.9 (C6*); 143.4 (C5**); 138.3 (C4*); 129.5 (C3); 115.8 (C3**); 111.7 (C5*); 110.2 (C4**); 107.8 (C3*). $C_{10}H_9N_3O$ (187.0746): C 64.0 (calcd. 64.2); H 4.9 (calcd. 4.9); N 22.3 (calcd. 22.5) %. **MALDI-TOF-MS**: *m/z* = 188 ($M+H^+$: 188). **3c**: Yield 75 %. **^{1}H NMR** ($CDCl_3$): δ = 9.35 (s, 1 H, NH); 8.13 (dd, 1 H, H6*); 7.96 (s, 1 H, H3); 7.61 (ddd, 1 H, H4*); 7.35 (ddd, 1 H, H5**); 7.28 (dd, 1 H, H3**); 7.13 (ddd, 1 H, H4**); 7.02 (dd, 1 H, H5*); 6.78 (dd, 1 H, H3*). **^{13}C NMR** ($CDCl_3$): δ = 156.8 (C2*); 146.9 (C6*); 140.2 (C2**); 138.2 (C4*); 133.9 (C3); 127.3 (C5**); 127.2 (C4**); 126.4 (C3**); 115.6 (C5*); 107.7 (C3*). $C_{10}H_9N_3S$ (203.0517): C 59.2 (calcd. 59.1); H 4.4 (calcd. 4.5); N 20.7 (calcd. 20.7) %. **MALDI-TOF-MS**: *m/z* = 204 ($M+H^+$: 204).

Synthesis of the Methylated Hydrazones (4a, 4b, 4c): To a solution of **2a** in EtOH (50 mL) were added 0.5 equivalents of acetic acid and one equivalent of the pyridine- (**4a**), furan- (**4b**) or thiophene-substituted (**4c**) ketone. The reaction mixture was stirred for 70 min at 55 °C. The volume was reduced to half, and H_2O (15 mL) was added. The solution was flash-frozen in liquid nitrogen, and the product crystallized at –26 °C overnight. **4a**: Yield 68 %. **^{1}H NMR** ($CDCl_3$): δ = 8.16 (s, 1 H, NH); 8.11 (dd, 1 H, H6**); 7.64 (dd, 1 H, H6*); 7.59 (dd, 1 H, H3**); 7.46 (ddd, 1 H, H4*); 7.36 (ddd, 1 H, H4**); 6.78 (dd, 1 H, H3*); 6.65 (ddd, 1 H, H5*); 6.45 (ddd, 1 H, H5**); 2.21 (s, 3 H, CH_3). **^{13}C NMR** ($CDCl_3$): δ = 156.8 (C2**); 152.8 (C2*); 147.2 (C6**); 144.8 (C6*); 142.9 (C3); 139.3 (C4*); 137.8 (C4**); 115.2 (C5**); 111.5 (C3**); 108.7 (C5*); 108.4 (C3*); 12.6 (CH_3). $C_{12}H_{12}N_4$ (212.1062): C 67.7 (calcd. 67.9); H 5.6 (calcd. 5.7); N 26.2 (calcd. 26.4) %. **MALDI-TOF-MS**: *m/z* = 213 ($M+H^+$: 213). **4b**: Yield 62 %. **^{1}H NMR** ($CDCl_3$): δ = 9.73 (s, 1 H, NH); 7.95 (dd, 1 H, H6*); 7.64 (ddd, 1 H, H4*); 7.48 (dd, 1 H, H5**); 7.46 (dd, 1 H, H3**); 6.68 (ddd, 1 H, H5*); 6.66 (dd, 1 H, H3*); 6.45 (ddd, 1 H, H4**); 2.28 (s, 3 H, CH_3). **^{13}C NMR** ($CDCl_3$): δ = 156.8 (C2*); 152.9 (C2**); 144.6 (C6*); 143.0 (C5**); 140.0 (C3); 138.0 (C4*); 115.1 (C3**); 112.5 (C5*); 108.8 (C4**); 108.5 (C3*); 12.7 (CH_3). $C_{11}H_{11}N_3O{\cdot}0.5\,CH_3COOH$: C 62.5 (calcd. 62.3); H 5.7 (calcd. 5.7); N 18.4 (calcd. 18.2) %. **MALDI-TOF-MS**: *m/z* = 202; ($M+H^+$: 202). **4c**: Yield 50 %. **^{1}H NMR** ($CDCl_3$): δ = 9.31 (s, 1 H, NH); 7.99 (dd, 1 H, H6*); 7.63 (ddd, 1 H, H4*); 7.42 (dd, 1 H, H5**); 7.24 (dd, 1 H, H3**); 7.19 (ddd, 1 H, H4**); 7.00 (ddd, 1 H, H5*); 6.76 (dd, 1 H, H3*); 2.32 (s, 3 H, CH_3). **^{13}C NMR** ($CDCl_3$): δ = 156.7 (C2*); 146.6 (C2**); 144.6 (C6*); 140.1 (C5**); 138.5 (C3); 127.1 (C4*); 126.4 (C3**); 124.7 (C5*); 115.6 (C4**); 108.0 (C3*); 13.0 (CH_3). $C_{11}H_{11}N_3S$ (217.0674): C 60.5 (calcd. 60.8); H 5.1 (calcd. 5.1); N 19.1 (calcd. 19.3) %. **MALDI-TOF-MS**: *m/z* = 218 ($M+H^+$: 218).

Synthesis of the Nucleosides (5a, 5b, 5c): To a solution of the hydrazone (**3a**, **3b**, **3c**) in CH_3CN (50 mL) 1.1 equivalents of NaH (60 %) were added. The resulting suspension was stirred for 40 min. Over the duration of 90 min, 1.1 equivalents of **1** were added in 4 portions. The suspension was stirred for further 3 h at ambient temperature, filtered, and washed with CH_2Cl_2 (120 mL). The filtrate was evaporated to dryness and re-dissolved in methanol (60 mL). After the addition 2.3 equivalents of K_2CO_3 the suspension was stirred for 20 h at ambient temperature. To the clear solution CH_2Cl_2 (50 mL) and H_2O (25 mL) were added. After separation of the organic layer, the aqueous layer was washed with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (15 mL), dried (Na_2SO_4), and the solvents evaporated to dryness. The crude product was purified by column chromatography (SiO_2, 0.035–0.070 mm, 60 Å), **5a**: CH_2Cl_2 (18):MeOH (1):Et_3N (1), **5b**: CH_2Cl_2 (18):MeOH (1): Et_3N (1), **5c**: CH_2Cl_2 (20):MeOH (1):Et_3N (1). **5a**: Yield 76 %. **^{1}H NMR** ([D_6]DMSO): δ = 8.56 (dd, 1 H, H6**); 8.33 (dd, 1 H, H6*); 8.32 (s, 1 H, H3); 7.95 (d, 1 H, H3**); 7.83 (ddd, 1 H, H4**); 7.81 (ddd, 1 H, H4*); 7.54 (d, 1 H, H3*); 7.33 (ddd, 1 H, H5**); 7.06 (ddd, 1 H, H5*); 6.80 (pt, 1 H, H1′); 5.24 (s, 1 H, 3′-OH); 4.87 (s, 1 H, 5′-OH); 4.31 (m, 1 H, H3′); 3.70 (m, 1 H, H4′); 3.62–3.52 (m, 2 H, H5′, H5′′); 2.66 (m, 1 H, H2′); 1.91 (m, 1 H, H2′′). **^{13}C NMR** ([D_6]DMSO): δ = 156.3 (C2*); 154.4 (C2**); 149.2 (C6**); 147.1 (C6*); 140.9 (C3); 138.5 (C4*); 136.5 (C4**); 123.2 (C5*); 119.1 (C3*); 118.1 (C5**); 112.9 (C3**); 86.0 (C4′); 85.9 (C1′); 70.2 (C3′); 61.5 (C5′); 34.2 (C2′). $C_{16}H_{18}N_4O_3{\cdot}0.3H_2O$: C 60.1 (calcd. 60.0); H 5.9 (calcd. 5.9); N 17.1 (calcd. 17.5) %. **ESI-MS**: *m/z* = 337.1272 ($M+Na^+$: 337.1277). **5b**: Yield: 63 %. **^{1}H NMR** ([D_6]DMSO): δ = 8.50 (s, 1 H, H3); 8.25 (dd, 1 H, H6*), 7.77 (dd, 1 H, H5**); 7.73 (ddd, 1 H, H4*); 7.38 (dd, 1 H, H3*); 6.94 (ddd, 1 H, H5*); 6.94 (pt, 1 H, H1′); 6.73 (dd, 1 H, H3**); 6.60 (ddd, 1 H, H4**); 5.20 (s, 1 H, OH); 4.96 (s, 1 H, OH); 4.31 (dt, 1 H, H3′); 3.68 (dd, 1 H, H4′); 3.61–3.56 (m, 2 H, H5′, H5′′); 2.52 (dd, 1 H, H2′); 1.82 (dd, 1 H, H2′′). **^{13}C NMR** ([D_6]DMSO): δ = 156.8 (C2*); 150.5 (C2**); 146.9 (C6*); 144.0 (C5**); 138.2 (C4*); 134.6 (C3); 116.8 (C5*); 111.8 (C4**); 111.6 (C3**); 111.3 (C3*); 85.8 (C4′); 85.6 (C1′); 69.8 (C3′); 60.9 (C5′); 33.8 (C2′). $C_{15}H_{17}N_3O_4$ (303.1219): C 59.0 (calcd. 59.4); H 5.7 (calcd. 5.7); N 13.5 (calcd. 13.8) %. **ESI-MS**: *m/z* = 326.1112 ($M+Na^+$: 326.1117). **5c**: Yield 61 %. **^{1}H NMR** ([D_6]DMSO): δ = 8.84 (s, 1 H, H3); 8.25 (dd, 1 H, H6*), 7.74 (ddd, 1 H, H4*); 7.57 (dd, 1 H, H5**); 7.30 (ddd, 1 H, H5*); 7.30 (dd, 1 H, H3**); 7.11 (ddd, 1 H, H4**); 6.93 (dd, 1 H, H3*) 6.93 (pt, 1 H, H1′); 5.20 (s, 1 H, OH); 5.00 (s, 1 H, OH); 4.32 (dt, 1 H, H3′); 3.69 (dd, 1 H, H4′); 3.62–3.57 (m, 2 H, H5′, H5′′); 2.52 (dd, 1 H, H2′); 1.83 (dd, 1 H, H2′′). **^{13}C NMR** ([D_6]DMSO): δ = 156.7 (C2*); 147.0 (C6*); 140.8 (C2**); 140.6 (C3); 138.2 (C4*); 129.0 (C3**); 127.6 (C4**); 127.3 (C5**); 116.7 (C5*); 111.0 (C3*); 85.8 (C4′); 85.7 (C1′); 69.9 (C3′); 61.0 (C5′); 34.0 (C2′). $C_{15}H_{17}N_3O_3S$ (319.0991): C 56.2 (calcd. 56.4); H 5.4 (calcd. 5.4); N 13.0 (calcd. 13.2) %. **ESI-MS**: *m/z* = 342.0883 ($M+Na^+$: 342.0888).

Synthesis of the Methylated Nucleosides (6a, 6b, 6c): Compounds **6a**–**6c** were synthesized in analogy to nucleosides **5a**–**5c**. After addition of **1** to a solution of **4a**–**4c** in CH_3CN, the reaction mixture was stirred for 5 h at ambient temperature. The deprotection with K_2CO_3 required 26 h. The crude product was purified by column chromatography (SiO_2, 0.035–0.070 mm, 60 Å), **6a**: CH_2Cl_2 (18):MeOH (2):Et_3N (1), **6b**: CH_2Cl_2 (18):MeOH (1):Et_3N (1), **6c**: CH_2Cl_2 (18):MeOH (1):Et_3N (1). **6a**: Yield 56 %. **^{1}H NMR** ([D_6]DMSO): δ = 8.68 (dd, 1 H, H6**); 8.24 (dd, 1 H, H6*); 8.20 (d, 1 H, H3**); 7.94 (ddd, 1 H, H4**); 7.59 (ddd, 1 H, H4*); 7.53 (d, 1 H, H3*); 6.86 (ddd, 1 H, H5**); 6.62 (pt, 1 H, H1′); 6.55 (ddd, 1 H, H5*); 5.03 (s, 1 H, 3′-OH); 4.55 (s, 1 H, 5′-OH); 4.14 (m, 1 H, H3′); 3.65 (m, 1 H, H4′); 3.44–3.38 (m, 2 H, H5′, H5′′); 2.24 (m, 1 H, H2′); 2.15 (s, 3 H, CH_3);

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1.96 (m, 1 H, H2′′). **^{13}C NMR** ([D$_6$]DMSO): δ = 171.7 (C3); 156.9 (C2*); 154.5 (C2**); 148.9 (C6**); 147.8 (C6*); 137.8 (C4*); 136.8 (C4**); 125.0 (C5**); 120.8 (C3**); 116.0 (C5*); 110.2 (C3*); 89.9 (C4′); 86.0 (C1′); 70.9 (C3′); 62.7 (C5′); 45.7 (C2′); 15.8 (CH_3). $C_{17}H_{20}N_4O_3$ (328.1535): C 61.9 (calcd. 62.2); H 6.1 (calcd. 6.1); N 16.6 (calcd. 17.1)%. **ESI-MS**: *m/z* = 351.1438 (M+Na$^+$: 351.1423). **6b**: Yield 49%. **^{1}H NMR** ([D$_4$]Methanol): δ = 7.67 (dd, 1 H, H6*), 7.65 (dd, 1 H, H5**); 7.32 (ddd, 1 H, H4*); 7.11 (dd, 1 H, H3*); 6.73 (ddd, 1 H, H5*); 6.53 (dd, 1 H, H3**); 6.20 (ddd, 1 H, H4**); 6.03 (pt, 1 H, H1′); 5.05 (s, 1 H, OH); 4.89 (s, 1 H, OH); 4.30 (dt, 1 H, H3′); 4.28 (dd, 1 H, H4′); 3.39–3.18 (m, 2 H, H5′, H5′′); 2.65 (dd, 1 H, H2′); 2.22 (s, 3 H, CH_3); 2.00 (dd, 1 H, H2′′). **^{13}C NMR** ([D$_4$]Methanol): δ = 155.1 (C2*); 152.1 (C2**); 146.4 (C6*); 143.7 (C3); 138.7 (C4*); 138.2 (C4**); 115.1 (C5*); 112.3 (C3*); 111.0 (C5**); 107.1 (C3**); 86.3 (C4′); 84.5 (C1′); 71.8 (C3′); 62.2 (C5′); 40.9 (C2′); 13.3 (CH_3). $C_{16}H_{19}N_3O_4$ · 0.5 MeOH: C 59.3 (calcd. 59.4); H 6.3 (calcd. 6.4); N 12.6 (calcd. 12.6)%. **ESI-MS**: *m/z* = 340.1268 (M+Na$^+$: 340.1273). **6c**: Yield 55%. **^{1}H NMR** ([D$_4$]Methanol): δ = 7.80 (dd, 1 H, H6*), 7.55 (dd, 1 H, H4*); 7.33 (ddd, 1 H, H5**); 7.11 (m, 3 H, H5*, H4*, H3**); 6.31 (pt, 1 H, H1′); 6.22 (ddd, 1 H, H3*); 5.25 (s, 1 H, OH); 4.41 (m, 1 H, OH); 4.34 (dt, 1 H, H3′); 4.34 (dd, 1 H, H4′); 3.69–3.60 (m, 2 H, H5′, H5′′); 2.74 (dd, 1 H, H2′); 2.53 (dd, 1 H, H2′′); 2.30 (s, 3 H, CH_3). **^{13}C NMR** ([D$_4$]Methanol): δ = 155.8 (C3); 150.3 (C2*); 150.0 (C6*); 146.7 (C2**); 134.6 (C4*); 131.8 (C4**); 126.9 (C5**); 125.4 (C3**); 124.1 (C5*); 113.1 (C3*); 88.6 (C4′); 86.4 (C1′); 71.1 (C3′); 62.4 (C5′); 40.8 (C2′); 14.1 (CH_3). $C_{16}H_{19}N_3O_3S$ · 0.25H_2O: C 56.9 (calcd. 56.9); H 5.7 (calcd. 5.8); N 12.3 (calcd. 12.4)%. **ESI-MS**: *m/z* = 356.1040 (M+Na$^+$: 356.1045).

Synthesis of the Model Nucleobase (7): To a solution of **2b** (0.99 g, 8.11 mmol) in EtOH (30 mL), acetic acid (0.8 mL) and 2-furancarboxaldehyde (0.67 mL, 0.79 g, 8.22 mmol) were added. The reaction mixture was stirred at 55 °C for 35 min. The solvent was evaporated; the residue was dissolved in CH_2Cl_2 (80 mL) and washed with water. After evaporation of the organic phase the product was obtained in 71% yield (1.16 g, 5.76 mmol). **^{1}H NMR** ($CDCl_3$): δ = 8.21 (ddd, 1 H, H6*); 7.69 (dd, 1 H, H5**); 7.59 (dd, 1 H, H4*); 7.53 (s, 1 H, H3); 7.46 (dd, 1 H, H5*); 6.78 (dd, 1 H, H3**); 6.61 (dd, 1 H, H3*); 6.46 (dd, 1 H, H4**); 3.61 (s, 3 H, CH_3). **^{13}C NMR** ($CDCl_3$): δ = 157.2 (C2*); 151.7 (C2**); 146.4 (C6*); 142.7 (C4**); 137.8 (C4*); 124.9 (C3); 115.6 (C5*); 111.6 (C4**); 110.2 (C3**); 108.8 (C3*); 29.5 (CH_3). $C_{11}H_{11}N_3O$ (201.0902): C 65.5 (calcd. 65.7); H 5.4 (calcd. 5.5); N 20.6 (calcd. 20.9)%. **ESI-MS**: *m/z* = 202.0980 (M+H$^+$: 202.0980).

Synthesis of [Cu(7)Cl$_2$] (8): The N,N,O-ligand **7** (120.0 mg, 597 µmol) was dissolved in EtOH (10 mL). A solution of $CuCl_2$·2 H_2O (100.8 mg, 598 µmol) in EtOH (10 mL) was added slowly. The resulting suspension was stirred for 2 h at ambient temperature. The solid was filtered off, washed with Et_2O, and dried at 40 °C. The product was obtained in 60% yield (120.2 mg, 360 µmol). $C_{11}H_{11}Cl_2CuN_3O$·0.25H_2O: C 38.8 (calcd. 38.8); H 3.2 (calcd. 3.4); N 12.3 (calcd. 12.4)%. **ESI-MS**: *m/z* = 298.9882 (M$^+$–Cl: 298.9887). **X-ray**: Single crystals of **8** were obtained by crystallizing the compounds from methanol in an atmosphere of Et_2O.

Synthesis of [Ni(7)Cl$_2$] (9): The N,N,O-ligand **7** (99.2 mg, 492 µmol) was dissolved in MeOH (8 mL). A solution of $NiCl_2$·6H_2O (117.0 mg, 492 µmol) in MeOH (2 mL) was added slowly. The resulting suspension was refluxed at 80 °C for 2 h. The solid was filtered off and washed with cold Et_2O. After drying at 40 °C, the product was obtained in 72% yield (118 mg, 357 µmol). $C_{11}H_{11}Cl_2CuN_3O$·0.25H_2O: C 39.9 (calcd. 39.9); H 3.4 (calcd. 3.4); N 12.6 (calcd. 12.7)%. **ESI-MS**: *m/z* = 293.9939 (M$^+$–Cl: 293.9944). **X-ray**: Single crystals of the composition [Ni(**7**)Cl$_2$(DMSO)]·DMSO (**9a**) were obtained by crystallizing the compounds from DMSO in an atmosphere of MeOH.

Synthesis of [Co(7)(NO$_3$)$_2$(H$_2$O)] (10): The N,N,O-ligand **7** (81.3 mg, 404 µmol) was dissolved in MeOH (10 mL). A solution of $Co(NO_3)_2$·6H_2O (118.1 mg, 406 µmol) in MeOH (5 mL) was added. The reaction mixture was refluxed at 80 °C for 3 h. The solvent was evaporated and the residue treated with Et_2O. The solid was filtered off and washed with Et_2O. After drying at 40 °C, the product was obtained in 64% yield (104.1 mg, 259 µmol). $C_{11}H_{13}CoN_5O_8$ (402.0096): C 32.7 (calcd. 32.9); H 3.4 (calcd. 3.3); N 17.5 (calcd.

Table 3. Crystallographic data for compounds **8**, **9a**, and **10**.

	8	**9a**	**10**
Empirical formula	$C_{11}H_{11}Cl_2CuN_3O$	$C_{15}H_{23}Cl_2N_3NiO_3S_2$	$C_{11}H_{13}CoN_5O_8$
Formula weight	335.67	487.09	402.19
Crystal system	monoclinic	triclinic	monoclinic
Space group	$P12_1/n1$	$P\bar{1}$	$P12_1/n1$
a /Å	13.2532(3)	8.3419(3)	9.6094(2)
b /Å	7.53314(13)	11.3177(5)	13.4147(3)
c /Å	13.7017(3)	12.5230(5)	12.0436(2)
α /°	90	97.372(4)	90
β /°	105.060(2)	100.634(3)	92.090(1)
γ /°	90	110.800(4)	90
V /Å^3	1320.97(4)	1061.82(7)	1551.47(5)
Z	4	2	4
$\rho_{calcd.}$ /g·cm^{-3}	1.688	1.523	1.722
μ(Mo-K_α) /mm^{-1}	2.054	1.381	1.161
Crystal size /mm	0.25 × 0.22 × 0.05	0.64 × 0.53 × 0.44	0.35 × 0.28 × 0.04
Temperature /K	183(2)	183(2)	153(2)
θ_{min}, θ_{max} /°)	2.48, 32.75	2.81, 31.51	2.27, 30.06
Dataset	–19:18, –11:11, –20:20	–12:12, –17:16, –17:17	–13:13, –18:18, –16:16
Tot., uniq. data	25088, 4511	18420, 6734	23682, 4548
Observed data [$I > 2\sigma(I)$]	3670	5331	4025
N_{ref}, N_{par}	4511, 175	6734, 244	4548, 233
R, wR_2, *S* [$I > 2\sigma(I)$][a)]	0.0357, 0.0807, 1.075	0.0360, 0.0934, 1.003	0.0274, 0.0764, 1.044
Resd. dens. min. and max. /e·Å^{-3}	0.48, –0.40	0.70, –0.64	0.75, –0.28

a) $R_1 = \Sigma||F_o|-|F_c||/\Sigma|F_o|$, $wR_2 = [\Sigma w(F_o^2-F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$.

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17.7)%. **ESI-MS**: m/z = 340.0212 (M^+–(NO_3): 340.0218). **X-ray**: Single crystals of **10** were obtained by crystallizing the product from MeOH in an atmosphere of Et_2O.

X-ray Crystallography: Crystal data were collected with graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å) with an Xcalibur system (**8**, **9a**) and a Bruker APEX diffractometer (**10**). The structures were solved by direct methods and were refined by full-matrix, least-squares on F^2 by using the SHELXTL PLUS and SHELXL-97 programs.[26] All non-hydrogen atoms were refined anisotropically, whilst hydrogen atoms were calculated on ideal positions. In compound **8**, the equatorial chlorido ligand was found to be disordered over two positions with occupancy factors of 0.60 and 0.40. Relevant crystallographic data are listed in Table 3.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre, CCDC, 12 Union Road, Cambridge CB21EZ, UK. Copies of the data can be obtained free of charge on quoting the depository numbers CCDC-922129, CCDC-922130, and CCDC-922131. (Fax: +44-1223-336-033; E-Mail: deposit@ccdc.cam.ac.uk, http://www.ccdc.cam.ac.uk)

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