Scientific paper

Synthesis and X-ray Structural Analysis of the Ruthenium(III) Complex Na[*trans*-$RuCl_4$(DMSO)(PyrDiaz)], the Diazene Derivative of Antitumor NAMI-Pyr

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Dedicated to Professor Emeritus Miha Tišler, University of Ljubljana, on the occasion of his 90th birthday.

Abstract

Novel tetrachloridoruthenium(III) complex Na[*trans*-$RuCl_4$(DMSO)(**PyrDiaz**)] (**3**) with pyridine-tethered diazenedicarboxamide **PyrDiaz** ligand (**PyrDiaz** = N^1-(4-isopropylphenyl)-N^2-(pyridin-2-ylmethyl)diazene-1,2-dicarboxamide) was synthesized by direct coupling of **PyrDiaz** with sodium *trans*-bis(dimethyl sulfoxide)tetrachloridoruthenate(III) (Na-[*trans*-$Ru(DMSO)_2Cl_4$]). Compound **3** is the analogue of the antimetastatic Ru(III) complex NAMI-A and NAMI-Pyr. Single crystal X-ray diffraction analysis revealed that the compound **3** is a polymeric complex with the ruthenium and sodium centres.

Keywords: Diazene, pyridine, ruthenium(III), sodium, polymeric complex

1. Introduction

Based on the WHO estimates, cancer is one of the leading causes of mortality worldwide accounting for 8.8 million deaths in 2015.[1] In addition to surgical removal of tumours and radiation therapy, chemotherapy is one of the most commonly applied treatments of cancer. Burden associated with chemotherapy, however, is intrinsic and acquired resistance,[2] and severe side-effects that are responsible for considerable morbidity, greatly reducing the effectiveness of the therapy. This, and the striking estimate that the global incidence of cancer continues to increase, urges for new strategies and chemical entities to be devised.[3]

Commenced with a group of platinum chemotherapeutic agents that has been in clinical use for half of a century,[4–6] other precious-metal-based alternatives lately enticed an army of chemists worldwide.[7] As a result, some ruthenium-based compounds of unique properties, surpassing cisplatin in activity, particularly on resistant tumours, and with reduced host toxicity at active doses have been discovered.[8,9]

In the treatment of a complex disease like cancer it is unlikely for a single drug to be effective. To increase the chemotherapeutic success, a combination of two or more active agents having separate targets is commonly administered at the therapy.[10] A promising alternative to these so-called cocktails are hybrid molecules that are composed of two or more covalently bound drugs; the compounds that can possess combined pharmacological properties of the individual drugs[10,11] yet superior synergistic effects.[12,13]

Over the past years, we have investigated redox-active[14] diazenecarboxamides as potential anti-cancer agents.[15] The results of the *in vitro* experiments suggested that they likely target tumour cell redox mechanism by oxidation of glutathione into glutathione disulphide.[16] A synergistic effect was noted by treating some tumour cell lines with the combination of cisplatin and selected diazenecar-

boxamides,[16e] prompting us to consider novel diazenecarboxamide-platinum conjugates (Figure 1).[6,17] This has led to complex **A**, possessing higher cytotoxicity against T24 bladder carcinoma cells as compared to the parent platinum precursor ([PtCl(DMSO)(en)]Cl; en = ethylenediamine) and organic ligand, for example.[18] Redox-active diazenecarboxamides were also combined with organometallic [Ru(II)–Arene] to generate complexes with interesting coordination modes and chemical reactivity (Figure 2).[19,20] In the context of our endeavour in the field of potential anti-cancer agents, complex **B** was identified as highly cytotoxic against tumour cell lines with IC_{50} values in the low micro-molar range.[19,21] The activity of **B** was cell-type specific and comparable in both cancer cell lines and their drug-resistant subline. A tenfold increase in the sensitivity of tumour cervical carcinoma cell lines (HeLa) with depleted intracellular glutathione level in comparison to the untreated HeLa suggested glutathione as the molecular target of **B**.[19]

Encouraged by these results and inspired by ruthenium(III) complexes NAMI-A (imidazolium *trans*-[tetrachlorido(dimethyl sulfoxide)imidazole ruthenium(III)]),[22] KP1019 (indazolium *trans*-[tetrachloridobis(1*H*-indazole)ruthenium(III)]) and its sodium salt KP1339[23] (Figure 3), we were prompted to examine the coordination ability of diazenedicarboxamide N^1-(4-isopropylphenyl)-N^2-(pyridin-2-ylmethyl)diazene-1,2-dicarboxamide (**1**) (Scheme 1). Compound **1** has been previously screened for anti-cancer activity.[24]

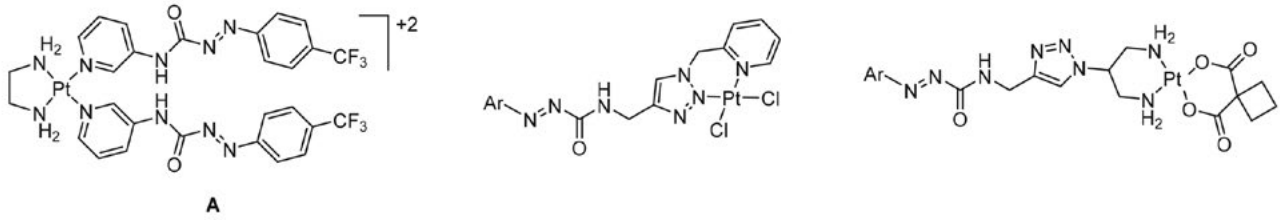


Figure 1. Selected diazenecarboxamide-platinum conjugates.

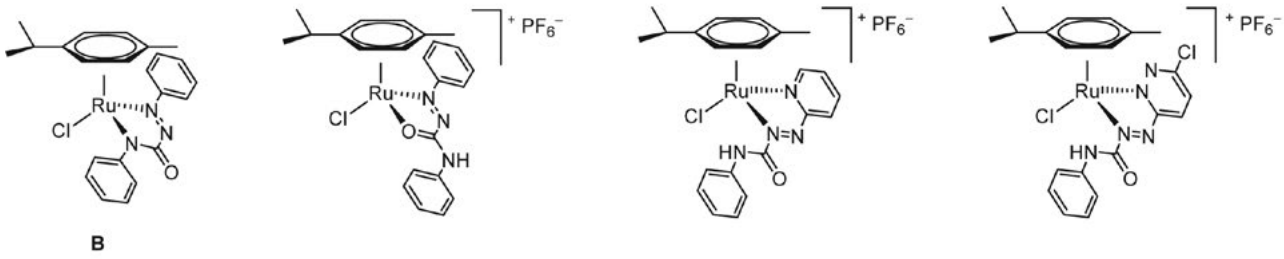
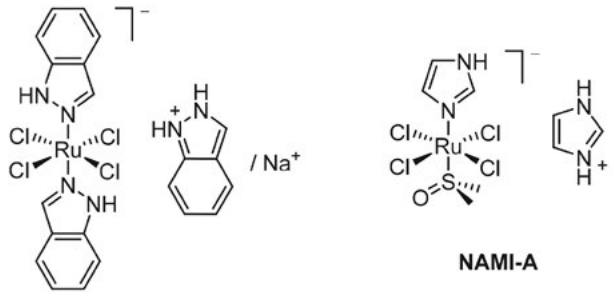


Figure 2. Selected organometallic [Arene–Ru^{II}–Diazenecarboxamide] compounds.



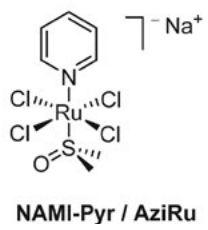


Figure 3. Selected Ru(III) complexes having anti-cancer activity.

2. Experimental

Starting materials and solvents for the synthesis of the examined compounds were used as obtained, and without further purification, from Aldrich, Fluka and Alfa Aesar. IR spectrum was obtained with a Bruker ALPHA Platinum ATR spectrometer on a solid sample support (ATR). NMR spectra were recorded in D_2O with a Bruker Avance III 500 MHz instrument operating at 500 MHz, at 296 K, and referenced to the peak of HOD (δ = 4.63 ppm). An Agilent 6224 time-of-flight (TOF) mass spectrometer equipped with a double orthogonal electrospray source at atmospheric pressure ionization (ESI) coupled to an Agilent 1260 HLPC was used for recording HRMS spectra.

Mobile phase composed of two solvents: A was 0.1% formic acid in Milli-Q water, and B was 0.1% formic acid in acetonitrile mixed in the ratio of 1:1. Compound was prepared by dissolving the sample in acetonitrile and injected (0.1 μL) into the LC-MS. Flow rate was 0.4 mL/min. Fragmentor voltage was 150 V. Capillary voltage 4000 V. Mass range 100–1100. Elemental analysis (C, H, N) was performed with Perkin Elmer 2400 Series II CHNS/O Analyser. Melting points were determined on the microscope hot stage.

2. 1. The Synthesis of Compound 3

N^1-(4-Isopropylphenyl)-N^2-(pyridin-2-ylmethyl)diazene-1,2-dicarboxamide[24] (**1**, 163 mg, 0.5 mmol) was added to a solution of sodium *trans*-bis(dimethyl sulfoxide)tetrachloridoruthenate(III) (Na[*trans*-Ru(DMSO-*S*)$_2$Cl$_4$])[25] (**2**, 106 mg, 0.25 mmol) in acetone (10 mL) and stirred at room temperature for 2 h. The solvent was removed under reduced pressure. Dry residue was re-suspended in dichloromethane and filtered off to remove unreacted ligand **1**. The precipitate was dried in air to give compound **3** (165 mg, 99%). Crystal suitable for X-ray structure determination was found in the crude product. Purple solid; mp >250 °C dec.; IR ν 3245, 3035, 2959, 1736, 1718, 1603, 1534, 1482, 1459, 1438 cm^{-1}; HRMS (ESI–) *m/z* for $C_{19}H_{25}Cl_4N_5O_3RuS^-$ [M – Na]$^-$: calcd 646.9462, found 646.9467, *m/z* for $C_{17}H_{18}Cl_3N_5O_2Ru^-$[M–Na–DMSO –HCl]$^-$: calcd 532.9560, found 532.9554; Anal. calcd for $C_{19}H_{25}Cl_4N_5O_3NaRuS \cdot 0.1\ H_2O$: C, 34.00; H, 3.78; N, 10.43; found: C, 34.48; H, 3.96; N, 10.60.

2. 2. X-ray Structure Determination

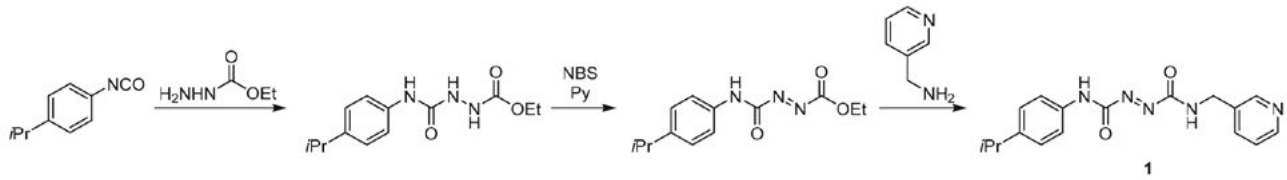
Crystal data and refinement parameters of **3** ([NaRuCl_4**1**(DMSO)]$_n$) are listed in Table 1. Single-crystal data were collected at 150 K on a Gemini A diffractometer equipped with an Atlas CCD detector, using graphite monochromated CuKα radiation (λ = 1.54184 Å). The data were treated using the CrysAlisPro software suite program package.[26] Analytical absorption correction was applied. Structure of compound **3** was solved using direct methods with SHELXS-97[27] and refined using the least-squares method on F^2 with SHELXL-2014[28] and using the graphical interface of OLEX2.[29] Figures were prepared using Diamond software.[30] CCDC 1569486 contains the supplementary crystallographic data for **3**. These data can be obtained free of charge from The Cambridge Crystallographic Data Center *via* www.ccdc.cam.ac.uk/data_request/cif.

3. Results and Discussion

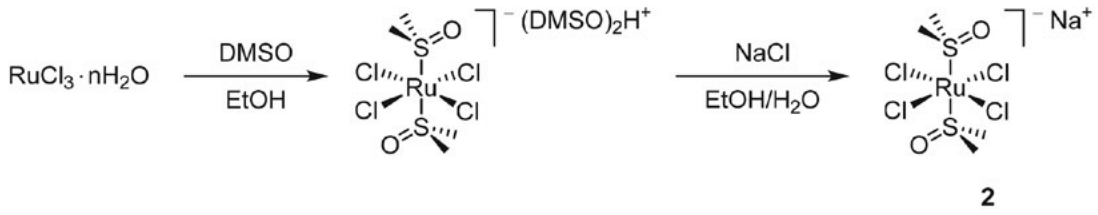
The pyridine-tethered diazenedicarboxamide, N^1-(4-isopropylphenyl)-N^2-(pyridin-2-ylmethyl)diazene-1,2-dicarboxamide (**1**), was prepared in a three step reaction sequence starting from the commercial reactants as previously described by us (Scheme 1).[24] Thus, the addition of carbazate to 4-isopropylphenyl isocyanate gave ethyl 2-((4-isopropylphenyl)carbamoyl)hydrazine-1-carboxylate, which was oxidized with *N*-bromosuccinimide (NBS) into ethyl 2-((4-isopropylphenyl)carbamoyl)diazene-1-carboxylate. Subsequent nucleophilic displacement with 3-picolylamine afforded the target compound **1**.

Sodium *trans*-bis(dimethyl sulfoxide)tetrachloridoruthenate(III) (Na-[*trans*-Ru(DMSO-*S*)$_2$Cl$_4$], **2**) was selected as the ruthenium(III) precursor. This compound was prepared by the literature procedure starting from the commercial hydrated $RuCl_3$ *via* hydrogen *trans*-bis(dimethyl sulfoxide)tetrachloridoruthenate(III) ([(DMSO)$_2$H][*trans*-Ru(DMSO-*S*)$_2$Cl$_4$]) as shown in Scheme 2.[25]

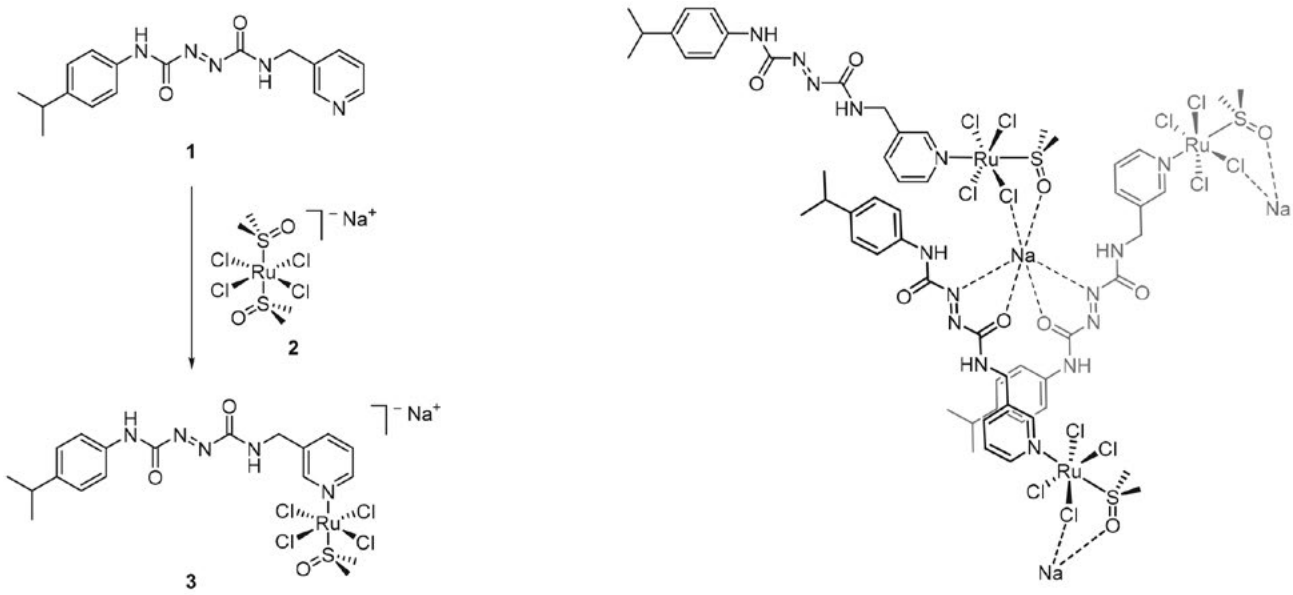
The coordination of ligand **1** to the ruthenium of **2** was performed using procedure based on that reported for



Scheme 1. Synthesis of pyridine-tethered diazenecarboxamide ligand **1** (**PyrDiaz**).[24]



Scheme 2. Preparation of Ru(III) precursor **2**.[25]



Scheme 3. Synthesis of Ru(III) complex **3** (left) and schematic presentation of sodium ion stabilized three-dimensional framework (right).

NAMI-A.[31] Combining complex **2** with an excess of ligand **1** in acetone solution resulted in displacement of one dimethyl sulfoxide ligand in the ruthenium coordination sphere and the formation of a new compound **3** shown in Scheme 3 (left). In contrast to our previous findings[19,20] for arene-ruthenium(II) compounds from Figure 2, in complex **3** diazene moiety did not participate in coordination to the metal centre. Instead, the pyridine part of the molecule replaced one axial dimethyl sulfoxide ligand. The charge compensation was provided by sodium ion. In solid state, the sodium ion interconnects the anionic ruthenium units into a three-dimensional framework, schematically presented in Scheme 3 (right).

The structure of the complex **3** was fully characterized by ^{1}H NMR, elemental analysis and ESI-HRMS. Complex **3** was analysed by high-resolution (HRMS) electrospray ionization mass spectrometry in negative ion mode (ESI–). The spectrum, shown in Figure 4, was dominated by the parent $[Ru^{III}Cl_4(DMSO)(\mathbf{PyrDiaz})]^-$ ion at *m/z* 646.9467 (calcd for $C_{19}H_{25}Cl_4N_5O_3RuS^-$: 646.9462). Another peak at *m/z* 532.9566 was interpreted as a result of in source collision-induced dissociation of the parent ion giving $[Ru^{III}Cl_3(\mathbf{PyrDiaz} - H)]^-$ ion at *m/z* 532.9554 (calcd for $C_{17}H_{18}Cl_3N_5O_2Ru^-$ ([M – Na – HCl]$^-$: 532.9560). In positive mode (ESI+), the spectrum of compound **3** was featureless.

The paramagnetic ruthenium(III) ion severely broadened the NMR signals of coordinated ligands, not allowing the assignment procedure. The ^{1}H NMR spectra of freshly prepared D_2O solutions of complexes **2** and **3** are shown in Figure 5. Chemical shifts of the coordinated DMSO ligand, peaks at ca. –15 ppm to –18 ppm, are in agreement with published data for the NAMI-type complexes.[31,32] Monitoring the D_2O solution of **3** for 24 h at

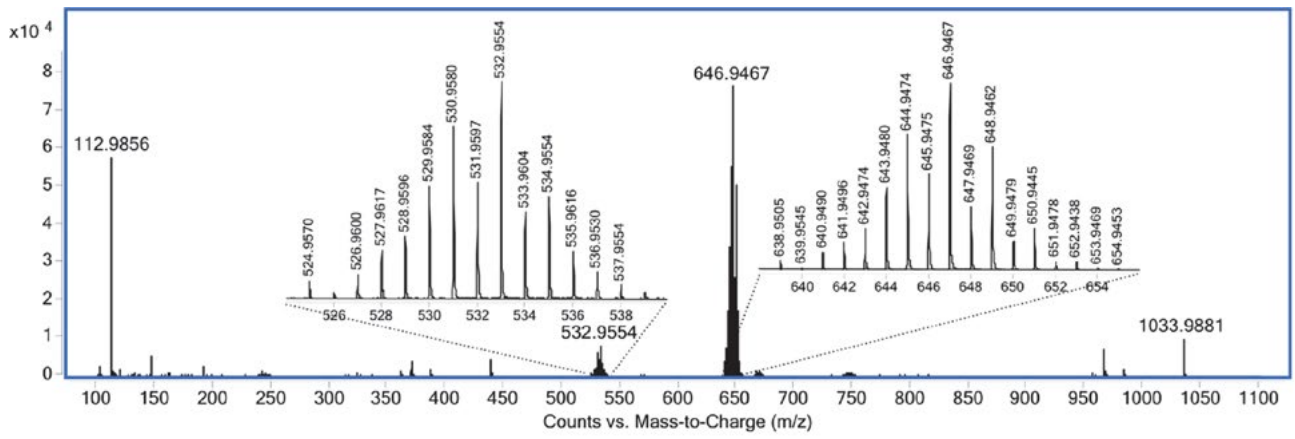


Figure 4. ESI– HRMS spectrum of compound **3**. Peaks at *m/z* 112.9856 and *m/z* 1033.9881 are due to calibrants.

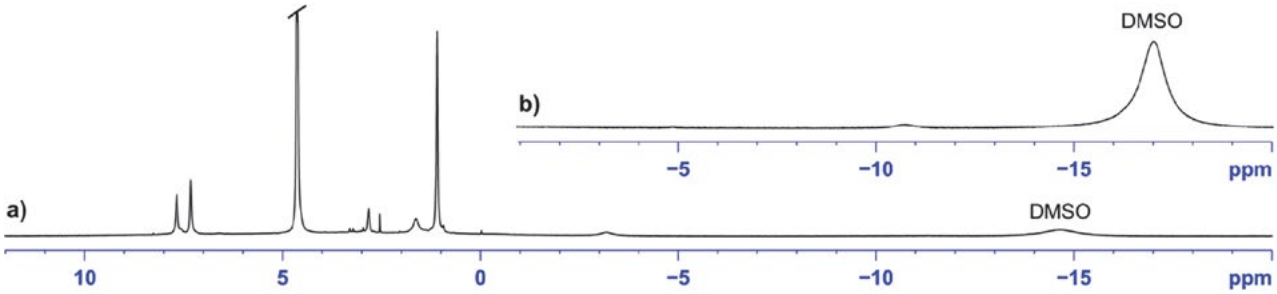


Figure 5. ^{1}H NMR spectrum of a) complex **3**, and b) complex **2** as D_2O solutions. Relevant insets are only shown (spectra were recorded with spectral width of 60 ppm, number of scans = 128).

room temperature by ^{1}H NMR indicated the formation of a complex mixture of products as seen by the appearance of several overlapping broad resonances in the spectra. The structures of these by-products could not be deduced from the spectra.

The structure of compound **3** could unambiguously be determined by a single crystal X-ray structure determination and is displayed in Figure 6. Selected bond lengths and angles are given in Table 2. Compound **3** is a polymeric complex with the ruthenium and sodium metallic atoms. Each of the Ru^{III} atoms are hexacoordinated by sulphur atom from DMSO molecule and the pyridine nitrogen of **1** in apical positions and four chlorido ligands in an equatorial plane. The sulphur-bound DMSO and ligand **1** are *trans* in nearly octahedral geometry of ruthenium central atom. The Ru–N and Ru–S bond distances of 2.109(6) and 2.2924(17) Å, respectively, are very similar to those found in the related structures containing *trans*-$RuNCl_4S$ donor set.[33–35,37] Three of the chlorido ligands are terminal while Cl4 forms a bridge between the ruthenium and sodium atoms. The DMSO ligand also forms a bridge between a ruthenium centre (through its sulphur atom) and a sodium (through its oxygen) thus forming a five membered RuClNaOS ring in the crystal structure. The sodium has six atoms in its distorted octahedrally coordinated environment with the resulting ClN_2O_3 donor set. Sodium atom is coordinated by two ligands **1**, each through one of the diazene nitrogen and one carbonyl oxygen atom. The coordination sphere of sodium atom in the structure of compound **3** is fulfilled by oxygen (bridging DMSO) and

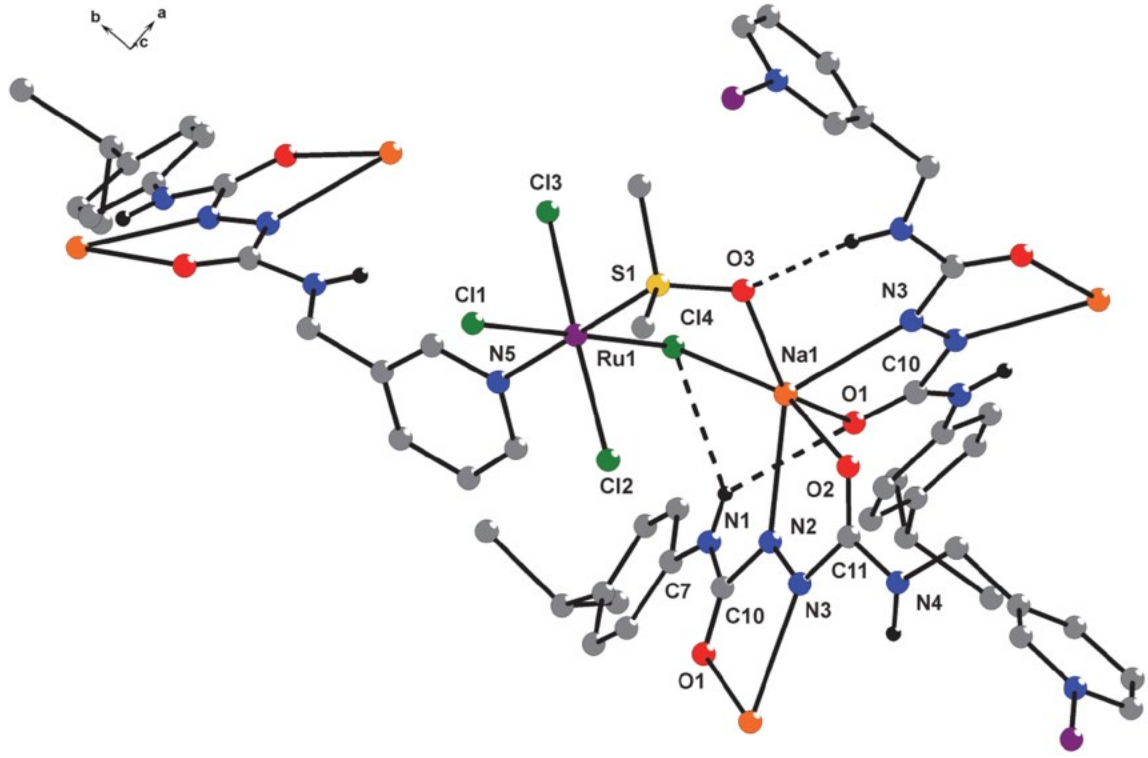


Figure 6. Part of the crystal structure of the compound **3**, showing atom numbering scheme and hydrogen bonding interactions. The hydrogens on carbon atoms have been omitted for clarity.

Table 1. Crystal data and structure refinement details for **3**.

	3
formula	$C_{19}H_{25}Cl_4N_5NaO_3RuS$
Fw (g mol^{-1})	669.36
crystal size (mm)	0.59 × 0.12 × 0.01
crystal color	Yellow
crystal system	Orthorhombic
space group	*P n a* 2_1
a (Å)	9.64914(19)
b (Å)	21.4978(6)
c (Å)	14.5013(3)
V (Å^3)	3008.07(12)
Z	4
calcd density (g cm^{-3})	1.478
F(000)	1348
no. of collected reflns	9948
no. of independent reflns	4713
R_{int}	0.0443
no. of reflns observed	4388
no. parameters	323
Flack parameter	–0.022(16)
$R[I > 2\sigma(I)]^a$	0.0415
wR_2 (all data)^b	0.1113
Goof, S^c	1.067
maximum/minimum residual electron density (e Å^{-3})	+0.909/–0.462

^{a} $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. ^{b} $wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$.
^{c} $S = \{\Sigma[(F_o^2 - F_c^2)^2]/(n/p)\}^{1/2}$ where n is the number of reflections and p is the total number of parameters refined.

Table 2. Selected bond lengths (Å) and angles (°) for **3**.

Ru1 – Cl1	2.3294(17)	Cl1 – Ru1– Cl2	92.44(7)
Ru1 – Cl2	2.3624(18)	Cl1 – Ru1 – Cl3	90.27(7)
Ru1 – Cl3	2.3387(17)	Cl1 – Ru1 – Cl4	175.82(7)
Ru1 – Cl4	2.3797(17)	Cl1 – Ru1 – S1	89.86(7)
Na1 – O1	2.397(7)	Cl1 – Ru1 – N5	89.57(18)
Na1 – O2	2.290(6)	N5 – Ru1 – S1	179.32(18)
Na1 – O3	2.319(6)	Cl2 – Ru1 – Cl3	177.29(7)
Na1 – N2	2.558(6)	O1 – Na1 – O2	104.3(3)
Na1 – N3	2.542(7)	O1 – Na1 – O3	141.3(2)
Na1 – Cl4	2.683(3)	O1 – Na1 – N2	77.2(2)
N1 – C10	1.321(11)	O1 – Na1 – N3	64.0(2)
N2 – N3	1.228(9)	O1 – Na1 – Cl4	83.72(19)
N2 – C10	1.490(9)	N2 – N3 – C11	109.5(6)
N3 – C11	1.474(9)	N3 – C11 – N4	110.1(6)
N4 – C11	1.345(10)	N3 – N2 – C10	111.3(6)
O1 – C10	1.198(9)	C10 – N1 – C7	127.7(7)
O2 – C11	1.204(9)	C11 – N4 – C12	119.4(6)

bridging chlorido ligand. Both diazene nitrogen atoms and both carbonyl oxygen atoms of ligand **1** are involved in the coordination to sodium atoms in the polymeric structure of compound **3**. A similar coordination environment around sodium ion has been found in related tetrachloridoruthenium(III) complexes.[33–36] The crystal structure of **3** is further stabilized by three intramolecular hydrogen bonds of the type N–H···O and N–H···F (Table 3).

A pyridine-heterocycle unsubstituted analogue of **3**, called NAMI-Pyr[37] and AziRu[38] (Figure 3), has been reported to show interesting reactivity profiles towards biologically relevant targets.[9] Derivatives with functionalized pyridine ligand have also been investigated.[32] Unfortunately, no biological studies of **3** were possible due to its instability and decomposition in protic solvents (*vide supra*).

4. Conclusions

We have reported the synthesis of novel tetrachloridoruthenium(III) complex Na[*trans*-$RuCl_4$(DMSO)(**PyrDiaz**)] (**PyrDiaz** = N^1-(4-isopropylphenyl)-N^2-(pyridin-2-ylmethyl)diazene-1,2-dicarboxamide), a pyridine-tethered derivative of NAMI-A that has a redox-active diazencarobxamide ligand (**PyrDiaz**) in the structure. It has been designed to target tumour cell-lines synergistically by means of known antiproliferative activity of NAMI-A and glutathione oxidation ability enacted by the diazene part of the molecule. Although in this particular case the instability and decomposition of Na[*trans*-$RuCl_4$(DMSO)(**PyrDiaz**)] in protic solvents disabled biological studies, work is in progress to improve the physicochemical properties of such **PyrDiaz**-ruthenium(III) complexes.

5. Acknowledgments

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Table 3. Hydrogen bonding geometry for **3**.

D – H ··· A	***d*(D – H)/ Å**	***d*(H ··· A)/ Å**	***d*(D ··· A)/ Å**	**<(DHA)/ °**
N1 – H1N1 ··· Cl4	0.88	2.72	3.455(5)	141.9
N1 – H1N1 ··· O1	0.88	2.53	3.236(7)	137.4
N4 – H1N4 ··· O3	0.88	2.05	2.922(6)	169.9

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Povzetek

Z neposredno reakcijo med **PyrDiaz** ligandom (**PyrDiaz** = N^1-(4-izopropilfenil)-N^2-(piridin-2-ilmetil)diazen-1,2-dikarboksamid)) in natrijevim *trans*-bis(dimetil sulfoksid)tetrakloridorutenatom(III) (Na-[*trans*-$Ru(DMSO)_2Cl_4$]) smo sintetizirali nov tetrakloridorutenijev(III) kompleks Na[*trans*-$RuCl_4$(DMSO)(**PyrDiaz**)] (**3**) s piridin-funkcionaliziranim diazenkarboksamidnim ligandom **PyrDiaz**. Spojina **3** je analog antimetastatičnega Ru(III) kompleksa NAMI-A in NAMI-Pyr. Rentgenska difrakcijska analiza monokristala je pokazala, da je spojina **3** polimeren kompleks z rutenijevimi in natrijevimi kovinskimi atomi.