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Identification of new selective BK1R bradykinin analogs and evaluation of their Antiproliferative activity on human Cancer cell lines

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Abstract

Bradykinin (BK) (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg) performs many functions in normal and pathological physiology through G-protein coupled receptors (GPCR) that have been pharmacologically classified as a kinin receptor subtype 1 (B1R) and kinin receptor subtype 2 (B2R). Numerous reports indicate that BK is involved in a number of processes related to cancer progression, and bradykinin antagonists have been tested for anti-tumor activity. However, the role of kinin receptors as potential targets in cancer therapy is still being studied, and the search for a new generation of selective BK receptor ligands is in progress. A number of new ligands for the above-mentioned receptors have been synthesized and tested in the present study. To assess the functional activity (EC50 and IC50 assessment) of these ligands at BK1 and BK2 receptors, two cell lines overexpressing the human BK1 or BK2 receptor in HEK 293 cell lines were prepared. The activity of these compounds was tested in a homogeneous time-resolved fluorescence assay for IP1 (IP-One HTRF; Cis-bio). Five of the tested compounds showed antagonistic properties at the BK1 receptor, and these compounds were selected for further evaluation in in vitro experiments, including the cell proliferation test by using an MTT assay and caspase-3 activation test on human cancer cell lines (glioblastoma astrocytoma U-87 MG, neuroglioma HTB-148, and small-cell lung carcinoma SHP-77). The compounds for which the most encouraging results were obtained in in vitro tests; i.e., showing a promising bioactive potential against cancer cells, were adsorbed at the solid/aqueous solution interface and spectra were measured by surface-enhanced Raman scattering (SERS). Different metallic surfaces (metal and metal oxide surfaces of different sizes and shapes of surface porosity) that significantly enhance the Raman signal for molecules on or near their surface, played the role of a solid. This is because SERS is a potential tool for modeling ligand-receptor interaction.

Biography

Grzegorz Burnat has completed his PhD at the age of 30 years from Friedrich-Alexander Erlangen-Nurnberg University, Germany. He is the bio-specialist of IF-PAS, Poland. His research topics are: GPCR functional assays, GPCR modulation and cancer research. He has over 25 publications that have been cited over 670 times, and his publication H-index is 16.

Publications

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