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Recent Trends in the Synthesis of Cisplatin Analogs*

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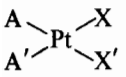
Abstract

Recent rationales in the design of cisplatin analogs will be briefly reviewed and discussed. These include: (i) Pt complexes with carrier molecules (e.g. amino acids, steroids, etc.) in the hope of increasing drug concentration in the tumor tissues; (ii) complexes of chemotherapeutic agents (e.g. alkylating agents, antimetabolites, etc.) in order to obtain polyfunctional drugs with synergistic action; (iii) polymeric Pt complexes which should modify the pharmacokinetics in a favorable way; (iv) Pt complexes designed to increase the effects of radiation therapy.

Introduction

The general formula of a cisplatin analog is shown in structure **1**, where A and A′ are amines, or other



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firmly bound ligands, and X and X′ are the so-called leaving groups. (For cisplatin $A = A' = NH_3$, and $X = X' = Cl$). In this structure the nature of X determines its rate of substitution, that is the reactivity of the drug towards biological macromolecules [1] and its likely target DNA [2]. Useful antitumor properties of an analog are associated with an intermediate lability of the Pt–X bond. Labile groups give rise to toxic compounds since **1** will react with almost any nucleophile present in the body fluids, whereas strongly bound ligands yield kinetically inert complexes. The role of A is less clear. Although a few examples of substitution of ammonia in the case of cisplatin have been reported [3], it is likely that A is not substituted *in vivo*, thus accompanying the PtX_2 moiety to the target macromolecule, and representing an important factor in the modulation of cytotoxicity and antitumor effects [1]. For instance the analogs in which two ammonia groups are substituted by diaminocyclohexane, are not crossresistant to cisplatin [4].

Results and Discussion

Literally thousands of analogs have been synthesized with different A (mainly amines) and X (mainly carboxylate anions). The screening for antitumor activity against experimental model tumors of these compounds led to the selection of approximately 15 analogs for clinical evaluation, but very few indeed are promising antitumor agents [5].

There are some recent reports, however, of Pt complexes in which either A or X is a biologically relevant molecule, in the hope of increasing selectivity towards tumor tissues and antitumor effectiveness.

(1) A number of Pt complexes have been reported in which the ligands are compounds which should accumulate in the cancer tissues. Examples are sulfadiazine [6], nutrients and metabolic precursors (amino acids [7] and their derivatives [8]), non-protein hormones (steroids [9] and molecules with estrogen-like activity [10]). Selectivity of Pt complexes of these ligands has seldom, if ever, been documented.

(2) Following what can be called a multifunctional approach, Pt has been bound to certain antitumor drugs possessing a mode of action different from that of cisplatin, in the hope of obtaining drugs displaying synergistic antitumor actions. Examples include doxorubicin [11, 12], mitoxantrone [13], and other intercalating drugs [14, 15]; and antimetabolites (such as mercaptopurine [16], selenoguanine [17], nucleoside derivatives [18] and amino sugars [19]). Melphalan (an alkylating agent) and *N*-phosphonacetyl-L-aspartate (PALA, an inhibitor of aspartate *trans*-carbamylase) have been used as leaving groups. In this latter case a very interesting complex, in which A_2 = diaminocyclohexane, has been obtained [20].

(3) There are some examples in the literature of molecules in which two [15, 21], or more [22], PtA_2 groups are bound to a same suitable ligand, or to a polymer. Presumably these substances slowly

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release- active moieties such as PtA_2X_2 ($X = H_2O$ or OH), thus modifying the pharmacokinetics in a favorable way. Very few activity data have however been published [22].

At least two examples of Pt complexed to antibodies have been reported [23].

(4) Cisplatin and many analogs enhance the effect of radiation therapy [24]. Pt complexes of derivatives of nitroimidazole, which is *per se* a radiosensitizer [25], have been specifically designed for this purpose.

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