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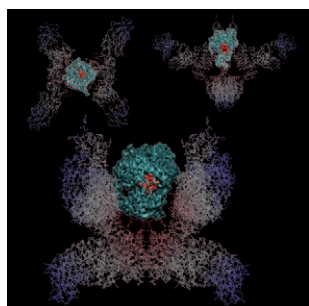
Full text:



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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 three views of a vitamin B₁₂-insulin conjugate bound to transcobalamin II, docked in the insulin receptor (IR). This study reveals how the structure of an orally deliverable insulin changes in solution after vitamin B₁₂ conjugation and its effect on IR binding capacity. The results demonstrate that chemical modification of insulin by linking relatively large pendant groups does not interfere with IR recognition. For more details, see the Full Paper by T. J. Fairchild, R. P. Doyle, et al. on p. 421 ff.

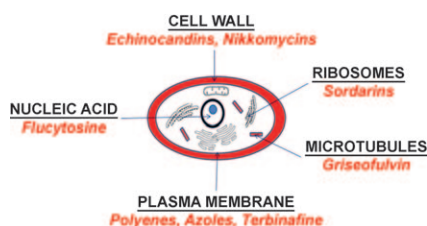
NEWS

Spotlights on our sister journals

308 – 309

REVIEWS

Antimycotic agents: Diverse classes of antimycotic drugs have been developed over the past decades with the goal of improving selectivity and efficacy. This review discusses both conventional and novel targets for antifungal agents and the possibility of vaccination in the treatment of invasive fungal infections.



B. P. Mathew, M. Nath*

310 – 323

Recent Approaches to Antifungal Therapy for Invasive Mycoses



ITALY



GERMANY



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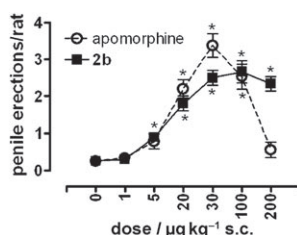
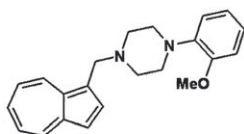
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COMMUNICATIONS



Azulene **2b** induces penile erection



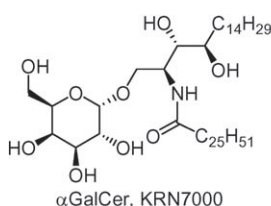
Blue makes it happen: The non-uniform charge distribution of the blue colored azulene framework is highly suitable for the bioisosteric replacement of bicyclic heteroarene moieties. Showing an analogous binding mode as hetero-

cyclic dopamine D4 receptor-selective lead compounds, the induction of penile erection in rats over a greater range of doses indicates a putative advantage of the rationally developed azulene derivative **2b** over apomorphine.

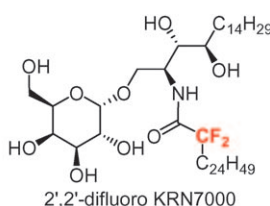
S. Löber, N. Tschammer, H. Hübner, M. R. Melis, A. Argiolas, P. Gmeiner*

325 – 328

The Azulene Framework as a Novel Arene Bioisostere: Design of Potent Dopamine D4 Receptor Ligands Inducing Penile Erection



The synthesis of 2',2'-difluoro KRN7000 is described. In vivo evaluation demonstrates that this fluorinated glycolipid

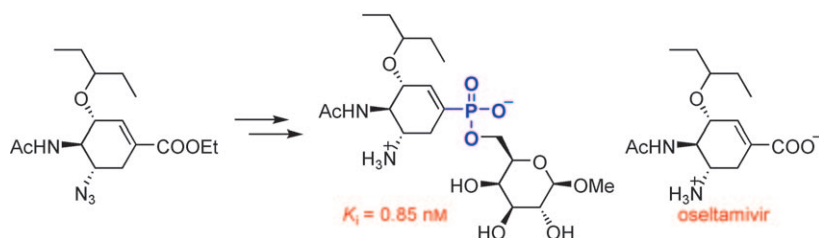


induces CD1d-dependent TCR activation of NKT cells, with a bias towards Th2 cytokine production.

L. Leung, C. Tomassi, K. Van Beneden, T. Decruy, M. Trappeniers, D. Elewaut, Y. Gao, T. Elliott, A. Al-Shamkhani, C. Ottensmeier, J. M. Werner, A. Williams, S. Van Calenbergh, B. Linclau*

329 – 334

The Synthesis and in vivo Evaluation of 2',2'-Difluoro KRN7000



With a Hunsdiecker–Barton iododecarboxylation strategy, we converted the carboxylate group of the oseltamivir precursor into exemplary phosphonate monoesters. In all cases, K_i values towards influenza virus sialidase remained

in the sub-nanomolar range. We have thus made valuable structural space available for the design of novel oseltamivir-based tools for influenza virus research.

B. Carbain, P. J. Collins, L. Callum, S. R. Martin, A. J. Hay, J. McCauley, H. Streicher*

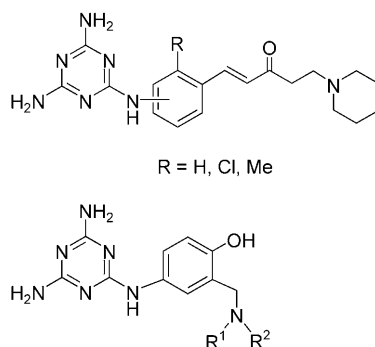
335 – 337

Efficient Synthesis of Highly Active Phospha-Isosteres of the Influenza Neuraminidase Inhibitor Oseltamivir



FULL PAPERS

Unsaturated Mannich bases with potent antitrypanosomal action against multidrug-resistant strains of *T. brucei brucei* were identified. Their observed activities correlated well with their high Michael acceptor properties but not with their affinities to the P2 purine transporter.



I. N. Wenzel, P. E. Wong, L. Maes, T. J. J. Müller, R. L. Krauth-Siegel, M. P. Barrett, E. Davioud-Charvet*

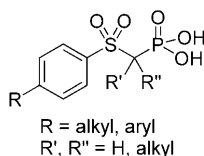
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Unsaturated Mannich Bases Active Against Multidrug-Resistant *Trypanosoma brucei brucei* Strains




M. T. Rubino, M. Agamennone,
C. Campestre, G. Fracchiolla, A. Laghezza,
F. Loiodice, E. Nuti, A. Rossello,
P. Tortorella*

352–362



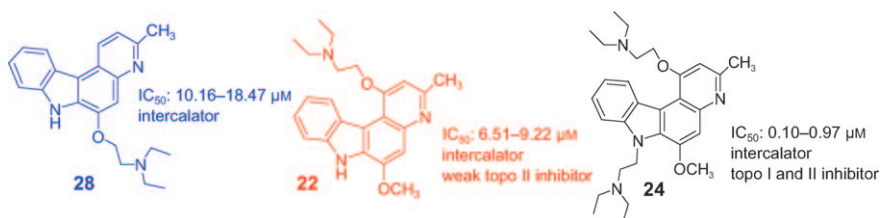
Selective MMP inhibitors: Eleven α -sulfonylphosphonates were synthesized and tested as MMP inhibitors. The IC_{50} values for most of them are in the nanomolar range against MMP-2, -8, -13, and -14, with an interesting selectivity profile versus MMP-9.

 **Synthesis, SAR, and Biological Evaluation of α -Sulfonylphosphonic Acids as Selective Matrix Metalloproteinase Inhibitors**

M. G. Ferlin,* C. Marzano, V. Gandin,
S. Dall'Acqua, L. Dalla Via

363–377

 **DNA Binding Ellipticine Analogues: Synthesis, Biological Evaluation, and Structure–Activity Relationships**



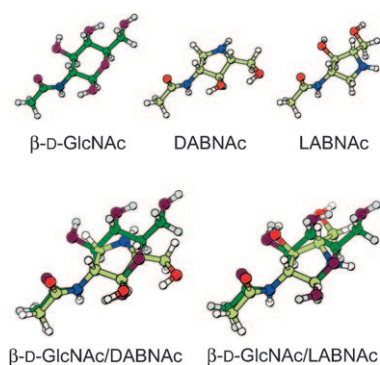
Novel angular and branched ellipticine-correlated anticancer agents were developed. In particular, compound **24**, with two basic side chains on opposite sides of the molecule, exhibits cytotoxicity in the nanomolar range, acting as a

DNA intercalator and topoisomerase II inhibitor. SAR studies with pyridocarbazole derivatives in comparison with corresponding smaller pyrroloquinolines are discussed.

J. S. S. Rountree,* T. D. Butters,*
M. R. Wormald, S. D. Boomkamp,
R. A. Dwek, N. Asano, K. Ikeda,
E. L. Evinson, R. J. Nash, G. W. J. Fleet*

378–392

Design, Synthesis, and Biological Evaluation of Enantiomeric β -N-Acetylhexosaminidase Inhibitors LABNAc and DABNAc as Potential Agents against Tay-Sachs and Sandhoff Disease

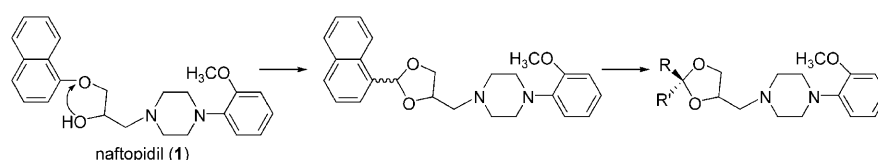


Combating glycolipid storage disorders: LABNAc was prepared in an efficient 11-step procedure from D-lyxonolactone. The enantiomer DABNAc was also prepared from L-lyxonolactone. Preliminary cellular studies indicate that these compounds may find utility as chemical chaperones for the treatment of Tay-Sachs and Sandhoff diseases.

C. Sorbi, S. Franchini, A. Tait, A. Prandi,
R. Galesi, P. Angeli, G. Marucci, L. Pirrona,
E. Poggesi, L. Brasili*

393–399

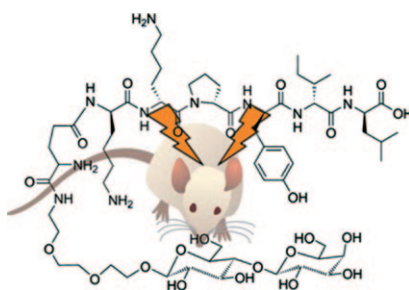
1,3-Dioxolane-Based Ligands as Rigid Analogues of Naftopidil: Structure–Affinity/Activity Relationships at α_1 and 5-HT_{1A} Receptors



Conformational restriction of naftopidil led to the discovery of a new class of ligands with a 1,3-dioxolane (1,3-oxathiolane, 1,3-dithiolane) structure that bind

to α_1 adrenoceptor subtypes and 5-HT_{1A} receptors. Adequate structural modifications address the selectivity toward one or the other receptor system.

The glycosylation of neuroactive peptides is a promising strategy to treat neurological and psychiatric disorders. Herein we investigated the effects of site-specific glycosylation of neurotensin (NT). The glycosylated analogues have low-nanomolar affinities and agonist activities toward NTS1, and suppress seizures with sub-picomolar potency. Our work points to a new research direction of exploring BBB-permeable NT analogues as potential first-in-class anti-epileptic drugs.

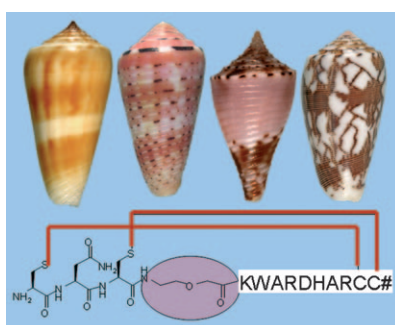


H.-K. Lee, L. Zhang, M. D. Smith,
H. S. White, G. Bulaj*

400 – 405

Glycosylated Neurotensin Analogues Exhibit Sub-picomolar Anticonvulsant Potency in a Pharmacoresistant Model of Epilepsy

Transforming the neuroactive toxins of cone snails into small-size compounds poses a challenge due to the presence of multiple disulfide bridges. Herein we describe our successful efforts in minimizing the size of μ -conotoxin while retaining its biological activity.

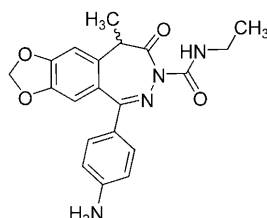


T. S. Han, M.-M. Zhang, A. Walewska,
P. Gruszczynski, C. R. Robertson,
T. E. Cheatham III, D. Yoshikami,
B. M. Olivera, G. Bulaj*

406 – 414

Structurally Minimized μ -Conotoxin Analogues as Sodium Channel Blockers: Implications for Designing Conopeptide-Based Therapeutics

2,3-Benzodiazepine derivatives: 1-(4-Aminophenyl)-3,5-dihydro-3-*N*-ethylcarbamoyl-5-methyl-7,8-methylenedioxy-4*H*-2,3-benzodiazepin-4-one was synthesized, and its enantiomers were separated by chiral HPLC. Pharmacological evaluation of each enantiomer showed that (*S*)-(-)-5 appears to be more potent than its optical antipode (*R*)-(+)-5 in an AMPA receptor binding assay.

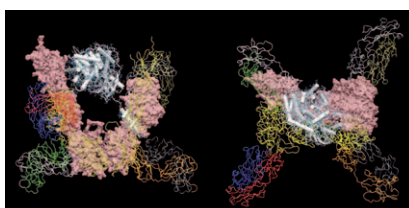


M. L. Calabrò, D. Raneri, P. Ficarra,
T. Mennini, S. Colleoni, G. Grazioso,
N. Micale,* M. Zappalà, S. Grasso

415 – 420

Synthesis, Chiral Resolution and Pharmacological Evaluation of a 2,3-Benzodiazepine-Derived Noncompetitive AMPA Receptor Antagonist

The dynamic behavior of insulin in solution and its binding geometry with the insulin receptor (IR) have been the focus of experimental and computational studies. We investigated how the structure of an orally deliverable insulin changes in solution after vitamin B₁₂ conjugation and its effect on IR binding capacity. In vitro immunoelectron microscopy confirms conjugate activity, IR binding, and cellular uptake.



A. K. Petrus, D. G. Allis, R. P. Smith,
T. J. Fairchild,* R. P. Doyle*

421 – 426

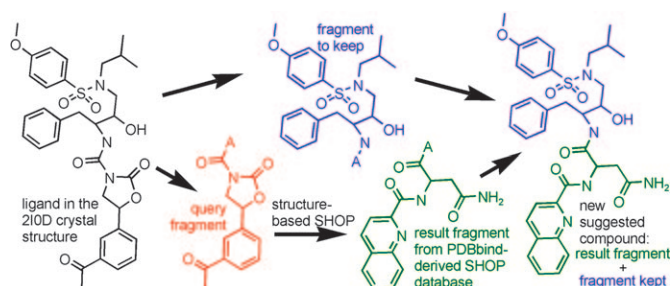
Exploring the Implications of Vitamin B₁₂ Conjugation to Insulin on Insulin Receptor Binding



F. Fontaine, S. Cross, G. Plasencia,
M. Pastor, I. Zamora*

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SHOP: A Method For Structure-Based Fragment and Scaffold Hopping



We present a method for fragment/
scaffold substitution based on protein–
ligand interactions. This concept goes
beyond bioisosteric replacement, which

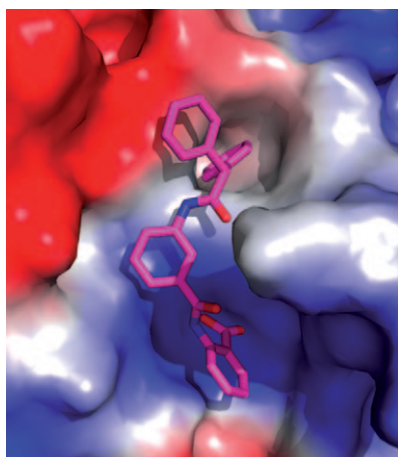
only uses the structure of the fragment
to replace as query. The methodology is
validated with more than 10 biological
targets relevant for drug discovery.

S. Wu, M. Bottini, R. C. Rickert, T. Mustelin,
L. Tautz*

440 – 444



In Silico Screening for PTPN22 Inhibitors: Active Hits from an Inactive Phosphatase Conformation



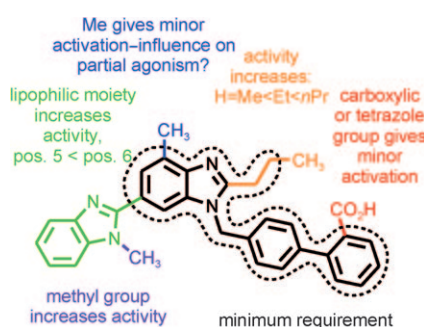
2-Benzamidobenzoic acids seem to sta-
bilize PTPN22 phosphatase in its inac-
tive 'open' conformation with the WPD
loop locked in a distal position. In silico
screening using both 3D structures in
open and closed conformations yielded
potent inhibitors of this potential drug
target for autoimmunity that specifically
dock into its open form. Tryptophan
fluorescence measurements support the
proposed binding mode.

M. Goebel, M. Clemenz, B. Staels,
T. Unger, U. Kintscher, R. Gust*

445 – 456



Characterization of New PPAR γ Agonists: Analysis of Telmisartan's Structural Components



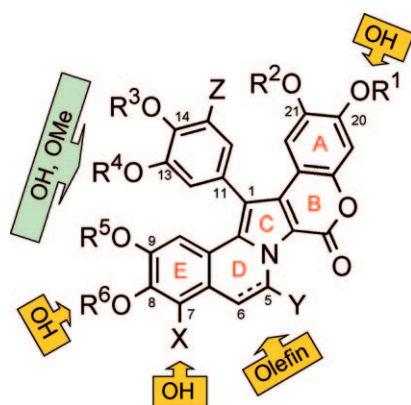
Telmisartan was originally designed as
an AT $_1$ antagonist but was later also
characterized as a selective PPAR γ mod-
ulator. This study focused on the iden-
tification of the essential structural
motifs of telmisartan for PPAR γ activa-
tion activity, elucidating the individual
SAR of each different component
(shown).

M. Chittchang, P. Batsomboon,
S. Ruchirawat, P. Ploypradith*

457 – 465

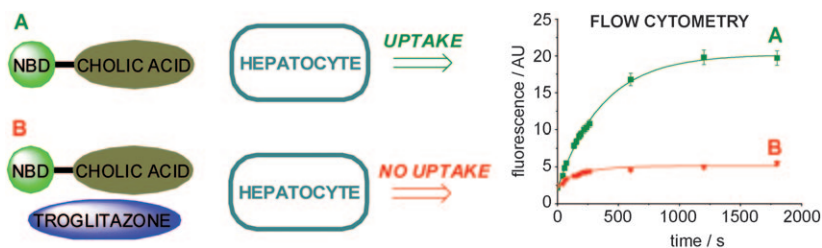


Cytotoxicities and Structure–Activity Relationships of Natural and Unnatural Lamellarins toward Cancer Cell Lines



Shedding light on the lamellarins:

Structural determinants for potent cyto-
toxic activity toward various cancer cell
lines were systematically investigated to
establish SARs for the marine alkaloids
in the lamellarin family. The C5=C6
double bond ensures not only the pla-
narity of the D-ring, but also proper
alignment of the substituents on the
E-ring with their respective moieties of
the target. The importance of the C7
OH group is also revealed for the first
time.



Fluorescent synthetic 7-nitrobenzo-2-oxa-1,3-diazole (NBD) conjugates of cholic acid were prepared and characterized. Their photophysical properties make them suitable for monitoring

uptake in freshly isolated rat hepatocytes using flow cytometry. This technique makes it possible to screen drug candidates for cholestatic (and thus hepatotoxic) liability.

J. Rohacova, M. L. Marín, A. Martinez-Romero, L. Diaz, J.-E. O'Connor, M. J. Gomez-Lechon, M. T. Donato, J. V. Castell, M. A. Miranda*

466–472

Fluorescent Benzofurazan–Cholic Acid Conjugates for in vitro Assessment of Bile Acid Uptake and Its Modulation by Drugs



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.

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C. Chan and X. Wang 473

Concerning Cytochromes P450: Role in the Metabolism and Toxicity of Drugs and other Xenobiotics • C. Ioannides (Ed.)

M. Ingelman-Sundberg 473

High-Throughput Analysis in the Pharmaceutical Industry • P. G. Wang (Ed.)

J. N. Kyranos 474

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