



**cresset**

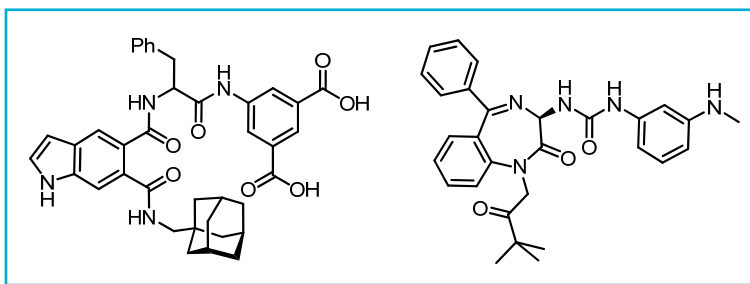
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## GPCR Inhibitors A - CCK<sub>2</sub> Class A peptide-activated GPCR

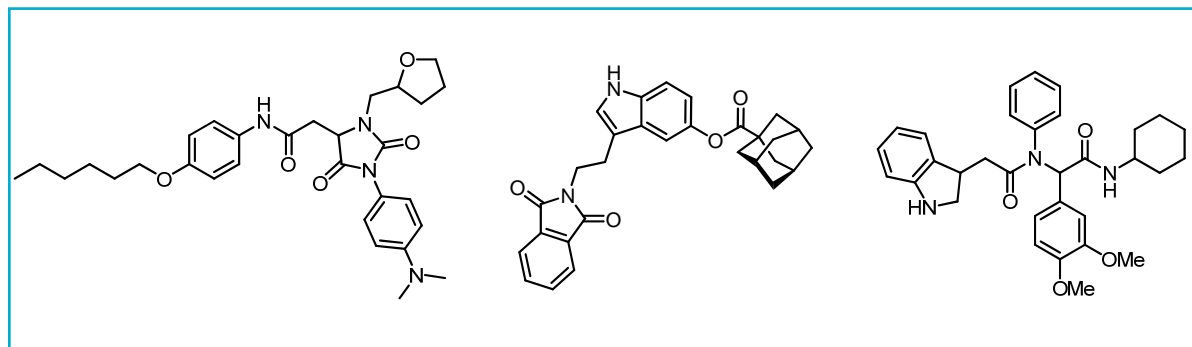
Antagonism of the cholecystinin 2 (CCK<sub>2</sub>) G-protein coupled receptor (GPCR) represents an attractive pharmaceutical target with a potential role in treating gastric-acid related conditions, as well as gastrointestinal and pancreatic cancers.

CCK<sub>2</sub> receptors regulate stomach acid release at a deeper control level than H/KATPases or histamine. These receptors are activated by the hormone gastrin, a 34-residue peptide that shares the same active C-terminal pentapeptide sequence with cholecystinin, a related hormone that activates both CCK<sub>1</sub> and CCK<sub>2</sub> receptors.

Two known selective CCK<sub>2</sub> inhibitors (opposite) were used to derive a Field template for the receptor. From this, the Fields of the bioactive conformations of each inhibitor were used as seeds to search our Field database (which at the time contained 2M commercially available compounds) using FieldScreen.



The top 500 ranked results from each of the searches were combined and visually distilled down to 200 diverse and interesting structures. Our clients subsequently purchased and tested 88 compounds of which 27 were found to be active below 10 $\mu$ M. Four of these were sub- $\mu$ M and all were in the 350-600 molecular weight range<sup>1</sup>. Three of the active structures identified are shown below:



<sup>1</sup> Low, C. M. R.; Vinter, J. G. Rationalizing the Activities of Diverse Cholecystinin 2 Receptor Antagonists Using Molecular Field Points J. Med. Chem. 2008, 51, 565–573.