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CHEMISTRY ENABLING DRUG DISCOVERY

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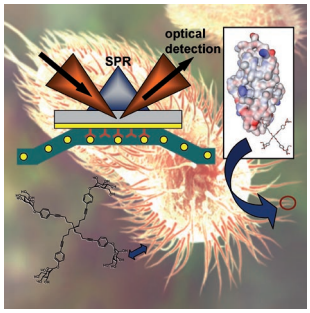
Some articles in this issue have already appeared online in Wiley InterScience. See www.chemmedchem.org under EarlyView®

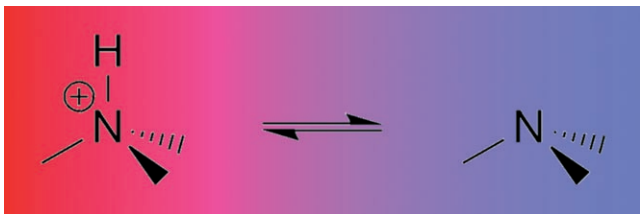
COVER PICTURE



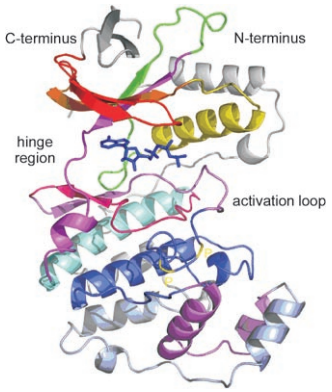
The cover picture shows fimbriated *E. coli* (background) expressing mannoside binding pili lectin (FimH) (Connolly surface insert with nanomolar tetrameric mannoside ligand). The FimH are primarily involved in bacterial adhesion to host tissues. The affinity constants of several glycodendrimers were 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 mannoside clusters (bottom left) was developed using Sonogashira coupling and click chemistry. These mannoside 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

REVIEWS

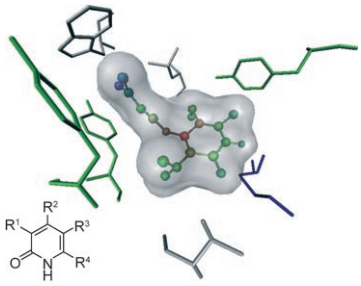


Predicting and tuning amine basicity is one of the crucial factors determining physicochemical properties of leads in drug-discovery research. We present simple-to-use rules for pK_a prediction based on extensive database mining and several case studies from our medicinal chemistry programs over the last years. Stereochemical and conformational factors influencing amine basicity are discussed, and the emergent computational approaches to pK_a predictions are briefly surveyed.



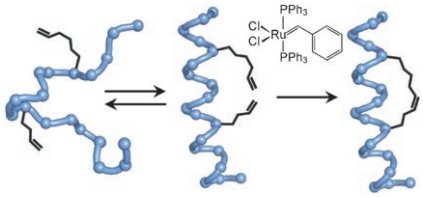
Difficult drug targets: MAP kinases represent one of the big areas of interest in pharmaceutical research and business. This review presents, through examples of different inhibitors and clinical candidates, an update in the definition of MAP kinases as drug targets with particular focus on p38 MAPK.

MINIREVIEWS



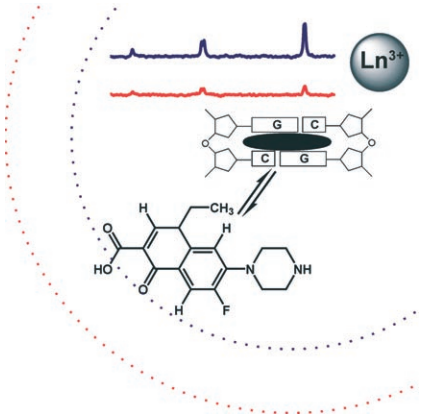
The HIV-1 reverse transcriptase (RT) is an attractive target in the treatment of AIDS. This minireview focuses on the advances in the development of non-nucleoside RT inhibitors of the pyridin-2(1*H*)-one class. Representative molecules, covering several subclasses are presented. Computational studies,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

HIGHLIGHTS



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.

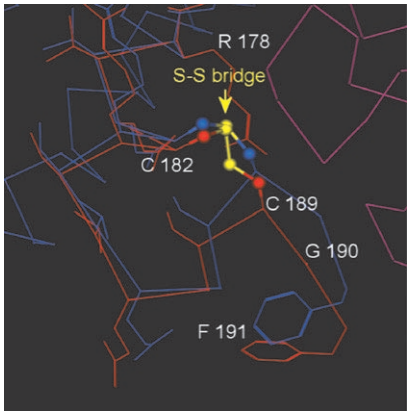
COMMUNICATIONS



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.

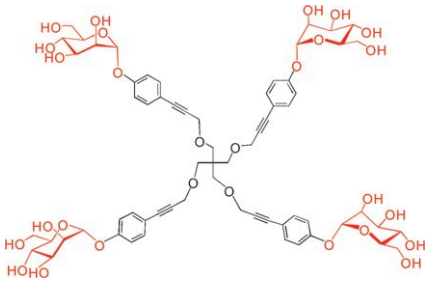
FULL PAPERS

*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



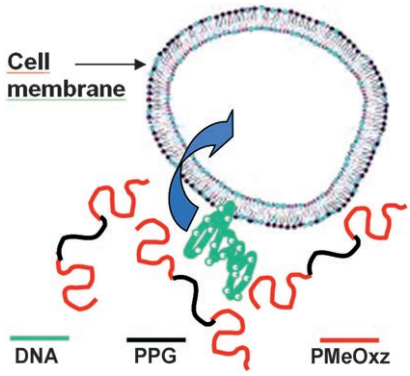
A novel variant of recombinant human growth hormone (r-hGH), containing a nonreducible thioether bridge near the C terminus between Cys182 and Cys189 was characterised. This modification was found to alter the higher order structure of the protein. The presence of this modified intramolecular link may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



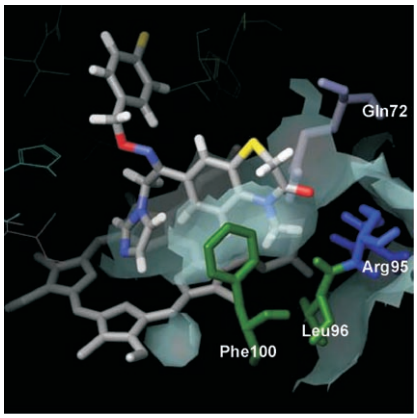
Mannosylated dendrimers: Pentaerythritol and bis-pentaerythritol scaffolds were used for the preparation of first generation glycodendrimers bearing aryl α-D-mannopyranoside residues assembled using Sonogashira and click chemistry. Surface Plasmon Resonance measurements showed these two mannosylated 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**



Giving muscle to gene therapy: Non-ionic amphiphilic triblock copolymers based on polypropylene glycol (PPG) as the central component and polymethyloxazoline (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**



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.

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

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