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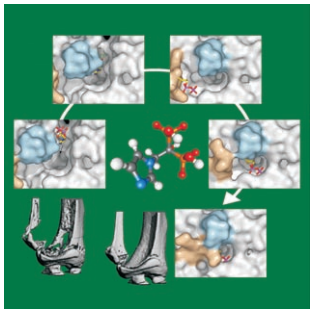
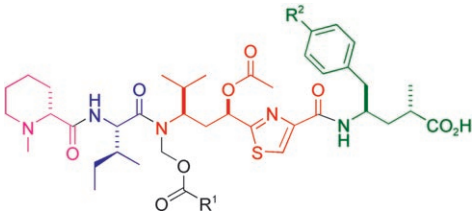
Some articles in this issue have already appeared online in Wiley InterScience. See www.chemmedchem.org under EarlyView®

COVER PICTURE



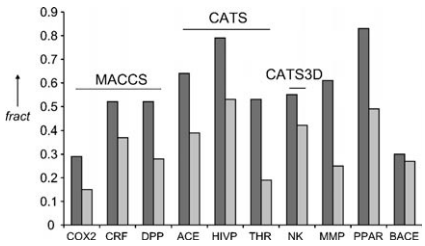
The cover picture shows micro computer tomography images that demonstrate the effect of zoledronate in the prevention of the tumor osteolytic response caused by local injection of human 4T1 mammary carcinoma cells into the tibia of nude mice. The circular arrangement shows interpolations between structural snapshots of farnesyl pyrophosphate synthase (FPPS), the molecular target of zoledronate and other bisphosphonates, upon inhibition by zoledronate and further complexation by IPP. It illustrates the structural basis for bisphosphonate treatment of bone metastasis, Paget's disease, osteoporosis, and other diseases. (Bone images courtesy of Dr. Jürg A. Gasser, Novartis Pharma AG). For more details, see the full paper by J.-M. Rondeau, W. Jahnke, et al. on p. 267 ff.

MINIREVIEWS

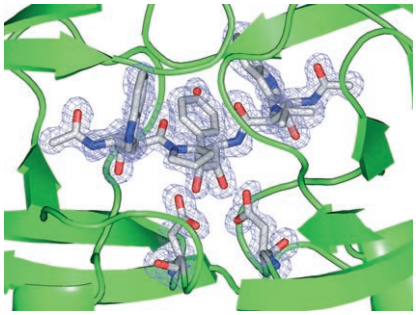


Tubulysins are potent cytotoxic natural tetrapeptides that have attracted great interest as potential drug payloads coupled with monoclonal antibodies for the targeting of tumors. Five years after the publication of their isolation from myxobacteria species, tubulysins (shown) remain a challenge for total synthesis efforts, as published reports of synthesized tubulysin have yet to appear.

COMMUNICATIONS

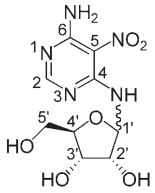


Virtual screening: Different similarity searching descriptors were compared for scaffold hopping. The pharmacophore pair CATS descriptor performed best for ligand classes with a high fraction (*fract*) of different scaffolds, MACCS fingerprints were best for classes with low scaffold diversity. The methods complemented each other in retrieving scaffolds.



Discovery by co-crystallization: High-resolution electron-density maps of HIV-1 aspartyl protease complexed with a potent Phe–Pro isostere-based inhibitor (shown) allowed the determination of the stereochemistry of the inhibitor and an initial assessment of the inhibition properties of this compound without its purification from the epimeric mixture.

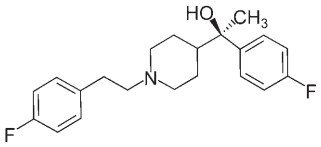
FULL PAPERS



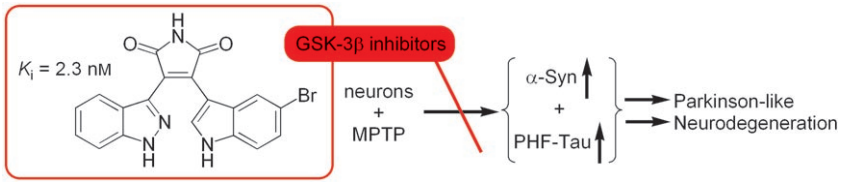
clitocine

From the forest floor: Clitocine, a nucleoside produced by the Basidiomycete mushroom *Lepista inversa*, was isolated, synthesized, and its stability was studied. Clitocine has potent in vitro activity toward cancer cell lines (with IC_{50} values in the nanomolar range), and apoptotic effects were observed. Potent in vivo antitumor activity was also observed in mouse models.

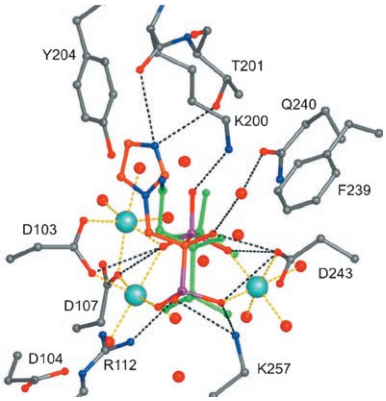
Leaving cytochromes alone: The inhibitory potency of the isoxazole compound (shown) toward p38 MAP kinase supports the important role of hydrogen bonding in the interaction between p38 inhibitors and Lys 53 of the kinase. A further advantage of the isoxazole scaffold is a decreased interaction with cytochrome isoenzymes.



Mind your 'A's and 'C's: The *R* enantiomer of the tertiary alcohol (shown) is a highly potent antagonist of the serotonin receptor subtype 2A (5-HT$_{2A}$) and has greater than 1300-fold selectivity for 5-HT$_{2A}$ over the 2C receptor subtype, 5-HT$_{2C}$. The affinity and selectivity of this compound toward 5-HT$_{2A}$ versus other relevant receptors (domaminergic D$_2$ and adrenergic α_1) was also optimized.



Analogues of the natural product staurosporine are able to inhibit Tau phosphorylation at a GSK-3β-specific site. Two members of this compound series can protect neuronal cells against cell death by decreasing the expression of α-synuclein. This work provides the chemical and biological information relevant to the identification of new chemical entities for the treatment of Tau-related neurodegenerative disease states.



The structural basis for bisphosphonate therapy has been elucidated by solving the first crystal structures of human farnesyl pyrophosphate synthase (FPPS), the molecular target of bisphosphonates. The structures uncover a particularly interesting and efficient mode of enzyme inhibition, and suggest novel routes for the treatment of bone metastasis and soft-tissue cancer.

Supporting information on the WWW (see article for access details).

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