Design, synthesis, characterisation and chemical reactivity of mixed-ligand platinum(II) oxadiazoline complexes with potential cytotoxic properties

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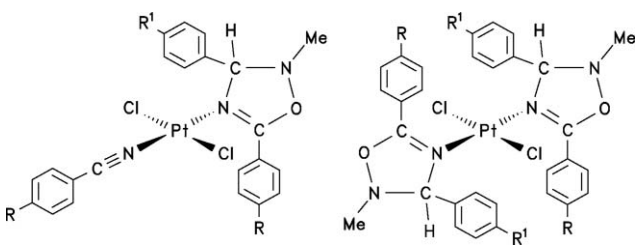
A series of mixed ligand platinum(II) oxadiazoline complexes bearing 7-nitro-1,3,5-triazaadamantane (7-NO_2TAA) as a labile and reactive nitrogen ligand has been synthesised from easily accessible starting materials. [2+3] cycloaddition of nitrones $R^1R^2C–N^+(Me)O^-$ to only one of the nitrile ligands in *trans*-[$PtX_2(PhCN)_2$] (X = Cl, Br) results in the selective formation of mono-oxadiazoline complexes *trans*-[PtX_2(PhCN){N=C(Ph)–O–N(Me)–CR^1R^2}] from which the remaining nitrile can be replaced by 7-NO_2TAA. The resulting complexes *trans*-[PtX_2(7-NO_2TAA) {N=C(Ph)–O–N(Me)–CR^1R^2}] and their precursors were characterised by elemental analysis, IR and multinuclear NMR spectroscopy. The suitability of the target complexes as anticancer agents was extrapolated from their general chemical reactivity. They are stable in DMSO, but react with thiols and undergo aquation of a chloro ligand. In the absence of a competing ligand, the coordinated 7-NO_2TAA ligand slowly hydrolyses in an aqueous medium under release of formaldehyde, and this could induce bioactivity independent of the one typically found with platinum compounds. With nitrogen heterocycles such as pyridine a slow exchange of the 7-NO_2TAA ligand occurs. A combined DFT/AIM study confirms the reaction observed in the experiment and predicts that other nitrogen heterocycles such as DNA nucleobases should react in the same way. Moreover, the 7-NO_2TAA should be even more labile in an aqueous medium where protonation of the remaining amines can occur. A PM6 molecular modelling study suggests that the PtCl(oxadiazoline) fragment formed after release of one chloro and the labile 7-NO_2TAA ligand fits well into the DNA groove and is able to form d(GpG) intrastrand crosslinks similar to the ones observed with cisplatin.

Introduction

Platinum based anticancer agents such as cisplatin, carboplatin and oxaliplatin are widely used in the treatment of human cancers,[1] and a variety of combinatorial chemotherapy regimens are in place for the treatment of ovarian, testicular, colon, head and neck cancer, as well as other solid tumor types.[2] Their clinical success, however, is often limited by the occurrence of resistance and severe side effects and, in the case of cisplatin, a dose limiting toxicity. In this light, the search is ongoing for new and improved platinum drugs with a high activity combined with less toxic side effects, an extended spectrum of activity to difficult-to-treat tumours, and an ability to overcome intrinsic and acquired resistance of cancer cells to currently used drugs. The past decades have seen the discovery of a number of compounds with high *in vitro* activity in the sub-micromolar range,[3] the development of tumour-seeking complexes,[4] as well as compounds that overcome cisplatin resistance, among which *trans*-configured complexes are prominent.[5] For instance, Pt(IV) complexes bearing NH_3 and aliphatic amines have been studied in Kelland's team,[6] and Pt(II) complexes with aromatic nitrogen heterocycles or one ammine or a sulfoxide were pioneered by Farrell.[7] Branched aliphatic amines as ligands were explored in Navarro-Ranninger's group,[8] whereas Natile successfully introduced Pt(II) compounds with imino-type ligands, which were synthesised in the metal coordination sphere by condensation of acetone to a platinum-ammine precursor,[9] or by alcoholysis of a coordinated nitrile.[10]

We recently found that Δ^4-1,2,4-oxadiazoline complexes such as the *trans*-[$PtCl_2(\Delta^4$-1,2,4-oxadiazoline$)_2$] and *trans*-[$PtCl_2$(nitrile)(Δ^4-1,2,4-oxadiazoline)] compounds shown in Scheme 1 exhibit *in vitro* cytotoxicities in platinum-sensitive human cancer cell lines which are comparable to those of cisplatin and carboplatin, and their activity is retained in cisplatin-resistant cells.[11] Δ^4-1,2,4-Oxadiazoline complexes can be synthesised straightforwardly by cycloaddition of nitrones across the C≡N bond of Pt-coordinated nitriles to give *trans*-[$PtCl_4(\Delta^4$-1,2,4-oxadiazoline$)_2$][12] and *trans*-[$PtCl_4$(nitrile)(Δ^4-1,2,4-oxadiazoline)] compounds[13] where the metal is a Pt(IV) center. Analogous Pt(II) complexes[14–16] and other mixed ligand Pt(II) complexes



Scheme 1 Pt(II) oxadiazoline complexes with potent *in vitro* cytotoxicity (R = H, OH, OCH_2CH_2OMe; R^1 = H, OH).[11]

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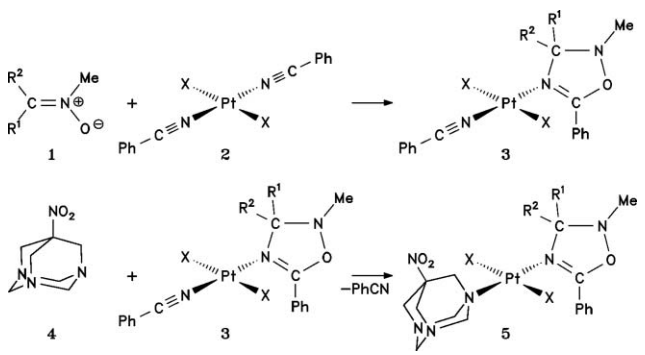
such as *trans*-[$PtCl_2$(heterocycle)(Δ^4-1,2,4-oxadiazoline)][13] and *cis*-[$PtCl_2$(sulfoxide)(Δ^4-1,2,4-oxadiazoline)] can be prepared as well, the latter ones also in an enantiomerically enriched form when a chiral sulfoxide is employed.[17] Given the ease with which the substitution pattern of the oxadiazoline ligand can be varied, a combinatorial chemistry approach can help to optimise pharmaceutically relevant properties such as solubility, polarity or cell uptake, or to enhance the DNA binding by secondary binding mechanisms. This could render this class of compounds particularly promising for medicinal applications.

Cytotoxic platinum compounds with a Cl,Cl,N,N coordination sphere are thought to bind to the DNA after loss of the labile chloro ligands whereas the nitrogen ligands remain unaffected. Herein, we report on our approach to design *trans*-configured mixed ligand Pt(II) oxadiazoline complexes with a labile nitrogen ligand whose reactivity is enhanced in an aqueous medium. This can be achieved if this ligand is labilised upon protonation at the nearly neutral pH of the cytoplasm,[18] or able to undergo slow hydrolysis. Concomitant loss of a labile chloro ligand then allows for DNA inter- and intrastrand adducts similar to the ones formed by cisplatin, except that now a *cis*-PtCl(oxadiazoline) moiety attaches to the DNA rather than a *cis*-$Pt(NH_3)_2$ fragment. The compounds, although initially *trans*-configured, could mimic the mode of action of classical *cis*-configured platinum drugs, but still retain the oxadiazoline moiety for the fine-tuning of the pharmacological properties.

Results and discussion

As a protonatable ligand we opted for the 1,3,5-triazaadamantane derivative **4** (7-NO_2TAA), shown in Scheme 2. Tertiary amines bind to Pt(II) moderately strongly, and protonation at the uncoordinated nitrogens ought to weaken the Pt–N bond to facilitate the release of the ligand since the nitrogens are close enough to each other to communicate. Other adamantyl-type ligands have been used before in anticancer-active transition metal compounds, *e.g.* Pt(IV) complexes bearing an adamantylamine moiety,[19] or Ru complexes with a 1,3,5-triaza-7-phosphaadamantane ligand,[20] but with a different intention. The variable oxadiazoline part is used to explore the effect of substituents. Both chloro and bromo compounds were prepared in this work, because the bromo analogue of cisplatin is known to be also active and less toxic than cisplatin itself.[21]

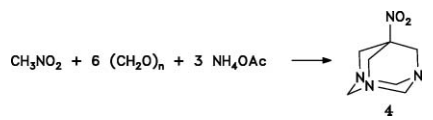


Scheme 2 Synthesis of the PtX_2(7-NO_2TAA)(oxadiazoline) complexes **5**.

Synthesis of the compounds

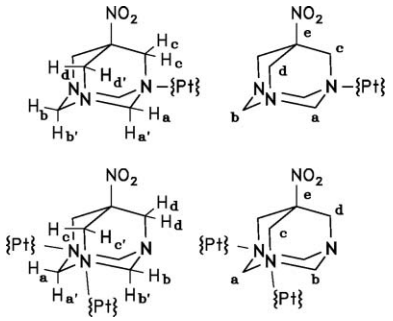
The synthesis of the target compounds **5a–5l** was straightforward and followed the outline shown in Scheme 2. The starting complexes *trans*-[$PtCl_2(PhCN)_2$] (**2a**) and *trans*-[$PtBr_2(PhCN)_2$] (**2b**) were prepared from $PtCl_2$ or $PtBr_2$ and hot benzonitrile as described previously.[13] Reaction with one equivalent of nitrones **1a–1f** provided the mono-cycloadducts *trans*-[PtX_2(PhCN)(N=C(Ph)–O–N(Me)–CR^1R^2)] **3a–3l** with high selectivity and in good yields. With the methoxy substituted nitrones **1a–1d**, this reaction took place at room temperature within 10–20 h. The nitrones **1e** and **1f** are less reactive and 3–4 days at room temperature or 20 h at 60 °C were required for the reaction to complete. The halogen attached to the platinum in the starting benzonitrile complex has little influence on the reactivity of the coordinated nitriles. This is also expected because the halogen and the nitrile are in *cis* position to each other and there is little electronic communication between them. The IR, ^{1}H and ^{13}C NMR data are in good agreement with those of similar compounds described previously,[13,16] and confirm the presence of one coordinated nitrile and one oxadiazoline moiety. The ^{195}Pt NMR chemical shift reports on the nature of the coordinated halogens (–2229 to –2232 ppm for the chloro complexes **3a–3f**, –2679 to –2708 for the bromo compounds **3g–3l**).

The ligand 7-nitro-1,3,5-triazaadamantane **4** was synthesised from nitromethane, paraformaldehyde and ammonium acetate as shown in Scheme 3, using a procedure described in the literature.[22] Alternatively, this compound can be prepared from nitromethane, formic acid and hexamethylenetetramine,[23] or from aqueous ammonia, paraformaldehyde and tris(hydroxymethyl)nitromethane.[22a]



Scheme 3 Synthesis of 7-nitro-1,3,5-triazaadamantane **4**.

The reaction of the mono-oxadiazoline complexes **3a–3l** with one equivalent of **4** results in a ligand exchange and selective replacement of the nitrile ligand. A similar reactivity has been observed previously with stoichiometric amounts of aromatic nitrogen heterocycles,[13] but this is the first example where such a reaction occurs with a tertiary aliphatic amine and an excess of amine relative to platinum. The resulting mixed ligand oxadiazoline/triazaadamantane Pt(II) complexes **5a–5l** were characterised by TLC, elemental analysis, IR and NMR spectroscopy. Additionally, the Pt content of **5a** was determined by thermogravimetric analysis of the residue after complete combustion. Compounds **5** are significantly more polar than their precursors **3**, as evidenced from their lower R_f value on TLC (*e.g.*, **5a**: 0.12; **3a**: 0.50 on SiO_2/CH_2Cl_2). In the IR spectrum the C≡N stretch is no longer present, indicating that the nitrile has been replaced. The oxadiazoline can be identified by its C=N stretching vibration at 1634–1645 cm^{-1}, and the presence of a coordinated triazaadamantane ligand is confirmed by the asymmetric NO_2 stretch at 1538 cm^{-1} (*vs.* 1520 cm^{-1} in the free ligand). The ^{1}H and ^{13}C NMR spectra show the typical signals of one oxadiazoline and one triazaadamantane ligand whose NMR designation is



Scheme 4 ^{1}H and ^{13}C NMR numbering of the coordinated 7-nitro-1,3,5-triazaadamantane ligand in compounds **5** (top) and **6** (bottom).

shown in Scheme 4. The coordinated triazaadamantane produces two ^{1}H signals for the C–CH_2–N groups at 3.66 (s, 4 $H_{d/d'}$) and 4.29 ppm (s, 2 H_c). The axial and equatorial N–CH_2–N protons appear at 3.88 and 4.23 (1 $H_{b/b'}$ each), 4.68 and 4.81 ppm (2 $H_{a/a'}$ each), as broad doublets with a geminal coupling of 12.8–13.8 Hz. Compared to free **4** (3.83 (s, 6H, C–CH_2–N), 4.12 (d, 13,2 Hz, 3H, N–CH_2–N equatorial), 4.48 (d, 13,2 Hz, 3H, N–CH_2–N axial)), the coordinated ligand is reduced in symmetry from C_{3v} to C_s, and the protons close to the platinum center are more deshielded, whereas the remote set of protons experiences a stronger shielding than in **4**. The ^{13}C pattern consists of four CH_2 signals at approximately 58 (2 C–CH_2–N, C_d), 64 (1 C–CH_2–N, C_c), 71 (1 N–CH_2–N, C_b) and 80 ppm (2 N–CH_2–N, C_a), and one quaternary carbon C_e at about 73 ppm. Again, the platinum atom deshields the nearer carbons with respect to the uncoordinated ligand **4** (59.7 (C–CH_2–N), 72.6 (C–NO_2), 73.4 (N–CH_2–N). The ^{1}H and ^{13}C patterns together with the elemental analysis provide evidence that only one of the amino nitrogens of the triazaadamantane is coordinated to a platinum center and a mononuclear 1 : 1 complex had formed, in spite of the initial equivalence of the three amino groups of ligand **4**. The oxadiazoline ligands exhibit a ^{1}H and ^{13}C NMR pattern similar to the one seen in the precursor compounds **3a–3l**. However, it is worth mentioning that the methoxy groups in positions 2 and 6 of the aromatic substituent attached to the oxadiazoline ligand are not equivalent in **5c**, **5d**, **5i** and **5j**, nor are the triazaadamantane protons H_c. This is ascribed to hindered rotation of the methoxy-substituted aromatic ring relative to the oxadiazoline. In the same sense, the broad ^{1}H and ^{13}C signals of the 6-position in the 2- and 2,4-derivatives **5a**, **5b**, **5g** and **5h** can be attributed to conformational changes in the NMR dynamic range. If the NMR spectra are run at 333 K (60 °C), these broad signals sharpen due to faster conformational exchange. The ^{195}Pt NMR signal of the chloro compounds **5a–5f** appears at a higher chemical shift than in **3a–3f**. This is the expected trend when a nitrile ligand is exchanged by an amine although the change in chemical shift for **5a–5f** is smaller (approx. 70 ppm) than the one observed for replacement of a nitrile with an aromatic amine (approx 200 ppm).[13,16] The ^{195}Pt NMR signal of the bromo compounds **5g–5l** reports more sensitively on the nature of the coordinated ligands and large downfield shifts of about 200 ppm relative to **3g–3l** are observed. Similar effects have been reported for other platinum bromo compounds.[24]

In the synthesis of **5a–5l** a small amount (up to 10%) of a byproduct is formed which can be easily separated off by chromatography. For the reaction of **3a** with **4** this product was isolated and characterised as the 2 : 1 complex **6a** where two $PtCl_2$(oxadiazoline) moieties bind to one and the same triazaadamantane ligand. Its ^{195}Pt signal is virtually the same as for **5a** and also the ^{1}H and ^{13}C signals of the oxadiazoline part of the molecule are very similar. The triazaadamantane ligand, however, shows a signal pattern clearly distinct from **5a** but consistent with the involvement of two amino groups in metal coordination. Thus, the two protons H_a and $H_{a'}$ appear at a relatively high chemical shift of 5.06 and 5.24 ppm as a result of the deshielding effect of two neighbouring platinum moieties. Protons H_b and $H_{b'}$ (4.3 and 4.74 ppm, 2 H each) and those in positions H_c and $H_{c'}$ (4.01 and 4.21 ppm, 2 H each) are flanked by one platinum moiety only and are less deshielded. The two protons H_d at a fairly low chemical shift of 3.52 ppm are more shielded than in **5a**. Similar trends are observed in the corresponding ^{13}C signals of **6a**.

Computational analysis of the ligand–Pt bond strengths in 2a, 3a and 5a and related compounds

For a better understanding of the chemical reactivity of compounds **2**, **3** and **5** and to establish evidence for the postulated weakening of the Pt–N bond upon protonation of the other amino nitrogens of the triazaadamantane ligand, a DFT study of compounds **2a**, **3a**, **5a** and the mono- and diprotonated forms **5a–H**$^+$ and **5a–2H**$^+$ was undertaken, using the B3LYP functional, the LANL08 basis set for Pt and Cl, and 6-31G* for all other atoms. This and similar computational methods have been used for other DFT studies of related compounds before,[25,26] and the geometry optimised structures compare well with the structures of related compounds examined by single crystal X-ray diffraction.[13,14,17] Since bond distances do not always accurately reflect the strength of a bond, other parameters such as bond orders and the charge density at the bond critical point were used as additional indicators. The latter property was obtained from a topological analysis of the charge densities[27] and the results are summarised in Table 1.

As expected from molecular orbital considerations, the Pt–Cl bonds of all compounds show similar properties and there is little influence from the nitrogen ligands in a *cis*-position to them. The properties of the Pt–N bonds, however, depend sensitively on the

Table 1 Bond distances and electronic properties of the Pt–N and Pt–Cl bonds in compounds **2a**, **3a**, **5a**, monoprotonated **5a–H**$^+$ and diprotonated **5a–2H**$^+$

Bond	Property	2a	3a	5a	5a–H$^+$	5a–2H$^+$
Pt–N(nitrile)	Dist/Å	1.950	1.958			
	Bond order	0.320	0.301			
	ρ_{BCP} (e/Å^3)	0.8824	0.8591			
Pt–N(oxa)	Dist/Å		2.026	2.035	2.008	1.989
	Bond order		0.382	0.354	0.405	0.458
	ρ_{BCP} (e/Å^3)		0.7960	0.7792	0.8489	0.9086
Pt–N(TAA)	Dist/Å			2.135	2.182	2.234
	Bond order			0.420	0.334	0.253
	ρ_{BCP} (e/Å^3)			0.6450	0.5551	0.4768
Pt–Cl(1)	Dist/Å	2.426	2.434	2.447	2.433	2.443
	Bond order	0.899	0.855	0.818	0.843	0.812
	ρ_{BCP} (e/Å^3)	0.4770	0.4665	0.4513	0.4670	0.4590
Pt–Cl(2)	Dist/Å	2.424	2.428	2.435	2.429	2.413
	Bond order	0.901	0.888	0.876	0.860	0.879
	ρ_{BCP} (e/Å^3)	0.4785	0.4710	0.4668	0.4683	0.4854

nature of the nitrogen ligand itself, as well as the nature of the ligand in the *trans*-position to it. The Pt–N bond parameters suggest that the coordination of the nitrile in **3a** is weaker, as compared to **2a**. This is plausible because the oxadiazoline ligand in the *trans*-position to it acts as an electron donor, making the Pt center less Lewis acidic and less prone to accept electrons from the nitrile lone pair. In consequence, the nitrile in **3a** is less activated towards cycloaddition with a nitrone, and this explains why the reaction with **2a** can be stopped at the mono-cycloadduct **3a**. The nitrile in **3a** should also be more labile and easier to exchange, which is indeed observed in the experiment when **3a** is reacted with the amine **4** to form **5a**. A comparison of **3a** with **5a** suggests that the Pt–N bond to the oxadiazoline does not change much upon ligand exchange, whereas the newly introduced 7-NO_2-TAA ligand seems to bind relatively weakly, as evidenced by the longer bond distance and the low charge density in the bond critical point. The bond order is comparatively high, but this can be attributed to the different hybridisation of the nitrogen lone pair (sp^3 *vs.* sp^2), where a better overlap is expected with increasing p-character.

When **5a** is protonated at the free amino groups of the 7-NO_2-TAA ligand to form **5a–H$^+$** and **5a-2H$^+$**, the Pt–N bond to 7-NO_2-TAA weakens with increasing degree of protonation and the Pt–N bond to the oxadiazoline concomitantly strengthens. Hence, the reactivity of **5** towards a replacement of the 7-NO_2-TAA ligand should be enhanced upon protonation. A similar effect is expected when a Lewis acidic Pt moiety coordinates to the 7-NO_2-TAA ligand, and this explains the preferred formation of a 1 : 1 (Pt:7-NO_2-TAA) complex such as **5a** over coordination of two Pt moieties to the 7-NO_2-TAA, as in **6a**.

To assess the possibility of replacement of the 7-NO_2-TAA ligand by nitrogen heterocycles such as pyridine or DNA nucleobases typically acting as targets for platinum binding in biological systems, the bond properties of the pyridine complex **7a** and the analogous guanine and adenine complexes **8a** and **9a** (see Scheme 5) were calculated and the results are summarised in Table 2. The pyridine ligand in **7a** binds far more strongly than the 7-NO_2-TAA ligand in **5a**, suggesting that a ligand exchange should be feasible, at least as long as the steric effects in the coordination sphere are small enough not to adversely affect the thermodynamics and the kinetics of the reaction. Accordingly, one might expect ligand exchange with the purine nucleobases guanine or adenine if **5a** was to form DNA adducts. This can be inferred from the very good agreement of the calculated Pt–N bond parameters of the pyridine complex **7a** and the complexes with guanine or adenine (**8a** and **9a**), suggesting similar reactivities and properties.

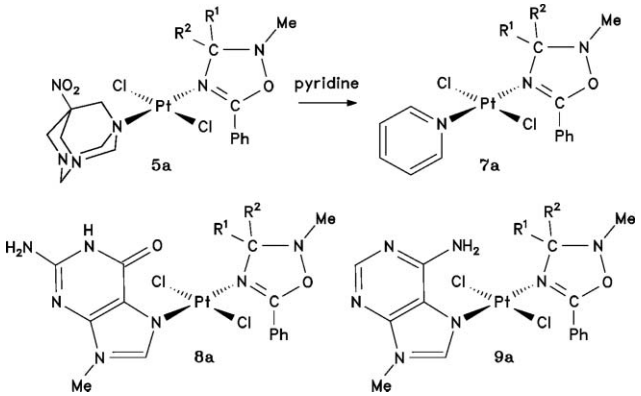
Molecular modelling of the DNA binding of the PtCl(oxadiazoline) fragment

Cisplatin is thought to act primarily through formation of 1,2-intrastrand d(GpG) adducts with the DNA, where the binding of a *cis*-Pt$(NH_3)_2$ moiety to the N7 of two adjacent guanine bases forces the DNA double helix to bend into a U-shaped turn.[28] If compounds such as **5a** reacted under loss of ligand **4** and a chloride, as postulated, one might expect the remaining *cis*-PtCl(oxadiazoline) moiety to form similar 1,2-intrastrand d(GpG) adducts. Whether these are bent (and thus dysfunctional to the cell) depends on how well the comparatively large PtCl(oxadiazoline) fragment fits into the groove of the DNA double helix. Moreover, the oxadiazoline ligand may allow for additional binding with the DNA, e.g through intercalation of the aromatic substituents with the nucleobases, or by hydrogen bonding to the DNA backbone, leading to a higher stability of the adduct.

We addressed these issues in a molecular modelling study with the semiempiric PM6 parametrisation[29] as implemented in MOPAC2009.[30] This method has been used successfully for the modelling of other biologically relevant systems such as proteins and nucleobases.[31] The input was generated from Lippard's DNA duplex dodecamer, d(CCTCTGGTCTCC. GGAGACCA-GAGG), containing a *cis*-diammineplatinum(II) d(GpG) 1,2-intrastrand cross-link at the central guanine pair. The structure of this complex has been determined in solution by high-resolution 2D NMR spectroscopy and restrained molecular dynamics refinement,[32] and the coordinates can be obtained from the RSCB Protein Data Bank.[33] The Pt$(NH_3)_2$ moiety was replaced by the PtCl(oxadiazoline) fragment present in **5a** and hydrogens were added to the phosphates to reduce the charges on the backbone. This structure was subjected to a geometry optimisation of the newly added hydrogens only, followed by a geometry optimisation of the PtCl(oxadiazoline) moiety only. The result is shown in Fig. 1 and demonstrates that the PtCl(oxadiazoline) moiety fits well into

Table 2 Calculated bond distances and electronic properties of the Pt–N and Pt–Cl bonds in compounds **5a**, **7a**, **8a** and **9a**

Bond	Property	5a	7a	8a	9a
Pt–N(oxa)	Dist/Å	2.035	2.040	2.034	2.037
	Bond order	0.354	0.357	0.360	0.363
	ρ_{BCP} (e/Å^3)	0.7792	0.7666	0.7733	0.7702
Pt–N(ligand)	Dist/Å	2.135	2.051	2.030	2.044
	Bond order	0.420	0.387	0.330	0.366
	ρ_{BCP} (e/Å^3)	0.6450	0.7591	0.7751	0.7585
Pt–Cl(1)	Dist/Å	2.447	2.435	2.435	2.443
	Bond order	0.818	0.838	0.861	0.814
	ρ_{BCP} (e/Å^3)	0.4513	0.4631	0.4635	0.4551
Pt–Cl(2)	Dist/Å	2.435	2.429	2.432	2.421
	Bond order	0.876	0.869	0.880	0.894
	ρ_{BCP} (e/Å^3)	0.4668	0.4678	0.4648	0.4748



Scheme 5 Synthesis of *trans*-$PtCl_2$(oxadiazoline)(pyridine) **7a** and structures of the calculated complexes *trans*-$PtCl_2$(oxadiazoline)(5-methyl-guanine) **8a** and *trans*-$PtCl_2$(oxadiazoline)(5-methyladenine) **9a**; R^1 = H; R^2 = 2-methoxyphenyl.

the groove of the bent DNA helix, and seems not to impose much strain.

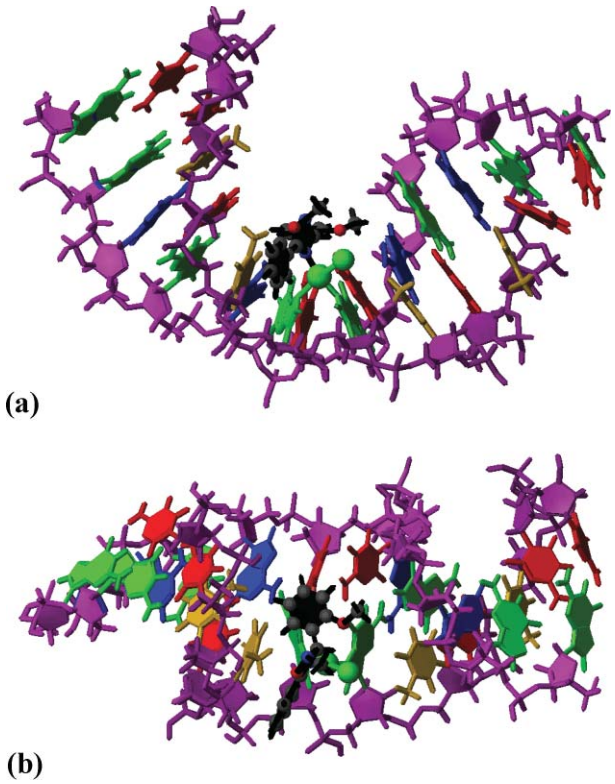


Fig. 1 Orthogonal views (a) and (b) of the structure of the d(GpG) intrastrand crosslink with a PtCl(oxadiazoline) moiety; only the PtCl(oxadiazoline) moiety was geometry optimised whereas the DNA fragment, taken from the corresponding cisplatin adduct,[32] was held fixed. Purple: phosphate–deoxyribose backbone; green: G; blue: A; red: C; yellow: T; green spheres: Pt and Cl; black: oxadiazoline ligand, with spheres depicting O(red), N (blue) and C (grey). The oxadiazoline ligand is the one present in compound **5a**.

Upon full geometry optimisation (Fig. 2) the U-turn of the DNA double helix widened a little and the oxadiazoline ligand changed its conformation, but the overall shape is very similar to the previous one where the DNA coordinates were held fixed in the positions of the *cis*-diammineplatinum(II) d(GpG) intrastrand cross-link. This can also be seen in Fig. 3 where a best fit overlay of the two structures is shown.

The oxadiazoline ligand spans about 2/3 through the double strand, with the phenyl group close to the phosphate backbone of one strand and the 2-methoxyphenyl group near the nucleobases of the other one. With this particular oxadiazoline, no evidence for intercalation or hydrogen bonding was found. However, the model suggests sites where the introduction of substituents may cause such additional bonding, and this could help with the design of more effective compounds in the future, and a better understanding of the activity of similar oxadiazoline complexes studied previously.[11] The most cytotoxic complex described in that paper bears an OH at the phenyl group that comes close to the phosphate backbone in the model presented here, and this might reflect in a stronger DNA binding through hydrogen bond formation.

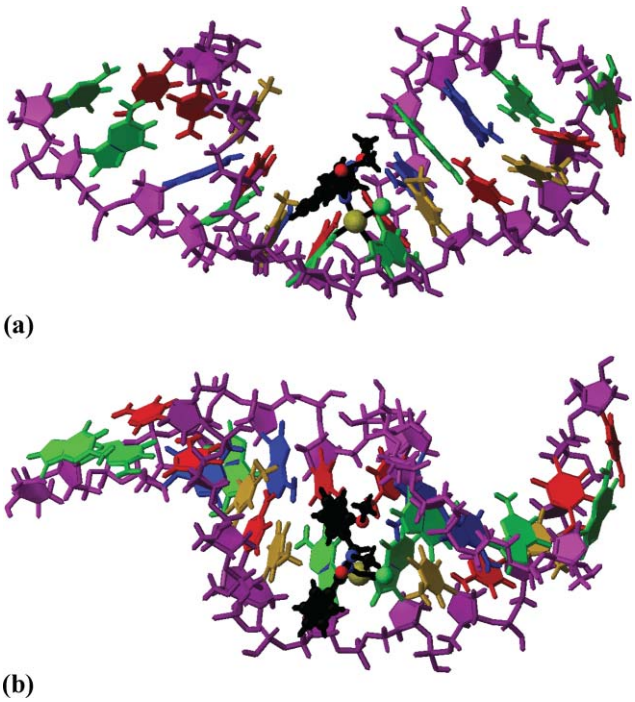


Fig. 2 Orthogonal views (a) and (b) of the structure of the d(GpG) intrastrand crosslink with a PtCl(oxadiazoline) moiety after full geometry optimisation of all atoms. For colour coding see Fig. 1.

Chemical reactivity of [$PtCl_2$(oxadiazoline)(7-NO_2-TAA)] complexes

A basic investigation of the chemical reactivity of **5a** was undertaken to confirm some of the predictions made on the basis of the computational study, and to further assess the potential of compounds of this type for medicinal applications. The hypothesis that complexes **5** react with nitrogen heterocycles by replacement of the 7-NO_2-TAA ligand was supported by the selective formation of the mixed $PtCl_2$(oxadiazoline)(pyridine) complex **7a** in the reaction of **5a** with one equivalent of pyridine. The analytical and spectroscopic data of **7a** confirm the absence of the 7-NO_2-TAA and the presence of a pyridine ligand, and agree well with those of a similar mixed $PtCl_2$(oxadiazoline)(pyridine) complex synthesised by a different route.[13] The reaction of **5a** with pyridine to give **7a** requires 96 h at 37 °C and is slower than the replacement of a nitrile from a related mixed oxadiazoline/nitrile complex (24 h at 60 °C).[13] This is also expected from the calculated properties of the Pt–N bond in **7a** as compared to **3a**, described in the previous section.

The reactivity of **5a** towards thiols, represented by N-acetyl-L-cysteine methyl ester, was studied as a model for the reactions with cysteine, methionine and glutathione, which were suggested as an important detoxification route for platinum compounds, but also as a pathway for the generation of compounds with enhanced renal toxicity.[34] With **5a**, an unselective reaction took place within 48 h at room temperature, to form a number of so far uncharacterized compounds, part of which precipitated as a brownish material. It can be concluded that thiols do react and will certainly affect the *in vivo* toxicity, the general metabolism and drug clearance pathways.

DMSO is a common solvent in medicinal chemistry, not only for the investigation of the biological activity of organic drug

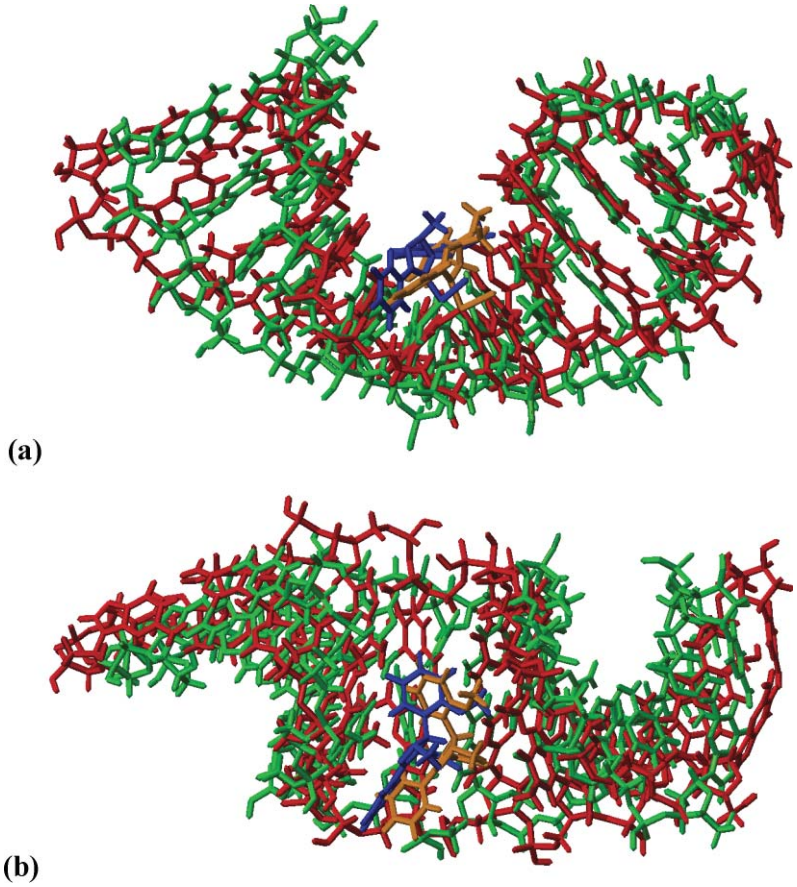


Fig. 3 Orthogonal views (a) and (b) of the best fit of the *cis*-PtCl(oxadiazoline) d(GpG) intrastrand crosslinks shown in Fig. 2 (DNA in red, Pt moiety in orange: fully optimised structure) and Fig. 1 (DNA in green, Pt moiety in blue: DNA conformation as in the cisplatin-adduct, only the Pt moiety was geometry optimised).

candidates but also for platinum compounds, although their affinity for sulfoxides is fairly high. Cisplatin, for example, is known to react with DMSO within a few hours to produce the less cytotoxic cationic complex *cis*-$[Pt(NH_3)_2(Cl)(DMSO)]^+$.[35] In view of these observations, the stability in DMSO should be generally checked for potential drug candidates before cytotoxicities are assessed. Compound **5a** is stable in DMSO for several weeks at room temperature and occupies an intermediate position between *trans*-$[PtCl_2(oxadiazoline)_2]$ compounds which are unchanged for months, and the *trans*-$[PtCl_2(oxadiazoline)(nitrile)]$ complexes which react within hours.[11] The first signs of replacement of the azaadamantane ligand by DMSO became apparent after six weeks with the emergence of signals of the free 7-NO_2-TAA ligand in the ^{1}H NMR spectrum. After three months the progress of the reaction was sufficient to reveal a new ^{195}Pt signal at –2966 ppm, at a similar chemical shift as the one observed for *cis*-$[PtCl_2(oxadiazoline)(DMSO)]$ compounds synthesized *via* a different route.[17] Complex **5a** thus closely mirrors the reactivity of $[PtCl_2(oxadiazoline)(nitrile)]$ with DMSO,[11] except that the ligand exchange is significantly slower. After prolonged reaction times (more than six months), an increasing number of compounds was detected by NMR spectroscopy. Among these a small amount of *cis*-$[PtCl_2(DMSO)_2]$ was identified on the basis of its ^{195}Pt NMR signal at –3440 ppm (lit. –3442 ppm[36]). Several ^{195}Pt signals in the range of –3040 to –3160 ppm and –2100 to –2280 ppm were tentatively assigned to complexes of the general type $[PtCl_2(N\text{-ligand})(DMSO)]$ or $[PtCl(N\text{-ligand})_2(DMSO)]^+$, and $[PtCl_2(N\text{-ligand})_2]$, respectively.

Aquation, *i.e.* chloride replacement by an aqua ligand, is a necessary requirement for cisplatin to be biologically active,[37] and occurs when the drug passes from the relatively high chloride concentration in the blood plasma to the cell cytoplasm, where the chloride concentration is significantly lower. The rates and extent of aquation of platinum compounds are usually measured by NMR techniques, based on the identification and quantitative determination of the different species in solution from the cross peaks in the [^{1}H,^{15}N] HMQC, for which ^{15}N-labelled compounds are required and a proton has to be attached to the nitrogen.[38] Compounds like **5**, lacking NH groups, cannot be studied by this method. Alternatively, the molar conductivity has been used as evidence for aquation of platinum(II) iminoether compounds,[39] on the basis that replacement of a chloro by an aqua ligand generates ionic species which enhance the conductivity. The chloro complex **5a** and its bromo counterpart **5g** were dissolved in dry DMSO and the conductivity was measured at regular intervals over a period of one week. The conductivity was negligibly low and unchanged with time, indicating the absence of ionic species. However, when water was added to these samples, the conductivity of **5a** increased within 7 days to stabilise at a final molar conductivity of 30–37 Ω^{-1} mol^{-1} cm^2, which is in a range expected for a 1 : 1 electrolyte in

DMSO or aqueous solution.[40] Compound **5g**, in contrast, did not show any conductivity even after 4 weeks. This observation is in agreement with previous reports that bromo compounds aquate to a lesser extent than the corresponding chloro compounds[21] and also excludes processes such as hydrolysis of the organic ligands as the source of ion formation because this should be similar in **5a** and **5g**. Also protonation of the azaadamantane ligand can be ruled out because this should have occurred instantaneously upon addition of water in both **5a** and **5g**.

The 7-NO_2-TAA ligand **4** is closely related to hexamethylene tetramine, which is known to release formaldehyde at pH <6.8.[41] A similar reaction is conceivable with the platinum complexes **5** where **4** acts as a ligand. Formaldehyde can be detected with phloroglucinol in alkaline medium, with a detection limit of about 0.00122%,[42] in a setup adapted from the literature[43] where nitrogen is bubbled through a flask containing the analyte and then through two micro impingers containing a freshly prepared solution of the test reagent. After 1 h the solutions from both impingers were analysed for their orange coloration (which should be intense in the first and negligible in the second sample for a positive result). Alternatively, formaldehyde can be detected with Schiff's test (fuchsin/sodium bisulfite solution) by the violet–red colour formed, using the same apparatus. The reliability of the two methods was checked with blind tests with aqueous formaldehyde solution, hexamethylene tetramine in acidic medium (both positive), hexamethylene tetramine in alkaline solution and the blank solvents water or aqueous DMSO (all three negative). No formaldehyde was detected with ligand **4** in aqueous DMSO, but the test became positive upon addition of 1 N H_2SO_4 to the analyte, indicating that the release of formaldehyde is promoted by acid. With compound **5a**, where ligand **4** is bound to a Lewis acidic Pt(II) center, the activation is strong enough to cause a slow formaldehyde release at neutral pH values already. The detection after about 2 h suggests a low equilibrium concentration, but since the formaldehyde is continuously removed from the equilibrium by the nitrogen stream and accumulates in the test solution it can be detected reproducibly after prolonged reaction time.

The formation of formaldehyde could have a positive effect on the pharmacological properties of platinum compounds such as **5**, because the release of a toxic compound could help to overcome resistance effects by introduction of a second mode of action which is independent of the action of the Pt center itself. On the other hand, one should keep in mind that formaldehyde has been classified as carcinogenic in humans by the IARC working group in 2004.[44] In spite of this, hexamethylene tetramine is still in use as a bacteriostatic in infections of the urinal tracts (in drugs such as Hiprex®), and its mode of action is attributed exactly to the release of formaldehyde. Interestingly, the use of hexamethylene tetramine in combination with cisplatin in squamous cell carcinoma has been reported.[45] The results suggested a cisplatin sensitivity-enhancing effect of hexamethylene tetramine, which might also operate with the platinum compounds suggested in this work.

Concluding Remarks

This work presents the facile synthesis of *trans*-configured mixed ligand platinum(II) oxadiazoline complexes with a labile and reactive 1-nitro-1,3,5-triazaadamantane ligand. The target compounds are promising candidates as cytotoxic agents in cancer therapy for a number of reasons: Firstly, there is precedence that Pt(II) oxadiazoline complexes have indeed cytotoxic properties,[11] and the compounds presented in this work are equally easy to modify at the oxadiazoline moiety for an optimisation of the pharmacological properties. The azaadamantane ligand can be selectively replaced by heterocycles such as pyridine, and DFT/AIM calculations suggest that this reaction should be enhanced in an aqueous medium when the azaadamantane is protonated. A similar ligand replacement should be feasible with purine nucleobases of the DNA, so that DNA binding is very likely to happen in the cell. After the exchange of a labile adjacent chloro ligand, d(GpG) intrastrand adducts analogous to the ones observed with cisplatin can be formed, and these have been shown in a PM6 molecular modelling study to cause a similar distortion of the DNA conformation.

However, there are also some issues that might question the medicinal properties. Although the compounds are comparatively stable in DMSO which is used as a common solvent for medicinal studies, they do react in an aqueous medium and with thiols. Since thiol-containing compounds are fairly widespread in the body and also thought to contribute to the metabolism and the toxicity of platinum compounds, this reaction needs to be studied in more detail and also kept in mind when the bioactivity of the compounds is evaluated. Secondly, the release of formaldehyde from the coordinated azaadamatane is an ambiguous issue. On one hand, it could add a second mode of action different from the DNA binding observed with Pt compounds and thus help to overcome resistance, but the fact that formaldehyde is classified as carcinogenic may restrict its medicinal use. Lastly, since the TAA ligand is released from the complex it will be necessary to study its biological activity in some depth, before a decision about the potential use of the platinum compounds discussed in this work can be made.

Experimental section

Computational details

DFT calculations were carried out with the PC GAMESS/Firefly package,[46] which is partially based on the GAMESS(US) source code.[47] Results were visualised with MacMOLPlt.[48] Molecular geometries were fully optimised using the B3LYP hybrid functional,[49] in its implementation which is based on the VWN1 formula.[50] The LANL08 core potential basis set[51] was used for Pt and Cl and the 6-31G* basis set[52] for all other atoms. Mayer bond orders[53] were calculated as implemented in PC GAMESS/Firefly. The topological analysis of the charge densities[27] was performed with the software package AIMPAC.[54] Molecular modelling of the DNA binding was performed with the program package MOPAC2009,[30] using the PM6 parametrisation[29] and a modified BFGS routine recommended for large molecules,[55] as implemented in the program. For the graphical evaluation the program MolMol 2 K.2 was used.[56]

Materials and instrumentation. Solvents and reagents were obtained from commercial sources and used as received. *Trans*-[$PtX_2(PhCN)_2$] **2a–2b**,[13] nitrone **1f**,[13] nitrones **1a–1e**[57] and 7-nitro-1,3,5-triazaadamantane **4**[22a] were synthesised according to published methods. C, H and N elemental analyses were run on a

Leeman CE 440 automatic analyser. Thermogravimetric analyses were carried out on a TA Instruments Q500 thermoanalyser, at heating rates of 10 K min^{-1} over a range of 20 to 800 °C and in an N_2 atmosphere, followed by a switch to synthetic air. The Pt content of the sample was calculated from the weight of the residue. Conductivities were measured with a WTW Cond315i conductivity meter and a TetraCon325 conductivity cell. Infrared spectra (4000–400 cm^{-1}) were recorded on Perkin Elmer 2000 FTIR, Nicolet Avatar 320 FT-IR and Bruker Equinox 55 FT-IR spectrometers in KBr pellets. ^{1}H, ^{13}C and ^{195}Pt NMR spectra were acquired on Bruker DRX 500 and Bruker AV 300 spectrometers at ambient temperature. ^{195}Pt chemical shifts are given relative to aqueous $K_2[PtCl_4] = -1630$ ppm, with half height line widths in parentheses.

Synthesis of the mixed nitrile/oxadiazoline complexes

Trans-$PtX_2(PhCN)_2$ **2a** or **2b** (0.1 mmol) and the corresponding nitrone **1a–1f** (0.1 mmol) were dissolved in chloroform (1 ml) and stirred at room temperature for 48 h. The solvent was evaporated and the residual crude products were purified by chromatography on silica using CH_2Cl_2 (**3a–3e** and **3g–3k**) or CH_2Cl_2–ethyl acetate 98 : 2 (**3f** and **3l**) as eluent.

***trans*-(Benzonitrile)-dichloro[2,3-dihydro-3-(2-methoxyphenyl)-2-methyl-5-phenyl-1,2,4-oxadiazole-κN⁴]platinum (3a).** Yield 75%. Elemental analysis calculated for $C_{23}H_{21}Cl_2N_3O_2Pt$: C 43.34; H 3.32; N 6.59; Pt 30.60; found: C 43.16; H 3.22; N 6.45. TGA (residue) Pt 30.71. IR (selected bands), cm^{-1}: 3065, 3006 and 2972 ν(C–H), 2841 ν(C–H of OMe), 2294 ν(C≡N), 1629 m ν(C=N). ^{1}H NMR in $CDCl_3$, δ (ppm): 3.08 (s, br., 3H, NMe), 3.92 (s, 3H, OMe), 6.44 (s, br., 1H, N–CH–N), 6.97 (d, 8.0 Hz, 1H), 7.01 (t, 8.0 Hz, 1H), 7.39 (td, 8.0 Hz, 1.5 Hz, 1H) and 7.53 (s, br., 1H)(aryl-H of N–CH(Ar)–N), 7.49 (t, 7.8 Hz, 2H) and 7.68 (m, 3H)(aryl-H of PhC≡N–Pt), 7.61 (t, 7.8 Hz, 2H), 7.69 (m, 1H) and 8.99 (dd, 7.9 Hz, 1.9 Hz, 2H)(aryl-H of PhC=N). ^{13}C NMR in $CDCl_3$, δ (ppm): 47.5 (NMe), 56.0 (OMe), 90.6 (N–CH–N), 111.3, 120.7, 129.7 and 130.9 (CH of N–CH(*Ar*)–N), 124.1 and 157.9 (C_q of N–CH(*Ar*)–N), 129.5, 133.6 and 135.0 (CH of *Ph*C≡N–Pt), 110.0 (C_q of *Ph*C≡N–Pt), 116.7 (C≡N), 128.8, 130.8 and 134.2 (CH of *Ph*C=N), 122.6 (C_q of *Ph*C=N), 165.5 (C=N). ^{195}Pt NMR in $CDCl_3$, δ (ppm): –2229 (740 Hz).

***trans*-(Benzonitrile)-dichloro[2,3-dihydro-3-(2,4-dimethoxyphenyl)-2-methyl-5-phenyl-1,2,4-oxadiazole-κN⁴]platinum (3b).** Yield 70%. Elemental analysis calculated for $C_{24}H_{23}Cl_2N_3O_3Pt$: C 43.19; H 3.47; N 6.29; found: C 43.01; H 3.31; N 6.27. IR (selected bands), cm^{-1}: 3063, 3003 and 2966 ν(C–H), 2837 ν(C–H of OMe), 2289 ν(C≡N), 1615 and 1590 m ν(C=N and C=C). ^{1}H NMR in $CDCl_3$, δ (ppm): 3.05 (s, br., 3H, NMe), 3.80 (s, 3H) and 3.89 (s, 3H)(2 × OMe), 6.33 (s, br., 1H, N–CH–N), 6.51 (s, 1H), 6.52 (d, 8.0 Hz, 1H) and 7.43 ("s", br., 1H)(aryl-H of N–CH(Ar)–N), 7.49 (t, 7.4 Hz, 2H) and 7.67 (m, 3H)(aryl-H of PhC≡N–Pt), 7.60 (t, 7.4 Hz, 2H), 7.67 (m, 1H) and 8.97 (d, 7.4 Hz, 2H)(aryl-H of PhC=N). ^{13}C NMR in $CDCl_3$, δ (ppm): 47.2 (NMe), 55.5 and 55.9 (2 × OMe), 90.5 (N–CH–N), 99.1, 104.3 and 130.7 (CH of N–CH(*Ar*)–N), 116.6, 159.0 and 162.1 (C_q of N–CH(*Ar*)–N), 129.4, 133.6 and 134.8 (CH of *Ph*C≡N–Pt), 109.9 (C_q of *Ph*C≡N–Pt), 116.7 (C≡N), 128.7, 130.7 and 134.0 (CH of *Ph*C=N), 122.7 (C_q of *Ph*C=N), 165.2 (C=N). ^{195}Pt NMR in $CDCl_3$, δ (ppm): –2229 (680 Hz).

***trans*-(Benzonitrile)-dichloro[2,3-dihydro-3-(2,6-dimethoxyphenyl)-2-methyl-5-phenyl-1,2,4-oxadiazole-κN⁴]platinum (3c).** Yield 79%. Elemental analysis calculated for $C_{24}H_{23}Cl_2N_3O_3Pt$: C 43.19; H 3.47; N 6.29; found: C 43.28; H 3.33; N 6.17. IR (selected bands), cm^{-1}: 3064, 3003, 2967 and 2939 ν(C–H), 2839 ν(C–H of OMe), 2289 ν(C≡N), 1645 and 1597 m ν(C=N and C=C). ^{1}H NMR in $CDCl_3$, δ (ppm): 3.06 (s, 3H, NMe), 3.67 (s, 3H) and 4.01 (s, 3H)(2 × OMe), 6.75 (s, 1H, N–CH–N), 6.56 (d, 8.3 Hz, 1H), 6.66 (d, 8.3 Hz, 1H) and 7.33 (t, 8.4 Hz, 1H)(aryl-H of N–CH(Ar)–N), 7.47 (t, 7.5 Hz, 2H) and 7.67 (m, 3H)(aryl-H of PhC≡N–Pt), 7.58 (t, 7.5 Hz, 2H), 7.65 (m, 1H) and 8.92 (d, 7.1 Hz, 2H)(aryl-H of PhC=N). ^{13}C NMR in $CDCl_3$, δ (ppm): 48.4 (NMe), 56.1 and 56.8 (2 × OMe), 86.9 (N–CH–N), 104.2, 105.2 and 131.4 (CH of N–CH(*Ar*)–N), 112.9, 158.7 and 160.6 (C_q of N–CH(*Ar*)–N), 129.4, 133.6 and 134.7 (CH of *Ph*C≡N–Pt), 110.1 (C_q of *Ph*C≡N–Pt), 116.4 (C≡N), 128.7, 130.5 and 134.8 (CH of *Ph*C=N), 123.0 (C_q of *Ph*C=N), 164.2 (C=N). ^{195}Pt NMR in $CDCl_3$, δ (ppm): –2231 (620 Hz).

***trans*-(Benzonitrile)-dichloro[2,3-dihydro-3-(2,4,6-trimethoxyphenyl)-2-methyl-5-phenyl-1,2,4-oxadiazole-κN⁴]platinum (3d).** Yield 89%. Elemental analysis calculated for $C_{25}H_{25}Cl_2N_3O_4Pt$: C 43.05; H 3.61; N 6.02; found: C 43.21; H 3.41; N 5.91. IR (selected bands), cm^{-1}: 3068, 3007 and 2974 ν(C–H), 2844 ν(C–H of OMe), 2293 ν(C≡N), 1631 m ν(C=N). ^{1}H NMR in $CDCl_3$, δ (ppm): 3.03 (s, br., 3H, NMe), 3.65 (s, 3H), 3.80 (s, 3H) and 3.98 (s, 3H)(3 × OMe), 6.64 (s, br., 1H, N–CH–N), 6.11 (s, 1H) and 6.20 (s, 1H)(aryl-H of N–CH(Ar)–N), 7.48 (t, 7.8 Hz, 2H) and 7.67 (m, 3H)(aryl-H of PhC≡N–Pt), 7.59 (t, 7.8 Hz, 2H), 7.66 (m, 1H) and 8.92 (d, 7.5 Hz, 2H)(aryl-H of PhC=N). ^{13}C NMR in $CDCl_3$, δ (ppm): 48.3 (NMe), 55.4, 56.1 and 56.8 (3 × OMe), 87.1 (N–CH–N), 91.0 and 91.8 (CH of N–CH(*Ar*)–N), 106.0, 159.5, 161.6 and 162.6 (C_q of N–CH(*Ar*)–N), 129.5, 133.5 and 133.7 (CH of *Ph*C≡N–Pt), 110.2 (C_q of *Ph*C≡N–Pt), 116.5 (C≡N), 128.7, 130.5 and 134.8 (CH of *Ph*C=N), 123.3 (C_q of *Ph*C=N), 164.0 (C=N). ^{195}Pt NMR in $CDCl_3$, δ (ppm): –2230 (640 Hz).

***trans*-(Benzonitrile)-dichloro[2,3-dihydro-3-(2-furyl)-2-methyl-5-phenyl-1,2,4-oxadiazole-κN⁴]platinum (3e).** Yield 65%. Elemental analysis calculated for $C_{20}H_{17}Cl_2N_3O_2Pt$: C 40.21; H 2.87; N 7.03; found: C 40.18; H 2.66; N 6.98. IR (selected bands), cm^{-1}: 3115, 3063, 3005 and 2968 ν(C–H), 2290 ν(C≡N), 1630 s and 1599 m ν(C=N and C=C). ^{1}H NMR in $CDCl_3$, δ (ppm): 3.05 (s, br., 3H, NMe), 6.15 (s, br., 1H, N–CH–N), 6.44 (dd, 3.4 Hz, 1.9 Hz, 1H), 6.84 (d, 3.3 Hz, 1H) and 7.51 (m, 1H)(furyl-H), 7.51 (t, 7.8 Hz, 2H) and 7.69 (m, 3H)(aryl-H of PhC≡N–Pt), 7.60 (t, 7.8 Hz, 2H), 7.70 (m, 1H) and 8.99 (d, 7.5 Hz, 2H)(aryl-H of PhC=N). ^{13}C NMR in $CDCl_3$, δ (ppm): 46.8 (NMe), 87.9 (N–CH–N), 110.8, 111.5 and 144.1 (CH of N–CH(*furyl*)-N), 147.8 (C_q of N–CH(*furyl*)-N), 129.5, 133.6 and 135.0 (CH of *Ph*C≡N–Pt), 109.8 (C_q of *Ph*C≡N–Pt), 116.9 (C≡N), 128.8, 130.9 and 134.5 (CH of *Ph*C=N), 121.9 (C_q of *Ph*C=N), 165.3 (C=N). ^{195}Pt NMR in $CDCl_3$, δ (ppm): –2248 (650 Hz).

***trans*-(Benzonitrile)-dichloro[2,3-dihydro-3-ethoxycarbonyl-3-ethoxycarbonyl-methyl-2-methyl-5-phenyl-1,2,4-oxadiazole-κN⁴]platinum (3f).** Yield 74%. Anal. Calcd for $C_{23}H_{25}Cl_2N_3O_5Pt$: C, 40.07; H, 3.65; N, 6.09. Found: C, 40.10; H, 3.67; N, 5.83. IR

spectrum (selected bands), cm^{-1}: 2289 w ν(C≡N), 1739 s ν(C=O), 1623 m ν(C=N). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.31 (t, 7.1 Hz, 3H) and 1.33 (t, 7.1 Hz, 3H)(2 × OCH_2CH_3), 3.06 (s, 3H, NMe), 3.56 (d, 17.5 Hz, 1H) and 4.88 (d, 17.5 Hz, 1H)(CH_2), 4.27 (m, 3H) and 4.34 (m, 1H)(2 × OCH_2CH_3), 7.53 (t, 8.0 Hz, 2H), 7.70 (m, 1H) and 7.74 (d, 8.0 Hz, 2H)(PhC≡N), 7.61 (t, 7.5 Hz, 2H), 7.70 (m, 1H) and 8.85 (d, 7.5 Hz, 2H)(N=C–Ph). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ (ppm): 14.1 and 14.4 (2 × OCH_2CH_3), 39.7 (CH_2), 42.0 (NMe), 61.6 and 63.3 (2 × OCH_2CH_3), 92.2 (N–C–N), 109.9 (C_q, N≡CPh), 116.8 (N≡C), 122.5 (C_q, N=CPh), 129.0 (CH, N≡CPh), 129.6 (CH, N=CPh), 131.2 (CH, N=CPh), 133.8 (CH, N≡CPh), 134.7 and 135.1 (CH, N≡CPh and N=CPh), 167.9 (C=N), 165.9 and 168.1 (C=O). ^{195}Pt NMR (107.3 MHz, $CDCl_3$) δ (ppm): –2232 (950 Hz).

***trans*-(Benzonitrile)-dibromo[2,3-dihydro-3-(2-methoxyphenyl)-2-methyl-5-phenyl-1,2,4-oxadiazole-κN^4]platinum (3g).** Yield 82%. Elemental analysis calculated for $C_{23}H_{21}Br_2N_3O_2Pt$: C 38.03; H 2.91; N 5.79; found: C 38.07; H 2.75; N 5.63. IR (selected bands), cm^{-1}: 3069, 2994 and 2968 ν(C–H), 2839 ν(C–H of OMe), 2286 ν(C≡N), 1631 m ν(C=N). ^{1}H NMR in $CDCl_3$, δ (ppm): 3.10 (s, br., 3H, NMe), 3.92 (s, 3H, OMe), 6.42 (s, br., 1H, N–CH–N), 6.95 (d, 8.3 Hz, 1H), 7.02 (t, 7.6 Hz, 1H), 7.39 (td, 8.3 Hz, 1.5 Hz, 1H) and 7.53 (s, br., 1H)(aryl-H of N–CH(Ar)-N), 7.48 (t, 7.8 Hz, 2H) and 7.66 (m, 3H)(aryl-H of PhC≡N–Pt), 7.60 (t, 7.8 Hz, 2H), 7.67 (m, 1H) and 8.99 (dd, 7.6 Hz, 1.9 Hz, 2H)(aryl-H of PhC=N). ^{13}C NMR in $CDCl_3$, δ (ppm): 47.6 (NMe), 56.0 (OMe), 91.2 (N–CH–N), 111.5, 120.7, 130.1 and 130.9 (CH of N–CH(*Ar*)-N), 124.1 and 158.0 (C_q of N–CH(*Ar*)-N), 129.5, 133.6 and 134.9 (CH of *Ph*C≡N–Pt), 110.1 (C_q of *Ph*C≡N–Pt), 118.5 (C≡N), 128.8, 131.3 and 134.0 (CH of *Ph*C=N), 122.8 (C_q of *Ph*C=N), 165.0 (C=N). ^{195}Pt NMR in $CDCl_3$, δ (ppm): –2681 (800 Hz).

***trans*-(Benzonitrile)-dibromo[2,3-dihydro-3-(2,4-dimethoxyphenyl)-2-methyl-5-phenyl-1,2,4-oxadiazole-κN^4]platinum (3h).** Yield 70%. Elemental analysis calculated for $C_{24}H_{23}Br_2N_3O_3Pt$: C 38.11; H 3.07; N 5.56; found: C 38.17; H 3.03; N 5.42. IR (selected bands), cm^{-1}: 3060, 3005 and 2968 ν(C–H), 2839 ν(C–H of OMe), 2286 ν(C≡N), 1622 and 1615 m ν(C=N and C=C). ^{1}H NMR in $CDCl_3$, δ (ppm): 3.07 (s, br., 3H, NMe), 3.80 (s, 3H) and 3.89 (s, 3H)(2 × OMe), 6.32 (s, br., 1H, N–CH–N), 6.50 (s, 1H), 6.53 (d, 8.2 Hz, 1H) and 7.45 ("s", br., 1H)(aryl-H of N–CH(Ar)-N), 7.49 (t, 7.6 Hz, 2H) and 7.68 (m, 3H)(aryl-H of PhC≡N–Pt), 7.60 (t, 7.6 Hz, 2H), 7.67 (m, 1H) and 8.97 (d, 7.2 Hz, 2H)(aryl-H of PhC=N). ^{13}C NMR in $CDCl_3$, δ (ppm): 47.2 (NMe), 55.4 and 55.7 (2 × OMe), 91.1 (N–CH–N), 99.1, 105.8 and 130.9 (CH of N–CH(*Ar*)-N), 116.6, 159.0 and 162.1 (C_q of N–CH(*Ar*)-N), 129.3, 133.6 and 135.2 (CH of *Ph*C≡N–Pt), 109.9 (C_q of *Ph*C≡N–Pt), 118.2 (C≡N), 128.5, 130.7 and 134.6 (CH of *Ph*C=N), 122.7 (C_q of *Ph*C=N), 164.5 (C=N). ^{195}Pt NMR in $CDCl_3$, δ (ppm): –2679 (850 Hz).

***trans*-(Benzonitrile)-dibromo[2,3-dihydro-3-(2,6-dimethoxyphenyl)-2-methyl-5-phenyl-1,2,4-oxadiazole-κN^4]platinum (3i).** Yield 79%. Elemental analysis calculated for $C_{24}H_{23}Br_2N_3O_3Pt$: C 38.11; H 3.07; N 5.56; found: C 38.18; H 2.89; N 5.36. IR (selected bands), cm^{-1}: 3063, 3000 and 2940 ν(C–H), 2836 ν(C–H of OMe), 2286 ν(C≡N), 1638 and 1596 m ν(C=N and C=C). ^{1}H NMR in $CDCl_3$, δ (ppm): 3.07 (s, 3H, NMe), 3.69 (s, 3H) and 4.02 (s, 3H)(2 × OMe), 6.79 (s, 1H, N–CH–N), 6.55 (d, 8.0 Hz, 1H), 6.65 (d, 8.2 Hz, 1H) and 7.32 (t, 8.0 Hz, 1H)(aryl-H of N–CH(Ar)-N), 7.47 (t, 7.6 Hz, 2H) and 7.67 (m, 3H)(aryl-H of PhC≡N–Pt), 7.59 (t, 7.6 Hz, 2H), 7.65 (m, 1H) and 8.94 (d, 7.5 Hz, 2H)(aryl-H of PhC=N). ^{13}C NMR in $CDCl_3$, δ (ppm): 48.5 (NMe), 56.1 and 57.0 (2 × OMe), 87.5 (N–CH–N), 104.4, 105.2 and 131.4 (CH of N–CH(*Ar*)-N), 113.0, 158.8 and 160.7 (C_q of N–CH(*Ar*)-N), 129.4, 133.7 and 135.5 (CH of *Ph*C≡N–Pt), 110.3 (C_q of *Ph*C≡N–Pt), 118.2 (C≡N), 128.7, 130.6 and 134.8 (CH of *Ph*C=N), 123.2 (C_q of *Ph*C=N), 164.1 (C=N). ^{195}Pt NMR in $CDCl_3$, δ (ppm): –2685 (580 Hz).

***trans*-(Benzonitrile)-dibromo[2,3-dihydro-3-(2,4,6-trimethoxyphenyl)-2-methyl-5-phenyl-1,2,4-oxadiazole-κN^4]platinum (3j).** Yield 76%. Elemental analysis calculated for $C_{25}H_{25}Br_2N_3O_4Pt$: C 38.18; H 3.20; N 5.37; found: C 37.93; H 3.18; N 5.14. IR (selected bands), cm^{-1}: 3060, 2995, 2955 and 2940 ν(C–H), 2839 ν(C–H of OMe), 2286 ν(C≡N), 1641 and 1610 m ν(C=N and C=C). ^{1}H NMR in $CDCl_3$, δ (ppm): 3.05 (s, 3H, NMe), 3.67, 3.80 and 4.00 (s, 3H, 3 × OMe), 6.68 (s, 1H, N–CH–N), 6.09 (d, 1.5 Hz, 1H) and 6.21 (d, 1.5 Hz, 1H)(aryl-H of N–CH(Ar)-N), 7.48 (t, 7.7 Hz, 2H) and 7.67 (m, 3H)(aryl-H of PhC≡N–Pt), 7.58 (t, 7.8 Hz, 2H), 7.65 (m, 1H) and 8.93 (d, 7.5 Hz, 2H)(aryl-H of PhC=N). ^{13}C NMR in $CDCl_3$, δ (ppm): 48.3 (NMe), 55.4, 55.9 and 56.8 (3 × OMe), 87.5 (N–CH–N), 90.9 and 91.7 (CH of N–CH(*Ar*)-N), 105.1, 159.4, 161.5 and 162.6 (C_q of N–CH(*Ar*)-N), 129.3, 133.6 and 135.4 (CH of *Ph*C≡N–Pt), 110.2 (C_q of *Ph*C≡N–Pt), 118.1 (C≡N), 128.5, 130.5 and 134.7 (CH of *Ph*C=N), 123.2 (C_q of *Ph*C=N), 163.8 (C=N). ^{195}Pt NMR in $CDCl_3$, δ (ppm): –2685 (650 Hz).

***trans*-(Benzonitrile)-dibromo[2,3-dihydro-3-(2-furyl)-2-methyl-5-phenyl-1,2,4-oxadiazole-κN^4]platinum (3k).** Yield 62%. Elemental analysis calculated for $C_{20}H_{17}Br_2N_3O_2Pt$: C 35.00; H 2.50; N 6.12; found: C 34.91; H 2.39; N 6.01. IR (selected bands), cm^{-1}: 3118, 3066, 3009 and 2969 ν(C–H), 2287 ν(C≡N), 1633 s and 1600 m ν(C=N and C=C). ^{1}H NMR in $CDCl_3$, δ (ppm): 3.08 (s, br., 3H, NMe), 6.14 (s, br., 1H, N–CH–N), 6.43 (dd, 3.3 Hz, 1.8 Hz, 1H), 6.81 (d, 2.7 Hz, 1H) and 7.50 (m, 1H)(furyl-H), 7.51 (t, 7.7 Hz, 2H) and 7.67 (m, 3H)(aryl-H of PhC≡N–Pt), 7.59 (t, 7.6 Hz, 2H), 7.68 (m, 1H) and 9.00 (d, 7.8 Hz, 2H)(aryl-H of PhC=N). ^{13}C NMR in $CDCl_3$, δ (ppm): 46.9 (NMe), 88.4 (N–CH–N), 110.8, 111.9 and 144.0 (CH of N–CH(*furyl*)-N), 147.6 (C_q of N–CH(*furyl*)-N), 129.4, 133.6 and 135.0 (CH of *Ph*C≡N–Pt), 109.9 (C_q of *Ph*C≡N–Pt), 118.6 (C≡N), 128.7, 131.0 and 134.4 (CH of *Ph*C=N), 122.0 (C_q of *Ph*C=N), 164.9 (C=N). ^{195}Pt NMR in $CDCl_3$, δ (ppm): –2708 (750 Hz).

***trans*-(Benzonitrile)-dibromo[2,3-dihydro-3-ethoxycarbonyl-3-ethoxycarbonyl-methyl-2-methyl-5-phenyl-1,2,4-oxadiazole-κN^4]platinum (3l).** Yield 64%. Anal. Calcd for $C_{23}H_{25}Br_2N_3O_5Pt$: C, 35.49; H, 3.24; N, 5.40. Found: C, 35.30; H, 3.28; N, 5.06. IR spectrum (selected bands), cm^{-1}: 3063, 2982 and 2938 ν(C–H), 2288 w ν(C≡N), 1739 s ν(C=O), 1622 m ν(C=N). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.28 (t, 7.3 Hz, 3H) and 1.34 (t, 7.3 Hz, 3H)(2 × OCH_2CH_3), 3.08 (s, 3H, NMe), 3.64 (d, 17.5 Hz, 1H) and 4.82 (d, 17.5 Hz, 1H)(CH_2), 4.25 (m, 3H) and 4.35 (m, 1H)(2 × OCH_2CH_3), 7.53 (t, 8.0 Hz, 2H), 7.71 (m, 1H) and 7.74 (d, 8.0 Hz, 2H)(PhC≡N), 7.61 (t, 7.5 Hz, 2H), 7.71 (m, 1H) and

8.84 (d, 7.5 Hz, 2H)(N=C–Ph). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ (ppm): 14.0 and 14.4 (2 × OCH_2CH_3), 39.9 (CH_2), 42.2 (NMe), 61.6 and 63.4 (2 × OCH_2CH_3), 92.3 (N–C–N), 110.0 (C_q, N≡CPh), 118.6 (N≡C), 122.7 (C_q, N=CPh), 129.0 (CH, N≡CPh), 129.6 (CH, N=CPh), 131.4 (CH, N=CPh), 133.7 (CH, N≡CPh), 134.7 and 135.1 (CH, N≡CPh and N=CPh), 167.9 (C=N), 166.0 and 168.0 (C=O). ^{195}Pt NMR (107.3 MHz, $CDCl_3$) δ (ppm): –2688 (850 Hz).

Synthesis of the mixed triazaadamantane/oxadiazoline complexes.

Trans-PtX_2(PhCN)(oxadiazoline) **3a–3l** (0.1 mmol) and 7-nitro-1,3,5-triaza-adamantane **4** (0.1 mmol) were dissolved in chloroform (1 ml) and stirred at room temperature for 2 weeks. The solvent was evaporated and the residual crude products were purified by chromatography on silica using CH_2Cl_2/diethylether 98 : 2 (**5a–5e** and **5g–5k**) or CH_2Cl_2/ethyl acetate 92 : 8 (**5f** and **5l**) as eluent. A small amount of a dinuclear side product **6** was detected in each reaction, and **6a** was isolated and characterised.

***trans*-Dichloro[2,3-dihydro-3-(2-methoxyphenyl)-2-methyl-5-phenyl-1,2,4-oxadiazole-κN^4][7-nitro-1,3,5-triazaadamantane κN^1]platinum (5a).** Yield 73%. Elemental analysis calculated for $C_{23}H_{28}Cl_2N_6O_4Pt$: C 38.45; H 3.93; N 11.70; Pt 27.15; found: C 38.42; H 4.08; N 11.43. TGA (residue) Pt 27.37. R_f (SiO_2/CH_2Cl_2): 0.12. IR (selected bands), cm^{-1}: 3065, 2991, 2961 and 2923 ν(C–H), 2839 ν(C–H of OMe), 1634 m ν(C=N), 1610 s ν(C=C), 1539 ν(NO_2). ^{1}H NMR in $CDCl_3$, δ (ppm): 3.03 (s, br., 3H, NMe), 3.92 (s, 3H, OMe), 3.65 (d, 14.1 Hz, 2H) and 3.67 (d, 14.1 Hz, 2H)(TAA H_d and $H_{d'}$), 4.21 ("s", 2H, TAA H_c), 3.88 (dm, 13.3 Hz, 1H) and 4.23 (d, 13.3 Hz, 1H)(TAA H_b and $H_{b'}$), 4.56 (dm, 13.3 Hz, 2H) and 4.78 (d, 13.3 Hz, 2H)(TAA H_a and $H_{a'}$), 6.29 (s, br., 1H, N–CH–N), 6.95 (d, 8.0 Hz, 1H), 6.98 (t, 7.8 Hz, 1H), 7.38 (td, 7.8 Hz, 1.5 Hz, 1H) and 7.48 ("s", br., 1H)(aryl-H of N–CH(Ar)-N), 7.58 (t, 7.6 Hz, 2H), 7.68 (t, 7.6 Hz, 1H) and 8.89 (dd, 7.7 Hz, 1.8 Hz, 2H)(aryl-H of PhC=N). ^{13}C NMR in $CDCl_3$, δ (ppm): 47.4 (NMe), 56.0 (OMe), 58.31 and 58.35 (TAA C_d), 62.8 (TAA C_c), 71.6 (TAA C_b), 78.37 and 78.42 (TAA C_a), 73.0 (TAA C–NO_2), 90.3 (N–CH–N), 111.1, 120.6, 129.5 and 131.0 (CH of N–CH(*Ar*)–N), 124.4 and 157.5 (C_q of N–CH(*Ar*)–N), 128.7, 130.6 and 134.1 (CH of *Ph*C=N), 123.1 (C_q of *Ph*C=N), 164.9 (C=N). ^{195}Pt NMR in $CDCl_3$, δ (ppm): –2164 (720 Hz).

[μ-(7-Nitro-1,3,5-triazaadamantane-κN^1:κN^3]tetrachlorobis[2,3-dihydro-3-(2-methoxyphenyl)-2-methyl-5-phenyl-1,2,4-oxadiazole-κN^4]diplatinum (6a). Yield 12%. Elemental analysis calculated for $C_{39}H_{44}Cl_4N_8O_6Pt_2$: C 37.39; H 3.54; N 8.94; found: C 37.33; H 3.60; N 8.61. R_f (SiO_2/CH_2Cl_2): 0.31. IR (selected bands), cm^{-1}: 3065, 2991, 2961 and 2923 ν(C–H), 2839 ν(C–H of OMe), 1632 m ν(C=N), 1610 s ν(C=C), 1542 ν(NO_2). ^{1}H NMR in $CDCl_3$, δ (ppm): 3.03 (s, br., 6H, NMe), 3.92 (s, 6H, OMe), 3.52 ("s", 2H, TAA H_d), 4.01 (m, 2H) and 4.21 (m, 2H)(TAA H_c and $H_{c'}$), 4.30 (m, 2H) and 4.72 (m, 2H)(TAA H_b and $H_{b'}$), 5.06 (m, 1H) and 5.24 (m, 1H)(TAA H_a and $H_{a'}$), 6.27 (s, br., 2H, N–CH–N), 6.94 (m, 2H), 6.99 (m, 2H), 7.38 (tm, 7.8 Hz, 2H) and 7.47 ("s", br., 2H)(aryl-H of N–CH(Ar)–N), 7.59 (m, 4H), 7.67 ("t", 7.6 Hz, 2H) and 8.89 (dm, 7.7 Hz, 4H)(aryl-H of PhC=N). ^{13}C NMR in $CDCl_3$, δ (ppm): 47.2 (NMe), 55.7 (OMe), 56.7 (TAA C_d), 61.7 (TAA C_c), 76.4 (TAA C_b), 79.4 (TAA C_a), 72.8 (TAA C–NO_2), 89.8 (N–CH–N), 110.9, 120.4, 129.1 and 130.8 (CH of N–CH(*Ar*)–N), 124.2 and 157.4 (C_q of N–CH(*Ar*)–N), 128.5, 130.3 and 133.8 (CH of *Ph*C=N), 122.9 (C_q of *Ph*C=N), 164.5 (C=N). ^{195}Pt NMR in $CDCl_3$, δ (ppm): –2160 (910 Hz).

***trans*-Dichloro[2,3-dihydro-3-(2,4-dimethoxyphenyl)-2-methyl-5-phenyl-1,2,4-oxadiazole-κN^4][7-nitro-1,3,5-triazaadamantane-κN^1]platinum (5b).** Yield 69%. Elemental analysis calculated for $C_{24}H_{30}Cl_2N_6O_5Pt$: C 38.51; H 4.04; N 11.23; found: C 38.39; H 3.97; N 11.00. IR (selected bands), cm^{-1}: 3063, 3005 and 2966 ν(C–H), 2838 ν(C–H of OMe), 1628 and 1615 m ν(C=N and C=C), 1538 ν(NO_2). ^{1}H NMR in $CDCl_3$, δ (ppm): 3.00 (s, br., 3H, NMe), 3.81 (s, 3H) and 3.90 (s, 3H)(2 × OMe), 3.66 (s, 4H)(TAA H_d and $H_{d'}$), 4.22 (s, 2H, TAA H_c), 3.85 (dm, 13.2 Hz, 1H) and 4.23 (d, 13.2 Hz, 1H)(TAA H_b and $H_{b'}$), 4.56 (dm, 13.2 Hz, 2H) and 4.78 (d, 13.2 Hz, 2H)(TAA H_a and $H_{a'}$), 6.21 (s, br., 1H, N–CH–N), 6.50 (m, 2H) and 7.40 ("s", br., 1H)(aryl-H of N–CH(Ar)–N), 7.58 (t, 7.6 Hz, 2H), 7.66 (tm, 7.5 Hz, 1H) and 8.89 (d, 7.2 Hz, 2H)(aryl-H of PhC=N). ^{13}C NMR in $CDCl_3$, δ (ppm): 47.1 (NMe), 55.5 and 55.9 (2 × OMe), 58.2 (TAA C_d), 62.7 (TAA C_c), 71.6 (TAA C_b), 78.3 (TAA C_a), 73.0 (TAA C–NO_2), 90.2 (N–CH–N), 98.9, 104.2 and 130.5 (CH of N–CH(*Ar*)–N), 117.0, 158.8 and 162.0 (C_q of N–CH(*Ar*)–N), 128.6, 130.5 and 133.8 (CH of *Ph*C=N), 123.2 (C_q of *Ph*C=N), 164.7 (C=N). ^{195}Pt NMR in $CDCl_3$, δ (ppm): –2164 (650 Hz).

***trans*-Dichloro[2,3-dihydro-3-(2,6-dimethoxyphenyl)-2-methyl-5-phenyl-1,2,4-oxadiazole-κN^4][7-nitro-1,3,5-triazaadamantane-κN^1]platinum (5c).** Yield 82%. Elemental analysis calculated for $C_{24}H_{30}Cl_2N_6O_5Pt$: C 38.51; H 4.04; N 11.23; found: C 38.33; H 3.91; N 10.97. IR (selected bands), cm^{-1}: 3054, 2968 and 2941 ν(C–H), 2839 ν(C–H of OMe), 1645 and 1598 m ν(C=N and C=C), 1538 ν(NO_2). ^{1}H NMR in $CDCl_3$, δ (ppm): 3.00 (s, 3H, NMe), 3.62 (s, 3H) and 4.02 (s, 3H)(2 × OMe), 3.64 (s, 4H)(TAA H_d and $H_{d'}$), 4.13 (d, 13.6 Hz, 1H) and 4.19 (d, 13.6 Hz, 1H)(TAA H_c), 3.87 (dm, 13.6 Hz, 1H) and 4.21 (d, 13.6 Hz, 1H)(TAA H_b and $H_{b'}$), 4.51 (dm, 13.2 Hz, 2H) and 4.73 (d, 13.2 Hz, 2H)(TAA H_a and $H_{a'}$), 6.62 (s, 1H, N–CH–N), 6.54 (d, 8.0 Hz, 1H), 6.65 (d, 8.0 Hz, 1H) and 7.33 (t, 8.0 Hz, 1H)(aryl-H of N–CH(Ar)–N), 7.58 (t, 7.6 Hz, 2H), 7.64 (m, 1H) and 8.83 (d, 7.6 Hz, 2H)(aryl-H of PhC=N). ^{13}C NMR in $CDCl_3$, δ (ppm): 48.6 (NMe), 56.1 and 56.8 (2 × OMe), 58.25 and 58.32 (TAA C_d), 62.6 (TAA C_c), 71.6 (TAA C_b), 78.2 (TAA C_a), 73.1 (TAA C–NO_2), 87.1 (N–CH–N), 104.1, 105.2 and 131.4 (CH of N–CH(*Ar*)–N), 113.3, 158.7 and 160.8 (C_q of N–CH(*Ar*)–N), 128.6, 130.3 and 133.5 (CH of *Ph*C=N), 123.5 (C_q of *Ph*C=N), 163.6 (C=N). ^{195}Pt NMR in $CDCl_3$, δ (ppm): –2170 (520 Hz).

***trans*-Dichloro[2,3-dihydro-3-(2,4,6-trimethoxyphenyl)-2-methyl-5-phenyl-1,2,4-oxadiazole-κN^4][7-nitro-1,3,5-triazaadamantane-κN^1]platinum (5d).** Yield 77%. Elemental analysis calculated for $C_{25}H_{32}Cl_2N_6O_6Pt$: C 38.57; H 4.14; N 10.79; found: C 38.19; H 4.44; N 10.65. IR (selected bands), cm^{-1}: 3008, 2965 and 2942 ν(C–H), 2841 ν(C–H of OMe), 1645 m ν(C=N), 1610 s ν(C=C), 1538 ν(NO_2). ^{1}H NMR in $CDCl_3$, δ (ppm): 2.97 (s, br., 3H, NMe), 3.60 (s, 3H), 3.80 (s, 3H) and 4.00 (s, 3H)(3 × OMe), 3.65 (s, 4H)(TAA H_d and $H_{d'}$), 4.23 (d, 14.1 Hz, 1H) and 4.19 (d, 14.1 Hz, 1H)(TAA H_c), 3.86 (dm, 13.4 Hz, 1H) and 4.26 (d, 13.4 Hz, 1H)(TAA H_b and $H_{b'}$), 4.53 (dm, 13.2 Hz, 2H) and 4.74 (d, 13.2 Hz, 2H)(TAA H_a and $H_{a'}$), 6.50 (s, br., 1H, N–CH–N), 6.08 (s, 1H) and 6.20 (s, 1H)(aryl-H of N–CH(Ar)–N), 7.58 (t, 7.6 Hz,

2H), 7.61 (m, 1H) and 8.82 (d, 7.6 Hz, 2H)(aryl-H of PhC=N). ^{13}C NMR in $CDCl_3$, δ (ppm): 48.5 (NMe), 55.4, 56.1 and 56.8 (3 × OMe), 58.26 and 58.33 (TAA C_d), 62.7 (TAA C_c), 71.6 (TAA C_b), 78.2 (TAA C_a), 73.0 (TAA C–NO_2), 87.2 (N–CH–N), 90.9 and 91.8 (CH of N–CH(*Ar*)-N), 106.4, 159.5, 161.7 and 162.6 (C_q of N–CH(*Ar*)–N), 128.5, 130.2 and 133.4 (CH of *Ph*C=N), 123.6 (C_q of *Ph*C=N), 163.4 (C=N). ^{195}Pt NMR in $CDCl_3$, δ (ppm): –2169 (600 Hz).

***trans*-Dichloro[2,3-dihydro-3-(2-furyl)-2-methyl-5-phenyl-1,2,4-oxadiazole-κN^4][7 - nitro - 1,3,5 - triazaadamantane-κN^1]platinum (5e).** Yield 69%. Elemental analysis calculated for $C_{20}H_{24}Cl_2N_6O_4Pt$: C 35.41; H 3.57; N 12.39; found: C 35.26; H 3.31; N 12.12. IR (selected bands), cm^{-1}: 3112, 3061, 2966, 2902 and 2880 w ν(C–H), 1634 m ν(C=N and C=C), 1538 ν(NO_2). ^{1}H NMR in $CDCl_3$, δ (ppm): 3.00 (s, br., 3H, NMe), 3.68 (d, 13.6 Hz, 2H) and 3.70 (d, 13.6 Hz, 2H)(TAA H_d and $H_{d'}$), 4.26 (s, 2H, TAA H_c), 3.90 (dm, 13.2 Hz, 1H) and 4.28 (d, 13.2 Hz, 1H)(TAA H_b and $H_{b'}$), 4.60 (dm, 12.8 Hz, 2H) and 4.84 (d, 12.8 Hz, 2H)(TAA H_a and $H_{a'}$), 5.99 (s, br., 1H, N–CH–N), 6.44 (dd, 3.3 Hz, 1.8 Hz, 1H), 6.77 (d, 3.2 Hz, 1H) and 7.50 (m, 1H)(furyl-H), 7.59 (t, 7.8 Hz, 2H), 7.70 (tm, 7.4 Hz, 1H) and 8.90 (dm, 7.3 Hz, 2H)(aryl-H of PhC=N). ^{13}C NMR in $CDCl_3$, δ (ppm): 46.8 (NMe), 58.3 (TAA C_d), 62.8 (TAA C_c), 71.6 (TAA C_b), 78.4 (TAA C_a), 72.9 (TAA C–NO_2), 87.9 (N–CH–N), 110.8, 111.3 and 143.9 (CH of N–CH(*furyl*)–N), 148.1 (C_q of N–CH(*furyl*)–N), 128.6, 130.6 and 134.2 (CH of *Ph*C=N), 122.4 (C_q of *Ph*C=N), 164.8 (C=N). ^{195}Pt NMR in $CDCl_3$, δ (ppm): –2187 (580 Hz).

***trans*-Dichloro[2,3-dihydro-3-ethoxycarbonyl-3-ethoxycarbonylmethyl-2-methyl-5-phenyl-1,2,4-oxadiazole-κN^4][7-nitro-1,3,5-triazaadamantane-κN^1]platinum (5f).** Yield 54%. Anal. Calcd for $C_{23}H_{32}Cl_2N_6O_7Pt$: C, 35.85; H, 4.19; N, 10.91. Found: C, 35.73; H, 3.99; N, 10.76. IR spectrum (selected bands), cm^{-1}: 2989, 2965 and 2935 w ν(C–H), 1742 s ν(C=O), 1628 m ν(C=N), 1536 ν(NO_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.26 (t, 7.2 Hz, 3H) and 1.35 (t, 7.2 Hz, 3H)(2 × OCH_2CH_3), 3.01 (s, 3H, NMe), 3.46 (d, 17.5 Hz, 1H) and 4.66 (d, 17.5 Hz, 1H)(CH_2), 4.26–4.32 (m, 4H)(2 × OCH_2CH_3), 3.71 (s, 4H)(TAA H_d and $H_{d'}$), 4.18 (d, 14.1 Hz, 1H) and 4.23 (d, 14.1 Hz, 1H)(TAA H_c), 3.92 (dm, 13.4 Hz, 1H) and 4.25 (d, 13.4 Hz, 1H)(TAA H_b and $H_{b'}$), 4.61 (dm, 13.2 Hz, 2H) and 4.85 (d, 13.2 Hz, 2H)(TAA H_a and $H_{a'}$), 7.61 ("t", 7.6 Hz, 2H), 7.72 (m, 1H) and 8.76 (d, 7.6 Hz, 2H)(N=C–Ph). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ (ppm): 14.0 and 14.2 (2 × OCH_2CH_3), 39.5 (CH_2), 42.0 (NMe), 61.5 and 62.9 (2 × OCH_2CH_3), 58.26 and 58.33 (TAA C_d), 62.7 (TAA C_c), 71.6 (TAA C_b), 78.2 (TAA C_a), 73.0 (TAA C–NO_2), 92.2 (N–C–N), 122.5 (C_q, N=CPh), 129.6 (CH, N=CPh), 131.2 (CH, N=CPh), 135.1 (CH, N≡CPh and N=CPh), 167.9 (C=N), 165.9 and 168.7 (C=O). ^{195}Pt NMR (107.3 MHz, $CDCl_3$) δ (ppm): –2168 (710 Hz).

***trans*-Dibromo[2,3-dihydro-3-(2-methoxyphenyl)-2-methyl-5-phenyl-1,2,4-oxadiazole-κN^4][7-nitro-1,3,5-triazaadamantane-κN^1]platinum (5g).** Yield 70%. Elemental analysis calculated for $C_{23}H_{28}Br_2N_6O_4Pt$: C 34.21; H 3.49; N 10.41; found: C 34.08; H 3.22; N 10.07. IR (selected bands), cm^{-1}: 3068, 2988, 2958 and 2920 ν(C–H), 2837 ν(C–H of OMe), 1631 m ν(C=N), 1534 ν(NO_2). ^{1}H NMR in $CDCl_3$, δ (ppm): 3.04 (s, br., 3H, NMe), 3.93 (s, 3H, OMe), 3.66 ("s", 4H, TAA H_d and $H_{d'}$), 4.29 ("s", 2H, TAA H_c), 3.88 (dm, 13.1 Hz, 1H) and 4.23 (d, 13.1 Hz, 1H)(TAA H_b and $H_{b'}$), 4.68 (dm, 13.2 Hz, 2H) and 4.81 (d, 13.3 Hz, 2H)(TAA H_a and $H_{a'}$), 6.26 (s, br., 1H, N–CH–N), 6.95 (d, 7.8 Hz, 1H), 7.00 (t, 7.8 Hz, 1H), 7.39 (td, 7.8 Hz, 1.5 Hz, 1H) and 7.50 ("s", br., 1H)(aryl-H of N–CH(Ar)–N), 7.59 (t, 7.6 Hz, 2H), 7.69 (t, 7.6 Hz, 1H) and 8.91 (dd, 7.8 Hz, 1.6 Hz, 2H)(aryl-H of PhC=N). ^{13}C NMR in $CDCl_3$, δ (ppm): 47.6 (NMe), 56.0 (OMe), 58.2 (TAA C_d), 64.3 (TAA C_c), 71.5 (TAA C_b), 80.38 and 80.45 (TAA C_a), 73.4 (TAA C–NO_2), 91.2 (N–CH–N), 111.3, 120.7, 129.4 and 131.2 (CH of N–CH(*Ar*)–N), 124.7 and 157.9 (C_q of N–CH(*Ar*)–N), 128.6, 130.6 and 133.8 (CH of *Ph*C=N), 123.3 (C_q of *Ph*C=N), 164.3 (C=N). ^{195}Pt NMR in $CDCl_3$, δ (ppm): –2471 (840 Hz).

***trans*-Dibromo[2,3-dihydro-3-(2,4-dimethoxyphenyl)-2-methyl-5-phenyl-1,2,4-oxadiazole-κN^4][7-nitro-1,3,5-triazaadamantane-κN^1]platinum (5h).** Yield 63%. Elemental analysis calculated for $C_{24}H_{30}Br_2N_6O_5Pt$: C 34.42; H 3.61; N 10.04; found: C 34.23; H 3.55; N 9.81. IR (selected bands), cm^{-1}: 3060, 3007 and 2938 ν(C–H), 2839 ν(C–H of OMe), 1630 and 1618 m ν(C=N and C=C), 1533 ν(NO_2). ^{1}H NMR in $CDCl_3$, δ (ppm): 3.02 (s, br., 3H, NMe), 3.82 (s, 3H) and 3.90 (s, 3H)(2 × OMe), 3.67 (s, 4H)(TAA H_d and $H_{d'}$), 4.29 (s, 2H, TAA H_c), 3.87 (dm, 13.5 Hz, 1H) and 4.25 (d, 13.5 Hz, 1H)(TAA H_b and $H_{b'}$), 4.69 (dm, 13.0 Hz, 2H) and 4.82 (d, 13.0 Hz, 2H)(TAA H_a and $H_{a'}$), 6.18 (s, br., 1H, N–CH–N), 6.49 (s, 1H), 6.51 (d, 8.2 Hz, 1H) and 7.43 ("s", br., 1H)(aryl-H of N–CH(Ar)–N), 7.58 (t, 7.5 Hz, 2H), 7.64 (m, 1H) and 8.89 (d, 7.3 Hz, 2H)(aryl-H of PhC=N). ^{13}C NMR in $CDCl_3$, δ (ppm): 47.3 (NMe), 55.5 and 55.9 (2 × OMe), 58.15 and 58.18 (TAA C_d), 64.2 (TAA C_c), 71.4 (TAA C_b), 80.26 and 80.34 (TAA C_a), 73.4 (TAA C–NO_2), 91.3 (N–CH–N), 98.9, 104.4 and 131.0 (CH of N–CH(*Ar*)–N), 117.2, 159.1 and 162.1 (C_q of N–CH(*Ar*)–N), 128.4, 130.4 and 133.6 (CH of *Ph*C=N), 123.3 (C_q of *Ph*C=N), 164.0 (C=N). ^{195}Pt NMR in $CDCl_3$, δ (ppm): –2467 (550 Hz).

***trans*-Dibromo[2,3-dihydro-3-(2,6-dimethoxyphenyl)-2-methyl-5-phenyl-1,2,4-oxadiazole-κN^4][7-nitro-1,3,5-triazaadamantane-κN^1]platinum (5i).** Yield 70%. Elemental analysis calculated $C_{24}H_{30}Br_2N_6O_5Pt$: C 34.42; H 3.61; N 10.04; found: C 34.18; H 3.48; N 9.79. IR (selected bands), cm^{-1}: 3052, 2966 and 2940 ν(C–H), 2838 ν(C–H of OMe), 1640 and 1605 m ν(C=N and C=C), 1534 ν(NO_2). ^{1}H NMR in $CDCl_3$, δ (ppm): 3.03 (s, 3H, NMe), 3.67 (s, 3H) and 4.05 (s, 3H)(2 × OMe), 3.65 (s, 4H)(TAA H_d and $H_{d'}$), 4.22 (d, 13.8 Hz, 1H) and 4.26 (d, 13.8 Hz, 1H)(TAA H_c), 3.86 (dm, 13.8 Hz, 1H) and 4.25 (d, 13.8 Hz, 1H)(TAA H_b and $H_{b'}$), 4.67 (dm, 13.0 Hz, 2H) and 4.79 (d, 13.0 Hz, 2H)(TAA H_a and $H_{a'}$), 6.66 (s, 1H, N–CH–N), 6.53 (d, 8.2 Hz, 1H), 6.66 (d, 8.0 Hz, 1H) and 7.33 (t, 8.1 Hz, 1H)(aryl-H of N–CH(Ar)–N), 7.57 (t, 7.6 Hz, 2H), 7.63 (m, 1H) and 8.85 (d, 7.6 Hz, 2H)(aryl-H of PhC=N). ^{13}C NMR in $CDCl_3$, δ (ppm): 48.5 (NMe), 56.0 and 56.8 (2 × OMe), 58.12 and 58.17 (TAA C_d), 64.1 (TAA C_c), 71.4 (TAA C_b), 80.19 and 80.22 (TAA C_a), 73.4 (TAA C–NO_2), 87.4 (N–CH–N), 104.0, 105.2 and 131.2 (CH of N–CH(*Ar*)–N), 113.2, 158.6 and 160.7 (C_q of N–CH(*Ar*)–N), 128.4, 130.3 and 133.4 (CH of *Ph*C=N), 123.4 (C_q of *Ph*C=N), 163.3 (C=N). ^{195}Pt NMR in $CDCl_3$, δ (ppm): –2478 (600 Hz).

***trans* - Dibromo[2,3 - dihydro - 3 - (2,4,6 - trimethoxyphenyl) - 2-methyl - 5 - phenyl - 1,2,4 - oxadiazole - κN^4][7 - nitro - 1,3,5-triazaadamantane-κN^1]platinum (5j).** Yield 65%. Elemental analysis

calculated for $C_{25}H_{32}Br_2N_6O_6Pt$: C 34.61; H 3.72; N 9.69; found: C 34.55; H 3.61; N 9.41. IR (selected bands), cm^{-1}: 2999, 2958 and 2938 ν(C–H), 2835 ν(C–H of OMe), 1640 m ν(C=N), 1533 $\nu(NO_2)$. ^1H NMR in $CDCl_3$, δ (ppm): 2.98 (s, br., 3H, NMe), 3.62 (s, 3H), 3.80 (s, 3H) and 4.01 (s, 3H)(3 × OMe), 3.65 (s, 4H)(TAA H_d and $H_{d'}$), 4.29 (d, 14.1 Hz, 1H) and 4.24 (d, 14.1 Hz, 1H)(TAA H_c), 3.86 (dm, 13.4 Hz, 1H) and 4.27 (d, 13.4 Hz, 1H)(TAA H_b and $H_{b'}$), 4.66 (dm, 13.2 Hz, 2H) and 4.78 (d, 13.2 Hz, 2H)(TAA H_a and $H_{a'}$), 6.52 (s, br., 1H, N–CH–N), 6.06 (s, 1H) and 6.20 (s, 1H)(aryl-H of N–CH(Ar)–N), 7.58 (t, 7.6 Hz, 2H), 7.62 (m, 1H) and 8.82 (d, 7.6 Hz, 2H)(aryl-H of PhC=N). ^{13}C NMR in $CDCl_3$, δ (ppm): 48.7 (NMe), 55.4, 55.9 and 56.8 (3 × OMe), 58.28 and 58.35 (TAA C_d), 64.7 (TAA C_c), 71.5 (TAA C_b), 80.2 (TAA C_a), 73.3 (TAA C–NO_2), 87.5 (N–CH–N), 90.8 and 91.7 (CH of N–CH(*Ar*)–N), 105.5, 159.4, 161.6 and 162.6 (C_q of N–CH(*Ar*)–N), 128.5, 130.4 and 133.4 (CH of *Ph*C=N), 123.6 (C_q of *Ph*C=N), 163.5 (C=N). ^{195}Pt NMR in $CDCl_3$, δ (ppm): –2477 (620 Hz).

***trans*-Dibromo[2,3-dihydro-3-(2-furyl)-2-methyl-5-phenyl-1,2,4-oxadiazole-κN⁴][7-nitro-1,3,5-triazaadamantane-κN¹]platinum (5k).** Yield 51%. Elemental analysis calculated for $C_{20}H_{24}Br_2N_6O_4Pt$: C 31.31; H 3.15; N 10.95; found: C 31.19; H 3.01; N 10.71. IR (selected bands), cm^{-1}: 3117, 3063, 2967 and 2887 w ν(C–H), 1632 and 1602 m ν(C=N and C=C), 1535 $\nu(NO_2)$. ^1H NMR in $CDCl_3$, δ (ppm): 3.01 (s, br., 3H, NMe), 3.67 (d, 13.6 Hz, 2H) and 3.69 (d, 13.6 Hz, 2H)(TAA H_d and $H_{d'}$), 4.32 (s, 2H, TAA H_c), 3.90 (dm, 13.2 Hz, 1H) and 4.28 (d, 13.2 Hz, 1H)(TAA H_b and $H_{b'}$), 4.67 (dm, 12.8 Hz, 2H) and 4.87 (d, 12.8 Hz, 2H)(TAA H_a and $H_{a'}$), 6.02 (s, br., 1H, N–CH–N), 6.44 (dd, 3.3 Hz, 1.8 Hz, 1H), 6.79 (d, 3.2 Hz, 1H) and 7.49 (m, 1H)(furyl-H), 7.59 (t, 7.8 Hz, 2H), 7.71 (tm, 7.4 Hz, 1H) and 8.90 (dm, 7.3 Hz, 2H)(aryl-H of PhC=N). ^{13}C NMR in $CDCl_3$, δ (ppm): 46.9 (NMe), 58.3 (TAA C_d), 63.8 (TAA C_c), 71.5 (TAA C_b), 80.2 (TAA C_a), 73.2 (TAA C–NO_2), 88.4 (N–CH–N), 110.8, 111.5 and 144.0 (CH of N–CH(*furyl*)–N), 148.0 (C_q of N–CH(*furyl*)–N), 128.6, 130.7 and 134.2 (CH of *Ph*C=N), 122.3 (C_q of *Ph*C=N), 164.7 (C=N). ^{195}Pt NMR in $CDCl_3$, δ (ppm): –2496 (720 Hz).

***trans*-Dibromo[2,3-dihydro-3-ethoxycarbonyl-3-ethoxycarbonylmethyl-2-methyl-5-phenyl-1,2,4-oxadiazole-κN⁴][7-nitro-1,3,5-triazaadamantane-κN¹]platinum (5l).** Yield 48%. Anal. Calcd for $C_{23}H_{32}Br_2N_6O_7Pt$: C, 32.14; H, 3.75; N, 9.78. Found: C, 32.11; H, 3.61; N, 9.55. IR spectrum (selected bands), cm^{-1}: 2991, 2963 and 2937 w ν(C–H), 1740 s ν(C=O), 1625 m ν(C=N), 1533 s $\nu(NO_2)$. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.24 (t, 7.2 Hz, 3H) and 1.36 (t, 7.2 Hz, 3H)(2 × OCH_2CH_3), 3.03 (s, 3H, NMe), 3.48 (d, 17.5 Hz, 1H) and 4.62 (d, 17.5 Hz, 1H)(CH_2), 4.27–4.33 (m, 4H)(2 × OCH_2CH_3), 3.71 (s, 4H)(TAA H_d and $H_{d'}$), 4.25 (d, 14.1 Hz, 1H) and 4.26 (d, 14.1 Hz, 1H)(TAA H_c), 3.93 (dm, 13.4 Hz, 1H) and 4.26 (d, 13.4 Hz, 1H)(TAA H_b and $H_{b'}$), 4.69 (dm, 13.2 Hz, 2H) and 4.90 (d, 13.2 Hz, 2H)(TAA H_a and $H_{a'}$), 7.61 ("t", 7.6 Hz, 2H), 7.72 (m, 1H) and 8.76 (d, 7.6 Hz, 2H)(N=C–Ph). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ (ppm): 14.1 and 14.3 (2 × OCH_2CH_3), 39.8 (CH_2), 42.2 (NMe), 61.5 and 62.9 (2 × OCH_2CH_3), 58.3 (TAA C_d), 64.1 (TAA C_c), 71.5 (TAA C_b), 80.2 (TAA C_a), 73.3 (TAA C–NO_2), 92.2 (N–C–N), 122.6 (C_q, N=CPh), 129.6 (CH, N=CPh), 131.3 (CH, N=CPh), 135.2 (CH, N≡CPh and N=CPh), 167.9 (C=N), 166.0 and 168.6 (C=O). ^{195}Pt NMR (107.3 MHz, $CDCl_3$) δ (ppm): –2480 (840 Hz).

Ligand substitution of the mixed triazaadamantane/oxadiazoline complex 5a.

A solution of **5a** (0.1 mmol) and pyridine (0.1 mmol) in chloroform (1 ml) was stirred at 37 °C for 96 h. The solvent was evaporated and the residual crude products were purified by chromatography on silica using CH_2Cl_2–ethyl acetate 98 : 2 as eluent.

***trans*-Dichloro[2,3-dihydro-3-(2-methoxyphenyl)-2-methyl-5-phenyl-1,2,4-oxadiazole-κN⁴][pyridine-κN¹]platinum (7a).** Yield 69%. Elemental analysis calculated for $C_{21}H_{21}Cl_2N_3O_2Pt$: C 41.12; H 3.45; N 6.85; Pt 31.80; found: C 40.99; H 3.39; N 6.59. TGA (residue) Pt 32.23. IR (selected bands), cm^{-1}: 3066, 2999, 2964 and 2924 ν(C–H), 2838 ν(C–H of OMe), 1628 and 1605 m ν(C=N, C=C). ^1H NMR in $CDCl_3$, δ (ppm): 3.05 (s, 3H, NMe), 3.73 (s, br., 3H, OMe), 6.41 (s, br., 1H, N–CH–N), 6.87 (d, 8.1 Hz, 1H), 6.81 (t, 7.8 Hz, 1H), 7.35 (m, 1.5 Hz, 1H) and 7.82 ("s", br., 1H)(aryl-H of N–CH(Ar)–N), 7.23 (t, 6.6 Hz, 2H), 7.74 (m, 1H), 7.82 (d, 6.8 Hz, 2H)(pyridine), 7.48 (t, 7.6 Hz, 2H), 7.67 (t, 7.7 Hz, 1H) and 9.23 (dd, 7.8 Hz, 1.8 Hz, 2H)(aryl-H of PhC=N). ^{13}C NMR in $CDCl_3$, δ (ppm): 47.7 (NMe), 56.1 (OMe), 91.5 (N–CH–N), 112.0, 121.1, 129.3 and 131.1 (CH of N–CH(*Ar*)–N), 124.8 and 158.0 (C_q of N–CH(*Ar*)–N), 125.1, 129.7 and 153.3 (CH, pyridine), 129.2, 130.8 and 133.9 (CH of *Ph*C=N), 123.1 (C_q of *Ph*C=N), C=N not detected. ^{195}Pt NMR in $CDCl_3$, δ (ppm): –2025 (940 Hz).

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