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Analytical Chemistry **61**

Tip-enhanced Raman spectroscopy with Ag tips

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We present a systematic study of the performance of Ag tips for tip-enhanced Raman spectroscopy (TERS), which has been attracting the interest of chemists for several years because of its potential to do nano-scale chemical analysis with single molecule sensitivity. In our experiment, a side-illumination scheme was adopted to excite the gap between tip and a metallic sample surface in order to obtain a high field enhancement [1]. Ag tips fabricated by both chemical etching and metallizing sharp glass fiber tips were tested with two wavelengths, 488 nm and 633nm, which are two of the most widely used laser lines. Our experiments show that the etched Ag tips illuminated with the red laser can give a good enhancement for different substrates, such as rough and crystallized, silver and gold surfaces. Clear TERS signals from different monolayers adsorbed on Au or Ag surface can be obtained with 10 sec collection time and low laser power (0.5 mW). With such an enhancement, real-time investigation of chemical reactions on metal surfaces is within reach.

[1] P. K. Aravind and H. Metiu, *Surf. Sci.* **1983**, *124*, 506.

Analytical Chemistry **62**

Railway induced particulate emissions: A one year WD-XRF survey in Zürich, Switzerland

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Public transportation systems are promoted especially in urban areas to reduce the use of individual vehicles. Compared to light duty vehicles, trains operated by electric engines have obviously no emissions of combustion aerosols per passenger and distance. Nevertheless, particulate emissions caused by railway traffic are detectable. Material abrasion from tracks, wheels, brakes and the overhead traction line enhance the concentration of typical railway specific elements in ambient air.
To get representative information about the contribution of railway traffic to the local concentrations of particulate matter with particle sizes below 10 micrometers (PM10), a field study was performed covering a time period of one year. The chemical composition of the aerosol samples was determined with WD-XRF. The measurement campaign involved daily sampling at three measuring sites influenced by railway traffic together with an urban background site without local railway exposition (Zeughaus). The sampling sites were situated at the entry to the main railway station of Zürich (Röntgenstrasse, Gamperstrasse) as well as at a very busy railway line with more than 700 trains per day (Juchhof). The aerosol particles were sampled on quartz filters in a distance of ~10 m from the railway tracks. To study the distance dependence of the railway induced concentrations of railway relevant elements such as iron, manganese and copper, additional samples were taken at Juchhof in a distance of 36 m and 120 m from the railway track. The WD-XRF results coincide well with hourly concentrations measured simultaneously at the same locations by RDI-SR-XRF [1].

[1] N. Bukowiecki et al., *Environ. Sci. Technol.* **2005**, *39*, 5754.

Medicinal Chemistry **63**

Exploring the Binding Site of E-Selectin

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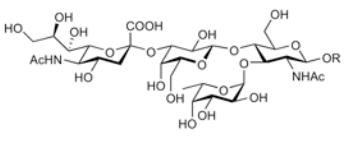
Selectins play a major role in the adhesion of leukocytes to the vascular endothelium in the early stage of the inflammatory cascade, associated with a number of diseases and pathological situations [1,2]. The sialyl Lewis^x (sLe^x, **1**) epitope, found on the surface of leukocytes is known to be a natural ligand of E-selectin [2].
Here, we present the synthesis of sLe^x mimics with improved pharmacokinetic and pharmacodynamic properties. First, the synthesis of a suitable azide-bearing precursor **2** was developed. The scaffold was then coupled to various alkynes using click chemistry [3] in order to get a small library of triazoles. The inhibitory activity of these compounds was then evaluated in a static cell-free bioassay.



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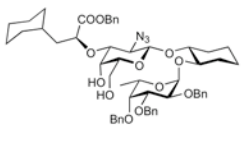

2

[1] R. P. McEver, *Glycoconj. J.*, **1997**, *14*, 585.
[2] L. Phillips, E. Nudelman, F. A. Gaeta, M. Perez, A. K. Singhal, S. Hakomori, J. Paulson, *Science*, **1990**, *250*, 1130.
[3] V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed. Eng.*, **2002**, *41*, 2596.

Medicinal Chemistry **64**

Design and Synthesis of 12-Aza-Epothilones (Azathilones)

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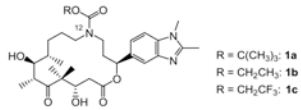
Department of Chemistry and Applied Biosciences, ETH Zürich, Wolfgang-Pauli-Str. 10, HCI, CH-8093 Zürich, Switzerland

Owing to their potent cytotoxicity against tumor cells and a taxol-like mode of action, the epothilones have attracted considerable research interest over the last few years. Several phase I-III clinical trials are ongoing with epothilone B and closely related analogues thereof. In contrast to these closely related structures and based on existing SAR data, our research aims at the creation of new structural scaffolds for microtubule stabilization, which could offer the potential for distinctly different overall pharmacological profiles. These considerations resulted in compounds **1a-1c** as initial targets for total synthesis and biological investigation.



Given the degree of structural divergence from the natural epothilone template, these analogs (which have been termed "azathilones") may be considered as members of a distinct group of hypermodified natural products with unique structural features. In this presentation we will report on the total synthesis of aza-macrolides **1a-1c**, either based on ring-closing olefin metathesis (RCM) as the key step or *via* a macrolactonization approach. All three compounds prepared proved to be highly potent inhibitors of human tumor growth *in vitro*, with **1a** being at least as potent as epothilone A, both in terms of cytotoxicity and tubulin polymerization. They should thus be attractive new lead structures for anticancer drug discovery.[1]

[1] Feyen, F.; Gertsch, J.; Wartmann, M. Altmann, K.-H. *Angew. Chem.* **2006**, in press.

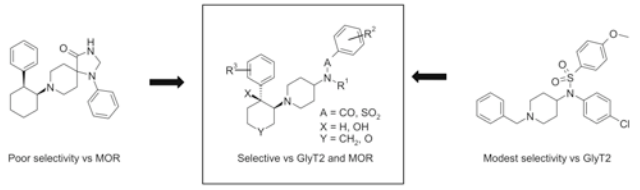
Medicinal Chemistry **65**

Design, synthesis and Structure-Activity Relationship of N(1)-(2-phenyl-cylohexyl)-4-amino-piperidine derivatives as potent and selective glycine reuptake inhibitors

Simona M. Ceccarelli, Emmanuel Pinard, Henri Stalder, Daniela Alberati

F. Hoffmann-La Roche Ltd., Pharmaceutical Division Basel, Discovery Chemistry, CH-4070 Basel, Switzerland

Glycine Transporter Type 1 (GlyT1) regulates synaptic glycine concentration in neurons and glial cells. According to the NMDA (N-Methyl-D-Aspartate Receptor) hypofuntion theory of the pathophysiology of schizophrenia, selective GlyT1 inhibitors may have therapeutic value in the treatement of psychoses.



The 2-phenyl-cyclohexyl motif was identified as a privileged substructure for GlyT1 inhibitors during a high throughput screening campaign. This finding prompted us to attempt the synthesis of chymeric compounds, combining the novel structural element with the known 4-aminopiperidine scaffold. The resulting class of N(1)-(2-phenyl-cylohexyl)-4-amino-piperidine derivatives shows high potency, a selective pharmacological profile and promising molecular properties. A broad SAR screen was performed and an optimal molecular property profile was achieved through introduction of a tertiary alcohol at position 2 of the 2-phenyl-cyclohexyl system.

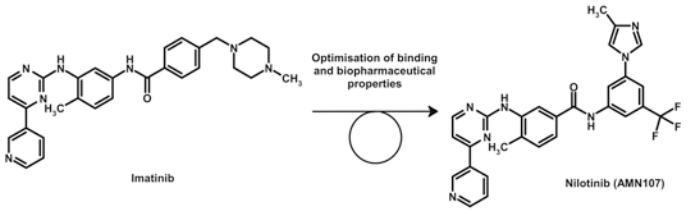
Medicinal Chemistry **66**

Nilotinib: A new agent for the treatment of imatinib-resistant CML

P.W. Manley, W. Breitenstein, S. Cowan-Jacob, M. Jensen, J. Mestan

Novartis Institutes for BioMedical Research, CH-4002, Basel, Switzerland

As an inhibitor of the tyrosine kinase activity of the Bcr-Abl oncoprotein, imatinib (Glivec®) is an effective therapy of chronic myelogenous leukemia (CML). However, patients with advanced stage disease frequently relapse due to the emergence of imatinib-resistant mutants of Bcr-Abl. Consequently, a potent Bcr-Abl inhibitor, which maintains activity against imatinib-resistant mutants, should provide patient benefit in CML. Based upon our x-ray crystallographic analysis of the binding mode of imatinib [1], we prepared libraries of compounds designed to probe the inactive conformation of the human Bcr-Abl kinase domain [2], and identified some key pharmacophore elements. Optimisation of the biopharmaceutical properties of lead compounds, afforded potent, selective Bcr-Abl kinase inhibitors, possessing good pharmacokinetic profiles and showing efficacy following oral administration in CML models [3]. Nilotinib, which has recently completed Phase II clinical trials, emerged from these studies [4]:



[1] S.W. Cowan-Jacob, V. Guez, J.D. Griffin, *et al*, *Mini Rev. Med. Chem.* **2004**, 4, 285. [2] P.W. Manley, W. Breitenstein, J. Brüggen, *et al*, *Bioorg. Med. Chem. Lett*. **2004**, 14, 5793. [3] E. Weisberg, P.W. Manley, W. Breitenstein, *et al*, *Cancer Cell* **2005**, *7*, 129. [4] H. Kantarjian, F. Giles, L. Wunderle, *et al*, *New Engl. J. Med*. **2006**, in press.

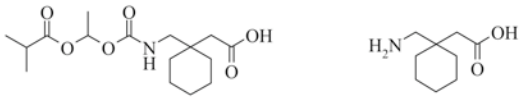
Medicinal Chemistry **67**

XP13512, a Transported Prodrug of Gabapentin, Overcomes the Saturable Oral Absorption of Neurontin® in Humans

Stephan Raillard

XenoPort, Inc., 3410 Central Expressway, Santa Clara, CA 95051, USA

Clinical data will be presented for XP13512, a prodrug of gabapentin currently undergoing Phase 3 studies for the treatment of restless legs syndrome and neuropathic pain disorders.



XP13512 **Gabapentin**

XP13512 was designed to be actively absorbed along the length of the GI tract by high-capacity transport pathways [1]. This has permitted development of an oral sustained-release formulation of XP13512 that provides higher levels of gabapentin in the blood for a longer period of time compared with administration of Neurontin®.

[1] K.C. Cundy, R. Branch, T. Chernov-Rogan, T. Dias, T. Estrada, K. Hold, K. Koller, X. Liu, A. Mann, M. Panuwat, S.P. Raillard, S. Upadhyay, Q. Wu, J. Xiang, H. Yan, N. Zerangue, C.X. Zhou, R.W. Barrett, M. A. Gallop, *J. Pharmacol. Exp. Ther.* **2004**, *311*, 315.

Medicinal Chemistry **68**

Novel hexahydropyrido[3',2':4,5]pyrrolo[1,2-*a*]pyrazines as potent and selective human 5-HT$_{2C}$ receptor agonists

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Over the last decades the prevalence of obesity has been rising significantly all over the world. Obesity is a major risk factor in the development of hyperglycemia, hypertension, dyslipidemia, coronary artery disease and some cancers.

The currently approved drugs for the long-term treatment of obesity are the appetite suppressant Sibutramine (Meridia®), a centrally acting mixed noradrenaline/serotonin-reuptake inhibitor, and Orlistat (Xenical®), a non-systemic acting lipase inhibitor which increases the fecal loss of undigested triglycerides. It is expected that another appetite suppressant, Rimonabant®, a cannabinoid (CB-1) receptor antagonist will reach the market this year.

In preclinical studies the involvement of the 5-HT$_{2C}$ receptor subtype in the control of feeding in animals has been established through the use of 5-HT$_{2C}$ receptor agonists, antagonists and transgenic mouse models. In clinical studies, the non-selective 5-HT$_{2C}$ receptor agonist mCPP decreases food intake and body weight of obese subjects. Recent Phase IIb clinical trials with the 5-HT$_{2C}$ receptor agonist Lorcaserin (APD356) showed significant body weight loss in obese patients.

In the presentation, the discovery and SAR of 5,5a,6,7,8,9-hexahydropyrido[3',2':4,5]pyrrolo[1,2-*a*]pyrazines, a novel class of potent and selective human 5-HT$_{2C}$ receptor agonists will be described. Several analogues had favorable *in vitro* phospholipidosis and hERG properties and were active **in rodent models of feeding after** oral administration.

Medicinal Chemistry **69**

Targeting Hepatocytes via the Asialoglycoprotein Receptor

Daniela Stokmaier, Oleg Khorev, Karin Johansson, Daniel Ricklin, Brian Cutting, Beat Ernst

Institute of Molecular Pharmacy,Pharmacenter of the University of Basel, Klingelbergstr.50, CH-4056 Basel, Switzerland

The asialoglycoprotein receptor (ASGP-R) is a liver specific membrane receptor responsible for the removal of desialylated glycoproteins with terminal galactose or *N*-acetylgalactosamine (Gal*N*Ac) residues from circulation via receptor mediated endocytosis. The human receptor consists of two subunits, designated H1 and H2, each of which contains a single C-type lectin carbohydrate recognition domain (CRD). Being a transport receptor exclusively expressed on hepatocytes, the ASGP-R is an interesting target for medicinal chemists in their effort to deliver drugs and genes specifically to the liver. Because of the generally low affinity of carbohydrates to their receptors (μM to mM range) as well as their unfavorable pharmacokinetic properties, small drug-like delivery systems have to be developed. In order to elucidate the uptake mechanism by the ASGP-R, assays with either the isolated H1-CRD alone or the whole receptor on living cells were developed. First, a competitive solid-phase assay with the recombinant H1-CRD was used to screen for monomeric, high affinity ligands. In a second step, the specific binding and uptake of selected synthetic oligovalent ligands by the whole functional receptor on living cells was monitored using fluorescence microscopy and flow cytometry.

The presented results served as a starting point for the design and synthesis of a high-affinity, small-molecule ligand capable of facilitating the targeted drug delivery to hepatocytes.

Medicinal Chemistry **70**

In vitro cytotoxicity studies of oxides nanoparticles and comparison to Asbestos

L.K. Limbach[1], T.J. Brunner[1], P. Wick[2], R.N. Grass[1], P. Manser[2], P. Spohn[2], A. Bruinink[2], W.J. Stark[1]

[1] ETH Zurich, Institute for Chemical and Bioengineering, Switzerland.
[2] Empa St. Gallen, Materials and Tissues for Medicine, Switzerland

Early indicators for nanoparticle derived adverse health effects should provide a relative measure for cytotoxicity of nanomaterials in comparison to existing toxicological data.
We have therefore evaluated a human mesothelioma and a rodent fibroblast cell line for in vitro cytotoxicity tests using industrially important nanoparticles. Their response in terms of metabolic activity and cell proliferation of cultures exposed to 0 to 30 ppm nanoparticles (μg g-1) was compared to the effects of non-toxic amorphous silica and toxic crocidolite asbestos. Solubility was found to strongly influence the cytotoxic response.
The results further revealed a nanoparticle specific cytotoxic mechanism for uncoated iron oxide and partial detoxification or recovery after treatment with zirconia, ceria or titania. While in vitro experiments may never replace in vivo studies, the relatively simple cytotoxic tests provide a readily available pre-screening method.

[1] L.K Limbach, Y. Li, R.N. Grass, T.J. Brunner, M.A. Hintermann, M. Muller, D. Gunther, W.J Stark, Oxide nanoparticle uptake in human lung fibroblasts: Effects of particle size, agglomeration, and diffusion at low concentrations. *Environmental Science & Technology* **2005** *39*, 9370-9376.
[2] T.J. Brunner, P. Wick, P. Manser, P. Spohn, R.N. Grass, L.K. Limbach, A. Bruinink, W.J. Stark, In vitro cytotoxicity of Oxide Nanoparticles: Comparison to Asbestos, Silica, and effects of particle solubility. *Environmental Science & Technology* **2006**, published online, 2006, DOI: 10.1021/es052069.

Medicinal Chemistry **71**

Discovery of a Novel Series of Quinazoline Derivatives as Competitive AMPA Receptor Antagonists: Design, Synthesis and SAR.

M. Koller, H. Allgeier,. W. Froestl,. P. Floersheim,. J. Kallen,.; K. Lingenhoehl,. S. Ofner, S. Urwyler, J..Renaud*

Novartis Institutes for BioMedical Research Basel, Global Discovery Chemistry, Neuroscience department, WKL-136.6.81, CH-4002 Basel, Switzerland

Epilepsy is a common neurological disorder which affects ca 1% of the population and 1/3 of the patients are poorly controlled by anti-epileptic drugs. Excessive stimulation of the glutamatergic system plays a role in triggering seizures associated with epilepsy. Inhibitors of glutamatergic neurotransmission may thus have anticonvulsive properties. Specifically, AMPA receptor antagonists may offer new hopes in the treatment of epilepsy. We wish to disclose herein the design, synthesis and SAR of a novel series of potent competitive AMPA receptor antagonists.

Medicinal Chemistry **72**

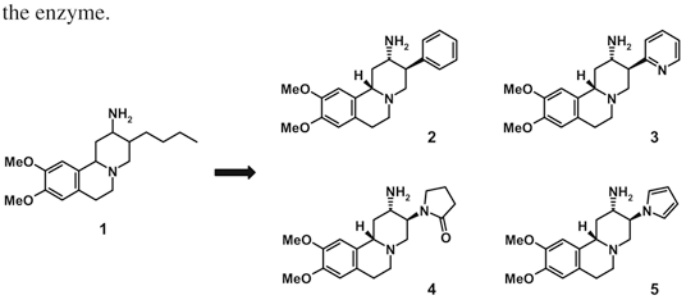
Aminobenzoquinolizines: A New Class of DPP–IV Inhibitors

Patrizio Mattei

F. Hoffmann-La Roche AG, Discovery Chemistry, CH-4070 Basel

DPP–IV (dipeptidyl peptidase IV) inhibitors have emerged in recent years as promising therapeutic agents for the treatment of Type 2 diabetes. DPP–IV rapidly cleaves and inactivates GLP–1, a stimulator of insulin secretion.

Aminobenzoquinolizine **1** was found as a hit in a high-throughput screening campaign. It had an interesting drug-like profile but needed improvement in terms of affinity with the target. The co-crystal structure of DPP–IV with **1** revealed a poor fit of the butyl side chain within the S1 specificity pocket of the enzyme.



The search for aminobenzoquinolizine-type inhibitors with alternative substituents for the S1 pocket was supported by structure-based design methods and led to compounds **2** – **5**, which served as leads for subsequent refinement. The lead optimization work was guided by a combination of X-Ray information with SAR that had been elaborated on a structurally unrelated lead series and provided markedly more potent DPP–IV inhibitors.

This lecture will illustrate the evolution of an HTS hit into DPP–IV inhibitors with highly promising characteristics.

Medicinal Chemistry **73**

Structural determinants of a miniprotein: The importance of individual aminoacids in porcine polypeptide YY (pPYY) for formation of secondary and tertiary structure and implications for folding

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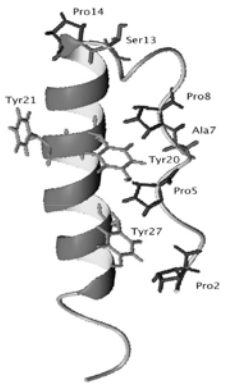
Institute of Organic Chemistry, University of Zurich, Winterthurerstr. 190, CH-8057 Zürich, Switzerland

The polypeptide YY (PYY), a 36-residue, C-terminally amidated polypeptide hormone is a member of the neuropeptide Y (NPY) family. Despite the high sequence similarity of NPY and PYY the latter displays the characteristic PP-fold in solution whereas no tertiary contacts are formed in NPY (see Figure, [1,2]).

In this work, we have developed methodology to characterize structural changes of PYY in aqueous solution upon systematic replacement of residues involved in forming tertiary contacts or imposing other structural restraints (see Figure). Studies of the internal backbone dynamics of PYY were performed to quantify the extent of tertiary contact formation [2]. Moreover, we developed methods to monitor the structural transition of PYY upon diffusing from solution to the membrane interface.

We obtained important insights into the role of individual amino acids for protein folding, using PYY as a model protein.



[1] M. Lerch, M. Mayrhofer, O. Zerbe, *J. Mol. Biol.* **2004**, *339*, 1153-68.
[2] R. Bader, A. Bettio, A.G. Beck-Sickinger, O. Zerbe, *J. Mol. Biol.* **2001**, *305*, 307-392.

Medicinal Chemistry **74**

Preorganization of E-Selectin antagonists in the bioactive conformation

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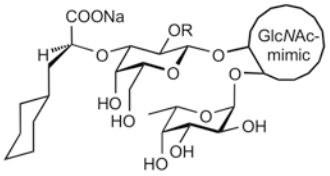
Institute of Molecular Pharmacy, Pharmacenter of the University of Basel, Klingelbergstrasse 50, Basel CH-4056, Switzerland

The activity of E-selectin antagonists benefits the from preorganization of the ligand in the bioactive conformation [1]. We have demonstrated that the optimal special presentation of the pharmacophores to the receptor site can be enforced by steric factors [2]. Along these lines, potent E-selectin antagonists based on novel Glc*N*Ac mimetics were developed. Biological evaluation in a static E-selectin binding assay and under flow conditions showed substantial improvement compared to ligands missing the steric compression. The conformational flexibility vs. preorganization was further evaluated by computational techniques and NMR studies.



[1] B. Ernst, H. C. Kolb, O. Schwardt in *The Organic Chemistry of Sugars*, (Eds.: D. E. Levy, P. Fügedi), CRC Press/Taylor & Francis, Boca Raton, **2006**, pp. 828-862.
[2] G. Thoma, J. L. Magnani, J. T. Patton, B. Ernst, W. Jahnke, *Angew. Chem. Int. Ed.* **2001**, *40*, 1941.

Medicinal Chemistry **75**

Discovery of Highly Potent and Selective CXCR4 Inhibitors Using Protein Epitope Mimetics (PEM) Technology

Alexander Lederer[1], Barbara Romagnoli[1], Heiko Henze[1], Reshmi Mukherjee[1], Steven J. DeMarco[1], Jürg Zumbrunn[1], Frank O. Gombert[1], Sergio Lociuro[1], Christian Ludin[1], Jan Willem Vrijbloed[1], Daniel Obrecht[1], François Hamy[2], Thomas Klimkait[2], Kerstin Moehle[3] and John A. Robinson[3]

[1]Polyphor AG, Gewerbestrasse 14, CH-4123 Allschwil
[2]InPheno AG, Vesalgasse 1, CH-4051, Basel
[3]University of Zurich, Winterthurerstr. 190, CH-8750 Zürich

In collaboration with Prof. J.A. Robinson at the University of Zurich Polyphor Ltd has developed the Protein Epitope Mimetics (PEM) Technology to generate modulators of protein-protein interactions, focusing on template-fixed (e.g. ^{D}Pro-^{L}Pro-dipeptide), cyclic peptide-like molecules.

As an example, PEM Technology has enabled the discovery of novel antagonists of the chemokine receptor CXCR4, which is used not only as a co-receptor for the entry of T-tropic (X4) HIV-1 but is also involved in the progression of various types of cancers, hematopoietic stem cell mobilization and inflammatory processes.

The beta-hairpin shaped natural product polyphemusin II, one of the first known CXCR4 antagonists, served as a starting point for the design of focused PEM libraries. Using a high throughput parallel synthesis approach, the potency and ADMET properties were optimized in iterative cycles resulting in the selective and potent CXCR4 antagonists POL2438 and POL3026. The potencies of these compounds were confirmed in a series of HIV-assays including *in vitro* cell fusion (FIGS) and virus replication (deCIPhR). POL3026 binds with a 100-fold greater affinity to CXCR4 than AMD3100, a current CXCR4 antagonist in clinical development for stem cell mobilization.

Currently, preclinical studies are being performed with our lead compound for application in stem cell transplant.

Medicinal Chemistry **76**

Atomistic Study of Feedback Inhibition in Guanylate Cyclase PLED

F. F.-F. Schmid, M. Meuwly

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Cyclic di-guanosine monophosphate (c-diGMP) is found to be an ubiquitous second messenger [1] in bacteria involved in various medicinally relevant processes such as biofilm formation and bacterial development. The synthesis of c-diGMP from two guanosine triphosphate molecules is catalyzed by the GGDEF domain. In many proteins, the catalytically active GGDEF domain is found in combination with various sensory input domains.

The ability of the GGDEF domain for product feedback inhibition to control the cellular c-diGMP level was first found in the multidomain protein PleD from *C. crescentus* [2]. However this process is not understood at a molecular level. Such an understanding will provide the necessary information to isolate structural motifs that are potentially relevant in controlling allostery in PleD.

In this work the molecular mechanism of inhibition is investigated at an atomistic level using computer simulations. Normal mode analysis shows that the flexibility of the inhibition and the active site are coupled which provides motional control between the two sites. Mutant screening experiments identify the RxxD motif in the inhibition-site necessary for feedback inhibition. The relation of these findings to structural and energetic changes is studied on a structurally related, smaller subsystem.

[1] U. Römling, M. Gomelsky, M.Y. Galperin, *Mol. Microbiol.* **2005**, 57, 629.
[2] C. Chan, R. Paul, D. Samoray, N.C. Amiot, B. Giese, U. Jenal, T. Schirmer, *PNAS* **2004**, *101*, 17084.
[3] B. Christen, M. Christen, R. Paul, F. Schmid, M. Folcher, P. Jenoe, M. Meuwly, U. Jenal, *J. Biol. Chem.*, submitted.

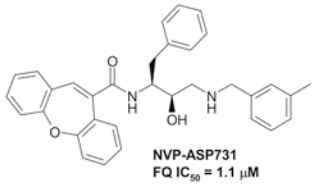
Medicinal Chemistry **77**

Identification and Optimisation of novel BACE Inhibitors based on the Hydroxyethylamine Transition State Mimetic

Oliver Simić

Expertise Program Proteases/Novartis Institute for Biomedical Research, Postfach, CH-4002 Basel, Switzerland

An established approach towards the development of a causal therapy against Alzheimer's disease is the inhibition of BACE (beta-site amyloid precursor protein cleaving enzyme). Like renin and HIV protease, BACE belongs to the class of aspartic proteases.
As high-throughput screening campaigns of the Novartis Compound Archive (NCA) for BACE inhibitors did not result in the identification of validated hits, attempts to develop BACE inhibitors from a peptidomimetic approach were undertaken.
In an effort to reduce the peptidic character of the inhibitors, a search for novel P2-P3 residues was performed using high-throughput docking. A set of low molecular weight carboxylic acids, available from the NCA and commercial sources, was screened and led to the identification of the dibenzo[b,f]oxepine-10-carboxamide motif.



NVP-ASP731
FQ IC_{50} = 1.1 μM

The dibenzo[b,f]oxepine-10-carboxamide fragment was then combined with various transition state mimetics, eventually giving rise to NVP-ASP731 as a lead compound. Starting with NVP-ASP731 we designed and synthesized several potent BACE inhibitors. The syntheses as well as structural and biological data of these compounds will be presented.

Medicinal Chemistry **78**

Pyrrolidinone based α-mannosidases inhibitors act as growth inhibitors of human glioblastoma cells

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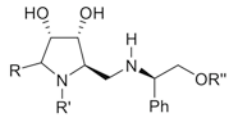
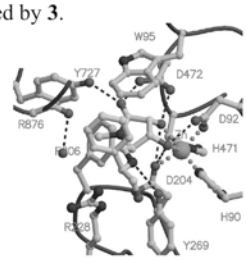
The specific inhibition of *N*-linked glycoprotein-processing α-mannosidases may provide a useful anti-cancer strategy.[1] Recently, we have demonstrated that ester derivatives of **1** presented promising anti-proliferative properties on human cancer cells.[2]
Synthesis of the more rigid pyrrolidinone analog **3** provided an increased inhibitory activity against α-mannosidase from jack-bean (IC_{50} = 705 nM for **1** *vs* 150 nM for **3**) resulting from additional interactions with residues of the enzyme [X-ray of *Drosophila melanogaster* Golgi α-mannosidase II (dGMII)]. Moreover, studies on cellular extracts from human cancer cells revealed that α-mannosidases are also inhibited by **3**.





1 R = R' = R'' = H
2 R = R' = H, R'' = OC(O)Ar
3 R = C(O), R' = Me, R'' = H
$IC_{50\ of\ Jack\text{-}bean}$ = 150 nM; $IC_{50\ of\ dGMII}$ = 500 nM; $IC_{50\ of\ cellular\ extracts}$ = 500 nM

[1] a) Dwek, M.V.; Brooks, S.A. *Curr. Cancer Drug Targets* **2004**, *4*, 425 b) Gerber-Lemaire, S.; Juillerat-Jeanneret, L. *Mini Rev. Med. Chem.* **2006**, in press.
[2] Fiaux, H.; Popowycz, F.; Favre, S.; Schütz, C.; Vogel, P.; Gerber-Lemaire, S.; Juillerat-Jeanneret, L. *J. Med. Chem.* **2005**, *48*, 4237.

Medicinal Chemistry **79**

Signal Enhancement and Pharmacophore Characterization in NMR Saturation Transfer Experiments

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Numerous biomolecular ligand-receptor interactions have been investigated by Saturation Transfer Difference (STD) experiments [1]. Information provided from these studies has permitted the high-throughput acquisition of structure activity relationships (SAR) and greatly enhanced role of NMR in drug design.

Herein, methods are described allowing a considerable gain in sensitivity with respect to numerous published schemes reported by various academic research groups and pharmaceutical companies. The second part of this contribution will describe a novel approach to the interpretation of the STD epitopes. The analysis will allow an accurate characterization of the similarity between binding modes of different ligands, and is independent of any structural information from the receptor.

[1] M. Mayer, B. Meyer, *Angew. Chem. Int. Ed.* **1999**, 38, 1784.

Medicinal Chemistry **80**

Cell Uptake and Radiotoxicity Studies of Bombesin-Intercalator Conjugates of Re / $^{99m}Tc(CO)^{3+}$

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Effective electrons to induce DNA single and double strand breaks by direct and indirect pathways are those with initial energy of 50 to 250 eV. These electrons are able to produce clusters of inelastic interactions within a radius of a few nm. In the case of ^{99m}Tc, the emitted electrons with a potentially cytotoxic potential would thus be the MXY Auger as well as MMX and NNX Coster-Kronig ones. The theoretical aspect of the *in vivo* toxicity of ^{99m}Tc has only been experimentally tested by few research groups. We would like to present preliminary results of the nuclear targeting of the Re/^{99m}Tc-complexes and their cytotoxic effects with cells , making use of this Auger and Coster-Kronig electrons. A DNA intercalator is thereby attached to the ^{99m}Tc-tricarbonyl moiety in addition to a targeting molecule (Bombesin) should allow the whole molecule, once internalized into a cancer cell, to intercalate into the DNA. The conversion electrons induce DNA double strand breaks which should lead to the death of the cell. The radiotoxicity of the ^{99m}Tc-complex on B16F1 mouse melanoma cells has been investigated to evaluate the activity of Auger and Coster-Kronig electrons on the viability of cells. The cellular uptake of the Re/^{99m}Tc-complexes has been also investigated on B16F1 and PC-3 cell line using fluorescence microscopy.

Medicinal Chemistry **81**

Total Synthesis of New Functionalized Epothilone Analogs for Prodrug Design and Tumor Targeting

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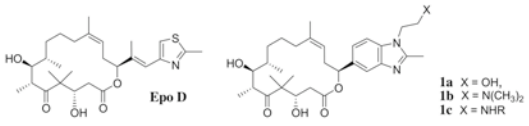
Epothilones (Epo's) are microtubule-stabilizing natural products which exhibit strong antiproliferative effects *in vitro* and potent antitumor activity *in vivo*, including tumor growth inhibition in multi-drug resistant human tumor models.[1] Although the SAR of this highly promising compound class has been extensively investigated, specific aspects still remain unaddressed. Moreover, an increase in the selectivity of these agents towards tumor cells would be highly desirable, in order to improve their therapeutic window. In this context we have synthesized a series of new Epo D analogs **1a-c** and investigated their biological activity. All three compounds proved to be potent inducers of tubulin polymerization and inhibitors of human cancer cell growth *in vitro*. Of particular interest is analog **1c**, where the 2-aminoethyl group could serve as attachment site for various tumor-targeting moieties, such as high molecular weight poly(ethylene glycol)s, folic acid, the peptide Mu-His-Ser-Ser-Lys-Leu-Gln-Leu (containing a prostate-specific-antigen (PSA) cleavage site; Mu = morpholinooxycarbonyl)), or human antibodies.



[1] Goodin, S.; Kane, M. P.; Rubin, E. H. *J. Clin. Onc.***2004**, *22(10)*, 2015.

Medicinal Chemistry **82**

Inhibitors for the Malarial Enzyme Plasmepsin II – Improvement of an Established System

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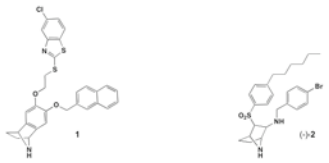
Malaria, caused by a parasite of the genus *Plasmodium*, remains one of the most widespread infectious diseases in the world, despite the efforts of thousands of researchers. A possible drug target is the Plasmepsin family of aspartic proteases which are involved in the first steps of the Hemoglobin degradation by the parasite.



Based on the knowledge acquired in our research group (see compounds **1** and (-)-**2**) we developed new inhibitors for the malarial protease Plasmepsin II [1, 2]. We subsequently changed the different vectors of the initial molecule and varied the substituents for the pockets as well as the needle binding to the two aspartates in the catalytic dyad. Our project aims at the improvement of binding affinity and pharmaceutical aspects of the lead structure.

[1] D. A. Carcache, S. R. Hörtner, A. Bertogg, C. Binkert, D. Bur, H. P. Märki, A. Dorn, F. Diederich, *ChemBioChem* **2002**, *3*, 1137.
[2] F. Hof, A. Schütz, C. Fäh, S. Meyer, D. Bur, J. Liu, D. E. Goldberg, F. Diederich, *Angew. Chem. Int. Ed.* **2006**, *45*, 2138.

Medicinal Chemistry **83**

Towards a QSAR Study of Furo[3,4-*c*]pyranones with Antiproliferative and Apoptotic Activity

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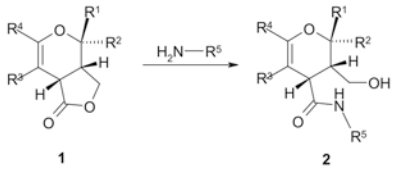
The synthesis of natural product analogues represents a key challenge for medicinal chemists since many natural products, or derivatives thereof, are used in modern medicine.[1] So we became keen to synthesise iridoid-like furo[3,4-*c*]pyranones [2] **1** due to interesting biological activities of naturally occurring iridoids and secoiridoids.[3] Subsequent derivatisations of **1** included the aminolysis of the lactone moiety with different amines.



In cell proliferation assays of two different human cancer cell lines (A549 and KB31), compounds **1** and **2** showed potent antiproliferative and apoptotic (KB31) activity. Both cell lines also showed a significant accumulation of cells in the G2/M phase when treated with compounds **1**.
The synthesis of different furo[3,4-*c*]pyranones **1** and their derivatives for QSAR studies and possible target identification is now in progress.

[1] R. Messer, C. A. Fuhrer, R. Häner, *Curr. Opin. Chem. Biol*. **2005**, *9*, 259-265.
[2] C. A. Fuhrer, R. Messer, R. Häner, *Tetrahedron Lett.* **2004**, *45*, 4297-4300.
[3] E. L. Ghisalberti, *Phytomedicine* **1998**, *5*, 147-163.

Medicinal Chemistry **84**

Structure-Based Design and Sythesis of a New Class of Antibiotics Against Bacillary Dysentery *(SHIGELLOSIS)*

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tRNA-guanine transglycosylase (TGT) is a tRNA-modifying enzyme common to nearly all organisms, including humans. Its substrate specificity [1] offers the possibility of selective inhibition of the eubacterial enzyme, which has been linked to the pathogenicity of *Shigellae* [2], the causative agents of bacillary dysentery (*Shigellosis*). Extensive crystallographic and biochemical characterization of this enzyme has been carried out, therefore TGT represents an ideal target for structure-based drug design, which might facilitate the development of new antibiotics against dysentery.
Molecular modeling tools, the existence of numerous X-ray crystal structures of TGT complexes with its substrate $PreQ_1$ [3] and previously described inhibitors [4] allow the structure-based design of two new, further elaborated series of inhibitors.

[1] C. Romier, J. E. W. Meyer, D. Suck, *FEBS Lett.* **1997**, *416*, 93-98.
[2] N. Okada, C. Sasakawa, T. Cobe, M. Yamada, S. Nagai, K. A. Talukde, K. Komatsu, S. Kanegasaki,, M. Yoshikawa, *Mol. Microbiol.* **1991**, *261,* 187-195.
[3] W. Xie, X. Liu, R. H. Huang, *Nat. Struct. Biol.* **2003**, *10,* 781-788.
[4] E. A. Meyer, M. Furler, R. Brenk, G. Klebe, F. Diederich, *Helv. Chim. Acta* **2004,** 87, 1333-1356.

Medicinal Chemistry **85**

Antisense mechanisms of fully modified tc-DNA and tc-DNA gapmer

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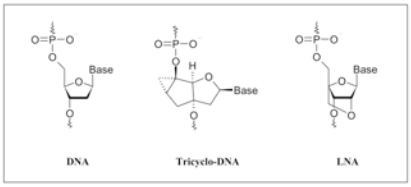
High potential in terms of antisense properties is given to the class of conformationally constrained oligonucleotide analogues such as for example LNA or tricyclo (tc)-DNA [1] (see Fig.), which show signifcantly enhanced target binding properties and enhanced biological stability.

We investigated the antisense mechanism (steric block vs. RNase H induced mRNA degradation) of a fully modified tc-oligonucleotide and a 5-8-5 tc-DNA gapmer that was directed to the coding region of the Enhanced Green Fluorescent Protein (EGFP) mRNA. A dual fluorescence reporter assay was used [2] consisting of two plasmids carrying EGFP and Red Fluorescent Protein (RFP, as a control) that were cotransfected with variable amounts of antisense oligonucleotides into HeLa cells.

The antisense effect was quantified on the protein level by Fluorescence Activated Cell Sorting (FACS) and on the RNA level by quantitative PCR. The antisense effects obtained with tc-DNA were compared to those obtained by LNA.



[1] D. Ittig, S. Liu, D. Renneberg, D. Schümperli, C. J. Leumann, *NAR*, **2004**, *32*, 346-353.

[2] Y.-L. Chiu, T. M. Rana, *Mol. Cell*, **2002**, *10*, 549-561.

Medicinal Chemistry **86**

Combinatorial Approach to Discovery of Glycopeptide Dendrimers Binding to Fucose-Specific Lectins

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The antibiotic-resistant pathogenic *pseudomonas aeruginosa* bacterium is known to be responsible for respiratory tract infections. Fucose specific lectin, biosynthesized by this bacterium, plays an important role in the colonization and the infection process. Previous studies have shown that fucose itself can inhibit this kind of pathology.[1] In this context, multivalent fucosyl-containing molecules appear to be relevant target. Our aim was then focused on synthesis and evaluation of antibacterial properties of glycopeptide dendrimers. Peptide dendrimers are tree-like molecules with amino acids in the branches and whose dendritic structure allows the display of multiple copies of the carbohydrate in the peripheral layer.[2] A combinatorial library of fucosylated-dendrimers was thus prepared using solid-phase peptide chemistry. Fucose-dendrimers with strong affinity for lectin, were discovered after on-bead screening of the dendrimer library, suggesting these may act as improved inhibitors of colonization and therefore provide interesting lead-compounds for drug design.

[1] D. Tielker, S. Hacker, R. Loris, M. Stratmann, Microbiology, **2005**, 151, 1313.

[2] A. Clouet, T. Darbre, J.-L. Reymond, Angew. Chem. Int. Ed. **2004**, 43, 4612

Medicinal Chemistry **87**

Towards Glycopeptide Dendrimers as Antibacterial Agents

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The chronic colonization of the lungs by P*seudomonas aeruginosa* is a major cause of infections and of mortality for cystic fibrosis patients. This bacterium expresses two intracellular lectins, one of which is specific for fucose and reveals unusually high affinity than that generally observed for lectins interacting with monovalent ligands.[1] It was shown that multivalent lectin binding inhibits attachment of the bacterium to its host cell and may block infection.[2] Thus, multivalent fucosylated dendrimers appear to be potential antibacterial agents. A combinatorial library of second-generation fucose-dendrimers was prepared using split-and-mix protocol.[3] High-affinity ligands to lectin were identified by on-bead screening of the dendrimer library. These resynthesized ligands show strong inhibition properties in solution under ELLA test. Polyvalency effect and dendritic peptide backbone-lectin interactions are under current investigation.

[1] E.P. Mitchell, C. Sabin, N. Gilboa-Garber, A. Imbety, *Proteins*. **2005**, *58*, 735.

[2] D. Tielker, S. Hacker, R. Loris, M. Strathmann, K.-E. Jaeger, *Microbiology*. **2005**, *151*, 1313.

[3] A. Clouet, T. Darbre, J.-L. Reymond, *Angew. Chem. Int. Ed*. **2004**, *43*, 4612.

Medicinal Chemistry **88**

The ^{99m}Tc(I)/Re(I)-Tricarbonyl Complexes of Diamino-propionic Acid Derivatives Recognized by LAT1

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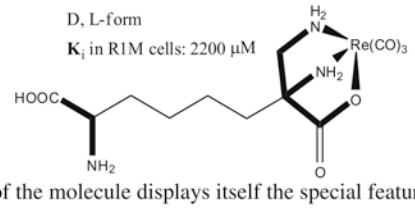
[1]Institute of Inorganic Chemistry, University of Zürich, Winterthurerstr. 190, CH-8057 Zürich, Switzerland [2]Radiopharmaceutical Chemistry, Vrije Universiteit Brussel, Laarbeeklaan 103, 1090 Brussel, Belgium

Diamino-propionic acid (DAP) was found to be a very good tripod ligand for the labeling of ^{99m}Tc(I)/Re(I) tricarbonyl core [1], forming the corresponding hydrophilic complexes which were stable to air, cysteine and histidine in aqueous media. Encouraged by these observations, A series of novel bifunctional ligands, with general formular $X(CH_2)_nY$ (n = 4, 5, 6, 7; X = -C(NH_2)(CH_2NH_2)COOH; Y = -CH(NH_2)COOH) were prepared. The complex formed by $X(CH_2)_4Y$ and *fac*-$[Re(CO)_3]^+$ was illustrated below.



The structure of the molecule displays itself the special features for potential radiopharmaceutical applications. The DAP part X in the ligand acted as a tripod ligand, while the pendant amino acid part Y was free for conjugation with biomolecules. The complex can be recognized and transported by LAT1, and thus, to the best of our knowledge, provided the first example that a labeled Re-complex can be transported into a cell, which is of great significance for the designing of new cancer-targeting agents [2].

[1] R. Alberto, *Comprehensive Coord. Chem. II,* **2004**, *vol.5*, .Technetium.

[2] R. Alberto, *Top. Curr. Chem.,* **2005**, *252*, 1-44.

Medicinal Chemistry **89**

Search for New Glycosidase Inhibitors: Conduramine Epoxides

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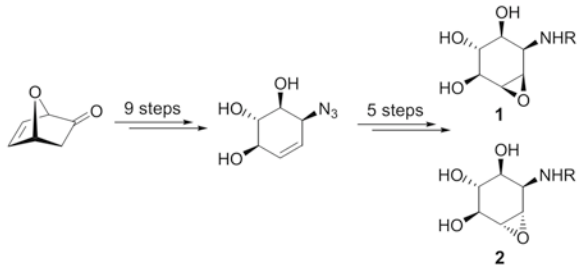
Inhibitors of α-glucosidases are used to treat diabetes of type II [1]. They are potential anti-HIV agents [2]. Inhibitors of β-glucosidases are drugs against Gaucher´s disease [3] [4]. Conduramine B-1 and F-1 derivatives have shown promising activities and selectivities as glycosidase inhibitors [5]. We have now developed stereoselective synthesis of conduramine F-1 epoxides and present their inhibitory activities toward several glycosidases.



Compound **1** (R = $CH_2C_6H_4$-4-Ph) is a good and selective inhibitor of yeast α-glucosidase, whereas **2** (R = $CH_2C_6H_4$-4-CF_3) is a good and selective inhibitor of β-xylosidase from *Aspergillus niger*.

[1] Treadway, J. L.; Mendys, P.; Hoover, D. J. *Expert Opin. Investig. Drugs* **2001**, *10*, 439–454.
[2] Robina, I.; Moreno-Vargas, A. J.; Carmona, A. T.; Vogel, P. *Curr. Drug Metab.* **2004**, *5*, 329–361.
[3] Butters, T. D.; Dwek, R. A.; Platt, F. M. *Curr. Top. Med. Chem.* **2003**, *5*, 561–574.
[4] Łysek, R.; Schütz, C.; Vogel, P. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3071–3075.
[5] Łysek, R.; Vogel, P. *Tetrahedron* **2006**, *62*, 2733–2768; Łysek, R.; Schütz, C.; Vogel, P. *Helv. Chim. Acta* **2005**, *88*, 2788–2811.

Medicinal Chemistry **90**

Antagonists of the Myelin-associated Glycoprotein (MAG)

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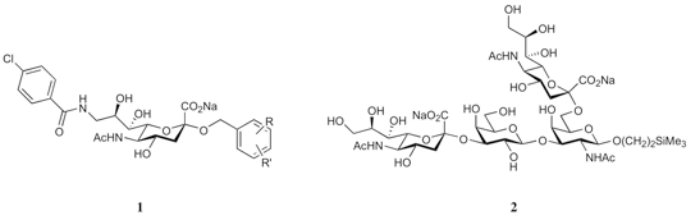
The myelin-associated glycoprotein (MAG) [1] belongs to the siglec family (sialic acid binding immunoglobulin like lectin) and was identified as one of the neurite outgrowth inhibitory proteins. In earlier studies, we identified the lead structure **1** (R, R'= H), which showed a 250-fold improved *in vitro* affinity towards MAG compared to the tetrasaccharide **2** (substructure of GQ1bα, the best physiological MAG ligand identified so far). With modifications (R, R'= Cl, F) at the reducing end of **1**, the affinity could be further improved. A homology model of MAG which is based on the crystal structure of sialoadhesin [2], another member of the siglec family, was used to dock the novel MAG antagonists and to rationalize their binding properties.



[1] M. T. Filbin, *Neuron,* **1994**, *13*, 757.
[2] A. P. May, R. C. Robinson, M. Vinson, P. R. Crocker, Y. Jones, *Molcular Cell*, **1998**, *1*, 719.

Medicinal Chemistry **91**

Virtual screening of the small-molecule chemical universe database for NMDA receptor ligands

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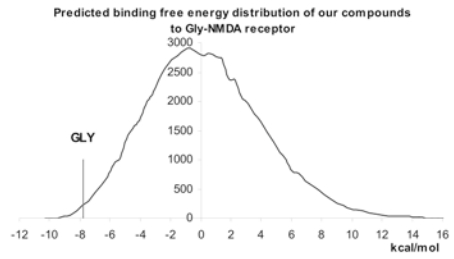
We recently reported a database listing all possible organic molecules up to 11 non-hydrogen atoms [1]. The database contains 13.9 million molecules below 160 Daltons, with a majority of drug-like structures suitable for drug discovery. We focused on the human central nervous system excitatory amino-acid receptors because their natural ligands are of comparable size, such as glutamate, GABA or glycine. Here we report a virtual screening approach to identify new ligands for the glycine site of the NMDA receptors, for which a high resolution X-ray structure is available [2]. A combination of 2D high-throughput screening and 3D-docking was developed to extract promising compounds from the database, and will be discussed in this paper.



[1] T. Fink, H. Bruggesser, J.L. Reymond. *Angew. Chem. Int. Ed.* **2005**, *44*, 1504-1508.
[2] H. Furukawa, S.K. Singh, R. Mancusso, E. Gouaux. *Nature* **2005**, *438*, 185-192.

Medicinal Chemistry **92**

New Diaryl Sulfides as Inhibitors for Trypanothione Reductase

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Trypanosomatids, the causative agents of African sleeping sickness differ from nearly all other prokaryotes in their specific sulfur redox metabolism which is based on the thiol-polyamine conjugate trypanothione and the flavoenzyme trypanothione reductase (TR) that protects the parasites from oxidant damage. It has been shown in the past that TR is essential for the parasite making it an attractive target for the development of new drugs.

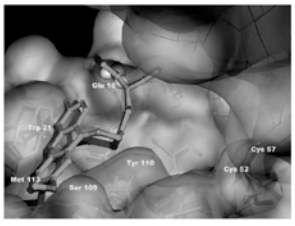

Fig.1: *The TR active site occupied by the antiparasitic drug mepacrine [2].*

2-Aminodiphenyl sulfides has been described as TR inhibitors [2]. A series of modified derivatives has been synthesized and tested for their affinity towards the enzyme to explore the ability of the TR active site to accommodate different functional groups.

[1] Fernandez-Gomez R., Moutiez M., Aumercier M., Bethegnies G., Luyckx M., Ouaissi A., Tartar A., Sergheraert C., Int. J. Antimicrob. Agents **1995**, *6*, 111.

Medicinal Chemistry **93**

Beyond empirical scoring functions for ligand docking: Post optimization with GRID based Molecular Dynamics

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In recent years virtual screening tools have become increasingly important for the drug discovery process [1]. However, the computational methods and their ability for quantitative prediction are still limited. For example, the currently used scoring functions are often ``knowledge based" instead of motivated by physio-chemical considerations, or the sampling of different conformations of the ligand-protein complex is insufficient. The question we want to answer is whether poses obtained from virtual screening (e.g. Autodock and Glide) can be improved by performing molecular dynamics simulations and if using MM-GBSA scoring method will result in a better ranking of ligands.

Recently, we have established a molecular dynamics method based on MM-GBSA to estimate the relative binding free energy of interaction of 16 HIV-1 protease inhibitor complexes and find that it correlates well with experimental data [2]. Using this system we can study how well poses obtained from virtual screening tools correlate to experimental data. This sort of calculation is computationally expensive, but by performing it on a computer GRID we obtain the necessary computing power.

[1] RX. Wang, XP. Lu, XL. Fang, SM. Wang, *J Chem Inf Comput Sci.* **2004**, *44*, 2114.
[2] HB. Thorsteinsdottir, T. Schwede, V. Zoete, M. Meuwly, *Proteins.* **2006**, in Press

Medicinal Chemistry **94**

The Preorganization of the Carboxylic Acid of Sialyl Lewis^x Mimetics is Essential for Binding to E-selectin

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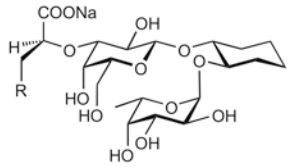
The selectins play a key role in the inflammatory process, i.e. the recruitment of leukocytes from blood vessels into inflamed tissues. Excessive infiltration of leukocytes can cause acute or chronic reactions, as observed in reperfusion injury, stroke or rheumatoid arthritis. Therefore, the antagonism of selectins is a valuable pharmaceutical approach. The tetrasaccharide epitope sialyl Lewis^x (sLe^x) which is present in all physiological ligands of the selectins, served as lead structure in the search for antagonists. The bioactive conformation of sLe^x has been elucidated [1]. It has been shown that the preorganization of the carboxylic acid in the bioactive conformation contributes substantially to the affinity of E-selectin antagonists [2].



The *(S)* configuration of C-2 of the neuraminic acid mimetics, as well as the substituents *R* are decisive elements for the preorganization of the acid in the bioactive conformation. In order to verify the above considerations, a series of E-selectin antagonists was synthesized and biologically evaluated.

[1] Scheffler, L. *et al. Angew. Chem. Int. Ed.* **1995**, *34*, 1841. Rinnbauer, M. *et al. Glycobiology* **2003**, *13*, 435.
[2] Kolb, H. C.; Ernst, B. *Chem. Eur. J.* **1997**, *3*, 1571.

Medicinal Chemistry **95**

Guided Travel Through the Chemical Universe

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The chemical universe of organic molecules in the range of 14-35 atoms (MW 200-500 Dal) is of particular interest as a reservoir for new drugs [1]. A molecular structure evolution algorithm is presented which enables one to travel between any two points in the chemical universe of drug-size organic molecules (MW 200-500). Movement in chemical space is understood as structural mutations in molecules, whereby nearest neighbours are related by single atom or bond changes. The "chemical spaceship" algorithm travels through chemical space continuum using structural point mutations for propulsion and a selection module ranking similarity to the set target as the compass for holding direction, which results in a detailed and continuous exploration of chemical space around and between molecules. The principle is demonstrated by traveling from methane to for example glutamate, sucrose, morphine, or the core of taxol, and back. It is also possible to travel between different points of interest in chemical space, as exemplified with the glutamate-receptor agonist-antagonist pair AMPA/CNQX. Intermediates encountered on the way between these two ligands might provide partial agonists and were evaluated by docking.

References
1. Fink T., Bruggesser H. and Reymond J.-L. Virtual Exploration of the Small Molecule Chemical Universe below 160 Daltons. *Angew. Chem. Int. Ed.* **2005**, *44*, p. 1504.

Medicinal Chemistry **96**

Interaction of N-terminal Domains of NPY Receptors with their Ligands

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Neuropeptide Y (NPY) is one of the most abundant signal peptides expressed in the central nervous system, that plays an important role in food uptake and vasoconstriction. Four subtypes of its receptors been better characterized in mammalian cells, named Y Receptors 1,2,4 and 5, which all belong to the class of G-Protein Coupled Receptors (GPCRs)[1]. GPCRs are important drug targets, accounting for around 30-50% of the drugs on the market. Because of the tremendous difficulties involved in expressing and purifying full-length GPCRs, we felt justified to study the interaction between NPY and the N-terminal domains. We have recently proposed a model for receptor recognition that postulates binding of the peptides to the membranes, but also requires the ligands to detach from the membrane in order to diffuse into the receptor binding pocket[2]. Such a process would be facilitated if at least transient binding between the peptides and the extracellular N-terminal domains would occur.
In our study, we have purified all the N termini of the four Y receptor subtypes, and studied the interaction of them with hormones of the NPY family by NMR. Our preliminary data demonstrate interactions between the N termini of receptors and their ligands. This finding indicates that the N termini might play an important role in the recognition or binding of ligands. Furthermore, phylogenetically related receptors dispay similar binding profiles of the N termini towards different peptides from the NPY family.

[1] Michel, M.C., Beck-Sickinger, A.G., Cox, H., Doods, H.N., Herzog, H., Larhammar, D., Quirion, R., Schwatz, T., Westfall, T. *Pharmacol.Rev.* **1998**, *50*, 143-50.
[2] Bader, R., Zerbe, O. *ChemBioChem.* **2005**, *6*, 1520-1534

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Medicinal Chemistry **97**

Cationic Lipidoids for RNA Interference Therapy

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RNA interference therapy — the specific inhibition of endogenous protein expression — shows great promise for the treatment of hitherto untreatable diseases. As with all nucleotide-based therapy systems, a formulation must be found to effciently transport the DNA or small interfering RNA molecules into a cell in vivo. Recently, we have reported on a library of cationic polymers that act as DNA transfection vectors, protecting DNA from the degradation in the blood-stream and releasing the DNA-prodrug into the cytoplasm of target cells[1,2]. At this meeting we would like to present a new library of hundreds of di erent cationiclipidoid molecules. All weretested in vitro for their effciency to mediate DNA or siRNA transfection. We have identified structures that surpass state-of-the-art delivery systems and we have tested the most promising candidates in an extensive in vivo study. The communication will reveal powerful systemic protein knockdown in various disease models.

[1] D. G. Anderson, D. M. Lynn, R. Langer,Angew. Chem. Int. Ed., 2003, 42, 3153–3158.

[2] D. G. Anderson, W. Peng, A. Akinc, N. Hossain, A. Kohn, R. Padera, R. Langer, J. A. Sawicki PNAS, 2004, 101, 16028–16033.

Computational Chemistry **98**

The Emergence of Density Functional Theory in Computational Quantum Chemistry

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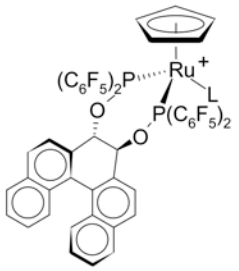
As a major method of computational quantum chemistry, Density Functional Theory (DFT) has made a remarkable breakthrough during the last 10-15 years. Today, DFT-based methodologies have become *de facto* standard techniques for routine modeling of organic, organometallic and inorganic systems, clusters, catalysts, new materials, surfaces, lead compounds in drug design, etc. In this presentation, some historical landmarks in the development of DFT will be outlined, emphasizing as well on its differencies with wavefunction-based methodologies. In addition, some recent DFT applications to large organic and organometallic systems, such as $[CpRu(PP)L]^+$ derivatives [1] will be discussed.



[1] V. Alezra, G. Bernardinelli, C. Corminboeuf, U. Frey, E.P. Kündig, A.E. Merbach, C.M. Saudan, F. Viton, J. Weber, J. Am. Chem. Soc. **2004**, *126*, 4843-4853.

Computational Chemistry **99**

Modeling Environmental Effects with Frozen Density Embedding

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An efficient implementation of the orbital free frozen-density embedding (FDE) scheme within density functional theory (DFT) [1] is presented. FDE is based on the partitioning of the electron density into an active embedded part and a frozen (environmental) part. It is demonstrated that FDE can, in combination with efficient approximations for the surrounding density [2], be used to model environmental effects on molecular properties, e.g., solvent effects on electronic spectra [3].
We also discuss the possibility to model the effect of more complex surroundings. In particular, the phenomenon of induced circular dichroism (ICD) is investigated, where the chiral compound is only described in terms of its frozen density. It is demonstrated that FDE can reproduce circular dichroism spectra of achiral compounds in complexes with chiral partner molecules very well [4].
The current implementation of FDE assumes excitations which are localized on the embedded system only. This offers some striking advantages in comparison to conventional TDDFT calculations for large systems. But there are also cases in which this approximation does not hold. This is discussed for the properties of a water molecule surrounded by water in a comparison of FDE with a classical polarizable force field [5]

[1] T.A. Wesolowski, A. Warshel, *J. Chem. Phys.*, **1993**, *97*, 8050.
[2] J. Neugebauer, M.J. Louwerse, E.J. Baerends, T.A. Wesolowski, *J. Chem. Phys.*, **2005**, *122*, 094115.
[3] J. Neugebauer, Ch.R. Jacob, T.A. Wesolowski, E.J. Baerends, *J. Phys. Chem. A*, **2005**, *109*, 7805.
[4] J. Neugebauer, E.J. Baerends, *J. Phys. Chem. A*, **2006**, accepted.
[5] Ch.R. Jacob, J. Neugebauer, L. Jensen, L. Visscher, *Phys. Chem. Chem. Phys.*, **2006**, *8*, 2349.

Computational Chemistry **100**

From Solvent Fluctuations to Quantitative Redox Properties of Quinones in Methanol and Acetonitrile

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We have employed a novel combination of density functional theory (DFT) and classical molecular dynamics simulations (MD) to provide quantitative values for key parameters of electron transfer reactions[1]. We have been able to rationalise the difference in redox potentials and reorganisation free energies of quinones due to chemical substitutions and to changes in their environments. Using two solvents with very similar dielectric properties, we are able to highlight the role of hydrogen bonding as a specific interaction that increases the reorganisation free energy.

Within our approach, redox properties are computed based on Marcus theory. An ensemble of configurations is generated using classical MD, but redox properties are obtained using the average and fluctuations of the vertical ionisation energy, which is computed using DFT[2]. This combines the strength of classical models, which lies in the accessibility of long time scales and thus in the statistical accuracy with which fluctuations can be evaluated, with the accuracy of the more elaborate quantum mechanical models. Indeed, DFT includes electronic relaxation and thus describes the solvent polarisation and changes in hydrogen bonding strength upon reduction. The new approach is both sufficiently general and efficient to allow e.g. for further exploration of redox properties of systems of biological interest in their native environment.

[1] VandeVondele J., Sulpizi M. and Sprik M., *Angew. Chem. Int. Ed.* **2006**, *45*, 1936.
[2] DFT calculations have been performed using the Gaussian and plane waves method (GPW) as implemented in CP2K: http://cp2k.berlios.de/