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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 a human affected with malaria, the disease vector *Anopheles*, a map from the WHO showing areas of malaria risk, and MAP-412, an antimalarial compound developed in our group. As the map shows, regions affected by malaria include a large proportion of developing countries. Therefore, there is a need for new antimalarials that can be synthesized and supplied inexpensively. Prepared in just two steps from an inexpensive starting material, isonicotinic acid, our bis-cationic antimalarial compounds may be useful as leads for inexpensive antimalarials. For details, see the Full Paper by H. Kakuta et al. on p. 1527 ff. (Cover design by H.K.)

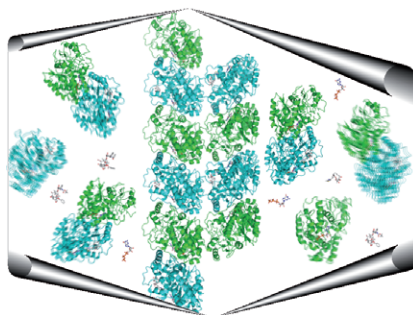
NEWS

Spotlights on our sister journals

1386 – 1387

REVIEWS

Computational tools are available that can increase the information content of experimentally determined structures far beyond gap filling, minor local conformational changes, and energy refinement.



E. Marco,* F. Gago*

1388 – 1401

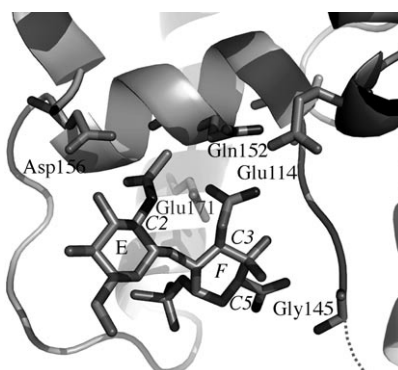
Overcoming the Inadequacies or Limitations of Experimental Structures as Drug Targets by Using Computational Modeling Tools and Molecular Dynamics Simulations

HIGHLIGHTS

J. Zuegg, W. Meutermaans*

1403 – 1404

**Crystal Structures of the PBP2
Glycosyltransferase Domain: New
Opportunities for Antibacterial Drug
Design**



The recent publication by Strynadka and colleagues, describing the first X-ray structures of a soluble truncated version of PBP2 containing both glycosyltransferase and transpeptidase domains facilitates more common and feasible approaches for the rational design and in turn clinically useful GT-inhibitors for the treatment of infections caused by highly resistant bacterial organisms.

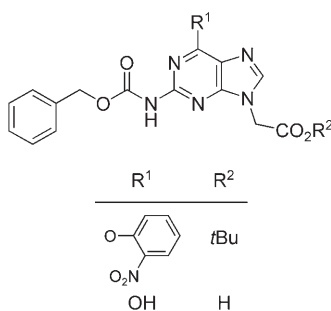
COMMUNICATIONS

K. F. Adebambo, S. Zanoli, M. G. Thomas, R. Cancio, N. M. Howarth,* G. Maga*

1405 – 1409



***N*²-Benzyloxycarbonylguan-9-yl Acetic
Acid Derivatives as HIV-1 Reverse
Transcriptase Non-Nucleoside
Inhibitors with Decreased Loss of
Potency Against Common Drug-
Resistance Mutations.**

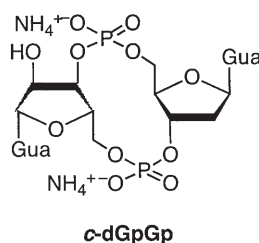


Beating the RT mutants: A novel class of *N*²-Cbz-guan-9-yl acetic acid derivatives is endowed with anti-HIV-1 reverse transcriptase (RT) activity in the low micromolar range. These compounds have improved efficacy towards drug-resistant RT mutants relative to nevirapine and efavirenz. Their unique scaffold and interesting resistance profiles warrant further development.

E. Mano, M. Hyodo, Y. Sato, Y. Ishihara, M. Ohta, Y. Hayakawa*

1410 – 1413

**Synthesis of Cyclic Bis(3'-5')-2'-
deoxyguanylic/guanylic Acid
(c-dGpGp) and Its Biological
Activities to Microbes**

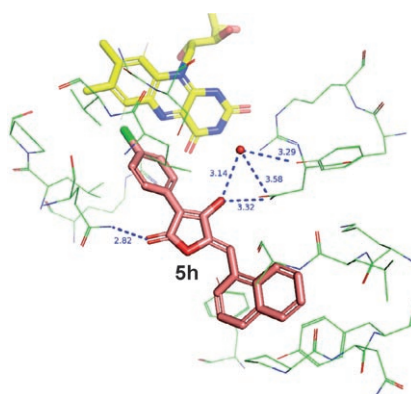


c-di-GMP is considered to play an important role in regulating exopolysaccharide production, biofilm formation, and other phenotypes in bacteria. These attractive biological properties of c-di-GMP prompted us to carry out a systematic study of the bioactivity of c-di-GMP-related compounds, including derivatives with modified nucleoside bases, carbohydrates, or internucleotide bonds. Synthesis of c-dGpGp and its biological activities is reported.

T. S. Mansour,* C. E. Caufield, B. Rasmussen, R. Chopra, G. Krishnamurthy, K. M. Morris, K. Svenson, J. Bard, C. Smeltzer, S. Naughton, S. Antane, Y. Yang, A. Severin, D. Quagliato, P. J. Petersen, G. Singh

1414 – 1417

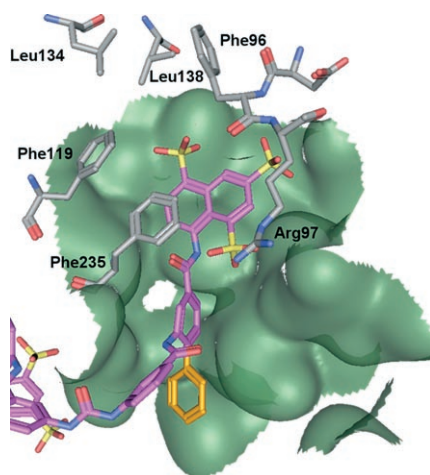
**Naphthyl Tetronic Acids as Multi-
Target Inhibitors of Bacterial
Peptidoglycan Biosynthesis**



A pathway screen targeting multiple muramyl peptide synthesis inhibitors identified the naphthyl tetronic acids series. Optimization of this series based on IC₅₀, K_d and MIC values led to potent inhibitors. Compound **5h** was co-crystallized in the active site of *E. coli* MurB.

FULL PAPERS

New inhibitors for sirtuins: Suramin emerged as an inhibitor of the NAD^+ -dependent histone deacetylase SIRT1. We found suramin-related compounds to be much more potent than the parent molecule and established structure–activity relationships for a large set of suramin derivatives. Molecular modelling accompanied the screening process and gives new insight into suramin binding on sirtuins.

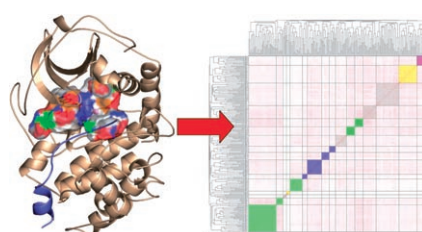


J. Trapp, R. Meier, D. Hongwiset, M. U. Kassack, W. Sippl, M. Jung*

1419 – 1431

Structure–Activity Studies on Suramin Analogues as Inhibitors of NAD^+ -Dependent Histone Deacetylases (Sirtuins)

A diverse set of 258 kinases has been analyzed and clustered based on the exposed physicochemical properties of their ATP binding sites using Cavbase. The resulting clustering provides a relevant grouping of the kinases. Furthermore, pairs of kinases are identified that show unexpected similarities in their binding sites independent of their distance in sequence space.



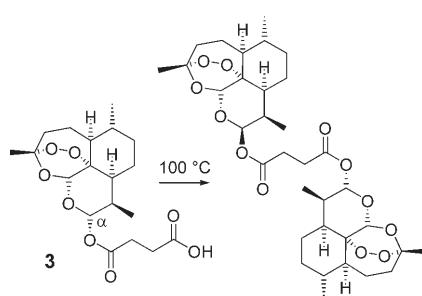
D. Kuhn, N. Weskamp, E. Hüllermeier, G. Klebe*

1432 – 1447

Functional Classification of Protein Kinase Binding Sites Using Cavbase



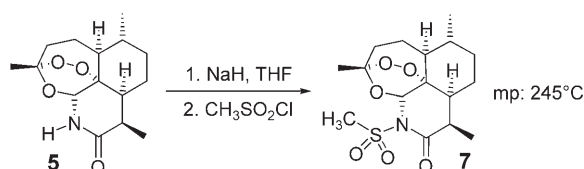
The front-line antimalarial drugs artesunate and DHA undergo thermal decomposition under mild conditions to give unusual dimeric peroxides, a glycal and a rearranged peroxide, in addition to benign decomposition products. The implications of the decomposition in relation to shelf-life determination according to the International Conference of Harmonization guidelines and use of DHA as an antimalarial drug are discussed.



R. K. Haynes,* H.-W. Chan, C.-M. Lung, N.-C. Ng, H.-N. Wong, L. Y. Shek, I. D. Williams, A. Cartwright, M. F. Gomes

1448 – 1463

Artesunate and Dihydroartemisinin (DHA): Unusual Decomposition Products Formed under Mild Conditions and Comments on the Fitness of DHA as an Antimalarial Drug



As a counter to the thermal lability of artemisinins in clinical use, we attached *N*-sulfonyl and *N*-carbonyl groups to the Ziffer 11-azaartemisinin to provide new derivatives, some of which possess sub-

stantially greater thermal stabilities than current artemisinins, whilst retaining good antimalarial activity against the malaria parasite.

R. K. Haynes,* H.-N. Wong, K.-W. Lee, C.-M. Lung, L. Y. Shek, I. D. Williams, S. L. Croft, L. Vivas, L. Ratray, L. Stewart, V. K. W. Wong, B. C. B. Ko

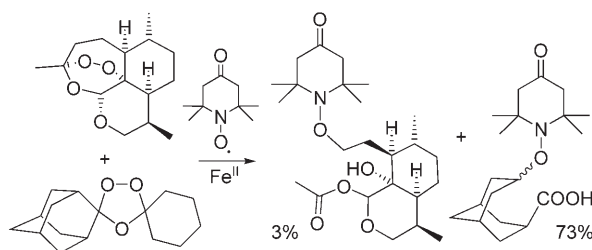
1464 – 1479

Preparation of *N*-Sulfonyl- and *N*-Carbonyl-11-Azaartemisinins with Greatly Enhanced Thermal Stabilities: in vitro Antimalarial Activities

R. K. Haynes,* W. C. Chan, C.-M. Lung,
A.-C. Uhlemann, U. Eckstein, D. Taramelli,
S. Parapini, D. Monti, S. Krishna*

1480 – 1497

The Fe²⁺-Mediated Decomposition, PfATP6 Binding, and Antimalarial Activities of Artemisone and Other Artemisinins: The Unlikelihood of C-Centered Radicals as Bioactive Intermediates



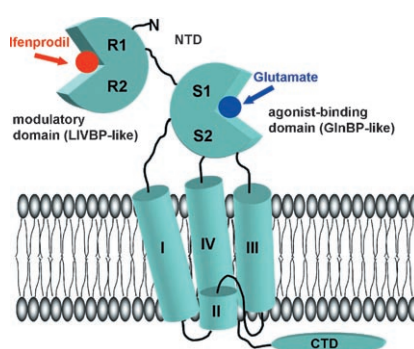
The Fe²⁺-induced decomposition of artemisinins in relation to the ability to intercept C radical intermediates, their antimalarial activities, inhibition of the parasite PfATP6, and the effect of ascorbate

and the iron chelator DFO on the biological properties have been examined. The artemisinins are intrinsically incapable of providing C radicals eminently suited for intermolecular reactions.

L. Marinelli,* S. Cosconati, T. Steinbrecher,
V. Limongelli, A. Bertamino, E. Novellino,
D. A. Case

1498 – 1510

Homology Modeling of NR2B Modulatory Domain of NMDA Receptor and Analysis of Ifenprodil Binding



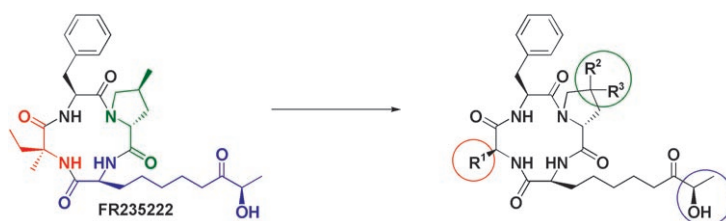
Open or closed? The construction of a 3D model for the NMDA NR2B domain is described along with docking, MD simulations, and MM-PBSA analysis. These calculations allowed the definition of ifenprodil binding pose at an atomic level in both the open and closed conformation of the NR2B domain. Finally, a hypothesis of the ifenprodil mechanism of action is proposed.

L. Gomez-Paloma, I. Bruno, E. Cini,
S. Khochbin, M. Rodriguez, M. Taddei,*
S. Terracciano, K. Sadoul

1511 – 1519



Design and Synthesis of Cyclopeptide Analogues of the Potent Histone Deacetylase Inhibitor FR235222



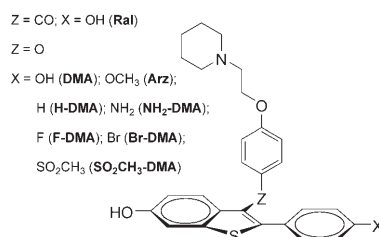
FR235222, one of the most potent HDAC inhibitors, is a natural tetrapeptide formed by some not easily available amino acids. We found that it is possible to build a structurally similar tetrapeptide made with simpler amino acids but

maintaining Ahoda (indispensable) which has the high activity of the parent natural product and shows selective inhibition of class 1 histone deacetylase.

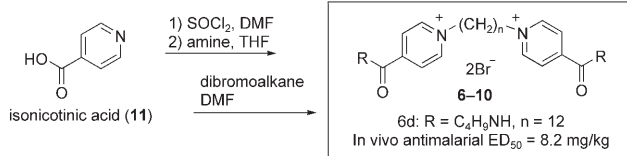
C. R. Overk, K.-W. Peng, R. T. Asghodom,
I. Kastrati, D. D. Lantvit, Z. Qin, J. Frasor,
J. L. Bolton, G. R. J. Thatcher*

1520 – 1526

Structure–Activity Relationships for a Family of Benzothiophene Selective Estrogen Receptor Modulators Including Raloxifene and Arzoxifene



The ideal estrogen receptor modulator. Development of the “ideal” selective estrogen receptor modulator (SERM) is of importance in postmenopausal women’s health. SERMs are generally oxidatively labile phenolic aromatics. Modification of the 4’-position of benzothiophene SERMs can modulate lability, but can the appropriate antiestrogenic profile be retained?



Managing malaria. As the area affected by malaria includes a large proportion of developing countries, there is a need for new antimalarials that can be synthesized and supplied inexpensively. In

this study, bis-cation dimers, MAP series **6–10** synthesized from an inexpensive isonicotinic acid (**11**) in just two steps, were designed. MAP-412 (**6d**) exhibited a potent in vivo antimalarial activity.

K. Motoshima, Y. Hiwasa, M. Yoshikawa,
K. Fujimoto, A. Tai, H. Kakuta,* K. Sasaki

1527 – 1532

**Antimalarial Cation-dimers
Synthesized in Two Steps from an
Inexpensive Starting Material,
Isonicotinic Acid**

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

* Author to whom correspondence should be addressed.

COMMENTARY

Lusucentics: Opportunity or Curse?

C. Djerassi 1533

BOOKS

**Nanotechnology in Biology and Medicine: Methods, Devices, and
Applications** · T. Vo-Dinh (Ed.)

D. Akin 1534

Bioinformatics—From Genomes to Therapies · T. Lengauer (Ed.)

J. E. Kerrigan 1535

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