Stabilization of Cisplatin *via* Coordination of Ethylenediamine

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ABSTRACT
While the chemotherapeutic cisplatin is used to treat a variety of cancers, metal toxicity and cisplatin resistance *via* genetic and epigenetic changes limits its use and calls for alternative therapies. To combat the observed toxicities and create a more stable compound, which avoids isomerization into a *trans* configuration, three cisplatin analogues including cispalladium, dichloro-(ethylenediamine)-platinum(II), and dichloro-(ethylenediamine)-palladium(II) were synthesized as potential cisplatin alternatives. Each compound was evaluated for cytotoxicity on SK-OV-3 cells against cisplatin. Synthesis of dichloro-(ethylenediamine)-platinum(II) yielded 20.5% of the theoretical yield, while dichloro-(ethylenediamine)-palladium(II) yielded 49.1%. Results from the cytotoxicity trial revealed that cispalladium was not effective against SK-OV-3 cells, and dichloro-(ethylenediamine)-palladium had minimal effects. The dichloro-(ethylenediamine)-platinum(II) was the most efficacious with an IC_{50} value of 0.77 μg/ml compared to the IC_{50} of 0.61 μg/ml for cisplatin. With a similar IC_{50} to cisplatin, these results suggest that dichloro-(ethylenediamine)-platinum(II) has the potential to serve as a cisplatin alternative for cancer patients who develop resistance following their clinical course of cisplatin. Future studies on the cytotoxicity of dichloro-(ethylenediamine)-platinum(II) to induce cell death on cisplatin-resistance cell lines are necessary to determine the ability of the compound to be utilized as a cisplatin alternative.

KEYWORDS
Cisplatin; Ovarian Cancer; SK-OV-3; Drug Resistance; Stability; Palladium; Ethylenediamine; Cispalladium; Dichloro-(ethylenediamine)-platinum(II); Dichloro-(ethylenediamine)-palladium(II)

INTRODUCTION

Cisplatin, a current chemotherapeutic used to treat lung and other cancers including bladder, head and neck, ovarian, and testicular cancers, prevents cell replication by crosslinking DNA nucleotides along the same strand forming DNA-platinum adducts, subsequently inducing apoptosis.[1] Though widely used, formation of *trans* isomers, metal toxicity and cisplatin resistance via genetic and epigenetic changes limits its use and calls for alternative therapies.[2]

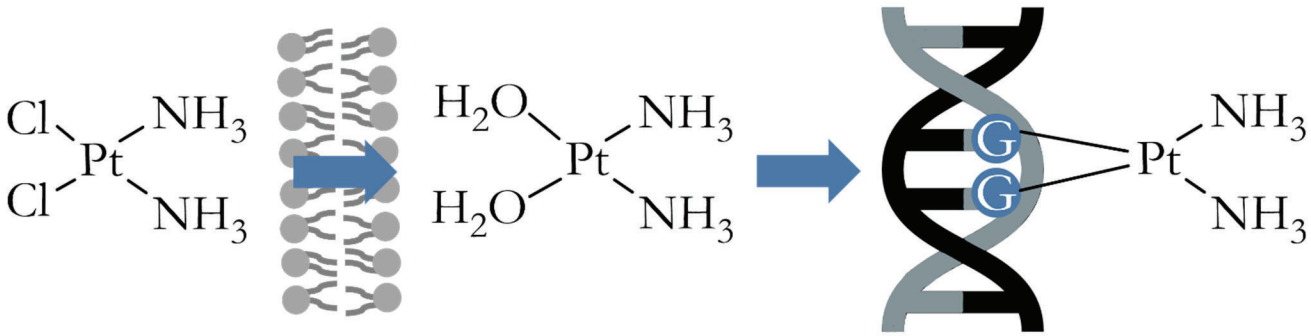


Figure 1. Once cisplatin passes through a cell membrane, it become aquated through ligand exchange, during which each chlorine atom is replaced with a water molecule.

One of the most common mechanisms of cisplatin resistance has been attributed to an observed decrease in accumulation of platinum compounds during cisplatin-resistant cell culture studies.[3] Many methods may contribute to this observation including active efflux, impaired influx, antioxidants, increases in DNA damage repair, DNA-methylation or de-methylation, membrane protein trafficking alterations via the cytoskeleton, overexpression of chaperones, inactivation of the apoptosis pathway, along with activation of the EMT and many other pathways.[3]

Severe nephrotoxicity induced by platinum compounds, is partly due to the transporter-mediated uptake in cells.[4] For cisplatin, the copper transporter 1 appears to play a role in its tumor cellular uptake, while its side effects may be due to the organic cation transporter (OCT) 2 based upon its placement and distribution among affected organs.[4] One proposed mechanism for cisplatin induced nephrotoxicity (CIN) is due to the platinum-glutathionine (GSH) conjugates formed within the kidneys.[5] Compared to metabolic intermediates, the platinum-GSH is highly unstable leading to damage in the proximal tubules.[5]

To combat the observed nephrotoxicity, secondary treatments such as amifostine, which binds to free radicals, have been approved by the FDA.[6] Previous work by these students[7] involved replacing the amine groups on cisplatin with the amine groups on amifostine, to form a singular, less toxic treatment, as seen in **Figure 2A,** which would retain the ability of cisplatin to bind to DNA, and the ability of amifostine to bind to free radicals. Though ultimately a bulky analogue with an unfavorable coordination to the platinum center was formed, as shown in **Figure 2B**, the intention was to form a less toxic compound that was stabilized through a formed ring structure. Additional methods to combat CIN include replacing the platinum center, which is the cause of the toxic side effects. While there are many other studies that have investigated cisplatin analogs as well as platinum substitutes,[8] this work will focus on the comparison of ring-stabilized analogs to their more traditional counterparts (**Figure 3**).

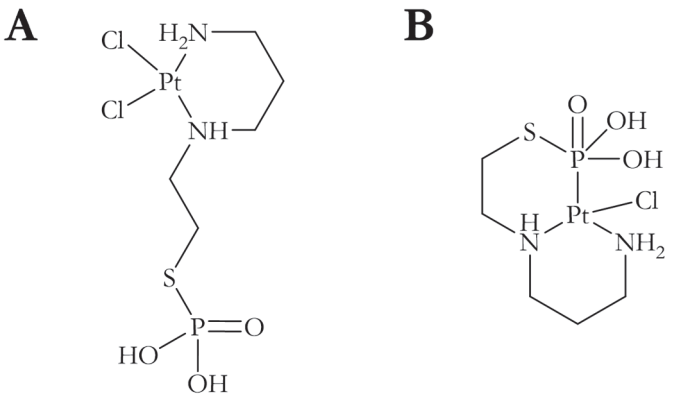


Figure 2. (A) The intended amifostine-incorporated cisplatin analogue, and (B) the analogue that was likely formed instead.

Combining the previous two strategies to combat toxicity and resistance, three cisplatin analogues shown in **Figure 3** were synthesized and analyzed for cytotoxicity in a SK-OV-3 cell line. Should resistance occur in patients receiving cisplatin treatment, these analogues have the potential to serve as cisplatin alternatives. To minimize the toxicity of the platinum component, palladium was used as a replacement metallic center to form cispalladium in hopes of minimizing toxic glutathione metabolites produced in the kidneys from cisplatin. Additionally, ethylenediamine was used to replace the amine groups in cisplatin, forming dichloro-(ethylenediamine)-platinum(II), with a stable five-membered cyclic group which may evade some of the observed mechanisms of cisplatin resistance while preventing formation of *trans* compounds. The amine groups of ethylenediamine also replaced the amine groups on cispalladium to create dichloro-(ethylenediamine)-palladium(II), a compound that utilizes both techniques. Through synthesis and cytotoxicity analyses of three cisplatin analogues, which replace the toxic platinum center and stabilize the compound through cyclic arrangements, alternative cisplatin treatments may be considered.

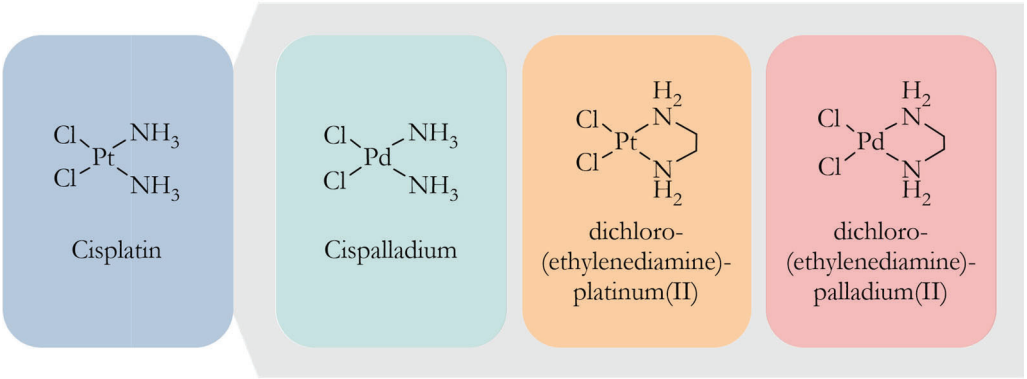


Figure 3. The chemical structures of cisplatin and the cisplatin analogues synthesized.

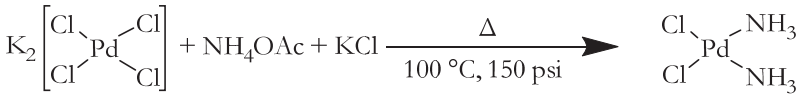
METHODS AND PROCEDURES

Materials

All reagents used to synthesize the cisplatin analogues were retrieved from Sigma Aldrich. Equipment utilized during analogue synthesis included the CEM Discover System Microwave (Matthews, NC) to synthesize cispalladium and a PerkinElmer Spectrum 100 FT-IR Spectrometer to obtain Infrared (IR) spectra (ATR) for each compound. For the cytotoxicity assay, SK-OV-3 ovarian cancer cells were retrieved September 2021 from Stevenson University after being frozen in 2016. Throughout the experiments, the cells were passaged a total of 12 times in 70% DMEM (20% FBS, 10% DMSO) media, retrieved from Sigma Aldrich. The absorbance of the cytotoxicity assays was measured on a Tecan Microplate Reader.

Cispalladium Synthesis

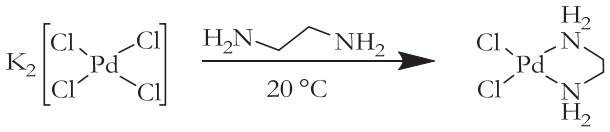
Cispalladium was synthesized using tetrachloropalladium (K_2PdCl_4) and potassium chloride (KCl) as shown in **Scheme 1** using procedures adapted from Pertruzzella *et al.*[9] Following the microwave and an ice bath, the precipitate and solute were separated through centrifugation, which was completed at 13.6 x 10^3 g for 10 minutes. After drying, the structure of the product was confirmed by IR (ATR).



Scheme 1. Synthesis of cispalladium using a microwave[9]

Dichloro-(ethylenediamine)-platinum (II) Synthesis

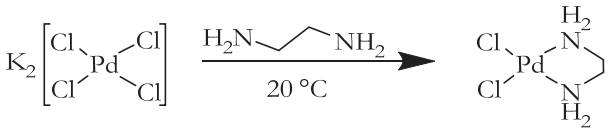
The cisplatin analogue was synthesized as shown in **Scheme 2**. Potassium tetrachloroplatinate (0.244 mol) and ethylenediamine (0.244 mol) were dissolved in a 1:1 mole ratio in deionized water so that each reagent had a final concentration of 0.11 M, while stirring at room temperature (~20 °C) for approximately 20 minutes. Following centrifugation (13.6 x 10^3 g, 10 mins.), the supernatant was discarded. After drying, the structure of the product was confirmed by IR (ATR) and produced a 20.5% yield.



Scheme 2. Synthesis of dichloro-(ethylenediamine)-platinum(II)

Dichloro-(ethylenediamine)-palladium (II) Synthesis

The cisplatin analogue was synthesized as shown in **Scheme 3**. Potassium tetrachloropalladate (0.244 mol) and ethylene diamine (0.244 mol) were dissolved in a 1:1 mole ratio in deionized water so that each reagent had a final concentration of 0.11 M, while stirring at room temperature (~20 °C) for approximately 20 minutes. Following centrifugation (13.6 x 10^3 g, 10 mins.), the supernatant was discarded. After drying the structure of the product was confirmed by IR (ATR) and produced a 49.1% yield.



Scheme 3. Synthesis of dichloro-(ethylenediamine)-palladium(II)

Cell Culture and Cytotoxicity Assay

Each of the cisplatin analogues was tested for cytotoxicity as shown in **Figure 4**. During the first trial, SK-OV-3 cells were plated in a 96-well round-bottom plate at 1000 cells/well. Following a 24-hour incubation (5% CO_2, 37 °C), four different treatments including cisplatin, cispalldium, dichloro-(ethylenediamine)-platinum(II), and dichloro-(ethylenediamine)-palladium(II) dissolved in 0.9% sodium chloride (NaCl) solution were separately administered in quadruplicates with five half-serial dilutions in concentrations ranging from 100 μg/ml to 6 μg/ml. The control wells received a 0.9% NaCl solution *in lieu* of a treatment.

Following a 72-hour incubation period, cells were washed with PBS (100 μl/well) and then incubated at 20 °C in 10% glutaraldehyde solution (100 μl/well). After another PBS (100 μl/well) wash, the cells were stained using 1X crystal violet solution (50 μl/well) and incubated at 37 °C. The wells were washed twice with PBS (100 μl/well) and any remaining crystal violet was solubilized with 33% acetic acid (100 μl/well). The wells were then shaken to dissolve the crystal violet and scanned on an absorbance plate reader at 580 nm with reference at 650 nm using cvsinglescan and cvsinglescancontrol. Cytotoxicity was

calculated by averaging the absorbances of each quadruplicate and then dividing the average treatment absorbance (A_{drug}) by the average absorbance of the control ($A_{control}$).

The procedures were repeated in a second trial using three treatments including cisplatin, dichloro-(ethylenediamine)-platinum(II), dichloro-(ethylenediamine)-palladium(II) in quadruplicates with seven half-serial dilutions ranging from 5 μg/ml to 0.08 μg/ml. The control wells received additional DMEM media *in lieu* of a treatment. The IC_{50} scores for cisplatin and dichloro-(ethylenediamine)-platinum(II) were determined using linear regression equations for doses between 0.16 and 1.3 μg/ml. The y-variable in each subsequent equation was substituted with 0.5 and solved for the x-variable.

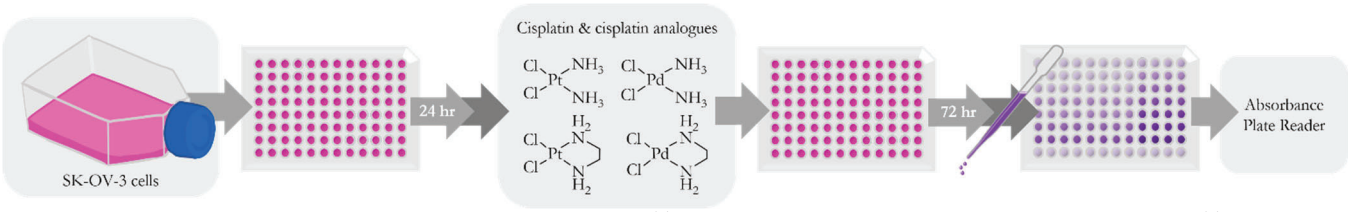


Figure 4. Cytotoxicity assay procedures were completed using SK-OV-3 cells. The cells were incubated and allowed to adhere on a 96 well plate. The following day, each drug was administered to the cells as separate treatments and allowed to incubate for 3 days. The remaining viable cells were stained with a crystal violet solution, and the absorbance was measured.

RESULTS

Analogue Synthesis

The synthesized dichloro-(ethylenediamine)-platinum(II) yielded 20.5% of the theoretical, and the dichloro-(ethylenediamine)-palladium(II) yielded 49.1%. Following synthesis of cispalladium, dichloro-(ethylenediamine)-platinum (II), and dichloro-(ethylenediamine)-palladium (II) IR spectra were obtained for each and plotted against cisplatin and ethylenediamine as shown in **Figure 5** (**(A)** cispalladium**, (B)** dichloro-(ethylenediamine)-platinum (II), **(C)** dichloro-(ethylenediamine)-palladium (II)). Peaks located at 3200 and 1560 nm^{-1} in cisplatin and each of the analogues confirmed the presence of the *cis* amine groups in each of the analogues. Additional peaks at 2800 nm^{-1} in the ethylenediamine, dichloro-(ethylenediamine)-platinum(II), and dichloro-(ethylenediamine)-palladium(II) confirm the presence of alkane groups, which are not existent in the cisplatin IR.

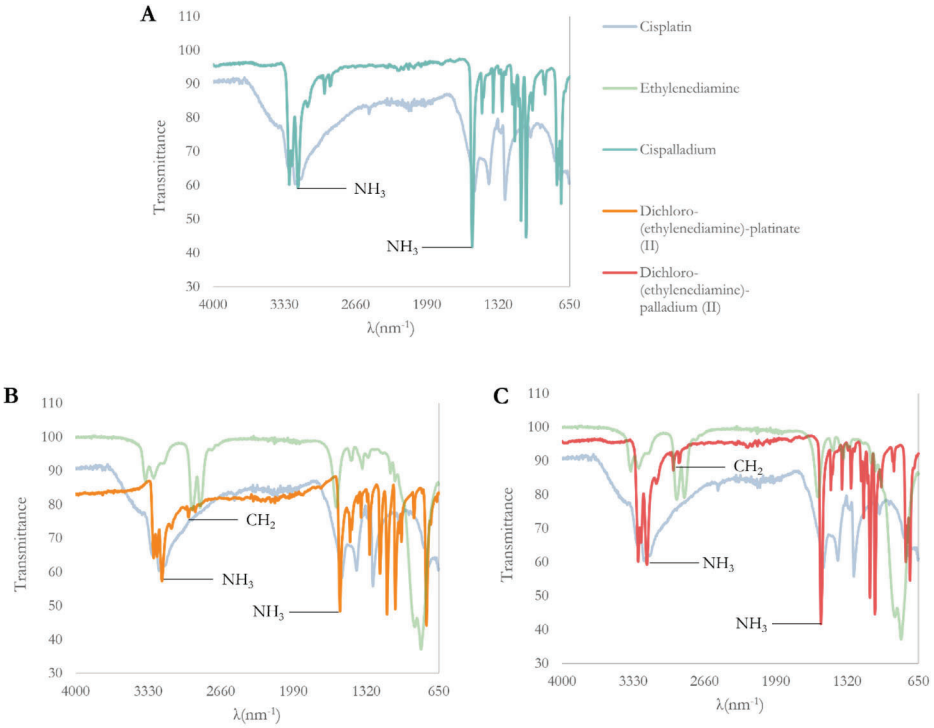


Figure 5. IRs (ATR) of each cisplatin analogue compared to the IR of **(A)** cisplatin. The IRs for **(B)** dichloro-(ethylenediamine)-platinum(II) and **(C)** dichloro-(ethylenediamine)-palladium(II) are also plotted against the IR of ethylenediamine. The peaks indicative of amines and alkanes on each analogue, which are shared with cisplatin or ethylenediamine, are labeled.

Cytotoxicity Trial 1

During the first cytotoxicity trial, cisplatin and each of the three proposed analogues were incubated with SK-OV-3 cells, which were then stained and measured for absorbance to indicate the proportion of remaining viable cells. The cytotoxicity scores of each compound at consecutive concentrations indicated in **Figure 6** reveals that the cytotoxicity scores for cispalladium at every concentration tested were greater than a value of one ($A_{cispalladium}/A_{control}$ >1). Of the three the other three treatments, dichloro-(ethylenediamine)-palladium(II) had the highest cytotoxicity scores beginning at 0.976 at the lowest concentration (100 µg/ml) and progressively decreasing to 0.610 at its highest concentration (100 µg/ml). The cisplatin had the second lowest cytotoxicity score of 0.218 at a concentration of 12.5 µg/ml, and the cytotoxicity scores progressively increased to 0.924 as concentration of the treatment increased to its maximum dose (100 µg/ml). The dichloro-(ethylenediamine)-platinum(II) treatment yielded the lowest cytotoxicity scores of 0.186 at a concentration of 25 µg/ml, and had a maximum cytotoxicity of 0.336 at the lowest administered dose (6.3 µg/ml).

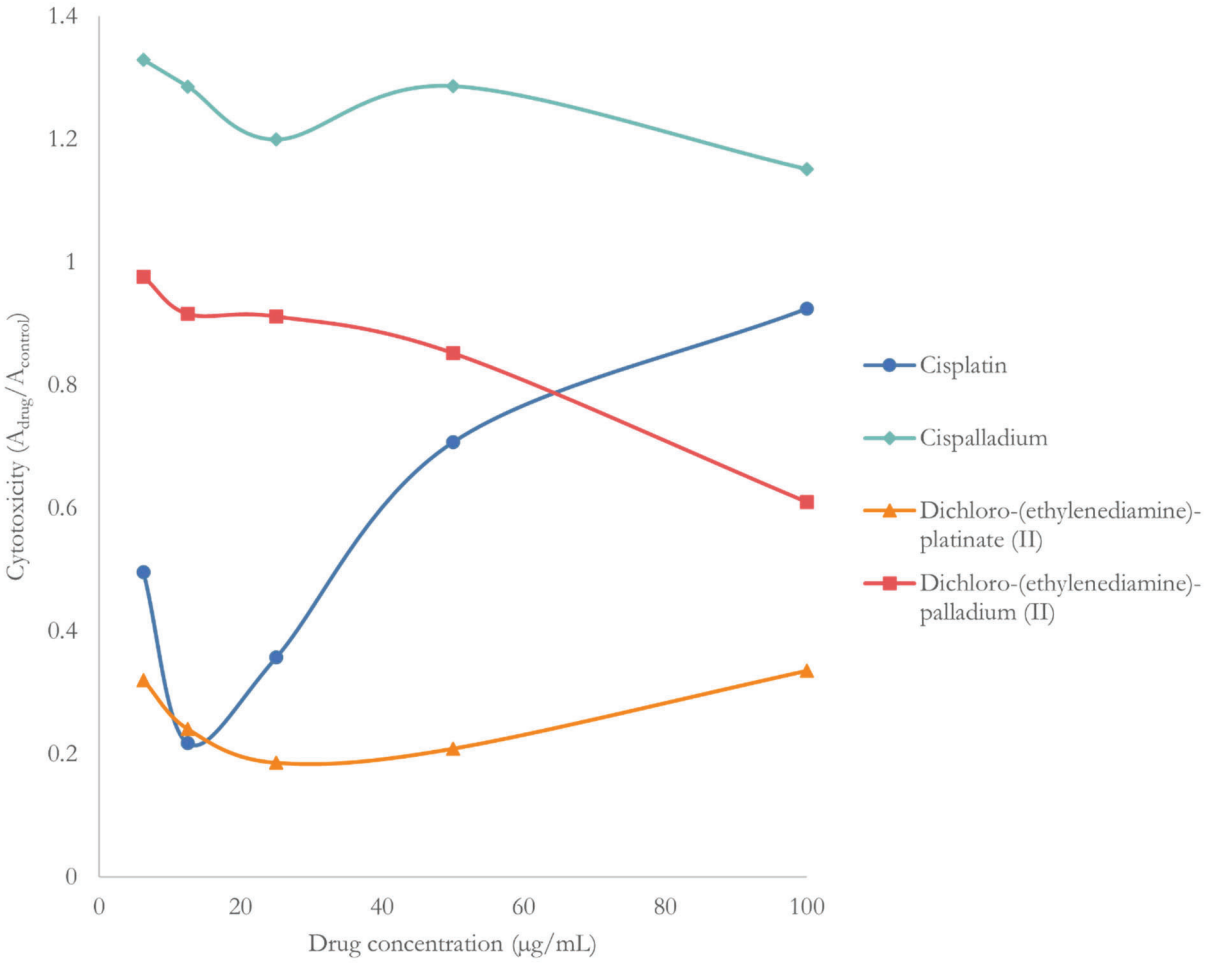


Figure 6. Cytotoxicity of cisplatin;(●), cispalladium (♦), dichloro-(ethylenediamine)-platinum (II) (▲), dichloro-(ethylenediamine)-palladium(II) (■) at five concentrations (100 µg/ml, 50 µg/ml, 25 µg/ml, 12.5 µg/ml, and 6.25 µg/ml).

Cytotoxicity Trial 2

The second trial included cisplatin, dichloro-(ethylenediamine)-platinum(II), and dichloro-(ethylenediamine)-palladium (II). The results shown in **Figure 7** indicate that dichloro-(ethylenediamine)-palladium was the least efficacious with the highest cytotoxicity scores between 0.830 and 1.098. The cytotoxicity scores for cisplatin and dichloro-(ethylenediamine)-platinum(II) followed a similar trend to each other. The IC_{50} scores of the two compounds were determined using linear regression equations

as shown in **Figure 8**. Substituting 0.5 for the y-variable and solving for the concentration indicated by the x-variable yielded an IC_{50} equal to 0.61 µg/ml for cisplatin and an IC_{50} equal to 0.77 µg/ml for dichloro-(ethylenediamine)-platinum(II).

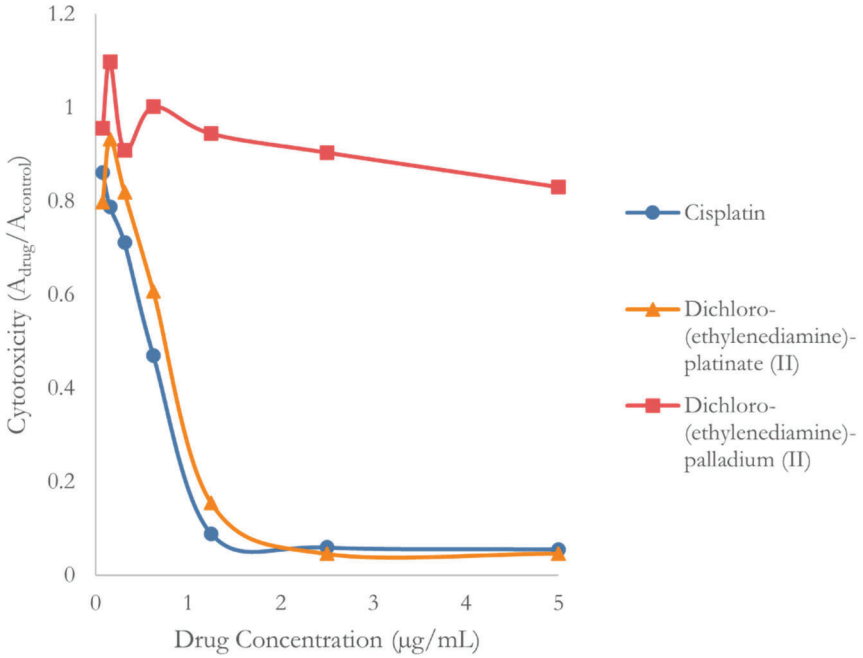


Figure 7. Cytotoxicity of cisplatin (●), dichloro-(ethylenediamine)-platinum(II) (▲), and dichloro-(ethylenediamine)-palladium(II) (■) in the second trial at seven concentrations (5 µg/ml, 2.5 µg/ml, 1.3 µg/ml, 0.63 µg/ml, 0.31 µg/ml, 0.16 µg/ml, 0.08 µ/ml).

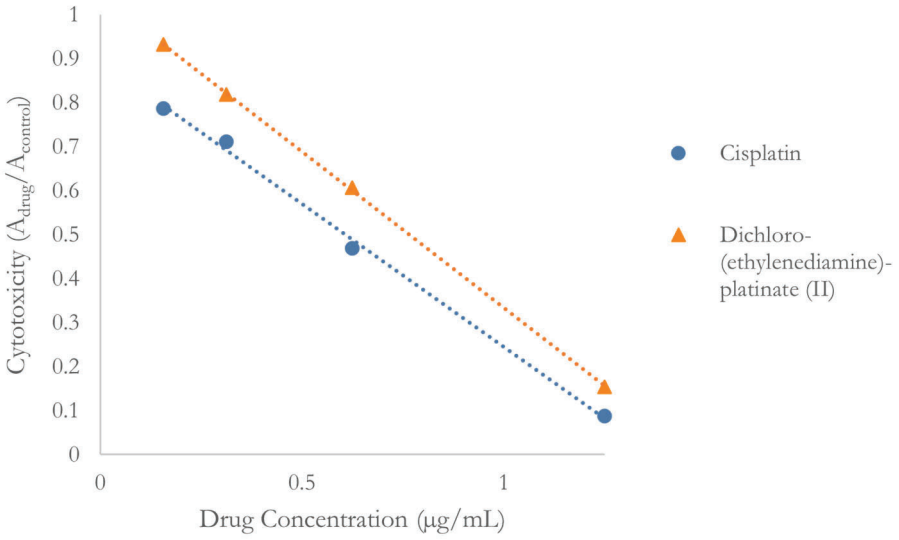


Figure 8. Linear regressions for the cytotoxicity of cisplatin and dichloro-(ethylenediamine)-platinum(II) between 0.16 and 1.3 µg/ml. The IC_{50} for each treatment was calculated using the linear regression equation associated with cisplatin (● $y = -0.6494x + 0.8944$; $R^2 = 0.9973$) or dichloro-(ethylenediamine)-platinum (▲ $y = -0.7095x + 1.0433$; $R^2 = 0.9998$) and found to be 0.61 µg/ml and 0.77 µg/ml, respectively.

DISCUSSION

Synthesis of the proposed analogues was completed to create a ring-stabilized alternative treatment to cisplatin, which may exhibit less toxicity than cisplatin or serve as a treatment once cisplatin resistance develops. The identity of each analogue was confirmed using IR spectra. The existence of amine groups is suggested by the similar peaks in the cisplatin and analogue IRs at 3200 and 1560 nm^{-1} as shown in **Figure 5**. Additionally, the existence of alkane groups at similar peaks in ethylenediamine and two of the analogue IRs, dichloro-(ethylenediamine)-platinum(II) and dichloro-(ethylenediamine)-palladium(II), suggests the presence of alkane groups which are not present in the cisplatin IR. Therefore, the similarities and differences in the IR of cisplatin, ethylenediamine, and the analogues confirm the identities of each of the analogues.

From the first cytotoxicity trial, it was determined that cispalladium was not efficacious as none of the cytotoxicity scores dipped below a value of 1.00 as shown in **Figure 6**. Since the cytotoxicity scores represent what ratio of SK-OV-3 cells were killed compared to the control which received no treatment based on absorbance readings ($A_{cispalladium}/A_{control}$), the results suggest that cispalladium did not cause any detectable cell death, and thus was not efficacious. Of the three treatments which did induce cell death ($A_{cispalladium}/A_{control}<1$), dichloro-(ethylenediamine)-palladium was the least efficacious, with a minimum cytotoxicity score of 0.610. The minimum cytotoxicity score for cisplatin was the second lowest at 0.218, while the dichloro-(ethylenediamine)-platinum(II) yielded the lowest cytotoxicity score of 0.186, providing initial evidence that the analogue may be more cytotoxic than cisplatin. The second trial, however, contradicted these results. Upon further inspection of the cytotoxicity scores in **Figure 6**, one can appreciate the increase in cytotoxicity of cisplatin as the dosage was increased. These results suggest that cisplatin solution had reached supersaturation, causing some of the drug to come out of solution. As a result, the cisplatin would have been unable to be taken up by the plated cells to induce damage to the DNA. Additionally, each of the compounds was dissolved in a 0.9% NaCl solution and applied to the cells rather than DMEM media which may have affected cell growth. The control for this group also received a volume of 0.9% NaCl equivalent to the DMEM media previously administered.

Given the results and limitations from the first cytotoxicity experiment, the experiment was rerun using three treatment groups: cisplatin, dichloro-(ethylenediamine)-platinum(II), and dichloro-(ethylenediamine)-palladium(II). Each drug was dissolved in the appropriate media, and the control cells received the same cell media to mitigate the potential limitations from the first experiment. Additionally. the concentrations at which the compounds were administered to the treatment groups was lowered to prevent supersaturation. As shown in **Figure 7**, dichloro-(ethylenediamine)-palladium(II) was the least efficacious and failing to reach a cytotoxicity score below 0.830 within the examined dosages, which is consistent with the previous results. On the contrary, the results suggest that cisplatin and dichloro-(ethylenediamine)-platinum(II) have similar efficacy, as their cytotoxicity scores followed a similar trend. This conclusion is further supported by the calculated IC_{50} values using linear regression equations for cisplatin and dichloro-(ethylenediamine)-platinum(II) which were 0.61 μg/ml for cisplatin and 0.77 μg/ml for dichloro-(ethylenediamine)-platinum(II). The calculated IC_{50} value in this work is also consistent with previously published IC_{50} concentrations for cisplatin.[10] One potential limitation to this cytotoxicity assay is the inconsistent cell incubation conditions. Throughout the incubation stages of the assay and prior passaging of the SK-OV-3 cells, the CO_2 concentration dipped below 5% multiple times, disrupting the ideal growth conditions.

Overall, the results suggest that dichloro-(ethylenediamine)-platinum(II) may serve as a cisplatin alternative due to its comparable IC_{50} value to that of cisplatin, while cispalladium and dichloro-(ethylenediamine)-palladium(II) are not effective. Should individuals receiving cisplatin, develop resistance to the drug, dichloro-(ethylenediamine)-platinum(II) may serve as a similarly efficacious alternative, which is stabilized in the *cis* confirmation by a ring structure. Since the arrangement of cisplatin is significant to its mechanism, the ring formed by ethylenediamine in this analogue may prevent formation of a *trans* isomer that would typically disrupt its mechanism of action.

Overall, the conflicting cytotoxicity levels between the cisplatin and dichloro-(ethylenediamine)-platinum(II) versus cispalladium and dichloro-(ethylenediamine)-palladium(II) are most likely due to the differences in the metallic center of the compounds. Palladium and platinum clearly have different binding affinities to both the temporary water ligands as well as the eventual guanine bases, which likely leads to the palladium-containing compounds binding less effectively to DNA, which is significant to the mechanism of cisplatin.

Furthermore, to confirm that dichloro-(ethylenediamine)-platinum(II) may serve as cisplatin alternative following the development of cisplatin resistance, future cytotoxicity studies on the compound in cisplatin-resistant cell lines should be

conducted. Additionally, the cytotoxicity of the compound should be tested at lower concentrations to confirm the calculated IC_{50} concentration, as previous work has cited the IC50 concentration of cisplatin have varied between 0.022 μg/ml and 0.56 μg/ml.

While, dichloro-(ethylenediamine)-platinum(II) may offer a favorable alternative treatment to cisplatin also due to its simplistic synthetic requirements, the procedures proposed in this work resulted in a minimal yield (20.5%). Therefore, other synthetic methods or adjustments to these procedures may be required to provide an appropriate yield for mass production of the compound. While the reagents tetrachloroplatinate and ethylenediamine for the synthesis of dichloro-(ethylenediamine)-platinum(II) are required to coordinate in a one to one (1:1) ratio, the formation of the analogue may be pushed to a greater yield by keeping tetrachlroplatinate as the limiting reagent and supplementing a greater equivalent of ethylenediamine as opposed to the 1:1 equivalents utilized in this work.

Based on the results from the IR spectra, and cytotoxicity assay, it can be concluded that all three cisplatin analogues were successfully synthesized, but only dichloro-(ethylenediamine)-platinum(II) provided an efficacious potential alternative to cisplatin.

CONCLUSIONS

While all three cisplatin analogues were successfully synthesized, only dichloro-(ethylenediamine)-platinum(II) was efficacious with an IC_{50} value of 0.77 μg/ml. Additionally, the proposed synthesis of the analogue is simplistic, though may require adjustments to increase synthetic yield. In the future, dichloro-(ethylenediamine)-platinum(II) must be tested on cisplatin-resistant cells to confirm their potential as a cisplatin alternative for individuals who develop resistance to cisplatin.

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ABOUT STUDENT AUTHORS

Samantha Rea and Brooke Hornberger will graduate from Stevenson University in December 2021, while Alexia Smith and Grace Fillmore will graduate in May 2022 also from Stevenson University.

PRESS SUMMARY

A widely used cancer chemotherapy drug called cisplatin has limited use due to its toxicity from the incorporated heavy metal platinum, and the resistance patients often develop to the drug, which results in cancer reoccurrence. Additionally, two configurations of the drug exist, one of which is ineffective and may reduce the efficiency of the cancer treatment. To mitigate

these challenges, three similar compounds were synthesized to serve as potential alternatives to cisplatin should an individual develop cisplatin resistance. Each of these structures either replaced the platinum within cisplatin using a less toxic metal called palladium, added a second structure called ethylenediamine to prevent formation of the ineffective version of cisplatin, or used a combination of both methods. Each of these compounds was tested against cisplatin for its ability to kill ovarian cancer cells. While two of the new compounds were ineffective, the third compound called dichloro-(ethylenediamine)-platinum(II) was able to kill the ovarian to a similar degree as cisplatin, suggesting that this new compound may provide an alternative treatment for cancer patients.