5th BCNP Brazilian Conference on Natural Products
XXXI RESEM
Atibaia – SP – Brazil
ISBN: 978-85-66836-10-3
Oct. 26–29th 2015

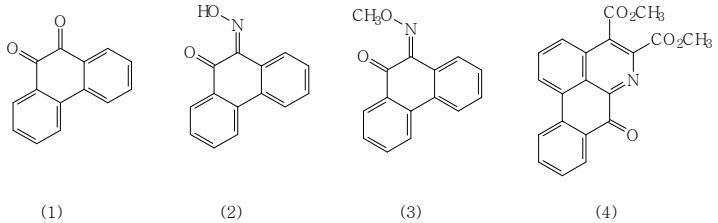
EVALUATION OF ANTIPROLIFERATIVE , MUTAGENIC AND ANTIOXIDANT ACTIVITIES *IN VITRO* OF AN APORFINIC ALKALOID AND ITS INTERMEDIATES OF SYNTHESIS

Tamires Carolina Sedano (IC)[1,2] Adriana Della Torre (PG)[2,3] Anderson Rogério dos Santos (PG)[4], Beatriz H. L. N. S. Maia (PQ)[4], Ana Lucia T. G Ruiz (PQ)[2,3].

1. Pharmaceutical Science, USF; 2. DFT, CPQBA/UNICAMP; 3. PPG BTPB, IB/UNICAMP; 4 Chemistry Department, UFPR tamires.sedano@yahoo.com.br

Purpose of study: The aporfinic alkaloids are a subtype of isoquinolínic alkaloids widely distributed in plants of Annonaceae family, among others [1], with many pharmacologic activities described, including antiproliferative activity [2]. The aim of this work was assess *in vitro* the antiproliferative, mutagenic and antioxidant activities of the aporfinic 7-oxo-7H-dibenzo-quinolina-4,5- dicarboxilato de dimetila (**4**) and its three synthetic precursors (**1-3**) (Figure 1) [3]. Methods and Results: The antiproliferative activity was assessed in tumor [U251 (glioma), UACC-62 (melanoma), MCF7 (breast), NCI/ADR-Res (ovarian, multidrug resistant), 786-0 (kidney), NCI-H460 (lung, NSC), PC-3 (prostate) and HT-29 (colon)] and no tumor human [HaCat (immortalized keratinocytes)] cell lines exposed for 48 h to **1-4** (0.25 - 250 µg/mL) and expressed as the concentration necessary to promote total growth inhibition (TGI). Considering mean TGI values against tumor human cell lines, compounds **1** (mean TGI < 0.71 µg/mL) and **2** (mean TGI < 0.53 µg/mL) showed the more promising antiproliferative activity followed by compound **3** (mean TGI = 3.96 µg/mL); showing that the precursors (**1-3**) of the alkaloid (**4**) were more active than the alkaloid (**4**) (Table **1**). The antiproliferative effect after 4 h-exposion on the CHO-K1 cell line (hamster´s ovary immortalized cells) pointed that the higher non cytostatic concentration to be used in the micronucleus induction assay (mutagenic activity) was 0.25 µg/mL. In comparison to untreated cells [negative (cells in the culture RPMI 1640)], the compounds **1** to **4** did not induce an increase on micronucleus (MN) frequency (0,82 ± 0,10 to 1,22 ± 0,22%) as it was observed for the positive group MMS (methylmethane sulfonate, 25 µg/mL, MN = 6,46 ± 4,56%). The antioxidant activity was assessed by the ability to scavenge DPPH radicals in EtOH solution. The alkaloid **4** showed the higher ability to scavenge free radicals (EC_{50} =1,6 ± 0,3 µg/mL), followed by **3** and **2**, while **1** showed inactive in the test conditions. Conclusions: Based on the results, compounds **1** to **3** showed a promising antiproliferative activity while **4** presented the best ability to scavenge free radicals. Moreover, compounds **1-4** did not show mutagenic effect.

Figure 1: Chemical structure of **1-4**.



(1) (2) (3) (4)

Acknowledgment: FAPESP (2014/23950-7), CPQBA/UNICAMP.

References

[1]. Zhang, A.; Zhang, Y.; Branfman, A. R.; Baldessarini, R. J.; Neumeyer, J. L. 2007. Advances in development of dopaminergic aporphinoids. J. Med. Chem. 50: 171-181.

[2]. Stevigny, C.; Bailly, C.; Quetin-Leclercq, J. 2005. Cytotoxic and antitumor potentialities of aporphinoid alkaloids. Curr. Med. Chem.: Anti-Cancer Agents 5: 173-182.

3. Santos, A. R. Alcaloides e constituintes voláteis de três espécies de *Guatteria*, avaliação da atividade antiproliferativa e antimicrobiana e estudos de biotransformação de um alcaloide oxoaporfínico e seus precursores sintéticos. Pós-Graduação em Química, Departamento de Química, Universidade Federal do Paraná - UFPR, 2014, 134 páginas.