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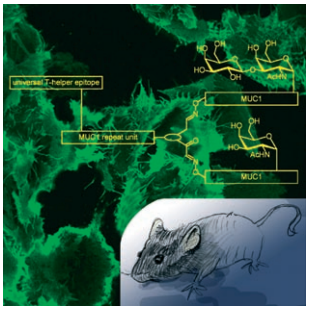
COVER PICTURE

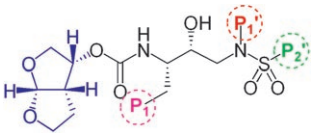


The cover picture shows human MCF7 mammary adenocarcinoma cells, a cell line which has been used extensively to characterize tumor-associated MUC1 glycoprotein. Cells were analysed by fluorescence-activated cell sorting after being labelled with antibodies induced in mice by a synthetic glycopeptide construct (structure shown) in association with a mild adjuvant suitable for human therapy. This construct, composed of a universal T-helper and three diversely glycosylated tumor-related epitopes, was assembled using a convergent strategy based on two successive oxime ligations. It is the most immunogenic synthetic construct reported to date and is able to elicit antibodies that recognize tumor-related MUC1 on MCF7 cells. (Thanks to T. Cantalupo for the image.) For more details, see the Communication by A. F. Delmas et al. on p. 965 ff.

NEWS

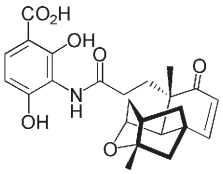
REVIEWS

MINIREVIEWS



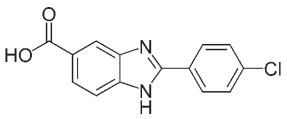
Two inhibitors that incorporate bis-THF as an effective high-affinity P_2 ligand for the HIV-1 protease substrate binding site maintain impressive potency against mutant strains resistant to currently approved protease inhibitors. Crystallographic structures of protein–ligand complexes help to explain the superior antiviral property of these inhibitors and their potency against a wide spectrum of HIV-1 strains.

HIGHLIGHTS

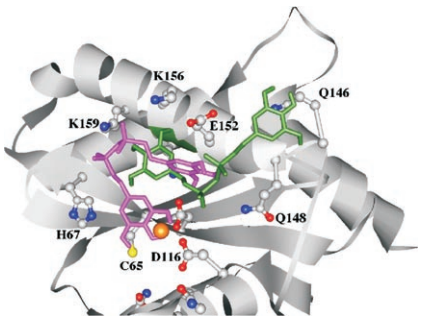


Natural products have once again proven their value as guideposts for unexplored targets. "Old-fashioned" extract screening integrated into an innovative assay set-up has opened a new playground for medicinal chemists. Platensimycin is the first member of a novel class of antibiotics that acts through a clinically unexploited target.

COMMUNICATIONS

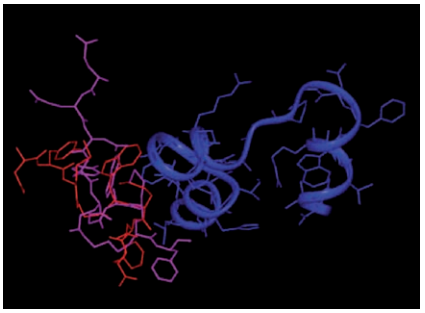


Benzimidazole-based Nurr1 agonists: Combinatorial chemistry and structure-based design were joined together to produce a lead-finding library of compounds focused on the nuclear receptor target family. A second-generation library directed against Nurr1, a specific orphan member of this family, was also prepared. This protocol allowed the discovery of a Nurr1 agonist with an EC_{50} value of 8 nM.

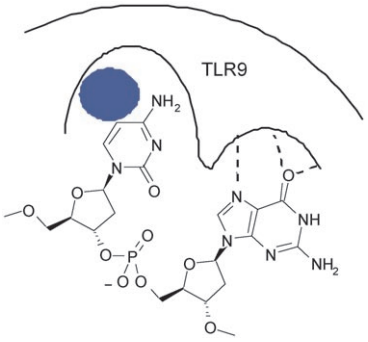


Binding modes of a series of potent geminal disulfone-containing HIV-1 integrase inhibitors were investigated using AutoDock 3.0. Two major conformations were shared for this series of compounds: a "U-shaped" conformation and an "L-shaped" conformation. The data presented suggest that the U-shaped conformer may be the more biologically relevant conformation and that the design of molecules that are structurally biased in that conformation could lead to more potent analogues.

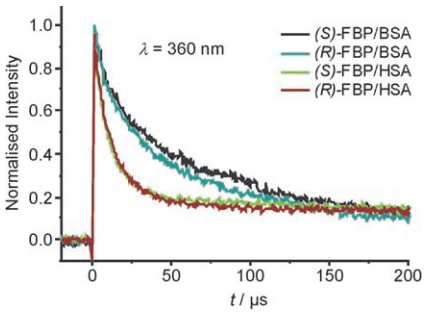
FULL PAPERS



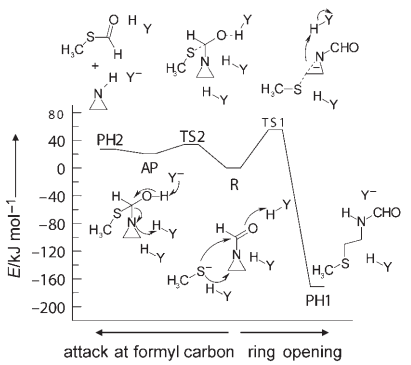
A rationally designed peptide library provided CCK8 analogues as new ligands (in red) for the cholecystokinin type B receptor (blue). In vitro cellular assays were used to determine the binding affinity of the ligands, and $IC_{50} \approx 10$ μM for the best compounds. NMR structural data of the lead compound confirm that the structure is stabilized by both the cyclic constraint and by interaction with the micelle.



Activation of Toll-like receptors (TLRs) results in stimulation of the innate immune response, including secretion of proinflammatory cytokines, up-regulation of co-stimulatory molecules, and secretion of cytokines and chemokines. In our SAR model, the CpG dinucleotide motif of immune stimulatory oligodeoxynucleotides is recognized by TLR9 by the Hoogsteen site of guanine and the C5 corner of cytosine resulting in potent stimulation of the innate immune response.



The triplet excited states of (*S*)- and (*R*)-flurbiprofen (FBP) were used as reporters for the microenvironments of the binding sites of serum albumins. Multiexponential fitting of the triplet decays ($\lambda = 360$ nm) can be satisfactorily correlated with the distribution of the drug among the two protein binding sites and the bulk solution. Triplet lifetimes and site occupancy are both sensitive to the type of serum albumin used.



Cysteine proteases are attractive targets for the development of new drugs, as they play pivotal roles in many diseases. Aziridine-containing cysteine protease inhibitors have been developed. To investigate the influence of the aziridine ring substituents on the kinetics and thermodynamics of the ring-opening reaction in detail, quantum chemical computations were performed. N-formylated aziridine was predicted to be much more effective than the nonformylated system.

SERVICE

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