doi:10.2533/chimia.2007.427 CHIMIA **2007**, *61*, No. 7/8

Analytical Chemistry **41**

Sensor Arrays for the Analysis of Sugars in Aqueous Solution

Friederike Zaubitzer, Kay Severin

Institut des Sciences et Ingénerie Chimiques, Ecole Polytechnique Fédérale de Lausanne (EPFL), CH-1015 Lausanne, Switzerland

Fluorescence sensors for sugars have received enormous interest in recent years. Most efforts have focused on the development of sensors with a highly selectivity for a particular sugar. This is generally accomplished with the help of synthetic receptors, which display a high specificity. An interesting alternative is the utilization of a sensor array technology. In a sensor array, several non-specific sensors are combined and the analyte is then identified with pattern recognition tools. This technique has successfully been applied for different analytical problems [1], but the utilization of sensor arrays for sugars is virtually unexplored [2]. We describe a sensor array, which is based on the reversible coupling of fluorescent hydrazides with the aldehyde group of reducing sugars.

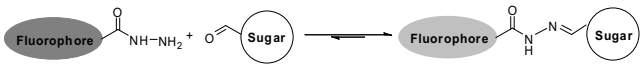


Fig.1.: Schematic representation of a fluorescence sensor for sugars

Discrimination is achieved by exploitation of differences in fluorescence emission intensities which depend on the nature of the dye-sugar derivate and the reaction equilibria in solution.

[1] K. J. Albert, N. S. Lewis, C. L. Schauer, G. A. Sotzing, S. E. Stitzel, T.P. Vaid, D. R. Walt, *Chem. Rev*. **2000**, 100, 2595.
[2] J. W. Lee, J.-S. Lee, Y.-T. Chang, *Angew. Chem. Int. Ed.* **2006**, 45, 6485.

Analytical Chemistry **42**

Investigation of *Hypericum* species by LC/MS

G. Sibailly, K. Ndjoko, A. Marston, and K. Hostettmann*

Laboratory of Pharmacognosy and Phytochemistry, School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Quai Ernest-Ansermet 30, CH-1211 Geneva 4, Switzerland

A characteristic of plant species from the genus *Hypericum* (Hypericaceae) is the presence of pigments belonging to the class of naphthodianthrones. These plants have many traditional uses and, notably, *Hypericum perforatum* is employed for the treatment of mild depression. Several studies deal with the activities of the numerous constituents of the genus or compare different *Hypericum* species [1, 2]. The genus is also reputed for cases of poisoning in cattle (hypericism) which also have their origin in the presence of these compounds. More recently, the naphthodianthrones have assumed importance for the photodynamic therapy of cancer.
In order to determine the relative contents of hypericin and pseudohypericin in these plants, extraction of several species of St.-John's wort was performed by different procedures in order to optimize the yield of the active constituents.
HPLC-UV/DAD and HPLC-MS methods were then developed for the analysis of naphthodianthrones in the plants. It was found that *Hypericum calycinum* L. does not contain this class of compounds.

[1] Fico G., Vitalini S., Colombo N., Tome F., *Hypericum perforatum* L.*, H. maculatum* Crantz.*, H. calycinum* L. *and H. pulchrum* L.*: phytochemical and morphological studies.*, **2006**, 1, 1129-1132.
[2] Ozturk Y., *Testing the andipressant effects of Hypericum species on animal models*, Pharmacopsychiatry, **1998**, 31, 37.

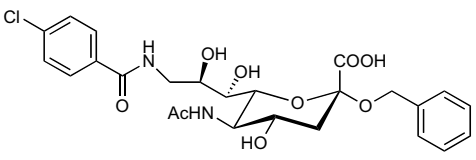
Medicinal Chemistry **43**

Thermodynamic and Kinetic Considerations of the Binding Process of MAG-Antagonists

Stefanie Mesch, Daniel Strasser, Morena Spreafico, Brian Cutting, Sachin Shelke, Oliver Schwardt, Beat Ernst

Institute of Molecular Pharmacy, University of Basel, Klingelbergstr. 50, 4050 Basel, Switzerland

The injured adult mammalian central nervous system is an inhibitory environment for axon regeneration due to specific inhibitory proteins. The myelin-associated glycoprotein (MAG) [1] was identified as one of these neurite outgrowth inhibitory proteins [2]. It belongs to the siglec family (sialic-acid binding immunoglobulin-like lectin). In earlier studies, we identified the lead structure **1** [3], which was further optimized yielding antagonists with nM affinities.



1

The kinetic and thermodynamic properties of these high affinity ligands were elucidated by Biacore studies. In addition, the binding mode was examined through STD NMR experiments and docking studies.

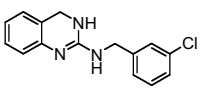
[1] Quarles, R. H., *J. Neurochem*. **2007**, *100*, 1431.
[2] Crocker, R. H., *Curr. Opin. Struct. Biol.* **2002**, *12*, 609.
[3] Shelke, S., Gao, G-P., Mesch, S., Gäthje, H., Kelm, S., Schwardt, O., Ernst, B., *Bioorg. Med. Chem*, *in press.*

Medicinal Chemistry **44**

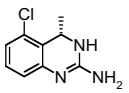
Novel guanidine-type 5-HT$_{5A}$ receptor antagonists

Jens-Uwe Peters,* Alexander Alanine, Andre Alker, Francesca Blasco, Arnulf Dorn, Alain Gast, Luca Gobbi, Sabine Kolczewski, Nicole Kratochwil, Thomas Lübbers, Pari Malherbe, Eric Prinssen, Diana Schuhbauer, Lucinda Steward

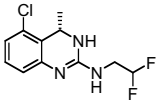
*Discovery Chemistry, F. Hoffmann-La Roche Ltd, CH-4070 Basel



1
K_i (5-HT$_{5A}$) = 160 nM
screening hit



2
K_i (5-HT$_{5A}$) = 2 nM
brain/plasma ~ 0.2



3
K_i (5-HT$_{5A}$) = 3 nM
brain/plasma ~ 4

The expression of the 5-HT$_{5A}$ receptor in the limbic brain areas suggests a potential role in the modulation of psychiatric diseases.[1] However until recently, no selective 5-HT$_{5A}$ receptor ligands were available to study its pharmacology in detail. We screened the Roche compound library to identify selective antagonists for this target, and found several guanidines such as **1** among the most selective compounds. A systematic exploration of small substituents (Cl, Me, MeO, F) around the core structure led to **2** with potent 5-HT$_{5A}$ antagonistic affinity *in vitro*, and improved selectivity, apart from 5-HT$_7$. Compound **2** had good PK properties, however a low brain-plasma ratio. The brain penetration was improved by the introduction of electron-withdrawing substituents, which afforded a compound with increased lipophilicity, and reduced basicity, **3**. The series refinement and structure activity relationship elucidated in progressing from the initial hit **1** to lead compound **3** will be further described in the presentation.

[1] Thomas, D. R. *Pharmacol. Ther.* **2006**, *111*(3), 707-714.

doi:10.2533/chimia.2007.427 CHIMIA **2007**, *61*, No. 7/8

Analytical Chemistry **41**

Sensor Arrays for the Analysis of Sugars in Aqueous Solution

Friederike Zaubitzer, Kay Severin

Institut des Sciences et Ingénerie Chimiques, Ecole Polytechnique Fédérale de Lausanne (EPFL), CH-1015 Lausanne, Switzerland

Fluorescence sensors for sugars have received enormous interest in recent years. Most efforts have focused on the development of sensors with a highly selectivity for a particular sugar. This is generally accomplished with the help of synthetic receptors, which display a high specificity. An interesting alternative is the utilization of a sensor array technology. In a sensor array, several non-specific sensors are combined and the analyte is then identified with pattern recognition tools. This technique has successfully been applied for different analytical problems [1], but the utilization of sensor arrays for sugars is virtually unexplored [2]. We describe a sensor array, which is based on the reversible coupling of fluorescent hydrazides with the aldehyde group of reducing sugars.

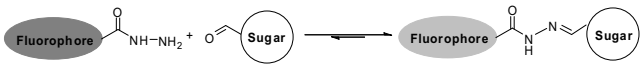


Fig.1.: Schematic representation of a fluorescence sensor for sugars

Discrimination is achieved by exploitation of differences in fluorescence emission intensities which depend on the nature of the dye-sugar derivate and the reaction equilibria in solution.

[1] K. J. Albert, N. S. Lewis, C. L. Schauer, G. A. Sotzing, S. E. Stitzel, T.P. Vaid, D. R. Walt, *Chem. Rev*. **2000**, 100, 2595.
[2] J. W. Lee, J.-S. Lee, Y.-T. Chang, *Angew. Chem. Int. Ed.* **2006**, 45, 6485.

Analytical Chemistry **42**

Investigation of *Hypericum* species by LC/MS

G. Sibailly, K. Ndjoko, A. Marston, and K. Hostettmann*

Laboratory of Pharmacognosy and Phytochemistry, School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Quai Ernest-Ansermet 30, CH-1211 Geneva 4, Switzerland

A characteristic of plant species from the genus *Hypericum* (Hypericaceae) is the presence of pigments belonging to the class of naphthodianthrones. These plants have many traditional uses and, notably, *Hypericum perforatum* is employed for the treatment of mild depression. Several studies deal with the activities of the numerous constituents of the genus or compare different *Hypericum* species [1, 2]. The genus is also reputed for cases of poisoning in cattle (hypericism) which also have their origin in the presence of these compounds. More recently, the naphthodianthrones have assumed importance for the photodynamic therapy of cancer.
In order to determine the relative contents of hypericin and pseudohypericin in these plants, extraction of several species of St.-John's wort was performed by different procedures in order to optimize the yield of the active constituents.
HPLC-UV/DAD and HPLC-MS methods were then developed for the analysis of naphthodianthrones in the plants. It was found that *Hypericum calycinum* L. does not contain this class of compounds.

[1] Fico G., Vitalini S., Colombo N., Tome F., *Hypericum perforatum* L.*, H. maculatum* Crantz.*, H. calycinum* L. *and H. pulchrum* L.*: phytochemical and morphological studies.*, **2006**, 1, 1129-1132.
[2] Ozturk Y., *Testing the andipressant effects of Hypericum species on animal models*, Pharmacopsychiatry, **1998**, 31, 37.

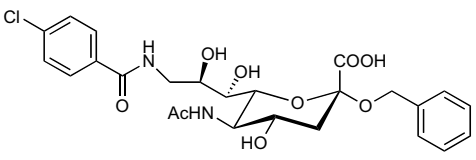
Medicinal Chemistry **43**

Thermodynamic and Kinetic Considerations of the Binding Process of MAG-Antagonists

Stefanie Mesch, Daniel Strasser, Morena Spreafico, Brian Cutting, Sachin Shelke, Oliver Schwardt, Beat Ernst

Institute of Molecular Pharmacy, University of Basel, Klingelbergstr. 50, 4050 Basel, Switzerland

The injured adult mammalian central nervous system is an inhibitory environment for axon regeneration due to specific inhibitory proteins. The myelin-associated glycoprotein (MAG) [1] was identified as one of these neurite outgrowth inhibitory proteins [2]. It belongs to the siglec family (sialic-acid binding immunoglobulin-like lectin). In earlier studies, we identified the lead structure **1** [3], which was further optimized yielding antagonists with nM affinities.



1

The kinetic and thermodynamic properties of these high affinity ligands were elucidated by Biacore studies. In addition, the binding mode was examined through STD NMR experiments and docking studies.

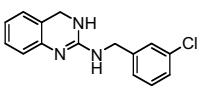
[1] Quarles, R. H., *J. Neurochem*. **2007**, *100*, 1431.
[2] Crocker, R. H., *Curr. Opin. Struct. Biol.* **2002**, *12*, 609.
[3] Shelke, S., Gao, G-P., Mesch, S., Gäthje, H., Kelm, S., Schwardt, O., Ernst, B., *Bioorg. Med. Chem*, *in press.*

Medicinal Chemistry **44**

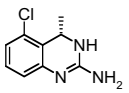
Novel guanidine-type 5-HT$_{5A}$ receptor antagonists

Jens-Uwe Peters,* Alexander Alanine, Andre Alker, Francesca Blasco, Arnulf Dorn, Alain Gast, Luca Gobbi, Sabine Kolczewski, Nicole Kratochwil, Thomas Lübbers, Pari Malherbe, Eric Prinssen, Diana Schuhbauer, Lucinda Steward

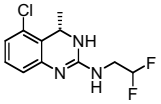
*Discovery Chemistry, F. Hoffmann-La Roche Ltd, CH-4070 Basel



1
K_i (5-HT$_{5A}$) = 160 nM
screening hit



2
K_i (5-HT$_{5A}$) = 2 nM
brain/plasma ~ 0.2



3
K_i (5-HT$_{5A}$) = 3 nM
brain/plasma ~ 4

The expression of the 5-HT$_{5A}$ receptor in the limbic brain areas suggests a potential role in the modulation of psychiatric diseases.[1] However until recently, no selective 5-HT$_{5A}$ receptor ligands were available to study its pharmacology in detail. We screened the Roche compound library to identify selective antagonists for this target, and found several guanidines such as **1** among the most selective compounds. A systematic exploration of small substituents (Cl, Me, MeO, F) around the core structure led to **2** with potent 5-HT$_{5A}$ antagonistic affinity *in vitro*, and improved selectivity, apart from 5-HT$_7$. Compound **2** had good PK properties, however a low brain-plasma ratio. The brain penetration was improved by the introduction of electron-withdrawing substituents, which afforded a compound with increased lipophilicity, and reduced basicity, **3**. The series refinement and structure activity relationship elucidated in progressing from the initial hit **1** to lead compound **3** will be further described in the presentation.

[1] Thomas, D. R. *Pharmacol. Ther.* **2006**, *111*(3), 707-714.

Medicinal Chemistry **45**

Identification of Novel Multi-functional Compounds for the Treatment of some Aging Related Neurodegenerative Diseases

Juan Bravo, Saviana Di Giovanni, Delphine Cressend, Francesca Bertolini; Laura Novaroli, Antoine Daina, Marianne Reist, Pierre-Alain Carrupt

Unité de Pharmacochimie, Section des sciences pharmaceutiques, Université de Genève, Université de Lausanne, Quai Ernest-Ansermet 30, CH-1211 Genève 4, Suisse

Aging related neurodegenerative disorders such as Parkinson disease (PD) and Alzheimer's disease (AD) are the result of multiple pathophysiological pathways that contribute to the neurodegenerative cascade. Hence, multi-functional drug candidates able to interact with several targets are of great interest for the treatment of such diseases. Therefore, an experimental and virtual screening pathway to generate multi-functional hits promising for the treatment of PD or AD was suggested [1].

Among the numerous potential targets, five were selected; two are common to both diseases, namely monoamine oxidase B (MAO B) and oxidative stress, and three are specific for only one of the two disorders, catechol-O-methyltransferase (COMT) for PD and acetylcholinesterase (AChE) as well as β-amyloid deposition for AD, respectively.

Suitable experimental and virtual screening methods to rapidly test pre-focused compound libraries were developed and validated. The proposed rational screening strategy was applied to a library of natural compounds and some focused synthetic libraries, leading to some interesting multi-functional hits. Refined molecular modelling approaches were also used to identify their binding modes and to suggest some guidelines for the pharmacomodulation of retained hits in order to obtain multifunctional virtual lead compounds.

[1] L. Novaroli et al, *Chimia*. **2005**, *59*, 315-320.

Medicinal Chemistry **46**

Medicinal chemistry efforts towards the identification and development of inhibitors of phosphatidylinositol 3-kinases (PI3Ks) and related protein kinases for cancer treatment.

Frédéric Stauffer, Carlos Garcia-Echeverria, Pascal Furet, Hans-Georg Capraro, Philipp Holzer, Christian Schnell, Christine M. Fritsch & Michel Maira.

Novartis Institutes for BioMedical Research, Klybeckstrasse 141, 4057 Basel, Switzerland.

Constitutive activation of the PI3K-pathway seems to be a prerequisite for a wide spectrum of cancers, either by loss / mutations of PTEN, acquisition of activating mutations in the PI3K catalytic subunit, or amplification / overexpression of receptor tyrosine kinases upstream of PI3K. In this respect, components of the PI3K/PKB/mTor pathway such as members of the class I PI3Ks represent well validated therapeutic targets for the discovery and development of new anticancer drugs. Although they have sub-optimal pharmaceutical properties, PI3K inhibitors like the fungal metabolite wortmannin and the morpholino derivative LY294002 have shown that this class of lipid kinases is "drug-able". Inactivators of the TORC1 complex -mTor/Raptor-, such as the rapamicine derivative RAD001, have shown anticancer activity in clinical trials. In addition to TORC1, the TORC2 complex -mTor/Rictor- has recently been linked to PKB phosphorylation and activation.[1]

Our medicinal chemistry efforts using the privilege kinase inhibitor scaffold imidazo[4,5-c]quinoline to identify and optimize new inhibitors of the PI3K/PKB/mTor-pathway will be disclosed. From this chemotype, a clinical candidate has been selected. This inhibitor, which has suitable pharmacological properties for clinical development, shows an efficient control of the PI3K-pathway in tumor cells by inhibiting the phosphorylation and activation of PKB in cellular and *in vivo* settings.

[1] Sarbassov, D. D.; Guertin, D. A.,; Ali, S. M.; Sabatini, D. M.; *Science* **2005**, *307*, 1098.

Medicinal Chemistry **47**

Receptor-Mediated Targeting of Metastatic Melanoma with Radiolabeled DOTA-α-MSH Analogs

Jean-Philippe Bapst, Martine Calame-Christe, Heidi Tanner and Alex N. Eberle

University Hospital Basel, Department of Research, Hebelstrasse 20, CH-4031 Basel, Switzerland

Melanotic and amelanotic melanomas express receptors for α-melanocyte-stimulating hormone (α-MSH; receptor name: MC1R). Radiolabeled α-MSH analogs are potential candidates for receptor-mediated melanoma targeting (diagnosis and therapy). Several short α-MSH peptides were designed and tested in the past, which showed high affinity for the MC1R *in vitro*, as well as a good incorporation in tumor xenografts *in vivo*, but also considerable uptake by the kidneys.

We now investigate glycosylated analogs of [Nle^4, Asp^5, D-Phe^7]-α-MSH$_{4-11}$ (NAPamide) [1], as glycosylation had been shown to improve tumor-to-kidney ratios in the case of somatostatin. Carbohydrate moieties such as glucose, galactose and maltotriose were introduced at various positions on the MSH peptide carrying the metal chelator DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) for labeling with ^{111}In. The peptides were evaluated *in vitro* for MC1R binding and cellular localization, and *in vivo* for tissue distribution. The tumor-to-kidney ratio for Gal-NAPamide (1.85), bearing an N-terminal galactose moiety, was comparable with that of NAPamide (1.92). Other glycopeptides showed very good binding affinities but lower selectivity *in vivo*.

Additionally, a class of non-glycosylated dimeric derivatives, bearing one or two moieties of the chelator complex, was developed and is currently being tested.

[1] Froidevaux S, Calame-Christe M, Tanner H, Sumanovski L, Eberle AN. *J Nucl Med*. **2002**, *43*, 1699

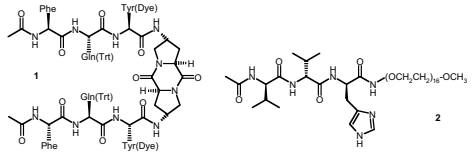
Medicinal Chemistry **48**

Vesicle Formation in Aqueous Solution Driven by Selective Non-Covalent Interactions

Jessica Grun[a], Corinne Vebert*[b], Matteo Conza[a], Wolfgang Meier[b], Helma Wennemers*[a]

[a]Organic Chemistry, University of Basel, St. Johanns-Ring 19, CH-4056 Basel, Switzerland
[b]Physical Chemistry, University of Basel, Kingelbergstr. 80, CH-4056 Basel, Switzerland

The Wennemers group has recently developed two-armed diketopiperazine receptors that bind peptides with high binding selectivities and affinities.[1] The highly selective intermolecular interaction between the diketopiperazine receptor **1** and the peptide, Ac-D-Val-D-Val-D-His-resin, was used to induce supramolecular assemblies by functionalizing the peptide with a PEG-chain. In chloroform, diketopiperazine receptor **1** mixed with the peptide-PEG conjugate **2** [2], forms a gel. In aqueous solution, the formation of vesicles was observed and studied using dynamic light scattering (DLS), transmission electron (TEM) and atomic force microscopy (AFM), surface pressure measurements, as well as, NMR titration.



This work is the first example of vesicle formation based on selective non-covalent interactions. We envision this concept to be of interest for encapsulation and drug delivery.

[1] (a) H. Wennemers, M. Conza, M. Nold, P. Krattiger, *Chem. Eur. J.* **2001**, *7*, 3342; (b) M. Conza, H. Wennemers, *J. Org. Chem*. **2002**, *67*, 2696; (c) M. Conza, H. Wennemers, *Chem. Commun*. **2003**, 866; (d) P. Krattiger, H. Wennemers, *Synlett* **2005**, *4*, 706.
[2] J. Grun, J. D. Revell, M. Conza, H. Wennemers, *Bioorg. Med. Chem*. **2006**, *14*, 6197.

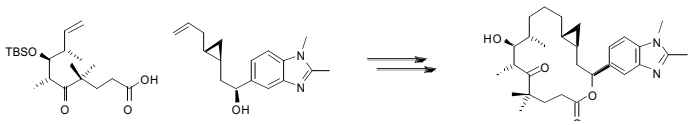
Medicinal Chemistry **49**

Hypermodified Epothilone Analogs as New Lead Structures for Anti-Cancer Drug Discovery

Christian Kuzniewski, Karl-Heinz Altmann

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

Epothilones are microtubule-stabilizing agents with potent *in vitro* and *in vivo* antitumor activity. Although the SAR of this highly promising compound class has been extensively investigated, specific aspects still remain unaddressed[1]. Benzimidazole-based analogs of epothilones exhibit enhanced antiproliferative activity against drug-sensitive cancer cells; however they also show increased susceptibility to P-gp170-mediated drug efflux[1,2]. In contrast, the corresponding cyclopropane analogs are poor substrates for P-gp-mediated drug efflux[3]. The major objective of this project is the development of an efficient synthesis for epothilone analogues of type **1**, that allow for the combined exploitation of the potent biological activity of the 3-deoxy *trans*-epothilone A scaffold and an activity-enhancing dimethylbenzimidazole side chain. To circumvent drug efflux, the epoxide moiety is replaced by an isosteric cyclopropane ring. These structural changes lead to hypermodified analogues with little structural resemblance to the original epothilone scaffold. The synthesis of **1** is based on the assembly of fragments **2** and **3** *via* an esterification/ring-closing-metathesis sequence. The preparation of these building blocks and their elaboration into target structure **1** will be described in detail.



[1] F. Cachoux *et al.*, *Angew. Chem. Int. Ed.* **2005**, *44*, 7469.
[2] F. Cachoux *et al.*, *ChemBioChem* **2006**, *7*, 54.
[3] K. C. Nicolaou *et al.*, *J. Am. Chem. Soc.* **2001**, *123*, 9313.

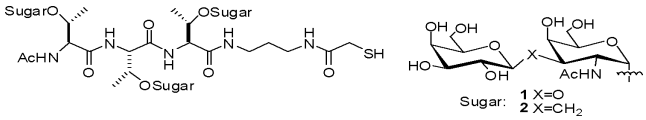
Medicinal Chemistry **50**

Synthesis of a C-linked Disaccharide Analogue of the Thomsen-Friedenreich (TF)-Epitope and Formation of a Clustery form as a Potential Anticancer Vaccine

Loay Awad, and Pierre Vogel*

LGSA, BCH, EPFL, CH-1015 Lausanne, Switzerland

The Thomsen-Friedenreich antigen (T antigen) is a cancer-associated disaccharide which plays an important role in tumor cell-cell recognition. The immunodominant part of the T antigen consists of the disaccharide Galβ1→3GalNAcα→O linked to serine or threonine. The great potential of clustered antigen motifs such as **1** for antitumor vaccines has been demonstrated. [1]



C-linked disaccharide analogues offer stability towards hydrolysis which is catalysed by ubiquitous glycosidases. We wish to present here the extension of our previous efforts [2] towards the synthesis of C-disaccharide analogues of the T antigen based on a Baylis-Hillman type of condensation between a D-galactose-derived aldehyde and isolevoglucosenone. [3-4]

[1] S. D. Kuduk, J. B. Schwarz, X.-T. Chen, P. W. Glunz, D. Sames, G. Ragupathi, P. O. Livingston, S. J. Danishefsky, *J. Am. Chem. Soc.* **1998**, *120*, 12474.
[2] Y.-H. Zhu, P. Vogel, *Synlett* **2001**, 79.
[3] Y.-H. Zhu, P. Vogel, *Tetrahedron Lett.* **1998**, *39*, 31; Y.-H. Zhu, R. Demange, P. Vogel, *Tetrahedron: Asymmetry* **2000**, *11*, 263;

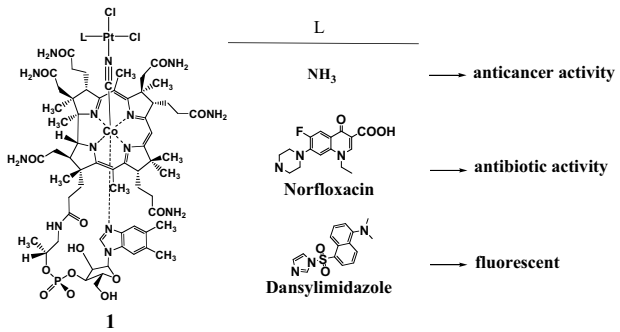
Medicinal Chemistry **51**

Vitamin B_{12} as a "trojan-horse" in therapy

Pilar Ruiz-Sánchez, Bernhard Spingler, Roger Alberto

University of Zürich, Winterthurerstr. 190, CH-8057 Zürich, Switzerland

We have synthesized and characterized a series of Pt(II) complexes containing vitamin B_{12} as a ligand.[1] The precursors $[PtCl_3L]^-$ {L=NH_3, antibiotics (norfloxacin, ciprofloxacin) or fluorescent markers (dansylimidazole, dansyl-L-lysine…)}, react with the cyanide of vitamin B_{12} to form the {Co-C≡N-Pt} conjugates, with a behaviour similar to that of cisplatin (example: compound **1**).
Enzymatic corrinoid adenosylation assays[2] of these adducts showed recognition and conversion to adenosylcobalamin and release of Pt(II) species.
These novel derivatives can be used for specific targeting of cancer cells or bacterial infections, since fast proliferation cells are high B_{12} consumers. Preliminary bacterial and cancer cell uptake studies will be discussed.



[1] Mundwiler, S.; Spingler, B.; Kurz, P.; Kunze, S.; Alberto, R. *Angew. Chem. Int. Edit.* **2005**, *11*, 4089.
[2] Fonseca, M.V.; Escalante-Semerena, J.C. *J. Biol. Chem.* **2001**, *276*, 32101.

Medicinal Chemistry **52**

From ASA to SAM: Introducing the PAMPA diagnostic mode

Frank Senner

F. Hoffmann-La Roche Ltd., Grenzacherstrasse, 4070 Basel, Switzerland

PAMPA is a 1st line permeability screen for pharmaceutical drugs [1-7]. When introduced first in 1998 it has been used to predict oral absorption in humans. Later on its application area has been extended to blood brain barrier (BBB) penetration and even skin permeation [8].
Nowadays a shift from "All Screen All (ASA)" to "Selected Assays and Molecules (SAM)" is becoming more and more important in order to support faster decision making in early drug development (LI, LO, CLS).
PAMPA diagnostic mode is such an example for "SAM". By applying a donor pH profile and acceptor sink conditions (blood pH 7.4, protein binding effects) low permeable and low soluble molecules are characterized in detail. Further extensions are possible. The keywords are: excipient screening and reduction of sample consumption (DiFi plates).

[1] Kansy, Manfred; Senner, Frank; Gubernator, Klaus, J. of Med. Chem. **1998**, 41(7), 1007.
[2] Avdeef, Alex, Cur. Top. in Med. Chem. **2001**, 1(4), 277.
[3] Wohnsland, Frank; Faller, Bernard, J. of Med. Chem. **2001**, 44(6), 923.
[4] Sugano Kiyohiko; Nabuchi Yoshiaki; Machida Minoru; Aso Yoshinori, Int. J. of Pharm. **2003**, 257(1-2), 245.
[5] Kansy, Manfred; Avdeef, Alex; Fischer, Holger, Drug Disc. Today: Tech. **2004**, 1(4), 349.
[6] Avdeef, Alex, Exp. Op. on Drug Met. & Tox. **2005**, 1(2), 325.
[7] Bendels, Stefanie; Tsinman, Oksana; Wagner, Bjoern; Lipp, Dana; Parrilla, Isabelle; Kansy, Manfred; Avdeef, Alex, Pharm. Res. **2006**, 23(11), 2525.
[8] Ottaviani, Giorgio; Martel, Sophie; Carrupt, Pierre-Alain, J. of Med. Chem. **2006**, 49(13), 3948.

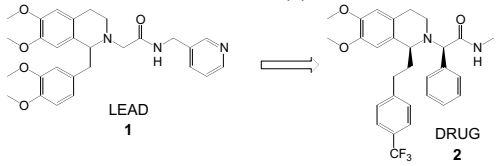
Medicinal Chemistry **53**

Orexin Receptor Antagonists: A New Therapeutic Principle in Neurology and Psychiatry?

Hamed Aissaoui, Christoph Boss, Thierry Sifferlen, Markus Gude, Thomas Weller, Catherine Brisbare-Roch, François Jenck, John Gatfield, Roberto Bravo, Ralf Koberstein

Drug Discovery, Actelion Pharmaceuticals Ltd., Gewerbestrasse 16, 4123 Allschwil, Switzerland

Orexins are hypothalamic peptides that play an important role in maintaining wakefulness in mammals. Permanent deficit in orexinergic function is a pathophysiological hallmark of rodent, canine and human narcolepsy. Here we report that in rats, somnolence without cataplexy is induced by pharmacological blockade of both orexin OX_1 and OX_2 receptors. We describe the medicinal chemistry efforts that led from the initial lead structure (**1**) to the clinical candidate ACT-078573 (**2**).



The specific challenge in this project was to find a compound, which crosses the blood-brain-barrier (BBB) in order to interact with the orexin receptors in the brain. It also needed to be devoid of cytochrome inhibition and to exhibit appropriate pharmacokinetic properties. Objective is to improve next-day performance that is often impaired with other insomnia drugs. The results found during preclinical and clinical investigations open new perspectives for studying the role of endogenous orexins in sleep-wake regulation.

[1] Catherine Brisbare-Roch et al, *Nature Medicine* **2007**, *13*, 150-155.
[2] Ralf Koberstein et al, *Chimia* **2003**, *57*, 270.

Medicinal Chemistry **54**

Efficient ligand affinity calculations using novel computational methods

Holmfridur B. Thorsteinsdottir, Michael Podvinec, Torsten Schwede, Markus Meuwly

University of Basel, Klingelbergstrasse 50/70, CH-4056 Basel, Switzerland

In recent years virtual screening tools are becoming increasingly important for the drug discovery process. However, the scoring functions many of these methods use are often found to be lacking in accuracy. Previously a MM-GBSA method to calculate binding free energies has been validated using the well characterized HIV-1 protease and 16 known ligands as a test system [1]. We would like to extend this method to improve poses generated from virtual screening methods by molecular dynamics simulations and use MM-GBSA as a more advanced scoring technique to obtain better ranking of ligands.

One of the main obstacles in the routine application of molecular dynamics simulations in large-scale virtual screening projects is the calculation time that is required. GRID computing is a possible solution to this problem, but molecular simulations are not well adapted to the parallelization required for calculations on a GRID. This work aims to develop a method for parallelization and show that parallelized molecular dynamics is able to reproduce binding free energies in a comparable way to classical molecular dynamics simulations and can therefore be applied to virtual screening projects.

[1] HB. Thorsteinsdottir, T. Schwede, V. Zoete, M. Meuwly, *Proteins.* **2006**, 65, 407

Medicinal Chemistry **55**

Ruthenium(II) η^6-Arene Imidazole Complexes: A New Promising Class of Organometallic Compounds in Anticancer Therapy

Carsten A. Vock† and Paul J. Dyson†

† Institut des Sciences et Ingénierie Chimiques, Ecole Polytechnique Fédérale de Lausanne (EPFL), CH-1015 Lausanne, Switzerland

During the last decade, ruthenium-based anticancer drugs have become an important field of research in organometallic chemistry. Ruthenium(III) complexes like NAMI-A[1] or KP1019[2] have shown promising antimetastatic activity and have successfully completed phase I clinical trials. Although imidazole ligands are frequently used with ruthenium(III) drugs, only a few examples of ruthenium(II) η^6-arene imidazole complexes are known, and none of them has been biologically evaluated so far.

Therefore, with the intention to combine aspects of both ruthenium(III) and ruthenium(II) η^6-arene anticancer drugs, our research has focussed on the synthesis, characterisation and biological evaluation of ruthenium(II) η^6-arene imidazole complexes.[3] Furthermore, the "imidazole strategy" has been used to attach bioactive organic ligands to ruthenium(II) η^6-arene fragments in order to obtain new and more powerful drugs.[4] The presentation will give a summary of our research in this field.

[1] J. M. Rademaker-Lakhai, D. van den Bongard, D. Pluim, J. H. Beijnen, J. H. Schellens, *Clin. Cancer Res.* **2004**, *10*, 3717–3727.
[2] M. A. Jakupec, V. B. Arion, S. Kapitza, E. Reisner, A. Eichinger, M. Pongratz, B. Marian, N. Graf von Keyserlingk, B. K. Keppler, *Int. J. Clin. Pharm. Ther.* **2005**, *43*, 595–596.
[3] C. A. Vock, C. Scolaro, A. D. Phillips, R. Scopelliti, G. Sava, P. J. Dyson, *J. Med. Chem.* **2006**, *49*, 5552–5561.
[4] C. A. Vock, W. H. Ang, C. Scolaro, A. D. Phillips, L. Lagopoulos, G. Sava, L. Juillerat-Jeanneret, P. J. Dyson, *J. Med. Chem.*, ASAP.

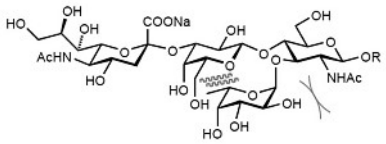
Medicinal Chemistry **56**

The Preorganization of the Trisaccharide Core of Sialyl Lewis^x Is Essential for Binding to E-selectin

Alexander Titz, Beatrice Wagner, Beat Ernst

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

The selectins play a key role in the inflammatory process. Since the physiological ligands of the selectins all contain the tetrasaccharide epitope sialyl Lewis^x (sLe^x), this epitope served as lead structure in the search for E-selectin antagonists. It has been shown that the preorganization of the core in the bioactive conformation [1] contributes substantially to the affinity of E-selectin antagonists [2].
In addition to the exoanomeric effects, there are two factors that stabilize the core conformation of sLe^x: (i) by steric compression with sterically demanding substituents of the Glc*N*Ac moiety and (ii) by lipophilic interaction between the alpha-face of fucose with the beta-face of galactose.



Stabilizing interactions of the bioactive conformation of sLe^x

In order to verify the above considerations, a series of E-selectin antagonists were synthesized and biologically evaluated.

[1] Scheffler, L.; Ernst, B. *et al. Angew. Chem. Int. Ed.* **1995**, *34*, 1841. Rinnbauer, M.; Ernst, B. *et al. Glycobiology* **2003**, *13*, 435.
[2] Kolb, H. C.; Ernst, B. *Chem. Eur. J.* **1997**, *3*, 1571. Thoma, G. *et al. Angew. Chem. Int. Ed.* **2001**, *40*, 1941.

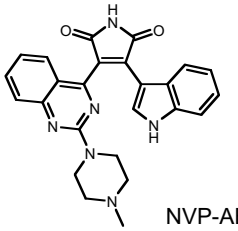
Medicinal Chemistry **57**

NVP-AEB071: Oral and Specific Inhibitor of T cell Activation for the Prevention of Graft Rejection and the Treatment of Autoimmune Diseases

Rainer Albert, Marc Bigaud, Nigel Cooke, Sylvain Cottens, Jean-Pierre Evenou, Randall Morris, Charles Pally, Richard Sedrani, Walter Schuler, Maurice van Eis, Jürgen Wagner, Gerhard Zenke, Peter von Matt

ATDA and Global Discovery Chemistry, Novartis Institutes for BioMedical Research, Postfach, 4002 Basel, Switzerland

Immunosuppressants with an improved therapeutic window represent a high medical need. The search for novel approaches to block T-cell activation led to NVP-AEB071, a selective and potent inhibitor of classical and novel protein kinase C (PKC) isoforms with K_i values in the low nM range.



NVP-AEB071

T-cell activation is effectively blocked as determined by inhibition of IL-2 production (IC_{50} ~ 5 nM). In contrast, IL-2-dependent T cell proliferation is not affected. NVP-AEB071 dose-dependently prolongs Brown-Norway heart grafts in Lewis rats with all animals reaching 28 days without clinical adverse events at an oral dose of 30 mg/kg bid.

This lecture describes the medicinal chemistry program that led to NVP-AEB071 and highlights its effectiveness as a novel immunosuppressant in animal models of transplantation and its tolerability in a Ph I clinical trial.

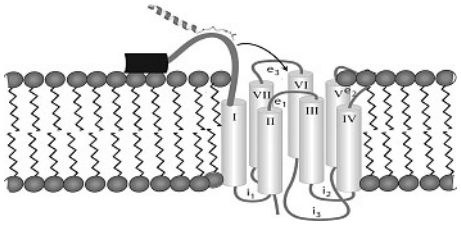
Medicinal Chemistry **58**

Structural and Functional Studies of the N-terminal domain of the Y4 GPCR

Chao Zou, Stefan Markovic, Reto Walser, Oliver Zerbe*

Institute of Organic Chemistry, 8057 Zurich, Switzerland

G-protein coupled receptors (GPCRs) comprises 2% of the human genome, and almost one third of the drugs on the market target GPCRs. Neuropeptide Y (NPY) receptors (Y receptors) are important in the regulation of blood pressure, memory retention and food intake[1]. In human organisms functional Y1, Y2, Y4 and Y5 subtypes have been identified. While NPY and PYY target all subtypes with nanomolar affinities, the pancreatic peptide (PP) preferentially binds to the Y4 receptor. We have proposed that peptides from the NPY family associate with the membrane prior to binding to the receptor[2]. Herein, we have structurally characterized the N-terminal extracellular domain of the Y4 (N-Y4) receptor and determined whether the hormones bind to the isolated domain:



N-Y4 was produced both by solid phase peptide synthesis and recombinant techniques in ^{15}N-labeled in *E.coli*. We compared the structure of N-Y4 in solution in the presence and absence of phospholid micelles by NMR. Binding affinities of peptides from the NPY family to N-Y4 have been measured by SPR and mutagenesis experiments revealed the interaction sites.

[1] Grundemar, L., and Bloom, S. R. (eds). *Neuropeptide Y and drug development*, **1997**, Academic Press.
[2] Bader, R., Zerbe, O. *ChemBioChem,* **2005**, 6, 1520-1534.

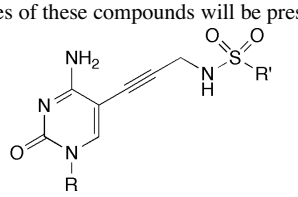
Medicinal Chemistry **59**

Non-phosphate inhibitors of IspE, a kinase in the non-mevalonate pathway and a potential target for antimalarial therapy

Anna K. H. Hirsch, S. Lauw, P. Gersbach, W. Bernd Schweizer, F. Rohdich, W. Eisenreich, A. Bacher, F. Diederich

Laboratorium für Organische Chemie, ETH Zurich, 8093 Zurich, Switzerland

Malaria remains the most important and devastating tropical disease known with 300-500 million clinical cases and around one million deaths a year. The emergence of drug and insecticide resistance the need for medicines with a novel mode of action has become increasingly important.
Plasmodium parasites, the causative agents of malaria, use the non-mevalonate pathway for the biosynthesis of the common isoprenoid precursors, which is distinct from that used by humans. Hence, the enzymes of this pathway are ideal targets in the fight against this important infectious disease [1].
The kinase IspE, at the center of the non-mevalonate pathway, was chosen as the target of a structure-based drug design project leading to potent competitive inhibitors with K_i values in the nanomolar range [2]. The syntheses and biological activities of these compounds will be presented.



[1] H. Jomaa *et al.*, *Science* **1999**, *285*, 1573.
[2] A. K. H. Hirsch, S. Lauw, P. Gersbach, W. B. Schweizer, F. Rohdich, W. Eisenreich, A. Bacher, F. Diederich, *ChemMedChem* **2007**, DOI: 10.1002/cmdc.200700014

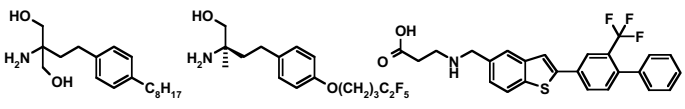
Medicinal Chemistry **60**

The Role of Sphingosine-1-Phosphate Receptor Modulators in the Prevention of Transplant Rejection and Autoimmunity

R. Albert, C. Beerli, M. Bigaud, V. Brinkmann, C. Bruns, N. Cooke, N. Gray, D. Guerini, K. Hinterding, B. Nüsslein-Hildesheim, C. Pally, S. Pan, C. Spanka, M Streiff, F. Zécri

Novartis Institutes for BioMedical Research,
Autoimmune Disease & Transplantation, CH-4002 Basel, Switzerland

FTY720 is a novel immunomodulator which is highly effective in animal models of organ transplantation and autoimmunity. Phase III clinical trials for *de novo* kidney transplantation were recently discontinued, while ***FTY720*** successfully completed Phase II clinical trials for relapsing-remitting multiple sclerosis and recently entered Phase III for this indication. FTY720-phosphate, the active metabolite generated upon *in vivo* phosphorylation, acts as a potent agonist on 4 of the 5 known sphingosine-1-phosphate (S1P) receptors.



FTY720 NIBR713 AUY954

NIBR713, shows selectivity over the S1P3 receptor while retaining its ability to reduce peripheral lymphocyte counts both in rats and monkeys after p.o. application. ***AUY954***, is a monoselective S1P1 agonist with nanomolar potency and good pharmacokinetic properties both in rats and monkeys inducing a profound and reversible reduction of lymphocyte counts and prolonged survival of cardiac allografts in rats. This demonstrates that targeting S1P1 is sufficient to achieve immunomodulation *in vivo*.

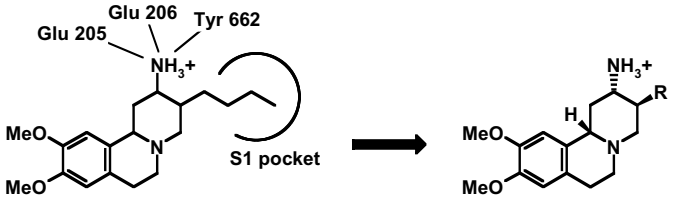
Medicinal Chemistry **61**

Structure-guided Optimization of Aminobenzoquinolizines Towards Low Nanomolar DPP-IV Inhibitors

Markus Böhringer, Holger Fischer, Luca Gobbi, Michael Hennig, Jörg Huwyler, Bernd Kuhn, Bernd Löffler, Thomas Lübbers, Patrizio Mattei, Robert Narquizian, Jörgen Nielsen, Hans Peter Wessel, Pierre Wyss

F. Hoffmann-La Roche Ltd., Pharmaceuticals Division, Preclinical Research PRBD, CH-4070 Basel, Switzerland

The serine protease dipeptidyl peptidase IV (DPP-IV) is a clinically validated target for the treatment of type II diabetes and has received great interest from the pharmaceutical industry over the last years [1]. Concomitant with a large variety of published small molecule DPP-IV inhibitors a considerable number of co-crystal structures have been solved providing a solid basis for the understanding of molecular recognition in this enzyme.



1 **2**

We describe our multidisciplinary approach to optimize the aminobenzoquinolizine HTS hit **1** to potent DPP-IV inhibitors of the general structure **2** (R = aryl, heteroaryl, 2-oxopyrrolidin-1-yl). The focus of this presentation is placed in the analysis of the central molecular interactions and their exploitation by structure-based design methods.

[1] D. Hunziker, M. Hennig, J.-U. Peters, *Curr. Top. Med. Chem.* **2005**, *5*, 1623-1637

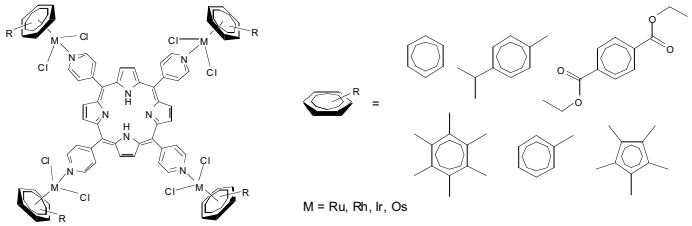
Medicinal Chemistry **62**

Ruthenium-Porphyrin Compounds for Photodynamic Cancer Therapy

Bruno Therrien

Institut de Chimie, Université de Neuchâtel, Case Postale 158, CH-2009 Neuchâtel, Switzerland.

Porphyrin derivatives are known to concentrate in cancer cells and they are used as photosensitising agents in the photochemotherapy of cancer. Ruthenium possesses several favourable properties suited to rational anticancer drug design. It is thought that ruthenium complexes reduce tumour growth by a mechanism of interaction with DNA although non-genomic targets also appear to be important. Therefore, we were interested in coordinating arene-ruthenium units to porphyrin moiety to combine the photodynamic action of porphyrin with the cytotoxicity of arene-ruthenium complexes. A series of organo-ruthenium modified porphyrin compounds has been prepared and the *in vitro* tumour cell growth inhibition effects assessed.



They show a strong photodynamic activity on melanomas after exposure to light. In particular, two of the eight complexes were only slightly cytotoxic towards two metastatic cancer cell lines, unless exposed to light. These complexes offer a considerable potential in terms of future drug and irradiation level optimisation [1].

[1] B. Therrien, P. Govindaswamy, G. Süss-Fink, W. H. Ang, P. J. Dyson, F. Schmitt, L. Juillerat-Jeanneret, submitted.

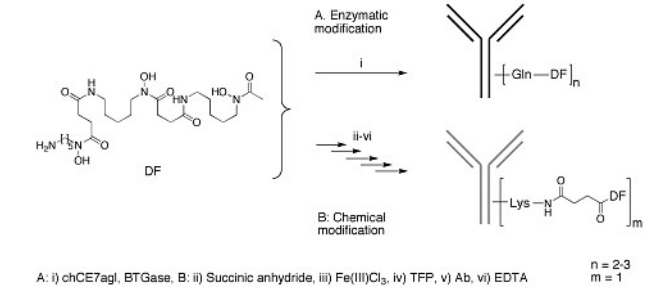
Medicinal Chemistry **63**

Enzymatic Functionalization and Radiolabeling of a Tumor Affine Monoclonal Antibody Using Transglutaminase

Simone Jeger[1,2], Alexander Hohn[2], Jürgen Grünberg[2] and Roger Schibli[1,2]

[1]Department of Chemistry and Applied Biosciences, ETHZ, 8093 Zurich, Switzerland. [2]Center for Radiopharmaceutical Science ETH-PSI-USZ, PSI, 5232 Villigen, Switzerland

Antibodies (mAb) functionalized with the chelator deferoxamine (DF) and radiolabeled with ^{89}Zr showed promising clinical results [1]. However, the five-step coupling of DF to the lysine (Lys) side chains of the mAb by chemical methods is laborious (see Figure, route B).
Using the enzymatic activity of bacterial transglutaminase (BTGase) we were able to link the primary pentyl amino residue of unmodified DF to glutamine (Gln) side chains of the tumor affine mAb chCE7agl, via formation of isopeptide bonds under physiological conditions in a single step (route A). The ligand-to-protein ratio was determined to be between 2 and 3, whereas for the chemical method the ratio was found to be 1 only.
The immunoconjugate was radiolabeled with ^{67}Ga. Addition of excess DF to [^{67}Ga-DF]-chCE7agl showed only slight transchelation of ^{67}Ga, proving the stability and specificity of the radiolabeling.
The implementation of the procedure for the functionalization of chCE7agl with other chelating systems suitable for radiolabeling with ^{67}Cu (e.g. CPTA, DOTA), as well as in vitro and in vivo studies are in progress.



[1] Verel et al. *J Nucl Med*, **2003**, *44*, 1271-1281.

Medicinal Chemistry **64**

Structural studies of fragments of Ste2p, a G-protein coupled receptor from yeast, in membrane-mimicking environments

A. Neumoin[1], L.S. Cohen[2], B. Arshava[2], J. Becker[3], F. Naider[2] and O. Zerbe[1]*

[1]Institute of Organic Chemistry, University of Zurich, [2]College of Staten Island, CUNY, [3]University of Knoxville, Tennessee

Structural studies of G-protein coupled receptors are often hampered by problems in expressing, purifying and reconstituting the receptors as well as in the spectroscopy of these large systems. To circumvent some of these problems we have looked at fragments comprising the transmembrane (TM) segments. Herein we report on the structure and dynamics of a large segments of Ste2p, the G-protein coupled α-factor receptor from yeast [1], using solution NMR spectroscopy. We investigated the 73-residue peptide TM7 consisting of the third extracellular loop, the 7th transmembrane helix and 40 residues from the cytosolic C-terminal domain [2] in dodecylphosphocholine (DPC) micelles. The structure reveals the presence of an α-helix for residues 10 to 30, which is perturbed around the internal Pro24 residue. Spin-label data indicate that the α-helix integrates into DPC micelles so that residues 22 to 26 are partially exposed to solution. Moreover, the data reveal a second site of interaction with the micelle within the cytosolic portion [3]. Our present efforts are concentrated on the structural studies of the 80-residue peptide TM1-TM2 consisting of the 19 residues from N-terminal domain, the 1st transmembrane helix, the first cytoplasmic loop, the second transmembrane helix and 7 residues from the first endoplasmic loop in lyso-palmitoylphosphatidylglycerol (LPPG) micelles.

[1] N. Nakayama, A. Miyajima, K. Arai, *EMBO J.* **1985**, 10, 2643-2648.
[2] R. Estephan, J. Englander, B. Arshava, K. Samples, J. Becker, F. Naider, *Biochemistry* **2005**, 44, 11795-11810.
[3] A. Neumoin, B. Arshava, J. Becker, O. Zerbe, F. Naider, *Biophys. J.* **2007**, in press

Medicinal Chemistry **65**

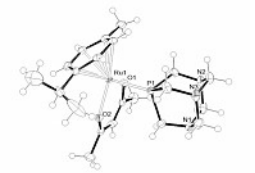
Synthesis, Crystallography and Biological Evaluation of Monocationic Complexes [Ru(η^6-*p*-cymene)(Racac)(PTA)][X] (Racac = Different Symmetric 1,3-Diketonates; X = BPh_4, BF_4)

Carsten A. Vock,[†] Anna K. Renfrew,[†] Hervé Pittet,[†] Lucienne Juillerat-Jeanneret[††] and Paul J. Dyson[†]

[†] *Institut des Sciences et Ingénierie Chimiques, Ecole Polytechnique Fedérale de Lausanne (EPFL), CH-1015 Lausanne*

[††] *University Institute of Pathology, CHUV, Rue de Bugnon 25, CH-1011 Lausanne, Switzerland.*

The development of new ruthenium(II) η^6-arene complexes as potential anticancer agents has gained considerable interest during the last years.[1,2] RAPTA complexes with PTA ligands (PTA = 1,3,5-triaza-7-phosphaadamantane) have shown promising antimetastatic activity,[1] and complexes with acetylacetone ligands exhibit strong cytotoxic effects.[2]



In order to combine both moieties, we will present synthetic and crystallographic aspects for the novel monocationic complexes [Ru(η^6-*p*-cymene)(Racac)(PTA)][X] (Racac = different symmetric 1,3-diketonates; X = BPh_4, BF_4). Results of biological *in vitro* studies will be included.

[1] W. H. Ang, P. J. Dyson, *Eur. J. Inorg. Chem.* **2006**, 4003–4018.
[2] A. Habtemariam, M. Melchart, R. Fernandez, S. Parsons, I. D. H. Oswald, A. Parkin, F. P. A. Fabbiani, J. E. Davidson, A. Dawson, R. E. Aird, D. I. Jodrell, P. J. Sadler, *J. Med. Chem.* **2006**, *49*, 6858–6868.

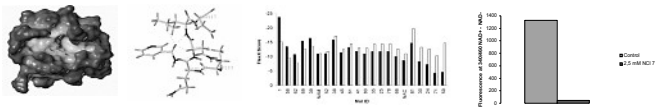
Medicinal Chemistry **66**

Strucure based discovery of potent selective inhibitors of *Leishmnia* sirtuin

Rameshwar U. Kadam[1], Joana Tavares[2], Kiran V. M[1], Anabela Cordeiro[2], Ali Ouaissi[3], and Nilanjan Roy[1]*

Centre of Pharmacoinformatics[1], National Institute of Pharmaceutical Education and Research, S.A.S Nagar-160062, India; Faculdade de Farmacia da Universidade do Porto[2], Portugal and "Pathogenie des Trypanosomatides[3]", 34394 Montpellier Cedex 5, France

In the recent years visceral leishmaniasis is rapidly emerging as an opportunistic infection in HIV patients, in pregnancy and organ transplant. Globalization and consequent travel of people across the world has increased the chances of spreading the infection. Since the available treatment for leishmaniasis poses many problems, researchers are looking for novel targets in order to develop new drugs. In this quest, we have built homology model of LmSir2, an emerging target and did comparative analysis of cofactor and substrate binding site of leishmania and human Sir2. Our finding indicates few subtle structural deference in NAD binding and catalytic domain of LmSir2 and human Sir2.[1] In a bid to identify compounds selective to LmSir2, we have screened 2 x 10^5 NCI compounds based on nicotinamide fingerprint followed by docking in both the active site. The compounds showed selectivity in docking study is subjected to *in-vitro* enzymatic and cell killing assay. We have successfully identified few compounds which are selective against LmSir2 and can kill axenic amastigotes in culture. Our result indicates that this strategy can be used for screening of more selective LmSir2 inhibitors.



[1] Kadam, R. U.; Kiran, V. M.; Roy, N, *Bioorg. Med. Chem. Lett.* **2006,** *16,* 6013-8**.**

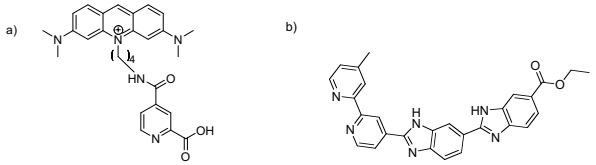
Medicinal Chemistry **67**

Nuclear targeted therapy using ^{99m}Tc-intercalating complexes

Patricia Antunes, Eszter Boros, Roger Alberto

Institute of Inorganic Chemistry, University of Zurich, Winterthurerstrasse 190, 8057 Zurich, Switzerland

Beside its usefulness for radioimaging the potential application of ^{99m}Tc for therapeutic purposes is based on its radiotoxicity as caused by low energy and high LET Auger electrons. Nevertheless, the therapeutic potential of this Auger-emitting radionuclide is critically dependent on the cellular localisation. An intranuclear decay is crucial to provoke cellular catabolism through DNA damage. For this purpose, the conjugation of DNA targeting and binding molecules in the ligands design is crucial. We have recently proved the principle that intercalators can be used as carriers for ^{99m}Tc into the nucleus. [1,2] In extending this principle to our work, DNA intercalators like acridine orange and Hoechst are attached to mono/bidentate ligands in order to target nuclear DNA with the corresponding Re/^{99m}Tc-complexes. The remaining position should then be occupied with a cell specific receptor-targeting agent. This [2+1] methodology is used with a variety of monodentate ligands, including a model dipeptide. The *in vitro* studies of these new Re/^{99m}Tc-intercalating agents will be presented.



Acridine Orange a) and Hoechst b) based ligands

[1] P. Haefliger, N. Agorastos, A. Renard, G. Giambonini-Brugnoli, C. Marty, and R. Alberto, *Bioconjugate Chem.* **2005**, *16*, 582.
[2] N. Agorastos, L. Borsig, A. Renard, P. Antoni, G. Viola, B. Spingler, P. Kurz, and R. Alberto, *Chem. Eur. J.* **2007**, 000.

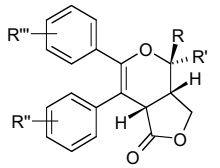
Medicinal Chemistry **68**

Natural Product-Like Furo[3,4-*c*]pyranones as Lead Structure for Novel Anticancer Agents

Cyril A. Fuhrer[a], Stephan Ruetz[b], Alina Nussbaumer[a], Fabian Wenger[a] and Robert Häner[a]

[a]Department of Chemistry, University of Bern, CH-3012 Bern, Switzerland
[b]Novartis Institutes of Biomedical Research, CH-4002 Basel, Switzerland

New drugs are required to combat drug resistance, for the improvement in the treatment of existing diseases, the treatment of newly identified diseases and the production of safer drugs by the reduction or removal of adverse side effects.
We have shown that natural product-like compounds can improve the drug discovery namely the hit/lead identification process.[1] In connection with this strategy we recently reported the synthesis of different natural product-like furo[3,4-*c*]pyranones.[2] These compounds like **1**, containing a *cis*-stilbene motif, exhibited interesting anticancer properties in different human cancer cell lines.[3] After identification of the *cis*-stilbene as pharmacophore we now investigate how the substitution pattern of this motif correlates to the biological activity. A short summary of this structure-activity relationships (SAR) study will be presented.



1
(+/-)

[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] C. A. Fuhrer, E. Grüter, S. Ruetz ,R. Häner, *ChemMedChem* **2007**, *2*, 441-444.

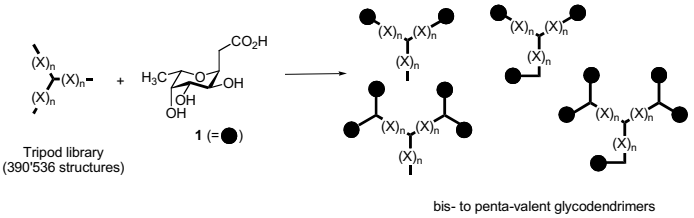
Medicinal Chemistry **69**

Combinatorial Variation of Branching Length and Multivalency in a Large (390'625 Member) Glycopeptide Dendrimer Library: Ligands for Fucose-specific Lectins

Emma M. V. Johansson, Tamis Darbre, Jean-Louis Reymond*

Department of Chemistry and Biochemistry, University of Berne, Freiestrasse 3, 3012 Berne, Switzerland

The antibiotic-resistant pathogenic *pseudomonas aeruginosa* bacterium causes lethal respiratory tract infections in cystic fibrosis patients. The fucose specific lectin PA-IIL (LecB) mediates tissue attachment and biofilm formation and can be inhibited by fucose.[1] We have discovered high-affinity ligands for PA-IIL by screening combinatorial fucosyl-peptide dendrimer libraries.[2] Here we report a study of multivalency effects in these ligands using an innovative combinatorial approach. [3]



[1] D. Tielker et al., *Microbiol.* **2005**, *151*, 1313.
[2] E. Kolomiets, E. M. V. Johansson, O. Renaudet, T. Darbre, J.–L. Reymond, *Org. Lett.* **2007**, *9*, 1465-1468.
[3] E. M. V. Johansson, E. Kolomiets, D. Tielker, K.-M. Bartels, F. Rosenau, K.-E. Jäger, T. Darbre, J.-L. Reymond, *N. J. Chem.* **2007**, DOI: 10.1039/b616051b.

Medicinal Chemistry **70**

Factors Modulating Time-Dependent Distribution of Chlorin Derivatives in Phospholipid Membranes

Martina Vermathen, Peter Bigler

University of Berne, Department of Chemistry and Biochemistry, Freiestrasse 3, 3012 Bern, Switzerland

Membrane penetration of porphyrinic drugs is believed to be one of the crucial factors for their efficiency in Photodynamic Therapy (PDT) of diseased tissues, since singlet oxygen, the actual cytotoxic species, unfolds its effect mainly in the immediate surrounding of the location where it is generated, i.e. the location of the excited photosensitizer [1]. In this study previous NMR-spectroscopic kinetic studies of chlorin e6 (CE) and mono-L-aspartyl chlorin e6 (MACE) transition across the phospholipid (PL)-bilayer [2] were extended to further determine the factors which modulate this distribution process. Addition of CE or MACE resulted in characteristic changes in the ^{1}H NMR spectrum of dioleoylphosphatidyl choline (DOPC) vesicles, most pronounced being a split of the PL-choline resonances. At neutral pH MACE remained surface attached while CE slowly distributed across the bilayer [2]. For CE an exponential relationship was found between the transition rate constant and the pH of the surrounding medium, while for MACE reduction of the pH had only little effect. In addition, the rate constant was found to depend on chlorin concentration. Increase in membrane rigidity reduced the transition rate of CE as was derived from studies performed with cholesterol containing DOPC vesicles. In conclusion, the above results demonstrate that membrane localization and distribution of the porphyrinic compound can be very sensitive to small changes in the physico-chemical properties of the chlorin vesicle system.

[1] A. Castano, T.N. Demidova, M.R. Hamblin, *Photodiagnosis and Photodynamic Therapy* **2004**, *1*, 279.
[2] M. Vermathen, U. Simonis, P. Bigler, *J. Porphyrins Phthalocyanines* **2006**, *10*, 519.

Medicinal Chemistry **71**

A Computational Study on the Dimerization of Insulin

Manuela Koch, Markus Meuwly*

University of Basel, Klingelbergstrasse 80, CH-4056 Basel, Switzerland

In recent years the number of social diseases has steadily increased. Diabetes mellitus is one of the biggest impacts on adults of working age and is reaching epidemic proportions in industrial countries.[1,2]
Patients suffering from Diabetes mellitus are not able to either produce or to assimilate insulin and have to be treated with insulin shots. Insulin is a peptide hormone which controls the concentration of glucose in the blood stream. In its native form insulin aggregates immediately into a hexamer under physiological conditions. In the human body only the monomeric form binds to the receptor what causes severe problems in insulin therapy. Experimentally, it was found that mutations at the end of the B chain of the protein, especially at position B24[3] have a significant influence on the receptor binding potency.[4]
In this study two B24-insulin monomer and dimer mutants were investigated using atomistically detailed computer simulations. Molecular dynamics simulations for the native and the two mutated forms showed differences in flexibility in particular at the dimerization interface. As a measure for aggregation potency the dimerization energies were calculated and were compared to the calculated energy of the native form and to the experiment respectively.

[1] World Health Org. http://www.who.int/diabetes/facts/en.2006
[2] Wicox G., *Clin. Biochem. Rev*, **2005**, *26*, 19.
[3] Hua Q. X., Shoelson S. E., Inouye K., Weiss M., *Proc. Natl. Acad. Sci.*, **1993**, *90*, 582.
[4] DeFelippis M.R., Chance R. E., Frank B. H., *Critical Reiews in Therapeutical Drug Carrier Systems*, **2001**, *18*, 201.

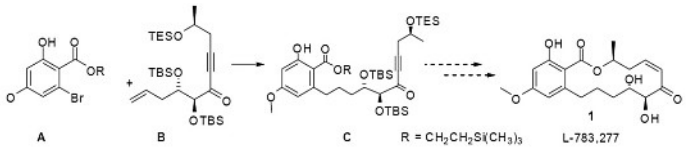
Medicinal Chemistry **72**

Studies on the Total Synthesis of Resorcyclic Lactone LE-783,277 – A New Lead Structure for Kinase Inhibition

Tatjana Hofmann, Karl-Heinz Altmann

Institute of Pharmaceutical Sciences, ETH Zurich, Wolfgang-Pauli-Strasse 10, 8093 Zurich, Switzerland

Kinases have emerged as important drug targets in cancer and inflammatory disease and several low-molecular-weight kinase inhibitors have now been introduced into clinical practice.[1] The natural product L-783,277 (**1**) belongs to the family of resorcyclic acid lactones (RALs), which includes compounds such as zearalenone, C292 (LL-Z1640-2), hypothemycin, or Radicicol, and which exhibit a diverse range of biological activities.[2]
L-783,277 (**1**) is a potent inhibitor of the Ser/Thr kinase MEK.[3] No total synthesis of **1** has been reported so far and the biological activity of the compound has not been characterized beyond its ability to inhibit a few selected kinases. The development of an efficient enantioselective synthesis of **1** and a more detailed characterization of its biological effects are the primary goals of this research project. The synthesis of macrolactone **1** is based on the consecutive assembly of the key fragments **A** and **B**, whose synthesis is already implemented. The preparation of the advanced intermediate **C** as well as their ongoing assembly will be described in detail. This approach will enable the synthesis of analogs for SAR studies and also biophysical investigations, in order to assess its usefulness as a potential lead structure for drug discovery.



[1] Krause, D. S. and Van Etten, *R. H. N. Engl. J. Med.* **2005**, *353,* 172-187. [2] Winssinger, N. and Barluenga, S. *Chem. Commun.* **2007**, *1*, 22-36. [3] Zhao, A.; Lee, S. H.; Mojena, M.; Jenkins, R. G.; Patrick, D. R.; Huber, H. E.; Goetz, M. A.; Hensens, O.D.; Zink, D. L.; Vilella, D.; Dombrowski, A. W.; Lingham, R. B.; Huang, L. *J. Antibiot.* **1999**, *52* (12), 1086-1094

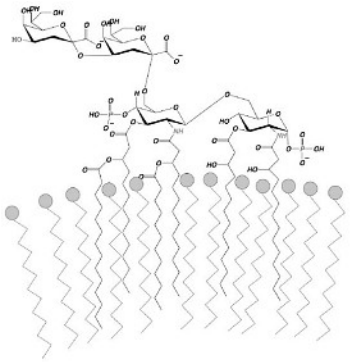
Medicinal Chemistry **73**

Interactions of a bacterial lipopolysaccharide with antibacterial peptides

Jiří Mareš, Sowmini Kumaran, Oliver Zerbe*

University of Zürich, Winterthurerstr. 190, CH-8057 Zürich, Switzerland

The action of many antibacterial (ATB) peptides starts by interacting with lipopolysaccharide (LPS), which largely forms the outer membrane of gram-negative bacteria. We purified isotopically labelled LPS from the deep rough mutant of Escherichia coli D31m4 [1] for NMR studies. Incorporation of LPS into dodecylphosphocholine (DPC) micelles provided a suitable model of a bacterial membrane. Heteronuclear 2D and 3D spectroscopy techniques were employed for assignment purposes. Interactions of LPS with ATB peptide were studied by chemical shift mapping experiments using proton-carbon correlation experiments. Moreover, contacts were additionally directly probed by isotope edited and isotope-filtered NOESY experiments The data allow to describe ATB peptide-LPS interactions at atomic resolution.



[1] Qureshi, *J. Biol. Chem.*, **1988**, *263*, 11971.

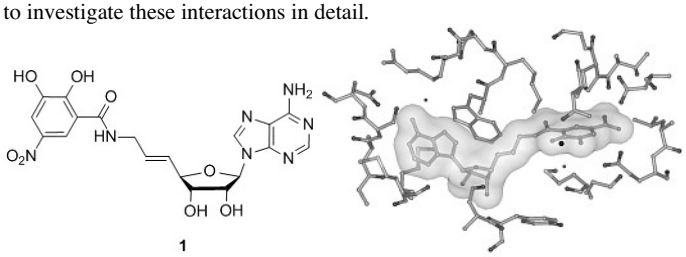
Medicinal Chemistry **74**

Novel Bisubstrate Inhibitors of Catechol-*O*-Methyltransferase (COMT): Investigation of the Ribose Structural Unit

Manuel Ellermann[a], Ralph Paulini[a], Edilio Borroni[b], Gerhard Zürcher[b], Roland Jakob-Roetne[b], François Diederich*[a]

[a]Laboratorium für Organische Chemie, ETH Zürich, Wolfgang-Pauli-Str. 10, 8093 Zürich
[b]Pharma Division, Präklinische Forschung, F. Hoffman-La Roche AG, Grenzacherstr. 124, 4070 Basel

Catechol-*O*-Methyltransferase (COMT) is one of the key enzymes involved in catecholamine catabolism. Therefore it is a valuable target for the treatment of CNS disorders such as Parkinson's disease [1]. Highly potent bisubstrate Inhibitors (e.g. **1**) have been developed by *de novo* design [2], but the exact binding motif at the ribose moiety still requires further explanation [3]. In our ongoing work we synthesize novel bisubstrate inhibitors in order to investigate these interactions in detail.



1

[1] P. T. Männistö, S. Kaakola, *Pharmacol. Rev.* **1999**, 51, 593-628.
[2] C. Lerner, A. Ruf, V. Gramlich, B. Masjost, G. Zürcher, R. Jakob-Roetne, E. Borroni, F. Diederich, *Ang. Chem. Int. Ed.* **2001**, 40, 4040-4042.
[3] R. Paulini, C. Trindler, C. Lerner, L. Brändli, W. B. Schweizer, R. Jakob-Roetne, G. Zürcher, E. Borroni, F. Diederich, *ChemMedChem* **2006**, 1, 340-357.

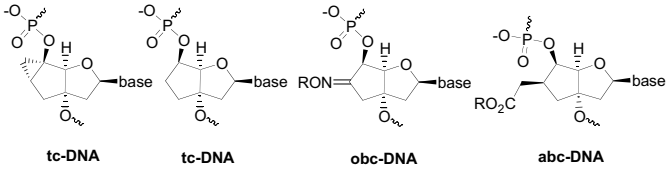
Medicinal Chemistry **75**

Synthesis of conformationaly constrained nucleotides with improved lipophilicity

Samuel Luisier, Christian Leumann

Department of chemistry and biochemistry, University of Bern, Freiestrasse 3, 3012 Bern, Switzerland

Tricyclo (tc)- and bicycle (bc)-DNA show promising properties as antisense oligonucleotides[1,2]. Due to the anionic character of the sugar-phosphate backbone, oligonuclceotides and modified oligonucleotides show restricted cellular uptake. The attachment of a lipophilic rest to the sugar analogue of bc-DNA is expected to increase the membrane permeability of the modified oligo-nucleotide[3]. In this context, we synthesized two different bicyclo-DNA analogues, with lipophilic side chains at the carbocyclic rings.



[1] D. Ittig, S. Liu, D. Renneberg, D. Schümperli, C. J. Leumann, *Nucleic Acids Res.*, **2004**, *32,* 346
[2] D. Renneberg, C. Leumann, *J. Am. Chem. Soc*, **2002**, *124*, 5993
[3] P. Chaltin, A. Margineanu, D. Marchand, A. Van Aerschot, J. Rozenski, F. C. De Schryver, F. Herrmann, K. Müllen, R. Juliano, M. Fisher, H. Kang, S. De Feyter, P. Herdewijn, *Bioconjugate Chem.*, **2005**, *16*, 827

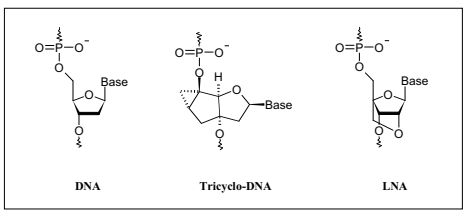
Medicinal Chemistry **76**

Antisense mechanisms of tc-DNA modified oligonucleotides

Damian Ittig[1], Daniel Schümperli[2], Christian J. Leumann[1]

[1]Department of Chemistry and Biochemistry, Freiestrasse 3, 3012 Bern,
[2]Department of Cell Biology, Baltzerstrasse 4, 3012 Bern,
University of Bern, Switzerland

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] (Fig.), which show signifcantly enhanced target binding properties and enhanced biological stability.
We investigated different antisense mechanisms (steric block, RNase H induced mRNA degradation and siRNA) of a fully modified tc-oligonucleotide, 5-8-5 tc-DNA gapmer and sense strand modified siRNAs that were 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.



[1] D. Ittig, S. Liu, D. Renneberg, D. Schümperli, C. J. Leumann, *Nucleic Acids Res*, **2004**, *32*, 346-353.
[2] Y.-L. Chiu, T. M. Rana, *Mol. Cell*, **2002**, *10*, 549-561.

Medicinal Chemistry **77**

Stereoselective block of hERG channel by (S)-methadone and detailed studies of mechanisms of interaction.

Liliana Sintra Grilo (1, 2), Pierre-Alain Carrupt (1), Hugues Abriel (2)

(1) Pharmacochemistry, School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Switzerland. (2) Department of Pharmacology and Toxicology, University of Lausanne, Switzerland.

Methadone, a widely used opioid μ-receptor agonist, blocks the hERG potassium channel essential in cardiac repolarization. As a result, methadone prolongs the QT interval and can trigger potentially lethal arrhythmias [1]. Methadone is given as a racemate, even though (R)-methadone has a higher μ-receptor activity [2].

We investigated how the hERG current (IhERG) is stereoselectively blocked by one enantiomer and investigated the state-dependency of the block. IhERG were recorded from HEK293 cells expressing the wild type channel or mutants, using the patch-clamp technique at 37° C or 25° C.

Methadone-induced block of IhERG was found to be stereoselective under both recording temperatures. At 37° C, we found that (S)-methadone is ~3.5-fold more potent in blocking IhERG than the (R)-form (IC_{50}= 2 μM and 7 μM respectively). Block is the contribution of both closed and open states, and stereoselectivity seems to happen in the open state. Residue F656 is important for the binding of methadone as the mutant F656A shows decreased block. Theses findings provide new insights into stereoselectivity in the field of drug-induced Long QT syndrome.

[1] Pearson EC, Woosley RL, *Pharmacoepidemiol. Drug Saf.* **2005,** *14,* 747-53
[2] Kristensen K, Christensen CB, Christrup LL, *Life Sci*. **1995**, *56*, L45-L50

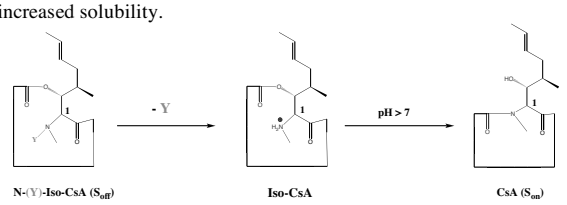
Medicinal Chemistry **78**

Synthesis of new prodrugs of cyclosporin A applying chemical and enzymatic triggering of O,N-acyl migrations in situ

J. Bérard, E. Condemi, R. Lysek, M. Mutter

Swiss Federal Institute of Technology (EPFL), CH-1015 Lausanne

The cyclosporin family is composed of cyclic undecapeptides among the cyclosporin A (CsA) is the most important representative due to its well known immunosuppressive, anti-inflammatory, antifugal and antiparasitic activities. The biological efficiency of the molecule is limited by its poor solubility that induces for example low oral absorption. To overcome this problem, the synthesis of prodrugs of CsA and its synthetic analogues has been a major topic of research over many years [1]. Here, we apply the concept of switch-peptides [2] in transforming CsA to its N(Y)-protected Iso-CsA derivative (Soff-state), which undergoes by chemical or enzymatic cleavage of Y spontaneous O,N-acyl migration to native CsA (Son). The chemical synthesis, the kinetics of cleavage, physico-chemical and biological properties of a series of Y-protected Iso-CsA derivatives are investigated. It will be shown, that the prodrugs (Soff state) are devoid of biological activity, exhibit high chemical stability at physiological conditions and show significantly increased solubility.



In modulating Y, the transformation of the CsA prodrugs to their bioactive state (Son) proceeds smoothly over a time scale up to several hours. Results on the design and synthesis of protecting groups Y exhibiting high solubilising power in water will also be presented.

[1] a) R. Oliyai, TJ. Siahaan, VJ. Stella, *Pharm. Res*., 12,323 (1995). b) A. Hamel, F. Hubler and M. Mutter, *J. Pept. Res*., 65(3), 364-374 (2005).
[2] a) M. Mutter, et al., *Angew. Chem. Int. Ed*., 43, 4172 (2004).b) S. Dos Santos, et al., *J. Am. Chem. Soc*., 127, 11888 (2005).

Medicinal Chemistry **79**

Screening for antioxidant properties by different *in vitro* assays

Delphine Cressend, Marianne Reist, Pierre-Alain Carrupt

Unité de Pharmacochimie, Section des sciences pharmaceutiques, Université de Genève, Université de Lausanne, Quai Ernest-Ansermet 30, CH-1211 Genève 4, Suisse

Oxidative stress, contributing to the pathophysiology of many diseases with a high incidence in the population, is resulting from an imbalance between the generation and detoxification of reactive oxygen species (ROS). To protect biomolecules form ROS, efficient antioxidants are needed.

Two complementary *in vitro* microplate assays were used to screen for new chemical entities (NCE) with antioxidant properties. One was a fluorimetric test [1] to assess the antioxidant capacity of compounds to protect proteins from loss of activity caused by ROS, using alkaline phosphatase (ALP) as model protein. $EC_{50(prot)}$, i.e. required concentrations to protect ALP to 50% from maximal activity decrease, were determined. The other assay was a spectrophotometric test [2] to evaluate the radical scavenging capacity of compounds able to participate in hydrogen transfer reactions, based on the scavenging of the stable radical 2,2-diphenyl-1-picrylhydrazyl (DPPH). Results were expressed as $EC_{50(DPPH)}$, the effective concentration to scavenge 50% of DPPH, and as log Z, a kinetic parameter derived from initial second-order rate constants and antioxidant/DPPH ratios.

These antioxidant parameters allowed to characterize the antioxidant properties of NCE and to compare them with those of known reference antioxidants.

[1] Bertolini F, Novaroli L, Carrupt PA, Reist M, *J. Pharm. Sci.* **2007,** in press.
[2] Ancerewicz J, Migliavacca E, Carrupt PA, Testa B, Brée F, Zini R, Tillement JP, Labidalle S, Guyot D, Chauvet-Monges AM, Crevat A, Le Ridant A, *Free Rad Biol Med*. **1998**. *25*, 113-120.

Medicinal Chemistry **80**

Rapid Identification of Protease Substrates by Direct On-bead Assay of Peptide Combinatorial Libraries

Ewelina Minta, Jacob Kofoed, Jean-Louis Reymond*

Department of Chemistry & Biochemistry, Freiestrasse 3, 3012 Bern, Switzerland

Proteolytic pathways have a crucial importance to biological regulation of the fundamental aspects of cell behaviour. Proteases are involved in different pathological processes such as cancer, neurodegenerative and cardiovascular diseases, i.e., thus these enzymes are important biomarkers and potential drug targets. As a result, specific and sensitive assays to monitor the activity of proteases are of the great interest. Activity-based protein profiling is a chemical proteomic method that characterizes protease specificity from the sequence of short peptidic or peptidomimetic substrates [1, 2, 3]
Here we report a method for the rapid discovery of selective protease substrates by screening a 65'536 member octapeptide split-and-mix combinatorial library. Proteolysis is carried out directly on-bead, followed by chemoselective staining of proteolyzed sequences and high-throughput decoding [4]. The method correctly identifies reactive subtrates for solution assays, and delivers original new reactive sequences to guide the design of inhibitors.

[1] O. Schilling, C. M. Overall, *Curr Opin Chem Biol*. **2007**, *11,* 36.
[2] M. J. Evans, B. F. Cravatt, *Chem Rev* **2006**, *106*, 3279.
[3] Y. Yang, J.-L. Reymond, *Mol BioSys* **2005**, *1*, 57.
[4] J. Kofoed, *PhD dissertation* **2006**, University of Bern.

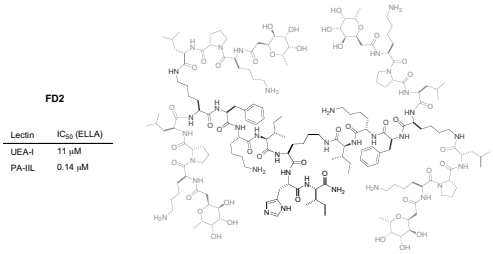
Medicinal Chemistry **81**

Neoglycopeptide Dendrimer Libraries as a Source of Lectin Binding Ligands

Elena Kolomiets, Tamis Darbre, Jean-Louis Reymond*

Department of Chemistry and Biochemistry, University of Berne, Freiestrasse 3, 3012 Berne, Switzerland

A microbal lectin PA-IIL involved in biofilm formation in the opportunistic pathogen P*seudomonas aeruginosa* responsible for lethal infections in cystic fibrosis patients. Micromolar affinity binding of this lectin to fucose inhibits attachment of the bacterium to its host cell and may block infection.[1] High-affinity ligands for PA-IIL lectin were revealed by screening of 2nd generation fucosylated peptide dendrimer library.[2] Under investigation of the structure-activity relationship in one of the most potent ligand **FD2**, the nanomolar ligand was find out with IC_{50} = 25nM. In continuation, the importance of amino acid sequence was shown and multivalency effect was studied.[3]



[1] D. Tielker, S. Hacker, R. Loris, M. Strathmann, K.-E. Jaeger, *Microbiology*. **2005**, *151*, 1313.
[2] E. Kolomiets, E. M. V. Johansson, O. Renaudet, T. Darbre, J.-L. Reymond, *Org. Lett.* **2007**, *9*, 1465.
[3] E. Kolomiets, T. Darbre, J.-L. Reymond, unpublished results.

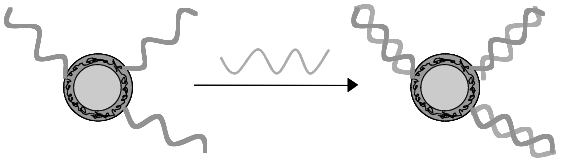
Medicinal Chemistry **82**

Development of a novel BNA biosensor based on DNA-core-shell nanoparticles

Caroline Fraysse-Ailhas[a], Sandrine Poux[a], Cornelia Palivan[a], Franck Vazquez[b], Wolfgang Meier[a]

[a] University Basel, Klingelbergstrasse 80,4056 Basel, Switzerland
[b] Friedrich Miescher Institute for Biomedical Research, Maulbeerstrasse 66, 4058 Basel, Switzerland

The increasing demand of DNA biosensing for medical applications increased dramatically since some years, and lead to the development of different systems [1, 2]. We present the design and development of a new DNA biosensor system based on core-shell nanoparticles [3].



The system is acting as a DNA biosensor *per se*, in aqueous solution and without any disturbance from the polymer particles. As they allow recovery of both the DNA biosensor and the precious DNA sample after measurement, for re-use and further analysis, respectively, our particles have a high potential for medical applications.

1. Brown, P. O.; Botstein, D. *Nature Genetics* **1999,** 21, 33-37.
2. McGlennen, R. C. *Clinical Chemistry* **2001,** 47, (3), 393-402.
3. Kong, X. Z.; Ruckenstein, E. *Journal Of Applied Polymer Science* **1999,** 73, (11), 2235-2245.

Medicinal Chemistry **83**

Preparation and characterization of $NaYF_4$:Yb,Er nanoparticles

Mireille Crittin, Michel J. Rossi, Hubert van den Bergh

Swiss Federal Institute of Technology, Air and Soil Pollution Laboratory, CH-1015 Lausanne, Switzerland

Up-converting phosphors, which emit visible light upon infrared excitation, have a great potential in biological labelling and imaging. The purpose of this project is to prepare ultra sensitive up-converting nanoparticles for cell biological studies. $NaYF_4$ has been reported as the most efficient host material for green (Yb/Er) up-conversion phosphors [1]. Water-soluble $NaYF_4$:Yb,Er nanoparticles have been prepared using the hydrothermal method [2]. We will focus on the details of the preparation as well as the characteristic properties of these nanoparticles such as morphology, photoemission yield and structure in relation to relevant parameters of their preparation method. Images of these up-converting nanoparticles upon Near-IR excitation within cells will also be presented.

[1] K. W. Krämer, D. Biner, G. Frei, H. U. Güdel, M. P. Hehlen and S. R. Lüthi, *Chem. Mater.*, **2004,** *16,* 1244.
[2] F. Wang, D. K. Chatterjee, Z. Li, Y. Zhang, X. Fan and M. Wang, *Nanotechnology*, **2006**, *17*, 5786.

Medicinal Chemistry **84**

Lipophilicity determination by RP-LC: the complex case of zwitterionic compounds

Amandine Guillot, Sophie Martel, Pierre-Alain Carrupt

Unité de Pharmacochimie, Section des sciences pharmaceutiques, Université de Genève, Université de Lausanne, Quai Ernest-Ansermet 30, CH-1211 Genève 4, Suisse.

Lipophilicity, a key parameter in the study of pharmacokinetic behaviour of NCE must be measured by rapid and accurate experimental methods in early stages of drug development. In this context, RP-LC methods, based on correlation between log P and log k_w (measured or extrapolated retention factors), were largely used for the determination of log Poct of neutral, acidic and basic compounds [1, 2]. However, 16 % of drugs are ampholytes (compounds containing a basic and an acidic function) and number of them are zwitterionic compounds (pK_a^{acidic}<pK_a^{basic}). The lipophilicity of such compounds is complex to evaluate due to the presence of the tautomeric equilibrium between neutral unionized and neutral zwitterionic forms. Systematic studies were performed using the Discovery® RP Amide C16 stationary phase demonstrating that two different log k_w, and thus two lipophilicity values were obtained with different mobile phase composition according to the position of the equilibrium between the neutral and the zwitterionic form. Therefore RP-LC could be a method of choice to determine, for the first time, the lipophilicity of the two tautomeric forms for a zwitterionic compound.

References

1. Lombardo F, Shalaeva MY, Tupper KA, Gao F, Abraham MH. *J.Med.Chem.* **2000**, *43*, 2922-2928

2. Nasal A, Siluk D, Kaliszan A. *Curr.Med.Chem.* **2003**, *10*, 381-426.

doi:10.2533/chimia.2007.438 CHIMIA **2007**, *61*, No. 7/8

Medicinal Chemistry **85**

New C-glucosylxanthones from the leaves of *Arrabidaea patellifera* (Bignoniaceae)

F. Martin[a], A.E. Hay[a], S. Vargas[a], L. Vivas[b], M.P. Gupta[c] and K. Hostettmann[a,*]

[a]Laboratory of Pharmacognosy and Phytochemistry, School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Quai Ernest-Ansermet 30, CH-1211 Geneva 4, Switzerland.
[b]London School of Hygiene and Tropical Medicine, Department of Infectious and Tropical Diseases, Keppel Street, London WC1E 7HT, UK
[c]Center for Pharmacognostic Research on Panamanian Flora (CIFLORPAN), College of Pharmacy, University of Panama, Panama

As a part of our ongoing investigations on Panamanian Bignoniaceae [1], seven methanolic extracts from six plants were submitted to a β-hematin polymerization inhibition test [2]. This reaction is one of the possible targets in the fight against parasites of the genus *Plasmodium*, responsible for malaria. The extract from the leaves of *Arrabidaea patellifera* (Schlecht) Sandw., a liana which grows from lowlands to mountain forest, was selected because of its good activity, corroborated by an *in vitro* test against *Plasmodium falciparum*. Moreover, this plant has never been investigated before.
The extract was first fractionated by vacuum liquid chromatography (VLC) and then by medium pressure liquid chromatography (MPLC). It afforded directly mangiferin and four of its derivatives, new C-glucosylxanthones, all active *in vitro* against *P. falciparum*. Further chromatographic separations gave other compounds, of which the identification is underway.
The structures were determined by means of spectrometric methods, including 1D and 2D NMR experiments and MS analysis.

[1] F. Martin, A.E. Hay, L. Corno, M. P. Gupta, K. Hostettmann, *Phytochemistry*. **2007**, in press
[2] K. K. Ncokazi, T. J. Egan, *Anal. Biochem*. **2005**, *338*, 306-319

Medicinal Chemistry **86**

Analyses and bioactivities of wild populations of *Rhodiola rosea* L. (Crassulaceae) from Switzerland

D. van Diermen, A. Marston, K. Ndjoko and K. Hostettmann

Laboratory of Pharmacognosy and Phytochemistry, School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Quai Ernest-Ansermet 30, CH-1211 Geneva 4, Switzerland

Rhodiola rosea L., also known as "Golden root", has been used for centuries in the traditional medicine of Eastern Europe and Asia. It has been classed as an adaptogen by Russian researchers due to its ability to increase resistance in humans to a variety of stressors.
According to the Soviet Pharmacopoeia (RFMHMI 1983), extracts of *Rhodiola rosea* L. are now standardized in both rosavin (min. 3%) and salidroside (min. 1%) content [1].
The efficacy observed in clinical studies is due to the synergistic activity of these two metabolites and other active ingredients.
An efficient analytical method by HPLC-UV/DAD was developed to quantify rosavin and salidroside in the roots of four wild populations of *R. rosea* L. coming from the same area in Switzerland. The analyses were performed in order to observe the variability in the populations, and to establish the dynamics of their rosavin and salidroside content over a one year period. The results obtained after the analysis of 20 samples will be useful in the selection of the most appropriate population for large scale cultivation.
Acetylcholinesterase-inhibitory activity was observed due to the presence in the plant of linoleic acid and cinnamic alcohol.
Further investigations on *R. rosea* are underway in order to discover new biological activities, especially in the area of depression (inhibition of monoamine-oxidase).

[1] Khanum F., Bawa A. S., Singh B., *Comp Rev Food Sci Food Safety*, **2005**, *4*, 55-62.

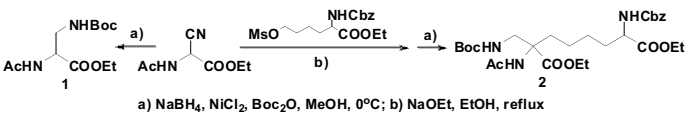
Medicinal Chemistry **87**

A New Protocol to the Syntheses of α,β-Diamino Acids

Y. Liu[1], P. Schmutz[1], M. Bauwens[2], J. Mertens[2], R. Alberto[1]

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

α,β-Diamino Acids have attracted the interests from both organic chemists and biochemists through years, because of its unique structural and ubiquitous role playing in biologically active compounds. Moreover, it has been demonstrated that the α,β-diamino acid can be used as efficient tripodal ligand for the labelling of Re(I)/Tc(I) tricarbonyl, the corresponding hydrophilic compound of which is stable to air and competition from cysteine or histidine. However, in the radiopharmaceutical context, only after being coupled to other biomolecules, could α,β-diamino acids be feasible for the further application [1].
Here we report a new method for the preparation of α,β-diamino acid, which entails also the convenient syntheses of α,β-diamino acids derivatized at α-position. The deprotected **2** formed stable Re(I)/Tc(I) tricarbonyl complex, which can be recognized and transported into a cell by LAT1 [2].



a) $NaBH_4$, $NiCl_2$, Boc_2O, MeOH, 0°C; b) NaOEt, EtOH, reflux

[1] R. Alberto, *Top. Curr. Chem.,* **2005**, *252*, 1-44.
[2] Y. Liu, J. K. Pak, P. Schmutz, M. Bauwens, J. Mertens, H. Knight, R. Alberto, *J. Am. Chem. Soc*., **2006**, *128,* 15996-15997.

Computational Chemistry **88**

DFT Study of Jahn-Teller Effect in Cobaltocene

Matija Zlatar[1,2], Emmanuel Penka Fowe[1], Carl-Wilhelm Schlapfer[1], Claude Daul[1⋆]

[1]Department of Chemistry, University of Fribourg, Chemin de Musée 9, CH-1700, Fribourg, Switzerland
[2]Center for Chemistry, IHTM, University of Belgrade, Njegoševa 12, P.O. Box 815, 11001 Belgrade, Serbia

The detailed analysis of Jahn-Teller (JT) effect in bis - cyclopentadyenyl-cobalt(II) - cobaltocene ($CoCp_2$), is given. Descent in symmetry goes from D_{5h} (eclipsed conformation of the two rings) to C_{2v}. The electronic ground state, $^2E_1''$, splits into $^2A_2$ and $^2B_1$. We have used the method developed by Daul et al. [1] for the calculation of the ground-state JT stabilization energy (E_{JT}) and the resulting properties of a JT-active molecules by DFT. The adiabatic potential energy surface is described by three parameters (E_{JT}, Δ and R_{JT}) which are related to the Bersuker's description [2] of $E \otimes e$ problem (K_E, F_E, G_E - force constant, first and second order vibronic coupling constants respectively). We obtained $E_{JT} = 750 - 850\ cm^{-1}$ (depending on the basis set and functional used) which is in agreement with experimentally estimated value of 1010 cm^{-1} [3]. There is no second order JT effect. The geometry changed mainly in the Cp rings. The results are interpreted by group theory, in both, the high, D_{5h}, and the low, C_{2v}, symmetry. In D_{5h}, the problem was considered as a multimode $E \otimes (\sum_i e_i)$ and in a C_{2v} as a multimode $(^2A_2 + ^2B_1) \otimes (\sum_i a_i)$ vibronic interactions. The contribution of the totally symmetrical vibrations in C_{2v} to the E_{JT} was analysed.

[1] R. Bruyndockx, C. Daul, P. T. Manoharan, E. Deiss, *Inorg. Chem.*, **1997**, *36*, 4251-4256.
[2] I. B. Bersuker, *The Jahn-Teller Effect*, Cambridge University Press, **2006**.
[3] R. Bucher, *ESR-Untersuchungen an Jahn-Teller-Aktiven Sandwitchkomplexen*, PhD Thesis, ETH Zuerich, **1977**.