CHEMMEDCHEM

CHEMISTRY ENABLING DRUG DISCOVERY

07/2008

http://www.chemmedchem.org

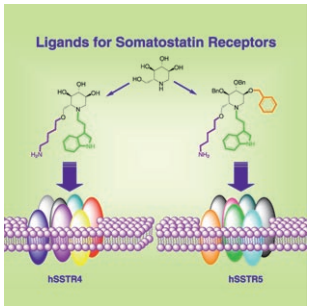
Full text:

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.

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

COVER PICTURE

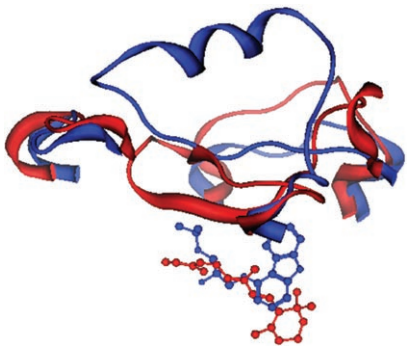


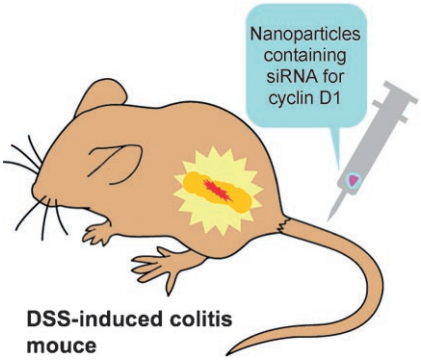
The cover picture shows two peptidomimetics based on 1-deoxynojirimycin (DNJ). The Lys-Trp mimetic on the left is a ligand for the human somatostatin receptor subtype 4 (hSSTR4) but has low affinity for hSSTR5. The Lys-Trp-Phe mimetic on the right displays higher affinity for hSSTR5. For details, see the Full Paper by P. V. Murphy et al. on p. 1071 ff.

NEWS

HIGHLIGHTS

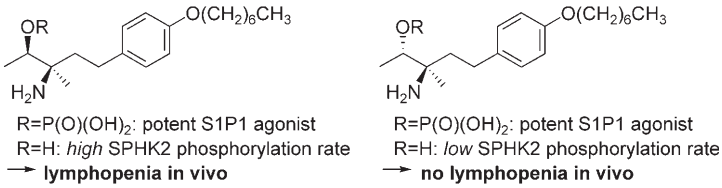
Long sought: The recently reported crystallographic structures of the β2-adrenergic receptor demonstrate that GPCR exhibit the strong structural conservation expected, in addition to some surprising structural differences. These structures were obtained through a number of methodological advances that are broadly applicable to studies of other GPCR.



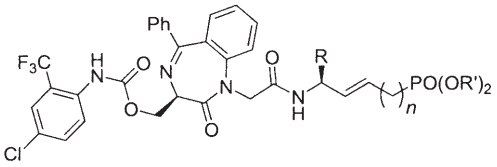


Leukocyte-targeted delivery of siRNA in stabilized nanoparticles: This Highlight article summarizes elegantly designed targeted nanoparticles that can be administered systemically to deliver siRNA for cyclin D1 to specific leukocyte subsets. Silencing of cyclin D1 in this way can reverse experimentally induced colitis in mice.

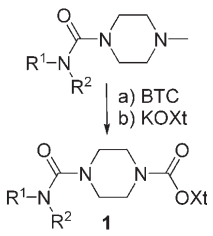
COMMUNICATIONS



Decisive diastereomers. Sphingosine kinase 2 (SPHK2) phosphorylation rate was found to be the major limiting factor for decreasing peripheral lymphocyte counts of FTY720-like derivatives in vivo. For a diastereomeric pair of potent S1P1 agonists, lymphopenia was only observed for the epimer showing an efficient SPHK2 phosphorylation rate of the parent amino alcohol.

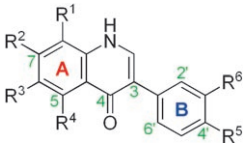


Antimalarials: The aim of our work was to investigate the ability of nonpeptidic vinyl and allyl phosphonates to inhibit falcipain-2 (FP-2), the main cysteine protease of *P. falciparum*. Some of the compounds synthesized, such as the one shown, moderately inhibit FP-2 activity.

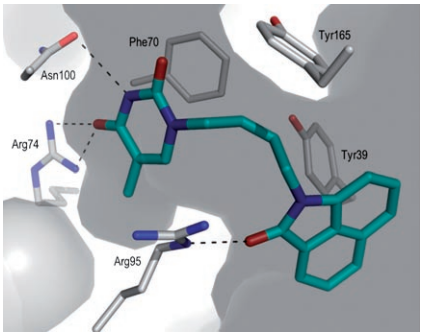


***N*-Methylpiperazine** is an excellent building block for the preparation of piperazine-based unsymmetrical ureas. The methyl group blocks one of the nitrogen atoms and is concomitantly removed during the reaction with phosgene or related reagents required for the preparation of an active carbamate intermediate, which, after reaction with the corresponding amine, renders the desired urea. This strategy allows the preparation of a library of bis-ureas, several of which have anti-HIV properties.

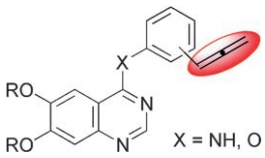
FULL PAPERS



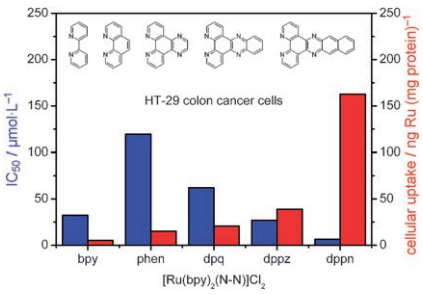
Selective cytotoxicity: Thirty-six 3-aryl-1*H*-quinolin-4-ones were synthesized, and their antiproliferative activity was determined against two cancer cell lines (Hep G2 and KB), and one human normal cell line (L02). Most of the compounds showed cytotoxicity against only the cancer cell lines; the SAR are also reported.



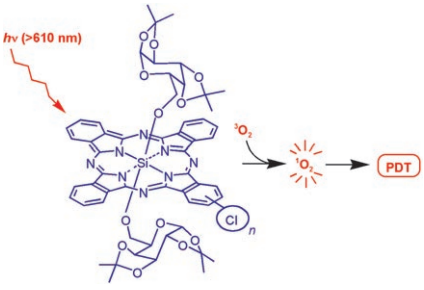
Tackling tuberculosis. Thymine derivatives with a distal naphtholactam or naphthosultam moiety potently and selectively inhibit TMPKmt with K_i values of 0.42 and 0.27 μM, respectively. Docking studies with the target enzyme followed by molecular dynamics simulations revealed a key interaction between the distal substituent and Arg 95.



Are allenes attractive functional groups for drug design? A series of allenic 4-anilino- and 4-phenoxyquinazolines were synthesized and evaluated. Among the compounds synthesized, the allenic quinazoline **1a** inhibits EGF-mediated phosphorylation of EGFR and its downstream kinases in A431 cells, which results in cell-cycle arrest and apoptosis.



Metal-based anticancer therapeutics: For a series of ruthenium(II) polypyridyl complexes $[Ru(bpy)_2(N—N)]Cl_2$, cellular uptake efficiency and cytotoxicity toward HT-29 and MCF-7 cancer cells increase with the aromatic surface area of the N—N ligand. The biological action seems to be related to modifications in cell morphology and adhesion properties.



Good or bad? Peripheral chloro substitution: A series of silicon(IV) phthalocyanines with two axial isopropylidene-protected galactose moieties and one, two, or eight chloro group(s) on the periphery of the macrocycle were synthesised and spectroscopically characterised. The photophysical properties of these compounds and their in vitro photocytotoxicity are discussed.

CONTENTS

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

SERVICE

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

Issue 6, 2008, was published online on June 5, 2008.