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

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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]diaminocyclohexane (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 antitumor 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.