# Copper(II) complexes of isoniazid-derived hydrazones: Synthesis, characterization and cytotoxicity against tumor cell lines

**Gisele dos S. S. Firmino[1] (PG), Marcus V. N. de Souza[2] (PQ), Claudia do Ó. Pessoa[3] (PQ), Jackson A. L. C. Resende[4] (PQ), Heloisa Beraldo[5] (PQ), Josane A. Lessa[1]* (PQ) *email: josane@uerj.br**

[1] *Instituto de Química, Universidade do Estado do Rio de Janeiro, Rio de Janeiro – RJ, Brasil*
[2] *Instituto de Tecnologia em Fármacos – Farmanguinhos, Fundação Oswaldo Cruz – FioCruz, 21041-250, Rio de Janeiro, RJ, Brazil*
[3] *Laboratório de Oncologia Experimental, Universidade Federal do Ceará, 60430-270, Fortaleza, CE, Brazil*
[4] *Instituto de Química, Universidade Federal Fluminense, 24020-141, Niterói, RJ, Brazil*
[5] *Departamento de Química, Universidade Federal de Minas Gerais, 31270-901, Belo Horizonte, MG, Brazil*

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## Introduction

Cancer is the leading cause of death in economically developed countries and the second leading cause in developing countries[1]. It is estimated that the overall incidence of cancer will reach 25 million of people in 2032[2]. Such estimative, together with other aspects, corroborate the importance of searching for compounds with potential cytotoxic effect. Coordination of organic molecules with known pharmacological activity to metals is one strategy to the development of possible metallodrugs. In this study we report the synthesis, characterization and the cytotoxic action against OVCAR-8 (ovarian cancer), HCT-116 (colon adenocarcinoma) and SF-295 (glioblastoma multiforme) tumor cell lines of copper(II) complexes with 2-pyridinecarbaldehyde- (HPCIH, **1**), 2-acetylpyridine- (HAPIH, **2**), 2-benzoylpyridine- (HBPIH, **3**), 2-pyridineformamide- (HPAmIH, **4**) and 2-pyridineformamide- (HPzAmIH, **5**) isonicotinoyl hydrazones (Fig. 1).

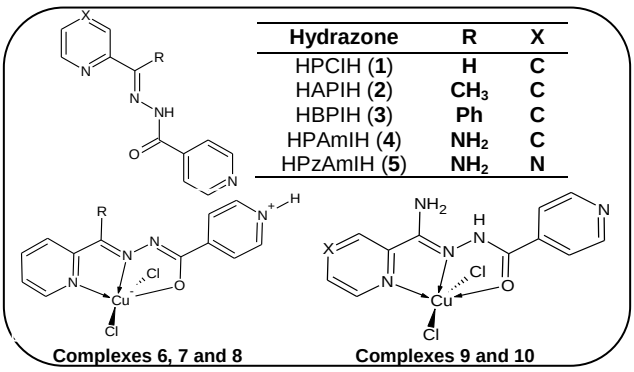


**Figure 1.** Structures of hydrazones **1–5** and its Cu(II) complexes **6–10**

## Results and Discussion

The complexes were prepared by reaction between the hydrazone and $CuCl_2$ (1:1) in methanol under reflux, and characterized by elemental analysis, infrared and electronic spectroscopies, conductimetry and magnetic susceptibility measurements. According to the analyses, the following complexes were obtained: $[Cu(HPCIH)Cl_2]\cdot 1/2H_2O$ (**6**), $[Cu(HAPIH)Cl_2]\cdot H_2O$ (**7**), $[Cu(HBPIH)Cl_2]\cdot 5/2\ H_2O$ (**8**), $[Cu(HPAmIH)Cl_2]\cdot H_2O$ (**9**) and $[Cu(HPzAmIH)Cl_2]\cdot H_2O$ (**10**), in which neutral hydrazones are attached to Cu(II) by the NNO system. For **6–8**, the hydrazones are in the zwitterionic form (Fig. 1). Crystal structures of **7**, **8** and **10** were determined by X- ray diffraction.

Cytotoxic activity assays showed INH, an antimycobacterial drug, presents low activity against the three cell lines, whereas **2** and **3** are the most effective hydrazones. In general, for the hydrazones, the higher the logP, the higher the activity. Coordination to Cu(II) leads to increasing or maintenance of the activity, as observed for complexes **6–9** (Table 1).

**Table 1.** Growth inhibition (%) of OVCAR-8, HCT-116 and SF-295 cell lines by **1–10**, $CuCl_2$ and INH (5 μg $mL^{-1}$)

| Compound | GI (Mean ± SD) | | |
|---|---|---|---|
| | HCT-116 | OVCAR-8 | SF-295 |
| **1** | 15.74 ± 3.82 | 15.47 ± 2.76 | -6.31 ± 21.46 |
| **2** | 49.79 ± 31.21 | 94.53 ± 3.46 | 72.20 ± 3.74 |
| **3** | 78.69 ± 3.22 | 98.63 ± 3.18 | 34.98 ± 46.73 |
| **4** | 22.37 ± 8.91 | 27.10 ± 6.91 | 38.39 ± 0.72 |
| **5** | 15.88 ± 0.27 | 6.91 ± 1.73 | 2.60 ± 0.79 |
| **INH** | 14.47 ± 6.42 | -3.79 ± 0.33 | 21.01 ± 2.85 |
| **6** | 74.18 ± 2.66 | 18.60 ± 3.26 | 29.49 ± 3.64 |
| **7** | 99.72 ± 0.13 | 101.23 ± 0.22 | 86.18 ± 3.83 |
| **8** | 100.09 ± 0.52 | 101.38 ± 0.44 | 101.39 ± 0.79 |
| **9** | 97.80 ± 2.59 | 93.00 ± 5.11 | 102.36 ± 0.20 |
| **10** | 35.98 ± 5.45 | 0.67 ± 3.37 | 45.61 ± 3.83 |
| **$CuCl_2$** | 42.99 ± 0.45 | 25.60 ± 5.55 | 75.20 ± 0.88 |

## Conclusion

Structural modification of isoniazid and posterior coordination to Cu(II) constituted an efficient way to obtain compounds with significant cytotoxic activity .

## Aknowledgements

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