Synthesis and characterisation of novel platinum-based drug candidates

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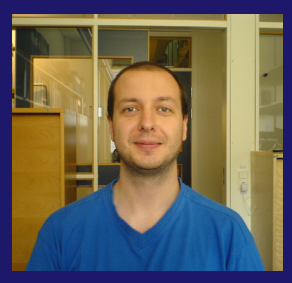


Introduction

Cisplatin, *cis*-$Pt(NH_3)_2Cl_2$ (*cis*-diamminedichloroplatinum(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.[1,2] 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 (dppf) and their corresponding *cis*-platinum complexes (Fig. 1). Earlier studies have shown that some dppf-based platinum complexes exhibit promising antineoplastic and antimicrobial activity.[3,4] 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 more specific interaction patterns towards biological targets.

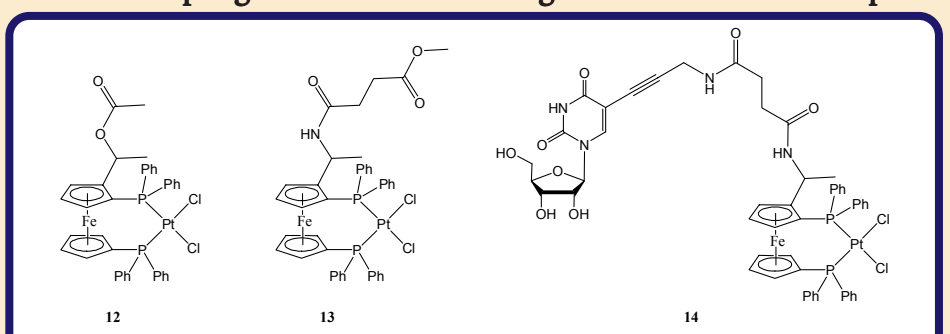
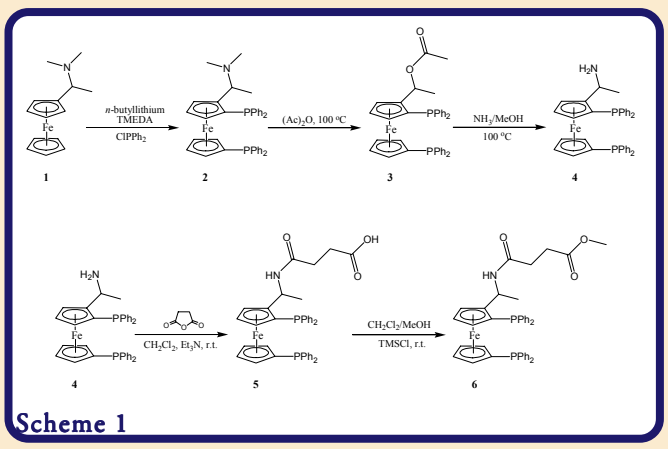


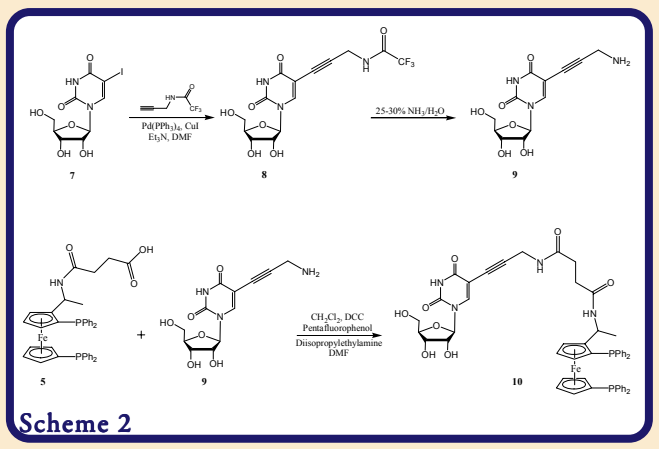
Fig. 1: Synthesised platinum compounds used in kinetic studies

Synthesis

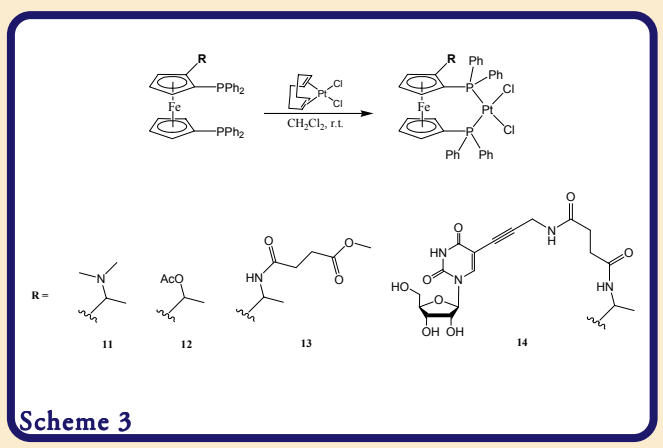
Compound (±)-*N,N*-dimethyl-1-ferrocenylethylamine was used as starting material (Scheme 1). First, the primary amine **4** was produced in three steps,[5] whereupon the succinamic acid linker was attached to the amino functionality to produce compound **5** (Scheme 1). Following, compound **5** was reacted with 5-(aminopropynyl)uridine **9** resulting in compound **10** (Scheme 2).[6] Compounds **2**, **3**, **6** and **10** were reacted with (1,5-cyclooctadiene)platinum(II)chloride, $[PtCl_2(cod)]$, to produce the platinated compunds **11-14** (Scheme 3).



Scheme 1



Scheme 2



Scheme 3

Cyclic voltammetry measurements

The CV of dppf contains two sets of redox reactions, those of the ferrocene moiety and those of the phosphino groups. The CV of $[PtCl_2(dppf)]$ and compounds **11-14** contains only one set of redox waves, with a considerably higher formal potential ($E^{0'}$) in comparison with that of uncoordinated dppf ($E^{0'}$ = 390 mV vs dppf).

Modification of the cyclopentadienyl ring resulted in an increased $i_{p,c}/i_{p,a}$ 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.

Voltammogram of complex **14** showed that the peak current of the reduction wave of the ferrocene moiety is larger then for the corresponding oxidation - the narrow shape and sweep rate dependance suggest that the oxidised species might be adsorbed on the electrode whereas the reduced specie is dissolved.

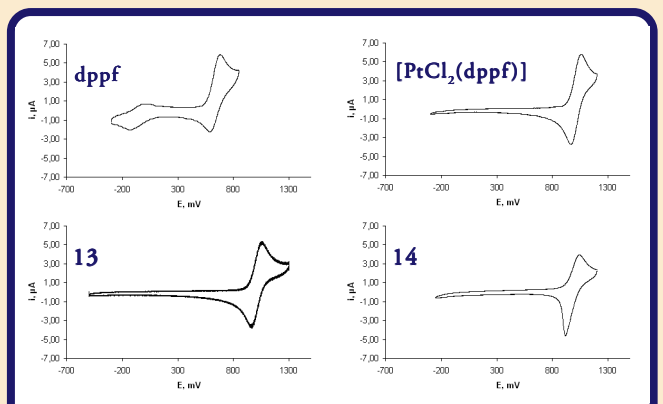


Fig. 2: CV voltammograms

Kinetic studies

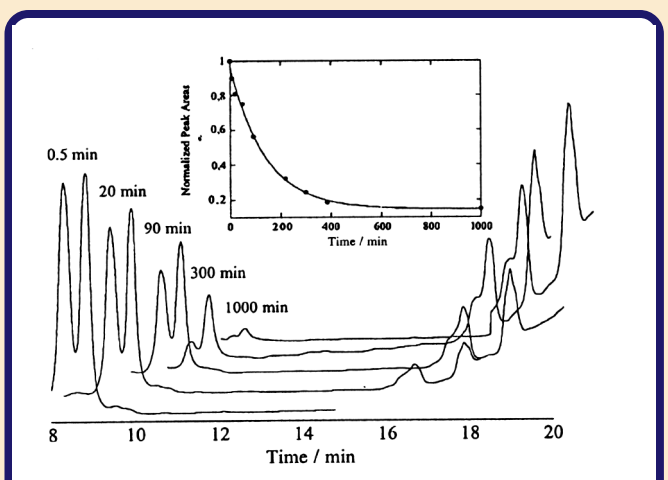


Fig. 3: Selected HPLC chromatograms, comp. 14

Compounds **12** and **13** were further investigated by studying their reactivity towards L-cysteine and L-methionine.[7] In addition, compound **14** was tested for its reactivity using DNA as target.[6] In this study, two types of oligomers were used, one containing the GG sequence, $d(T_7GGT_7)$, and the other containing the slightly more reactive phosphorothioate group $d(T_6p(S)T_6)$.

Figure 3 shows selected HPLC chromatograms at differrent reaction times illustrating the platination of $d(T_6p(S)T_6)$. The two diastereomers of the unplatinated oligonucleotides are eluting at t_r~8 and t_r~9 min, and the product peaks start to elute at t_r~16 min. The inserted graph displays the fit of a single exponential function to normalised, integrated peak areas versus time for the unplatinated oligonucleotide. Reaction conditions: $[Pt(II)]=1.0\times10^{-5}$ M, $[d(T_6p(S)T_6)]=2.0\times10^{-6}$ M, $[Na^+]=10.0$ mM.

Conclusions

Compounds **12** and **13** showed increased reactivity towards L-cys and L-met compared to dppf 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.

Ref.: [1] B. Rosenberg, *Plat. Met. Rev.* **15**, 42 (1971); [2] J.M. Pascoe and J.J. Roberts, *Biochem. Pharmacol.* **23**, 1345 (1974); [3] V. Scarcia, A. Furlani, B. Longato, B. Corain and G. Pilloni, *Inorg. Chim. Acta* **153**, 67 (1988); [4] R.W. Mason, K. McGrouther, P.R. Ranatunge-Bandarage, B.H. Robinson and J. Simpson, *Appl. Organomet. Chem.* **13**, 163 (1999); [5] T. Hayashi, T. Miese, M. Fukushima, M. Kagotani, N. Nagashima, Y. Hamada, A. Matsumoto, S. Kawakami, M. Konishi, K. Yamamoto and M. Kumada, *Bull. Chem. Soc. Jpn.* **53**, 1138 (1980); [6] H. Bjelosevic, C. Spégel, Å. Sykfont Snygg, L. Gorton, S.K.C. Elmroth and T. Persson, *Tetrahedron* **62**, 4519 (2006); [7] G. Puxty, H. Bjelosevic, T. Persson and S.K.C. Elmroth, *Dalton Trans.* **18**, 3032 (2005).

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