Response to the reviewers JMCS Manuscript 563

**Synthesis, characterization and cytotoxic activity of tioconazole coordination compounds with nickel(II), palladium(II) and platinum(II)**

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We thank the reviewers for all their suggestions and observations that contributed to improve our manuscript

Referee: A

Review for Manuscript 563, titled: Synthesis, characterization and cytotoxic activity of tioconazole coordination compounds with nickel(II), palladium(II) and platinum(II)

After a careful review of the manuscript, several points have to point out:

- “There are several techniques for coordination compounds involved in biological activity that were not done, such as electrochemical studies or EPR for Ni paramagnetic compounds”

**Reply**

*For the inert palladium(II) and platinum(II) metal, it is not possible to change their oxidation state under the conditions used in this work. For this reason the electrochemical studies were not carried on.*

*The nickel(II) oxidation state, may undergo redox reactions under severe experimental conditions, to Ni(III) or Ni(I), which is not favored under the experimental conditions used in this work. The EPR technique is not useful for the silent d8 Ni(II) compounds, only for d7 Ni(III) or d9 Ni(I).*

- “The stoichiometry for reaction made as 1:1, giving; an octahedral geometry. In [Ni(tcnz)2(NO3)2].H2O the coordinated nitrate presented a bidentate coordination mode, while for the [Ni(tcnz)2(OAc)2].3H2O compound, the acetate behaves as a bridging ligand.

But for 1;3 they said on the reaction synthesis, three or six ligands were coordinate to the nickel(II) atom, [Ni(tcnz)3Br2(H2O)], [Ni(tcnz)6]Cl2 and [Ni(tcnz)6]Br2. The palladium(II) and platinum(II) compounds, [Pd(tcnz)2Cl2], [Pt(tcnz)2Cl2].2H2O and [Pd(tcnz)2(OAc)2], stabilized a trans-square planar geometry. The compounds [Ni(tcnz)6]X2 are octahedral…..”

Not analysis or explication is made for these differences

**Reply**

*Compound [Ni(tcnz)3Br2(H2O)] was obtained when using a 1:1 ratio, while the [Ni(tcnz)6]Cl2 and [Ni(tcnz)6]Br2 compounds were obtained from a 1:3 ratio. This was corrected in the abstract and in the discussion.*

*Regarding the geometry stabilized for the metal ions, it is well establish that platinum(II) and paladium(II) stabilize only square planar geometries, and due to the steric effect of the bulky ligand a* *trans isomer for the compounds is stabilized, as it was shown from their NMR spectra. The octahedral geometry for the nickel(II) compounds was corroborated for their electronic spectra and X-ray crystal structures for compounds 4 and 5.*

- Crystal report

Compound 4 is described as colorless in Table 1 but in the experimental part says purple??

**Reply**

*It was an error on Table 1, this was corrected to purple, which is the color of the obtained compound.*

- In the In vitro experimental part says

…in 5% DMSO and saline to give a 1 mM stock solution by initial dissolution in DMSO followed by dilution with saline .

Should be clarified as saline what?? serum??

**Reply**

*The text was modified as follows:*

*“The metal complexes (cisplatin and tioconazole control was added to the plates to act as a positive and comparative control) were tested in 5% DMSO and in a physiological solution to 0.9% NaCl to give a 1 mM stock solution”*

- Page3

Palladium(II) compounds have the advantage of having fewer side effects, as well as greater lipophilicity. Reference should be given.

**Reply**

*This observation is for the compounds on reference 17, but is not true for other similar compounds, so we removed this discussion. .*

- Page 4

Coordination compounds of Ni(II) salts were synthesized by similar procedures. A solution of one mole equivalent of the corresponding transition metal salt in acetone was added to a solution of one mole equivalent of tioconazole in acetone, with exception of Ni(OAc)2∙4H2O where ethanol was used as solvent. What was obtained ?, should say 1,2,3…

**Reply**

*This text was modified to:*

*“A solution of one equivalent of the corresponding transition metal salt in acetone was added to a solution of one equivalent of tioconazole in acetone, with exception of the [Ni(tcnz)2(OAc)2]2∙3H2O* ***3*** *compound where ethanol was used as solvent”*

- Printing or spelling mistakes

Experimental part

page 3

--Says plating must say placing

-- says wthi must said with

**Reply**

*It was corrected*

- p4

as their biological activity as possible anticancer agents in HCT-15, HeLa, MCF-7 and PC-3 cell lines, were studied, must be, was studied

**Reply**

*It was corrected*

- The complexes [PdCl2(CH3CN)2] and [PtCl2(CH3CN)2] was synthesized; must say were synthesized with a universal ATR, must be an universal ATR

**Reply**

*It was corrected*

- The discussion is very superficial; no evidences are given or discussed. For instance not specific reason about the structures proposed, as trans isomers, or bidentated NO3 ligands or AcO bridge betwen 2 metals. Not experimental conditions, or stereochemical reasons are given for these proposals.what are the

The same is for cytotoxicity, no discussion for the different behaviors, is presented.

**Reply**

*The discussion was improved regarding the proposed structures. The nitrate and acetate binding modes are based on the experimental characterization: IR, electronic spectra and conductivity.*

The manuscript cannot be accepted as is presented, for lack of discussion and more studies should have been done.

**Referee: B**

The manuscript deals with the synthesis, characterization and biological evaluation of Ni(II), Pd(II) and Pt(II) complexes of the monodentate ligand tioconazole. The work has been properly performed but I have some concerns:

- Keywords: platinum(II)

**Reply**

*The Keywords regarding the metal ions were corrected*

-English should be revised, there are some mistakes.

**Reply**

*The English throughout the manuscript was revised*

- Resumen: los compuestos sintetizados fue estudiada en dos diferentes líneas celulares de carcinoma humano. There are four cell lines and not two.

**Reply**

*It was corrected*

- under Introduction: Authors state: Palladium(II) compounds have the advantage of having fewer side effects, as well as greater lipophilicity.

Please, put references for these statements. Do Pd compounds really have fewer side effects than analogous Pt compounds? In addition, are authors stating that Pd compounds show higher lipophilicity than their Pt analogues? Why?

**Reply**

*This observation is for the compounds on reference 17, but is not true for other similar compounds, so we removed this discussion.*

- Do authors have idea about the stability in solution of the synthesized metal complexes? Are they stable in solution during the time needed for the biological tests?

**Reply**

*The stability of the compounds in a DMSO solution was studied for 24 hours and they were stable. Their spectra were included in the Supplementary Information, and it is mentioned in the text.*

- Authors put the results of conductivity measurements under the title Magnetic susceptibility: The conductivity was measured for all compounds, showing good agreement for the neutral compounds with coordinated halides, nitrate or acetate, compounds 1-3 and 6-8, while 4 and 5 presented a 1:2 conductivity, Table 2.

I do not agree. Please, change place.

**Reply**

*The title of the table was changed to: “Electronic transitions, magnetic moments and molar conductivity of tcnz coordination compounds with NiII, PdII and PtII”*

- About conductivity measurements results (page 13): Authors interchange electrolyte 2:1 with electrolyte 1:2. Please, decide and put a reference.

**Reply**

*It was corrected to 1:2.*

*Compounds 1-3 and 6-8 were measured in acetone, while compounds 4 and 5 in acetonitrile. The experimental data for the compounds is in accordance with the reported ones: ΛM**molar conductance (µS cm-1) for 1x10-3 M solutions in acetone (no-electrolyte = 0-50 µS cm-1) and acetonitrile (electrolyte 1:2 = 220-300 µS cm-1) at 293 K., and it was included the reference [43]: Robert J. Angelic, Synthesis and technique in inorganic chemistry, University Science Books, 2nd Ed. 1986, page 213.*

Kind regards

Prof. Norah Barba-Behrens