Synthesis and antitumor evaluation of novel chiral platinum and palladium complexes bearing new (1R)-(–)-myrtanyl-based nitrogen ligands

Adnan S. Abu – Surrah, * [a] Mika Kettunen,[b] Markku Leskelä, [b] Yousef Al-Abed [c]

[a] Hashemite University, Department of Chemistry, P. O. Box 150459, Zarqa-13115, Jordan. E-mail address: asurrah@hu.edu.jo (A. S. Abu-Surrah)
[b] University of Helsinki, Laboratory of Inorganic chemistry, P. O. Box 55, FIN-00014 Helsinki, Finland
[c] Feinstein Institute for Medical Research, 350 Community Drive, Manhasset, NY 11030

Keywords: Platinum(II)-, Palladium(II) complexes, Bidentate nitrogen ligands, Chirality, Anticancer, Drug

ABSTRACT

The reaction of (1R,2R)-(–)-1,2-diaminocyclohexane (**1**) [*DACH*] with the enantiomerically pure aldehyde (1R)-(–)-Myrtenal (**2**) in MeOH afforded the bidentate diimine ligand, N,N´-1R,2R-(–)-bis[(1R)-(–)-myrtenyl]diiminocyclohexane (*MYRDICH*, **3**) in a high yield. Reduction of compound **3** utilizing $LiAlH_4$ selectively afforded the diamine **4**, while catalytic reduction using PtO_2/H_2 led to the formation of the desired ligand (**5**) (N,N´-1R,2R-(–)-bis[(1R)-(–)-myrtanyl]diaminocyclohexane (*MYRDACH*, **5**), where both the imine and the olefinic groups have been reduced. Treatment of compound **5** with K_2PtCl_4 or K_2PdCl_4 yielded the corresponding platinum(II) and palladium(II) complexes, **Pt-6** and **Pd-7,** respectively. For comparison, the diimine complex **Pt-8** was prepared by the reaction of **3** with K_2PtCl_4. The antitumor activity of the complexes **Pt-6, Pd-7** and **Pt-8** was tested and compared to the approved drugs, cisplatin (***Cis*-Pt**) and oxaplatin (**Ox-Pt**). The complexes (**Pt-6, Pd-7** and **Pt-8**) inhibit L1210 cell line proliferation with an IC_{50} of 0.6, 4.2, and 0.7 μM, respectively as evidenced by measuring thymidine incorporation. Compound **6** was 17 fold more potent as an anti-tumor agent in comparison to Cis-Pt and Ox-Pt. An insight into the mechanism of action revealed that compound **Pt-6** and **Pt-8** suppress proliferation by turning on apoptosis.