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A B S T R A C T

**Introduction/Justification:** Cancer remains one of the leading causes of death worldwide. Among the various tumor sites, the central nervous system is particularly significant, with gliomas accounting for the majority of primary brain tumors. In gliomas, alterations in the tyrosine kinase pathway lead to the overexpression of the Epidermal Growth Factor receptor (EGFr). Over the past decades, radiolabeled peptides with high affinity for EGFr have emerged as promising molecular targets with potential applications in both diagnosis and therapy. **Objectives:** This study aimed to evaluate the affinity of the peptide DEDEYFELV, radiolabeled with iodine-131 ($^{131}$I), for EGFr-overexpressing receptors in adult-type diffuse gliomas using tumor tissue samples. **Materials and Methods:** The peptide was synthesized using solid-phase peptide synthesis following the Fmoc/tBu strategy. Upon completion of the synthesis, the peptide was characterized and purified via high-performance liquid chromatography (HPLC). DEDEYFELV (20 nmol) was radiolabeled with [$^{131}$I]NaI (18.5 MBq) using the chloramine-T method. The radiochemical yield of [$^{131}$I]I-DEDEYFELV was determined via chromatography on Whatman 3MM strips using a 95% MeOH / 5% $H_2O$ eluent. Binding studies of [$^{131}$I]I-DEDEYFELV with neoplastic tissue homogenates were conducted at 1 and 4 h of incubation and quantified using an automatic gamma counter. Tumor tissue homogenates were obtained from surgical resections performed by a designated neurosurgeon, following informed consent. Gliomas were confirmed through pathological analysis, and tumor samples were preserved at -80°C. All human protocols adhered to local ethical guidelines (Protocol number CEP – FCMSCSP: CAAE 79336124.7.0000.5479). Statistical analysis was conducted using ANOVA or Student's t-test. **Results:** The peptide DEDEYFELV was successfully synthesized with a yield of approximately 92%. Mass spectrometry and HPLC analyses confirmed efficient synthesis, cleavage, and purification, as evidenced by a single peak and a molecular mass corresponding to the expected peptide. Radiolabeling was achieved with a radiochemical yield exceeding 95%. Binding studies of [$^{131}$I]I-DEDEYFELV with neoplastic tissue homogenates showed values of 3.25 ± 0.31% for high-grade tumors, 2.62 ± 0.34% for low-grade tumors, and 1.61 ± 0.25% for tumors of unknown grade at 1 h of incubation (n = 5). At 4 h, the binding values increased to 6.45 ± 0.66% for high-grade tumors, 10.27 ± 1.58% for low-grade tumors, and 7.74 ± 1.21% for tumors of unknown grade (n = 5). **Conclusion:** These findings demonstrate that the radiolabeled peptide [$^{131}$I]I-DEDEYFELV exhibits specific binding to EGFr-overexpressing tumor tissues, with an increasing affinity over time. The higher binding observed at 4 h suggests favorable interaction dynamics, particularly in low-grade gliomas. These results highlight the potential of [$^{131}$I]I-DEDEYFELV as a theranostic agent for EGFr-targeted imaging and therapy, warranting further investigations into its in vivo stability and clinical applicability.

**Keywords:** EFFr-targeting peptide, Glioma, Tumor tissue, [$^{131}$I] I-labeled peptide.

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## EXPRESSÃO DE GENES ASSOCIADOS COM RESISTÊNCIA À CISPLATINA EM LINHAGEM DE CÉLULAS DE CÂNCER DE CAVIDADE ORAL: PASSOS INICIAIS PARA O DESENVOLVIMENTO DE UM PAINEL MOLECULAR

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R E S U M O

**Introdução/Justificativa:** A cisplatina (CDDP) é um dos principais agentes quimioterápicos utilizados no tratamento do carcinoma de células escamosas de cavidade oral (CCECO). No entanto, a resistência ao tratamento representa um desafio clínico, reduzindo a eficácia terapêutica e impactando negativamente o prognóstico dos pacientes. A quimiorresistência à CDDP envolve mecanismos moleculares complexos, incluindo alterações na expressão de genes relacionados ao reparo do DNA e ao metabolismo do fármaco. Nesse contexto, genes como AKR1C1, CCND1, CCND3, ERCC1 e SLC31A1 têm sido implicados em processos biológicos associados à resistência, como detoxificação de drogas, regulação do ciclo celular e transporte de íons. **Objetivos:** O objetivo deste estudo foi avaliar a expressão desses genes em células do CCECO sensíveis e resistentes à CDDP, buscando identificar potenciais biomarcadores de resistência e novas abordagens para otimizar a terapia em pacientes com o CCECO. **Materiais e Métodos:** A linhagem celular SCC-25 (câncer de língua, CRL-1628, ATCC) sensível à CDDP foi cultivada seguindo protocolo padrão. A resistência celular foi induzida com 10,64 $\mu$M de CDDP, conforme protocolo previamente estabelecido. Os modelos experimentais utilizados foram: SCC-25 e SCC-25 resistente à CDDP (SCC-25-R). O cDNA de cada amostra foi amplificado por qPCR para avaliar a expressão dos genes AKR1C1, CCND1, CCND3, ERCC1 e SLC31A1 utilizando iniciadores específicos e reagentes do kit com o corante SYBR green no equipamento QuantStudio 3, seguindo as recomendações do fabricante. O gene GAPDH foi utilizado como controle endógeno. A comparação entre os grupos foi realizada por meio do teste t e os resultados foram expressos como fold change (FC). Valores de $p < 0,05$ foram considerados significativos. **Resultados:** A expressão dos genes AKR1C1 (FC: 74,19, $p = 0,001$), CCND1 (FC: 1,91, $p = 0,003$), CCND3 (FC: 1016,29, $p = 0,009$) e ERCC1 (FC: 14,90, $p = 0,004$) foi maior nas células SCC-25-R em comparação com as células sensíveis à CDDP. Em contraste, o gene SLC31A1 apresentou uma expressão reduzida na linhagem SCC-25-R (FC: 0,56, $p = 0,005$) em relação às células sensíveis ao tratamento. **Conclusão:** Nossos

resultados indicam que a resistência à CDDP na linhagem SCC-25 pode estar associada ao aumento da expressão dos genes AKR1C1, CCND1, CCND3 e ERCC1, bem como à redução da expressão do gene SLC31A1, o que sugere que esses genes desempenham um papel na quimiorresistência. Esses achados reforçam o potencial desses genes como biomarcadores para um futuro painel de predição de resistência à cisplatina no CCECO. No entanto, novos estudos devem ser realizados em outras linhagens de tumores, assim como em modelos animais, para validar esses resultados.

**Palavras-chave:** Biomarcadores, Câncer de cabeça e pescoço, Cisplatin, Quimiorresistência.

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## A BORON COMPLEX DESIGNED FOR FLUORINE-18 LABELING AIMING FOR PET IMAGING APPLICATION

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A B S T R A C T

**Introduction/Justification:** Positron emission tomography (PET) is a rapidly expanding clinical modality worldwide due to the availability of compact medical cyclotrons and automated chemistry for the production of radiopharmaceuticals. Despite the availability of various positron-emitting radionuclides such as carbon-11 [11C], fluorine-18 [18F], and gallium-68 [68Ga], 18F has gained more importance and preeminence in research and diagnostic nuclear medicine due to its appropriate half-life of 110 min. Currently, 18F-fluorodeoxyglucose [18F]FDG is the most used radiopharmaceutical for the detection of various neurological disorders and cancer diseases. Since standard 18F-fluorination methods to form carbon-fluorine bonds have some limitations, such as low yield and the requirement for harsh reaction conditions, inorganic approaches, including the formation of boron-fluorine-18 bonds, have the potential to give high specific activities at room temperature, forming a bond that is stable in vivo. The boron complex is planned to be used in fluorine-18 labeling, aiming to develop a potential radiopharmaceutical for PET. **Objectives:** This work aims to produce a new boron compound with a trivalent and tetradentate chelating agent, relatively stable in air and in solution, but reactive in the presence of fluoride ions, to form an inert fluorinated species, aiming for its use in fluor-18 labeling and application in PET imaging. **Materials and Methods:** A tetradentate trivalent chelator, named 3-((bis-(2-hydroxyethyl)amino)methyl)-2-hydroxy-5-methylbenzaldehyde (abbreviated as H3L), was synthesized as previously described and used to prepare a neutral tetracoordinated boron complex, named [BL], by its equimolar quantitative reaction with boric acid in acetonitrile under reflux conditions overnight, as a white solid, which was filtered, dried, and characterized. By spectroscopic monitoring, the formation of a new species was observed in methanol solution from [BL] and NaF, supposedly forming Na[BFL]. The structures of the [BL] molecule and of the [BFL]1- anion were theoretically calculated by DFT methods. **Results:** The H3L free ligand and the boron complex were satisfactorily characterized by diverse techniques, including mass spectrometry, FT-IR, UV-Vis, and NMR spectroscopies (1H, 13C, and 11B) and single crystal X-ray diffraction. The complex [BL] was formed upon deprotonation of three hydroxyl groups in the free ligand, whose oxygens formed the coordination sphere together with the nitrogen atom. The coordination compound has a distorted tetrahedral coordination geometry, which might favor the formation of the bond between the boron atom and the fluoride ion, which is a strong nucleophile, by weakening the boron-nitrogen bond but keeping the oxygen donor atoms strongly coordinated to the boron center. **Conclusion:** Both, the free ligand and the boron complex have been successfully synthesized and characterized. The complex forms a new species in the presence of fluoride. X-ray diffraction on a single crystal of [BL] confirms its structure. The boron center is tetracoordinate with the ligand L3-, which coordinates trianionically and tetradentate through one nitrogen and three oxygen donor atoms. The obtained boron complex exhibited reactivity upon fluoride in solution, resulting in the formation of a novel species, confirming its potential application in [18F]fluoride labeling.

**Keywords:** Boron, Fluorine-18, Polyvalent chelator, Radiopharmaceutical.

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## PREPARATION OF PHOSPHATIDYLSERINE LIPOSOMES FOR 99MTC RADIOPHARMACEUTICALS ENCAPSULATION

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