Bioorganic & Medicinal Chemistry Letters 27 (2017) 3591–3594

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

The synthesis, structure-toxicity relationship of cisplatin derivatives for the mechanism research of cisplatin-induced nephrotoxicity

Jing Hu, Tian-Ming Wu, Hong-Ze Li, Ze-Ping Zuo, Ying-Lan Zhao *, Li Yang *

Cancer Center, West China Hospital, Sichuan University and Collaborative Innovation Center, Chengdu 610041, China

ARTICLE INFO

Article history:
Received 4 January 2017
Revised 28 March 2017
Accepted 25 April 2017
Available online 26 April 2017

Keywords:
Cisplatin
Nephrotoxicity
Structure-toxicity relationship (STR)
Biotin labeling
Chemical proteomics
Target identification

ABSTRACT

Cisplatin is a widely used antineoplastic drug, while its nephrotoxicity limits the clinical application. Although several mechanisms contributing to nephrotoxicity have been reported, the direct protein targets are unclear. Herein we reported the synthesis of 29 cisplatin derivatives and the structure-toxicity relationship (STR) of these compounds with MTT assay in human renal proximal tubule cells (HK-2) and pig kidney epithelial cells (LLC-PK1). To the best of our knowledge, this study represented the first report regarding the structure-toxicity relationship (STR) of cisplatin derivatives. The potency of biotin-pyridine conjugated derivative **3** met the requirement for target identification, and the preliminary chemical proteomics results suggested that it is a promising tool for further target identification of cisplatin-induced nephrotoxicity.

In recent years, target identification of small bioactive molecules received increasing attention for its important role in both academic and pharmaceutical research.[1–4] For instance, the target identification of thalidomide teratogenicity[5,6] offered a hint to the development of novel thalidomide drugs without teratogenic activity.

Cisplatin (*cis*-diamminedichloroplatinum (II), CDDP) is one of the most important anti-cancer drugs, which is widely used in the treatment of various solid tumors, e.g., germ cell tumor, head and neck cancer, ovarian cancer and bladder cancer. However, its clinical application is greatly hampered by its side effects, including nephrotoxicity, neurotoxicity, ototoxicity, etc.[7] Among them, nephrotoxicity is the most severe adverse effect of cisplatin for clinic patients.[8]

After decades of investigation, several mechanisms contributing to nephrotoxicity have been uncovered. DNA has conventionally been considered as the target, as cisplatin can crosslink with DNA, thereby interfering with DNA repair and causing DNA damage, and eventually inducing apoptosis in cancer cells.[9] Some cell death pathways were found to be involved in nephrotoxicity.[10] Cisplatin can also be transported into renal epithelial cells by some specific transporters, such as organic cation transporters (OCT) and copper transporter 1 (Ctr1), contributing to the accumulation of cisplatin in kidney cells.[11] Cisplatin can be metabolized to a reactive toxic thiol derivative through a biotransformation pathway that requires γ-glutamyl transpeptidase, aminopeptidase and renal dipeptidase.[12] Moreover, oxidative stress, inflammation and immunity are believed to be involved in nephrotoxicity as well.[13,14]

Although many mechanistic studies of cisplatin-induced neurotoxicity have been reported previously, the direct protein targets are unclear. Among the frequently used protocols for target identification, biotin is a widely used tag. Therefore, a biotin-conjugated cisplatin derivative with comparable cisplatin-induced neurotoxicity will be of great help for target identification. In this study, we synthesized for the first time such a derivative as **3** (Scheme 2) on the basis of synthesis of a series of cisplatin derivatives and demonstrated that **3** might be a powerful tool for target identification based on the STR studies and pull-down assays.

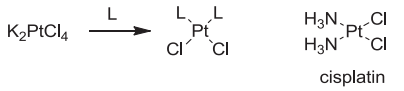
As illustrated in Scheme 1 and Fig. 1, 29 cisplatin derivatives were prepared in parallel through the reaction of various ligands with K_2PtCl_4 by reported methods (Scheme 1).[15,16]

The renal epithelial toxicity of these compounds was evaluated in human renal proximal tubule cells (HK-2) and pig kidney epithelial cells (LLC-PK1) by methyl thiazolyl tetrazolium assay (MTT).[17] The results are summarized in Table 1.

In the first round screening, compounds **1a** (aliphatic amine), **1b** (alicylic amine), **1c**–**1e** (aniline) and **1f**–**1m** (heteroarylic amine) were selected based on the structure-diversity exploration of ligand. The toxicity study showed that compounds **1d**, **1i** and **1j**

* Corresponding authors.
E-mail addresses: zhaoyinglan@scu.edu.cn (Y.-L. Zhao), yangli@scu.edu.cn (L. Yang).

http://dx.doi.org/10.1016/j.bmcl.2017.04.077
0960-894X/



Scheme 1. Synthetic scheme for cisplatin derivatives. L denotes ligand.

exhibited comparable renal epithelial toxicity to cisplatin, indicating pyridine is a promising ligand for further study, given the easy availability and promising potency.

In the second round screening, the substitute effects on the pyridine ring were first studied, with 2-aminopyridine (**2a**),

Table 1
The nephrotoxicity profile of cisplatin and its analogues **1a–7a**, **2a–2o** and **3**.

Compounds (Ligand)	**IC50** (μM)		**Compounds** (Ligand)	**IC50** (μM)	
	HK-2	**LLC-PK1**		**HK-2**	**LLC-PK1**
Cisplatin	17.0	15.8	**2b** (pyridine)	32.0	>100
1a(ethylenediamine)	55.2	7.75	**2c** (3-Br Pyridine)	12.9	24.4
1b (*N*-(2-Hydroxyethyl)piperazine)	>100	>100	**2d** (2-Br pyridine)	64.0	37.2
1c (aniline)	36.6	>100	**2e** (4-Br pyridine)	19.5	>100
1d (2-NH_2 aniline)	20.9	16.6	**2f** (3-F pyridine)	28.3	36.1
1e (4-Cl-2-NH_2 aniline)	>100	43.1	**2g** (3-Cl pyridine)	10.1	9.40
1f (2-NH_2 thiazole)	>100	>100	**2h** (3-Br 5-OH pyridine)	64.0	>100
1g (2-pyrimidinamine)	>100	>100	**2i** (5-Br 3-NH_2 pyridine)	19.8	26.2
1h (2-pyrimidinamine dimer)	78.4	37.0	**2j** (5-Br 3-COOH pyridine)	>100	>100
1i (2-NH_2-3-Br-5-methyl pyridine)	28.0	8.19	**2k** (3-OH pyridine)	33.1	>100
1j (2-NH_2-5-Br-pyridine)	26.2	27.6	**2l** (3-NH_2 pyridine)	32.0	>100
1k (indole)	>100	>100	**2m** (3-COOH pyridine)	>100	>100
1l (benzothiazole)	>100	>100	**2n** (3-F 5-NH_2 pyridine)	45.8	41.6
1m (HOBT)	>100	49.4	**2o** (3-Cl 5-NH_2 pyridine)	34.6	36.3
2a (2-NH_2 pyridine)	>100	>100	**8** (Ligand of **3**)	>100	>100
3 (biotinylated 3-Br 5-NH_2 pyridine)	44.8	53.2			

[a]The cytotoxic effects of various compounds on HK-2 and LLC-PK1 cells are determined by the MTT assay, and the results are expressed as the mean IC_{50} calculated from three independent experiments.

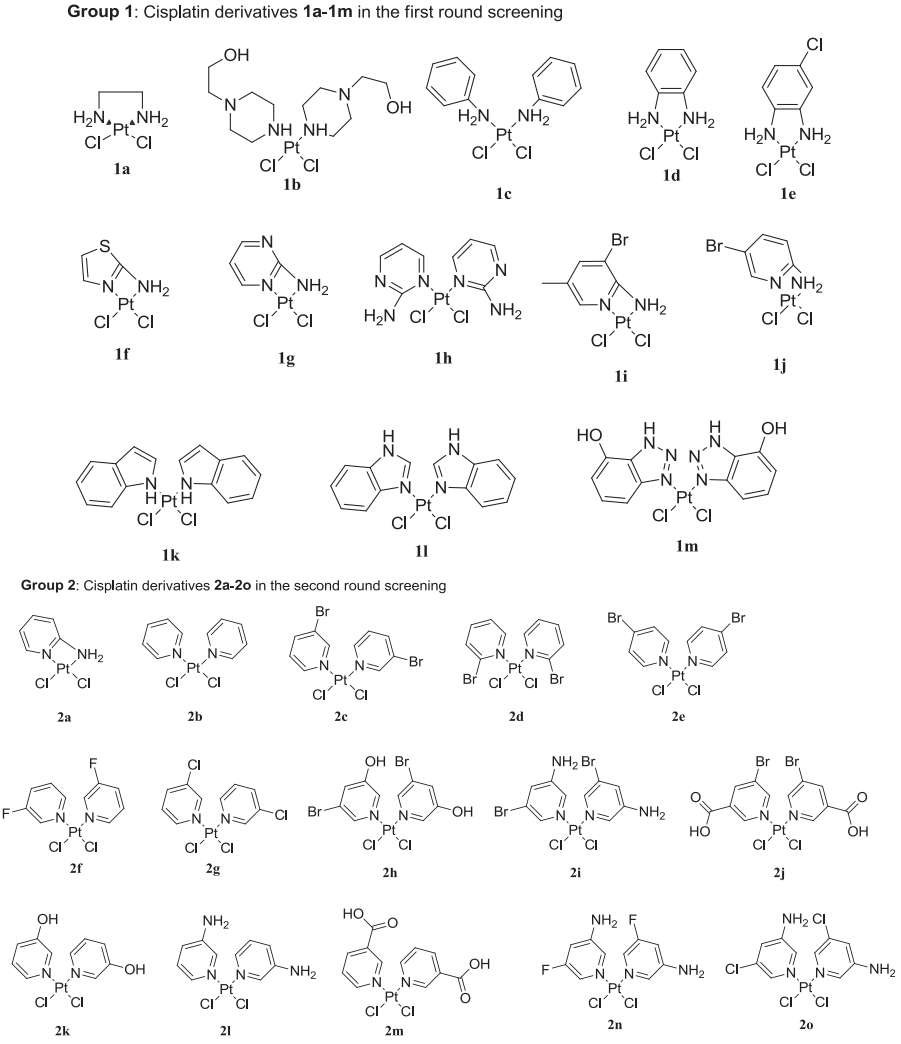


Fig. 1. Structure of cisplatin derivatives **1a**–**1m** and **2a**–**2o.**