

CHEMICAL & MEDICINAL CHEMISTRY

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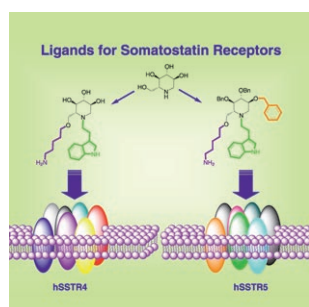
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COVER PICTURE



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.

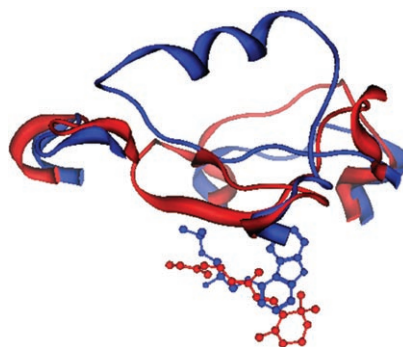
NEWS

Spotlights on our sister journals

1018 – 1019

HIGHLIGHTS

Long sought: The recently reported crystallographic structures of the β 2-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.



A. L. Parrill*

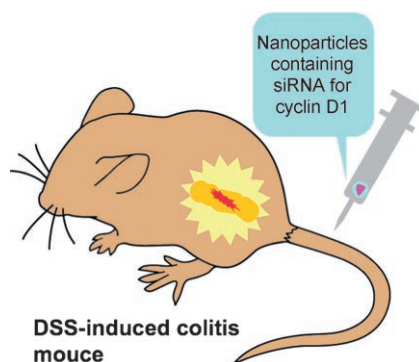
1021 – 1023

Crystal Structures of a Second G Protein-Coupled Receptor: Triumphs and Implications

H. Kakuta*

1024–1025

Necessity is the Mother of Invention: An Ingenious Method for Leukocyte-Targeted Delivery of siRNA in Stabilized Nanoparticles Demonstrates a Role of Cyclin D1 in Inflammation



DSS-induced colitis mouse

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.

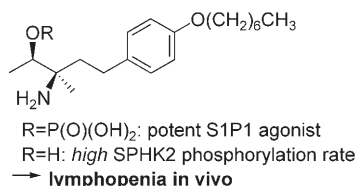
COMMUNICATIONS

K. Högenauer,* A. Billich, C. Pally, M. Streiff, T. Wagner, K. Welzenbach, P. Nussbaumer

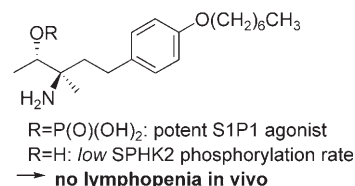
1027–1029



Phosphorylation by Sphingosine Kinase 2 is Essential for in vivo Potency of FTY720 Analogues



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

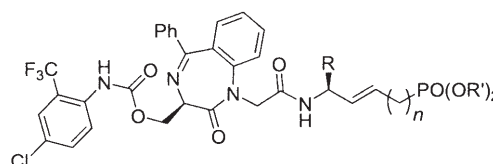


in vivo. For a diastereomeric pair of potent S1P1 agonists, lymphopenia was only observed for the epimer showing an efficient SPHK2 phosphorylation rate of the parent amino alcohol.

R. Ettari,* E. Nizi, M. E. Di Francesco, N. Micale, S. Grasso, M. Zappalà, R. Vičák, T. Schirmeister

1030–1033

Nonpeptidic Vinyl and Allyl Phosphonates as Falcipain-2 Inhibitors



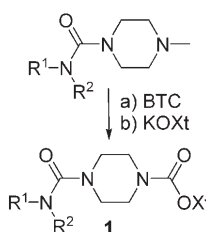
Antimalarials: The aim of our work was to investigate the ability of nonpeptidic vinyl and allyl phosphonates to inhibit falcipain-2 (FP-2), the main cysteine pro-

tease of *P. falciparum*. Some of the compounds synthesized, such as the one shown, moderately inhibit FP-2 activity.

A. El-Faham,* M. Armand-Ugón, J. A. Esté,* F. Albericio*

1034–1037

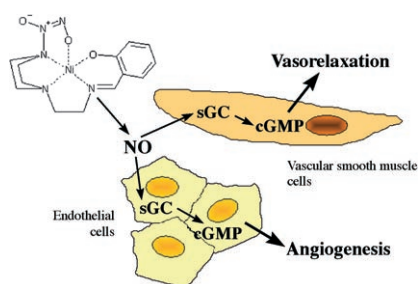
Use of N-Methylpiperazine for the Preparation of Piperazine-Based Unsymmetrical Bis-Ureas as Anti-HIV Agents



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 phosphene 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

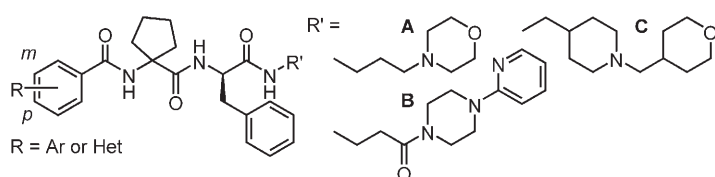
NO release in sight: New NO-releasing compounds based on *N*-aminoethylpiperazine-*N*-diazoniumdiolate ligands bound to transition metal ions release NO by hydrolysis with water at variable rates. The compounds are endowed with powerful vascular relaxation properties and have marked effects on the migration and proliferation of endothelial cells. These biological activities are completely blocked by inhibitors of guanylate cyclase.



M. Ziche, S. Donnini, L. Morbidelli, E. Monzani, R. Roncone, R. Gabbini, L. Casella*

1039 – 1047

Nitric Oxide Releasing Metal–Diazoniumdiolate Complexes Strongly Induce Vasorelaxation and Endothelial Cell Proliferation



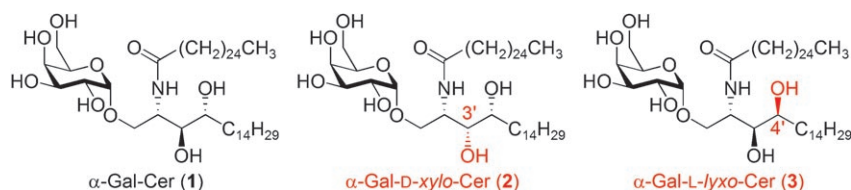
Three potent in vitro antagonists of the NK₂ receptor, which emerged from in-house capped dipeptide libraries, were elaborated to produce a panel of compounds endowed with significant

antagonist activity in our animal model after intravenous administration. An NMR conformational analysis was done on selected molecules.

M. Porcelloni, P. D'Andrea, C. Rossi, A. Sisto, A. Ettore, A. Madami, M. Altamura, S. Giuliani, S. Meini, D. Fattori*

1048 – 1060

α,α -Cyclopentaneglycine Dipeptides Capped with Biaryls as Tachykinin NK₂ Receptor Antagonists



Probing the immunoregulatory effects of α -GalCer epimers: CD1d-mediated NKT cell activation by α -GalCer analogues such as KRN7000 (1) induces the immediate release of IL-4 and IFN γ . To

assess the stereochemical requirements of the phytosphingosine portion of 1, the 3' and 4' epimers 2 and 3, respectively, of KRN7000 were synthesized by starting from phytosphingosine.

M. Trappeniers, S. Goormans, K. Van Beneden, T. Decruy, B. Linclau, A. Al-Shamkhani, T. Elliott, C. Ottensmeier, J. M. Werner, D. Elewaut, S. Van Calenbergh*

1061 – 1070

Synthesis and in vitro Evaluation of α -GalCer Epimers

The synthesis of peptidomimetics based on 1-deoxynojirimycin (DNJ) provides novel ligands for somatostatin receptors. The positioning of benzyl groups on the derivative shown on the right could potentially mimic interactions of phenylalanine residues of DNJ with its receptors. Results of this work could help in the design of selective inhibitors of two human somatostatin receptor subtypes based on iminosugar scaffolds.



V. Chagnault, J. Lalot, P. V. Murphy*

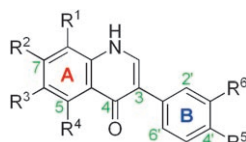
1071 – 1076

Synthesis of Somatostatin Mimetics Based on 1-Deoxynojirimycin

Z.-P. Xiao, H.-Q. Li, L. Shi, P.-C. Lv,
Z.-C. Song, H.-L. Zhu*

1077 – 1082

Synthesis, Antiproliferative Activity, and Structure–Activity Relationships of 3-Aryl-1H-quinolin-4-ones

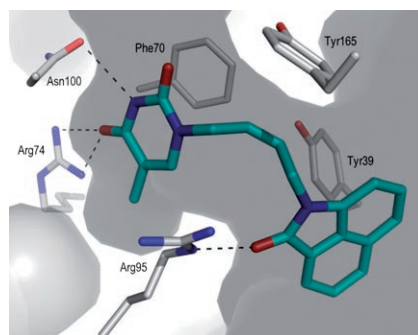


Selective cytotoxicity: Thirty-six 3-aryl-1H-quinolin-4-ones were synthesized, and their antiproliferative activity was determined against two cancer cell lines (Hep G2 and KB), and one human normal cell line (L02). Most of the compounds showed cytotoxicity against only the cancer cell lines; the SAR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

O. Familiar, H. Munier-Lehmann, A. Negri,
F. Gago, D. Douquet, L. Rigouts,
A.-I. Hernández, M.-J. Camarasa,
M.-J. Pérez-Pérez*

1083 – 1093

Exploring Acyclic Nucleoside Analogues as Inhibitors of *Mycobacterium tuberculosis* Thymidylate Kinase

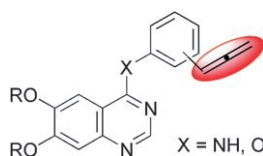


Tackling tuberculosis. Thymine derivatives with a distal naphtholactam or naphthosultam moiety potently and selectively inhibit TMPKmt with K_i values of 0.42 and 0.27 μM , respectively. Docking studies with the target enzyme followed by molecular dynamics simulations revealed a key interaction between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

H. S. Ban, S. Onagi, M. Uno,
W. Nabeyama, H. Nakamura*

1094 – 1103

Allene as an Alternative Functional Group for Drug Design: Effect of C–C Multiple Bonds Conjugated with Quinazolines on the Inhibition of EGFR Tyrosine Kinase

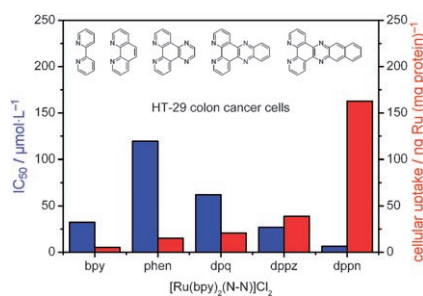


Are allenes attractive functional groups for drug design? A series of allenic 4-anilino- and 4-phenoxyquinazolines were synthesized and evaluated. Among the compounds synthesized, the allenic quinazoline **1a** inhibits EGF-mediated phosphorylation of EGFR and its downstream kinases in A431 cells, which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

U. Schatzschneider,* J. Niesel, I. Ott,*
R. Gust, H. Alborzinia, S. Wölfl*

1104 – 1109

Cellular Uptake, Cytotoxicity, and Metabolic Profiling of Human Cancer Cells Treated with Ruthenium(II) Polypyridyl Complexes $[\text{Ru}(\text{bpy})_2(\text{N}-\text{N})]\text{Cl}_2$ with N–N = bpy, phen, dpq, dppz, and dppn

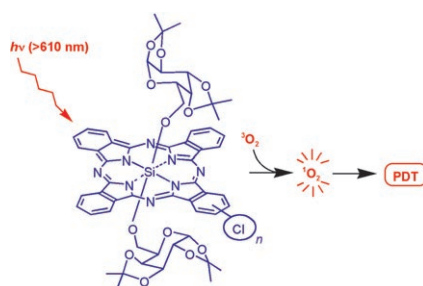


Metal-based anticancer therapeutics: For a series of ruthenium(II) polypyridyl complexes $[\text{Ru}(\text{bpy})_2(\text{N}-\text{N})]\text{Cl}_2$, cellular uptake efficiency and cytotoxicity toward HT-29 and MCF-7 cancer cells increase with the aromatic surface area of the N–N ligand. The biological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

P.-C. Lo, W.-P. Fong, D. K. P. Ng*

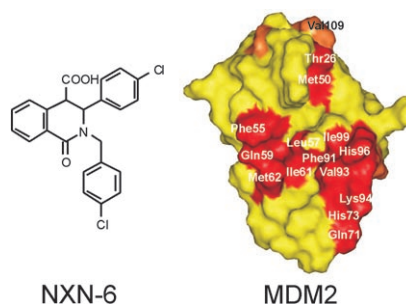
1110 – 1117

Effects of Peripheral Chloro Substitution on the Photophysical Properties and in vitro Photodynamic Activities of Galactose-Conjugated Silicon(IV) Phthalocyanines



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.

Protein interaction inhibitors: We report the design and characterisation of a new class of isoquinolinone inhibitors of the MDM2–p53 interaction. The p53 tumour suppressor protein is dysregulated in most cancers. The restoration of the impaired function of a single gene, *p53*, by disrupting the MDM2–p53 interaction, offers a fundamentally new avenue for anticancer therapy.

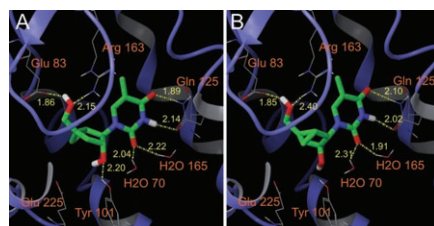


U. Rothweiler, A. Czarna, M. Krajewski, J. Ciombor, C. Kalinski, V. Khazak, G. Ross, N. Skobeleva, L. Weber,* T. A. Holak*

1118 – 1128

Isoquinolin-1-one Inhibitors of the MDM2–p53 Interaction

Herpes thymidine kinase recognizes exclusively the (+)-D enantiomer of racemic *iso*-methanocarbothymidine (*iso*-MCT). This was shown after achieving the stereoselective syntheses of both (+)-D and (–)-L enantiomers of the active racemate. The bicyclo-[3.1.0]hexane scaffold seems to provide an optimal combination of sugar pucker, nucleobase orientation, and disposition of hydroxy groups for efficient substrate activity.



M. J. Comin, B. C. Vu, P. L. Boyer, C. Liao, S. H. Hughes, V. E. Marquez*

1129 – 1134

D-(+)-*iso*-Methanocarbothymidine: a High-Affinity Substrate for Herpes Simplex Virus 1 Thymidine Kinase

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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