

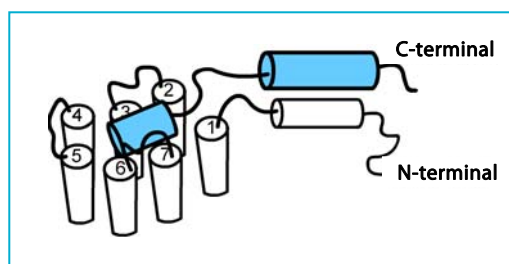


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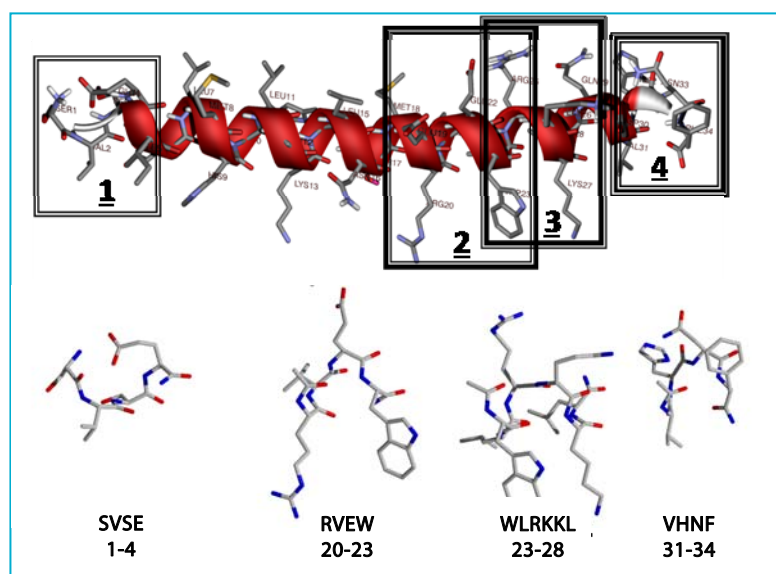
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GPCR Inhibitors B - PTH Class B peptide-activated GPCR

The PTH-1 receptor is a member of the class-II (or class B) G-protein coupled receptor (GPCR) subfamily, which includes glucagon, secretin and vasoactive intestinal peptide receptors. No definitive picture of the details of the binding of parathyroid hormone (PTH) with its receptor could be derived at the time of the project.



Although PTH is secreted as an 84-amino acid peptide, the first 34 residues have been shown to be fully active. There was reasonable evidence that the hormone remained as a helix when binding. Like other members of the class-II GPCRs, the signal transduction from the PTH-1 receptor can occur via both the cAMP and inositol triphosphate/intracellular calcium second messenger pathways. There is considerable homology with the related VIP (VPAC) receptor agonist family.



From sparse NMR, X-ray and mutagenesis evidence, four areas could be tentatively identified as major binding regions (opposite). The first comprised four residues of the N-terminal putative agonist region along with two 4-mers and a 6-mer identified across the first 14 residues from the N-terminal of PTH. These regions were cut out with their Fields and used as seeds to search the Field database, which at that time was comprised of 2M commercially available compounds.

The top 500 ranked results from each of the searches were visually distilled down to a total of 50. Our client subsequently purchased 41 compounds for testing. Although many of the purchases showed probable activity at PTH, the assays proved capricious and quantitative results could not be trusted. However, on a related VPAC test, 12 were found to be active below 30 μ M and six of these were sub-10 μ M. All were in the 360-500 molecular weight range.

No further definitive structural data have emerged to date beyond the solution NMR of PTH. All the active compounds in the final list have been retained as proprietary property by the client.