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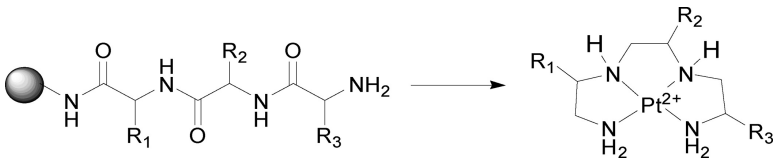

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Synthesis of Platinum(II) Chiral Tetraamine Coordination Complexes

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The individual and combinatorial syntheses of individual as well as a mixture-based diversity of 195 112 platinum(II) coordination complexes of chiral tetraamines are described. The use of both solid-phase synthesis and solution phase follow-on approaches were found to best afford the title compounds.

Metal coordination complexes are known to be useful chemotherapeutic and diagnostic agents in a wide range of applications.[1] One of the earliest therapeutic coordination compounds (*cis*-diaminedichloroplatinum(II), known as "*cis*-platin"), is widely used as an anticancer agent.[2,3] Metal coordination complexes have also shown efficacy against a wide range of drug targets, including HIV-integrase, α-thrombin, and P-glycoprotein.[4]

Since its inception in 1983−1985,[5] diversity-oriented synthetic approaches, which involve either the parallel synthesis of large numbers of individual compounds (hundreds to thousands) or of mixtures of compounds (thousands to millions), are now practiced in virtually all pharmaceutical companies and in a large number of research labs throughout the world.[6] Over the past 10 years, the focus of these approaches has been directed toward the preparation of both low molecular weight acyclic and heterocyclic compounds.[6d−g] Despite the therapeutic potential of metal coordination complexes, publications describing the generation and use of large diversity-oriented libraries of metal complexes remain scarce, with only a limited number of metal coordination complexes presented in formats useful for biological and medicinal applications.[7]

In 1994, our laboratory presented two important and efficient solid-phase synthesis approaches. The first involves general "libraries from libraries",[11] and the second involves the diversity-oriented synthesis of individual and mixture-based diversities of chiral polyamines.[8] In both instances, support-bound peptides were used as starting materials[8] to generate diversities of compounds having completely different physical−chemical properties relative to the starting peptides. These have been successfully used in the identification of highly active individual, biologically active polyamines.[9] The ability of polyamines to serve as multidentate ligands in the formation of metal coordination complexes, along with various reported medicinal applications of amine−metal coordination compounds,[10] prompted us to extend our "libraries from libraries" approach used for the preparation of polyamines[11] to include the synthesis of metal−polyamine complexes. Comparison of the biological activity of the uncoordinated polyamines versus their metal coordinated counterparts can be expected to provide unique structure−activity relationship information and facilitate the discovery of potential new therapeutic and diagnostic agents. We report herein a general approach for synthesis of large numbers of individual platinum(II) coordination complexes of chiral tetraamines (Scheme 1). Additionally, this same approach was used to generate a mixture-based diversity of 195 112 tetraamine−Pt(II) complexes in positional scanning format.[15]

In an initial study, the eight possible chiral tetraamines **2** were synthesized by exhaustive reduction of eight separate resin-bound tripeptides **1** (Scheme 1: R^1 = L- or D-Phe, R^2 = L- or D-Phe, R^3 = L- or D-Ala). Following cleavage of these eight individual polyamines from their resins, virtually quantitative conversion to the corresponding tetraamine−Pt(II) complexes **3** was achieved by solution-phase interaction of these individual chiral tetraamines with K_2PtCl_4.[3] Coordination of platinum(II) with such tetraamines converts the two secondary nitrogen atoms to chiral stereocenters, yielding four possible Pt−NH stereoisomers. Depending on steric hindrance and ring torsion, the four steroisomers would be expected to be rank-ordered in terms of their thermodynamic stability. The eight separate corresponding chiral tetraamine Pt(II) coordination complexes (70−80% yield), formed from their respective phenylalanyl−phenylalanyl−alanine amides, yielded four matching enantiomeric pairs of peaks (LLL and DDD, etc.; see Supporting Information) using a shallow gradient on analytical RP-HPLC (Figure 1). Preparative separation and characterization of the major stereoisomers is in progress (Figure 1). The eight chiral polyamine platinum complexes (steroisomers not separated) were then examined by ^1H and ^{13}C NMR spectroscopy. The NMR spectra of the tetraamine−Pt(II) complexes were compared to the spectra of the corresponding free tetraamines **2**. Signals were found at 5.20−5.62 ppm for the platinum-

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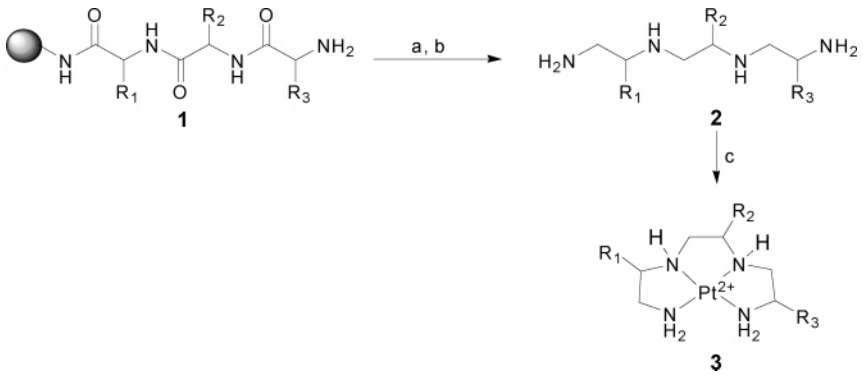
Scheme 1[a]



[a] Reactions: (a) BH_3−THF, 65 °C, 4 days; (b) HF, anisole, 0 °C, 7 h; (c) K_2PtCl_4, DIPEA, DMF/H_2O (50/50), 60 °C, 48 h.

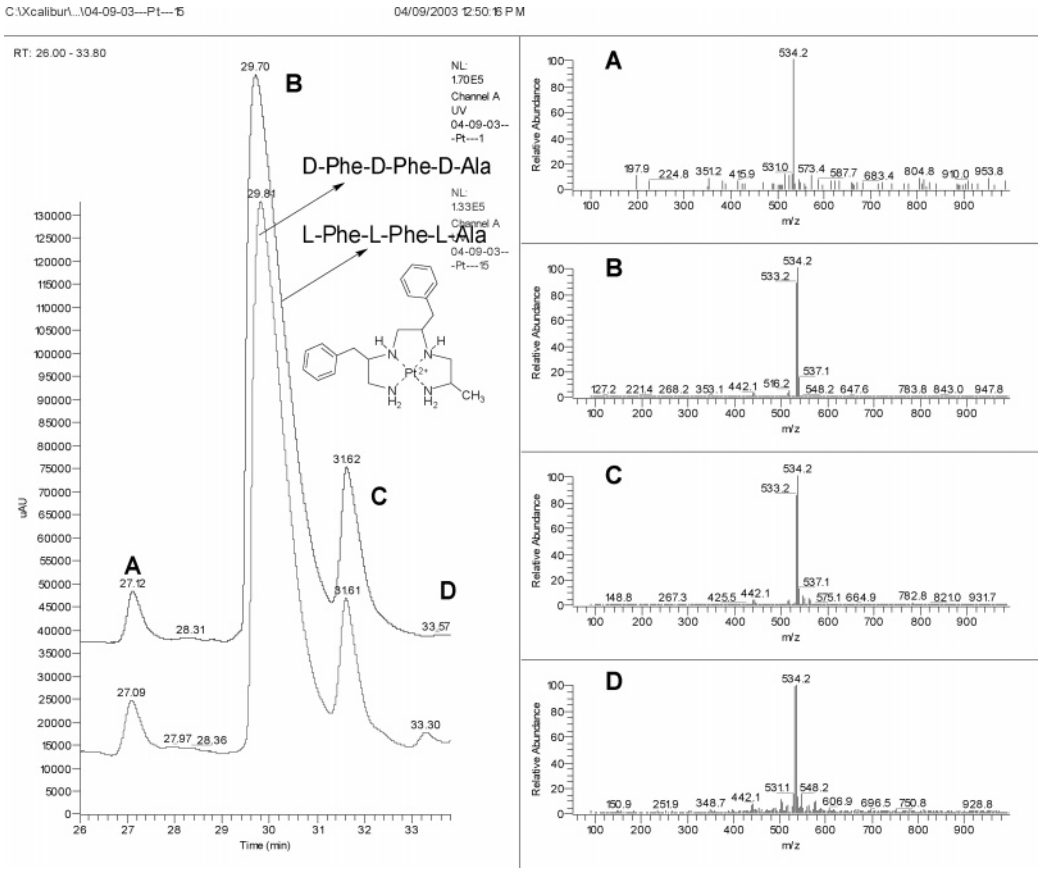


Figure 1. RP-HPLC separation of stereoisomers found for matched pairs of LLL and DDD tetraamine-Pt(II) complexes.

complexed NH_2 protons and at 7.04−7.25 ppm for the platinum-complexed NH protons. These chemical shift values for the coordinated amino protons were comparable to literature values.[12,13] When compared to the spectrum of the linear polyamines **2**, the signals of the ethylene carbon atoms in the ^{13}C NMR spectrum of the Pt(II) complexes **3** were shifted downfield ($\delta = 8.8-11.3$ ppm). The $\Delta\delta$ values are in the range of those reported for comparable platinum complexes.[14]

The CD spectra of the DLL and LDD mirror Pt(II) tetraamine enantiomers are shown in Figure 2 (related mirror image spectra were found for the other pairs (see Supporting Information).

In preliminary studies, we have found that the described library of 195 112 platinum chiral polyamine coordination conplexes strongly inhibit the interaction of an Eph receptor tyrosine kinase with its ephrin ligands. The coordinating effects of platinum(II) were critical for the inhibitory activity toward the Eph receptor, since the chiral tetraamines that were used to prepare the platinum complexes were substantially less active. In addition, the platinum chiral polyamine library was much more active relative to other libraries tested, including libraries of low molecular weight heterocyclic and acyclic compounds **16n** and **16h**. Since the receptor tyrosine kinases of the Eph family regulate numerous biological processes, including pathological forms of angiogenesis and cancer progression,[16] this result illustrates the potential biomedical value of combinatorial libraries of polyamines containing platinum as a coordinating agent.

To determine the breadth and scope of this approach, potential amino acids used to form the individual chiral tetraamines (75 different L-, D- or unnatural amino acids)

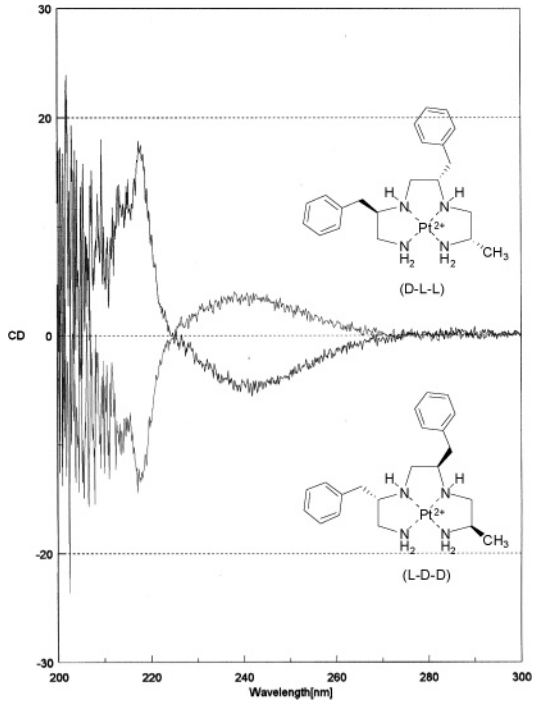


Figure 2. Circular dichroism spectra of matching DLL and LDD Pt(II) chiral tetraamine enantiomeric coordination complexes.

were examined by varying the first position of the tripeptide while keeping the two other positions fixed with L-phenylalanine. This was repeated for the second and the third positions. For >90% of the amino acids examined, Pt(II) tetraamine complexes were obtained in purities >80%. In all cases, the conversion to the platinum(II)−tetraamine coordination complexes appeared to be complete, with no free tetraamine detected by RP-HPLC. Those polyamines having an amino functionality on their side chains (derived from lysine, reduced asparagine, reduced glutamine, etc.) contained <10% of an additional $PtCl_3$ complexed to these side chain amino moieties, as observed by LC/MS. Cysteine, methionine, and histidine were found to yield complex side reaction product profiles and were omitted from further use. β-Alanine, aspartic acid (αBzl), and glutamic acid (αBzl) were also included (as building blocks) and yielded Pt(II) tetraamine complexes having six- and seven-membered ring systems, respectively. These results enable the preparation of a very large number of individual Pt(II)−tetraamine complexes in high yield and purity.

Using 58 different amino acids, three separate sets of mixtures (one for each of the three positions) were then incorporated at each position in a tripeptide to generate a positional scanning[15] library of 195 112 (58^3) resin-bound tripeptides. Following the reduction of the 174 peptide mixtures, a mixture-based diversity of chiral tetraamines was generated by the exhaustive reduction of the amides of the resin-bound tripeptides.[6] Thus, the 174 separate tetraamine mixtures (three sublibraries, 58 separate mixtures for each position with each mixture containing 3364 tetraamines) were cleaved from their respective resins and reacted with K_2PtCl_4 as described above. Concurrent with the library synthesis, three sets of 58 individual control compounds (one for each position, for a total of 174 tetraamines; each set addresses the functionalities making up a single position with the other two positions fixed with L-phenylalanine) were prepared to verify completeness and reproducibility of the mixture-based library.

Both the resulting tetraamine−Pt(II) mixtures and the individual tetraamine−Pt(II) control compounds were analyzed by LC/MS. The mass spectra of the mixture of 3364 tetraamines generated from L-Leu−X−X (each X being a mixture of 58 amino acids) and the resulting mixture of the corresponding 3364 platinum(II) coordinated tetraamines and their epimers were examined. The maximum of the resulting mass distribution was shifted from an average of M = 400 for the tetraamines to an average of M = 600 for the platinum complexes. This agrees well with the expected mass increase for the addition of a platinum atom (MW = 195) (see Supporting Information).

We have presented herein a general means for the synthesis of individual and mixture-based diversities of 195 112 Pt-(II)-coordinated chiral tetraamines. We believe that these approaches can be extended to include a wide range of other metals as well as a variety of additional multidentate ligands to yield platinum(II) coordination complexes having potential use as therapeutic or diagnostic agents. Over the past decade, computational methods have improved to the extent that the structure and many properties of molecules the size of those typically found in Pt complexes with organic ligands can now be treated quite accurately. This holds out the exciting prospect that these methods can now be applied effectively to assist in the design of new ligands with potential bioactivity, and we fully intend to investigate this possibility in our future work in this area.

General Procedure for the Pt(II) Complexation of Tetraamines 2 (GP 3). Ethyldiisopropylamine (4.8 equiv, 0.072 M in DMF) was added to tetraamine **2** (1.0 equiv). K_2PtCl_4 (2.0 equiv, 0.02 M in H_2O) was added, and the reaction mixture was stirred at 60 °C for 2 days. Following centrifugation, the desired product was lyophilized, dissolved in AcCN/water (50/50), and lyophilized again.

(2*R*)-*N*′-[(1*S*)-2-Amino-1-benzylethyl]-*N*″-[(2*S*)-2-aminopropyl]-3-phenylpropane-1,2-diamine (2a). ^{1}H NMR (500 MHz, DMSO-d_6), δ (ppm) 7.38−7.08 (m, 10H), 3.60 (dd, J = 12.3 Hz, J = 6.1 Hz, 1H), 3.40 (dd, J = 10.1 Hz, J = 4.1 Hz, 1H), 3.24 (dd, J = 13.1 Hz, J = 6.8 Hz, 1H), 3.14 (dd, J = 13.1 Hz, J = 5.5 Hz, 1H), 3.05 (dd, J = 13.4 Hz, J = 3.6 Hz, 1H), 2.98 (m, 1H), 2.82 (m, 3H), 2.79 (m, 2H), 2.59 (m, 2H), 1.29 (d, J = 6.7 Hz, 6H). ^{13}C NMR (125 MHz, DMSO-d_6), δ (ppm) 159.0, 158.7, 137.5, 136.3, 129.2, 129.0, 128.6, 128.5, 126.8, 126.4, 117.7, 115.3, 58.8, 57.1, 47.5, 44.7, 43.6, 41.4, 37.2, 34.2.

(2*R*)-*N*′-[(1*S*)-2-Amino-1-benzylethyl]-N″-[(2*S*)-2-aminopropyl]-3-phenylpropane-1,2-diamineplatinum(II) (3a). ^{1}H NMR (500 MHz, DMSO-d_6), δ (ppm) (4 diastereomers) 7.59−7.13 (m, 10 H), 5.37 (br s, 1H), 5.16 (br s, 1H), 5.12 (br s, 1H), 4.79 (br s, 1H), 4.78 (br s, 1H), 4.03 (m, 1H), 3.61 (m, 1H), 3.42 (m, 1H), 3.31 (m, 1H), 2.99 (m, 3H), 2.89 (dd, J = 13.8 Hz, J = 5.6 Hz, 1H), 2.68 (m, 4H), 2.54 (m, 2H), 1.34 (d, J = 7.0 Hz, 6H, diastereomer), 1.30 (J = 6.9 Hz, 6H, diastereomer), 1.26 (J = 6.3 Hz, 6H, diastereomer), 1.22 (d, J = 6.7 Hz, 6H, diastereomer). ^{13}C NMR (125 MHz, DMSO-d_6), δ (ppm) (4 diastereomers) 158.2,

157.9, 157.7, 137.5, 137.4, 137.1, 136.6, 136.4, 130.1, 129.6, 129.4, 129.1, 128.8, 128.7, 128.6, 128.5, 127.1, 126.7, 118.2, 69.9, 68.6, 67.3, 65.9, 65.6, 65.3, 58.2, 57.8, 55.3, 54.9, 53.7, 53.1, 52.1, 44.2, 42.7, 41.7, 37.7, 35.4, 34.7, 33.7, 31.7, 17.2, 17.0, 16.9.

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Supporting Information Available. Experimental procedure and representative spectroscopic data for **3a**−**3j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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