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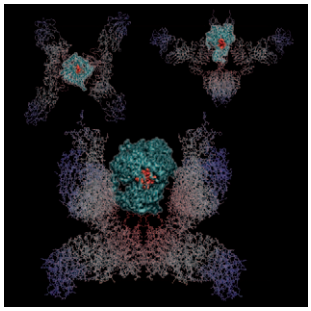
COVER PICTURE



The cover picture shows three views of a vitamin B_{12}–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 B_{12} 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

REVIEWS

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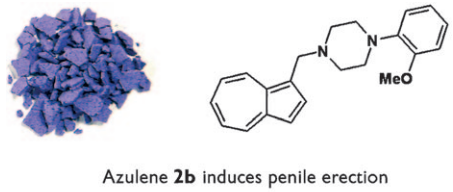
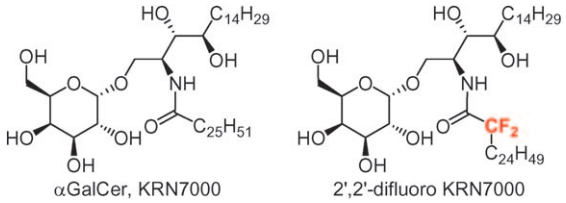
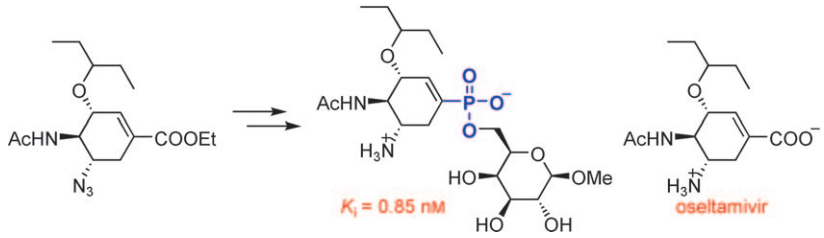
COMMUNICATIONS



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 heterocyclic 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.



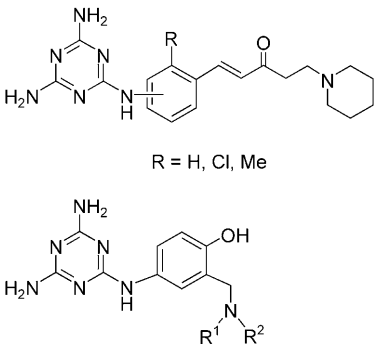
The synthesis of 2′,2′-difluoro KRN7000 is described. In vivo evaluation demonstrates that this fluorinated glycolipid induces CD1d-dependent TCR activation of NKT cells, with a bias towards Th2 cytokine production.



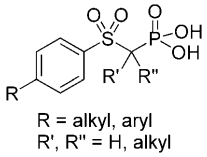
With a Hunsdiecker–Barton iododecarboxylation strategy, we converted the carboxylate group of the oseltamivir precursor into exemplary phosphonate monoesters. In all cases, K_i values towards influenza virus sialidase remained in the sub-nanomolar range. We have thus made valuable structural space available for the design of novel oseltamivir-based tools for influenza virus research.

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.

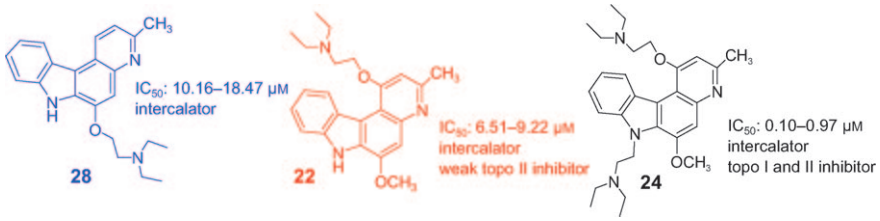


*M. T. Rubino, M. Agamennone, C. Campestre, G. Fracchiolla, A. Laghezza, F. Loiodice, E. Nuti, A. Rossello, P. Tortorella**



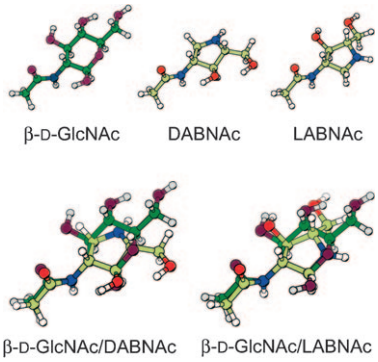
Selective MMP inhibitors: Eleven α-sulfonylphosphonates were synthesized and tested as MMP inhibitors. The IC_{50} values for most of them are in the nanomolar range against MMP-2, -8, -13, and -14, with an interesting selectivity profile versus MMP-9.

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



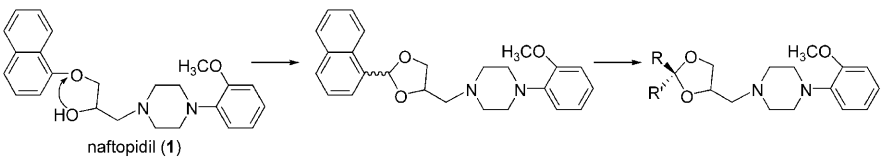
Novel angular and branched ellipticine-correlated anticancer agents were developed. In particular, compound **24**, with two basic side chains on opposite sides of the molecule, exhibits cytotoxicity in the nanomolar range, acting as a DNA intercalator and topoisomerase II inhibitor. SAR studies with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

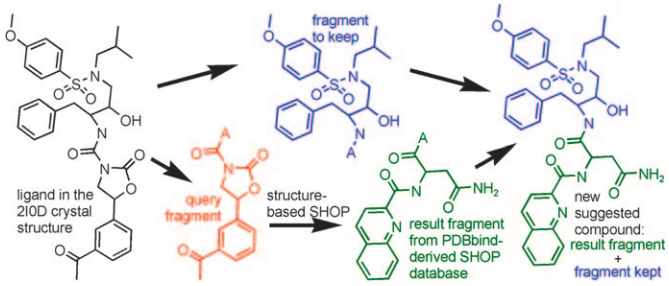


Combating glycolipid storage disorders: LABNAc was prepared in an efficient 11-step procedure from D-lyxonolactone. The enantiomer DABNAc was also prepared from L-lyxonolactone. Preliminary cellular studies indicate that these compounds may find utility as chemical chaperones for the treatment of Tay-Sachs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

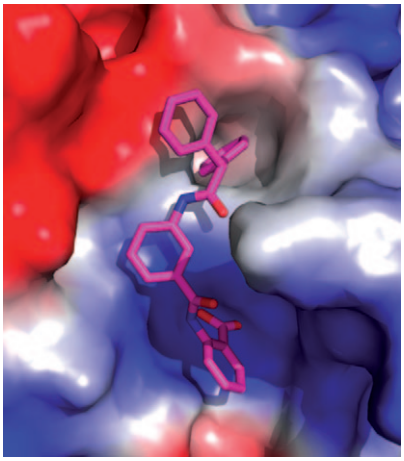
*C. Sorbi, S. Franchini, A. Tait, A. Prandi, R. Gallesi, P. Angeli, G. Marucci, L. Pirona, E. Poggesi, L. Brasili**



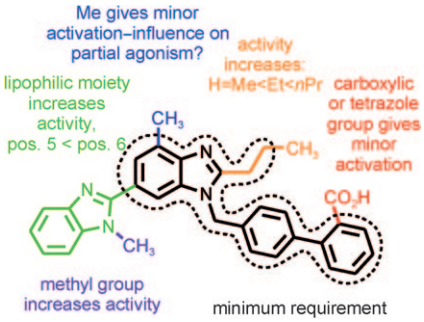
Conformational restriction of naftopidil led to the discovery of a new class of ligands with a 1,3-dioxolane (1,3-oxathiolane, 1,3-dithiolane) structure that bind to α_1 adrenoceptor subtypes and 5-HT_{1A} receptors. Adequate structural modifications address the selectivity toward one or the other receptor system.



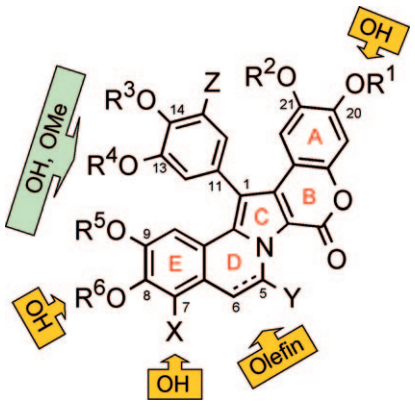
We present a method for fragment/scaffold substitution based on protein–ligand interactions. This concept goes beyond bioisosteric replacement, which only uses the structure of the fragment to replace as query. The methodology is validated with more than 10 biological targets relevant for drug discovery.



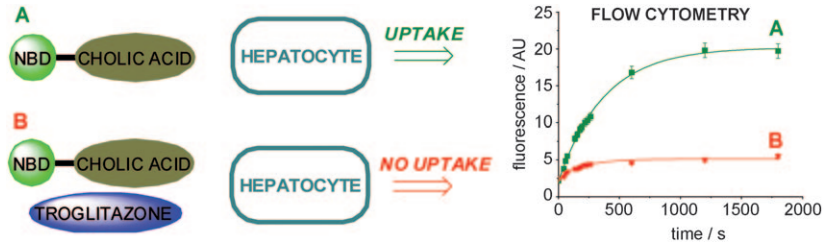
2-Benzamidobenzoic acids seem to stabilize PTPN22 phosphatase in its inactive 'open' conformation with the WPD loop locked in a distal position. In silico screening using both 3D structures in open and closed conformations yielded potent inhibitors of this potential drug target for autoimmunity that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



Telmisartan was originally designed as an AT_1 antagonist but was later also characterized as a selective PPARγ modulator. This study focused on the identification of the essential structural motifs of telmisartan for PPARγ activation activity, elucidating the individual SAR of each different component (shown).



Shedding light on the lamellarins: Structural determinants for potent cytotoxic 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 planarity 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.

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).

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BOOKS

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