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MOLECULES

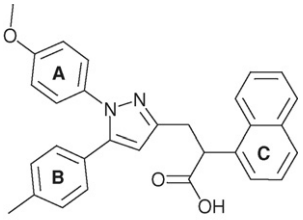
Pyrazole CCK1 receptor antagonists

Cholecystokinin (CCK) is an endogenous 33-amino acid peptide hormone that was first identified by its pharmacological actions early in the 20th century, and later purified and sequenced during the 1970s. Subsequently, it was shown that CCK was released in response to food intake and that it regulated gallbladder contraction, pancreatic enzyme secretion, gastric acid secretion and colonic motility, among other pharmacological effects. CCK is abundant in the CNS and is believed to be involved in aspects of nociception, satiety and anxiogenesis (e.g. Ref. [1]). The biological actions of CCK are mediated through two G protein-coupled receptors, CCK_1 and CCK_2. The pharmacological actions of CCK appear to be mediated through agonism of the CCK1 receptor. As a corollary, several CCK_1 antagonists have been evaluated in the clinic for pancreatic disorders, IBS and biliary colic.

Encouraging clinical results from a phase II trial of constipation-dependent IBS with a peptide-derived CCK_1 antagonist gave encouragement to the research community to further pursue differentiated non-peptide-derived antagonists of CCK_1 [2]. Recent work along this theme has been disclosed [3]. These workers based their design efforts upon the lead compound **(i)**, which was identified from an in-house HTS as a potent and selective antagonist of the CCK1 receptor (pK_I 7.6). This compound displayed promising physical properties and represented a novel chemical scaffold for SAR investigations. Work directed towards SAR elucidation via the construction of a solution phase library was undertaken.

During these studies, a novel method for the evaluation of SAR in combinatorial matrices was discovered. In particular, this new methodology provided for a quantitative assessment of additive and non-additive relationships in the SAR, enabling identification of potential changes in the binding modes of these antagonists. The synthetic scheme involved varying positions around aromatic centers B and C [see **(i)**], giving compounds with pK_I varying between the limits of 6.2–8.1 as antagonists of CCK1.

Additive models of SAR were first described by Free and Wilson in 1964 [4] and later modified by Fujita and Ban in 1971 [5]. The assumption with these models is that one variable in the structure does not effect the binding or conformation of the second variable. However, in many documented cases, this assumption is invalid, thus limiting the predictive power of additive models [4]. With the advent of combinatorial methods, a full matrix of compounds can be readily accessed synthetically. In this situation, the presence of non-additive relationships in the full matrix can suggest either a different binding mode in the biological target or direct interactions between different parts of a ligand. A modification of the Fujita-Ban equation [5] was applied to determine predicted activities for the combinatorial matrix generated in the work described here. The results from this study indicated that all compounds tested bind in a similar binding mode to the receptor. This work is of interest as it describes a novel class of potent pyrazole-based CCK_1 antagonists. The SAR was evaluated using a matrix synthesis approach, enabling the quantitative determination of additive relationships between substituents in the matrix. Further *in vivo* data and SAR on these compounds are warranted through future studies.



(i)

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Paul Edwards
mepauledwards@fsmail.net

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