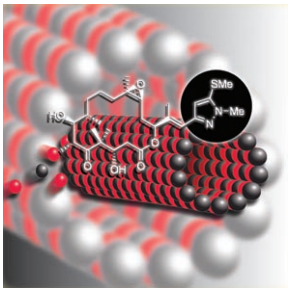
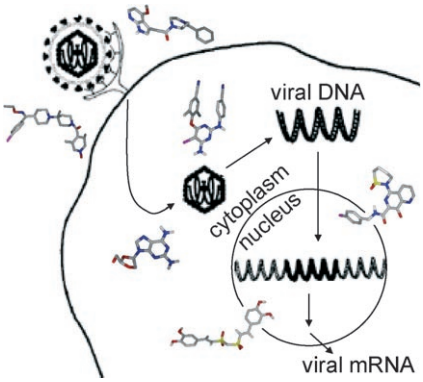
COVER PICTURE



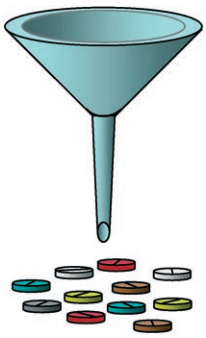
The cover picture shows a potent epothilone derivative with a schematized tubulin microtubule in the background. Epothilones exert their antitumor activity through the stabilization of microtubules by binding with tubulin; cell division stops if microtubules cannot disassemble properly. The structure shown here is the most potent epothilone reported to date. It is more potent than epothilone B in a wide range of cancer cell types, and shows excellent promise against taxol- and epothilone A-resistant cell lines. For more details, see the communication by K. C. Nicolaou et al. on p. 41 ff.

REVIEWS



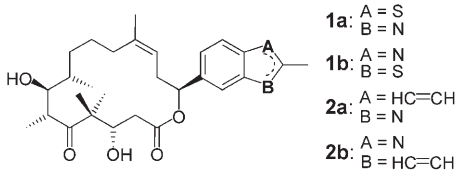
Barriers to integration: Specific blockage of HIV integrase, which inserts the viral genome into human DNA, has become an attractive approach toward future antiviral therapies. The development of small-molecule inhibitors of all the main stages of HIV infection (virus entry, reverse transcription, and integration) is a story of both success and failure. In all cases, however, valuable lessons are learned which lead to more effective anti-HIV drugs.

CONCEPTS

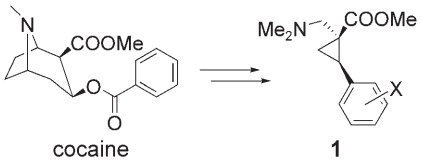


Funneled more effectively: High-throughput screening is prominently used in the pharmaceutical industry to identify novel hit structures. In modern drug discovery, processes have been established to convert hits into high-quality leads, which serve as starting points for lead-optimization projects. The hit-to-lead process at Schering AG is described with a focus on strategic aspects.

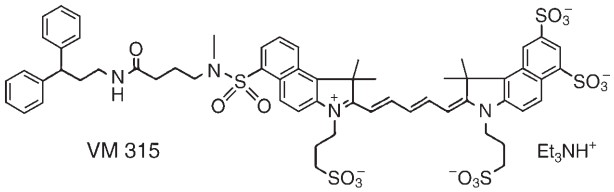
COMMUNICATIONS



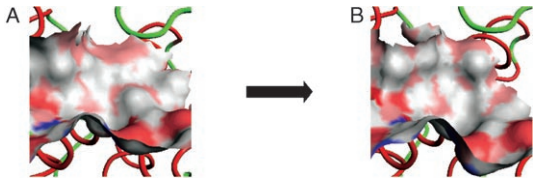
Side-chain-modified epothilone analogues **1b**, **2b**, and **3b** were prepared through stereoselective total synthesis to assess the importance of N-atom positioning in the side chain for tubulin polymerization and antiproliferative activity. Surprisingly, **1b**, **2b**, and **3b** appear to induce tubulin polymerization with activities similar to those of **1a**, **2a**, and **3a**, respectively. Substantial differences in antiproliferative activity were observed between **1a** and **2a**, and **1b** and **2b**, but not between **3a** and **3b**.



Blocking transporters: A series of novel cyclopropane analogues **1** structurally related to cocaine were synthesized by using a sulfonium ylide based cyclopropanation reaction of benzylidenemalonate. As selective serotonin reuptake inhibitors (SSRIs) have proven effective against depression and other neurological disorders, these easily synthesized ligands are of potential therapeutic interest.

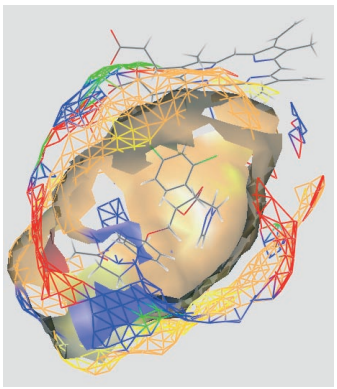


The far-red indocyanine fluorochrome VM315 significantly increases its fluorescence upon binding albumin, but not other proteins. Experimental tumor detection in multiple xenograft cancer models is greatly improved. This small-molecule probe is expected to find wide-spread application in the in vivo fluorescence imaging of various disease processes.



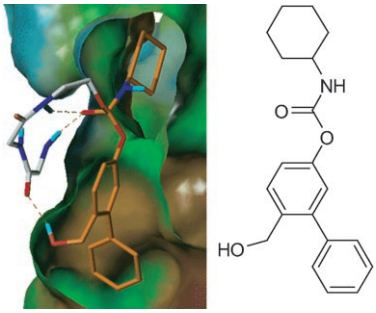
Drug targeting: The incorporation of protein binding-pocket fluctuations into the calculation of protein druggability improves the agreement between experimental data and predictions based on assessment of static protein structures alone. The predicted druggability of Bcl-xL benefits from the incorporation of multiple conformations taken from molecular dynamics simulation, which captures fluctuations in binding pocket shape and size (two such structures shown in A and B).

FULL PAPERS

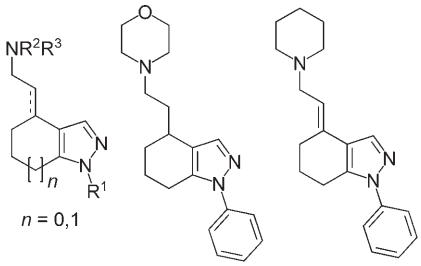


Undesired drug–drug interactions often result from small-molecule binding and inhibition of cytochrome P450 3A4 (CYP3A4, modeled binding site shown). Flexible docking and multidimensional QSAR were used to develop a computational model to predict the inhibitory potential of a diverse set of molecules that bind CYP3A4. The model successfully predicted the experimentally determined binding affinity of all compounds.

CONTENTS



FAAH away: Derivatives of the carbamate inhibitor URB524 substituted at the proximal phenyl ring were prepared for further investigations of the mechanism of FAAH inhibition. SAR studies revealed that the recognition step is fundamental for potency, with small polar substituents giving the best results. Kinetic experiments demonstrated the irreversible mechanism of these inhibitors.



The sigma 1 (σ1) receptor was recently rediscovered as a target for the treatment of such indications as drug abuse, pain, depression, anxiety, and psychosis. Three classes of novel cycloalkyl-annelated pyrazoles (general structure (left) and examples from two classes shown) are druglike, selective high-affinity ligands, which serve as powerful tool compounds for future drugs that target σ1.

CONFERENCE REPORTS

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

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