Synthesis and characterisation of novel platinum-based drug candidates

Bjelosevic, Haris; Sykfont Snygg, Åse; Spegel, Christer; Gorton, Lo; Elmroth, Sofi; Persson, Tina

2006

Link to publication

Citation for published version (APA):

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.
Introduction

Cisplatin, cis-Pt(NH₃)₂Cl₂ (cis-diaminedichloroplatinum(II)) was introduced in the clinic around 1980. Its use as a chemotherapeutic agent has been particularly successful in the treatment of testicular and ovarian cancers. The cytotoxicity of cisplatin is thought to be related to its ability to modify nuclear DNA. Unfortunately, factors such as toxic side effects and development of drug resistance in tumors limit the use of the drug. Therefore, there is a great interest in developing new Pt-based drug candidates with improved clinical efficacy and reduced toxicity.

In this study, we have synthesised derivatives of 1,1'-bis(diphenylphosphino)-ferrocene (dpff) and their corresponding cis-platinum complexes (Fig. 1). Previous studies have shown that some dpff-based platinum complexes exhibit promising antineoplastic and antimicrobial activity. Our ambition is to improve water solubility as well as reactivity profile of this class of compounds. The long term goal is to obtain substances which allow for specific interaction patterns towards biological targets.

Synthesis

Compound (a)-N,N-dimethyl-1-ferrocenylethylamine was used as starting material (Scheme 1). First, the primary amine was produced in three steps, whereupon the succinamic acid linker was attached to the amino functionality to produce compound 5 (Scheme 1). Following, compound 5 was reacted with 5-(aminopropynyl)uridine resulting in compound 9 (Scheme 2). Compounds 2, 3, 6 and 10 were reacted with (1,5-cyclooctadiene)platinum(II)chloride, [PtCl₂(cod)], to produce the platinated compounds 11-14 (Scheme 3).

Cyclic voltammetry measurements

The CV of dpff contains two sets of redox reactions, those of the ferrocene moiety and those of the phosphino groups. The CV of [PtCl₂(dpff)] and compounds 11-14 contains only one set of redox waves, with a considerably higher formal potential (E°) in comparison with that of uncoordinated dpff (E° = 390 mV vs dpff).

Modification of the cyclopentadienyl ring resulted in an increased i/i° ratio, which probably depends on the electron donating ability of the substituent. The three substituted compounds 11, 12 and 13 showed no significant difference in electrochemical behaviour.

Figure 3 shows selected HPLC chromatograms at different reaction times illustrating the platination of d(T₃p(S)T₃). The two distances of the unplatinated oligonucleotides are eluting at 5-8 and 1-9 min, and the product peaks start to elute at 1-16 min. The inserted graph displays the fit of a single exponential function to normalised, integrated peak areas versus time for the unplatinted oligonucleotide. Reaction conditions: [Pt(II)] = 1.0 x 10⁻⁵ M, d(T₃p(S)T₃) = 2.0 x 10⁻⁵ M, [Na⁺] = 10.0 mM.

Conclusions

Compounds 12 and 13 showed increased reactivity towards L-cys and L-met compared to dpff and cisplatin. The proposed mechanism involves establishment of a hydrogen bond between the substituent and the entering ligand, and subsequent outer-sphere complex stabilisation. Compound 14 showed reactivity similar to cisplatin towards selected oligonucleotides.