

CHEM MED CHEM & MEDICINAL CHEMISTRY

<http://www.chemmedchem.org>

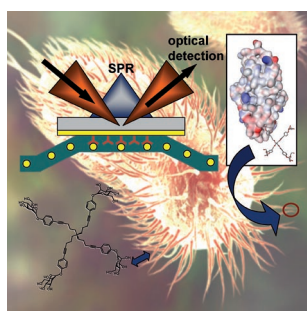
Full text:

WILEY
InterScience®
DISCOVER SOMETHING GREAT
<http://www.interscience.wiley.com>

ChemMedChem, European in origin but international in scope, deals with all aspects of drug discovery. It is co-owned by a group of European chemical societies and is published by Wiley-VCH. Contributions in *ChemMedChem* cover medicinal and pharmaceutical sciences, drug design, drug development and delivery, molecular modeling, combinatorial chemistry, target validation, lead generation, and ADMET studies, that is, research from the overlapping areas between biology, chemistry, and medicine. *ChemMedChem* publishes Communications and Full Papers, as well as Reviews, Minireviews, Highlights, Concepts, Essays, Book Reviews, and occasionally Conference Reports. Authors can submit manuscripts to *ChemMedChem* online through our homepage (see left) by clicking on "Online Submission" and following the simple instructions.

Some articles in this issue have already appeared online in Wiley InterScience. See www.chemmedchem.org under EarlyView®

COVER PICTURE



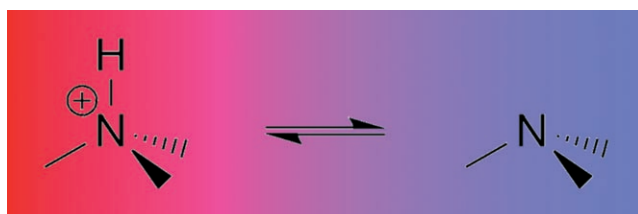
The cover picture shows fimbriated *E. coli* (background) expressing mannose binding pili lectin (FimH) (Connolly surface insert with nanomolar tetrameric mannose ligand). The FimH are primarily involved in bacterial adhesion to host tissues. The affinity constants of several glycodendrimers were evaluated with surface plasmon resonance (SPR). The understanding of these adhesion phenomena at the molecular level is crucial and presents promising alternatives to traditional antibiotic therapies. A novel class of mannose clusters (bottom left) was developed using Sonogashira coupling and click chemistry. These mannose clusters have the potential to inhibit the initial recognition events that lead to adhesion and colonization of host tissues by multiple attachments to *E. coli* FimH. For details, see the Full Paper by J. Bouckaert, R. Roy, et al. on p. 1190 ff.

NEWS

Spotlights on our sister journals

1098 – 1099

REVIEWS



Predicting and tuning amine basicity is one of the crucial factors determining physicochemical properties of leads in drug-discovery research. We present simple-to-use rules for pK_a prediction based on extensive database mining and several case studies from our me-

dicinal chemistry programs over the last years. Stereochemical and conformational factors influencing amine basicity are discussed, and the emergent computational approaches to pK_a predictions are briefly surveyed.

M. Morgenthaler, E. Schweizer,
A. Hoffmann-Röder, F. Benini, R. E. Martin,
G. Jaeschke, B. Wagner, H. Fischer,
S. Bendels, D. Zimmerli, J. Schneider,
F. Diederich,* M. Kansy,* K. Müller*

1100 – 1115

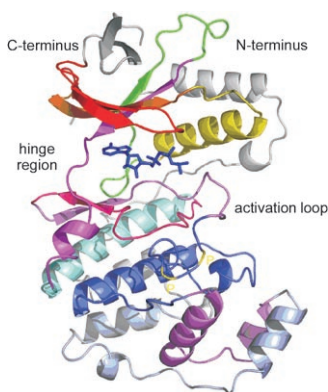
Predicting and Tuning
Physicochemical Properties in Lead
Optimization: Amine Basicities



S. Margutti, S. A. Laufer*

1116 – 1140

Are MAP Kinases Drug Targets? Yes, but Difficult Ones



Difficult drug targets: MAP kinases represent one of the big areas of interest in pharmaceutical research and business. This review presents, through examples of different inhibitors and clinical candidates, an update in the definition of MAP kinases as drug targets with particular focus on p38 MAPK.

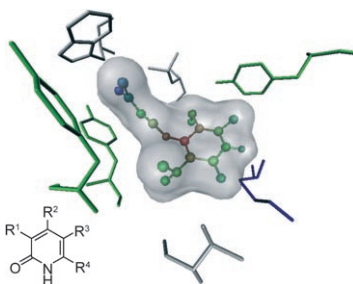
MINIREVIEWS

J. L. Medina-Franco,*

K. Martínez-Mayorga, C. Juárez-Gordiano,
R. Castillo*

1141 – 1147

Pyridin-2(1H)-ones: A Promising Class of HIV-1 Non-nucleoside Reverse Transcriptase Inhibitors



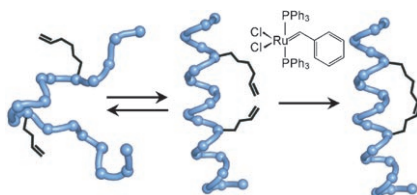
The HIV-1 reverse transcriptase (RT) is an attractive target in the treatment of AIDS. This minireview focuses on the advances in the development of non-nucleoside RT inhibitors of the pyridin-2(1H)-one class. Representative molecules, covering several subclasses are presented. Computational studies, including automated docking and QSAR, are also discussed.

HIGHLIGHTS

P. T. Wilder, T. H. Charpentier, D. J. Weber*

1149 – 1151

Hydrocarbon-Stapled Helices: A Novel Approach for Blocking Protein-Protein Interactions



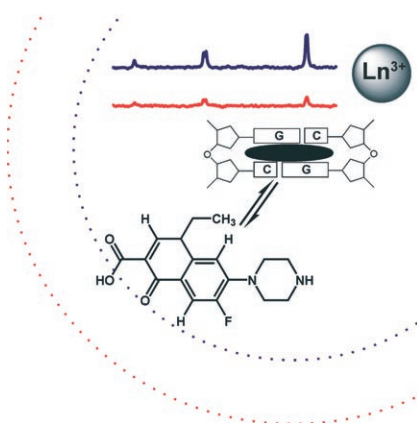
Stapling proteins. Modulating protein-protein interfaces for therapeutic intervention has long been a vision of the research and pharmaceutical community. In a recent paper published by Verdine and co-workers, they developed and implemented a new technique termed “peptide stapling” and have applied it to inhibiting the Hdm2–p53 interaction. Herein, the implications of this work are discussed.

COMMUNICATIONS

E. Chirivino, C. Giordano, S. Faini,
L. Cellai, M. Fragai*

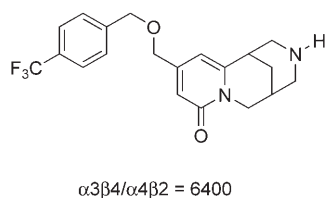
1153 – 1156

Tuning Sensitivity in Paramagnetic NMR Detection of Ligand–DNA Interactions



Pulsed paramagnetics: The presence of an EDTA-functionalized nucleotide on a synthetic fragment of DNA permits the insertion of metal ions with various paramagnetic properties. Therefore, the paramagnetic contribution to the transverse relaxation rate of ligand protons, exploited to increase the sensitivity of NMR screening, can be tuned to get long-range effects and qualitative information on binding specificity.

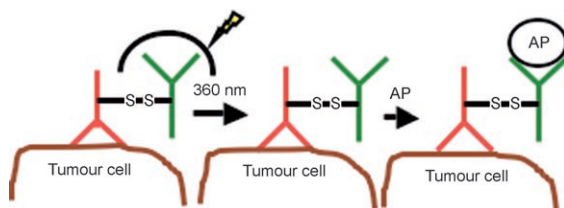
Neuronal nicotinic acetylcholine receptors are widely distributed in the central and peripheral nervous systems. Several lines of evidence suggest that the $\alpha 4\beta 2$ nAChRs mediate addiction to nicotine in tobacco smoking. Novel 10-substituted cytosine derivatives with increased selectivity for $\alpha 4\beta 2$ nicotinic acetylcholine receptors were synthesized and may be of use in smoking cessation.



A. P. Kozikowski,* S. K. Chellappan, Y. Xiao, K. M. Bajjuri, H. Yuan, K. J. Kellar, P. A. Petukhov

1157 – 1161

Chemical Medicine: Novel 10-Substituted Cytosine Derivatives with Increased Selectivity for $\alpha 4\beta 2$ Nicotinic Acetylcholine Receptors



Masked Invader: we constructed a “cloaked” bispecific antibody conjugate in which only one antibody is initially biologically active. The other antibody is rendered inert with a coating of photolabile 2-nitrobenzyl groups until its ac-

tivity is restored on irradiation with UV-A light. Such activatable conjugates could be used to target enzymes and drugs to tumours whilst minimising side effects in the rest of the body.

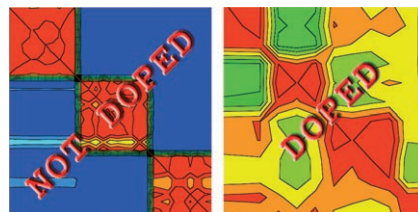
S. Thompson,* M.-C. Fawcett, C. H. Self*

1162 – 1164

The Construction of a Functional Photoactivatable Cancer Targeting Bispecific Antibody Conjugate



Detection of drug abuse in sports (doping) is a top priority for sport organizations due to a number of factors including enhancement of athletic performance and potential health risks to the athletes. Today, recombinant protein abuse is an evolving form of doping that poses a far more challenging target for analytical chemists. Herein we describe a SERS-based method for the ultrasensitive detection and classification of closely related peptidic performance enhancers.



R. A. Alvarez-Puebla, J. P. Bravo-Vasquez, B. Cui, T. Veres, H. Fenniri*

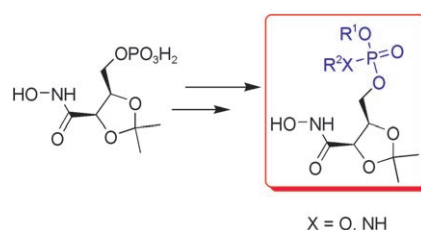
1165 – 1167

SERS Classification of Highly Related Performance Enhancers



FULL PAPERS

A series of prodrugs of the *T. brucei* 6PGDH inhibitor 4-phospho-D-erythronohydroxamic acid were synthesised and evaluated in vitro against the parasite. The compounds showed increased trypanocidal activity compared to the parent compound. Correlation of the antiparasitic activity with the prodrug stability was found.



G. F. Ruda, V. P. Alibu, C. Mitsos, O. Bidet, M. Kaiser, R. Brun, M. P. Barrett, I. H. Gilbert*

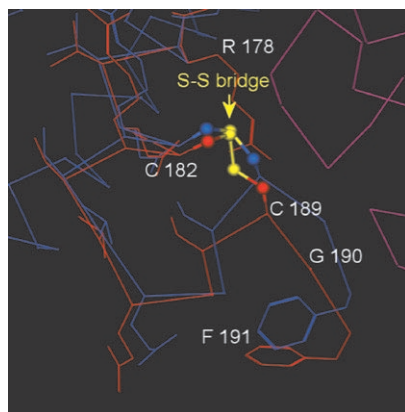
1169 – 1180

Synthesis and Biological Evaluation of Phosphate Prodrugs of 4-Phospho-D-erythronohydroxamic Acid, an Inhibitor of 6-Phosphogluconate Dehydrogenase

A. Datola, S. Richert, H. Bierau,*
D. Agugiaro, A. Izzo, M. Rossi, D. Cregut,
H. Diemer, C. Schaeffer, A. Van Dorsselaer,
C. E. Giartosio, C. Jone

1181 – 1189

Characterisation of a Novel Growth Hormone Variant Comprising a Thioether Link between Cys182 and Cys189

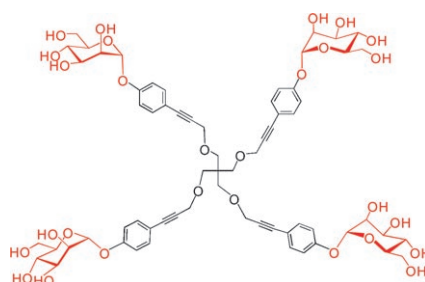


A novel variant of recombinant human growth hormone (r-hGH), containing a nonreducible thioether bridge near the C terminus between Cys182 and Cys189 was characterised. This modification was found to alter the higher order structure of the protein. The presence of this modified intramolecular link may have important implications with regard to the biological behaviour of the molecule.

M. Touaibia, A. Wellens, T. C. Shiao,
Q. Wang, S. Sirois, J. Bouckaert,* R. Roy*

1190 – 1201

Mannosylated G(0) Dendrimers with Nanomolar Affinities to *Escherichia coli* FimH



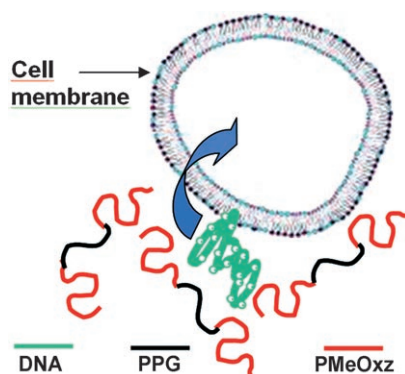
Mannosylated dendrimers: Pentaerythritol and bis-pentaerythritol scaffolds were used for the preparation of first generation glycodendrimers bearing aryl α -D-mannopyranoside residues assembled using Sonogashira and click chemistry. Surface Plasmon Resonance measurements showed these two mannosylated clusters as the best ligands known towards FimH from *Escherichia coli* at subnanomolar concentrations.

B. Brissault, A. Kichler, C. Leborgne,
N. Jarroux, H. Cheradame, C. Guis*

1202 – 1207



Amphiphilic Poly[(propylene glycol)-block-(2-methyl-2-oxazoline)] Copolymers for Gene Transfer in Skeletal Muscle



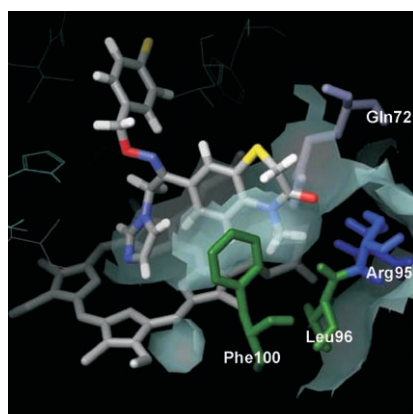
Giving muscle to gene therapy: Non-ionic amphiphilic triblock copolymers based on polypropylene glycol (PPG) as the central component and polymethyl-oxazoline (PMeOxz) termini significantly increase the in vivo gene expression of plasmid DNA in skeletal muscle. These data show that this potential approach to gene delivery is not restricted to Pluronic copolymers.

L. Milanese, N. Giacchè, F. Schiaffella,
A. Vecchiarelli, A. Macchiarulo,
R. Fringuelli*

1208 – 1213

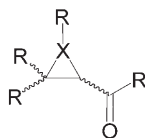


Oxime and Oxime Ether Derivatives of 1,4-Benzothiazine Related to Oxiconazole



The opportunistic human pathogen *Candida albicans* has acquired considerable significance in recent years because of the enhanced susceptibility of immunocompromised patients. Therefore, there is increased need to develop new antifungal drugs. The aim of this work was to synthesize new azole derivatives containing the 1,4-benzothiazine nucleus, that, in itself, shows a moderate antifungal activity and to extend the SAR for this class of compounds.

Proteases, in particular cysteine proteases, of malaria parasites play pivotal roles in the process of the disease. Therefore, the inhibition of cysteine proteases presents a promising strategy for combating the infection. A broad protease- and cell-based screening of 88 protease inhibitors containing an epoxide or aziridine ring yielded highly potent falcipain-2 and falcipain-3 inhibitors with antiparasmodial activity in the submicromolar range.



*F. Schulz, C. Gelhaus, B. Degel, R. Vicik, S. Heppner, A. Breuning, M. Leippe, J. Gut, P. J. Rosenthal, T. Schirmeister**

1214 – 1224

Screening of Protease Inhibitors as Antiplasmodial Agents. Part I: Aziridines and Epoxides



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

* Author to whom correspondence should be addressed.

SERVICE

Author Index 1225 Preview 1226

Keyword Index 1225

All the Tables of Contents may be found on the WWW under:
<http://www.chemmedchem.org>

Issue 7, 2007, was published online on June 27, 2007.

... the ultimate global JobMachine for scientists and engineers.

www.scitec-career.com

Online vacancies worldwide in physics, chemistry, materials science and life sciences.

WILEY-VCH