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Synthesis and evaluation of cholecystokinin trimers: A multivalent approach to pancreatic cancer detection and treatment

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ABSTRACT

In the quest for novel tools for early detection and treatment of cancer, we propose the use of multimers targeting overexpressed receptors at the cancer cell surface. Indeed, multimers are prone to create multivalent interactions, more potent and specific than their corresponding monovalent versions, thus enabling the potential for early detection. There is a lack of tools for early detection of pancreatic cancer, one of the deadliest forms of cancer, but CCK2-R overexpression on pancreatic cancer cells makes CCK based multimers potential markers for these cells. In this Letter, we describe the synthesis and evaluation of CCK trimers targeting overexpressed CCK2-R.

For the last decade, our group and others have investigated the use of multivalent interactions to enhance ligand–receptor binding properties.[1,2] Indeed, multivalent interactions are higher in affinity and more specific than monovalent ones. It is our belief that by targeting the appropriate cancer cell surface receptor combinations, cancer cells could be selectively targeted with a high sensitivity thanks to the creation of such multivalent interactions.[3]

We previously described an efficient synthetic strategy to afford libraries of multivalent molecules and successfully generated MSH multimer libraries for melanoma targeting.[4] These molecules have shown interesting properties and binding affinities were enhanced up to 350-times that of the monovalent ligand, resulting in the successful creation of powerful multivalent interactions with a dendrimer-like structure.

Pancreatic cancer is one of the most virulent and lethal cancers with a poor prognosis with less than 5% five year survival and on average six months of survival after diagnosis.[5,6] In the case of pancreatic cancer, a lack of evident symptoms is the source of such prognosis. Therefore, novel and sensitive detection methods are required in order to afford early detection and treatment to increase the chances of recovery and survival.

Cholecystokinin (or CCK, a gastrin-like peptide) by binding to its cognate receptors CCK1-R and CCK2-R, is involved in multiple physiological responses, especially in the gastrointestinal tract, where it regulates pancreatic secretion, gastric function and gall bladder contraction.[7–9] In cancer, the CCK ligand–receptor system is known to be involved in gastrointestinal tract tumor growth via autocrine and paracrine functions resulting in receptor overexpression such as in pancreatic cancer, in which the CCK2-R is overexpressed.[10–13] This receptor overexpression constitutes an ideal target for the creation of molecular markers specific to pancreatic cancer cells via the formation of multivalent interactions. Thus, we decided to apply our new strategy and synthesize multimers targeting CCK2-R. In this Letter, we describe the synthesis and evaluation of multimers bearing CCK ligands for CCK-2R targeting.

Our molecules are based on a trimeric template which upon modification with the desired ligand results in the multimer of interest.[4] In our previous studies, we established that the use of the minimal pharmacophores as ligands was optimal due to their short size (easy synthesis) and their relative weak binding affinities (micromolar). However, CCK1-R and CCK2-R share the same pharmacophore: Trp-Met-Asp-Phe. Fortunately, SAR studies provided ways to differentiate the two subtypes and the following CCK(4) agonist peptide: Trp-NMeNle-Asp-Phe, known to be 6000 times more selective for the CCK2-R,[14,15] was selected as our ligand. This

Abbreviations: CCK, cholecystokinin ligand; CCK1-R, cholecystokinin 1 receptor; CCK2-R, cholecystokinin 2 receptor; MSH, melanotropin ligand; SAR, structure–activity relationship; Trp, tryptophan; Met, methionine; Asp, aspartic acid; Phe, phenyl alanine; Nle, norleucine; TFA, trifluoroacetic acid; Ala, alanine; βAla, 3-aminopropanoic acid; Pro-Gly, proline-glycine; HF, hydrogen fluoride; MeCN, acetonitrile; TRF, time-resolved fluorescence

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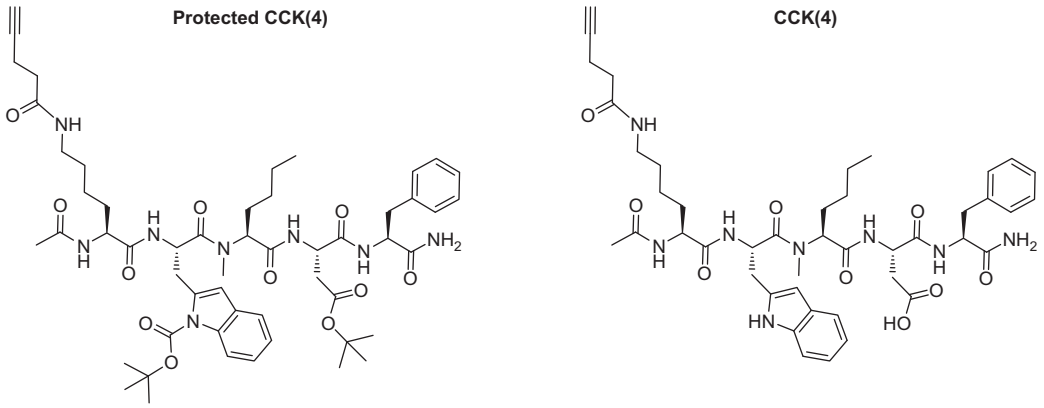
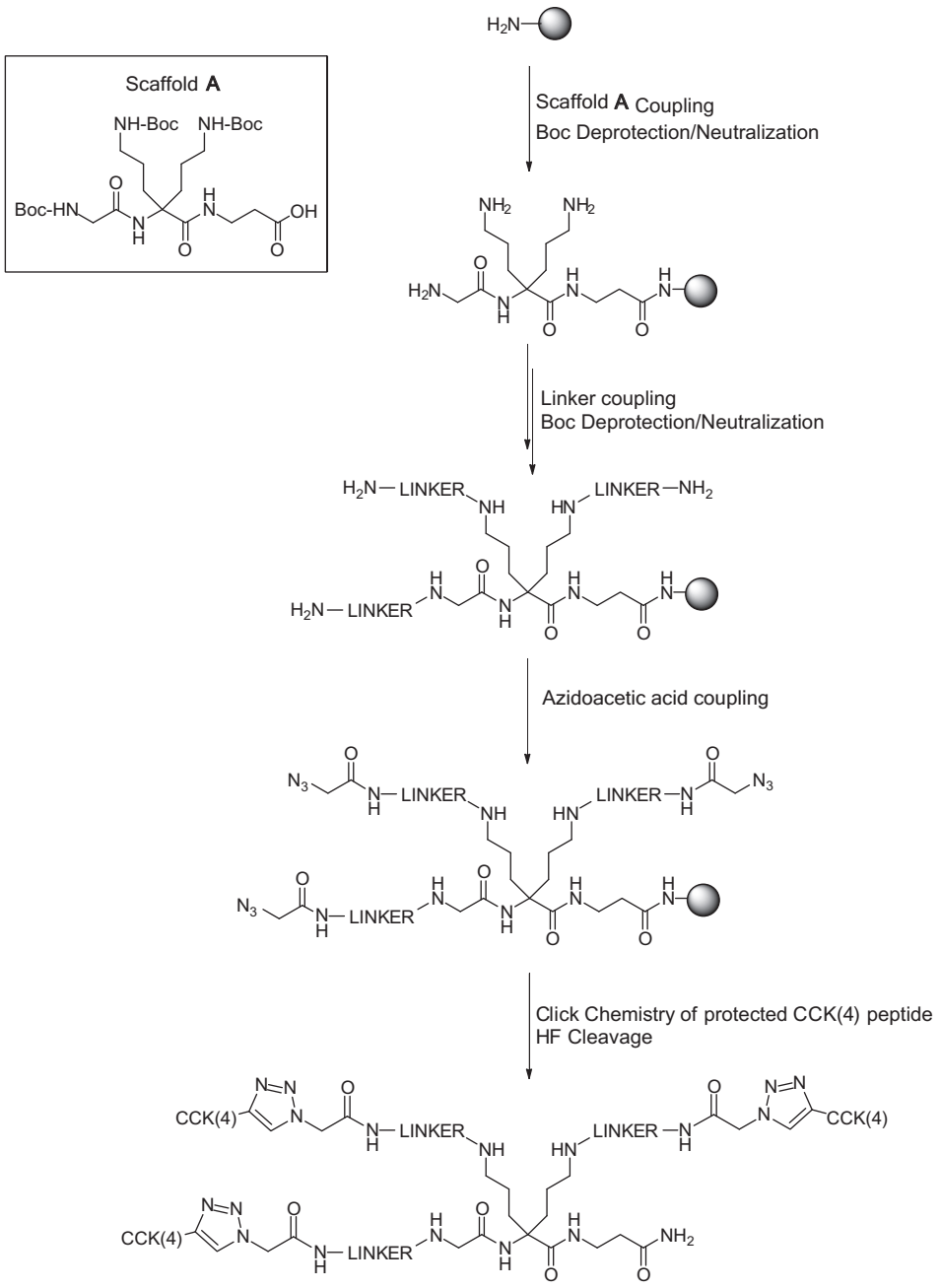


Figure 1. Sequence for selective monovalent ligand for CCK2-R targeting.



Scheme 1. Synthesis of CCK(4) trimers.