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Design, synthesis and comparative cytotoxic investigation of platinum(II) complexes with some derivatives of 5-methyl-5-(4-pyridyl)hydantoin

Adriana Bakalova [a,*], Rossen Buyukliev [a], Hristo Varbanov [b], Georgi Momekov [c]

[a] Medical University of Sofia, Faculty of Pharmacy, Department of Chemistry, Sofia, Bulgaria
[b] University of Vienna, Faculty of Chemistry, Institute of Inorganic Chemistry, Vienna, Austria
[c] Medical University of Sofia, Faculty of Pharmacy, Department of Pharmacology, Pharmacotherapy and Toxicology, Sofia, Bulgaria

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ABSTRACT

A series of Pt(II) complexes with 3-ethyl-5-methyl-5-(4-pyridyl)hydantoin, 3-propyl-5-methyl-5-(4-pyridyl)hydantoin and 3-benzyl-5-methyl-5-(4-pyridyl)hydantoin with general formulae *cis*-$[Pt(L)_2Cl_2]$, *cis*-$[Pt(NH_3)LCl_2]$ and *trans*-$[Pt(NH_3)LCl_2]$ were synthesized.

The new compounds were characterized by means of elemental analysis, IR, ^1H and ^{13}C NMR spectroscopy. The studies showed that the ligands coordinate to the platinum ions in a monodentate manner through the nitrogen atom from the pyridine ring. The cytotoxic activity *in vitro* of the complexes as well as of their previously prepared Pt(II) analogues with other derivatives of 5-methyl-5-(4-pyridyl)hydantoin was screened against a panel of human tumor cell lines. Cytotoxicity was strongly dependent on their lipophilicity, while the most lipophilic Pt(II) complex, carrying 3-benzyl-5-methyl-5-(4-pyridyl)hydantoin as carrier ligand inhibited the viability of tested cells at low micromolar concentrations with IC_{50} values comparable to that of cisplatin. A preliminary pharmacodynamic investigation showed that its cytotoxicity is mediated through induction of apoptosis. The *cis*- and *trans*-analogues consisting one ammine group in the molecules exhibited far less cytotoxicity in corroboration to the well established structure–activity rules for dia(m)mine platinum(II) complexes.

1. Introduction

The serendipitous discovery of the cytotoxic activity of cisplatin and its further clinical success in the therapy of various cancers has led researchers worldwide to investigate the antitumor potential of thousands of platinum and other metal-containing compounds [1–6]. The generation of new platinum complexes was based on early structure–activity relationships, which stated that potentially active complexes should be neutral and contain two inert amine/ammine ligands in *cis*-orientation and two semilabile leaving groups [7–9]. Beside cisplatin, over twenty platinum compounds have been tested in clinical trials. However, only few (e.g. carboplatin and oxaliplatin) received worldwide approval for clinical practice, while nedaplatin, lobaplatin and heptaplatin gained regional clinical approval [10]. Main problems, associated with the existing platinum-based chemotherapy are severe side effects, such as nephrotoxicity, neurotoxicity, and emetogenesis [6] and drug resistance [11]. Therefore, development of new platinum-based drugs, which can overcome the mentioned limitations, remains a main focus of current anticancer research [12–16].

Recently, interest was directed towards the development of cisplatin analogues which possess N-heterocyclic carrier ligands, coordinated to the cytotoxic platinum(II) moiety, instead of one or both of the am(m)ines. A number of platinum(II) complexes with benzimidazole, benzoxazole, imidazole, thiazole or benzoxazole, which demonstrated significant cytotoxicity have been reported in literature [6]. Furthermore, compounds of the type $[PtL(NH_3)Cl_2]$, where L is a pyridine derivative have shown enhanced activity in cisplatin resistant cell lines. Picoplatin, (SP-4-3)-amminedichlorido(2-methylpyridine)platinum(II)), for instance, has demonstrated anticancer activity in cell lines, resistant to the clinically applied platinum drugs as well as in tumor models *in vivo*. At the moment, it is in various phase II clinical trials [10,17,18].

Alternatively, cytotoxic platinum complexes, featuring N-heterocyclic carrier ligands with their own pharmacological activity, e.g. hydantoin derivatives were developed [19–22].

* Corresponding author. Address: Department of Chemistry, Faculty of Pharmacy, Medical University of Sofia, 2 Dunav Str., 1000 Sofia, Bulgaria. Tel.: +359 2 9236578; fax: +359 2 9879874.
E-mail address: adrigebk@abv.bg (A. Bakalova).

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Lipophilicity is one of the most important factors that have influence on drugs' biological activity [23,24]. Structure–cytotoxicity relationship studies revealed that for many compounds increased lipophilicity is often accompanied by increased cytotoxicity [25]. Taking into account our previous experience with cytotoxic platinum(II) complexes, carrying hydantoin ligands [26,27] and the approach for increasing lipophilicity via alkylation, herein we have prepared more lipophilic 3-subsituted-5-methyl-5-(4-pyridyl) hydrations and their Pt(II) complexes. The present study represents the synthesis, physicochemical evaluation and pharmacological investigation of three new Pt(II) complexes with 3-ethyl-5-methyl-5-(4-pyridyl)hydantoin (**4**), 3-propyl-5-methyl-5-(4-pyridyl)hydantoin (**5**) and 3-benzyl-5-methyl-5-(4-pyridyl)hydantoin (**6**) with general formula *cis*-[Pt(L)$_2$Cl$_2$]. Two new mixed am(m)ine Pt(II) complexes with 3-propyl-5-methyl-5-(4-pyridyl)hydantoin (**L5**) as ligand in *cis*- and *trans*-position with chemical formulae *cis*-[Pt(NH$_3$)(L5)Cl$_2$] (**5a**) and *trans*-[Pt(NH$_3$)(L5)Cl$_2$] (**5b**) were also synthesized and studied. All obtained platinum complexes were chemically and pharmacologically examined in comparison with previously synthesized and published Pt(II) complexes with 3-amino-5-methyl-5-(4-pyridyl)hydantoin, 5-methyl-5-(4-pyridyl)hydantoin, 3,5-dimethyl-5-(4-pyridyl)hydantoin, (**1**–**3**) and the clinically applied drug cisplatin [20,26,27]. General scheme of the investigated compounds is shown in Fig. 1.

2. Experimental

2.1. Materials and physical measurements

Potassium tetrachloroplatinate(II) utilized for the synthetic procedures was purchased from Merck – Germany, potassium threechloridoammineplatinate(II) – from Aldrich – USA and *cis*-dichloridodiammineplatinum(II) – from Fluka – Switzerland. All other chemicals were of analytical grade.

The newly synthesized Pt(II) complexes with 3-ethyl-5-methyl-5-(4-pyridyl)hydantoin, 3-propyl-5-methyl-5-(4-pyridyl)hydantoin and 3-benzyl-5-methyl-5-(4-pyridyl)hydantoin were characterized by elemental analysis, IR, ^{1}H, ^{13}C NMR spectra.

The carbon, nitrogen and hydrogen contents of the compounds were determined by elemental analysis, carried out on a "EuroEA EuroVector apparatus.

The IR spectra were recorded on Thermo Scientific Nicolet iS10 spectrophotometer in the range of 4000–400 as pellets KBr and on IFS 113 v Bruker FTIR spectrophotometer in the range of 400–150 cm^{-1} in polyethylene. Intensities of reported IR bands are defined as br = broad, s = strong, m = medium, and w = weak. The ^{1}H and ^{13}C NMR spectra were registered on a Bruker WM 250 (250 MHz) spectrometer in DMSO-d$_6$. The splitting of proton resonances in the ^{1}H NMR spectra is defined as s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet and m = multiplet (see Fig. 1 for NMR numbering scheme). Corrected melting points were determined, using a Bushi 535 apparatus.

Lipophilicity of the investigated compounds (**1**–**6**) was estimated by calculation of the log*P* values of the carrier heterocyclic ligands (**L1**–**L6**), using the ALOGPS 2.1 applet [28]. In addition, the extended version of ALOGPS, especially parameterized for Pt(II) complexes, was employed for prediction of the log*P* values of the complexes [29].

2.2. Synthesis of the Pt(II) complexes

2.2.1. Preparation of cis-dichlorido-bis(3-ethyl-5-methyl-5(4-pyridyl)hydantoin)platinum(II) – cis-[Pt(L4)$_2$Cl$_2$]·H$_2$O (*4*)

Water/ethanol solution of **L4** (0.2766 g, 1.4482 mmol) was added dropwise to water solution of K$_2$[PtCl$_4$] (0.1000 g, 0.2410 mmol) at constant stirring. After the addition of the ligand, the homogenous solution was stirred for 5–6 h at room temperature. Subsequently, the reaction mixture was concentrated and cooled to 4 °C. The obtained yellow precipitate was filtered off, washed several times with diethyl ether and dried in a vacuum desiccator. The product is soluble in DMSO and slightly soluble in water and ethanol. Purity is proved by thin layer chromatography with the eluent CH$_3$COOC$_2$H$_5$/C$_2$H$_5$OH – 2:1 and elemental analysis. Yield: ca. 36%, m.p.: >219 °C (dec.). IR (KBr disc. and polyethylene): 3503 br, 3312 br, 1785 m, 1716 s, 1620 m, 364 br, 336 br; ^{1}H NMR (DMSO-d$_6$, δ, ppm): 9.02 (s, NH-1); 8.83 (d, 2H, *J* = 7.1 Hz, H-2 + H-6); 7.61 (d, 2H, *J* = 7.1 Hz, H-3 + H-5); 3.40 (q, 2H, *J* = 7.5 Hz, N–*CH*$_2$); 1.67 (s, 3H, CH$_3$– C-5′); 1.06 (t, 3H, *J* = 7.5 Hz, N–CH$_2$–*CH*$_3$); ^{13}C NMR (DMSO-d$_6$, δ, ppm): 173.2 (C=O – 4′); 156.0 (C=O – 2'); 153.6 (C-2 + C-6); 150.0 (C-4); 123.0 (C-3 + C-5); 62.2 (C-5′); 33.3 (N–*CH*$_2$); 24.6 (CH$_3$–C-5′); 13.1 (N–CH$_2$–*CH*$_3$). *Anal.* Calc. for [Pt(C$_{11}$H$_{13}$N$_3$O$_2$)$_2$Cl$_2$]·H$_2$O: C, 36.57; H, 3.91; N, 11.63. Found: C, 36.29; H, 4.17; N, 11.64%.

2.2.2. Preparation of cis-dichlorido-bis(3-propyl-5-methyl-5-(4-pyridyl)hydantoin)platinum(II) – cis-[Pt(L5)$_2$Cl$_2$]·2H$_2$O (*5*)

The complex *cis*-[Pt(L5)$_2$Cl$_2$]·2H$_2$O (**5**) was synthesized analogously to the procedure for complex **4**. The compound is soluble

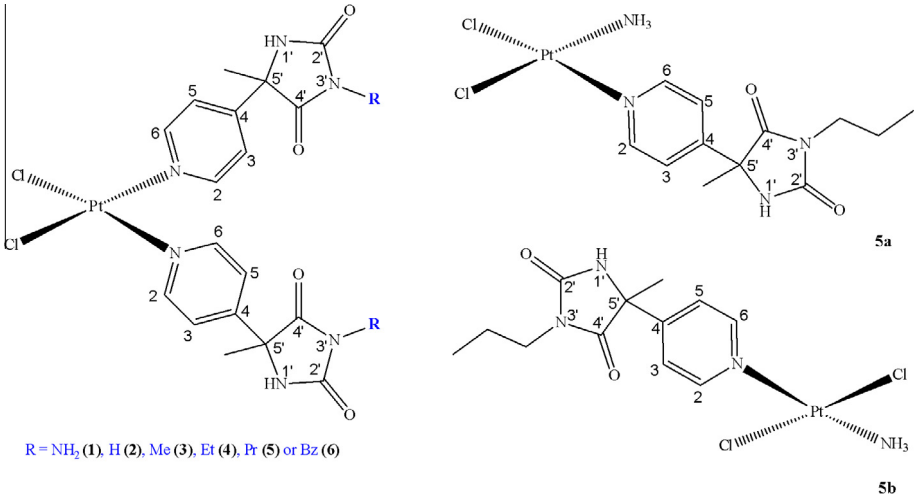

Fig. 1. Scheme of the complexes, object of the recent study.