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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 a bit pattern reflecting relative frequencies of a molecular fingerprint and molecules belonging to different activity classes. A divergence function is derived that captures differences in bit frequencies between active and database compounds. The function is applied to establish a linear relationship (black line) between bit divergence and expected compound recall in similarity searching. For a fingerprint, a screening database, and set of known active reference molecules, the linear model can be used to estimate the probability to identify hits in similarity search calculations. For details, see the Full Paper by M. Vogt and J. Bajorath on p. 1311 ff.

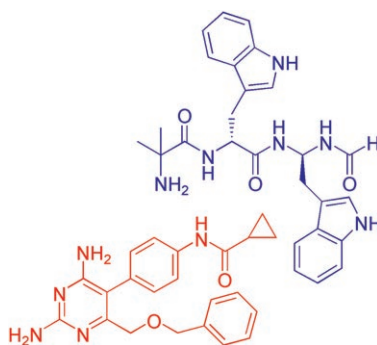
NEWS

Spotlights on our sister journals

1238 – 1239

REVIEWS

A healthy appetite for GHS-R1a ligands: This review summarizes the various types of growth hormone secretagogue receptor type 1a (GHS-R1a) ligands that have been described in the literature and highlights the recent progress made in this important area of research.



A. Moulin, J. Ryan, J. Martinez,
J.-A. Fehrentz*

1242 – 1259

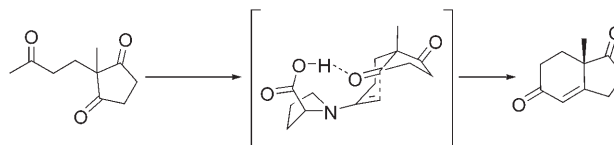
Recent Developments in Ghrelin Receptor Ligands

MINIREVIEWS

S. Jarocho,* H. Weinmann,* K. Zeitler*

1261 – 1264

Asymmetric Organocatalysis



Despite considerable efforts to explore and extend the scope of asymmetric organocatalytic reactions throughout the last years, their use in medicinal and process chemistry is still rather low. This minireview highlights some of the

recent developments in the rapidly evolving field of organocatalysis recently presented at the Schering Foundation organized symposium on "Organocatalysis".

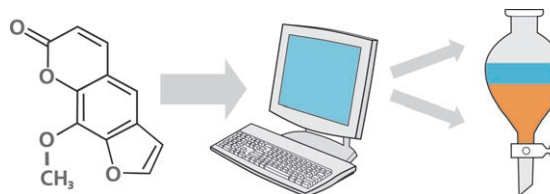
COMMUNICATIONS

T. S. Schroeter,* A. Schwaighofer, S. Mika,
A. Ter Laak, D. Suelzle, U. Ganzer,
N. Heinrich, K.-R. Müller

1265 – 1267



Predicting Lipophilicity of Drug-Discovery Molecules using Gaussian Process Models



The lipophilicity of 14556 library compounds at Bayer Schering was modeled using Gaussian process methodology. In a blind test with 7013 new drug-discovery molecules from the last few months, 81 % were predicted correctly within

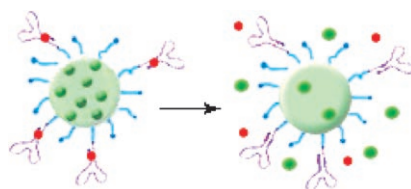
one log unit, compared with only 44 % achieved by commercial software. Predicted error bars exhibit close to ideal statistical properties, thereby allowing assessment of the model's domain of applicability.

L. Zhang, A. F. Radovic-Moreno, F. Alexis,
F. X. Gu, P. A. Basto, V. Bagalkot, S. Jon,
R. S. Langer, O. C. Farokhzad*

1268 – 1271



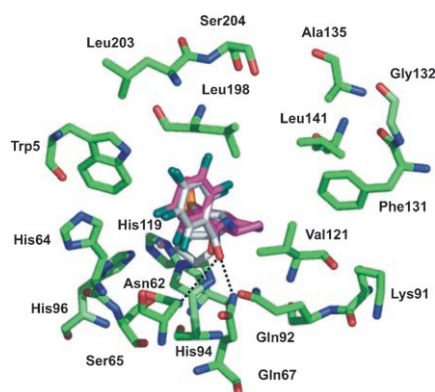
Co-Delivery of Hydrophobic and Hydrophilic Drugs from Nanoparticle-Aptamer Bioconjugates



Herein we report a novel targeted drug delivery system consisting of nanoparticle-aptamer bioconjugates, which can carry both hydrophobic and hydrophilic chemotherapeutic drugs simultaneously, and deliver them selectively in a targeted and temporally distinct manner. This work provides a robust platform for targeted co-delivery of chemotherapeutic agents with the hope of both leveraging the synergistic effects of multiple drugs and also potentially suppressing the likelihood of drug resistance by the treated tissues.

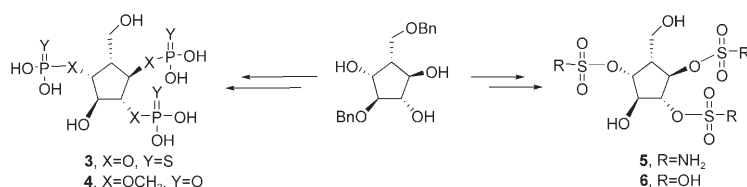
FULL PAPERS

The binding mode of (*R*)- (magenta) and (*S*)-1-pentafluorophenylamido-5-sulfonamide (light gray) inside the human carbonic anhydrase VII active site is shown. A shared hydrogen bond between the carbonyl group of each compound and Gln67 and Asn62 is observed. To increase hCA VII selectivity, structural modifications of these compounds are proposed in order to design new anticonvulsant agents.



A. Thiry,* B. Masereel, J.-M. Dogné,
C. T. Supuran, J. Wouters, C. Michaux
1273 – 1280

Exploration of the Binding Mode of Indanesulfonamides as Selective Inhibitors of Human Carbonic Anhydrase Type VII by Targeting Lys 91



Ins(1,4,5)P₃ analogues: Four phosphatase-resistant analogues of Ins(1,4,5)P₃ were synthesized and evaluated. Tris(phosphorothioate) **3** and the parent tris(phosphate) bound to an InsP₃R con-

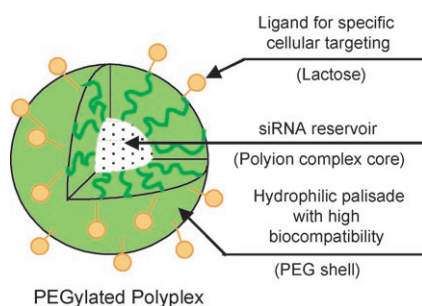
struct in vitro and elicited calcium release in breast cancer cells. The agonist activity was rationalized by computational docking of the ligands to the binding domain of the InsP₃R.

L. Zhang, W. Huang, A. Tanimura,
T. Morita, S. Harihar, D. B. DeWald,
G. D. Prestwich*

1281 – 1289

Synthesis and Biological Activity of Metabolically Stabilized Cyclopentyl Trisphosphate Analogues of D-myo-Ins(1,4,5)P₃

Multicellular tumor spheroids (MCTSs) are a versatile in vitro model for estimating the penetration of carriers into 3D tumor tissues as well as the long-term (up to 21 days) therapeutic efficacy of siRNA. Indeed, the PEGylated polyplexes showed a remarkable growth-inhibitory effect on the HuH-7 spheroids, inducing apoptotic cell death in the long term by means of siRNA.

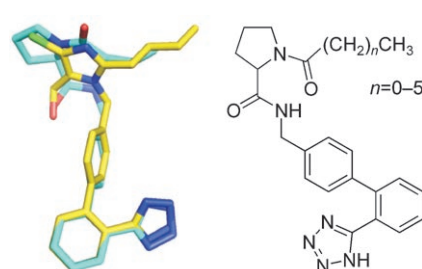


M. Oishi, Y. Nagasaki,* N. Nishiyama,
K. Itaka, M. Takagi, A. Shimamoto,
Y. Furuichi, K. Kataoka*

1290 – 1297

Enhanced Growth Inhibition of Hepatic Multicellular Tumor Spheroids by Lactosylated Poly(ethylene glycol)-siRNA Conjugate Formulated in PEGylated Polyplexes

A virtual approach that uses TOPP 3D descriptors to explore the AT₁ receptor is presented. It features a new series of sartan analogues (shown), which were synthesized and biologically evaluated on CHO-hAT₁ cells stably expressing the human AT₁ receptor.

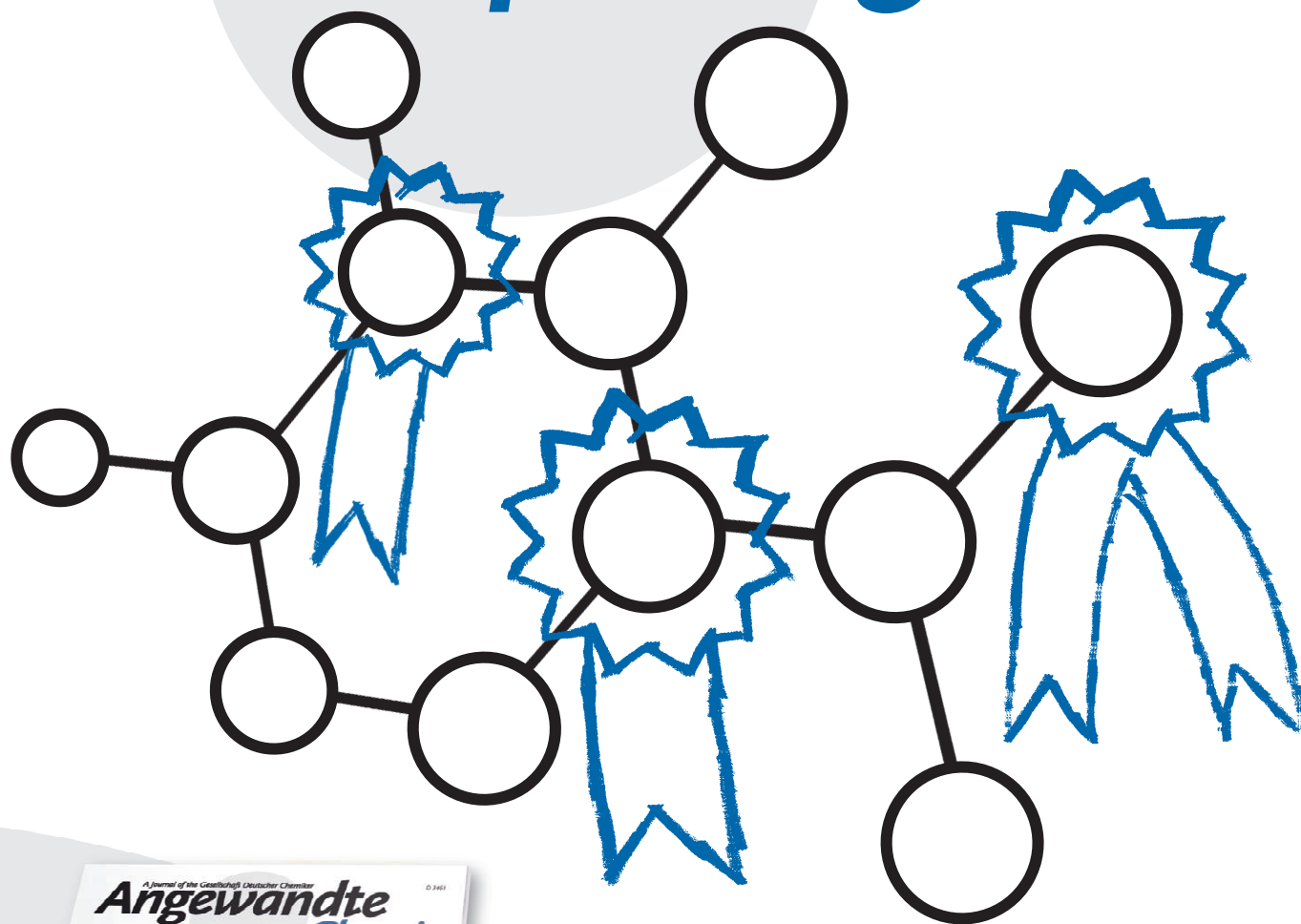


C. Lamanna, A. Catalano, A. Carocci,
A. Di Mola, C. Franchini,* V. Tortorella,
P. M. L. Vanderheyden, M. S. Sinicropi,
K. A. Watson, S. Sciabola

1298 – 1310

AT₁ Receptor Ligands: Virtual-Screening-Based Design with TOPP Descriptors, Synthesis, and Biological Evaluation of Pyrrolidine Derivatives

Incredibly prestigious!



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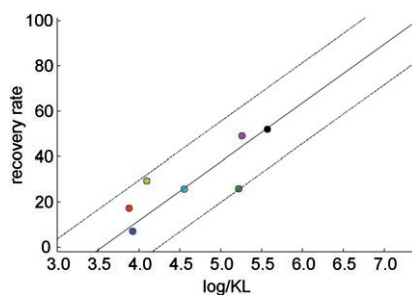
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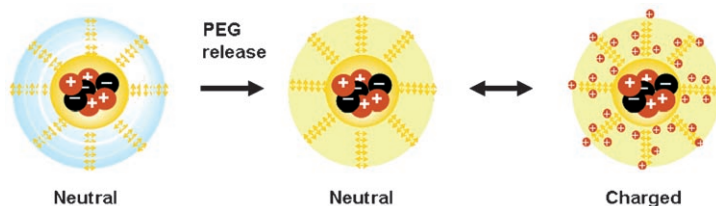
Fingerprinting molecules. For seven different compound activity classes (colored dots), recovery rates for fingerprint similarity searching were predicted from Kullback-Leibler divergence using a linear regression model and compared to the observed recovery rates. The solid line represents the linear regression curve and the dotted lines average error margins.



M. Vogt, J. Bajorath*

1311 – 1320

Introduction of a Generally Applicable Method to Estimate Retrieval of Active Molecules for Similarity Searching using Fingerprints



Charged to deliver: The intelligent design and characterization of dynamic cationic nanoparticles formed from the self-association of a pH-responsive block copolymer is described. The plat-

form allows pH-sensitive multilevel PEGylation and imparts nanoparticles with the ability to transition from neutral to charged at pH 5.

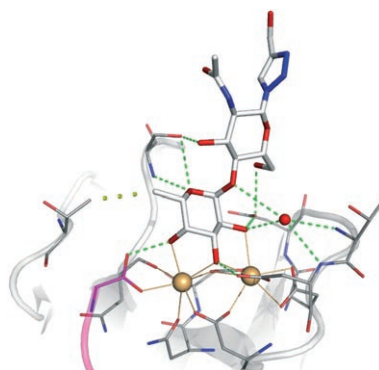
M. P. Xiong, Y. Bae, S. Fukushima, M. L. Forrest, N. Nishiyama, K. Kataoka,* G. S. Kwon*

1321 – 1327

pH-Responsive Multi-PEGylated Dual Cationic Nanoparticles Enable Charge Modulations for Safe Gene Delivery



The disaccharide α Fuc1-4GlcNAc has been used as a scaffold toward the synthesis of a series of derivatives targeting the fucose binding lectin from *Pseudomonas aeruginosa*. High affinity has been measured by titration microcalorimetry and structural studies rationalized the difference observed for the thermodynamics of binding between the natural and the synthetic ligands.



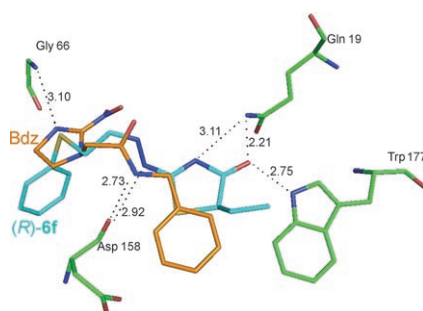
K. Marotte, C. Sabin, C. Prévile, M. Moumé-Pymbock, M. Wimmerová, E. P. Mitchell, A. Imberty,* R. Roy*

1328 – 1338

X-ray Structures and Thermodynamics of the Interaction of PA-ILL from *Pseudomonas aeruginosa* with Disaccharide Derivatives



Aiming for a key target: Aryl-4-oxothiazolylhydrazones such as (*R*)-**6 f** (in blue) are capable of inhibiting the growth of *Trypanosoma cruzi* cell cultures at non-cytotoxic concentrations. Their role as potential inhibitors of the *T. cruzi* cysteine protease cruzain (TCC) is explored in relation to drugs in current use such as benzimidazole (Bdz, in orange).



A. C. L. Leite,* D. R. de M. Moreira, M. V. de O. Cardoso, M. Z. Hernandez, V. R. Alves Pereira, R. O. Silva, A. C. Kiperstok, M. da S. Lima, M. B. P. Soares

1339 – 1345

Synthesis, Cruzain Docking, and in vitro Studies of Aryl-4-Oxothiazolylhydrazones Against *Trypanosoma cruzi*

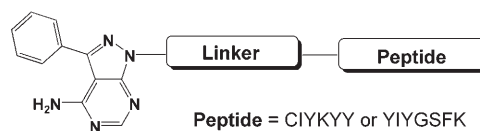


A. Kumar, Y. Wang, X. Lin, G. Sun,
K. Parang*

1346 – 1360



Synthesis and Evaluation of 3-Phenylpyrazolo[3,4-d]pyrimidine-Peptide Conjugates as Src Kinase Inhibitors



3-Phenylpyrazolopyrimidine-peptide conjugates

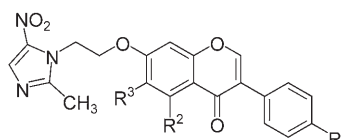
A series of 3-phenylpyrazolo[3,4-d]pyrimidine (PhPP)-peptide conjugates were synthesized using PhPP as an ATP mimic and CIYKYY or YIYGSKF as a peptide substrate to improve the inhibitory potency against active c-Src kinase.

PhPP-CH₂CO-CIYKYY improved the inhibitory potency against active c-Src by approximately 650- and 1000-fold higher than those of the parent compounds, PhPP-CH₂COOH and Ac-CIYKYY, respectively.

H.-Q. Li, C. Xu, H.-S. Li, Z.-P. Xiao, L. Shi,
H.-L. Zhu*

1361 – 1369

Metronidazole-Flavonoid Derivatives as Anti-*Helicobacter pylori* Agents with Potent Inhibitory Activity against HPE-Induced Interleukin-8 Production by AGS Cells



The anti-*H. pylori* properties of a series of metronidazole-flavonoid derivatives were demonstrated, and their ability to suppress the *H. pylori* water extract (HPE)-induced release of IL-8 from AGS cells was investigated. The conjugation of metronidazole with genistein produced a highly potent inhibitor (compound 6) of the growth of *H. pylori* which also potently inhibits the release of IL-8 from AGS cells.



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

* Author to whom correspondence should be addressed.

BOOKS

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Dendrimers in Medicine and Biotechnology · U. Boas, J. B. Cristensen,
P. M. H. Heegaard

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