Scientific paper

Design and Evaluation of Biological Activity of Diazenecarboxamide-extended Cisplatin and Carboplatin Analogues

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Dedicated to Professor Slovenko Polanc on his 65th birthday.

Abstract

Construction of a library of structurally diverse diazenecarboxamide-extended *cis*-[Pt(2-picolyl-1,2,3-triazole)Cl_2] and *cis*-[Pt(propan-1,3-diamine)CBDCA] (CBDCA = 1,1-cyclobutanedicarboxylate) complexes **1**–**4** is described. These compounds retain oxidative properties of parent diazenecarboxamides against glutathione as demonstrated by NMR spectroscopy and high resolution mass spectrometry experiments. Cytotoxic activity of **1**–**4** was investigated against human cervical carcinoma HeLa cells. Four library members were found to possess moderate cytotoxic activity. Some model compounds were also examined, returning [$PtCl_2L_2$] (L = 1-(2-picolyl)-4-phenyl-1*H*-1,2,3-triazole) as the most potent under this investigation with IC_{50} of 19.05 μM, comparable to that of cisplatin (IC_{50} = 16.3 μM).

Keywords: Cisplatin, carboplatin, diazenecarboxamide, glutathione, anti-cancer activity

1. Introduction

Cisplatin, *cis*-[diamminedichloridoplatinum(II)] (Figure 1), has been clinically approved for many years to be used as a single agent or in combination with other anti-cancer drugs to treat solid tumors including lung carcinoma, cervical carcinoma, head and neck tumors, as well as carcinoma of ovaries, bladder and testis.[1] Despite the fact that it is one of the most effective and commonly used agents, nephro-, neuro- and ototoxicities are the main side effects of this drug.[2] Its major obstacle to successful chemotherapy, significantly reducing the effectiveness of the cancer treatment, is development of cisplatin-resistance in tumors. Cisplatin-resistance is multifactorial, i.e. it is based on several molecular mechanisms.[3] Among others, it can emerge as a result of increased inactivation of cisplatin by intracellular thiol-containing molecules, such as glutathione (GSH).[3a,b] Increased GSH level may cause resistance by binding/inactivating cisplatin, enhancing DNA repair or reducing cisplatin-induced oxidative stress.[3c] Glutathion-S-transferase (GST) may augment the resistance by catalyzing GSH-cisplatin binding. The increased expression of GST along with elevated GSH level in resistant tumor cells suggests that the increased inactivation of cisplatin contributes significantly to the resistance phenotype.[3a,b]

In so advanced diseases such as cancer it is unlikely that a single mono functional targeted drug would be sufficient to cure the cancer. Combined drugs (cocktails) that impact multiple targets simultaneously are better at controlling complex disease systems and are the standard of care in cancer treatment.[4] In order to further improve the efficiency of using a two-drug cocktail, one approach involves the use of the so-called hybrid molecules, which comprises the incorporation of two drugs covalently bound into a single entity that combines pharmacological effects of independently acting drugs.[4,5] For such molecules, it has been even demonstrated that superior synergistic effects can be achieved that is beyond mere simultaneous administration of two separate agents.[6] An important example of hybrid molecules in

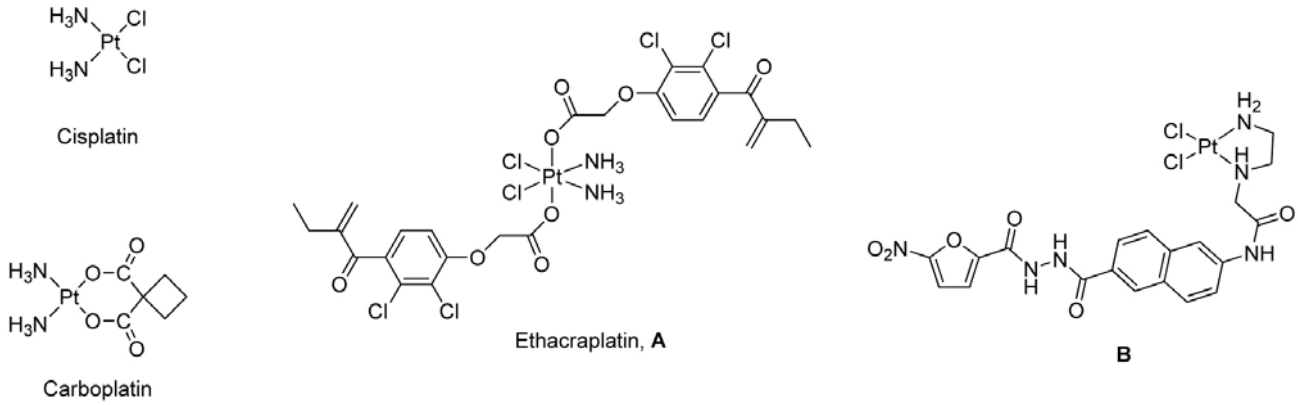


Figure 1. The structure of cisplatin, carboplatin and selected hybrid molecules.

the field of metal-based anticancer drugs includes the development of platinum complexes having bioactive carrier ligands, which are capable to revert resistances that tumor cells acquire during chemotherapy. This has been exemplified by ethacraplatin (**A**, Figure 1) in which GST-inhibitory ethacrynic acid was attached to the platinum,[7] as well as platinum complexes of nitrofuran carbohydrazide (**B**, Figure 1),[8] which is a human thioredoxin reductase inhibitor.

We have shown previously that diazenecarboxamides[9] (Figure 2) are cytotoxic for different tumor cell lines and act synergistically with cisplatin.[10] These compounds are powerful modulators of intracellular GSH concentration.[10a,c,e] In a combined (cocktail) diazenecarboxamide–cisplatin treatment, the GSH-depleting diazenecarboxamides led to the reversal of the acquired tumor resistances. The synergistic effect with cisplatin was shown on different tumor-cell lines as well as some cisplatin-resistant sublines.[10c,i,11] Besides the GSH-depleting activity, in selected examples an activation some alternative cell-death pathways has been observed, indicating that GSH may not be the only cellular target of diazenecarboxamides.[10h]

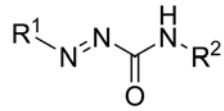
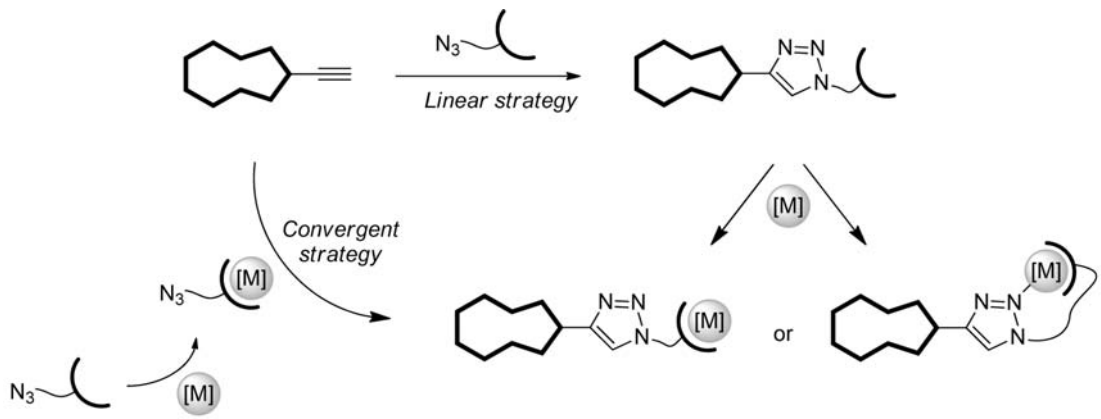


Figure 2. Diazenecarboxamides

The above results prompted design and screening an array of different diazenecarboxamide-extended platinum complexes. For these hybrid molecules a dual targeting that combines the advantages of diazenecarboxamide and cisplatin (and carboplatin) structural motif is expected. However, the synthesis of a diverse library of ligand-arm functionalized diazenecarboxamides that are capable of binding to platinum(II), as well as the corresponding complexes, is expected to be cumbersome and associated with redesign of synthetic routes for any specific type of the molecule. To increase the efficacy of the preparation of such a library of compounds we[12–15]and others[16] developed strategies that are based on recently discovered copper-catalyzed azide-alkyne cycloaddition protocol,[17,18] also known as "Click chemistry", as outlined in Scheme 1.[19]



Scheme 1. Schematic representations of the linear strategy *versus* the convergent strategy.

Figure 3. Diazenecarboxamide-extended platinum complexes

2. Results and Discussion

We have designed and prepared four types of diazenecarboxamide-extended platinum complexes, which differ in *i.* functionality R, *ii.* ligand arm that coordinates to platinum and consequently *iii.* platinum(II) coordination environment, and *iv.* linker that joins the diazenecarboxamide and complex parts together (Figure 3). Briefly, it has been demonstrated that the oxidative properties of diazenecarboxamides can be modulated through the choice of group R attached directly to the diazene –N=N– moiety,[20] whereas specific hydrolytic and coordinative properties towards DNA of tumor cells can be tuned by ligand variation around platinum center. Finally, through the choice of the linker, one can in principle adjust the lipophilicity of the compound, an important pharmacological characteristic that correlates with cellular uptake of a drug.[21]

The syntheses of compounds **1**–**4** were accomplished through the strategies shown in Scheme 1.[12–15] More specifically, the synthetic routes are outlined in Scheme 2.

Following the linear strategy shown in Scheme 1 propargyl functionalized diezenecarboxamides **5** were by copper-catalyzed azide-alkyne cycloaddition ("Click chemistry") with picolyl azide transformed into the corresponding picolyl-triazole derivatives **6** (Scheme 2).[12,15] Although the power of this strategy lies in potential combinatorial approach to diazenecarboxamides, conjugated with different ligand-arms, by using different organoazides, at this point of the research we only used picolyl azide as a "click" partner. In the final stage, the ability of picolyl-triazole group at **6** to serve as bidentate ligand[22,23] was employed to access the desired platinum-diazenecarboxamide conjugates **1** and **2** of *cis*-[Pt(diamine)Cl_2] structure.[13]

Concerning the coordination chemistry, this is a "classical" strategy, which considers the ligand to metal coordination at the very last step. The major drawback of this linear strategy is a potential redesign of synthetic routes for any specific type of the ligand. Alternatively, convergent strategy relies on the post-functionalization of metal complexes with the introduction of specific features

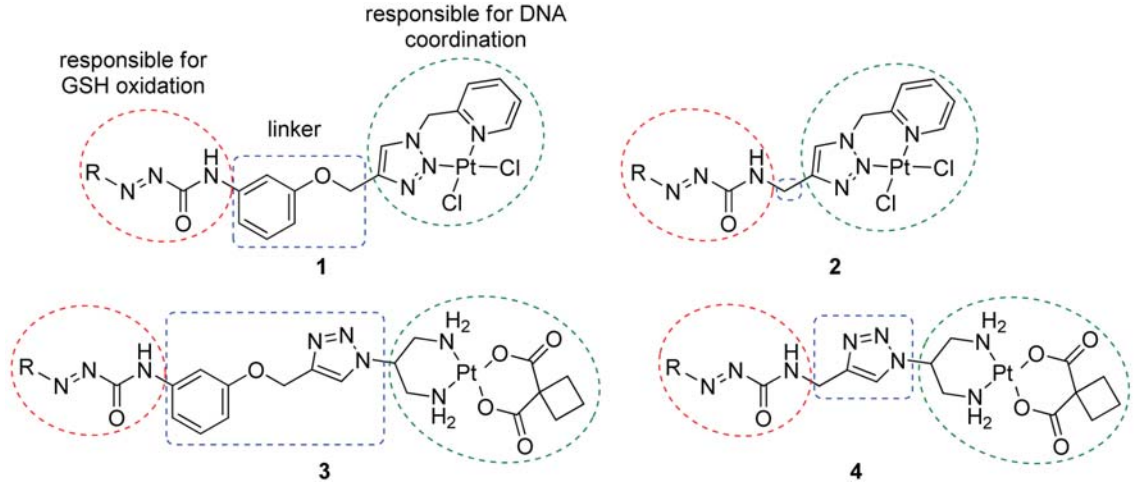
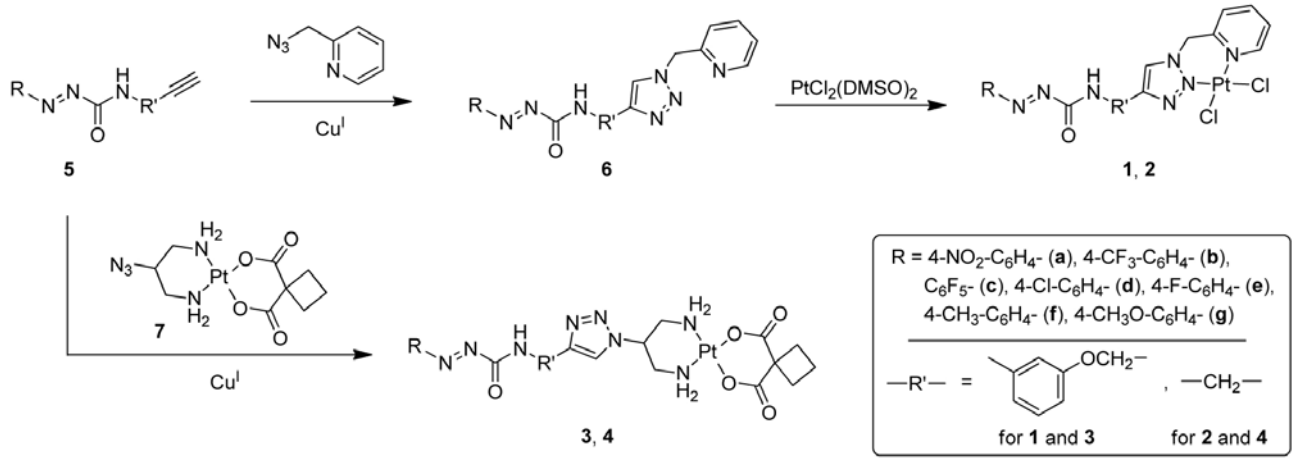


Figure 3. Diazenecarboxamide-extended platinum complexes.

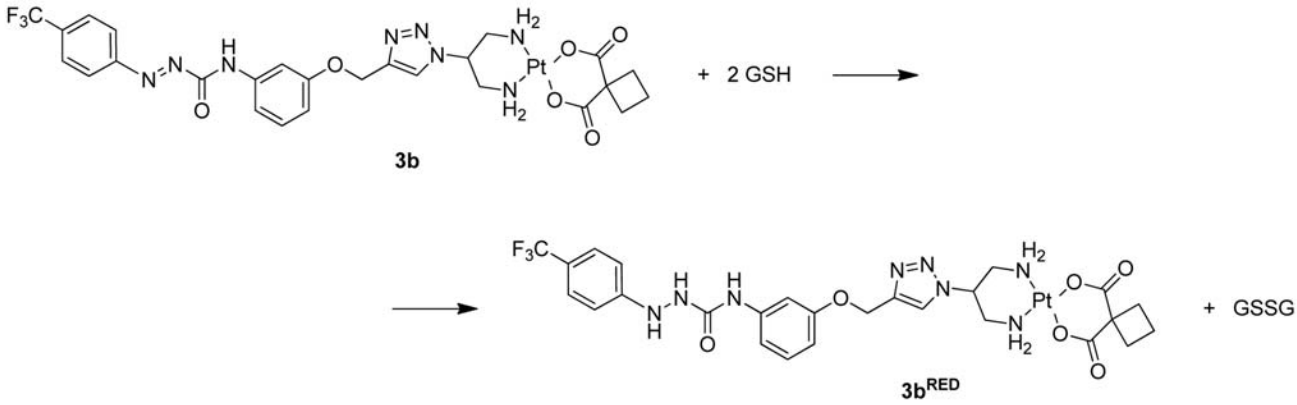


Scheme 2. Selected details showing the preparation of diazenecarboxamide-extended platinum complexes **1**–**4** using the strategies presented in Scheme 1.

at the very last step (Scheme 1). Following this convergent strategy, "click" reaction between propargyl functionalized diezenecarboxamides **5** and azide-tagged platinum(II) complex **7** allowed post-functionalization directly into the metalated "click" cycloadducts **3** and **4** of structure *cis*-[Pt(diamine)CBDCA] (CBDCA = 1,1-cyclobutanedicarboxylate) (Scheme 2).[14]

The oxidative properties of diazenecarboxamide moiety in complexes **1**–**4** towards GSH is preserved as demonstrated by the following experiment. Compound **3b** and slight excess of GSH (3.7 mol equiv.) were dissolved in a mixture of DMF-d_7 and D_2O at 23 °C. The progress of the reaction shown in Scheme 3 was monitored by ^{1}H NMR spectroscopy. Figure 4 demonstrates clean and fast transformation of diazenecarboxamide **3b** and GSH into semicarbazide **3b**$^{\mathbf{RED}}$ and GSSG. The resulting reaction mixture after the NMR experiment was analyzed by ESI+ LC-MS spectrometry, which confirmed the presence of semicarbazide **3b**$^{\mathbf{RED}}$ (*m/z* found for $C_{26}H_{30}F_3N_8O_6Pt^+$ $[M + H]^+ = 802.1886$) and GSSG (See Experimental).

To ascertain the oxidative properties of **3b** under biological conditions, it was incubated with GSH (4.4 mol equiv.) in a mixture of DMSO and growth medium supplemented with 10% fetal serum (Experimental). Similar conditions were used for determination of **3b** cytotoxicity (vide infra). Analysis of the reaction mixture by ESI+ LC-MS revealed nearly quantitative conversion of **3b** into **3b**$^{\mathbf{RED}}$ within 3.5 hours.



Scheme 3. Oxidation of GSH with diazenecarboxamide **3b** into GSSG and semicarbazide **3b**$^{\mathbf{RED}}$.

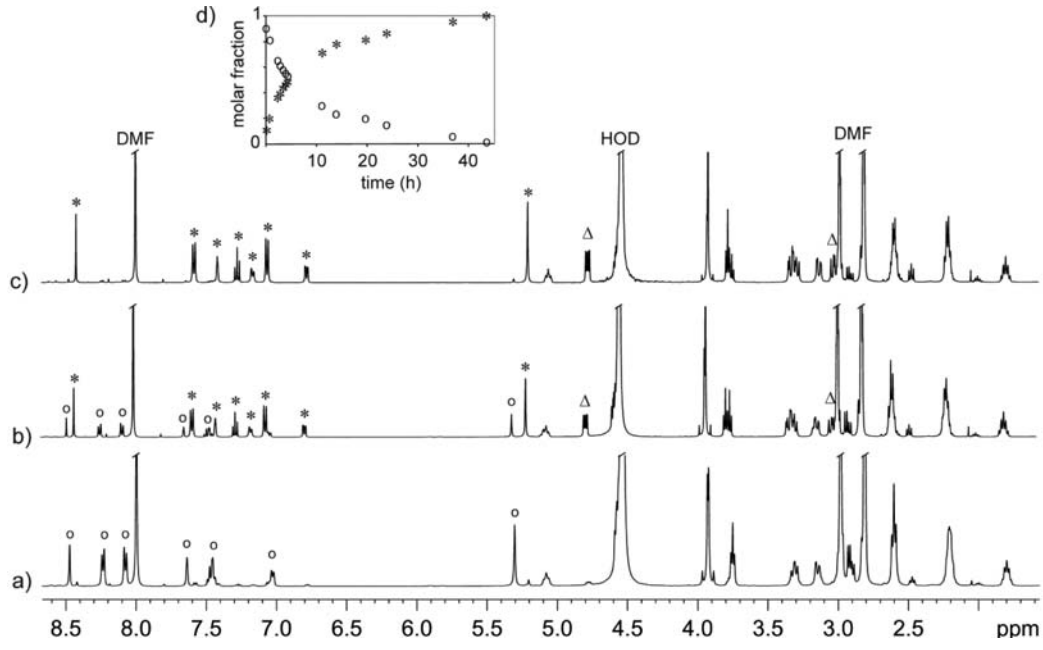


Figure 4. Monitoring the course of the reaction from Scheme 3 between **3b** (6.7 mM) and GSH (24.7 mM) in a mixture of DMF-d_7 (0.50 mL) and D_2O (0.25 mL) at 23 °C by ^{1}H NMR spectroscopy. Spectra shown after a) 6 min, b) 11 h, and c) 43 h of the reaction. Well separated resonances of **3b** (o), **3b**$^{\mathbf{RED}}$ (*), and GSSG (Δ) are indicated. Diagram d) shows the progress of the reaction as determined by integration of resonances of **3b** and **3b**$^{\mathbf{RED}}$.

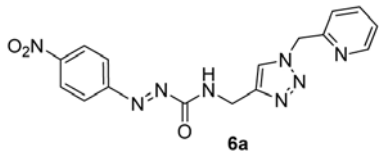
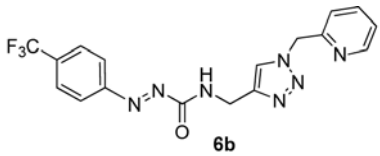
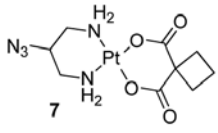
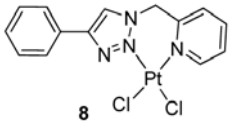
Compounds **1–4** were tested using MTT assay for their *in vitro* anticancer activity against human cervical carcinoma HeLa cells (see Experimental section for details). The results for compounds **1** and **2** (Table 1) with *cis*-[diamminedichloroplatinum(II)] coordination sphere were compared to cisplatin (Table 2). In analogy, the results for compounds **3** and **4** with *cis*-[Pt(diamine) CBDCA] structure were compared to carboplatin. Compounds **2a** and **2b** having strongly electron-withdrawing *p*-nitrophenyl and *p*-(trifluoromethyl)phenyl substituents attached to the diazene –N=N– group were quite cytotoxic. Interestingly, this was not the case for **3a** and **3b** from the carboplatin-like series, where **3d** and **4e** were the most active compounds.

In attempt to experimentally evaluate this idea of combining separate components into hybrid molecules **1–4**, cytotoxic activities of compounds **6a**, **6b**, **7** and **8** were determined. The results are summarized in Table 2. *cis*-[Pt(2-azidopropan-1,3-diamine)CBDCA] (**7**) proved to be inactive. Unexpectedly, uncoordinated picolyl-triazole functionalized diazenecarboxamides **6a** and **6b** (IC_{50} = 22.33 μM and 162.40 μM, respectively) as well as model [Pt(picolyl-triazole)Cl_2] complex **8** (IC_{50} = 19.05 μM) were all more active than the corresponding hybrids **2a** and **2b** (IC_{50} = 78 μM and 277 μM). The activity of **8** was in the range of cisplatin (IC_{50} = 16.3 μM).

Table 1. Cytotoxic activity of complexes **1–4** against cervical carcinoma HeLa cells expressed as IC_{50} values (μM) obtained after 72 h incubation.

R	1	IC_{50}	2	IC_{50}	3	IC_{50}	4	IC_{50}
4-NO_2-C_6H_4-	**1a**	>300	**2a**	87	**3a**	>1000		
4-CF_3-C_6H_4-	**1b**	300	**2b**	277	**3b**	>1000		
C_6F_5-	**1c**	>300						
4-Cl-C_6H_4-	**1d**	>300	**2d**	>300	**3d**	614 ± 161.9		
4-F-C_6H_4-			**2e**	>300			**4e**	649.6
4-CH_3-C_6H_4-							**4f**	>1000
4-CH_3O-C_6H_4-							**4g**	990

Table 2. Cytotoxic activity of cisplatin, carboplatin, **6a**, **6b**, **7**, and **8** against cervical carcinoma HeLa cells expressed as IC_{50} values (μM) obtained after 72 h incubation.

Compound	IC50 (μM)
Cisplatin	16.3 ± 3.6
Carboplatin	441.1 ± 91.8
 **6a**	22.33 ± 3.19
 **6b**	162.40 ± 21.98
 **7**	>1000
 **8**	19.05

In an easy explanation for severely reduced activity of **1–2** when coming from their "parent" compounds **6** and **8** is impossible but it could be a result of change in lipophilicity, molecular size, shape, etc.[24] Before these factors are taken into the consideration, however, the issue of solubility has to be addressed first as compounds **1–4** are completely insoluble in water.

3. Conclusions

We have demonstrated a design of a library of diazenecarboxamide-extended cisplatin and carboplatin analogues. The advantage of this strategy is modular, combinatorial approach, taking advantages of "Click chemistry" and offering timely preparation of organic-inorganic conjugates in general. The library was designed and evaluated for improved efficiency in antitumor therapy. Although several members were quite cytotoxic, in contrast to expectations, none performed better than carboplatin or cisplatin. This can be due to their limited solubility. Work is in progress to diazenecarboxamide-extended cisplatin and carboplatin analogues with improved water solubility.

4. Experimental

4. 1. General

Cisplatin, carboplatin and NMR solvents were used as obtained from commercial sources (Sigma-Aldrich,

USA). Compounds **1**,[13] **2**,[13] **3**,[14] **4**,[14] **5**,[15] **6**,[22] and **7**[14] and **8**[22] were prepared as described in the literature. NMR spectra were measured on a Bruker Avance III 500 spectrometer, using $Si(CH_3)_4$ as internal standard. ESI+ HRMS spectra were recorded with Agilent 6224 Accurate Mass TOF LC/MS system.

4. 2. NMR and HRMS Experiments

a) Monitoring the course of the reaction between **3b** and GSH in DMF-d_7/D_2O:

A mixture of **3b** (4.0 mg, 0.0014 mmol) and GSH (5.7 mg, 0.0185 mM) was dissolved in DMF-d_7 (0.50 mL) and D_2O (0.25 mL). The reaction mixture was kept at 23 °C and ^1H NMR spectra were recorded at the same temperature at the times indicated in Figure 4d. Resonances of **3b**,[14] **3b^{RED}**, GSH and GSSG were assigned on the basis of literature data and 2D ^1H-^1H COSY spectra of the reaction mixture. After 44 h a drop of the reaction mixture was dissolved in 0.1% formic acid in Milli-Q water (1 mL) and left for 24 h to allow complete deuterium exchange. HRMS spectrum was recorded, which revealed unreacted GSH, GSSG and **3b^{RED}** (*m/z* found: 802.1886. Calcd. for $C_{26}H_{30}F_3N_8O_6Pt^+$ $[M + H]^+$ = 802.1890).

b) Monitoring the course of the reaction between **3b** and GSH in a mixture of DMSO and growth medium with fetal serum:

A mixture of **3b** (1.1 mg, 0.0014 mmol) and GSH (1.9 mg, 0.00618 mmol) was dissolved in DMSO (0.50 mL), diluted with growth medium supplemented with 10% fetal serum (0.20 mL) and kept at 23 °C. The reaction was followed by dissolving an aliquot (one drop) in acetonitrile (1 mL) and measuring HRMS spectra.

4. 3. Cells

Human cervical carcinoma HeLa cells were obtained from cell culture bank (GIBCO BRL, Invitrogen, Grand Island, USA). They were cultured as a monolayer culture according in Dulbecco's medium supplemented with 10% fetal serum (Gibco BRL, Invitrogen, USA) and cultured in a humidified atmosphere of 5% CO_2 at 37 °C.

4. 4. Compounds

Carboplatin and cisplatin were dissolved in water whereas compounds **1**–**8** were dissolved in DMSO. They were and stored at –20 °C, and diluted to the appropriate concentrations with growth medium just before use.

4. 5. Cytotoxicity Assay

Cytotoxic effect of compounds under investigation was determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (Sigma Aldrich, USA) assay, modified as described. Cells were seeded into 96-well tissue culture plates (3000 cells/0.18 mL medium/well). Different concentrations of new compounds were added (0.02 mL) to each well on the following day. Each concentration was tested in quadruplicate. Following 72 h incubation at 37 °C, the medium was aspirated, and 20 mg of MTT dye/0.04 mL medium/well was added. Four hours later, formazan crystals were dissolved in DMSO (0.17 mL/well), the plates were mechanically agitated for 5 min and the optical density at 545 nm was determined on a microtiter plate reader (Awareness Technology Inc, Palm City, FL). Each experiment was repeated three times.

5. Acknowledgments

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Povzetek

Opisali smo knjižnico strukturno različnih *cis*-[Pt(2-pikolil-1,2,3-triazol)Cl_2] in *cis*-[Pt(propan-1,3-diamin)CBDCA] (CBDCA = 1,1-ciklobutandikarboksilat) kompleksov **1**–**4**, funkcionaliziranih z diazenkarboksamidno skupino. Te spojine ohranjajo oksidativne sposobnosti diazenkarboksamidov do glutationa, kar smo dokazali na osnovi NMR in HRMS eksperimentov. Citotoksičnost spojin **1**–**4** smo testirali na humanih tumorskih celicah materničnega vratu HeLa. Štiri spojine so pokazale zmerno aktivnost. Prav tako smo testirali nekatere modelne spojine, od katerih je bil [$PtCl_2L_2$] (L = 4-fenil-1-(2-pikolil)-1*H*-1,2,3-triazol) najbolj aktiven z IC_{50} = 19.05 μM, kar je primerljivo z aktivnostjo cisplatina (IC_{50} = 16.3 μM).