Triazolo-Peptidomimetics: Novel Radiolabeled Minigastrin Analogs for Improved Tumor Targeting

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Author(s) Grob, Nathalie M.; Häussinger, Daniel; Deupi, Xavier; Schibli, Roger; Behe, Martin; Mindt, Thomas L.
Author(s) at UniBasel Häussinger, Daniel ;
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MG11 is a truncated analog of minigastrin, a peptide with high affinity and specificity toward the cholecystokinin-2 receptor (CCK2R), which is overexpressed by different tumors. Thus, radiolabeled MG11 derivatives have great potential for use in cancer diagnosis and therapy. A drawback of MG11 is its fast degradation by proteases, leading to moderate tumor uptake; in vivo; . We introduced 1,4-disubstituted 1,2,3-triazoles as metabolically stable bioisosteres to replace labile amide bonds of the peptide. The ”triazole scan” yielded peptidomimetics with improved resistance to enzymatic degradation and/or enhanced affinity toward the CCK2R. Remarkably, our lead compound achieved a 10-fold increase in receptor affinity, resulting in a 2.6-fold improved tumor uptake; in vivo; . Modeling of the ligand-CCK2R complex suggests that an additional cation-π interaction of the aromatic triazole moiety with the Arg; 356; residue of the receptor is accountable for these observations. We show for the first time that the amide-to-triazole substitution strategy offers new opportunities in drug development that go beyond the metabolic stabilization of bioactive peptides.
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