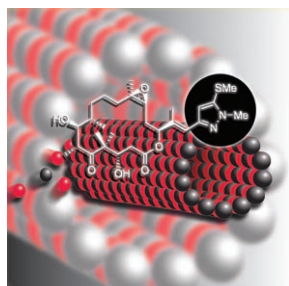


## COVER PICTURE



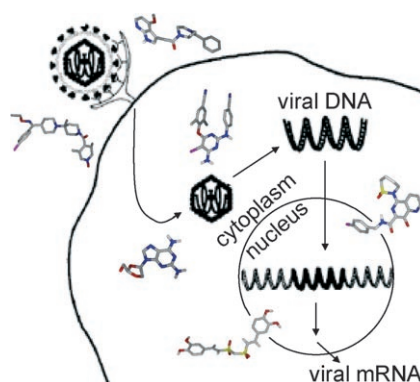
The cover picture shows a potent epothilone derivative with a schematized tubulin microtubule in the background. Epothilones exert their antitumor activity through the stabilization of microtubules by binding with tubulin; cell division stops if microtubules cannot disassemble properly. The structure 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

D. C. Meadows, J. Gervay-Hague\*

16 – 29

Current Developments in HIV  
Chemotherapy



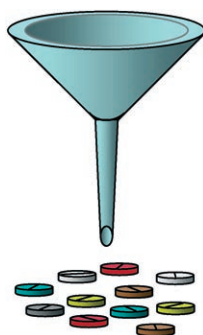
**Barriers to integration:** Specific blockage of HIV integrase, which inserts the viral genome into human DNA, has become an attractive approach toward future antiviral therapies. The development of small-molecule inhibitors of all the main stages of HIV infection (virus entry, reverse transcription, 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

A. Steinmeyer\*

31 – 36

The Hit-to-Lead Process at  
Schering AG: Strategic Aspects



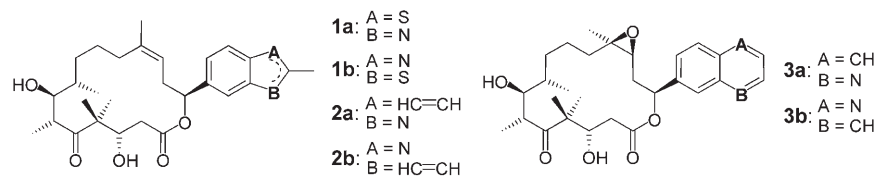
**Funneled more effectively:** High-throughput screening is prominently used in the pharmaceutical industry to identify novel hit structures. In modern drug discovery, processes have been established to convert hits into high-quality leads, which serve as starting points for lead-optimization projects.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

## COMMUNICATIONS

G. Bold, S. Wojeik, G. Caravatti,  
R. Lindauer, C. Stierlin, J. Gertsch,  
M. Wartmann, K.-H. Altmann\*

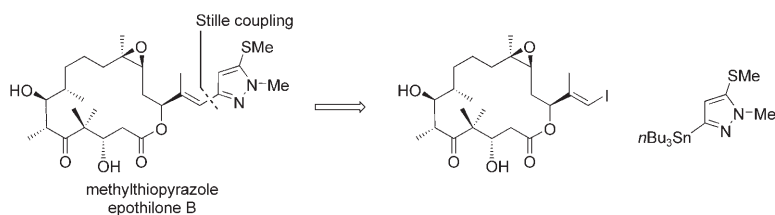
37 – 40

Structure–Activity Relationships in  
Side-Chain-Modified Epothilone  
Analogues—How Important is the  
Position of the Nitrogen Atom?



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**.



**De novo designed and synthesized** methylthiopyrazole epothilone B boasts a stunning biological profile against

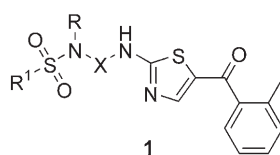
tumor cells, with activity at sub-nanomolar ( $IC_{50} = 0.06$  nM) concentrations.

K. C. Nicolaou,\* B. A. Pratt, S. Arseniyadis,  
M. Wartmann, A. O'Brate, P. Giannakakou

41 – 44

## Molecular Design and Chemical Synthesis of a Highly Potent Epothilone

**Potential appetite control:** A straightforward parallel solution-phase synthesis of novel thiazole derivatives with varying linker moieties gave access to a set of compounds **1**. Assessments of artificial membrane permeability and solubility show that some members of this compound class may be suitable antagonists for the neuropeptide Y5 receptor, which is involved in the stimulation of food intake.

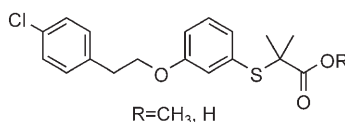


M. Nettekoven,\* W. Guba, W. Neidhart,  
P. Mattei, P. Pflieger, J.-M. Plancher,  
S. Taylor

45 – 48

## Aminothiazole Derivatives as Neuropeptide Y5 Receptor Ligands: Finding the Balance between Affinity and Physicochemical Properties

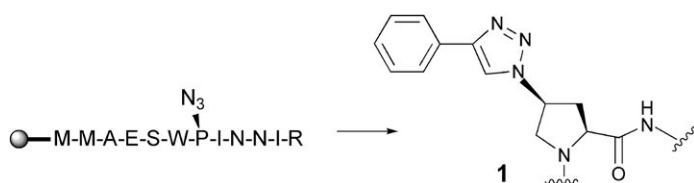
**Combating diabetes:** The new fibrate-like compounds **1** were synthesized and showed antidiabetic and hypolipidemic activities in diabetic mice and in models of hyperlipidemia and PPAR $\alpha$  activation. The acid form is an especially promising candidate for further investigation and preclinical development as a hypolipidemic and insulin-sensitizing agent.



N. Dell'Uomo, E. Tassoni, T. Brunetti,  
P. Pessotto, A. F. Sciarroni, F. M. Milazzo,  
F. De Angelis,\* A. Pescechera, M. O. Tinti,  
P. Carminati, F. Giannessi\*

49 – 53

## 2-{3-[2-(4-Chlorophenyl)ethoxy]-phenylthio}-2-methylpropanoic Acid: a Fibrate-Like Compound with Hypolipidemic and Antidiabetic Activity



**High affinity dual antagonist:** The envelope glycoprotein gp120 of HIV-1 mediates the first steps of viral entry into the host cell. An azidoproline-based peptide conjugate **1** blocks the interac-

tion of gp120 with both the CD4 cell-surface receptor and 17b (an antibody surrogate of the CCR5 co-receptor). It represents a potentially effective approach in preventing HIV infection.

H. N. Gopi, K. C. Tirupula, S. Baxter,  
S. Ajith, I. M. Chaiken\*

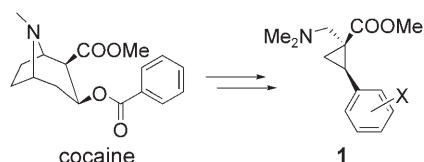
54 – 57

## Click Chemistry on Azidoproline: High-Affinity Dual Antagonist for HIV-1 Envelope Glycoprotein gp120

A. P. Kozikowski,\* L. Zhao, A. Zhang,  
C. Z. Wang, J. Flippen-Anderson,  
K. M. Johnson

58 – 65

## Structural Remodeling of Cocaine: Design and Synthesis of Trisubstituted Cyclopropanes as Selective Serotonin Reuptake Inhibitors

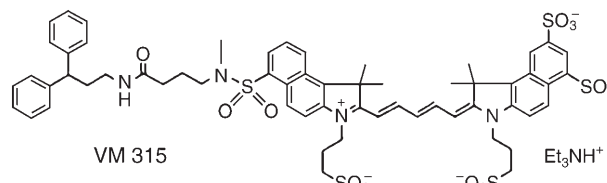


**Blocking transporters:** A series of novel cyclopropane analogues **1** structurally related to cocaine were synthesized by using a sulfonium ylide based cyclopropanation reaction of benzylidenemalonate. As selective serotonin reuptake inhibitors (SSRIs) have proven effective against depression and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

X. Montet, M. Rajopadhye, R. Weissleder\*

66 – 69

## An Albumin-Activated Far-Red Fluorochrome for In Vivo Imaging



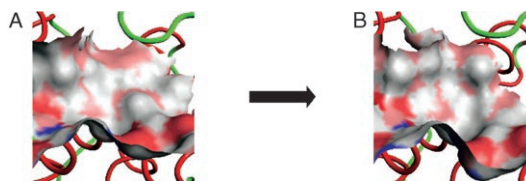
**The far-red indocyanine fluorochrome** VM315 significantly increases its fluorescence upon binding albumin, but not other proteins. Experimental tumor detection in multiple xenograft cancer

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.

S. P. Brown, P. J. Hajduk\*

70 – 72

## Effects of Conformational Dynamics on Predicted Protein Druggability



**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

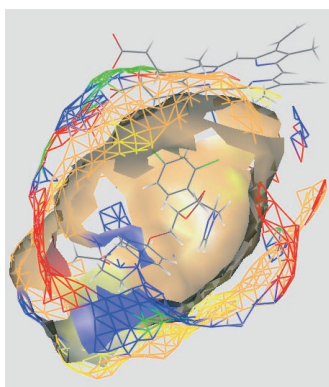
of Bcl-xL benefits from the incorporation of multiple conformations taken from molecular dynamics simulation, which captures fluctuations in binding pocket shape and size (two such structures shown in A and B).

## FULL PAPERS

M. A. Lill,\* M. Dobler, A. Vedani

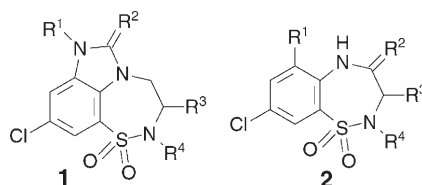
73 – 81

## Prediction of Small-Molecule Binding to Cytochrome P450 3A4: Flexible Docking Combined with Multidimensional QSAR



**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.

**Sulfone analogues** of TIBO that target HIV-1 reverse transcriptase (RT), are more easily synthesized than the most potent TIBO antivirals. Compounds **1** and **2** were active against HIV-1 in cell-based assays, and predictive 3D QSAR models were obtained with a receptor-based alignment by docking these sulfone derivatives into the non-nucleoside binding site of RT.

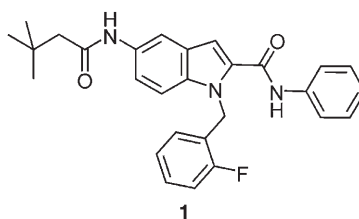


*R. Di Santo,\* R. Costi, M. Artico, R. Ragno, A. Lavecchia, E. Novellino, E. Gavuzzo, F. La Torre, R. Cirilli, R. Cancio, G. Maga*

82 – 95

**Design, Synthesis, Biological Evaluation, and Molecular Modeling Studies of TIBO-Like Cyclic Sulfones as Non-Nucleoside HIV-1 Reverse Transcriptase Inhibitors**

**Blocking heart disease:** A novel class of indole-based inhibitors **1** of endothelin converting enzyme (ECE) has been identified. Docking studies with an ECE model structure have revealed a unique binding mode in which the Zn center of the enzyme is not directly addressed by the inhibitor, but key interactions take place at the central amide group. In vivo efficacy is observed in hypertensive Dahl S rats and mouse models of acute myocardial infarction.

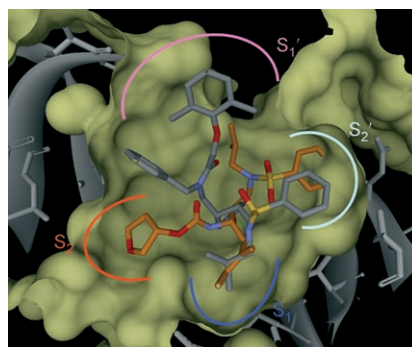


*M. Brands, J.-K. Ergüden, K. Hashimoto,\* D. Heimbach, T. Krahn, C. Schröder, S. Siegel, J.-P. Stasch, H. Tsujishita, S. Weigand, N. H. Yoshida*

96 – 105

**Selective Indole-Based ECE Inhibitors: Synthesis and Pharmacological Evaluation**

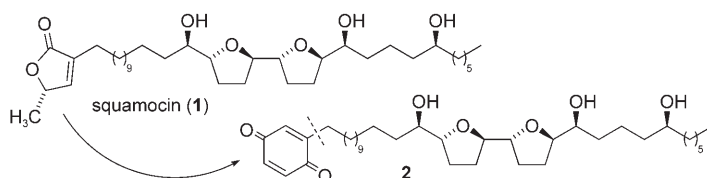
**An unexpected binding mode** for pyrrolidinedimethylene diamines designed as HIV-1 protease inhibitors was revealed through X-ray crystallography of the protease-inhibitor complex (shown). In addition to the identification of highly potent HIV-1 protease inhibitors, the results of this study underscore the importance of crystallography in the process of drug discovery through ligand design.



*E. Specker, J. Böttcher, S. Brass, A. Heine, H. Lilie, A. Schoop, G. Müller, N. Griebenow, G. Klebe\**

106 – 117

**Unexpected Novel Binding Mode of Pyrrolidine-Based Aspartyl Protease Inhibitors: Design, Synthesis and Crystal Structure in Complex with HIV Protease**



**Cell killers:** Radical decarboxylation and quinone addition provided the squamoquinone analogue **2** from the natural pro-apoptotic product, squamocin (**1**).

The squamoquinone form is tenfold more potent than its parent compound in the induction of a mitochondrial caspase-mediated cell-death process.

*S. Derbré, R. Duval, G. Roué, A. Garofano, E. Poupon,\* U. Brandt, S. A. Susin,\* R. Hocquemiller*

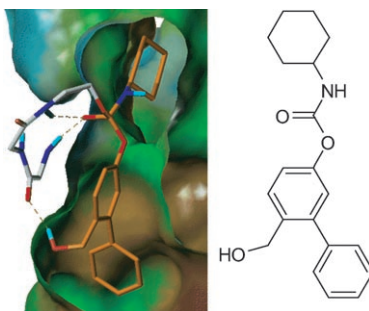
118 – 129

**Semisynthesis and Screening of a Small Library of Pro-Apoptotic Squamocin Analogues: Selection and Study of a Benzoquinone Hybrid with an Improved Biological Profile.**

G. Tarzia, A. Duranti, G. Gatti, G. Piersanti, A. Tontini, S. Rivara, A. Lodola, P. V. Plazzi, M. Mor,\* S. Kathuria, D. Piomelli

130 – 139

## Synthesis and Structure–Activity Relationships of FAAH Inhibitors: Cyclohexylcarbamic Acid Biphenyl Esters with Chemical Modulation at the Proximal Phenyl Ring

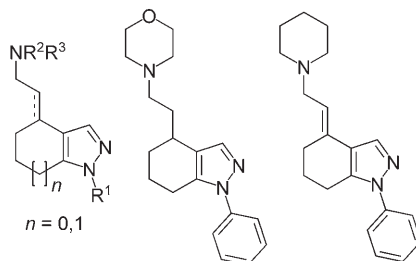


**FAAH away:** Derivatives of the carbamate inhibitor URB524 substituted at the proximal phenyl ring were prepared for further investigations of the mechanism of FAAH inhibition. SAR studies revealed that the recognition step is fundamental for the potency, with small polar substituents giving the best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

J. Corbera, D. Vaño, D. Martínez, J. M. Vela, D. Zamanillo, A. Dordal, F. Andreu, E. Hernandez, R. Perez, M. Escriche, L. Salgado, S. Yeste, M. T. Serafini, R. Pascual, J. Alegre, M. C. Calvet, N. Cano, M. Carro, H. Buschmann, J. Holenz\*

140 – 154

## A Medicinal-Chemistry-Guided Approach to Selective and Druglike Sigma 1 Ligands




**The sigma 1 ( $\sigma_1$ ) 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-annealed 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  $\sigma_1$ .

## CONFERENCE REPORTS

J. Cramer,\* M. Berger

155 – 157

### European Medicinal Chemistry—Strategies, Targets, and Drugs under the Spotlight

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

\* Author to whom correspondence should be addressed.

## BOOKS

**Methods and Principles in Medicinal Chemistry 25: Microwaves in Organic and Medicinal Chemistry** · C. O. Kappe, A. Stadler  
**Biopolymers for Medical and Pharmaceutical Applications** · A. Steinbüchel, R. Marchessault (Eds.)

C. Strauss ..... 158

X.-L. Sun ..... 159

## SERVICE

Author Index .....	160
Keyword Index .....	161
Preview .....	162

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