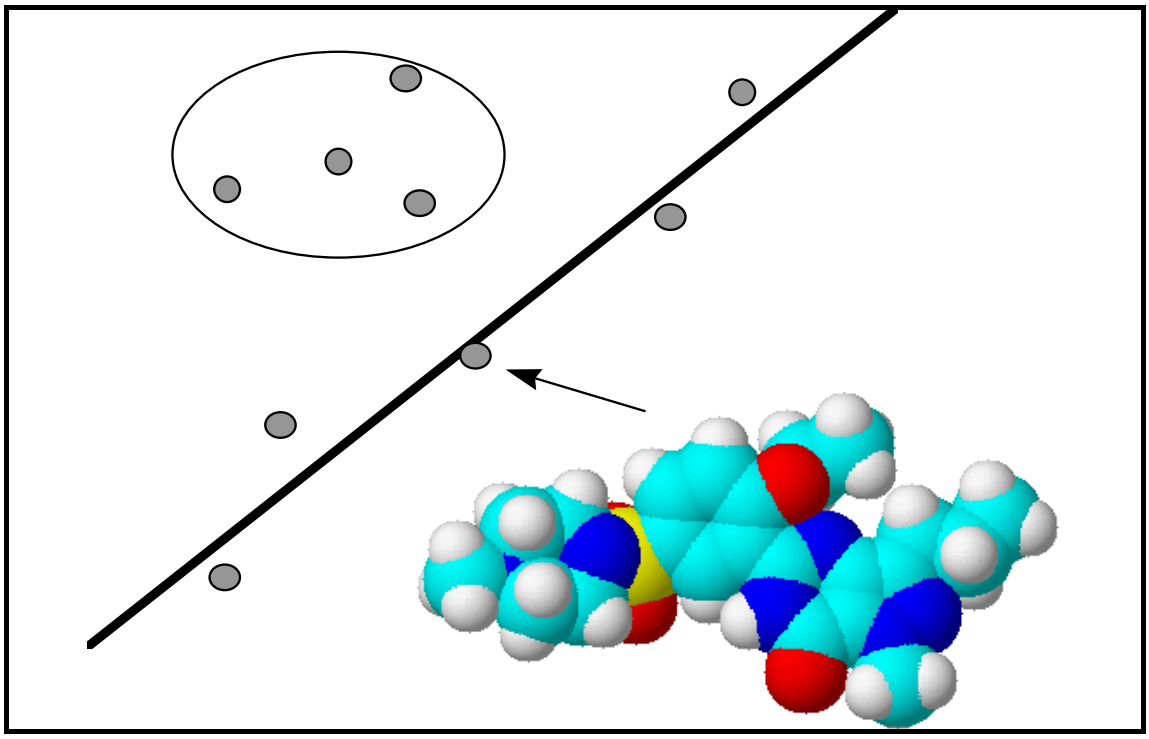
The QSAR and Modelling Society

NEWSLETTER

http://www.qsar.org

Issue No. 14 November 2003



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Report of the Chair

Editorial Summary

The QSAR and Modelling Society continues to provide a forum for those who are interested to use chemical structure to predict molecular properties, with emphasis on biological activity. As you will see in this newsletter, such interests provide the focus for meetings around the globe, innovative software, and of course scientific publications. As computer power grows and the internet proliferates members of the Society are presented with unique opportunities to further scientific knowledge to benefit mankind. There are exciting years ahead.

Two board members deserve special recognition. Han van de Waterbeemd and Stefan Balaz have each contributed many hours to the Society. Han has gathered the information and organized this Newsletter. It is neither quick to do nor an easy task. He also keeps the list of names and addresses of members, again a large effort. Stefan keeps our finances and importantly keeps our web site updated and lively. This requires much diligence to maintain current information and to supply sites of interest to members.

I would also like to thank Osman Guner and Accelrys for supporting the QSAR mailing list.

The Society is only as strong and active as its members--I ask you to do several things for the Society:

- *Pay your dues to Stefan Balaz or Han van de Waterbeemd.*
- *Check the web site to be sure that your contact information (and perhaps that of your colleagues) is correct. With companies merging, changing names, and being purchased, it is easy for this information to get out of date. Send corrections to Han van de Waterbeemd.*
- *Consider carefully if there is someone, even someone that you don't personally know, that should be nominated for the Hansch Award.*
- *Consider if your next publication should be in one of the Society's journals: QSAR and Combinatorial Science or Journal of Computer-Aided Molecular Design..*
- *If you organize a meeting, consider co-sponsorship by the QSAR and Modelling Society.*
- *Keep the web page current by telling Stefan Balaz of any meeting that you are organizing and resources that are of interest to all members.*
- *Contribute to the mail exploder. We have had some interesting discussions, but I'm sure that you have more questions or topics for discussions.*
- *Contribute your published data or a link to it to the Society's archives.*

Finances

The financial state of the Society is good. Our typical expenses include the Hansch award and support of students to attend a scientific meeting. Please send me proposals for student support. Are there other ways that we could use our funds to foster the development or recognition of QSAR and Modelling? Send me e-mail and I will follow from there with a discussion with the board or the whole society as seems fit.

Some members aren't paying their dues! Please pay your dues of $10.00/year, preferably for multiple years. Send either US cash or a check drawn on a US bank to

Stefan Balaz, North Dakota State University, College of Pharmacy, Department of Pharmaceutical Sciences, Sudro Hall, Rm 8, Fargo, ND 58105, USA

Treasurer's Reports:

US Account – November 2003

Starting balance (October 2001)		$7,204.79
Income		
Due collection	cash	$1,930
	checks	$1,270
Donations	checks	$100
Expenditures		
www.qsar.org domain	(2001-2002)	-$100
www.qsar.org domain	(2003-2012)	-$189
Hansch Award (Oprea)		-$1,000
Hansch Award plaque		-$100
Current balance		$9,115.79

Europe Account – November 2003

October 2002	£ 1,380.07
Current balance	£ 1,437.72

The Society E-mail List:

Osman Güner and Accelrys deserve a big vote of thanks for their support of the mailing list. Osman has worked diligently to solve the problems that have arisen. Although his work is in the background, we all appreciate the smooth way that the list operates. Now it is up to us to keep the messages coming.

The Hansch Award:

As you may know, this award is presented annually to a young investigator who, in the opinion of the society, has contributed to the advance of QSAR and Modelling of biological activity from structure and will continue to contribute to this field. To facilitate this process we have constituted two committees. The Nominations Committee, chaired by Prof. Kubinyi, will solicit and process nominations for this award. The Hansch Awards Committee will make the selection. It is not too early to be thinking about nominating a young investigator whose work has impressed you.

The Society Web Site:

Stefan Balaz also deserves a big vote of thanks for convincing the North Dakota State University to host our web site and for working very hard to update and expand it with interesting facts and links. If you haven't looked at it lately, you will be surprised at how much is there.

Please check that your contact information on the Society web site is current. Are we sending e-mail to the best long-term address? Is your telephone number correct? Corrections should be sent to Han van de Waterbeemd who keeps very accurate records.

Data sets:

Drs. Dave Winkler and Frank Burden have agreed to spearhead an effort to expand the number of datasets on the web page. Start thinking now about what data you could share. Anything that has been published would be interesting with others. To get the ball rolling, I am collecting the set of propynylamines that I published in 1975. This dataset is interesting because although there are 66 compounds in the dataset, the published QSAR included only 47 compounds.

The Corwin Hansch AWARD

2003 Award Goes to David Cark

Dr. Clark is a young investigator, just 10 years since his PhD. In this time he has published extensively on his imaginative work on 3D database searching, genetic algorithms in computational chemistry, de novo structure design, and more recently using QSAR to predict ADME properties. I have been very impressed with David's ability to move from one problem to another and to then present innovative solutions to the issues. I fully expect that in future years he will move the field forward in ways that we cannot anticipate now.

Yvonne Martin

Details:
Date of birth: 1st December 1966.

Education:
BSc: Oxford doing his first degree 1984-88
Library Trainee: Bodleian Library at Oxford, 1988-1989
MSc: Sheffield University, Information Science 1989-90
PhD: Sheffield University, Information Science 1990-93

Publications:
Clark, D. E., P. Willett and P. W. Kenny (1991). "Pharmacophoric Pattern Matching in Files of Three-Dimensional Chemical Structures: Use of Smoothed Bounded Distances for Incompletely Specified Query Patterns." Journal of Molecular Graphics **9**: 157-163.

Clark, D. E., P. Willett and P. W. Kenny (1992). "Pharmacophoric Pattern Searching in Files of Three-Dimensional Structures: Use of Bounded-Distance Matrices for the Representation and Searching of Conformationally Flexible Molecules." Journal of Molecular Graphics **10**(4): 194-204.

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Waszkowycz, B., D. E. Clark, D. Frenkel, J. Li, C. W. Murray, B. Robson and D. R. Westhead (1994). "Pro_Ligand: An

Approach to De Novo Molecular Design. 2. Design of Novel Molecules from Molecular Field Analysis (MFA) Models and Pharmacophores." Journal of Medicinal Chemistry **37**: 3994-4002.

Westhead, D. R., D. E. Clark, D. Frenkel, J. Li, C. W. Murray, B. Robson and B. Waszkowycz (1995). "Pro_Ligand: An Approach to De Novo Molecular Design. 3. A Genetic Algorithm for Structure Refinement." Journal of Computer-Aided Molecular Design **9**(00): 139-148.

Clark, D. E., A. D. Frenkel, S. A. Levy, J. Li, C. W. Murray, B. Robson, B. Waszkowycz and D. R. Westhead (1995). "Pro_Ligand: An Approach to De Novo Molecular Design. 1. Application to the Design of Organic Molecules." Journal of Computer-Aided Molecular Design **9**: 13-.

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Clark, D. E., M. A. Firth and C. W. Murray (1996). "Molmaker - De Novo Generation of 3D Databases for Use in Drug Design." Journal of Chemical Information & Computer Sciences **36**(1): 137-145.

Westhead, D. R., D. E. Clark and C. W. Murray (1997). "A Comparison of Heuristic-Search Algorithms for Molecular Docking." Journal Of Computer Aided Molecular Design **11**(3): 209-228.

Van de waterbeemd, H., R. E. Carter, G. Grassy, H. Kubinyi, Y. C. Martin, M. S. Tute, P. Willett, C. Haasnoot, L. B. Kier, K. Muller, S. V. Rose, J. Weber, K. S. Wibley, S. Wold, D. B. Boyd, D. E. Clark, C. Dehaen, N. D. Heindel, P. Kratochvil, B. Kutscher, R. A. Lewis, M. Mabilia, W. V. Metanomski, E. E. Polymeropoulos, J. P. Tollenaere, M. D. Turnbull, W. E. Vanderlinden and E. J. Vanlenten (1997). "Glossary of Terms Used in Computational Drug Design." Pure And Applied Chemistry **69**(5): 1137-1152.

Murray, C. W., D. E. Clark, T. R. Auton, M. A. Firth, J. Li, R. A. Sykes, B. Waszkowycz, D. R. Westhead and S. C. Young (1997). "Pro-Select - Combining Structure-Based Drug Design and Combinatorial Chemistry for Rapid Lead Discovery .1. Technology." Journal Of Computer Aided Molecular Design **11**(2): 193-207.

Brown, R. D. and D. E. Clark (1998). "Genetic Diversity - Applications of Evolutionary Algorithms to Combinatorial Library Design [Review]." Expert Opinion on Therapeutic Patents **8**(11): 1447-1459.

Baxter, C. A., C. W. Murray, D. E. Clark, D. R. Westhead and M. D. Eldridge (1998). "Flexible Docking Using Tabu Search and an Empirical Estimate of Binding Affinity." Proteins **33**(3): 367-382.

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Lewis, R. A., S. D. Pickett and D. E. Clark (2000). "Computer-Aided Molecular Diversity Analysis and Combinatorial Library Design." Reviews In Computational Chemistry **16**(16): 1-51.

Pickett, S. D., I. M. McLay and D. E. Clark (2000). "Enhancing the Hit-to-Lead Properties of Lead Optimization Libraries." Journal of Chemical Information & Computer Sciences **40**(2): 263-272.

Clark, D. E. (2001). "Prediction of Intestinal Absorption and Blood-Brain Barrier Penetration by Computational Methods." Combinatorial Chemistry & High Throughput Screening **4**(6): 477-96.

Clark, D. E. (2002). "Computational Methods for the Prediction of ADME and Toxicity - Preface." Advanced Drug Delivery Reviews **54**(3): 253-254. Editor of this volume.

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Yvonne Martin, Chair 2000-2005

In Memoriam JEAN-LUC FAUCHÈRE (1941-2003)

The death of Jean-Luc Fauchère on May 30, after a long and brave battle against cancer, was a tragic blow for his wife and his four children, as well as for so many of us. Jean-Luc was a talented and very creative peptide chemist. Soon after his Ph.D. in physical chemistry at the University of Fribourg (Switzerland) in 1970, he began his research at the Department of Molecular Biology and Biophysics at the ETH in Zürich. After a period of careful peptide synthetic work, he focused his interest on the relationships between peptide structure and their physicochemical and mainly biological properties. His physicochemical background turned out to be an excellent starting point for what became known as "Quantitative structure-activity relationships" (QSAR). Indeed, one of his sabbaticals was spent with two founding fathers of QSAR, Corwin Hansch and Albert Leo at Pomona College in Claremont (CA, USA). Very soon, he became a recognized player in this field. In 1984, he moved his group within the ETH to a newly established Department of Biotechnology where he found not only excellent conditions and support for his work but also many friends, among them the department chairman Prof. Klaus Mosbach. The same year, he was appointed Adjunct Professor of Biophysical Chemistry at the University of Fribourg. During this period, Jean-Luc published many QSAR studies on various peptide classes, as well as an impressive dataset of QSAR descriptors which have added significantly to our biophysical understanding of these compounds. His international recognition and fame grew rapidly as a result of his contributions, and in 1988 he was the Chairman of a memorable European QSAR Meeting held in Interlaken (Switzerland). During his career, he published more than 180 papers and was the supervisor of 23 PhD students. His manifold teaching activities can also be stressed, be it at the ETH or in Fribourg. He was also an active member of numerous scientific societies such as the Swiss Chemical Society, the French Society of Medicinal Chemistry, the American Peptide Society, the European Neuropeptide Club and the QSAR and Modelling Society.

In 1989, he was called as Chemistry Division Director at the Institut de Recherches Servier in the Paris area. Within this company, he created and developed a highly successful research group focused on therapeutic peptides and peptidomimetics. His contributions were both methodological, with the pioneering of automated synthetic technologies in combinatorial and parallel modes, and medicinal, with the discovery, patenting and publication of numerous active compounds in a number of therapeutic areas such as melatonin receptor ligands, MMP inhibitors, and neuropeptide Y receptor ligands.

Jean-Luc impressed all his friends and colleagues with his integrity, dedication to careful and original science, communication skills, friendly humour and engaging personality. We mourn his death, but we cherish his memory and example.

Vladimir Pliska
ETHZ

Bernard Testa
University of Lausanne

A selection of Jean-Luc papers, witnessing his wide interests:

Le Diguarher T, Ortuno JC, Dorey G, Shanks D, Guilbaud N, Pierre A, Fauchere JL, Hickman JA, Tucker GC, Casara PJ.
Parallel liquid synthesis of N,N'-Disubstituted 3-amino azepin-2-ones as potent and specific farnesyl transferase inhibitors.
Bioorg Med Chem. 2003 Jul 17;11(14):3193-204.

Boutin JA, Suply T, Audinot V, Rodriguez M, Beauverger P, Nicolas JP, Galizzi JP, Fauchere JL.
Melanin-concentrating hormone and its receptors: state of the art.
Can J Physiol Pharmacol. 2002 May;80(5):388-95. Review.

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Synthesis, conformational analysis and biological activity of cyclic analogs of the octadecaneuropeptide ODN. Design of a potent endozepine antagonist.
Eur J Biochem. 2001 Dec;268(23):6045-57.

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Substrate specificity and inhibition studies of human serotonin N-acetyltransferase
J Biol Chem. 2000 Dec 15;275(50):39799. No abstract available.

Ferry G, Loynel A, Kucharczyk N, Bertin S, Rodriguez M, Delagrange P, Galizzi JP, Jacoby E, Volland JP, Lesieur D, Renard P, Canet E, Fauchere JL, Boutin JA.
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J Biol Chem. 2000 Mar 24;275(12):8794-805. Erratum in: J Biol Chem 2000 Dec 15;275(50):39799.

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Screening of ligand binding on melatonin receptor using non-peptide combinatorial libraries.
J Recept Signal Transduct Res. 2000 Jan;20(1):105-18.

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Structure-activity relationships of a series of analogues of the octadecaneuropeptide ODN on calcium mobilization in rat astrocytes.
J Med Chem. 1998 Nov 5;41(23):4433-8.

Ferry G, Boutin JA, Hennig P, Genton A, Desmet C, Fauchere JL, Atassi G, Tucker GC.
A zinc chelator inhibiting gelatinases exerts potent in vitro anti-invasive effects.
Eur J Pharmacol. 1998 Jun 19;351(2):225-33.

Grassy G, Yasri A, Sans P, Armbruster AM, Lahana R, Fauchere JL.
Molecular dynamics simulations as a tool to investigate the three-dimensional diversity of peptide and pseudopeptide libraries.
Computer-assisted lead finding and optimisation, 11th European Symposium on QSAR, Wiley-VCH, edited by H van de Waterbeemd, B Testa and G Folkers, 1997, 209-21.

Jacoby E, Boudon A, Kucharczyk N, Michel A, Fauchere JL.
A structural rationale for the design of water soluble peptide-derived neurokinin-1 antagonists.
J Recept Signal Transduct Res. 1997 Nov;17(6):855-73.

Fauchere JL, Henlin JM, Boutin JA.
Peptide and nonpeptide lead discovery using robotically synthesized soluble libraries.
Can J Physiol Pharmacol. 1997 Jun;75(6):683-9. Review.

Thurieau C, Feletou M, Hennig P, Raimbaud E, Canet E, Fauchere JL.
Design and synthesis of new linear and cyclic bradykinin antagonists.
J Med Chem. 1996 May 10;39(10):2095-101.
Boutin JA, Hennig P, Lambert PH, Bertin S, Petit L, Mahieu JP, Serkiz B, Volland JP, Fauchere JL.

Combinatorial peptide libraries: robotic synthesis and analysis by nuclear magnetic resonance, mass spectrometry, tandem mass spectrometry, and high-performance capillary electrophoresis techniques.
Anal Biochem. 1996 Feb 15;234(2):126-41.
Hennig P, Raimbaud E, Thurieau C, Volland JP, Michel A, Fauchere JL.

Solution conformation by NMR and molecular modeling of three sulfide-free somatostatin octapeptide analogs compared to angiopeptin.
J Comput Aided Mol Des. 1996 Feb;10(1):83-6.

Paladino J, Thurieau C, Morris AD, Kucharczyk N, Rouissi N, Regoli D, Fauchere JL.
Synthesis and in vitro activities of new tryptophan-modified and thiomethylene-containing pseudopeptide antagonists of the neurokinins.
Int J Pept Protein Res. 1993 Sep;42(3):284-93.

Feuilloley M, Stolz MB, Delarue C, Fauchere JL, Vaudry H.
Structure-activity relationships of monomeric and dimeric synthetic ACTH fragments in perifused frog adrenal slices.
J Steroid Biochem. 1990 Apr;35(5):583-92.

Fauchere JL, Quarendon P, Kaetterer L
Estimating and representing hydrophobicity potential
J Mol Graph. 1988 Dec;6(4):203-6.

Fauchere JL, Charton M, Kier LB, Verloop A, Pliska V.
Amino acid side chain parameters for correlation studies in biology and pharmacology.
Int J Pept Protein Res. 1988 Oct;32(4):269-78.

Nisato D, Wagnon J, Callet G, Mettefeu D, Assens JL, Plouzane C, Tonnerre B, Pliska V, Fauchere JL.
Renin inhibitors. Free-Wilson and correlation analysis of the inhibitory potency of a series of pepstatin analogues on plasma renin.
J Med Chem. 1987 Dec;30(12):2287-91.

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FEBS Lett. 1985 Apr 22;183(2):283-6.

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A quantitative structure-activity relationship study of the inhibitory action of a series of enkephalin-like peptides in the guinea pig ileum and mouse vas deferens bioassays.
J Med Chem. 1982 Dec;25(12):1428-31.

Fauchere JL, Do KQ, Schwyzer R, Robson LE, Gillan MG, Paterson SJ, Kosterlitz HW.
Interaction of p-nitrophenylalanine enkephalins with mu-, delta- and kappa-subtypes of the opiate receptor.
Eur J Pharmacol. 1982 Feb 5;77(4):339-42.

Fauchere JL, Petermann C.
Synthesis of gamma-methyl-L-leucine (neopentylglycine, Neo) and derivatives suitable for peptide synthesis.
Int J Pept Protein Res. 1981 Sep;18(3):249-55.

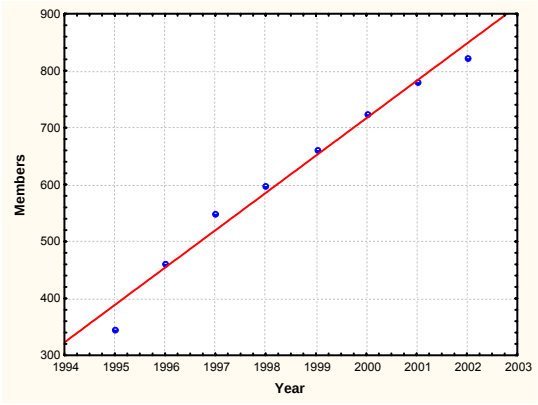
Do KQ, Fauchere JL, Schwyzer R, Schiller PW, Lemieux C.
Electronic, steric, and hydrophobic factors influencing the action of enkephalin-like peptides on opiate receptors.
Hoppe Seylers Z Physiol Chem. 1981 Jun;362(6):601-10.

Fauchere JL, Do KQ, Jow PY, Hansch C.
Unusually strong lipophilicity of 'fat' or 'super' amino-acids, including a new reference value for glycine.
Experientia. 1980 Oct 15;36(10):1203-4.

From the Secretary

Since 1995 Society kept showing a nearly linear growth in the number of its members.

August 1995	346 members
August 1996	463 members
July 1997	549 members
July 1998	599 members
July 1999	660 members
August 2000	725 members
October 2001	780 members
October 2002	823 members
October 2003	880 members



Distribution of the Newsletter

An alert will be send to all members via our Mailbox that the Newsletter is available in pdf format at our web site. No printed copies will be sent to save costs.

Update of (e-mail) addresses & affiliation

Please support our work, especially for the distribution of messages, by regularly updating e-mail and/or affiliation addresses. If you detect a wrong address in the members list in our Web page (http://www.qsar.org/members.htm), please inform
han_waterbeemd@sandwich.pfizer.com

Following email addresses generate an error:

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yarim.mine@pharma.anbi.ethz.ch
rlc@rti.org
markf@pharmeco.com
mreca@kaiser.alma.unibo.it
emmanuel.polymeropoulos@astamedica.de
dennis@mdli.com
fseisph@ku.ac.th
eoregan@healthtech.com

Lost email addresses

Although we all work with computers, still some email addresses are missing. Can you help finding them? Let me know so that we can get these folks back on line.

Allen	Mark	Novartis Pharma UK	UNITED KINGDOM
Alho	Sari	University of Helsinki	FINLAND
Araki	Koichi	Mitsubishi Petrochem. Co.	JAPAN
Ashman	William P.	U.S. Army Chem. Res.Dev.	USA
Ashton	Michael	Rhône Poulenc Rorer Ltd	UNITED KINGDOM
Barlett	Bob	834 Estates St.	USA
Bauman	Norman	Innapharma	USA
Berner	Heinz	Novartis	AUSTRIA
Biagi	Gian Luigi	Istituto di Farmacologia	ITALY
Blaschke	Heinz	Cl Pharma AG	AUSTRIA
Blum	Diane J. W.	112 Clwyd Road	USA
Bolton	Evan	American Cyanamid Company	USA
Boxall	Alistair	WRC	UNITED KINGDOM
Brannigan	Lawrence H.	9411 Cimarron Court	USA
Burgot	Jean Louis	Laboratoire Chimie Analytique	FRANCE
Burgot	Gwenola	Maitre de Conférences	FRANCE
Cativiela Marin	Carlos	Dpto. Quimica Organica	SPAIN
Cato	Stephen, J.	Chemical Design Inc.	USA
Caumel	Yves	SANOFI Recherche	FRANCE
Chau	Pak-Lee	University of Cambridge	UNITED KINGDOM
Cholinski	Jacek	Instytut Farmaceutyczny	POLAND
Cipriano	Robyn	SciVision	USA
Coe	Chris	BioTeknik Rational Drug Design	UNITED KINGDOM
Coats	Joel	Iowa State University	USA
Colombo	Lino	University of Pavia	ITALY
Cossement	E. R.	UCB Pharm. Sector	BELGIUM
Csorvasi	Istvan	Alkaloida Rt.	HUNGARY
De Paulis	Tomas	Vanderbilt University	USA
Donescu	Alexandrina	Universitatea Bucuresti	ROMANIA
Dragos	Dan	University of Medicine and Pharmacy	ROMANIA
Dross	Karl	Inst. Brain Research	GERMANY
Elenes	Florin	Institutul de Chimie al Academeie	ROMANIA
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Engle	Thomas	Rhône-Poulenc AG Products	USA
Escobar	Jose-Luis	College of Pharmacy 4.214	USA
Evans	Suzanne	Anaquest, Inc	USA
Fadhil	G. F.	Chemistry Department	IRAQ
Farahi	Asgar Kh.	Drug Design Center	IRAN
Fisanick	William	Chemical Abstracts Service	USA
Fukami	Harukazu	Suntory Limited Research Center	JAPAN
Gange	David M.	Row2 Technologies	USA
Gao	Ying-Duo	Merck	USA
Golender	Valery	DCL Systems International Ltd.	ISRAEL
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Govers	H.	Dept of Environmental &Toxicological Chem.	THE NETHERLANDS
Hadzi	Dusan	Boris Kidric Institute	SLOVENIA
Helmes	C. Tucker	ETAD	USA
Hillenbrand	Mihaela	Universitatea Bucuresti	ROMANIA
Hoeschele	James D.	6865 Montfort Dr.	USA

Holzgrabe	Ulrike	Universität Bonn (Poppelsdorf)	GERMANY
Howe	W. Jeffrey	Pharmacia & Upjohn	USA
Izumi	Keiichi	Sumitomo Chemical Co. Ltd.	JAPAN
Jerman-Blazic	Borka	Institut Josef Stefan	SLOVENIA
Kamoshita	Katsuzo	Sumitomo Chemical Co. Ltd.	JAPAN
Khambay	B. P. S.	Crop & Environ. Protection Div.	UNITED KINGDOM
Kido	Masaru	Otsuka Pharmaceutical Ind.	JAPAN
Kint	Saima	USDA	USA
Klitzenko	Olga	Institute of Medical Training	RUSSIA
Knjasev	Boris Ananjevich	Lenin Street 30, 63	RUSSIA
Kortagere	Sandya	Mount Sinai School of Medicine	USA
Kuchar	Miroslav	Research Institute Pharmacy & Biochemistry	CZECH REPUBLIC
Kuchcaev	Boris Irikovich	Molodesznaya Street 9, 27	RUSSIA
Kumita	Izumi	Nippon Soda Co.	JAPAN
Kuyper	Lee	Burroughs Wellcome Co.	USA
Ladner	David W.	American Cyanamid Co.	USA
Lau	Wan	Bristol-Meyers Squibb	USA
Lee	On	School of Pharmacy	TAIWAN
Lehmann	Pedro A.	Depto. Farmacologi y Toxicologi	MEXICO
Leonardi	A.	Recordati S.p.A	ITALY
Lopez	Manel	Almirall Prodesfarma SA	SPAIN
Luca	Costantino	Dip. di Scienze Farmaceutiche	ITALY
Mager	Harry	Bayer AG, Bldg. 470	GERMANY
Makino	Kenzi	Central Research Institute	JAPAN
Mattie	Renee	AstraZeneca Pharmaceuticals	USA
McKinney	James D.	Pharmacokinetics Branch	USA
Miller	Joseph	Universidade Federal da Paralba	BRAZIL
Moser	Peter	Gempengasse 71	SWITZERLAND
Moyer-Zirpoli	Susan	Slippery Rock University	USA
Mracec	Mioara	Institutl de Chimie al Academiei	ROMANIA
Mutsukado	Motoo	Patent Department	JAPAN
Negrié	Cristina	Lacer SA, R&D Dept.	SPAIN
O'Connor	Mary V.	Exxon Biomedical Sciences, Inc.	USA
Oda	Kengo	Mitsui Toatsu Chemicals, Inc.	JAPAN
Ohtaka	Hiroshi	Kanebo Ltd	JAPAN
Omata	Kenzo	Mitsubishi Kasei Corporation	JAPAN
Ordukhanian	A. Ashot	GRICC	RUSSIA
Pallakoff	Pamela A.	SRI International	USA
Pankkioyj	Leonia	Unioninkatu 22	FINLAND
Parodi	Silvio	Inst.Nat. Ricerca Sul Cancro	ITALY
Parton	Richard	Eastman Kodak	USA
Phillips	Richard B.	975 California Ave.	USA
Pillan	Antonio	Pharmacia R&D	ITALY
Potashnikov	Piotr	Altufievskoye shosse 40, Apt.219	RUSSIA
Pouplana Sole	Ramon	Universitat de Barcelona	SPAIN
Ramsden	C. A.	Department of Chemistry	UNITED KINGDOM
Rejholec	Valcav	Research Institute	CZECH REPUBLIC
Ren	Shijng	University of Southern California	USA
Roush	David	FMC Corporation	USA
Roy	Timothy	Mobil Oil Corp	USA
Rozenblit	Anatoly	Latvian Institute Organic Synthesis	LATVIA

Sahini	Victor Emanuel	Universitatea Bucuresti	ROMANIA
Salama	Zoser	L.A.B. GmbH & Co	GERMANY
Seclaman	Eduard	Institutul de Chimie al Academeie	ROMANIA
Shorter	John	29 Esk Terrace	UNITED KINGDOM
Siegel	Sidney	Office Hazardous Substances Information	USA
Singh	Bupinder	Institute Pharmaceutical Sciences	INDIA
Singh	Suresh B.	Wyeth-Ayerst Research	USA
Smith	Eric W.	School of Pharmacy	SOUTH AFRICA
Southwick	Rett	Philip Morris USA	USA
Speece	R. E.	Civil & Environmental Engineering Dept.	USA
Stein	Mark M.	ICI Americas, Inc.	USA
Stein	Reinhardt	Wyeth-Ayerst Research	USA
Szalkowski	Mary B.	Prisma Corp.	
Torchilin	Ekaterina	Tufts University	USA
Tosato	Maria Livia	Embassy of Italy	USA
Turner	James E.	Health and Safety Research Division	USA
Umeda	Yoshihisa	Takara Shuzo Co., LTD.	JAPAN
Volanschi	Elena	Universitatea Bucuresti	ROMANIA
Vorpagel	Erich, R.	Biosym Technologies, Inc	USA
Weber	Hans-Peter	Nova Research Services	SWITZERLAND
Weinberg	Josette	Universitatea Bucuresti	ROMANIA
Wolters	Fred	Clorox Technical Center	USA
Wong	Rosalind Y.	USDA Western Regional Research Center	USA
Xie	Qian	Laboratory of Computer Chemistry	P.R.CHINA
Yalcin	Ismail	Faculty of Pharmacy	TURKEY
Yamakawa	Masumi	Shionogi Pharmaceutical Co.	JAPAN
Yoshimura	Yoshinobu	Takeda Chemical Industries	JAPAN
Yoshioka	Hirosuke	Bioregulator Design & Synthesis Laboratory	JAPAN
Yuta	Kohtaro	Fujitsu Makuhari Systems Laboratory	JAPAN

Webmaster

The webmaster is Stefan Balaz at North Dakota University (stefan.balaz@ndsu.nodak.edu). The Societies' URL is in the heading of this Newsletter.

Contributions to the Newsletter and our website

All members are invited to contribute our Newsletter and to our web site. This Newsletter shall not be a one-man-show, it gains from your experience. Our publishing policy will not allow us to accept scientific contributions, which better should be sent to a reviewed journal. However, tips and tricks, key references, conferences, books, shareware, even the announcement of new commercial software, are welcome. We depend on your active participation!

Please send your comments and contributions to: Han van de Waterbeemd, c/o Pfizer Global Research and Development, Sandwich Laboratories, PDM, IPC 351 Sandwich, Kent CT13 9NJ, UK, E-MAIL han_waterbeemd@sandwich.pfizer.com

FROM OUR BRANCHES

RUSSIA

Contact: Oleg Raevsky (raevsky@ipac.ac.ru), secretary Yulia Borodina (borodina@ibmh.msk.su) http://www.ibmh.msk.su/qsar/

During the past year Russian Section of the QSAR and Modelling Society organized one Symposium and six seminars. The Symposium "Bioinformatics and Computer-Aided Drug Discovery" was held in Moscow in April 7-8, 2003 in the Framework of X Russian National Congress "Man and Drugs". Seven plenary lectures and eleven oral talks were presented at the Symposium. List of the plenary lectures is given below:

Vladimir Tumanyan (Institute of Molecular Biology of Rus. Acad. Sci., Moscow).
Relationships between the proteins polimorphysm and ethiology of certain diseases.

Alexey Ivanov (Institute of Biomedical Chemistry of Rus. Acad. Med. Sci., Moscow). Cytochromes P450 as a targets for computer-aided design of new drugs.

Nikolay Zefirof (Chemical Department of Moscow State University).
Quantitative structure-activity relationships: from Hansch models to ANN and 5-D QSAR.

Oleg Raevsky (Institute of Physiologically Active Compounds, Chernogolovka, Moscow Region).
Physical-chemical models of drigs' transport properies in the organism.

Vladimir Poroikov (Institute of Biomedical Chemistry of Rus. Acad. Med. Sci., Moscow).
Bioinformatics: virtual and real integration of knowledge in discovery of new drugs.

Yuri Vorob'ev (Novosibirsk Institute of Biorganic Chemistry, Novosibirsk).
An effective method for estimating free energy of ligand's binding with a biopolymer molecule.

Seminars were as follows.

Fedor Kolpakov ("BIOSOFT.RU", Novosibirsk).
BioUML: Integrative computer environment for modelling of biological processes at the molecular-genetics level.

John Dearden (School of Pharmacy and Chemistry, Liverpool John Moores University).
QSAR modelling of drug toxicity.

Patrick Sofarelli (Prous Science, Barcelona, Spain).
Prous Science products for pharma science and industry.

Andreas Loeffler and Ulrike Uhrig. (Tripos GmbH, Muenchen, Germany).
Tripos computational chemistry software: present and future.

Petr Vlassov (Institute of Molecular Biology of Rus. Acad. Sci., Moscow).
Analysis of conformation for amino acid residues in globular proteins. Prediction of left-handed helix polyproline II.
Anatoly Silberstein (Institute of Experimental and Theoretical Biophysics, Russian Academy of

Sciences, Puschino, Moscow Region).
Fragmental linear notation of molecular structures. Language and applications: database of metabolites, query language, generation of libraries.

The members of Russian Section of The QSAR and Modelling Society have presented several oral talks at the International symposia and conferences:

Archakov A. Bioinformatic Insight into the Structural Unity and Diversity of Cytochromes P450. 13th International Conference on Cytochromes P450, Ed. Pavel Anzenbacher and Jiri Hudecek, Prague, Czech Republic, 2003.

Bachurin S. Rational design of novel neuroprotectors and cognition-enhancers in series of glutamate receptors ligands. Second Joint French-Swiss Meeting on Medicinal Chemistry, Beaune, France, 2003.

Baskin I. Molecular Modeling of the N-methyl-D-aspartate receptor and design of neuroprotective drugs, Fourth International Symposium on Pharmaceutical Chemistry, Istanbul, Turkey, 2003.

Belenikin M. Molecular Modeling and Model of Functioning of Metabotropic Glutamate Receptor mGluR1. 14-th Silver Camerino-Noordwijkerhout Symposium “Ongoing Progress in the Receptor Chemistry”, Camerino, Italy, 7 – 11 September 2003.

Borodina Yu. Computer predicting of biotransformation potential from molecular structure. Computational Methods in Toxicology and Pharmacology Integrating Internet Resources (CMTPI-2003). Thessaloniki, Greece, 17-19 September 2003.

Filimonov D. PASS-based self-consistent regression for QSAR/QSPR problems. Computational Methods in Toxicology and Pharmacology Integrating Internet Resources (CMTPI-2003). Thessaloniki, Greece, 17-19 September 2003.

Ivanov A. General trends in 3D modelling of cytochromes P450. 13th International Conference “Cytochromes P450, Biochemistry, Biophysics and Drug Metabolism” Prague, 2003.

Ivanov A. The use of active site mould for the database mining of new ligands for enzymes with unknown 3D structure: focus on monoamine oxidase A. 5th International Conference on Molecular Structural Biology, Vienna, 2003.

Lisitsa A. Balance Sheet for Cytochrome P450 Knowledgebase. 13th International Conference on Cytochromes P450, Ed. Pavel Anzenbacher and Jiri Hudecek, 2003.

Milchevsky Yu. V. Acids Substitutions in Collagen in Connection with Structure and Diseases. International Moscow Conference on Computational Molecular Biology, 2003, Moscow.

Palyulin V. The joint application of QSAR and molecular modeling techniques in the design of new ligands of AMPA and NMDA receptors. 3rd Indo-US Workshop on Mathematical Chemistry. Duluth, USA, 2003.

Poroikov V. Computer prediction of biological activity spectra as a tool for determining the priorities in testing. The Ist International Conference of the Moldavian Chemical Society "Achivements and Perspectives of Modern Chemistry".Chisinau, Moldova, October 6-8, 2003.

Poroikov V. Computer prediction of drug-like substances biotransformations. E-Drug Discovery Symposium, Seoul, Korea, 20-24 May 2003.

Poroikov V. Computer-aided drug discovery by prediction of biological activity spectra for substances. International Symposium on Drud Discovery and Process Research (DDPR-2003), Kolhapur, India, 21-24 January 2003.

Poroikov V. Postgenomic chemistry in drug discovery. IUPAC Workshop "Postgenomic Chemistry", Moscow, Russia, September 5-7, 2003.

Poroikov V. Prediction of biological activity spectra via Internet. Computational Methods in Toxicology and Pharmacology Integrating Internet Resources (CMTPI-2003). Thessaloniki, Greece, 17-19 September 2003.

Sadym A. Computer predicting of drig-like substances' metabolism: from biotransformation reactions to metabolic network. 4th International Symposium on Pharmaceutical Chemistry, Istanbul, Turkey, 2003.

Tikhonova I. AMPA and NMDA receptors targeted virtual screening. Fourth International Symposium on Pharmaceutical Chemistry, Istanbul, Turkey, 2003.

Vorobjev Y.N. Molecular modeling program complex BISON. International conference "Targeting RNA: artificial ribonucleases, conformational traps and RNA interference", 2003, Novosibirsk, Russia.

ITALY

Contact: Sergio Clementi (sergio@chemiome.chm.unipg.it)

No news!

UK

Contact: Sally Rose (s.rose@cresset-bmd.com)
http://www.ukqsar.co.uk/

Report from the UK QSAR and Chemoinformatics Group

Siew Kuen Yeap, Pfizer, stepped down as secretary of the UK QSAR and Chemoinformatics Group in November 2002. Kuen has been an outstanding secretary and contributed a great deal to the efficient running of the group over the last few years. I would like to extend my thanks to her. She will be a difficult act to follow. Mark Smith, GSK, has kindly volunteered to take over the position.

The Group held two meetings in 2003. Both meetings were well attended and the group continues to operate a no fee basis for attending the meetings, thanks to the generosity of the host companies.

The Spring meeting in April was hosted by Lilly at their research centre at Windlesham and organised locally by Richard Lewis. The agenda is given below.

Chair: Richard Lewis and Mike Bodkin
Mark Mackey, Cresset Biomolecular Discovery Ltd
Structureless virtual screening for novel small molecule leads
Trudie Wright, Sheffield University
Multiobjective optimisation of combinatorial libraries
Céline Lebailly, University Catholique de Louvain

A fast exchange algorithm for designing focused library design in lead optimisation
Nick Stiefl, Wurzburg University
MaP: A 3D QSAR technique based on the distribution of molecular surface properties - Applications, validation and parameter settings
Dave Morley, Ribotargets
rDock: A virtual screening platform for hit identification and lead optimisation
Francesca Toschi, Southampton University
The computational investigation of protein/ligand complexes: ligand binding induced- fit
Ron Knegtel, Vertex
A structure-based approach to the design of genuinely broad caspase inhibitors

The Autumn meeting in October was hosted by Cyprotex at a magnificent manor house, Adlington Hall, Macclesfield. The meeting was organised locally by Dave Leahy, Karen Jones and Tracey Tomlinson. The agenda is given below.

Chair: David Leahy
Alexey Lagunin, Institute for Biomedical Chemistry, Moscow
Recent developments in the PASS approach
Ian Nabney, Aston University
Data visualisation and chemometrics
Martyn Ford, Portsmouth University
Hits or misses? Selecting compounds for gene family targeted high throughput screening
Pranas Japertas, PharmAlgorithms
Automated approaches to QSAR model building
Brian Hudson, Portsmouth University
Application of the TREPAN rule extraction method to chemoinformatic data
Kamaldeep Chohan, AstraZeneca
Development of local or global models for the prediction of DMPK and other properties
Russell Viner, Syngenta
A fragment based design approach to ACP-enoyl reductase inhibitors

Further details and abstracts from both meetings are available on the society's web page http://www.ukqsar.co.uk.

The Spring 2004 Meeting will be hosted by Pfizer at Sandwich and the Autumn Meeting will be held at AstraZeneca, Charnwood. I would like to thank both these companies and our generous hosts in 2003 for their support for the Group.

For further information on the society, please contact
Sally Rose, Chairwoman, srose@biofocus.co.uk or
Mark Smith, Secretary, mark.d.smith@gsk.com

HUNGARY

Contact: Antal Lopata (lopata@chemicicro.hu)
http://www.qsar.mtesz.hu (in Hungarian!)

During the past year we organized a two-day meeting together with the Chemometrics Group of the Hungarian Academy of Sciences. The meeting was held in Szeged on April 24-25, 2003. Altogether 22 lectures were given, 17 in four QSAR and Modeling sessions and 5 in a chemometrics session. The former 17 lectures are as follows (titles are translated from Hungarian):

L. Poppe (Budapest University of Technology and Economics):
Homology Modeling of B12-Dependent Mutases

Z. Bikádi, G. Maksay, M. Simonyi (Chemical Research Center, Hung. Acad. Sci.):
A Theoretical Study of the Binding of Antagonists Using a 5HT3A Receptor Model

I. Kolossváry (Budapest University of Technology and Economics & Biokol Research):
Low-Mode Protein Modeling

G. Tusnády (Institute of Enzymology, Hung. Acad. Sci.):
Topology of Transmembrane Proteins

T. Körtvélyesi, S. Dennis, S. Vajda (University of Szeged):
Identification of Protein Binding Sites Using Computational Methods

I. G. Csizmadia (University of Toronto):
Peptide Conformations

T. Beke, A. Perczel (Eötvös University):
Intrinsic Secondary Structures of Peptides Built Up from β-Amino Acids

A. Láng, A. Perczel (Eötvös University):
Conformational Analysis of N-Formyl-L-Methionine Amide Using Ab Initio Method

S. Fejér, Z. Jenei (University of Szeged):
Conformational Analysis of the ALA-VAL and VAL-ALA Dipeptides

G. M. Keserű (Gedeon Richter Ltd.):
QSAR Methods for the Prediction of HERG Potassium Channel Affinity

W. Győrffy, A. Lopata (CheMicro Ltd.):
Comparison of Classical and Quantum Chemical Electrostatic Potential Fields in CoMFA Models

K. Héberger (Chemical Research Center, Hung. Acad. Sci.):
Prediction of Rate Constants for Addition Reactions of Various Radicals on Styrene Using Partial Least Squares

M. Gáspár, I. Kövesdi, P. Mátyus (Semmelweis University & EGIS Ltd.):
Estimation of the Solubility of Organic Compounds Using a Computational Method

T. Veszprémi (Budapest University of Technology and Economics):
Modeling the Addition Reactions of Disilenes

T. Gunda (University of Debrecen):
Computation of the Geometries of β-Lactam Antibiotics

I. Lukovits (Chemical Research Center, Hung. Acad. Sci.):
Enumeration of Conjugated Circuits in Nanotubes

F. Bogár (University of Szeged):
A Simple Solid State Physical Model of the D.C. Conductivity of DNA

The Hungarian QSAR Group has got a web site since November, 2000 (in Hungarian): www.qsar.mtesz.hu

Dr. Antal Lopata
CheMicro Research & Development Co. Ltd.

Károly kőrút 1, H-1075 Budapest, Hungary
Tel: +36-1-4110492
Fax: +36-1-4110494
E-mail: lopata@chemicro.hu

ROMANIA

Contact: Zeno Simon (mailto:zsimon@cbg.uvt.ro) & Tudor Oprea (mailto:toprea@salud.unm.edu)

No news!

Z. Simon

MEETING REPORTS

None!

OPINIONS & ALERTS

See also the regular debates in our mailbox!

"The importance of not turning off your mind when switching on the computer is one of the points discussed in Hugo Kubinyi's article, which highlights several important issues in modern drug discovery research in which hype or false conclusions could be hindering the chances of success."
See Hugo Kubinyi, "Drug research: myths, hype and reality", Nature Rev. Drug Discov. 2(8), 665-668 (2003).
Article can be down-loaded from http://home.t-online.de/home/kubinyi

"ADME/Tox Informatics: Adding Innovation to Structure-Based Drug Design", in "Current Topics in Medicinal Chemistry", Vol 3, Number 11.
Ed. R. Bursi, Bentham Science Publishers Ltd., U.A.E.

CONTRIBUTIONS

Peptide Ligands to Non-peptide Ligands from Virtual Screening? You'd better believe it!

Tim Cheeseright, Mark Mackey, Sally Rose and Andy Vinter.
tim@cresset-bmd.com, mark@cresset-bmd.com, sally@cresset-bmd.com, andy@cresset-bmd.com
Cresset Biomolecular Discovery Ltd., The Spirella Building, Letchworth, SG6 4ET UK
www.cresset-bmd.com

The application of molecular similarity in terms of structure or shape-based models to the *in silico* design of lead compounds has proved to be disappointing. High Throughput Screening and combinatorial chemistry have so far failed to produce a large increase in the numbers of robust, diverse leads progressing through the drug discovery cycle. There remains a clear need for alternative approaches to molecule design. Factors affecting molecular recognition need to be better understood and applied by fast and cheap computational methods.

The structural topology of a ligand is not what the protein target recognizes. This must be so since we know many examples of diverse structural classes that act at the same biological site. The trick is to define what the protein sees and this is almost certainly the electron cloud of the ligand at and beyond its van der Waals surface. The Molecular Electrostatic Potential (MEP) has traditionally been used to characterise this cloud but has not had the success it deserves: It is slow to compute, complex to analyse and most importantly, it is inaccurate when derived from atom-centred partial charges (ACCs). ACCs are the usual way most molecular mechanics define charge distribution and is too gross an approximation to tolerate. Cresset has developed a new approach, called XED[1], to the electronic definition of molecules. It successfully reproduces experimental observations such as aromatic ring stacking[2] and furnishes the correct starting point for the calculation of accurate MEPs.

Using XED, the MEP map can be distilled into a simple set of 3D points in space we call molecular field points[3] localising the positive (electron deficient) and negative (electron rich) regions around the ligand. When combined with molecular field points describing the van der Waals and hydrophobic properties of the molecule, this set of four field point types uniquely defines the surface of the molecule as it appears to other molecules, without direct reference to the molecule's chemical structure.

Once we were able to define what is seen by a target protein, it was easy to set up a database of chemicals, each with its own set of accessible conformations, stored as field point patterns or FieldPrints™ rather than structures. A 'template' consisting of the FieldPrint™ of an active compound would be used to scan the database for similar FieldPrints™. Hits would, by definition, have no direct structural similarity and would therefore return a set of compounds broad enough to provide new and truly diverse structural leads.

Funded by the Wellcome Trust, Cresset was formed two years ago to put together this Virtual Screening idea and come up with a working tool. This done, a collaboration with the James Black Foundation (JBF) served to validate the FieldPrints™ technology. We used the field points of a known gastrin GPCR antagonist in its active conformation as a template to search though a database of 30 million field point entries from 600,000 commercially available chemical compounds. 88 candidates were distilled out, purchased and tested on the JBF gastrin peptide GPCR

binding assay. 27 of the 88 had a $pK_b > 5.0$ (K_i 10μm). 10 of the 27 had a $pK_b > 5.5$ and the top 4 pK_bs were greater than 6.0 (K_i ~1μm). The 27 active hits were in the molecular weight range 300 and 600 and all but two represented structural classes never before associated with gastrin antagonism. These results reflect the success of the approach in the case of a GPCR which has a natural peptide ligand. The object of the exercise was to validate a new virtual screening technology developed by Cresset that does not use structural topology to define chemical similarity.

The FieldPrints™ encode the surface properties of a molecule, not its chemical structure. As a result, our method is equally applicable to peptide and non-peptide agonists or substrates and provides a truly novel way to progress from peptidic leads to druglike molecules. For those problems that cause drug developers the most heartache: patent cover, poor ADME and toxicology, intractable chemistry or just frustration at the lack of positive progress, Cresset's Virtual Screening Technology offers a simple and effective solution.

References

1. **a) C. A. Hunter, and J. K. M. Sanders (1990), J. Am. Chem. Soc. 112 , 5525-5534. b) J. G. Vinter (1994), J Comp-Aid Mol Design, 8, 653-668. c) J. G. Vinter (1996), J Comp-Aid Mol Design, 10, 417-426.**
2. **a) G. Chessari, C. A. Hunter, C. M. R. Low, M. J. Packer, J. G. Vinter and C. Zonta. (2002) ' An Evaluation of Force Field Treatments of Aromatic Interactions.' Chem. Eur. J.,** 8**, No 13, 2860-2867. b) C. A. Hunter, C. M. R. Low, C. Rotger, J. G. Vinter and C. Zonta. (2002) 'Substituent effects on cation-p interactions: A quantitative study'. Proc. Natl. Acad. Sci.** 99**, No. 8, 4873-4876.**
3. **a) A. Davis, B. Warrington and J. G. Vinter (1987), J Comp-Aid Mol Design, 1, 97-120. b) J. G. Vinter and K. I. Trollope (1995), J. Comp-Aid Mol Design, 9, 297-307. c) J. G. Vinter and M. R. Saunders (1991), in 'Host-Guest Molecular Interactions: from Chemistry to Biology', Ciba Foundation Symposium No 158. p 249-261 (Wiley)**

Chemometrics Note II:

Onion Designs for Selecting Representative Subsets of Molecules

by Mark Earll and Oliver Whelehan of Umetrics UK Ltd

With the advent of higher throughput chemistries and 384 well plates there is a need for ways of selecting representative subsets of molecules spanning a range of molecular properties. QSAR models built on the subsets are then used to predict the activity of the remaining untested compounds.

Design of Experiments

The use of Design of Experiments (DOE) for selecting training sets is well established within statistical molecular design. Principal properties found by Principal Components Analysis (PCA) are used as orthogonal design variables. Approaches such as D-Optimal designs are ideal for selecting small subsets of compounds but do not perform so well when larger selections are required. Space-filling designs may be used for selecting larger subsets but, unlike DOE approaches, are not based on

statistical models. A new design has been developed (Onion Design) which works for large subset selection and is based on a statistical model.

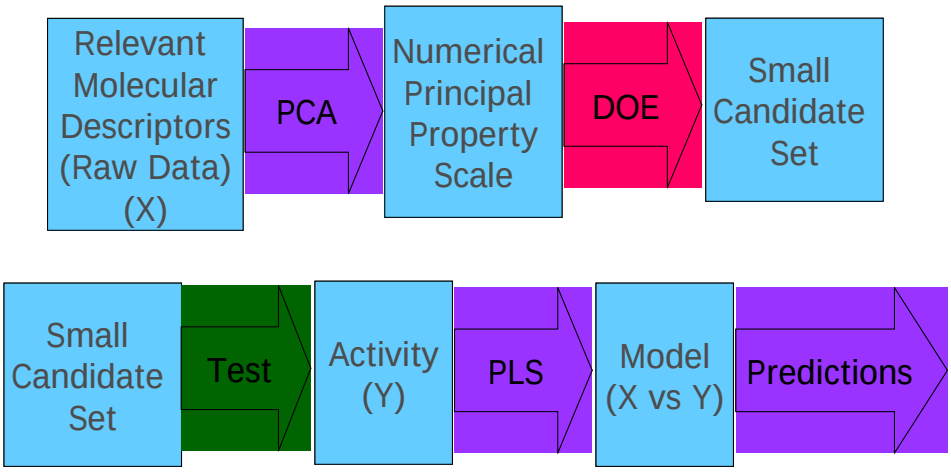

Fig 1. The Statistical Molecular Design Process

Onion Designs

In an Onion Design the chemical space is split into two or more concentric layers or shells and a D-Optimal design is built within each layer based on an underlying model. The number of experiments is easily controlled by varying the number of layers and the layer models.

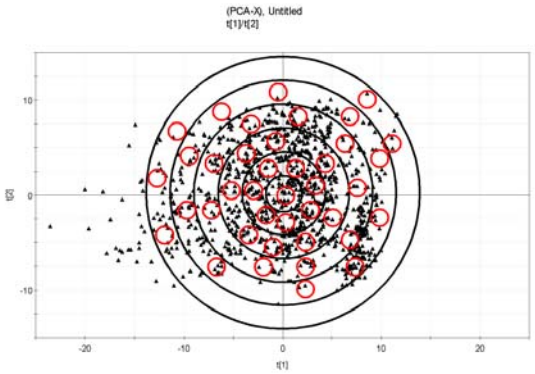

Figure 2 - Onion Design in Principal Properties

The benefit of onion designs is illustrated by an example. A set of 80 molecules is required from a library of 1107 molecules described by 6 principal properties. Constructing a conventional factorial design is unwieldy as many design points are not well represented by any compounds. A D-Optimal design has the disadvantage that many duplicate points are found.

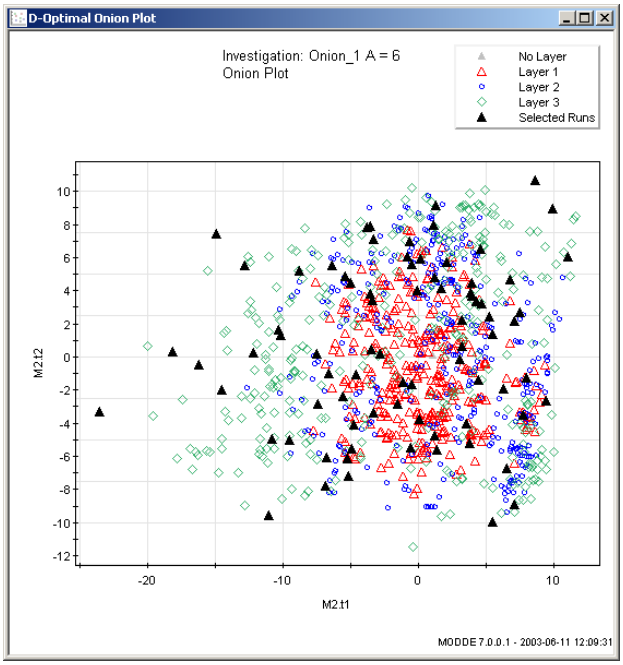

Fig 3. A set of 80 molecules selected from a library of 1107 molecules

An Onion Design with 3 layers and one centre point has 25 + 24 + 30 + 1 = 80 molecules and supports interaction, interaction and quadratic models in each layer respectively.

Onion Designs are supported in the new release of MODDE 7 software from Umetrics with principal component scores directly importable from SIMCA-P 10.

Further Reading

(1) D-Optimal Onion Designs (DOOD) in Statistical Molecular Design. Ing-Marie Olsson
Johan Gottfries, Svante Wold Presented at SSC 8 2003

For further information please email **mark.earll@umetrics.co.uk**

The Role of Topological Structure Descriptors in Modeling ADME Properties

Lowell H. Hall, Department of Chemistry, Eastern Nazarene College, Quincy, MA 02170 and Hall Associates Consulting, 2 Davis Street, Quincy, MA 02170;
Lemont B. Kier, Department of Medicinal Chemistry, School of Pharmacy, Virginia Commonwealth University, Richmond, VA 23298; and
L. Mark Hall, Hall Associates Consulting, 2 Davis Street, Quincy, MA 02170

Over the past few years, significant efforts have been applied to developing QSAR type models for ADME-Tox properties. Among the prominent efforts in this arena is the use of topological structure descriptors, including the electrotopological state (E-State), molecular connectivity chi, and kappa shape indices. We present a brief summary with several references for those who wish to follow these developments.

1. Protein Binding. The binding of drugs to serum proteins is an important part of early drug design. We have shown that topological descriptors provide a strong basis for modeling protein binding of penicillins, with a data set of 74 compounds: r^2 = 0.80. The model, based on both E-State and chi indices, was tested on a set of 13 commercial drugs with excellent results: q^2 = 0.84 [1]. Further, the model was extended to include cephalosporins for a total data set of 115 beta-lactams: q^2 = 0.78 (10% leave out). The same method was applied to a set of 84 commercial drugs whose albumin binding affinity was measured by HPLC [2], producing a sound model: q^2 = 0.70 (LOO) [3]. The model was tested on an external test set of 10 commercial drugs: q^2 = 0.74. The topological-based approach gave a model better than earlier published results [2]. ChemSilico Inc. extended this same approach to a set of 345drugs (with a test set of 40 drugs), providing a good predictive model [4].

2. Blood-Brain Barrier Partitioning. A data set of 106 compounds was collected from 11 literature sources by Rose, Hall and Kier [5]. A three variable model was published in 2002. That model, based on two E-State indices and one chi index, produced reasonable results for such an eclectic data set [5]. A subsequent analysis (yet to be published) was based on a training set of 93 compounds and produced a significantly better model with five descriptors: q^2 = 0.79 (LOO) [6]. Two external test sets were predicted: q^2 = 0.79 (n = 11 compounds) and q^2 = 0.72 (n = 10). To produce a commercial model, ChemSilico has analyzed a training set of 103 compounds (MAE = 0.30) and tested the model on an external validation set of 74 compounds (MAE = 0.39) [4].

3. Human Carcinogenicity. The Center for Drug Evaluation and Research of the US FDA (FDA CDER) has made their rodent carcinogenicity database available for model building. Based on two-year data (male and female mouse and rat), the FDA has created an assessment for high or low risk for an organic compound to produce cancer in humans [7]. MDL Information Systems, as part of a Cooperative Research and Development Agreement, has recently released their model for long-term human carcinogenicity risk. The MDL model is based on topological descriptors and was developed with the use of discriminant analysis. For an external test set (108 compounds) exclusively managed and tested by FDA CDER, the percent of known carcinogenic compounds predicted as carcinogenic is 91% (sensitivity) and the percent known non-carcinogens was predicted as 94% (specificity). These statistics are significantly better than those developed using other modeling approaches, especially for false positives [8].

4. Partition Coefficient, logP. Many models have been developed for logP (octanol/water). Several papers have demonstrated the usefulness of topological descriptors, using both artificial neural network and linear regression modeling [9,10]. Recently, a highly successful commercial model has been released by ChemSilico [4] based on a training set of 16, 893 organic compounds, yielding: q^2 = 0.87 for 10% multiple leave out cross-validation.

5. Aqueous Solubility. Another area of interest for drug design is water solubility. Several authors have published papers that indicate the effectiveness of topological descriptors as the basis for modeling aqueous solubility [11-13]. A large database of

5650 organic compounds has been used as a training set by ChemSilico to produce an excellent aqueous solubility model [4].

6. Fish Toxicity. In recent years several papers have demonstrated the usefulness of topological descriptors in modeling toxicity [14-17]. Recently Rose and Hall published a four variable model for the fish toxicity of 92 organic compounds (phenols, anilines and aromatic hydrocarbons): $q^2 = 0.85$ (LOO) [18]. The model was also tested with two external validation test sets. The results of this model were significantly better than those developed from a quantum mechanical approach [19].

Other ADME properties are also being addressed for the purpose of developing topological structure models. Gute et al have provided a model for dermal penetration of polyaromatic hydrocarbons (PAHs) [20]. ChemSilico is developing a model for human intestinal absorption, based on a large database [4]. We expect to see growing interest in models of this type because they are economical to calculate and very fast for screening large virtual compound structure libraries.

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Current trends for an efficient cheminformatics / QSAR support of drug discovery.

Baurin, N. and Morley, D., Computational Technology, Vernalis (Cambridge) Ltd
Granta Park, Cambridge, CB1 6GB, UK. n.baurin@vernalis.com +44 (0) 1223 895 418.

Several biological parameters are now taken into account in early stages of drug discovery to minimize the high attrition rate of drug candidates in pre-clinical and clinical trials. It's not only binding affinity (IC_{50}) to a macromolecular target that needs to be optimized[1,2], but also an increasing number of Absorption Distribution Metabolism, Excretion and Toxicity (ADME/TOX) properties[3,4]. This increasing flow of structure-activity data is a global challenge for cheminformatics/QSAR teams, who must intervene at several levels to maximize the impact of information mining technologies on early drug discovery projects. These activities are quickly described below.

Development and Validation of new Algorithms. Table 1 reflects the increasing number of innovations, both conceptual and practical, which are reported in the literature and can inspire the in-house development and upgrade of algorithms.

	1995	1996	1997	1998	1999	2000	2001	2002
QSAR	77	101	78	140	153	252	455	575
ADME	5	3	3	4	7	19	35	55
Structure-based	86	112	156	186	203	254	361	389

Table1: Number of references per year of publication and keyword which were retrieved using Pubmed http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed .

Deployment. Some *in-silico* tools (e.g. drug-like filters, general and local ADMET models) should be made accessible to a broad panel of non-specialist users, from managers to bench workers[5], to assist in decision making and compound prioritisation. The intranet provides an attractive option for the controlled deployment of robust, well-validated models, combining ease of use with ease of management. Designing and upgrading a simple, user-friendly web page can be done quickly. It's all about making several software components interact together[6]. Whilst a client desktop component enables the drawing/copying/pasting of molecular structures, elsewhere a property engine calculates the model predictions in batch mode on the intranet server. The other benefit of intranet deployment is training and education. Publishing convincing validation data about each *in-silico* tool is essential to help a broad audience of users adopt new computer-assisted standard practices in their daily work.

Fast design->validation->deployment cycle. For both development and deployment of any new cheminformatics/QSAR algorithm, the whole process must be achieved as quickly as possible[7]. When an idea has been clearly formulated, a prototype can be deployed in weeks, sometimes days, pending on the diversity and quality of the

cheminformatician toolbox. The quality of this toolbox depends largely on the use of a versatile and robust core molecular modelling package.

Last but not least, a **pro-active attitude** is necessary to identify needs, design and deploy prototypes and to finally impact project decisions.

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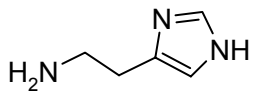
How small can high-activity molecules be?

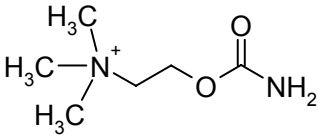
Tudor Oprea [toprea@salud.unm.edu]

A survey of *WOMBAT 2003.2* reveals 120 unique structures, with 188 recorded activities on 30 targets, all with activity better than 10 nM (higher than 8 on the negative Log scale) and MW ≤ 200. Of these, 108 are likely to be charged at pH 7.4: aliphatic amines, amidines or guanidines, and occasionally carboxylic acids. This indicates that low molecular weight compounds are likely to require salt bridge interactions with the receptor in order to achieve high activity.

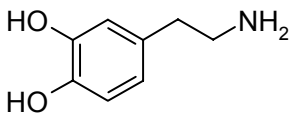
Below are some examples of small molecules (MW ≤ 200) that have biological activity in the nanomolar range. Under each molecule, the following information is included: molecule name (if available), molecular weight, LogP (calculated with LogKow), the biological activity type, value and target. Target names are as follows: H_3, histamine receptor subtype 3; m – muscarine receptor; D_2 – dopaminergic type 2; nACh – nicotine receptor; α_2 – alpha adrenergic receptor subtype 2; $mGLU_2$ - metabotropic glutamate receptor subtype 2; BChE – Butyrylcholinesterase receptor; GABA-B – GABA receptor subtype B; m1 – muscarinic receptor subtype 1.



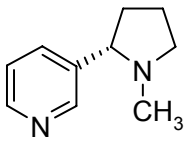
Histamine
MW = 111
LogP = -0.7
K_i = 8.2 (H_3)



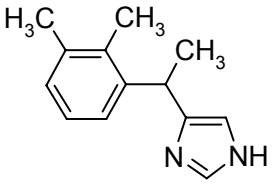
Carbachol
MW = 143
LogP = -3.8
IC_{50} = 8.2 (m)



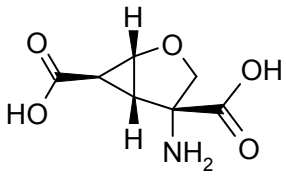
Dopamine
MW = 153
LogP = -1.0
IC_{50} = 8.7 (D_2)



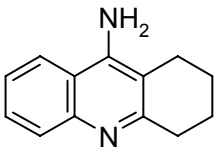
Nicotine
MW = 162
LogP = 1.2
K_i = 9.0 (nACh)



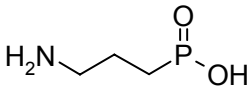
Medetomidine
MW = 200
LogP = 3.8
EC_{50} = 8.5 (α_2)



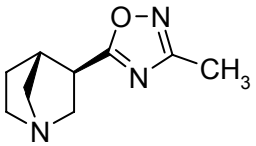
LY-379268
MW = 187
LogP = -4.6
EC_{50} = 8.6 ($mGLU_2$)



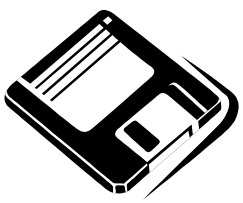
Tacrine
MW = 198
LogP = 2.7
IC_{50} = 8.2 (BChE)



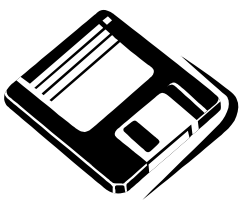
CGP-27492
MW = 123
LogP = -1.7
IC_{50} = 8.6 (GABA-B)



L-670548
MW = 179
LogP = 0.77
K_i = 9.7 (m1)



SOFTWARE



Bio-Loom

For some twenty years the CLOGP program (first offered by the Pomona College Medchem Project and later by BioByte Corp.) has been the world standard for calculating the hydrophobic parameter, log P (oct). Additional functionalities recently added to this program should encourage users to view it in an entirely new light. Since it offers a number of new 'threads' to weave into the 'fabric' of rational drug design, we are calling it **Bio-Loom**.

Bio-Loom now offers access, via Windows PC or Macintosh computers, to databases containing measured log P, log D, pKa, H-donor values, QSAR equations and Hammett-Taft parameters which were previously available only on large workstations operating in OpenVMS, UNIX etc. It's calculation of molar refractivity (as CMR), McGowan volume and molecular weight has proven useful in constructing Hansch-type QSAR. It also offers an exhaustive Activity Type listing which enables one to quickly survey the past successes (both rational and lucky) in drug design and development. This list can be viewed on the BioByte home page. www.biobyte.com.

One can search for compounds acting on any of over 450 Targets, some of which are well-known, such as hmg-coa reductase inhibitor [ec 1.1.1.34](27 hits) and some that are not so well-known, such as : kynurenine hydroxylase inhibitor (2 hits) Similarly the 'Results' section of the Activity Type file has over 700 entries, and enables the user to find compounds effective as 'immunosuppressants' (116 hits) as well as the lesser-known 'treatment of acute myelogenous leukemia [aml]'(8 hits).

We believe the new features in Bio-Loom will be especially useful in schools of pharmaceutical and medicinal chemistry as well as in industry when new areas of research are being considered. The file of over 67,000 drug names and synonyms makes Bio-Loom an excellent Drug Dictionary.

A fully-capable, complimentary evaluation copy of Bio-Loom can be downloaded from the following URL: http://www.biobyte.com/downloads/clogp5b.zip

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ul. Starowislna 13-15
31-038 Krakow, Poland
Tel.: (+48 12) 429 43 45
Fax: (+48 12) 429 61 24
e-mail: ccs@fqspl.com.pl
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Complete hydrogen bond description for QSAR, Drug Design and ADMET by means of the program HYBOT-PLUS / HYBOT 3-D

HYBOT program package contains
- the largest in the word the data bases of thermodynamic parameters of H-binding,
- the data bases of enthalpy, free energy and overall H-bond factors,
- the program for H-bond factor prediction for any organic compound.

HYBOT calculates:
- nineteen 2-D molecular descriptors connected with steric, electrostatic interatomic interactions and hydrogen binding;
- ten 3-D H-bonding molecular descriptors;
- volume-related, electrostatic and hydrogen binding parameters for each atom in a molecule;
- H-bond enthalpy of complexation between any organic molecules.

Platforms:
- Windows-95/98/NT/2000
- UNIX/LINUX
- HYBOT PLUS / HYBOT 3D is command line program and can be compiled under any computer platforms.

Application:
- The calculation of all descriptors on line for 100 first molecules is free.
- Further use of the program package is realized in framework of license on short-term, long-term or permanent application. ***The essential academic discount !***

Patents:
- Raevsky, O.A., Grigor'ev, V.Ju., Trepalin, S.V., HYBOT program package, Registration by Russian State Patent Agency N 990090 of 26.02.99.

- Raevsky, O.A., Skvortsov, V.S., Grigor'ev, V.Ju., Trepalin, HYBOT in UNIX/LINUX, Registration by Russian State Patent Agency N 2002610496 of 05.02.02.

Test online version: http://www.ibmh.msk.su/molpro/webhybot

Contacts: raevsky@ipac.ac.ru

Molecular 2-D descriptors calculated by HYBOT-PLUS

NN	Desriptor	Symbol
1	Molecular polarizability	α
2	Maximal positive atomic charge in a molecule	Max Q^+
3	Maximal negative atomic charge in a molecule	Max Q^-
4	Maximal enthalpy H-bond acceptor factor	Max E_a
5	Maximal enthalpy H-bond donor factor	Max E_d
6	Maximal free energy H-bond acceptor factor	Max C_a
7	Maximal free energy H-bond donor factor	Max C_d
8	Maximal overall H-bond acceptor factor	Max $C_a(o)$
9	Sum of all positive atomic charges in a molecule	ΣQ^+
10	Sum of all negative atomic charges in a molecule	ΣQ^-
11	Sum of absolute values for all atomic charges	$\Sigma\|Q\|$
12	Sum of all enthalpy H-bond acceptor factors	ΣE_a
13	Sum of all free energy H-bond acceptor factors	ΣC_a
14	Sum of all overall H-bond acceptor factors	$\Sigma C_a(o)$
15	Sum of all enthalpy H-bond donor factors	ΣE_d
16	Sum of all free energy H-bond factors	ΣC_d
17	Sum of absolute values of all enthalpy H-bond acceptor and donor factors	$\Sigma\|E\|$
18	Sum of absolute values of all free energy H-bond acceptor and donor factors	$\Sigma\|C\|$
19	Sum of absolute values of all overall H-bond acceptor factors and all free energy H-bond donor factors	$\Sigma C_a(o)+\Sigma\|C_d\|$

HYBOT-PLUS calculates also volume-related, electrostatic and hydrogen binding parameters for each atom in a molecule

References:

O.A.Raevsky.Ju.Grigor'ev, D.Kireev, N.S.Zefirov, Complete Thermodynamic Description of H-Bonding in the Framework of Multiplicative Approach, *Quant.Struct.-Act.Relat., 1992, v.11, 49-64.*

O.A.Raevsky, Hydrogen Bond Strength Estimation by means of HYBOT, *in "Computer-Assisted Lead Finding and Optimization", eds.H.Waterbeemd, B.Testa, G.Folkers, 1997, Basel: Verlag, pp. 367-378.*

O.A.Raevsky, Hydrogen Bond Description in Framework of Multiplicative Approach, *J.Phys.Org.Chem., 1997, 10, 369-376.*

Molecular Descriptors calculated by HYBOT 3-D

NN	Descriptor	Symbol
1	Van der Waals'acceptor surface area in Å^2 which is proportional to H-bond enthalpy factors E_a of acceptor atoms. *n* is number of acceptors in the molecule of interest. $k_a = \frac{1}{5}(\frac{1}{3}S_O)$. S_o is a surface sphere with a radius of 1.36 Å (O_{sp3})	$WEASA = \sum_n k_a E_a$
2	Van der Waals acceptor surface area in Å^2 which is proportional to H-bond overall free energy factors C_a(o) of acceptor atoms.	$WOFEASA = \sum_n k_a C_{a(o)}$
3	Van der Waals donor surface area in Å^2 which is proportional to H-bond enthalpy factors of donor atoms.*n* is number of donors in a molecule, $k_d = \frac{1}{5}(\frac{1}{3}S_H)$, S_H is a surface sphere with a radius of 1.08 Å (H atom).	$WEDSA = \sum_n k_d E_d$
4	Van der Waals donor surface area in Å^2 which is proportional to H-bond free energy factors of donor atoms.	$WFEDSA = \sum_n k_d C_d$
5	Surface area around a molecule in Å^2 where interactions of acceptor atoms of a molecule with a H-bond donor probe have been optimumly placed and which is proportional to product of H-bond enthalpy factor absolute values of those atoms. $E_{d(probe)}$ is the enthalpy factor of the probe H-bond donor, $k_a = \frac{1}{20}(\frac{1}{3}S_{rm})$, S_{rm} is the surface area of sphere with a radius of r_m = 2.45 Å for the strongest H-bonding	$OEASAprobe = \sum_n k_a(H_d)E_a E_{d(probe)}$
6	Surface area around a molecule in Å^2 where interactions of acceptor atoms of a molecule with H-bond donor probe have been optimumly placed and which is proportional to product of H-bond (overall) free energy factor absolute values of those atoms.	$OFEASAprobe = \sum_n k_a(H_d)C_a(o)C_{d(probe)}$
7	Surface area in Å^2 around a molecule where interactions of donor atoms of a molecule with H-bond acceptor probe have been optimumly placed and which is proportional to product of its H-bond enthalpy factor absolute values.	$OEDSAprobe = \sum_n k_d(H_a)E_d E_{a(probe)}$
8	Surface area in Å^2 around a molecule where interactions of donor atoms of a molecule with H-bond acceptor probe have been optimumly placed and which is proportional to product of its H-bond free energy factor absolute values.	$OFEDSAprobe = \sum_n k_d(H_a)C_d Ca(o)_{probe)}$
9	Surface integral for enthalpy values (kcal/M*Å^2) of interactions between acceptor atoms of a molecule and a donor probe on the surface *OEASA* .	$SIEAprobe = \oint H \cdot d(s)$
10	Surface integral for enthalpy values (kcal/M*Å^2) for interactions between donor atoms of a molecule and an acceptor probe on the surface *OEDSA*	$SIEDprobe = \oint H \cdot d(s)$

HYBOT 3-D calculated also enthalpy values for all H-bonding interactions in organic complexes.

Reference:

O.A.Raevsky, V.Skvortsov, 3D hydrogen bond thermodynamics (HYBOT) potentials in molecular modelling, *J. Comput.-Aided Molecular Design,* 2002*, 16,* 1-10.

New Software for Clustering Scientific Data

QCluster provides a comprehensive suite of fast clustering algorithms, optimized for quickly analyzing large chemical structure databases. It contains over a dozen clustering methods, including proven techniques and novel approaches designed specifically for libraries containing up to millions of compounds. QCluster's built-in tools streamline the data analysis process and deliver results with "one-click."

Benefits

- Cluster large data sets quickly
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- Match your approach to your unique data and research needs
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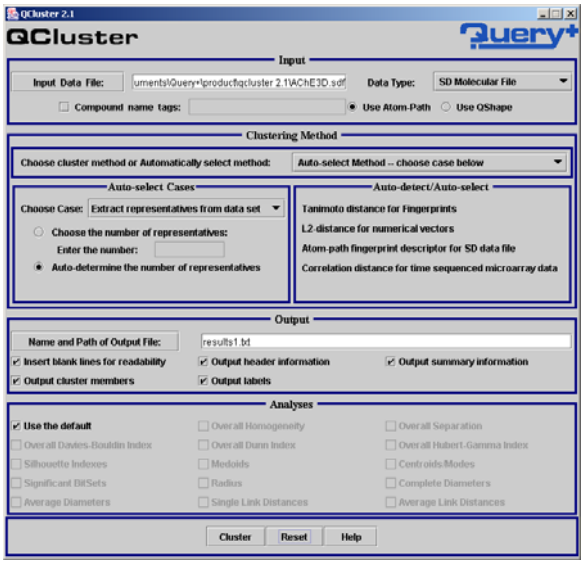
- Easy to use by both novices and experts

QCluster can read numerical/vector data, bitset/fingerprint data, or molecular structural data in SDF format. For cheminformatics workflow – SAR analysis, characterizing library diversity, in-silico screening, and a host of other applications – QCluster provides the widest range of algorithms, metrics and downstream analysis options of any clustering solution. It clusters both vector and bitset data using a wide choice of distance metrics. Almost every clustering algorithm is available for both bitset and vector data.



QCluster runs on Linux, Windows, Solaris, IRIX, OS X, and other UNIX environments.

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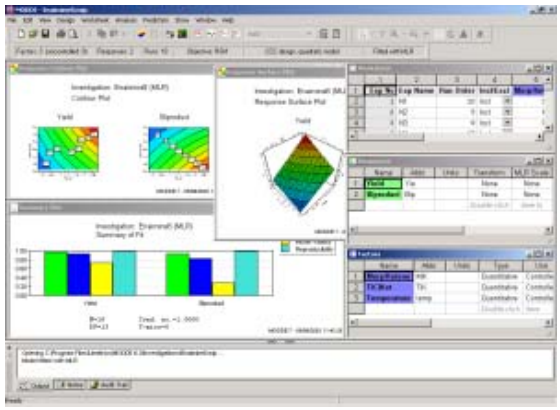
News from Umetrics

MODDE 7.0 imminent release



Umetrics software for Design of Experiments MODDE 7.0 is due for release in late September. The latest version has several new features which build on the success of MODDE 6.0
The software is aimed at end user scientists and guides you through to a successful experimental design with the help of the design wizard. Once you have defined the factors and responses MODDE will suggest appropriate designs for you to choose depending on how many experiments you can afford. Model refinement is interactive and an easy to use optimiser leads you to the best possible results.

New features include

- Onion Designs – for QSAR plus automatic import of SIMCA-P PCA scores
- Sweet Spot plots – for optimising multiple responses
- Blocking – Both for classical and D-Optimal designs
- HTML Report Generator – Customised reports
- 21 CFR part 11 features – Audit trail, Lock and Encrypt, Authority check, Validation

General MODDE features

- Wide variety of experimental designs – FD, FFD, Placket Burman, CCC, CCF D-Optimal
- Analysis of worksheet – Scatter plots, histograms, correlation matrix, replicate plots etc.
- Fit models with MLR or PLS – Handles mixture designs
- Analysis Advisor – guides you through the design process
- Comprehensive model review features – Q2, R2, Model Validity, Reproducibility, ANOVA
- Interactive model refinement – graphical refinement with automatic updating
- Predictions – Contour plots, 2D 3D and 4D plots, Linked responses
- Optimiser – Multidimensional Simplex, set target criteria

Autumn Courses

Umetrics will now be running residential courses at Umetrics UK Offices in Woodside near Windsor. The course fees of £850 include all course material, lunch, refreshments and the course meal in Windsor. Hotel accommodation is arranged in Windsor at a discounted rate of £99/night.

The courses are composed of a mixture of lectures, demonstrations and exercises. In addition delegates may bring their own data for analysis with the assistance of Umetrics' consultants.

The courses are intended as training in the techniques of DoE and Multivariate, not only for Umetrics software users.

October 7th – 9th Design of Experiments and Optimisation
Scientific problems are typically affected by several variables. Design of Experiments (DoE) provides a logical and cost-effective framework for planning experiments to improve and optimise products and processes.

October 28th-30th Multivariate QSAR Modelling
The aim of QSAR Modelling is to relate chemical and physical properties, both measured and calculated, to biological activity so that future potency may be predicted. Discover how to construct effective multivariate models in order to direct synthetic programmes towards optimal molecular structures.

November 18th-20th Design of Experiments and Optimisation in Organic Chemistry
This course is aimed specifically at organic chemists, at the bench and in the plant, and the problems they face in planning and optimising chemical reactions.

December 16th-18th Intermediate Multivariate Data Analysis NEW!
By popular demand, this course has been developed for users of multivariate methods wishing to brush up their existing skills and/or learn some new ones. We will take you through data preparation, pre-processing, wavelet compression, advanced PLS methods and advanced process analysis techniques.

In-House Training
Umetrics also run in-house courses in all of the above topics. These often offer the most cost effective training solution for larger organisations and can be individually tailored.

Academic Discount Scheme
Academic users qualify for heavily discounted prices on software and 10% off training course costs. Please contact Umetrics for details.
For more information on Umetrics training courses and Software please contact:

Umetrics UK Ltd, Woodside House, Woodside, Winkfield, Windsor SL4 2DX

Tel: +44 (0)1344 885605 Email:info.uk@umetrics.com
Fax: +44 (0)1344 885410 Web: www.umetrics.com

MDL Drug-like Key Set

At the 2003 QSAR Gordon Conference, a couple of talks and posters referenced the MDL Drug-like Key Set, obtained using the approach in Durant, et. al.,"Reoptimization of MDL Keys for use in Drug Discovery", JCICS, 42(6), 2002, 1273-1280. A generator for this key set from SMILES is available from Mesa Analytics (http://www.mesaac.com/). Users of MDL ISIS/Host(R) and or Cheshire(R) programs can compute this key set directly from ISIS/Host databases and SDfiles, using scripts and a key definition file. A Scitegic Pipeline Pilot(R) protocol is also available. These can be obtained freely by contacting Keith Taylor (k.taylor@mdl.com).

Douglas Henry
MDL
14600 Catalina St.
San Leandro, CA (usa)
d.henry@mdl.com

Molinspiration Drugability Calculator

This free interactive web tool allows easy calculation of activity scores for potential GPCR ligands, ion channel modulators and kinase inhibitors.
This tool, available at

http://www.molinspiration.com/cgi-bin/properties

is an enhancement of our already well established web-based molecular property calculation service. Molinspiration virtual screening and property calculation toolkits are available also in batch versions for in-house use. Additionally, for a limited period of time, we offer to academic and non-commercial institutions free calculation of activity scores (virtual screening) for their compound collections. Do not hesitate to contact us for more information.

Martin Leonard (leonard@molinspiration.com)
Molinspiration Cheminformatics

eduSoft, LC markets some very unique QSAR software. The offerings include Molconn-Z Toolkit and HINT Toolkit. These Toolkits are libraries of easily accessible computational functions that can be used with minimal programming in custom applications or compiled and used with provided example applications. Calculated data objects and results are accessed with persistent handles, not complex data structures. The Toolkits interface seamlessly with OpenEye, Daylight and in-house informatics. The toolkits are available on a variety of computational platforms including Sun Solaris, SGI Irix, LINUX, Windows 2000. Featured HINT handles include LogP for both small molecules and biomolecules (calculated at both atom and molecule level), free energy of interaction and docking score, 3D QSAR fields, solvent optimization including group pK titration, more. Featured Molconn-Z handles include the largest set of Kier-Hall descriptors (improved from the standards developed by Kier and Hall over the past 20 years), E-State (atom- and group-type) descriptors, H-bond (donor and acceptor) descriptors, polarity descriptors, 3D QSAR descriptor fields, more. Please visit www.edusoft-lc.com/toolkits.

Summary of Recent Molconn-Z Literature Studies

Rose, Hall and Kier (J. Chem. Inf. Comput. Sci. 2002, 42:651-666) used Molconn-Z to develop a QSAR model for blood-brain barrier partitioning. The model includes only 3 descriptors, an E-State for H-bond donors, and E-State for aromatic CH, and a second order difference valence molecular connectivity index. The logBB model was successfully used to evaluate a database of over 20,000 and drug-like compounds.

Rose and Hall (SAR QSAR Environ Res. 2003, 14:113-29) used Molconn-Z to develop a QSAR model for a set of 92 compounds, including phenols, anilines and aromatic hydrocarbons that predicts fish toxicity. The model is based on molecular connectivity valence chi-1 index, the atom type E-State indices for chlorine and for ether oxygen, and the maximum hydrogen E-State atom value in a molecule, and it yields excellent statistics with r2=0.87 and q2=0.85.

Summary of Recent HINT Literature Studies

Cozzini, Pornabaio, Marabotti, Abraham, Kellogg and Mozzarelli (J.Med.Chem. 2002, 45:2469-83) used HINT to evaluate the protein-ligand free energy of interaction for 53 complexes. An excellent correlation is found between the free energy of binding and the HINT interaction score, such that predictions within a protein series can be calculated with an error of about 1 kcal/mol or between protein series with an error of about 2.6 kcal/mol. Similarly, Cashman, Scarsdale and Kellogg (Nucleic Acids Res. 2003, 31:4410-4416) showed that the free energy of interaction of 8 anthracycline antibiotics with 32 DNA octamers could be predicted within less than 1 kcal/mol.

Fornabaio, Cozzini, Mozzarelli, Abraham and Kellogg (J. Med. Chem. 2003, 46:4487-4500) used HINT to perform "computational titration" of functional ligands at the binding site on nine inhibitors of neuraminidase. The maximum HINT score,

when comparing all ionization options, indicates the optimum ionization state. This helps improve free energy predictions for protein-ligand complexes. An additional observation that resulted from this "computational titration" study was that some structures are greatly improved with minor alternate crystallographic assignments. Because there are many changes that can be made to a crystal structure that are "iso-crystallographic", such as moving protons around on side-chains like -OH on TYR and SER, or rotating amide groups on ASN and GLN, HINT-assisted molecular modeling can build better molecular models for virtual screening.

ChemTree®
HTS ANALYSIS SOFTWARE
The power of sequential screening™

On October 3rd, Golden Helix released version 3.2 of ChemTree® HTS Analysis Software. ChemTree accelerates the drug discovery process by building structure activity models on screening data to understand mechanisms of action and drive the sequential screening compound optimization process. Multiple tree univariate and multivariate recursive partitioning techniques are used to "cherry-pick" compounds with optimal potency, ADME/Tox and other drug-like properties.
ChemTree can be purchased in 3 different modules all built around an intuitive user interface with strong visualization capabilities. A full-featured 30-day free demo, can be downloaded at: http://www.goldenhelix.com/.

Important new features and improvements are:

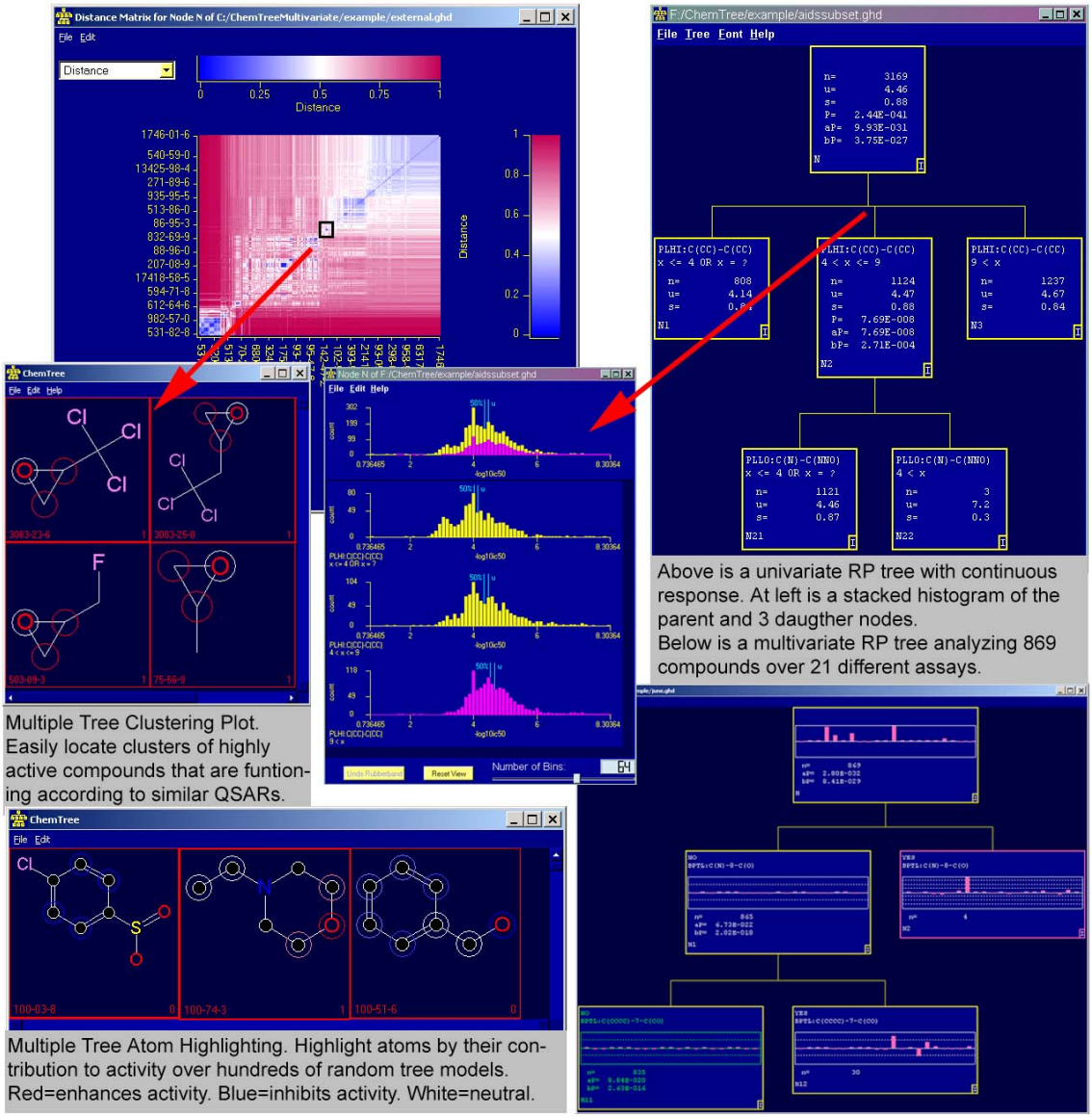
- The ability for multiple tree weighting of the atoms in a given molecule according to their relative contribution to the activity of the molecule across all descriptors in all trees that involve the given atom. This enables a chemist to see which parts of a molecule may be enhancing activity and which may be inhibiting activity.
- The ability to rotate a molecule in 3D.
- The ability output the model of a tree to C/C++ source code to be used in custom applications.
- The ability to run ChemTree from the command line, enabling batch mode execution of script files, possibly in conjunction with a data analysis pipeline.
- The user manual has been completely revised and rewritten, and is now also available as context-sensitive help within the software.
- Runs up to 3 times faster while building trees on large datasets.

ChemTree offers the following key benefits.

Reduce clinical failures through better discovery:

- Weed out failures before they enter clinical trials by optimizing for efficacy, safety and ADMET earlier.
- Enable earlier and more cost-effective ADMET optimization through low throughput invitro/insilico screening.

- Reduce attrition rate of compounds in later stages of pipeline by optimizing for efficacy, safety and ADME/Tox at the same time.
- Simultaneously optimize many screening endpoints with multivariate recursive partitioning (RP).



Above is a univariate RP tree with continuous response. At left is a stacked histogram of the parent and 3 daugther nodes.
Below is a multivariate RP tree analyzing 869 compounds over 21 different assays.

Multiple Tree Clustering Plot. Easily locate clusters of highly active compounds that are funtioning according to similar QSARs.

Multiple Tree Atom Highlighting. Highlight atoms by their contribution to activity over hundreds of random tree models. Red=enhances activity. Blue=inhibits activity. White=neutral.

Save time and resources by prioritizing what to screen next:

- Increase hit rates 10-100 fold through intelligent "Cherry Picking".
- Generate nanomolar concentration leads with the sequential screening process.
- Maximize hit rates through focused combinatorial synthesis.
- Automate screening analysis tasks to accelerate the drug discovery pipeline.
- Resurrect failed screening attempts.

Uncover QSAR relationships to accelerate lead optimization:

- Give lead optimization chemists a jump start by automatically highlighting the 'business end' of a molecule.
- Capture the most from screening expenditures by learning from both actives and inactives.
- Accelerate the identification of lead series through structure/activity clustering.
- Gain deeper chemical insight by automatic detection of interacting molecular features.
- Derive value from noisy HTS data using ensemble averaging of many RP trees.

For more detailed product and company info please visit:
http://www.goldenhelix.com

Contact:
Golden Helix, Inc.
716 S 20th Ave., Ste. 102
Bozeman, MT 59718 USA
Rudy Parker
parker@goldenhelix.com
406-585-8137 x 204

ChemSilico

ChemSilico is a new company with a mandate to provide robust, *in silico* models for ADMET properties. In 2003, the company introduced the following models under CSPredict, the parent program:

CSLogWS™ ***Intrinsic aqueous solubility*** and ***pH solubility profiles***
CS*pKa™** ***Up to five pKas per compound based on 12 identified, ionizable centers
CSLogD™ **O*ctanol/water partition coefficient*** and ***pH profiles*** for **charged** molecules
CSLogP™ **O*ctanol/water partition coefficient*** for **neutral** molecules
CSPB™ ***Plasma protein binding*** as percent of fraction bound
CSBBB™ ***Blood-brain barrier*** partition ratio
CSGenoTox™ ***Genotoxicity*** (Ames)
CSHIA™ **Human % oral absorption**

The *in silico* models are based on artificial neural net techniques using topological descriptors, several bulk properties, and polar surface areas. These predictors have undergone ***extensive cross validation and external validation testing*** with ***resultant validation R^2s above 0.8 on thousands of NCEs.*** The high degrees of accuracy demonstrated by our predictors assure maximal accuracy for the user when evaluating NCEs. Our models are based on experimental results from over 35,000 chemically diverse compounds that were selected and screened to ensure use of reliable end-points. The majority of the training sets used to develop our predictors ranged in size

from 150 to ~17,000 compounds (e.g., CSLogWS was built using ~5,700 diverse compounds). Reports on independent, competitive, testing on many of these predictors by major pharmas and biotechs have been highly favorable to CSPredict.

Our suite of ADMET predictors runs under **Windows 2000/XP** or **Linux** (web version). All predictors run in batch mode with rates of 600-800 compounds min^{-1} firing all eight (8) predictors with a standard PC and upwards of 2000 or more min^{-1} on a Linux server.

CSPredict comes with an easy-to-use front end with output in SDF or Excel-XLS. For more features such as data visualization, databasing, and graphical output, CSPredict is the principle ADMET property predictor in Bio-Rad's KIA Informatics software system running under Windows (www.knowitall.com/adme.

We cordially invite you to see technical information and validation results on all our *in silico* models on our web site (www.chemsilico.com). Free trials are also available over the Web by signing up at our Web site. For more extensive trials using a downloadable version of CSPredict, please e-mail us at sales@chemsilico.com or fill out our "information request" form residing on our Web site.

ChemSilico LLC
48 Baldwin Street
Tewksbury, MA 01876
1-888-636-8777

NEWS from BioSolveIT

Here are the latest developments from BioSolveIT:

FlexX and associated modules:

Download the latest versions of our docking and superpositioning software including new and updated modules such as

FlexX-Pharm - run pharmacophore constrained dockings
FlexX-C - docking combinatorial libraries
PyFlexx - the Python-wrapped version of FlexX

More goodies:
- The Flex* tools now read SDF (molfiles)
- FlexX for Windows is out! Download from http://www.biosolveit.de/download
- FlexSC: Our small compound superpositioning tool FlexS has been extended to superpose combinatorial libraries
- FlexE has been released: dock into ensembles of protein structures and treat side chain flexibility and different protonation choices efficiently

TopNet beta-Version released:

The toolbox for protein networks (TopNet) helps you explore gene networks and expression data by analysis facilities and intuitive visualisation. Moreover, significant sub-networks can be detected by user-provided expression measurements. Use this JAVA application on basically any platform and work with your hyperlinked data sources.

Extract knowledge from HTS data: HTSview:

Our fast "2.5D" similarity descriptor, Feature Trees, has been extended with a powerful vHTS data analysis GUI, "HTSview". Clustering, pharmacophore-like alignment of Feature Trees to so-called "models" is now just a few clicks away. HTSview is distributed for free to selected prototype testers now.

If you require more details, please visit
http://www.biosolveit.de or contact us directly
under contact@biosolveit.de, phone: ++49-2241-9736660.

WOMBAT
WOrld of Molecular BioAcTivity

WOMBAT 2003.2 **contains** 53126 entries **(47872 unique SMILES), totaling** 98662 biological activities **on** 506 unique targets**. Its activity list also includes 236 inactives, 7982 activities "less than" and 159 activities "greater than".** WOMBAT 2003.2 **contains** 2148 different series **from 2143 papers published in medicinal chemistry journals between 1975 and 2002, as follows:**

Journal Title	Publication Year
Biochem. Pharmacol.	2001 [partial coverage]
Bioorg. Med. Chem. Lett.	2002 [numbers 1-16]
Chembiochem	2002 [partial coverage]
Eur. J. Med. Chem.	2001 [partial coverage]
J. Amer. Chem. Soc.	1975,1992,1993 [partial coverage]
J. Med. Chem.	1992,1994-1998 [complete] 1999 [partial coverage]
Quant. Struct.-Act. Relat.	1998-2000 [partial coverage]

A vast majority of the biological activities are related to **antagonists** and **inhibitors**: **35.5%** $\mathbf{K_i}$ and **56.6%** $\mathbf{IC_{50}}$ values, respectively; only **5.5%** of the biological activities are $\mathbf{EC_{50}}$ or $\mathbf{A_2}$ values; the rest of **2.4%** includes: $\mathbf{D_2}$, $\mathbf{K_b}$, $\mathbf{K_{ii}}$, $\mathbf{K_{is}}$, $\mathbf{K_{act}}$ and $\mathbf{K_d}$ values. Biological activities indexed in WOMBAT are ranked by target in the Table below.

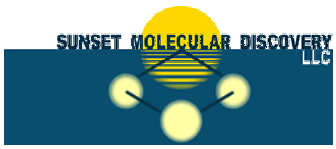
Target Class	Compounds [(a)]	Percentage
G-Protein Coupled Receptors	19839	37.3
Ion Channels	6090	11.5
Aspartyl Proteases	2656	5.00
Serine Proteases	2582	4.86
Kinases	2111	3.97
Transporters	1689	3.18
Cysteine Proteases	504	0.95
Nuclear Hormone Receptors	448	0.84
Others	19233	36.2

(a) number of structures active at least once/target, % of total entries

WOMBAT also includes, for convenience, calculated LogP (octanol/water partition coefficients) and LogSw (the intrinsic aqueous solubility), as computed by the EPA Suite. This software was developed at the Syracuse Research Corporation for the United States Environmental Protection Agency. WOMBAT 2003.2 includes 1230 measured LogP and 527 measured LogSw values (as provided by the EPA Suite software).

WOMBAT, indexed by **Sunset Molecular Discovery LLC**, is updated twice a year - in mid-September and mid-February. Each update provides approximately 10000 new entries, with their associated biological activities. **WOMBAT** is marketed by **Daylight Chemical Information Systems.** A demo version of the WOMBAT server in **FEDORA** is available for a 60-days trial period**.** Click here to download WOMBAT samples.

Disclaimer: WOMBAT is sold "as is", only on a non-exclusive basis, in Isis/Base or ASCII (RDF) format. The WOMBAT@FEDORA server is available from Daylight. Upgrades, post-processing or derivative databases are available separately. Sunset Molecular Discovery LLC assumes no responsibility for any inaccuracies or errors that may be present in WOMBAT – related, but not limited to, chirality information, biological activity and chemical structure.



Software for free from Gabriele Cruciani

Free softwares (for academic and non-profit institutions):

GRID - a computational procedure for determining energetically favourable binding sites on molecules of known structure. It may be used to study individual molecules such as drugs, molecular arrays such as membranes or crystals, and macromolecules such as proteins, nucleic acids, glycoproteins or polysaccharides. Several different molecules can be processed one after the other.

MetaSite - MetaSite is a computational procedure specially designed to predict the site of metabolism for xenobiotics starting from the 3D structure of a compound. The site of metabolism can be described by a probability function Psm that is correlated to, and can be considered, the free energy of the Cyp-substrate recognition and

reactivity process.The MetaSite methodology has been developed to predict the site of metabolism for substrates of 2C9, 2D6 and 3A4 cytochromes.

ChemoDock (available March 2004) - a new docking algorithm based on GRID force field which perform particularly well when hydrophobic interactions occur.

At reduced prices (very small fee):

VolSurf - is a computational procedure to produce 2D molecular descriptors from 3D molecular interaction energy grid maps. The basic idea of VolSurf is to compress the information present in 3D maps into a few 2D numerical descriptors which are very simple to understand and to interpret. VolSurf descriptors are specifically designed for the optimisation of in silico pharmacokinetic properties (eADME or IS-DMPK).
Almond - is a program specifically developed for generating and handling alignment independent descriptors called GRIND (GRid INdependent Descriptors). These are a new generation of 3D-molecular descriptors with application in 3D-QSAR, QSAR, virtual screening, design of combinatorial libraries, selectivity studies and in any field where 3D quantitative pharmacophoric description for (macro)molecules is needed.

PASS

PASS 1.809 (October, 2003) includes a knowledgebase of about ~46,000 biologically active substances. PASS predicts simultaneously the probabilities of presence/absence for ~900 biological actions (main and side pharmacological effects, mechanisms, specific toxicity). The system is open; the user can add some new biologically active compounds and new activities to the training set, and create his own knowledgebase. Mean accuracy of prediction in LOO cross-validation is ~85%. Calculation of biological activity spectra for 10,000 compounds on an ordinary PC takes about 5 min. PASS can be effectively used to analyze very large databases. Vendor, see: www.akosgmbh.de/pass.

TerraBase Inc. - *Advancing your R&D with innovative software*

Product lines:

TerraTox™ databases

TerraQSAR™ computation programs

For details, see **www.terrabase.ca**

Software from the Chem21 Group

4D-QSAR – Constructs quantitative 3D-pharmacophore QSAR models as a function of conformation, alignment and embedded pharmacophore of the molecules of the training set. The resultant 4D-QSAR models can be graphically displayed and used as virtual screens. Active conformations can be postulated for both training set and screening set compounds using the 4D-QSAR models. The loss in biological activity of a compound owing to conformational entropy can be estimated. Non-4D-QSAR descriptors can be added to the training set descriptor pool in building QSAR models. The software runs on both SGI Unix

and PC Linux platforms. For additional information contact *The Chem21 Group, Inc., 1780 Wilson Drive, Lake Forest, IL 60045, USA, hopfingr@uic.edu.*

4D-MS Module to 4D-QSAR - Performs 2D and 4D molecular similarity measurements of molecules independent of conformation and/or alignment, and as a function of conformation, alignment and pharmacophore types. Molecular similarity measurements can be made as a function of atom-types composing the molecules. Display of molecular similarity can be tabular and/or graphical. Graphical display of multiple atom types of molecular similarity is achieved using *molecular similarity wheels*. The software runs on both SGI Unix and PC Linux platforms. For additional information contact *The Chem21 Group, Inc., 1780 Wilson Drive, Lake Forest, IL 60045, USA, hopfingr@uic.edu.*

MI-QSAR Analysis - Constructs 2D- and 3D-QSAR models to predict ADME properties and "mild" toxicity endpoints like eye irritation. The program can be sued to construct models for most ADMET endpoints, but is particularly well-suited to model those properties involving interactions with cellular membranes like caco-2 cell permeation. The program permits the explicit simulation of the interaction of test molecules with model phospholipids mono- and bi-layers, or any membrane model a user wishes to provide. A set of membrane interaction (MI) descriptors is extracted from the simulations and added to the pool of descriptors used to build the ADMET QSAR model.
For more information contact *The Chem21 Group, Inc., 1780 Wilson Drive, Lake Forest, IL, 60045, USA, hopfingr@uic.edu.*

NEW BOOKS

H. van de Waterbeemd, H. Lennernas and P. Artursson (Eds), Drug Bioavailability – Estimation of Solubility, Permeability, Absorption and Bioavailability, Wiley-VCH, Weinheim, Germany (2003). ISBN 3-527-30438-X.

Handbook of Chemoinformatics, 4 volume set, Ed. Johann Gasteiger, Wiley-VCH, Weinheim, Germany

An Introduction to Chemoinformatics, by Andrew R. Leach, GlaxoSmithKline Research and Development, Stevenage, UK
Valerie J. Gillet Dept. of Information Studies, University of Sheffield, UK.
http://www.wkap.nl/prod/b/1-4020-1347-7

> Chemoinformatics draws upon techniques from many disciplines including computer science, mathematics, computational chemistry and data visualisation to tackle these problems.
>
> This, the first text written specifically for this field, aims to provide an introduction to the major techniques of chemoinformatics. The first part of the book deals with the representation of 2D and 3D molecular structures, the calculation of molecular descriptors and the construction of mathematical models. The second part describes other important topics including molecular similarity and diversity, the analysis of large data sets, virtual screening, and library design. Simple illustrative examples are used throughout to illustrate key concepts, supplemented with case studies from the literature.

The book is aimed at graduate students, final-year undergraduates, and professional scientists. No prior knowledge is assumed other than a familiarity with chemistry and some basic mathematical concepts.

Kluwer Academic Publishers, Dordrecht
Hardbound, ISBN 1-4020-1347-7
May 2003, 260 pp.
EUR 75.00 / USD 74.00 / GBP 48.00

Available at a reduced price for course adoption when ordering six copies or more. Please contact the Publisher (peter.butler@wkap.nl) for further details.

Kluwer Academic Publishers is pleased to offer a year-round 25% discount on the following book titles. Any QSAR and Modelling Society member interested in buying any copies, should contact the Publisher, Peter Butler <peter.butler@wkap.nl>, for ordering details.

An Introduction to Chemoinformatics
Andrew R. Leach, GlaxoSmithKline Research and Development, Stevenage, UK
Valerie J. Gillet, Dept. of Information Studies, University of Sheffield, UK
http://www.wkap.nl/prod/b/1-4020-1347-7

Computational Chemistry
Introduction to the Theory and Applications of Molecular and Quantum Mechanics
Errol G. Lewars; Dept. of Chemistry, Trent University, Peterborough, ON, Canada
http://www.wkap.nl/prod/b/1-4020-7285-6

Applying Molecular and Materials Modeling
edited by Phillip R. Westmoreland, University of Massachusetts, Amherst, USA
Peter A. Kollman, University of California, San Francisco, USA
Anne M. Chaka, National Institute of Standards and Technology, Gaithersburg, MD, USA
Peter T. Cummings, University of Tennessee, Knoxville, USA
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Ellen B. Stechel, Ford Motor Company, Dearborn, MI, USA
Priya Vashishta, Louisiana State University, Baton Rouge, USA
http://www.wkap.nl/prod/b/1-4020-0906-2

Erythrocyte Engineering for Drug Delivery and Targeting
edited by
Mauro Magnani
University of Urbino, Italy
http://www.wkap.nl/prod/b/0-306-47691-6

The CDK-Activating Kinase (CAK)
Philipp Kaldis
National Cancer Institute, Frederick, MD, USA
http://www.wkap.nl/prod/b/0-306-47438-7

3D QSAR in Drug Design
Volume 1: Theory Methods and Applications
edited by
Hugo Kubinyi
BASF AG, Ludwigshafen, Germany
http://www.wkap.nl/prod/b/90-72199-14-6

In the series Methods and Principles in Medicinal Chemistry by Wiley-VCH appeared:

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Editor:	Oliver Zerbe
Volume 17:	Quantum Chemical Methods in Medicinal Chemistry
Editors:	Paolo Carloni and Frank Alber
Volume 18:	Drug Bioavailability: Estimation of Solubility, Permeability, and Absorption
Editors:	Han van de Waterbeemd, Hans Lennernäs, Per Artursson
Volume 19:	Protein-Ligand Interactions. From Molecular Recognition to Drug Design
Editors:	Hans-Joachim Böhm and Gisbert Schneider

CALL FOR PAPERS

The Editorial Board of the Journal *Molecular Diversity* (http://www.kluweronline.com/issn/1381-1991) has planned to publish a special issue on *Topological Descriptors in Drug Design and Modeling Studies* (visit http://www.mdpi.org/modi/specialissues.htm **)**

The last date for paper submission is: **January 01, 2004**

Kindly go through the Journal website (http://www.kluweronline.com/issn/1381-1991) for the Instructions for Authors and other relevant information for manuscript submission. For further details, you may contact the Editorial Office:

Dr. Shu-Kun Lin, Editor-in-chief, Molecular Diversity,
Molecular Diversity Preservation International (MDPI), Matthaeusstrasse 11 CH-

4057 Basel, Switzerland
Phone: +41 79322 3379, Fax: +41 61302 8918, E-mail: modi@mdpi.org

Manuscripts may be submiited as WORD files via email to

Dr. Kunal Roy (*Guest Editor***:** Special issue on *Topological Descriptors in Drug Design and Modeling Studies*)
Division of Medicinal and Pharmaceutical Chemistry, Department of Pharmaceutical Technology
JADAVPUR UNIVERSITY, Kolkata 700 032 (INDIA)
Phone: (O): 91-33-2414 6676; (R): 91-33-2435 6547
Email: kunalroy_in@yahoo.com, kunalroy_in@hotmail.com, kunalroyindia@rediffmail.com

BOOK REVIEWS

none

POSITIONS

See http://www.qsar.org/position.htm

JOURNALS

- **QSAR and Combinatorial Science**

This VCH journal is considered to be the "home" journal of THE QSAR AND MODELLING SOCIETY. Editors are Prof. Michael Wiese, University of Bonn, Gisbert Schneider, University of Frankfurt, and Jean Martinez, University of Montpellier.

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Prof. Dr. Michael Wiese
Rheinische Friedrich-Wilhelms-Universitaet Bonn
Pharmazeutisches Institut
Pharmazeutische Chemie
An der Immenburg 4
D-53121 Bonn
Germany
Tel. +49-228-73 5212
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Consider that a publication in this journal will reach your audience of QSAR and modelling colleagues much better than a publication in JACS, JCICS, JMC, Biochemistry, etc. Of course, Ferenc Darvas remains the Editor of the Abstracts Section. Please consider also to subscribe personally to the QSAR journal. It's good and it's cheap, extremely cheap for members of our Society (call VCH, phone +49-6201-6060, for the current price).

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At the discretion of the co-ordinating Editor-in-Chief, up to a maximum of 4 (four) pages of color illustrations will be published free of charge. All other color illustrations will be published at the author's expense.

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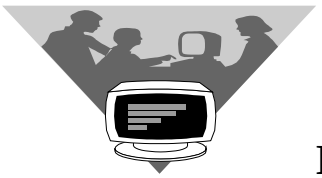
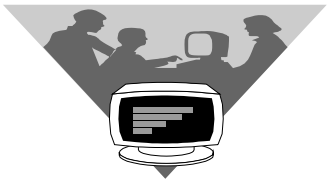


Meetings /Courses



See also http://www.qsar.org/meetings.htm

2004

- Winter International Symposium on Information and Communication Technologies, January 5 – 8, 2004, Cancun, Mexico. Info: http://www.cs.tcd.ie/publications/tech-reports/wisict04/wisict04.html
- ADMET Conference. February 11 – 13, 2004, San Diego CA, USA. Info: http://www.scherago.com/admet/
- 3rd Winter School on Chemometrics, February 16-20, 2004, Pushkinskiye Gory, Russia. Info: http://rcs.chph.ras.ru/drushba.htm
- LogP2004, February 29-March 4, 2004, Zurich, Switzerland. Info: http://www.logp2004.ethz.ch
- American Chemical Society Spring Meeting, March 28 – April 1, 2004, Anaheim CA, USA.Info below and www.acs.org
- 3rd Joint Scheffield Conference on Chemoinformatics. April 21-23, 2004. Sheffield. UK. Info: http://cisrg.shef.ac.uk/shef2004
- The 11th International Workshop on Quantitative Structure-Activity Relationships in Environmental Sciences, May 9-13, 2004, Liverpool, England. Info: http://www.toxqsar.org/
- American Chemical Society Fall Meeting, August 22-26, 2004, Philadelphia PA USA. Info: www.acs.org
- EuroQSAR 2004, Istanbul (Turkey), September 5-10, 2004. Info: http://www.euro-qsar2004.org
- 6th Swiss School on Medicinal Chemistry, 10-15 October 2004, Leysin, Switzerland. Contact: Gerd Folkers (gerd.folkers@pharma.ethz.ch), Bernard Testa, Han van de Waterbeemd.

Spring National ACS Meeting in Anaheim CA (28 March-1 April 2004)

Division of Chemical Information

Program Chair: O. F. Güner, Accelrys Inc, 9685 Scranton Road, San Diego, CA 92121-3752, 858-799-5341, fax 858-799-5100, e-mail: osman@accelrys.com

1- Advances in pharmacophores and 3D searching (Cosponsored with comp and medi). O. F. Güner

2- Chemical information needs for industrial and engineering chemistry (Cosponsored with iec). T. Wright, MDL Information Systems, Inc, 14600 Catalina Street, San Leandro, CA 94577, 510-357-2222, fax 510-614-3652, e-mail: terryw@mdli.com

3- CINF serves SCHB: Patent information for small chemical businesses (Cosponsored with chal and schb). A. Engel, Paterra, Inc, 526 N Spring Mill Road, Villanova, PA 19085-1928, 610-527-4500, fax 610-527-2041, e-mail: aengel@paterra.com

4- Electronic Lab Notebooks R. Lysakowski Jr., Executive Director, Collaborative Electronic Notebook Systems Association, 800 West Cummings Park, Suite 5400, Woburn, MA 01801, 781-935-9600, fax 781-935-3113, e-mail: rich@censa.org

5- Environmental Chemistry: Where to find your information (Cosponsored with envr and toxi). E. Kajosalo, Libraries, Massachusetts Institute of Technology, 77 Masschusetts Avenue, Room 14S-134, Cambridge, MA 02155, 617-253-9795, fax 617-253-6365, e-mail: kajosalo@mit.edu

6- General papers O. F. Güner

7- How do the changes in 21-CFR part 11 affect you? (Cosponsored with anyl, chas, laba and medi). D. A. Evans, MDL Information Systems, 14600 Catalina Street, San Leandro, CA 94577, 510-357-2222 x1145, fax 510-614-3651, e-mail: davide@mdli.com

8- Informatics challenges in Nanotechnology (Cosponsored with comp and inor). S. C. McGrother, Accelrys Inc, 9685 Scranton Rd, San Diego, CA 92121, 858-799-5355, fax 858-799-5100, e-mail: smcgrother@accelrys.com

9- Poster session O. F. Güner

10- Research collaboratories, virtual laboratories, and Grid computing (Cosponsored with comp). G. Grethe, Consultant, 352 Channing Way, Alameda, CA 94502-7409, 510-333-7526, fax 510-865-5152, e-mail: ggrethe@comcast.net; W. A. Warr, Wendy Warr & Associates, 6 Berwick Court, Holmes Chapel, Cheshire, CW4 7HZ, United Kingdom, 011 44 1477 533837, fax +44-1477-533837, e-mail: wendy@warr.com

11- The bigger picture: linking bioinformatics to cheminformatics (Cosponsored with biot, medi and comp). M. A. Miller, LION bioscience, Inc, 955 Ridge Hill Lane, Suite 30, Midvale, UT 84047, 801 569 1390, fax 801 365 3949, e-mail: mitchell.miller@lionbioscience.com

The following provides some guidelines on submitting your abstract through OASYS.

SUBMIT A TEST ABSTRACT IF YOU HAVE NEVER USED OASYS.
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2. Enter the author submittal site at http://oasys.acs.org/oasys.htm.
3. Click the link to the CINF division, and select the appropriate symposium
4. Follow the prompts to submit an abstract.
5. When you come to the Submit Abstract Text page, answer "yes" to "does your abstract contain an image?".
6. Follow the prompts to submit the abstract text and image. If you have entered it successfully, you will see the Submit to Program Officials page.

7. Complete the submission by clicking the next Submit button. You will receive an email showing you an example of the confirming email authors receive.
8. To retrieve your abstract, you can click the View/Modify/Withdraw Abstract or Preprint on the OASYS home page and enter your abstract ID and password.

Note that authors who submit an email address will receive this confirming email. Other authors will get no notice of receipt.

Scheduling notices will be sent by ACS after the final program has been submitted. Presenting authors will receive an email message telling them when and where their presentations are scheduled.

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GETTING IT RIGHT: VARIABLE SELECTION AND MODEL VALIDATION IN (Q)SAR

Spring National ACS Meeting in Anaheim CA (28 March - 1 April 2004)
Sponsored by the Division of Computers in Chemistry (COMP) and by the QSAR and Modelling Society

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Despite the ascendance of combinatorial chemistry, high throughput screening, and various 'omics technologies in recent years, delineating structure/property relationships remains key to effective drug discovery. The models in question may be quantitative ones relating structure to biochemical activity (QSARs) or to some physical property (QSPRs), or they may be more qualitative, as in many in silico ADME/Tox applications. Whether the tool used is linear regression or PLS, discriminant analysis or SIMCA, a support vector machine or a neural net, there is always an over-arching need to pick appropriate variables as input to the model and to get some sense of how much confidence one can have in the model(s) produced.

The general topic of variable selection and validation in (Q)SAR will form the basis of a multi-session symposium at the Spring 2004 meeting of the American Chemical Society in Anaheim CA. Methods development papers are welcome, as are abstracts for any application that involves variable selection or validation in some way. Selected papers will be considered for inclusion in a special "Perspectives in Drug Discovery and Design" ("PD3") issue of the Journal of Computer-Aided Molecular Design.

If you would like to present a paper on some aspect of QSAR, QSPR, or a related area of chemometrics, please use the OASYS system to do so:

http://oasys.acs.org/acs/227nm/comp/papers/index.cgi

to submit your abstract directly. The deadline for submission is 17 November 2003.

Bob Clark (bclark@tripos.com)
Tripos, Inc., 1699 S. Hanley Road, St. Louis MO 63144

The 11th International Workshop on QSAR in the Human Health and Environmental Sciences (www.toxqsar.org) will be held at the Britannia Adelphi Hotel in Liverpool, England from 9 - 13 May 2004.

The main sessions in the meeting will be:

Knowledge Discovery and Data Mining
Toxicogenomics / Molecular Mechanisms
QSAR Methods: Statistical Analysis and Physicochemical Properties
Predicting Environmental Toxicity
Modelling Environmental Fate
In silico ADMET
Prediction of Human Health Endpoints
Regulatory Use of QSAR
Validation of QSARs
Hot Topics

Plenary Lectures will be given by:

Dr Kees van Leuwen, Joint Research Centre, European Commission, Italy
Dr Gil Veith, United States Environmental Protection Agency, USA
Dr Ulf Norinder, AstraZeneca, Sweden
Dr Lowell Hall, Eastern Nazarene College, Boston, USA
Prof Gerrit Schüürmann, UFZ Centre for Environmental Research, Leipzig, Germany
Dr Christoph Helma, University of Freiberg, Germany
Dr Andrew Worth, ECVAM, Joint Research Centre, European Commission, Italy
Prof Michael McLachlan, Institute of Applied Environmental Research, Stockholm University,
Sweden

Registration Details: Registration will open in December 2003, with discounted registration available until the end of February 2004. Further discounts and discretionary bursaries will be available for students. Full details of registration fees, discounts and bursaries are available now from www.toxqsar.org.

Submission of Abstracts: The deadline for abstract submissions for oral presentations is 31st December 2003 and for poster presentations is 15th April 2004. In order to broaden the program, attendees will normally be allowed only one oral presentation. Please choose your topic carefully! Attendees are encouraged to submit as many poster presentations as they wish. Submission of Abstracts will be via the Workshop web-site: www.toxqsar.org

About Liverpool: Liverpool is unique and is proud to be European Capital of Culture for 2008. No trip to Liverpool is complete without a trip on the ferry, investigating the stunning architecture and both our cathedrals, taking in an art gallery and museum, and sampling the local ales in one of our many friendly pubs.

Building Better QSARs - A Training Course for New and Experienced QSAR Practitioners: A unique training course is planned for scientists of all capabilities. This will be held before the main Workshop on Sunday 9th May 2004. The full program for this event is listed on the Workshop web-site : www.toxqsar.org.

Full details of the Workshop are available from: www.toxqsar.org

We look forward to welcoming you in Liverpool.

Dr Mark Cronin and Prof John Dearden
(Co-Chairmen of QSAR2004)

Third Joint Sheffield Conference on Chemoinformatics
April 21-23, 2004

The Chemical Structure Association Trust and the Molecular Graphics and Modelling Society announce their Third Joint Sheffield **Conference on Chemoinformatics**. The conference will be held in The Octagon Centre and Tapton Hall of Residence, University of Sheffield, UK, from 21st to 23rd April 2004. Offers of papers are welcomed in all aspects of chemoinformatics. Possible topics include (but are not limited to):

* High-Throughput Screening including: assay QC and its influence on data mining; design of screening collections; systems based design

* Virtual Screening including: docking and pharmacophore analysis; similarity methods; clustering

* Computational Methods for Lead Identification and Optimisation including: structure-activity methods; structure-based design

* New Algorithms and Technologies including: machine learning algorithms; data handling and visualisation

* Case histories incorporating any of the above

cisrg.shef.ac.uk/shef2004

The conference is being organised jointly by the Chemical Structure Association Trust (CSAT), the Molecular Graphics and Modelling Society (MGMS) and the Department of Information Studies, University of Sheffield.
The organising committee consists of:
Val Gillet, University of Sheffield;
John Holliday, University of Sheffield;
Stephen Pickett, Glaxo SmithKline; on behalf of the Molecular Graphics and Modelling Society;
Helen Schofield, UMIST; on behalf of the Chemical Structure Association Trust;
Peter Willett, University of Sheffield.

Authors wishing to submit a paper for consideration should send a title and abstract to Val Gillet (v.gillet@sheffield.ac.uk) by 31st October 2003. Submissions will be selected as either oral contributions or posters by the Organising Committee. In selecting papers for oral presentation we will seek to achieve a balance between new methodologies and successful applications of methods. Further details of the conference and registration information will follow later in the year and will be posted at cisrg.shef.ac.uk/shef2004.

Molecular Discovery Ltd. Users Meeting 2004: Novel Computational Methods for Rational Drug Design, ADME and DMPK Prediction, Cheminformatics

mailto:meeting2004@moldiscovery.com

We are pleased to announce the first MD Users meeting, which will be held in Perugia, Italy, from the 18th to 22nd of May, 2004. The main focus of the meeting will be on the practical use of the MD programmes in real research applications, and participants will be able to work with the latest release of each programme. They will also have a unique opportunity to evaluate and criticize some of the novel software projects which are currently being developed by the scientists at Molecular Discovery. Feedback and suggestions from all participants will be greatly appreciated, so that our future programmes can be as useful, reliable and effective as possible.

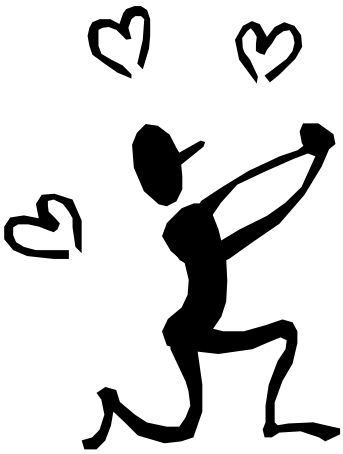
Lectures, Case Work and Computer Studies will be given by:

* Dr. Peter Goodford (the father of the well-known GRID force field).
* Prof. Gabriele Cruciani, showing practical applications of MIFs in ADME, DMPK, SBDD
* Prof. Manuel Pastor, on 3D-QSAR grid-independent methods
* Prof. Tudor Oprea, reporting on the Penguins projects
* Dr. Ismael Zamora, reporting of the MetaSite project
* Dr. Massimo Baroni, the author of our main cheminformatic tools
* Dr. Silvio Mecucci, the VolSurf project developer
* Dr. Emanuele Carosati, Dr. Paolo Benedetti, Dr. Gianluca Sforna, Dr. Riccardo Vianello on practical Case Works

The number of attendees is limited, so a definitive registration should be made as soon as possible.

The meeting will take place at the Relais San Clemente resort. It is "an old noble residence named after che millenary church which forms part of the complex" located near Perugia in "an atmosphere of suggestive naturalness".

More info: http://www.moldiscovery.com/meeting2004.php



Please send annual fees of **$10** to Stefan Balaz, or **£6** or **10 Euros** to Han van de Waterbeemd.

Dr. Stefan Balaz
The QSAR and Modelling Society
North Dakota State University
College of Pharmacy
Dept. Pharm.Sci.
Fargo, North Dakota 58105-5055
USA

Or to Han van de Waterbeemd in the UK (Eurocheques should be drafted in £).

MAILBOX

Mailbox of The QSAR and Modelling Society

qsar_society@accelrys.com

WWW HOMEPAGE

The best source for current information is our Web Home Page. You are encouraged to participate actively in improving and updating this site by sending us information and suggestions.

http://www.qsar.org

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'Biorelevant' chemistry is a multidisciplinary field that has undergone explosive growth in recent decades: chemical methodologies have long been employed in molecular- biology studies; wild-type and recombinant enzymes are used in stereo-selective chemical syntheses; natural products chemistry is making a comeback, as limitless 'active principles' from an ever widening range of species from every imaginable habitat are explored and exploited as potential clinical successes. *Chemistry & Biodiversity* will serve as a *high-quality* publishing forum covering a wide range of biorelevant topics for a truly *international* audience and will function as an official journal of the *Center for the Study of Biological Complexity* at Virginia Commonwealth University, USA. *Chemistry & Biodiversity* will publish both field-specific and interdisciplinary contributions on all aspects of *biologically relevant* chemistry research. The journal will cover all research fields straddling the border between the chemical and biological sciences, with the ultimate goal of broadening our understanding of how nature works at a molecular level.

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