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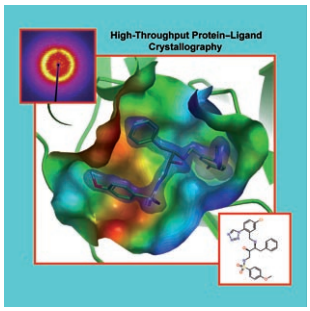
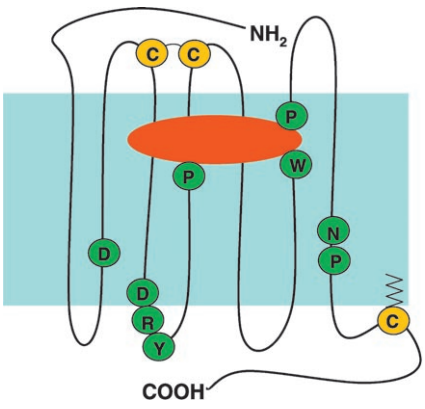
COVER PICTURE



The cover picture shows a compound bound to thrombin, as determined by automated protein–ligand crystallography. The picture illustrates how a diffraction pattern can be automatically analysed to reveal the binding mode of a compound given a 2D chemical structure and a known 3D structure for the protein. The compound shown was developed by means of fragment-based drug discovery, in which the binding of small, low-affinity molecules is determined by crystallography. This approach to drug discovery is enabled by the automation of protein–ligand crystallography. For details, see the full paper by W. T. M. Mooij et al. on p. 827 ff.

NEWS

REVIEWS



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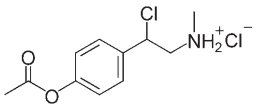
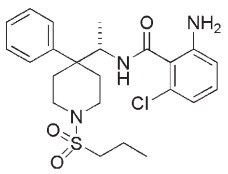
Devotion: In 1984 Barry Marshall performed a risky self experiment. Against a backdrop of skepticism from the mainstream in gastroenterology, the only way he was able to demonstrate that peptic ulcers are caused by bacterial infection was to drink a culture of *H. pylori*. For this discovery and the ensuing improvements in the treatment of ulcers, Marshall and J. Robin Warren shared the 2005 Nobel Prize for Physiology or Medicine.

HIGHLIGHTS



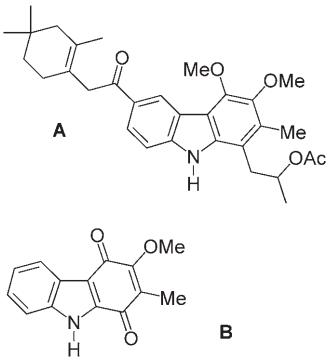
Glucocorticoids (GCs) represent the most effective therapy for acute and chronic inflammatory disorders, yet they can elicit severe side effects. New classes of GC receptor ligands appear to have all of the benefits and fewer side effects and have prompted new research into an old drug target. Compound A (shown) is the latest addition to this exciting development.

COMMUNICATIONS



(*S*)-**13h**

An iterative analogue library synthesis approach rapidly delivered (*S*)-**13h**, a potent, reversible, and selective GlyT1 inhibitor. (*S*)-**13h** selectively increased glycine levels in the prefrontal cortex to 340% of basal levels and significantly enhanced prepulse inhibition in mice. Thereby, providing strong support for the development of novel antipsychotics based on the NMDA hypofunction hypothesis of schizophrenia.



A series of carbazole derivatives was tested for inhibition of *Mycobacterium tuberculosis* growth and a mammalian cell line. Among several compounds with anti-TB activity, carbazoles **A** and **B** showed MIC values of 4.0 $\mu g\,mL^{-1}$ (8 μM) and 2.2 $\mu g\,mL^{-1}$ (9 μM) respectively, against *M. tuberculosis* and were relatively nontoxic for the mammalian cell line.

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FULL PAPERS

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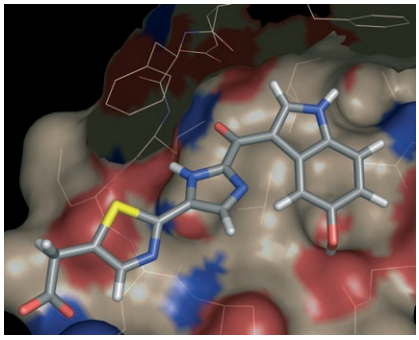
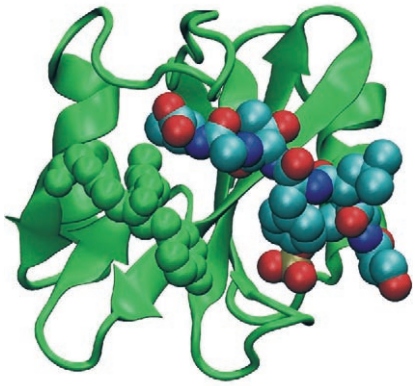
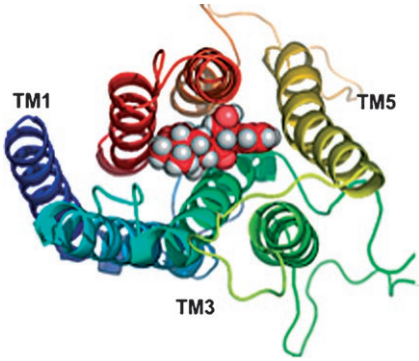


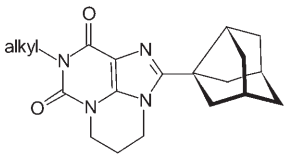
Filtering through: A novel molecular design software package, FlexNovo, based on the concept of chemical fragment spaces, has been applied to inhibitor design for four targets of pharmaceutical interest. FlexNovo is shown to reproduce known structural motifs and binding modes. The results underline the importance of using target-specific (tailored) filter functions as well as pharmacophore-type constraints for guiding the search process.

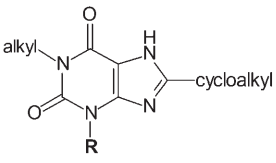


High-affinity peptides that target the N-terminal SH2 domain of SHP-1 were investigated for their ability to stimulate the phosphatase activity of both wild-type and mutant enzyme forms. This study is based on initial investigations of the structural requirements for the SHP-1 N-SH2 ligand binding of peptides derived from the natural interaction partner Ros EGLN-pY2267-MVL (image: PDB code 1aya).



The power of prediction: The 3D structure of the human M1 muscarinic receptor and the binding sites of seven agonists and antagonists were predicted using the MembStruk and HierDock methods. The results correlate well with mutagenesis data and measured binding affinities. The predicted binding site provides structural insight that will aid structure-based drug design for better ligands.





The structure–activity relationships of 3-substituted xanthine derivatives were investigated. 1-Butyl-3-(3-hydroxypropyl)-8-(3-noradamantyl)xanthine exhibited sub-nanomolar K_i values for rat and human adenosine A_1 receptors and was highly A_1-selective. 8-Alkyl-2-(3-noradamantyl)pyrimido[1,2,3-*cd*]purine-8,10-diones represent a new class of potent, selective adenosine A_1 receptor antagonists.

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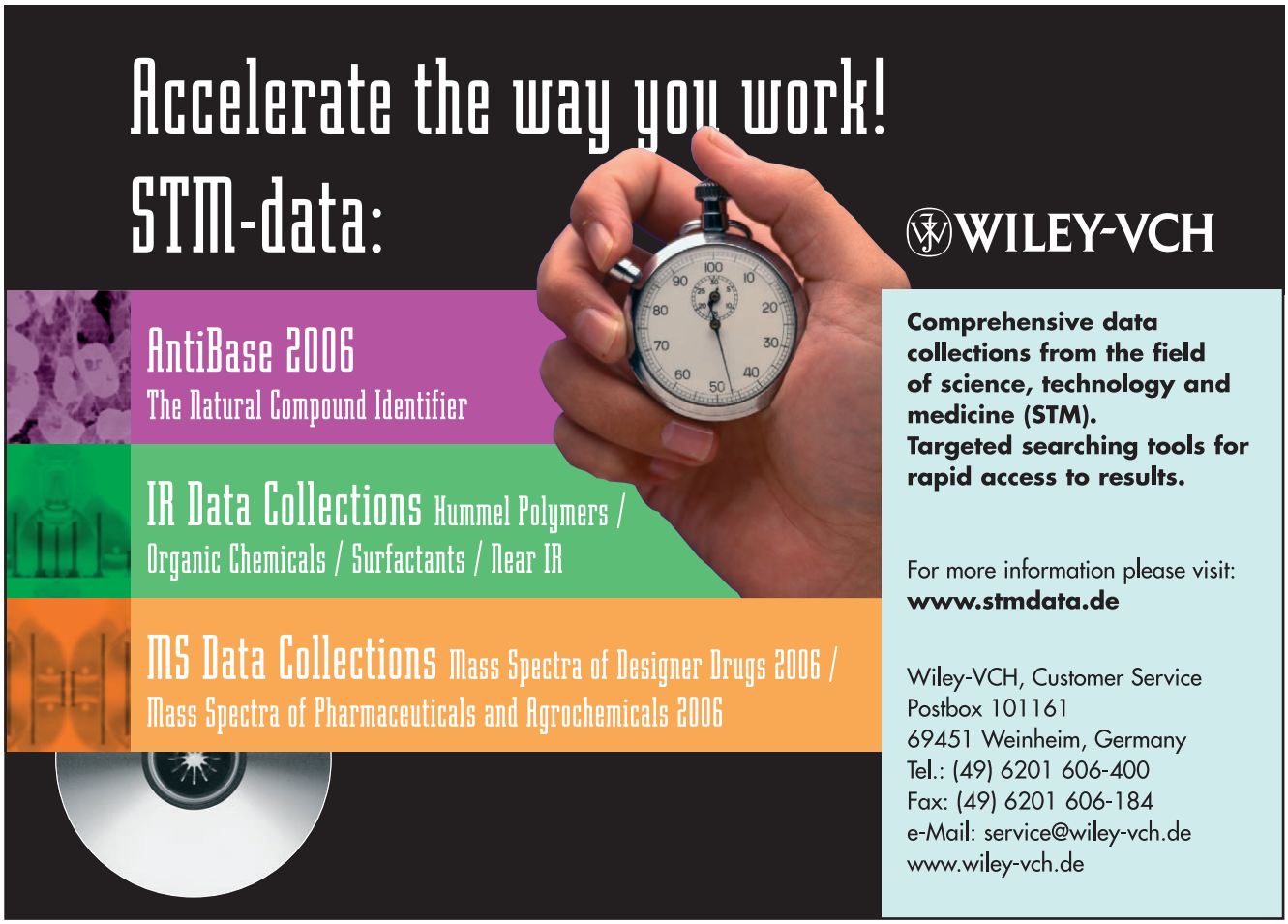

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