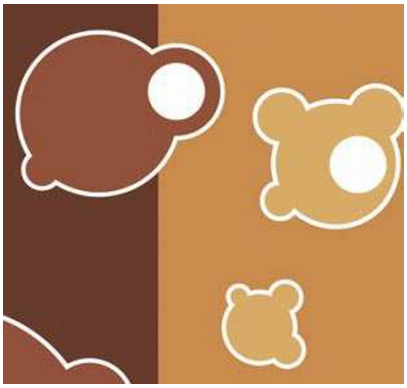
IN BRIEF



NUCLEAR RECEPTORS

Cytosporone B is an agonist for nuclear orphan receptor Nur77.

Zhan, Y. *et al. Nature Chem. Biol.* **4**, 548–556 (2008)

The nuclear orphan receptor Nur77 has important roles in apoptosis and glucose homeostasis. This paper describes how cytosporone B, an octaketide isolated from fungi, is a naturally occurring agonist for Nur77 that stimulates transactivational activity towards target genes including *Nr4a1* (*Nur77*) itself. In mice, the ligand enhanced gluconeogenesis and retarded xenograft tumour growth. So, cytosporone B could be used as a tool for understanding Nur77 function, and may represent a potential therapeutic compound for cancers and hypoglycaemia.

LEAD IDENTIFICATION

Discovery of the first potent and orally efficacious agonist of the orphan G-protein coupled receptor 119.

Semple, G. *J. Med. Chem.* **51**, 5172–5175 (2008)

GPR119 is a G-protein-coupled receptor expressed on pancreatic β-cells and incretin-releasing cells in the gastrointestinal tract, and is an attractive potential target for the treatment of diabetes. Semple and colleagues report the first potent, selective GPR119 agonist — AR231453 — identified from an inverse agonist screening hit and subsequent structure–activity relationship studies. The compound showed *in vivo* activity in rodents and was active in an oral glucose tolerance test in mice following oral administration, and so represents a lead molecule for further optimization for anti-diabetes drugs.

ANTIVIRAL DRUGS

The structural basis for an essential subunit interaction in influenza virus RNA polymerase.

Obayashi. E. *et al. Nature* **454**,1127–1131 (2008)

Most current anti-influenza drugs target viral proteins with a single known function and there is concern about the ease with which resistance to these drugs might emerge. This paper describes a subunit interface in the influenza viral polymerase complex that is important in viral replication. Crystallography studies showed that the interaction site is crucial to many viral functions and is highly conserved between different strains. The authors also highlight a peptide that might represent a useful starting point for lead discovery against all types of influenza A virus.

MUSCULAR DISORDERS

AMPK and PPARδ agonists are exercise mimetics.

Narkar, V. A. *et al. Cell* **134**, 405–415 (2008)

As well as increasing athletic performance, exercise has beneficial effects in pathophysiological conditions including metabolic and muscle diseases. Narkar and colleagues found that a peroxisome proliferator-activated-δ (PPAR-δ) agonist and exercise training synergistically increased oxidative myofibres and running endurance in mice. Furthermore, 4 weeks of treatment with an orally active agonist of AMPK (a protein kinase that is activated by training) induced metabolic genes and enhanced running endurance by 44%, without the need for exercise.