Naphthalimide Platinum(IV) Compounds as Antitumor Agents with Dual DNA Damage Mechanism to Overcome Cisplatin Resistance

Zuojie Li[a], Yan Chen[a], Qingpeng Wang[a,*]

[a] *Institute of Biopharmaceutical Research, Liaocheng University, Liaocheng 252059, P.R. China*

KEY WORDS: Platinum, DNA damage, Antitumor agents; Naphthalimide; Prodrugs

ABSTRACT: A new series of naphthalimide platinum(IV) compounds with dual DNA damage mechanism were designed, synthesized and evaluated for antitumor activities. The platinum(IV) compounds could combine with DNA and cause DNA damage via naphthalimide fragment. Then the platinum(II) complexes released in reductive microenvironment would cause remarkable secondary DNA lesions. Some title compounds exhibit good antitumor activities and are of great potential in overcoming the drug resistance of cisplatin. Moreover, the accumulation of the tested platinum(IV) compounds in whole cells and DNA is remarkably enhanced in comparison with cisplatin and oxaliplatin.

1. Introduction

Platinum compounds as the most prominent metallic drugs are widely applied in the treatment of various malignancies in clinic including testicular, ovarian, bladder, head and neck cancers.[1,2] Platinum(II) drugs account for approximately 50% of total expenditures of anticancer drugs and play a vital role in anticancer treatments. It has been fully demonstrated that platinum(II) compounds achieve their therapeutic effects by forming DNA lesions, which interfere with the genomic activities and ultimately trigger apoptosis.[3] However, with the wide use of platinum drugs for decades, the undesirable side effects have rather limited their clinical efficiency. Especially the increasingly serious drug resistance which mainly arise from the increased DNA repair and/or DNA damage tolerance etc., has badly reduced the cancer-cure effects of platinum drugs.[4–6] Therefore, the development of new platinum complexes with novel DNA binding modes hitting one or more therapeutic targets to overcome the drug resistance has become an urgent task for pharmaceutical researchers.[7,8]

Platinum(IV) compounds are of great potential to be developed as the new generation of platinum anticancer drugs and display many attracting pharmaceutical superiorities in contrast to the platinum(II) drugs. [9–12] It is widely accepted that platinum(IV) complexes as pro-drugs of platinum(II) drugs exhibit antitumor activities via reduction to bivalence by intracellular reductants including high molecular reducing biomolecules and low molecular ascorbic acid (AsA), glutathione (GSH) etc. which occur at higher concentrations in neoplasm[13,14]. Consequently, platinum(IV) compounds tend to possess high stabilities, low toxicities and

* Corresponding authors.
E-mail: lywqp@126.com (Q. Wang)