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Keywords: Anti-integrin peptide, Cell migration, Glioblastoma.

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COMPETITION RESPONSE OF PSMA-I&T RADIOLABELED WITH LUTETIUM-177 TO LNCAP, PC-3 AND RWPE-1 CELLS

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A B S T R A C T

Introduction/Justification: 177Lu-PSMA-I&T stands out as a promisor radiopharmaceutical for therapy of prostate cancer based on the specific bind of Glu-urea-Lys pharmacophoric group prostate-specific membrane antigen (PSMA), anchored in the epithelial prostate cell membrane, overexpressed in prostate cancer and increased in metastatic castration-resistant prostate cancer (mCRPC). To study the affinity of 177Lu-PSMA-I&T to target receptor, in vitro competition assay is frequently evaluated. **Objectives:** The purpose of this study was to compare the binding of 177Lu-PSMA-I&T in competition assay to three cell lines. LNCaP and PC-3 are the most used in vitro cell lines studies of prostate cancer research and LNCaP cells are known to have a mutated androgen receptor (AR) (T877A), PC3 is negative for AR expression, and RWPE-1 is frequently used as non-cancerous control. **Materials and Methods:** Radiochemical purity (%RP) of radiolabeling 177Lu-PSMA-I&T was determined by High Performance Liquid Chromatography (HPLC) and Thin Layer Chromatography (TLC) with results of > 95% of main peak and < 3% of free 177Lu, respectively. In vitro assays were performed with LNCaP (ATCC® CRL- 1740, American Type Culture Collection), RWPE-1 and PC-3 (LIM55, FMUSP) cell lines, cultivated in RMPl 1640 medium (Life Technologies, MD, USA) plus 10% v/v Fetal Bovine Serum (FBS) with 100 UI/mL of penicillin and 300 μg/mL of streptomycin. 6-well plates were used, and to each well 2×105 cells. For the total binding, cell incubation medium was removed and replaced with 1 mL of 177Lu-PSMA-I&T (2.22 MBq (60 μCi), approximately 0.076 nmol of peptide, diluted with RMPl 1640 medium/10% v/v FBS) and 1 mL of RMPl 1640 medium, per well. The plates were incubated for 1 h at 37 °C. Cells were washed two times with 1 mL of 0.1 M PBS pH 7.4, followed by an incubation step of 5 minute at room temperature with 1mL ice-cold glycine buffer (0.05 M glycine pH 2.8) and lysed with 2 mL of 1 M sodium hydroxide and incubation step of 10 minutes at room temperature. The same procedure was repeated replacing 1 mL of RMPl 1640 medium with 1mL of competitor (PSMA I&T, molar excess of 7.6 nmol in RMPl 1640 medium). To have the same geometry, the tubes were filled to the same volume (1mL) at each step. An automatic gamma counter with NaI (TI) crystal (D5002 Cobra II, Packard) was used to measure the radioactivity (as cpm) at each tube, and the concentration of 177Lu-PSMA-I&T bonded to the cells was determined in fmol. The assays were performed in quintuplicate for each cell. **Results:** The binding of 177Lu-PSMA-I&T to LNCaP cells showed 1309.3 $\pm$ 176.8 fmol without competitor and 928.5 $\pm$ 84.7 fmol in the presence of competitor, with significant difference (P= 0.0152, GraphPad Prism®). PC-3 cell line showed 28.8 $\pm$ 15.2 fmol without competitor and 25.3 $\pm$ 6.2 fmol with competitor, showing no significant variation (P = 0.6599). The results of binding with RPWE-1 cell line showed 74.3 $\pm$ 6.2 fmol without competitor and 37.9 $\pm$ 7.7 fmol with competitor, a significant difference ($P \leq 0.0001$). **Conclusion:** These results demonstrated the affinity of 177Lu-PSMA-I&T for binding receptors in LNCaP cells and low uptake by PC-3 cells due to the lack of expression of specific receptors. RWPE-1 cell line is positive for AR/PSA mRNA/protein and sensitive to androgens. However, it expresses low levels of PSMA, which likely explains the reduced binding of the radiopharmaceutical.

Keywords: Binding, Lutetium-177, PSMA-I&T, Radiopharmaceutical;.

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SYNTHETIC QUINAZOLINONES AS NEW ANTILEUKEMIC AGENTS

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A B S T R A C T

Introduction/Justification: Acute leukemias are aggressive malignancies characterized by the uncontrolled proliferation of hematopoietic progenitor cells in the bone marrow, leading to impaired production of normal blood cells. Nitrogen heterocycles have attracted the attention of researchers from various fields, with an extensive list of different biological activities. Among the heterocycles, quinazolines stand out, which have been widely investigated for the development of new drugs. **Objectives:** Evaluation of the anticancer activity of quinazolinones against acute leukemic cell lines. **Materials and Methods:** The quinazolinones (A1-A20) were synthesized in the Laboratory of Synthesis of Natural Products and Drugs (Institute of Chemistry, Unicamp). In total 2×104 cells of T cell acute lymphoblastic leukemia (T-ALL), Jurkat, and acute promyelocytic leukemia (APL), NB4, per well were seeded in a 96-well plate in the appropriate medium in the presence of vehicle or different concentrations of compounds (ranged

from 0.8 to 50 μM) for 72 h. Leukemic cells were exposed to the presence of vehicle or different concentrations of compounds (ranged from 0.8 to 50 μM) for 24, 48 and 72 h. Next, 10 μl methylthiazoletetrazolium (MTT, Sigma-Aldrich) solution (5 mg.mL^{-1}) was added and incubated at 37°C, 5% CO2 for 4 h. The reaction was stopped using 100 μL 0.1 N HCl in anhydrous isopropanol. Cell viability was evaluated by measuring the absorbance at 570 nm. IC50 values were calculated using non-linear regression analysis in GraphPad Prism 5 (GraphPad Software, Inc., San Diego, CA, USA). SwissADME and pkCSM software were used to predict the properties of the compounds. **Results:** Of the compounds synthesized, A1, A2, A3 and A4 showed antileukemic activity. Compounds A1 and A4 were the least cytotoxic for both cell lines. A2 showed strong activity against Jurkat cells. The best compound in the study, A3, showed strong activity against both Jurkat and NB4 cells. In the investigation of apoptosis by flow cytometry, the baseline cell viability was greater than 85%, which indicates a good quality cell culture and reliability in the data obtained. A2 showed greater efficacy, but still limited in Jurkat cells compared to NB4 cells. Compound A4 was the most effective in both models tested. For Log P (consensus), all the molecules are within the molecular filters, with A3 having the highest value, 3.79. The final analysis of all those described in this study indicates that all the quinazolinones synthesized meet the parameters for oral bioavailability. **Conclusion:** In this study, we prepared a series of quinazolinones that exhibited antiproliferative activities in T-ALL and APL. The most promising result of the study was A3 for both T-ALL and APL cells, respectively. In the analysis of apoptosis by flow cytometry, the highlight was also A3, which was the most effective against both cell lines.

Keywords: Antileukemic, Jurkat, NB4, Quinazolinone.

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NEW FUNCTIONALIZED QUINAZOLINES AS POTENTIAL AGENTS AGAINST HEAD AND NECK AND LUNG CANCER

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A B S T R A C T

Introduction/Justification: Lung cancer (LC) and head and neck cancer (HNC) are high incidence tumors around the world. Patients with the tumors have been treated for years with cisplatin alone or in combination with other agents. More recently, hyperexpression of the epidermal growth factor receptor (EGFR) has been identified in most LC and HNC, and anti-EGFR agents have been incorporated into the treatment of tumor carriers. However, a substantial number of patients with tumors still die, which justifies the search for new antineoplastic agents. **Objectives:** Evaluate the antiproliferative activity of new functionalized quinazolines against FaDu, HaCat, SCC-25 and NCI-H460 cell lines. **Materials and Methods:** The quinazolines (Q1-Q6) were synthesized in the Laboratory of Synthesis of Natural Products and Drugs (Institute of Chemistry, Unicamp). Non-small cell lung cancer (NCI-H460), squamous cell pharyngeal cancer (FaDu), squamous cell carcinoma of the tongue (SCC-25), and epidermal keratinocytes (HaCaT) were selected for this study, and all cell lines comply with the International Organization for Standardization (ISO 10993-5 and ISO 10993-1). The cytotoxicity of each compound in the cell lines was determined by the MTT (3-(4,5-dimethylthiazol-2-yl)-2-5 diphenyl tetrazolium bromide) assay. Cisplatin and gefitinib were used as positive controls. MTT is captured by cells and reduced intra-cellularly in a mitochondrion-dependent reaction to yield a formazan product. The ability of cells to reduce MTT provides an indication of their intactness and mitochondrial activity that serves as a measure of viability. After a 48 h incubation with compounds (seven concentrations on a logarithmic scale from 1 to 1000 μg.mL-1), the plates were centrifuged to pellet the cells, the supernatant was removed, and 10 μL of MTT (Sigma, M5665) dissolved in 100 μL of phosphate-buffered saline (Sigma P4417) was added followed by incubation for 4 h at 37°C in a humid, 5% CO_2 atmosphere. After this period, the plates were centrifuged again, the supernatant was removed, and the insoluble formazan crystals were dissolved in 150 μL of Isopropyl alcohol. The absorbance was read in a Synergy ELISA plate reader (Bio Tek Instruments, Highland Park, Winooski, USA) at 570 nm. The results were expressed as percentage inhibition relative to control cells (considered as 100%). **Results:** Compounds Q1 and Q6 showed no cytotoxic activity. The synthetic intermediate, Q2 and the target compound Q3 showed an unexpected but interesting cytotoxic activity for the HaCat cells. Compound Q4 showed strong and selective cytotoxic activity against the FaDu cells. Analyzing the NCI-H460 cells, compound Q5 showed strong and selective cytotoxic activity. **Conclusion:** Compounds Q2 and Q3 deserve attention as potential agents for the treatment of actinic keratosis patients. The Q4 and Q5 compounds emerge as new potential agents for the treatment of patients with HNC and LC, respectively. Studies focusing on response and toxicity to agents in animal models are necessary to verify the efficacy and safety of agents before starting studies in humans.

Keywords: Antiproliferative, Lung cancer, Quinazoline.

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GOLD(I)-BASED COMPLEX AUDMAP: A PROMISING ANTIPROLIFERATIVE AGENT FOR MELANOMA TREATMENT

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