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*The editorial staff and the publishers thank all readers, authors, referees, and advertisers for their interest and support over the past year and wish them all a **Happy New Year**.*

COVER PICTURE



The cover picture shows an orally active, glucose-lowering vitamin B₁₂–insulin conjugate bound to the B₁₂ uptake protein transcobalamin II (TCII). The inset shows a close-up view of the TCII binding pocket. (Insulin is in red; vitamin B₁₂ is in bright yellow.) For details, see the Communication by T. J. Fairchild, R. P. Doyle, et al. on p. 1717 ff.

NEWS

Spotlights on our sister journals

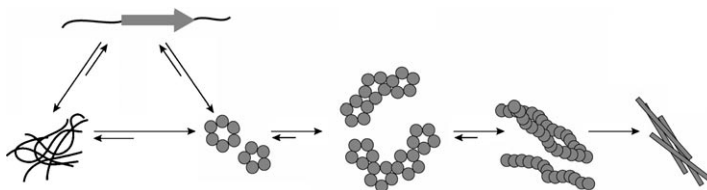
1672 – 1673

REVIEWS

C. I. Stains, K. Mondal, I. Ghosh*

1674 – 1692

Molecules that Target beta-Amyloid



Targeting amyloid. A review of molecules that target β -amyloid ($A\beta$) is presented. Particular attention is given to natural protein ligands, $A\beta$ -derived peptides and peptidomimetics, anti- $A\beta$ antibodies, in vitro anti- $A\beta$ selected pep-

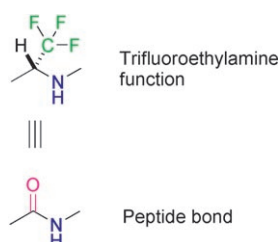
tides and proteins, and small molecules that bind $A\beta$. Moreover, the described anti-amyloid molecular toolbox will also provide an avenue for the design of new diagnostic and therapeutic reagents.

MINIREVIEWS

M. Sani, A. Volonterio, M. Zanda*

1693 – 1700

The Trifluoroethylamine Function as Peptide Bond Replacement



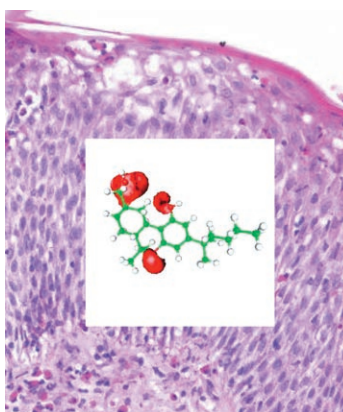
3D instead of 2D. That's the main difference between the tetrahedral stereogenic trifluoroethylamine function and the planar peptide bond. This property, together with other remarkable features such as high metabolic stability and low basicity, turns out to be of great importance to allow trifluoroethylamines to be excellent peptide bond replacements.

HIGHLIGHTS

D. M. Lambert*

1701 – 1702

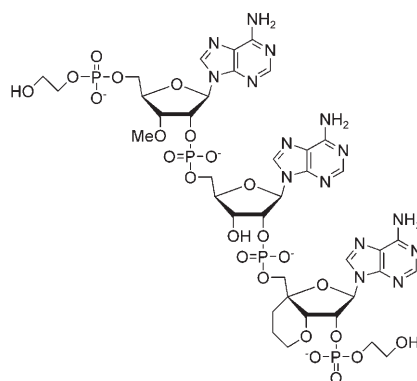
Allergic Contact Dermatitis and the Endocannabinoid System: From Mechanisms to Skin Care



A therapeutic endocannabinoid-based strategy could be useful in numerous and diverse pathological conditions, including CNS disorders, cancer, and cardiovascular diseases. However, Karsak et al. have explored a poorly investigated area: the endocannabinoid system and its ability to elicit a protective role in allergic contact dermatitis. Herein, the significance of this work is discussed.

COMMUNICATIONS

2',5'-Oligoadenylate 5'-triphosphate, referred to as 2-5A, plays an important role in an interferon-regulated RNA degradation pathway with antiviral, growth-inhibitory, and apoptotic activities in mammalian cells. However, its short half-life limits its therapeutic usefulness. Herein, we describe 2-5A analogues synthesized to be more biologically stable and therefore may be developed as chemotherapeutics for viral diseases and cancer.



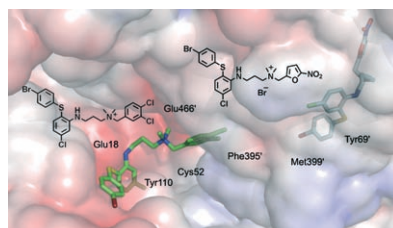
K. Morita, M. Kaneko, S. Obika,
T. Imanishi, Y. Kitade, M. Koizumi*

1703 – 1707

Biologically Stable 2-5A Analogues containing 3'-O,4'-C-bridged Adenosine as Potent RNase L Agonists



Subversive substrates. Replacing the 3,4-dichlorophenyl entity of diphenyl sulfide-based trypanothione reductase (TR) inhibitors for a nitrofur moiety led to a new class of inhibitors with a distinctively changed inhibition mode. These ligands do not only undergo mixed competitive–uncompetitive inhibition but additionally act as subversive substrates for TR.



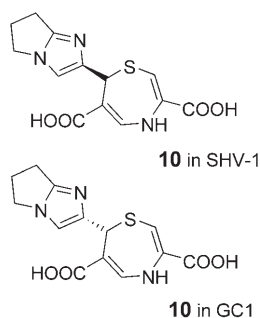
B. Stump, M. Kaiser, R. Brun,
R. L. Krauth-Siegel, F. Diederich*

1708 – 1712

Betraying the Parasite's Redox System: Diaryl Sulfide-Based Inhibitors of Trypanothione Reductase: Subversive Substrates and Antitrypanosomal Properties



Bacterial resistance is addressed clinically by combining a β -lactamase inhibitors with a β -lactam antibiotic. Whereas this strategy is effective with the class A β -lactamase inhibitors, there is an urgent need to extend the spectrum of activity to the other classes of serine β -lactamases. Interaction energies and modeling studies on penem inhibitors described herein, show that β -lactamases of the different classes prefer different stereochemistries.

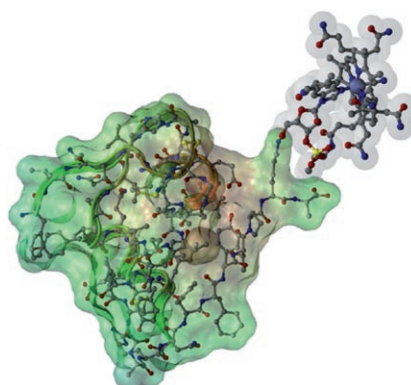


T. S. Mansour,* A. Agarwal,
A. Venkatesan, T. Abe, A. Mihira,
T. Takasaki, K. Sato, H. Ushiroguchi,
I. Yamamura, T. Isoda, Z. Li, Y. Yang,
T. Kumagai

1713 – 1716

On the Absolute Configuration in 1,4-Dihydrothiazepine Covalent Complexes Derived from Inhibition of Class A and C β -Lactamases with 6-Methylidene Penems

The noninvasive delivery of insulin continues to be a major goal for the treatment of diabetes mellitus. Oral–enteric administration would make insulin delivery easier and more effective, as higher patient compliance and improved glycemic control are likely; yet the oral–enteric pathway has been unfeasible owing to insulin's susceptibility to proteolytic degradation and inefficient enteric uptake. Herein we show that a noninvasive oral delivery route for insulin is possible through the vitamin B₁₂ uptake pathway. In diabetic rat models, insulin–B₁₂ conjugates can significantly lower blood glucose levels when administered orally.



A. K. Petrus, A. R. Vortherms,
T. J. Fairchild,* R. P. Doyle*

1717 – 1721

Vitamin B₁₂ as a Carrier for the Oral Delivery of Insulin

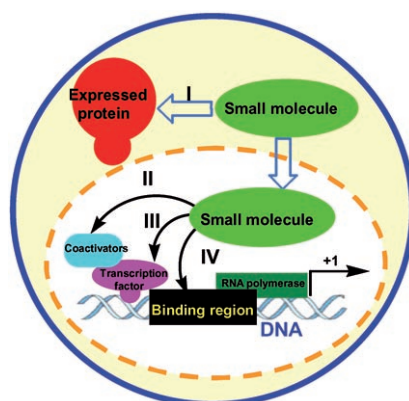


FULL PAPERS

J. Gao,* Y.-G. Liu, Y. Zhou, R. A. Zingaro*

1723 – 1729

Chiral Salicyl Diamines: Potent Anticancer Molecules

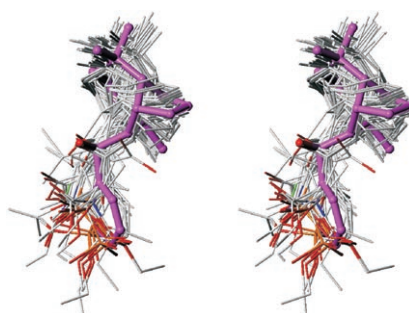


A grand challenge for chemical biologists involves the identification of small molecules that can effectively manipulate the transcription of encoded genes in cancer cells. Chiral *N,N'*-bis-salicyl diamino compounds have now been identified as an effective anticancer agent in the downregulation of Bcl-2 family gene expression in human breast cancer cells.

I. Bichlmaier, M. Finel, W. Sippl, J. Yli-Kauhaluoma*

1730 – 1740

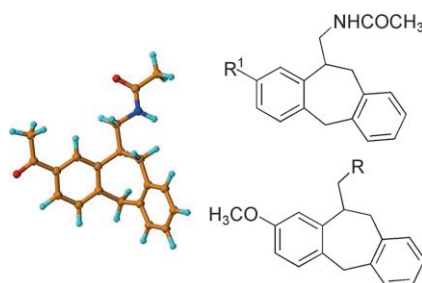
Stereochemical and Steric Control of the UDP-Glucuronosyltransferase-Catalyzed Conjugation Reaction: A Rational Approach for the Design of Inhibitors for the Human UGT2B7



Detailed structure–activity relationships for the design of potent inhibitors for UGT isoforms have not been reported to date. This study provides a rational approach for the design of potent inhibitors for the UGT-isoform 2B7 based on the analysis of functional, stereochemical, and steric properties of a large set of tricyclic sesquiterpenoid derivatives.

G. Spadoni, A. Bedini, G. Diamantini, G. Tarzia, S. Rivara,* S. Lorenzi, A. Lodola, M. Mor, V. Lucini, M. Pannacci, A. Caronno, F. Fraschini

1741 – 1749

Synthesis, Enantiomeric Resolution, and Structure–Activity Relationship Study of a Series of 10,11-Dihydro-5*H*-Dibenzo[*a,d*]cycloheptene MT₂ Receptor Antagonists

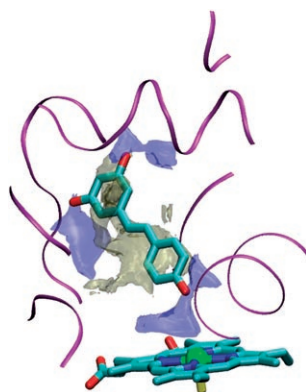
Tricyclic melatonin receptor antagonists: a series of MT₂ melatonin receptor antagonists, characterized by a 10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene scaffold, were synthesized, and SARs were investigated. Enantiomeric resolution by MPLC allowed the testing of enantiomer selectivity, and docking studies with the MT₂ receptor suggested possible binding modes.

M. A. C. Neves, T. C. P. Dinis, G. Colombo,* M. L. Sá e Melo*

1750 – 1762

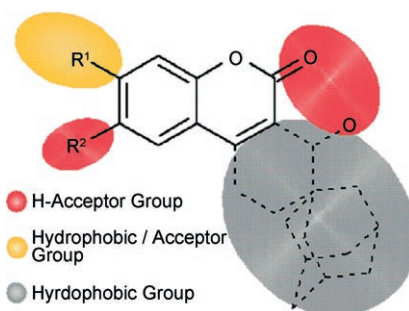


Combining Computational and Biochemical Studies for a Rationale on the Anti-Aromatase Activity of Natural Polyphenols



New strong aromatase inhibitors were identified experimentally. The physicochemical determinants for their productive binding to the active site of the enzyme were characterized through a combination of molecular modeling techniques based on grid-independent descriptors, molecular interaction fields and docking into the 3D homology model structure of the enzyme.

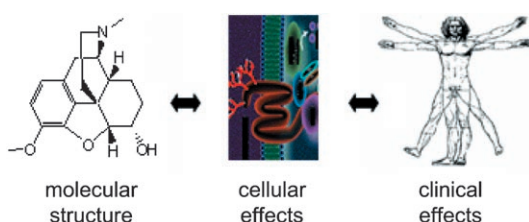
Coumarine mGluR1 antagonists. The important role of allosteric antagonists of metabotropic glutamate receptors (mGluRs) in diseases involving neurodegeneration, anxiety, pain, epilepsy, neuroprotection, and schizophrenia has been investigated. A virtual screening study and activity optimization program of a series of coumarine derivatives facilitated the discovery of novel and subtype selective noncompetitive antagonists of the mGluR1.



*T. Noeske, A. Jirgensons, I. Starchenkovs, S. Renner, I. Jaunzeme, D. Trifanova, M. Hechenberger, T. Bauer, V. Kauss, C. G. Parsons, G. Schneider, T. Weil**

1763 – 1773

Virtual Screening for Selective Allosteric mGluR1 Antagonists and Structure–Activity Relationship Investigations for Coumarine Derivatives



Improving success rates of new medicines in clinical trials requires the capture, standardization, and comparison of vast amounts of heterogeneous structure–effect information. Herein we

describe an approach for relating the molecular structure of medicines to the corresponding “system-wide” effects observed at the cellular and organism levels.

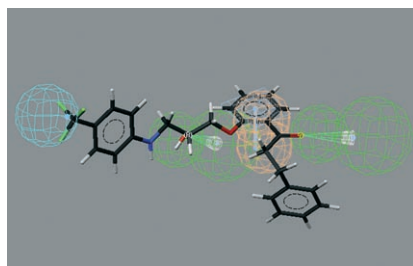
*A. F. Fliri, W. T. Loging, R. A. Volkmann**

1774 – 1782

Analysis of System Structure–Function Relationships



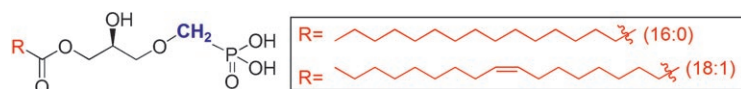
Multidrug resistance transporters ABCB1 and ABCG2 demonstrate broad and partly overlapping ligand specificity. Herein we show that within the chemical scaffold of propafenone-type efflux pump inhibitors, selectivity indices up to 1000 can be obtained by triggering hydrophobicity, number of rotatable bonds, and the number of H-bond acceptors.



J. Cramer, S. Kopp, S. E. Bates, P. Chiba, G. F. Ecker**

1783 – 1788

Multispecificity of Drug Transporters: Probing Inhibitor Selectivity for the Human Drug Efflux Transporters ABCB1 and ABCG2



Surprising subtype selectivity is observed with alkoxymethylenephosphonate (MP) analogues of lysophosphatidic acid (LPA) and phosphatidic acid (PA) that possess a stabilized phosphonate group, the glyceryl 3-oxygen atom,

and the dianionic head group. The MP analogues selectively activate signaling via the LPA₂ receptor subtype, while simultaneously suppressing signaling through the LPA₁ and LPA₃ subtypes.

*J. Gajewiak, R. Tsukahara, T. Tsukahara, S. Yu, Y. Lu, M. Murph, G. B. Mills, G. Tigyi, G. D. Prestwich**

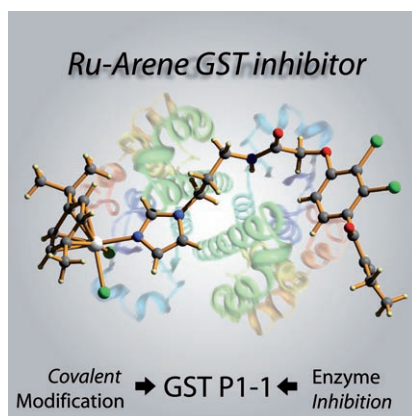
1789 – 1798

Alkoxymethylenephosphonate Analogues of (Lyso)phosphatidic Acid Stimulate Signaling Networks Coupled to the LPA₂ Receptor

W. H. Ang,* A. De Luca,
C. Chapuis-Bernasconi,
L. Juillerat-Jeanneret, M. Lo Bello,*
P. J. Dyson*

1799 – 1806

Organometallic Ruthenium Inhibitors of Glutathione-S-Transferase P1-1 as Anticancer Drugs

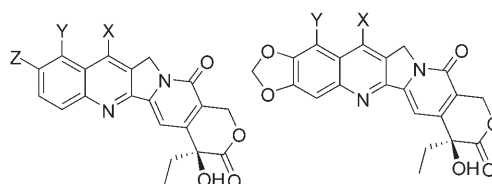


Two-pronged attack: By combining organometallic ruthenium fragments with ethacrynic acid, novel inhibitors of glutathione-S-transferase (GST) P1-1 were obtained. The complexes exhibit greater reactivity towards the enzyme and also represent potent anticancer compounds.

C. Hansch, R. P. Verma*

1807 – 1813

20-(S)-Camptothecin Analogues as DNA Topoisomerase I Inhibitors: A QSAR Study



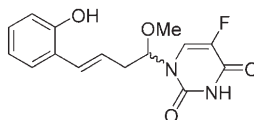
Revealing relationships: Quantitative structure–activity relationships were developed for two series of camptothecin derivatives with respect to their DNA topo I inhibition. The results show that

these activities of camptothecin derivatives are largely dependent on the hydrophobic (and steric) properties of the molecules/substituents.

J. A. Marchal, F. Rodríguez-Serrano,
O. Caba, A. Aránega, M. A. Gallo,
A. Espinosa, J. M. Campos*

1814 – 1821

Antiproliferative Activity, Cell-Cycle Dysregulation, and Cellular Differentiation: Salicyl- and Catechol-Derived Acyclic 5-Fluorouracil O,N-Acetals against Breast Cancer Cells



Looking for a differentiating agent.

The concept of differentiation therapy is based on the conversion of malignant cells to a more benign phenotype using chemical substances. Compounds represented by the formula shown may be useful for differentiation therapy against the MCF-7 human breast cancer cell line.

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

* Author to whom correspondence should be addressed.

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