

COVER PICTURE



The cover picture shows the evolutionary development of peptidic, peptidomimetic, and small-molecule inhibitors of the oncogenic signal transducer and activator of transcription 3 (Stat3) protein dimerization and biological function. For details, see the Minireview by S. Fletcher, J. Turkson, and P. T. Gunning on p. 1159 ff.

NEWS

Spotlights on our sister journals

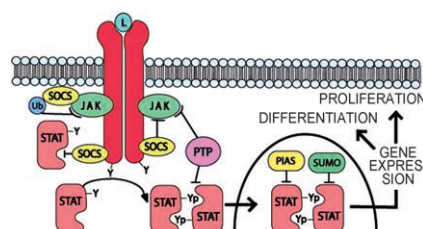
1156 – 1157

MINIREVIEWS

S. Fletcher, J. Turkson,* P. T. Gunning*

1159 – 1168

Molecular Approaches towards the Inhibition of the Signal Transducer and Activator of Transcription 3 (Stat3) Protein



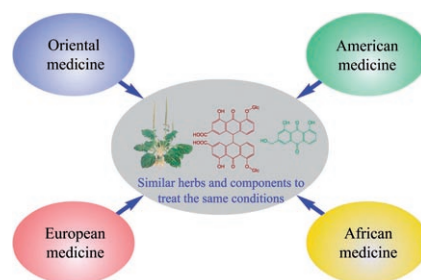
Molecular approaches towards Stat3 inhibition: Stat3 inhibition represents an exciting new approach to the treatment of cancer. The advances in the direct molecular inhibition of Stat3 are highlighted through discussion of the various inhibitors currently under investigation, including peptide sequences, peptidomimetics, small molecules and platinum-based agents.

ESSAY

D.-X. Kong, X.-J. Li, H.-Y. Zhang*

1169 – 1171

Convergent Evolution of Medicines



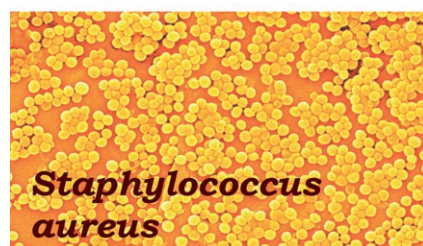
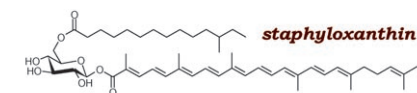
Applying a biological theory to a medicinal problem. By analyzing the phylogenies of Chinese, Western, and other medicinal systems and probing their chemical space, the phenomenon of convergent evolution has been found to exist within medicines.

HIGHLIGHTS

D. Haebich,* F. von Nussbaum*

1173 – 1177

“Superbugs Bunny” Outsmarts Our Immune Defense



A new, non-traditional antibacterial approach that targets the carotenoid pigment staphyloxanthin in *S. aureus* demonstrates that future anti-infective therapy could eventually be boosted by bacterial virulence factor neutralization.

COMMENTARY

Group Efficiency: A Guideline for Hits-to-Leads Chemistry

M. L. Verdonk,* D. C. Rees*

1179 – 1180

CONFERENCE REPORT

A meeting of innovation: The scenic college town of Regensburg in eastern Bavaria hosted a meeting of scientists working in GPCR research, antiviral drugs, cardiovascular and metabolic diseases, and molecular imaging. Conference highlights are discussed.

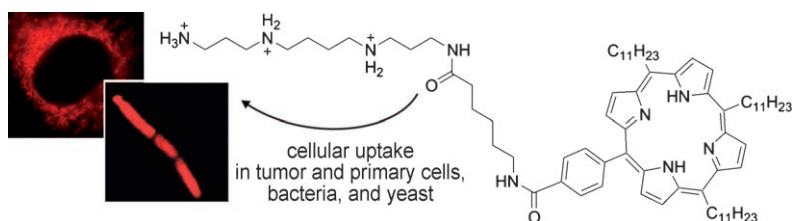


S. Dove, R. Seifert, S. Elz, A. Buschauer*

1181 – 1184

Frontiers in Medicinal Chemistry in Regensburg

COMMUNICATIONS



cellular uptake in tumor and primary cells, bacteria, and yeast

F. Hahn, K. Schmitz, T. S. Balaban, S. Bräse,* U. Schepers*

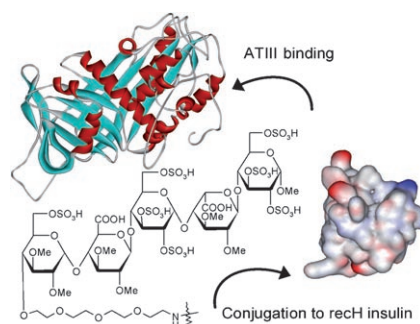
1185 – 1188

Conjugation of Spermine Facilitates Cellular Uptake and Enhances Antitumor and Antibiotic Properties of Highly Lipophilic Porphyrins

Photodynamic therapy: The application of porphyrins in photodynamic therapy has been limited by their low solubility and cellular uptake efficiency. The introduction of a charged polyamine moiety

to the lipophilic porphyrin ring can enhance the amphiphilicity of a compound of this class and ultimately lead to greater therapeutic efficacy.

CarboCarrier™: Site-specific conjugation of insulin to a synthetic antithrombin III (ATIII)-binding pentasaccharide (PS) improves the protein's half-life and extends the duration of action. The half-life can be adjusted by changing the PS affinity for ATIII.

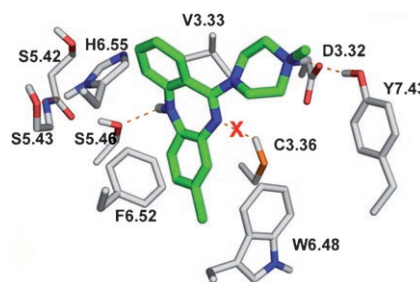


M. de Kort,* B. Gianotten, J. A. J. Wisse, E. S. Bos, M. H. M. Eppink, E. Mattaar, G. M. T. Vogel, W. H. A. Dokter, M. Honing, S. Vonsovic, M.-J. Smit, J. C. H. M. Wijkmans, C. A. A. van Boeckel

1189 – 1193

Conjugation of ATIII-Binding Pentasaccharides to Extend the Half-Life of Proteins: Long-Acting Insulin

The relationships between the multi-receptor binding profile of clozapine and olanzapine and their therapeutic properties were analyzed by using novel complexes built from the recently solved β_2 adrenergic receptor structure. While interactions with position 3.36 determine the binding profile of clozapine-like ligands, diversity in TM5 and TM6 is responsible for subtle differences between clozapine and olanzapine.




J. Selent, L. López, F. Sanz, M. Pastor*

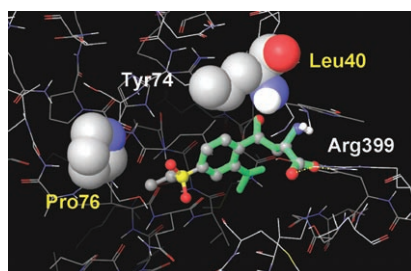
1194 – 1198

Multi-Receptor Binding Profile of Clozapine and Olanzapine: A Structural Study Based on the New β_2 Adrenergic Receptor Template

R. Pellicciari,* F. Venturoni, D. Bellocchi,
A. Carotti, M. Marinozzi, A. Macchiarulo,
L. Amori, R. Schwarcz

1199 – 1202


 **Sequence Variants in Kynurenine Aminotransferase II (KAT II) Orthologs Determine Different Potencies of the Inhibitor S-ESBA**

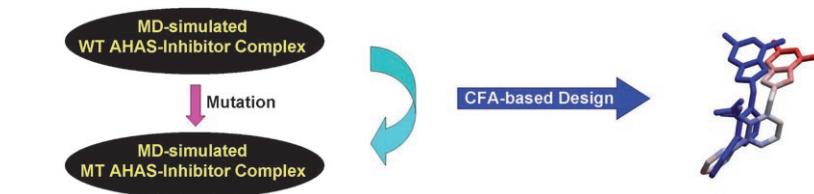


We report a novel and more efficient synthesis of S-ESBA and an analysis of its inhibitory activity toward recombinant human KAT II. The data are discussed in light of the crystal structure of human KAT II and on the basis of conserved and nonconserved residues of species-specific orthologs of KAT II (human, rat, and mouse).

F.-Q. Ji, C.-W. Niu, C.-N. Chen, Q. Chen,
G.-F. Yang,* Z. Xi,* C.-G. Zhan*

1203 – 1206

 **Computational Design and Discovery of Conformationally Flexible Inhibitors of Acetohydroxyacid Synthase to Overcome Drug Resistance Associated with the W586L Mutation**



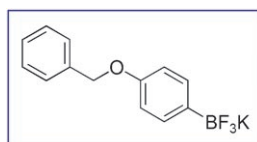
Rational design: A series of 2-aryloxy-1,2,4-triazolo[1,5-c]pyrimidine derivatives were computationally designed (see scheme) and synthesized as conforma-

tionally flexible AHAS inhibitors. These compounds could find use as new leads for combating drug resistance.

N. Lecat-Guillet, Y. Ambroise*

1207 – 1209

Discovery of Aryltrifluoroborates as Potent Sodium/Iodide Symporter (NIS) Inhibitors




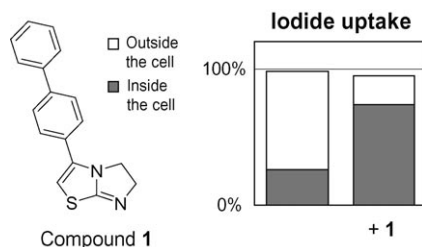
The structure-based design of sodium/iodide symporter (NIS) inhibitors identified new active compounds. The organotrifluoroborate shown was found to inhibit iodide uptake with an IC_{50} value of $0.4 \mu\text{M}$ on rat-derived thyroid cells. The biological activity is rationalized by the presence of the BF_3^- ion as a minimal binding motif for substrate recognition at the iodide binding site.

FULL PAPERS

N. Lecat-Guillet, Y. Ambroise*

1211 – 1216

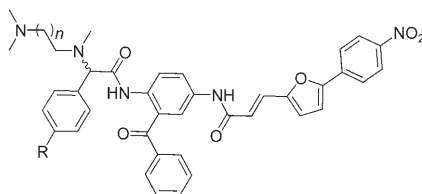
 **Enhanced Iodide Sequestration by 3-Biphenyl-5,6-dihydroimidazo[2,1-b]thiazole in Sodium/Iodide Symporter (NIS)-Expressing Cells**



A step toward selective cancer cell destruction using radioiodide therapy was achieved with the discovery of 3-biphenyl-5,6-dihydroimidazo[2,1-b]thiazole (Compound 1). This compound is a powerful iodide-sequestering agent that blocks radioiodide release from cells, and thus enhances $^{131}\text{I}^-$ residence time and killing efficacy.

Developing improved antimalarials:

The development of farnesyltransferase inhibitors directed against *Plasmodium falciparum* is a strategy towards new antimalarial drugs. Previously, we described benzophenone-based farnesyltransferase inhibitors with high in vitro antimalarial activity but no in vivo activity. Herein, a structure-based design approach is described in order to further improve the antimalarial activity of this type of inhibitor.



K. Kohring, J. Wiesner, M. Altenkämper, J. Sakowski, K. Silber, A. Hillebrecht, P. Haebel, H.-M. Dahse, R. Ortman, H. Jomaa, G. Klebe, M. Schlitzer*

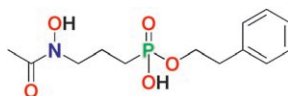
1217 – 1231

Development of Benzophenone-Based Farnesyltransferase Inhibitors as Novel Antimalarials



Hydrogen bonds alone are not

enough: Fosmidomycin derivatives with only one instead of two negative charges and an additional hydrophobic residue display micromolar antimalarial activity.

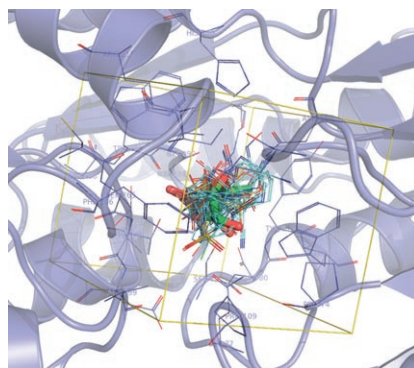


J. Perruchon, R. Ortman, M. Altenkämper, K. Silber, J. Wiesner, H. Jomaa, G. Klebe, M. Schlitzer*

1232 – 1241

Studies Addressing the Importance of Charge in the Binding of Fosmidomycin-Like Molecules to Deoxyxylulosephosphate Reductoisomerase

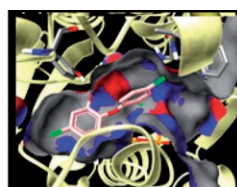
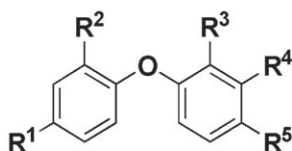
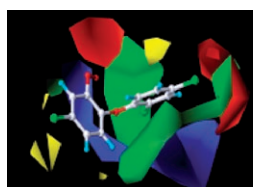
Inhibition of quorum sensing is recognized as a feasible approach to developing new antimicrobial agents. Virtual screening was conducted using the *V. harveyi* LuxP crystal structure. Two compounds were found to antagonize AI-2-mediated quorum sensing in *V. harveyi* without associated cytotoxicity. These two compounds have unique structures and will be very useful as probes for mechanistic studies and as leads for further structural optimization.



M. Li, N. Ni, H.-T. Chou, C.-D. Lu, P. C. Tai, B. Wang*

1242 – 1249

Structure-Based Discovery and Experimental Verification of Novel AI-2 Quorum Sensing Inhibitors against *Vibrio harveyi*



Aryl ether inhibitors of enoyl-ACP reductase. Fatty acid biosynthesis is essential for bacterial growth and is a validated target for antibiotic development. A structure-based design approach was

employed to develop novel aryl ether inhibitors that target BaENR, the product of the *fabI* gene, from *Bacillus anthracis*.

S. K. Tipparaju, D. C. Mulhearn, G. M. Klein, Y. Chen, S. Tapadar, M. H. Bishop, S. Yang, J. Chen, M. Ghassemi, B. D. Santarsiero, J. L. Cook, M. Johlfs, A. D. Mesecar,* M. E. Johnson,* A. P. Kozikowski*

1250 – 1268

Design and Synthesis of Aryl Ether Inhibitors of the *Bacillus Anthracis* Enoyl-ACP Reductase

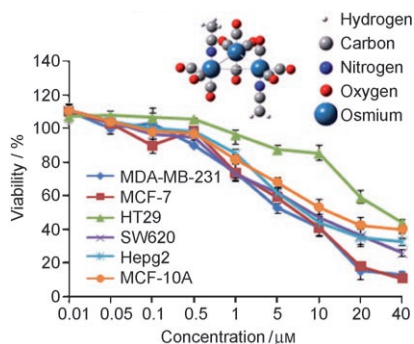


K. V. Kong, W. K. Leong,* S. P. Ng,
T. H. Nguyen, L. H. K. Lim

1269–1275



Osmium Carbonyl Clusters: A New Class of Apoptosis Inducing Agents



Putting the 'Os' in apoptosis: Osmium carbonyl clusters were found to induce apoptosis in four cancer cell lines, namely, ER+ breast carcinoma (MCF-7), ER- breast carcinoma (MDA-MB-231), metastatic colorectal adenocarcinoma (SW620), and hepatocarcinoma (Hep G2). The metal clusters are more cytotoxic towards these cancer cells than they are towards normal epithelial cells.



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



A video clip is available as Supporting Information on the WWW (see article for access details).

* Author to whom correspondence should be addressed.

BOOKS

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