Synthesis and NMR characterization of a new ligand, 2-acetylpyrazine-tert-butylthiosemicarbazone, and its palladium (II) and platinum (II) complexes

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Abstract

The new ligand, 2-acetylpyrazine-tert-butylthiosemicarbazone (APT-tBTSC) and its palladium (II) complex have been synthesized. After the synthesis process, the ligand and Pd complex were characterized and analyzed by ^{1}H Nuclear Magnetic Resonance spectrometry (NMR), ^{13}C NMR, ^{1}H-^{13}C HSQC, and ^{1}H-^{15}N HSQC. The acronym HSQC stands for Heteronuclear Single Quantum Coherence. We have determined that this thiosemicarbazone compound ligates to Pd in a tridentate monoanionic fashion forming a metal complex with the formula [Pd(APZ-tBTSC)Cl]. The metal complex was tested for biological behavior with a panel of seven microbes. The palladium complex was found to be highly active against Gram positive bacteria.

Synthesis of APZ-tBTSC Ligand

The ligand, APZ-tBTSC, was synthesized by combining 0.5079g of acetylpyrazine and 0.6123g of 4-tert-butyl-3-thiosemicarbazide (equimolar amounts) in a small Erlenmeyer flask. Approximately 20 mL of isopropanol was added to help dissolve the mixture along with one drop of concentrated H_2SO_4 as a catalyst. The mixture was equipped with a stir bar and covered. The mixture was left to stir for approximately 48 hours and heated at 60℃ for 24 hours. The white precipitate was filtered and washed with approximately 5-8 mL of isopropanol and left to dry for approximately 24 hours. The final product weighed 0.4035g. The MIC was determined using various bacteria, yeast and molds, and ^{1}H NMR spectra were obtained in DMSO-d6 using a Bruker Ascend 500MHz NMR.

Synthesis of [Pd(APZ-tBTSC)Cl] Complex

The palladium complex was synthesised by combining 0.1011g of dichlorobis (benzonitrile) palladium (II) and 0.0669g of the ligand, APZ-tBTSC, in a 25mL Erlenmeyer flask accompanied by a small stir bar. Approximately 15 mL of acetone was added to the mixture in order to help dissolve the two components. The mixture was left and stirred for approximately 48 hours with no heat. The red precipitate was filtered and washed with approximately 5 mL of acetone and then dried. The dry product weighed 0.0815 g. MIC studies and ^{1}H NMR spectra were collected (Fig. 1).

Synthesis of [Pt(APZ-tBTSC)Cl] Complex

The platinum complex was synthesised by measuring out 0.151g of platinum and 0.08g of APZ-tBTSC. Each reactant was individually dissolved in 10 mL ethanol and combined by pipetting each into a 50mL Erlenmeyer flask. The mixture was equipped with a stir bar and condenser and placed in an oil bath at 75℃. The mixture was left on heat and stirred for 24 hours. After the first few seconds of stirring a color change from light red to dark red was noted. The red precipitate was filtered and washed with approximately 10 mL of ethanol and dried. The final product weighed 0.1388g. MIC studies (Fig. 3) and ^{1}H NMR spectra were collected (Fig. 2).

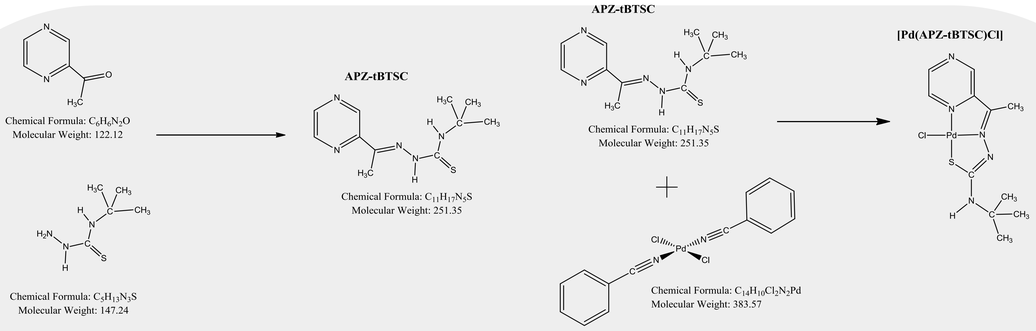


Figure 1. The synthesis schemes for synthesis of APZ-tBTSC and [Pd(APZ-tBTSC)Cl]

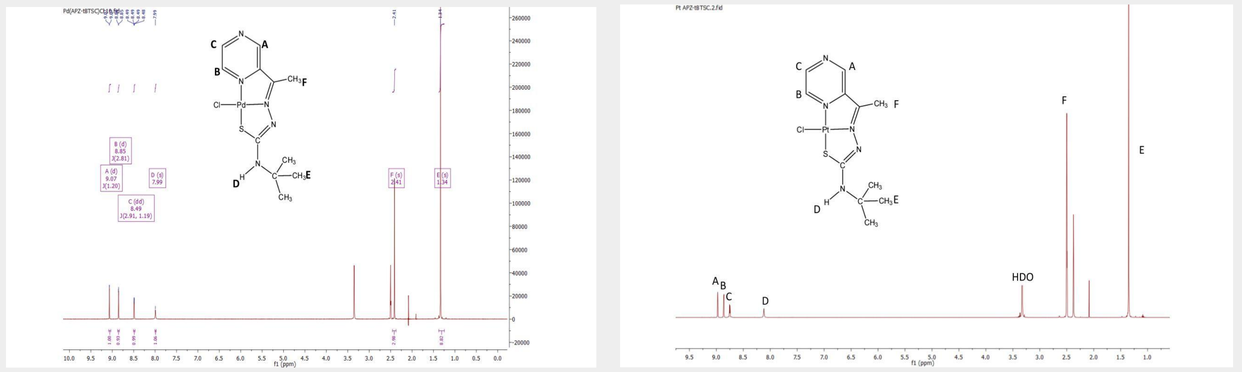
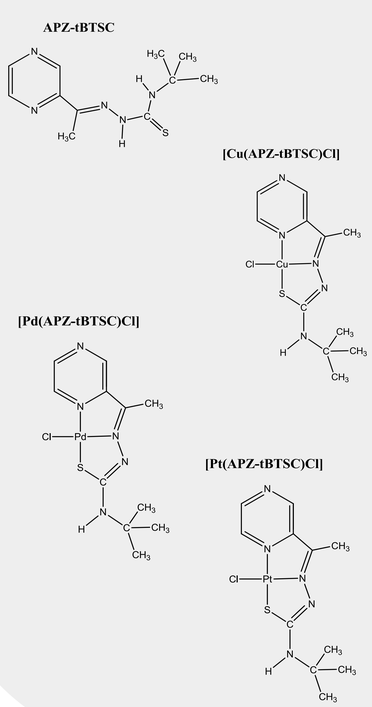


Figure 2. The ^{1}H NMR spectra of the metal complexes [Pd(APZ-tBTSC)Cl] and [Pt(APZ-tBTSC)Cl]



APZ-tBTSC

Conc	1	2	3	4	5	6	7	8	9	10	Bact control
ug/mL	500.0	250.0	125.0	62.50	31.25	15.625	7.813	3.906	1.953	0.9766	
Microrganisms											
Escherichia coli	+	+	+	+	+	+	+	+	+	+	+
Staphylococcus aureus	–	–	–	–	–	–	–	–	–	–	+
Bacillus subtilis	–	–	–	–	–	–	–	–	–	–	+
Pseudomonas aeruginosa	+	+	+	+	+	+	+	+	+	+	+
Aspergillus niger	–	–	–	–	–	–	–	–	–	+	+
Candida albicans	–	–	–	–	–	–	+	+	+	+	+
Sacchromyces cerevisiae	–	–	–	–	–	–	–	–	+	+	+

[Cu(APZ-TbTSC)Cl]

Conc	1	2	3	4	5	6	7	8	9	10	Bact control
ug/mL	250.0	125.0	62.5	31.25	15.625	7.8125	3.906	1.953	0.977	0.4883	
Microrganisms											
Escherichia coli	–	–	–	–	–	–	–	–	–	+	+
Staphylococcus aureus	–	–	–	–	–	–	–	–	–	–	+
Bacillus subtilis	–	–	–	–	–	–	–	–	–	–	+
Pseudomonas aeruginosa	–	+	+	+	+	+	+	+	+	+	+
Aspergillus niger	–	–	–	+	+	+	+	+	+	+	+
Candida albicans	–	–	–	+	+	+	+	+	+	+	+
Sacchromyces cerevisiae	–	–	–	–	–	+	+	+	+	+	+

[Pd(APZ-tbTSC)Cl]

Conc	1	2	3	4	5	6	7	8	9	10	Bact control
ug/mL	250.0	125.0	62.5	31.25	15.625	7.8125	3.906	1.953	0.977	0.4883	
Microrganisms											
Escherichia coli	–	–	+	+	+	+	+	+	+	+	+
Staphylococcus aureus	–	–	–	–	–	–	–	–	–	–	+
Bacillus subtilis	–	–	–	–	–	–	–	–	–	–	+
Pseudomonas aeruginosa	+	+	+	+	+	+	+	+	+	+	+
Aspergillus niger	–	–	–	+	+	+	+	+	+	+	+
Candida albicans	–	–	–	–	+	+	+	+	+	+	+
Sacchromyces cerevisiae	–	–	–	–	–	+	+	+	+	+	+

[Pt(APZ-tBTSC)] (100mg)

Conc	1	2	3	4	5	6	7	8	9	10	Bact control
ug/mL	250.0	125.0	62.5	31.25	15.625	7.8125	3.906	1.953	0.977	0.4883	
Microrg											
Sacchromyces cerevisiae	+	+	+	+	+	+	+	+	+	+	+
Aspergillus niger	+	+	+	+	+	+	+	+	+	+	+
Candida albicans	+	+	+	+	+	+	+	+	+	+	+
Pseudomonas aeruginosa	+	+	+	+	+	+	+	+	+	+	+
Escherichia coli	+	+	+	+	+	+	+	+	+	+	+
Bacillus subtilis	–	–	+	+	+	+	+	+	+	+	+
Staphylococcus aureus	–	–	–	+	+	+	+	+	+	+	+

Figure 3. The Minimum Inhibitory Concentrations (MIC) needed to inhibit microbe growth. Red Blocks indicate inhibition.

Results and Discussion

The metal complexes of Cu(II), Pd(II) and Pt(II) with certain thiosemicarbazone ligands have anti-cancer properties. (1-5) The new ligand APZ-tBTSC has been synthesized by our traditional thiosemicarbazone synthesis, as shown in Figure 1 and the ^{1}H NMR spectrum (Figure 2) gives evidence that our proposed structures are correct. We observe the thiazole ring proton, the hydrazinic proton, the thioamide proton, as well as the benzylic protons. The palladium and platinum complexes are similar, but different, and have no hydrazinic proton, confirming the coordination mode.

Conclusion

The synthesis of these ligands coordinate transition metals such as Pd^{2+} and Pt^{2+} in a tridentate, mono-anionic fashion by loss of the hydrazinic proton. The MIC studies reveal that at least against microbes, several of the compounds have high activity against proliferation, especially against Gram positive bacteria.

The future work will be to increase the number of thiosemicarbazone ligands based on this substrate, and to synthesize new metal complexes, including the use of Cu^{2+}, and to look for activity against the Topoisomerase IIα enzyme, which is essential in proliferation of breast cancer tumors and cell lines.

Acknowledgements

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