Metallanucleosides based on Adenosine

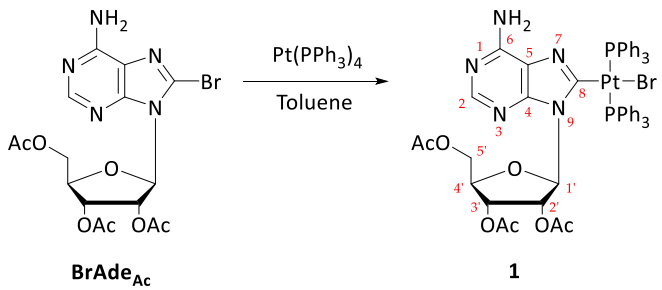
M. Inês P. S. Leitão, Giulia Francescato, Ana Petronilho*
NOVA ITQB, EAN, Avd República, 2780-157, Oeiras, Portugal. email: inesleitao@itqb.unl.pt
INSTITUTO DE TECNOLOGIA QUÍMICA E BIOLÓGICA ANTÓNIO XAVIER | WWW.ITQB.UNL.PT

Introduction

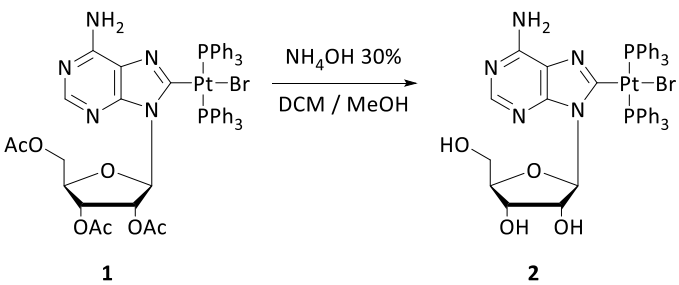
Adenosine is a crucial extracellular modulator, involved in several biological processes. This multi-signalling molecule restores the intracellular energy levels and mediates tissue protection. High extracellular levels of adenosine are associated with several pathological states.[1] Considering its biological importance, several agonists and antagonists of adenosine receptors (ARs) have been developed,[2] with some being derived from adenine with modifications at C-8 position. Moreover, metal-based drugs are of upmost importance in cancer therapy and as antimicrobials. Metallanucleosides have shown great potential as selective anticancer agents,[3–5] hydrogels with antimicrobial properties[6,7] and to promote tissue regeneration in vivo[7,8]. Herein, we report the synthesis of adenosine derivatives with a platinum centre, aiming at a later study of their biological applications. This connectivity allows keeping intact all the sites involved in base pairing, favouring molecular recognition.

Results and Discussion

Reaction of the acetate-protected bromoadenosine (**BrAde$_{Ac}$**) with $Pt(PPh_3)_4$ in toluene, afforded complex **1** by C-Br oxidative addition, in good yields (Scheme 1). Deprotection of **1** can be easily performed under basic conditions, affording complex **2** in good yields (Scheme 2). Deprotection under such conditions does not compromise the Pt–C bond or the glycosidic bond, as confirmed by NMR.

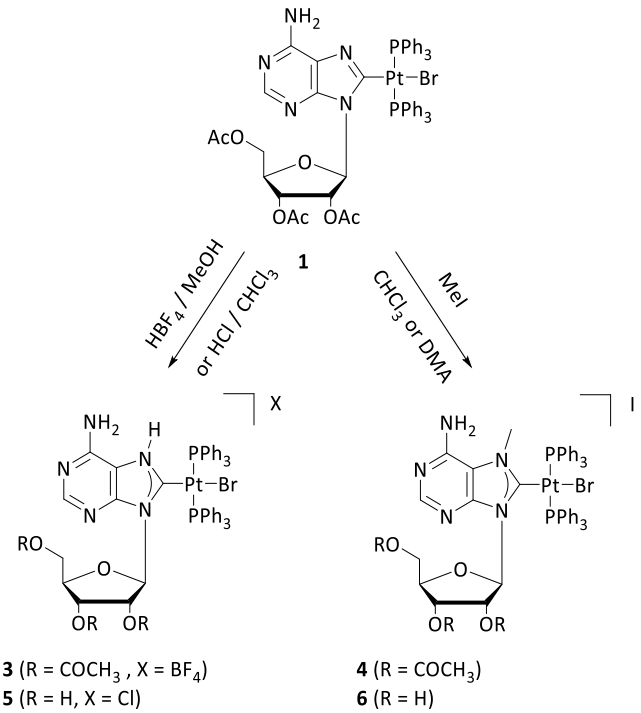


Scheme 1. C-Br oxidative addition of ligand precursor $BrAde_{Ac}$ to $Pt(PPh_3)_4$, affording complex **1**.



Scheme 2. Deprotection of the sugar moiety of complex **1**, affording **2**.

Compounds **1** and **2** react readily at N7 in the presence of acid or methyl iodide leading to the formation of NHCs **3**-**4** (acetate-protected) and **5**-**6**, respectively (Scheme 3).



Scheme 3. Synthesis of NHCs **3**-**6** by functionalization of N7-postion of the adenine moiety of compounds **1** and **2**.

Unlike our reported guanosine NHCs,[4,9] we noted that solutions of compound **5** in DMSO-d_6 are not stable and after a few days another compound starts to form. We hypothesized that this second compound is the result of the exchange of the bromine present as co-ligand to the metal centre and the chloride as counterion. NMR and HRMS analysis support this hypothesis. Indeed, changes in the chemical shift of ^{1}H NMR signals of NH groups, associated with different electronegativity values of the two ions. The same effect is also observed in the ^{31}P and ^{195}Pt NMR spectra, and supported by MS.

Conclusions

The synthesis of N-Heterocyclic carbenes derived adenosine was successfully achieved via N-7 protonation or methylation of two adenosine complexes, with and without acetate-protected sugar moieties. Once deprotected, the adenosine NHC can undergo halide exchange in DMSO solutions.

References: 1) P. A. Borea et al., *Trends Pharmacol. Sci.* 2016, **37**, 419–434. 2) K. A. Jacobson and Z. G. Gao, *Nat. Rev. Drug Discov.*, 2006, **5**, 247–264. 3) G. K. Voeltz et al., *Cell*, 2006, **124**, 573–586. 4) M. I. P. S. Leitão, F. Herrera and A. Petronilho, *ACS Omega*, 2018, **3**, 15653–15656. 5) R. Kaczmarek et al., *ChemistryOpen*, 2018, **7**, 237–247. 6) T. Bhattacharyya et al., *ACS Appl. Bio Mater.*, 2019, **2**, 3171–3177. 7) Q. Tang et al., *ACS Appl. Mater. Interfaces*, 2019, **11**, 19743–19750. 8) M. Xiao et al., *Mater. Sci. Eng. C*, 2019, **105**, 110067. 9) M. I. P. S. Leitão, Gonzalez, C.; Francescato, G.; Filipiak, Z.; Petronilho, A. *Chem. Comm.* 2020, **56**, 13365–13368.

Acknowledgments: This work was financially supported by: Project LISBOA-01-0145-FEDER-007660 (Microbiologia Molecular, Estrutural e Celular) funded by FEDER funds through COMPETE2020 - Programa Operacional Competitividade e Internacionalização (POCI) and by national funds through FCT - Fundação para a Ciência e a Tecnologia, and FCT project IF/00109/2014/CP1244/CT0007. Leitão thanks the PhD fellowship PD/BD/135483/2018 funded by FCT.