IN BRIEF

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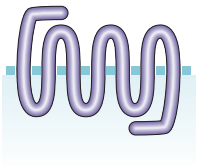

G-PROTEIN-COUPLED RECEPTORS

Nongenomic actions of bile acids. Synthesis and preliminary characterization of 23- and 6,23-akyl-substituted bile acid derivatives as selective modulators for the G-protein coupled receptor TGR5.

Pellicciari, R. *et al. J. Med. Chem.* **50**, 4265–4268 (2007)

TGR5, a G-protein-coupled receptor for bile acid, is a promising target for metabolic control but no selective and potent ligands are available. Pellicciari and colleagues identified alkyl-substituted derivatives of chenodeoxycholic acid that were potent and selective agonists of TGR5. Methylation at the C-23(S) position of natural bile acids conferred selectivity for TGR5 over the nuclear receptor for bile acids. These results show for the first time a pharmacological differentiation of genomic versus nongenomic effects mediated by bile-acid derivatives.

GENE SILENCING

MicroRNA sponges: competitive inhibitors of small RNA in mammalian cells.

Ebert, M. S. *et al. Nature Methods* **4**, 721–726 (2007)

MicroRNAs — 20–24 nucleotide RNAs derived from hairpin precursors — are predicted to silence many mammalian genes, but few targets have been experimentally validated. Ebert and colleagues developed competitive microRNA inhibitors termed microRNA sponges. When vectors encoding the sponges were transiently transfected into cells, microRNA targets were de-repressed as strongly as with chemically modified antisense oligonucleotides. The authors show that such sponges can be used to validate target predictions and in assays for microRNA loss-of-function phenotypes.

PROTEASE INHIBITORS

Highly potent inhibitors of methionine amino-peptidase-2 based on a 1,2,4-triazole pharmacophore.

Marino, J. P. *et al. J. Med. Chem.* **50**, 3777–3785 (2007)

Methionine aminopeptidase 2 (METAP2) is an important anti-angiogenesis target, but most existing inhibitors of this enzyme are derived from peptides. Marino and colleagues identified a class of heterocyclic triazole metalloproteinase compounds that were potent inhibitors of endothelial cell proliferation, and presented structure–activity relationships and X-ray crystallographic studies that determined key binding-site interactions. Furthermore, two compounds inhibited new blood vessel growth in an aortic model of angiogenesis, highlighting the potential utility of METAP2 inhibitors as anticancer agents.

NEURODEGENERATIVE DISEASES

Clearance of amyloid-β by circulating lipoprotein receptors.

Sagare, A. *et al. Nature Med.* 12 Aug 2007(doi:10.1038/nm1635)

Sagare and colleagues show that native soluble low-density lipoprotein receptor-related protein 1 (LRP1) normally controls 70–90% of the circulating neurotoxin amyloid-β (Aβ) in humans through peripheral binding, and is compromised in Alzheimer's disease. Recombinant LRP1 sequestered Aβ in plasma from Alzheimer's disease-affected humans. In mouse models of the disease, there was Aβ efflux from the brain and reduced Aβ-related pathology and dysfunction. So, recombinant LRP1 could serve as an Aβ clearance and soluble LRP1 replacement therapy for Alzheimer's disease.