CMTPI 2009

04 - 08 JULY'09 ISTANBUL TURKEY

Fifth International Symposium on Computational Methods in Toxicology and Pharmacology Integrating Internet Resources

Dedicated to the 80th Birth Anniversary of Professor Toshio Fujita

Abstract Book

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Fifth International Symposium on
Computational Methods in Toxicology and Pharmacology
Integrating Internet Resources
(CMTPI-2009)

Abstract Book

Istanbul, Turkey
July 04-08, 2009

ABSTRACT BOOK

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ABSTRACT BOOK

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ABSTRACT BOOK

Scientific Programme

Scientific Programme

04.07.2009, Saturday

12:00 - 18:00	***Registration***	
18:00 - 18:30	***Opening Ceremony***	
18.30 - 18.45	***The 80th Birth Anniversary of Professor Toshio FUJITA***	
18:45 - 19:30	Opening Lecture	Toshio FUJITA, Professor Emeritus at Kyoto University, Kyoto, Japan. LIGAND-BASED SAR-OMICS AS A PARADIGM FOR THE LEAD EVOLUTION IN DRUG DESIGN
19:30 - 21:00	***Welcome Party***	

05.07.2009, Sunday

Internet Tools & Databases (I)

Chairs: B.O. VILLOUTREIX and M. VRAČKO

09:00 - 09:45	Plenary Lecture	**Stephen H. BRYANT**, *Computational Biology Branch, Natinoal Center for Biotechnology Information (NCBI) National Library of Medicine (NLM), NIH Rockville Pike, Bethesda, MD, U.S.A PUBCHEM:* AN OPEN RESPOSITORY FOR CHEMICAL STRUCTURE AND BIOACTIVITY INFORMATION.
09:45 - 10:15	Major Talk	**James DEVILLERS**, *CTIS, Rillieux La Pape, France* INTERNET RESOURCES FOR AGENT- BASED MODELING.
10:15 - 10:45	Major Talk	**Vladimir POROIKOV**, *Institue of Biomedical Chemistry of Russian Academy of Medical Sciencis, Moscow, Russia.* COMPUTATIONAL TOOLS AND DATABASES FOR TOXICOLOGY AND PHARMACOLOGY: IS THERE REAL INTEGRATION VIA THE INTERNET?
10:45 - 11:15	*Coffee Break*	

Internet Tools & Databases (II)

Chairs: S.H.BRYANT and M. NOVIČ

11:15 - 12:00	Plenary Lecture	**Bruno O. VILLOUTREIX**, *Director Inserm-Paris 7 Unit U973, Bioinformatics - Chemoinformatics, Paris, France* STRUCTURE-BASED IN SILICO SCREENING COMPUTATIONS: FREE ACADEMIC AND CORPORATE SOFTWARE SOLUTIONS, FROM VISUALIZATION TO POST- PROCESSING.
12:00 - 12:20	Oral Communication	**Fabian BUCHWALD**, *Informatic Institute, München Technical University. Müchen, Germany.* *INTEGRATING BACKGROUND KNOWLEDGE FROM INTERNET DATABASES INTO PREDICTIVE TOXICOLOGY MODELS.*
12:20 - 12:40	Oral Communication	**Nathalie MARCHAND-GENESTE**, *Bordeaux University, France* e-ENVIRONMENTAL POLLUTANT SHORT AND LONG TERM TOXICOLOGICAL EFFECT DATABESES
12:40 - 14:00	*Lunch*	
15:00 - 19:00	*Sightseeing Tour*	

06.07.2009, Monday

QSAR in Toxicology (I)

Chairs: J. DEVILLERS and S. KULKARNI

09:00 - 09:45	Plenary Lecture	**Barry HARDY**, *Douglas connect GmbH, Zeiningen Switzerland.* COLLABORATIVE DEVELOPMENT OF PREDICTIVE TOXICOLOGY APPLICATIONS
09:45 - 10:15	Major Talk	**Paola GRAMATICA**, *Department of Structural and Funtional Biology, (DBSF), University ofInsubria, Varese, Italy.* QSAR MODELLING OF TOXICITY ENDPOINTS OF EMERGINIG POLLUTANTS: FRAGRANCES AND PERFLUORINATED COMPOUNDS.
10:15 - 10:35	Oral Communication	**Simona FUNAR-TIMOFEI**, *Institue of Chemistry of the Romania Academy Timisoara, Romania.* A QSAR STUDY OF DYE ACUTE TOXICITY.
10:35 - 11:05	*Coffee Break*	

QSAR in Toxicology (II)

Chairs: P. GRAMATICA and B.HARDY

11:05 - 11:25	Oral Communication	**James DEVILLERS**, *CTIS, Rillieux La Pape, France.* PREDICTION OF ACUTE MAMMALIAN TOXICITY FROM QSARs AND INTERSPECIES CORRELATIONS.
11:25 - 11:45	Oral Communication	**Elena FIORAVANZO**, *S-IN Soluzioni Informatiche, Vicenza, Italy.* APPLICATION OF STRUCTURE- ACTIVITY RELATIONSHIPS IN THE CHEMIAL HAZARD ASSESSMENT.
11:45 - 12:05	Oral Communication	**Marjan VRAČKO**,*National Institue of Chemistry, Ljublijana, Slovenia* CAESAR MODELS FOR PREDICTION OF FIVE ENDPOINTS.
12:05 - 12:25	Oral Communication	**Melek TÜRKER-SAÇAN** ,*Bogazici University, Institue of Environmental Sciences. Istanbul,Turkey.* MODELING THE RELATIVE TOXICITY OF METALS ON RESPIRATION OF NITRIFIERS USING ION CHARACTERISTICS.
12:25 - 12:45	Oral Communication	**Natalja FJODOROVA**,*Laboratory of Chemometrics, National nstitue of Chemistry, Ljubljana, Slovenia.* NEW PUBLIC QSAR MODEL FOR PREDICTION OF CARCINOGENICITY
12:45 - 14:15	*Lunch*	

"OMIC" -Sciences and Bioinformatics (I)

Chairs: T. FUJITA and MANALLACK

14:15 - 15:00	Plenary Lecture	**Danail BONCHEV**, *Director of Research on Bioinformatics, Collage of Humanities and Sciences, Virginia Commonwealth University, Virginia, U.S.A.* CELLULAR AUTOMATA IN MODELING COMPLEX BIOLOGICAL SYSTEMS.
15:00 - 15:20	Oral Communication	**Julie GONZALEZ**, *Bordeaux University, Talence. France.* MOLECULAR HODELLING OF STRUCTURAL AND ENERGETIC PROPERTIES OF CARCINOGEN DNA.
15:20 - 15:40	Oral Communication	**Timothy V. PYRKOV**,*Institute of Bioorganic Chemistry, Russian Academy of Sciences, Moscow, Russia.* ANALYSIS OF HYDROPHOBIC ORGANISATION OF PROTEIN- LIGAND COMPLEXES: USING PLATINUM WEB-SERVER TO IMPROVE THE RESULTS OF MOLECULAR DOCKING.
15:40 - 16:10	*Coffee Break*	
16:10 - 18:30	*Poster Session*	

07.07.2009, Monday

"OMIC"- Sciences and Bioinformatics (II)

Chairs: D.BONCHEV and A.SAXENA

09:00 - 09:30	Major Talk	**Kimito FUNATSU**, *Department of Chemical System Engineering The University of Tokyo, Japan.* DEVELOPMENT OF A METHOD FOR PREDICTING METABOLITES BY USING CHEMOINFORMATICS METHODS.
09:30 - 09:50	Oral Communication	**Marjana NOVIČ**, *National Institute of Chemistry, Ljubljana, Slovenia.* CHEMOMETRICS EXPLORATION OF TRANS MEMBRANE PROTEINS AVAILABLE IN THE PUBLIC DATA BASES. FROM STATISTICAL MODELS TOWARS STRUCTURE AND MECHANISM OF TRANSPORT.
09:50 - 10:10	Oral Communication	**Márcia M.C. FERREIRA**, *Laboratory for Theoretical and Applied Chemometrics, Institute of Chemistry, University of Campinas, Brazil.* LQTA-QSAR: ANEW 4D-QSAR METHODOLOGY.
10:10 - 10:30	Oral Communication	**Anna TSANTILI-KAKOULIDODU**, *Department of Pharmaceutical Chemistry, School of Pharmacy, University of Athens, Athens, Greece* A QSAR STUDY ON PPAR -α/γ GENE TRANSACTIVATION DATA USING MULTIVARIATE STATISTICS.
10:30 - 11:00	*Coffee Break*	

Computer-Aided Drug Discovery (I)

Chairs: E.AKI and P.POROIKOV

11:00 - 11:30	Major Talk	**Athina A. GERONIKAKI**, *Aristotle University of Thessaloniki, School of Pharmacy, Pharmaceutical Chemistry Department, Thessaloniki, Greece* COMPUTER-AIDED DISCOVERY OF ANTI-INFLAMMATORY THIAZOLIDINONES WITH DUAL CYCLOOXYGENASE/ LIPOXYGENASE INHIBITION.
11:30 - 11:50	Oral Communication	**Anna Yu. GOLOVACHEVA**, *Research Computing Center, Moscow State University, Moscow, Russia.* A NEW METHOD TO ESTIMATE STABILITY OF CHELATE COMPLEXES AND ITS APPLICATION FOR HIV-1 INTEGRASE INHIBITOR DESIGN.
11:50 - 12:10	Oral Communication	**György DORMÁN**, *Targetex, Hungary.* GRID AIDED COMPUTER SYSTEM FOR ACCELERATED ANTI-CANCER DRUG DESIGN: CANCERGIRD.
12:10 - 12:30	Oral Communication	**Olga N. KOBOROVA**, *Institute of Biomedical Chemistry Rus.Acad. Med. Sci., Moscow, Russia.* IN SILICO METHOD FOR IDENTIFICATION OF PROMISING ANTICANCER TARGETS.
12:30 - 14:00	*Lunch*	

Computer-Aided Drug Discovery (II)

Chairs: D.DOMINE and D.W.OLIVER

14:00 - 14: 45	Major Talk	**Pekka TIIKKAINEN**, *University of Turku and VIT Medical Biotechnology, Turku, Finland.* CRITICAL VALIDATION OF VIRTUAL SCREENING METHOD AGAINST THE MUV DATASET.
14:45 - 15:15	Major Talk	**Anil Kumar SAXENA**, *Central Drug Research Institute, Lucknow, India.* MOLECULER MODELING AND DOCKING STUDIES ON HSP90 INHIBITORS.
15:15 - 15:35	Oral Communication	**Annick PANAYE**, *ITODYS, University Denis Diderot, CNRS Paris, France.* CLASSIFICATION OF THE ESTROGEN RECEPTOR BINDING AFFINITY OF XENOBIOTICS FROM A MIXED 2D-SUBSTRUCTTURAL AND 3D-PARAMETRIC APPROACH.
15:35 - 16:05	*Coffee Break*	

Drug Design & Discovery Applications (I)

Chairs: J.P. DOUCET

16:05 - 16:50	Pleanary Lecture	**David MANNALLACK**, *Faculty of Pharmacy and Pharmaceutical Sciences, The University of Melbourne, Melbourne, Australia.* THE pKa DISTRIBUTION OF DRUGS: APPLICATION TO DRUG DISCOVERY.
16:50 - 17:20	Major Talk	**Douglas W. OLIVER**, *Faculty of Health Sciences, North- West University, Potchefstroom, South Africa.* OZONE IN MEDICINAL RESEARCH AND APPLICATION.
17:20 - 17:50	*Presentation of CMTPI-2011*	
19:30	*Gala Dinner*	

08.07.2009, Wednesday

Drug Design & Discovery Applications (II)

Chairs: A.GERONIKAKI and I. YALCIN

09:00 - 09:30	Major Talk	**Vladimir A. PALYULIN**, *Department of Chemistry, Moscow State University, Moscow, Russia.* EFFICIENT 2D APPROACHES TO VIRTUAL SCREENING: MFTA-AND FRAGMENT- BASED TECHNIQUES.
09:30 - 10:00	Major Talk	**Umpei NAGASHIMA**, *Research Institute for Computational Science, National Institute of Advanced Industrial Science and Technology, Tsukuba, Ibraki, Japan.* MOLECULER ORBITAL CALCULATION FOR LARGE MOLECULE WITH SAKURAI-SUGIURA METHOD ON GRID COMPUTING ENVIRONMENT.
10:00 - 10:20	Oral Communication	**Petro I. PETKOV**, *Laboratory of Mathematical Chemistry, Bourgas As. Zlatarov University, Bourgas, Bulgaria,* MECHANISTICALLY BASED CATEGORIZATION OF AROMATASE INHIBITORS.
10:20 - 10:50	*Coffee Break*	

Drug Design & Discovery Applications (II)

Chairs: M.C. FERREIRA and K. FUNATSU

10:50 - 11:10	Oral Communication	**Dimitry A. FILIMONOV**, *Institute of Biomedical Chemistry of Russian Academy of Medical Sciences, Moscow, Russia.* QNA BASED "STAR TRACK" QSAR APPROACH.
11:10 - 11:30	Oral Communication	**Semra ŞARDAŞ**, *Marmara University, Faculty of Pharmacy, Toxicology Department, Istanbul, Turkey.* SERIOUS ADVERSE DRUG EVENTS IN CURRENTLY MARKETED BIOTECHNOLOGY PRODUCTS.
11:30 - 11:50	*Closing of the Symposium*	
12:00 - 14:00	*Lunch*	

End of the Meeting

Opening Lecture

OL LIGAND - BASED SAR-OMICS AS A PARADIGM FOR THE LEAD EVOLUTION IN DRUG DESIGN.
Toshio Fujita

Plenary Lectures

PL-1 PUBCHEM: AN OPEN REPOSITORY FOR CHEMICAL STRUCTURE AND BIOACTIVITY INFORMATION.
Stephen Bryant

PL-2 STRUCTURE-BASED *IN SILICO* SCRENINIG COMPUTATIONS: FREE ACADEMIC AND CORPORATE SOFTWARE SOLUTIONS, FROM VISUALIZATION TO POST-PROCESSING.
Bruno O. Villoutreix

PL-3 COLLABORATIVE DEVELOPMENT OF PREDICTIVE TOXICOLOGY APPLICATIONS.
Barry Hardy, Christoph Helma, Nina Jeliazkova, Romualdo Benigni, Stefan Kramer, Andreas Karwath, Haralambos Sarimveis, David Gallagher, Vladimir Poroikov, Sunil Chawla, Sylvia Escher

PL-4 CELLULAR AUTOMATA MODELING OF BIOMOLECULAR NETWORKS.
Danail Bonchev

PL-5 THE pKa DISTRIBUTION OF DRUGS-APPLICATION TO DRUG DISCOVERY.
David Manallack

Major Talks

MT-1 INTERNET RESOURCES FOR AGENT-BASED MODELING.
J.Devillers, A.Decourtye ahd P. Aupinel

MT-2 COMPUTATIONAL TOOLS AND DATABASES FOR TOXICOLOGY AND PHARMACOLOGY: IS THERE REAL INTGERATION VIA THE INTERNET?
Vladimir Poroikov, Dmitry Druzhilovsky, Alexey Zakharov, Alexey Lagunin and Dmitry Filimonov

MT-3 QSAR MODELLING OF TOXICITY ENDPOINTS OF EMERGINIG POLLUTANTS: FRAGRANCES AND PERFLUORINATED COMPOUNDS.
Barun Bhhatarai, Paola Gramatica, Mara Luini and Ester Papa

MT-4 DEVELOPMENT THE METHOD FOR PRECITING METABOLITES BY USING CHEMOINFORMATICS METHODS.
Kimito Funatsu, Michio Koyama and Masamoto Arakawa

MT-5 COMPUTER-AIDED DISCOVERY OF ANTI-INFLAMMATORY THIAZOLIDINONES WITH DUAL CYCLOOXYGENASE/LIPOXYGENASE INHIBITION.
Athina A. Geronikaki, Alexey A.Lagunin, Dimitra I. Hadjipavlou-Litina, Phaedra T. Eleftheriou, Dmitrii A. Filimonov, Intekhab Alam, Anil K. Saxena and Vladimir V. Poroikov

MT-6 CRITICAL VALIDATION OF VIRTUAL SCREENING METHODS AGAINST THE MUVDATASET.
Pekka Tiikkainen, Patrick Markt, Gerhard Wolber, Antti Poso and Olli Kallioniemi

MT-7 MOLECULAR MODELING DOCKING STUDIES ON HSP90 INHIBITORS.
Anil K.Saxena, Shalini Saxena and Shailendra S. Chaudhary

MT-8 OZONE IN MEDICINAL RESEARCH AND APPLICATION.
Douglas W.Oliver, C.B.Brink, D.P.Venter, B.P.J.van Niekerk, A. Pretorius and J. Lotriet

MT-9 EFFICIENT 2D APPROACHES TO VIRTUAL SCREENING: MFTA-AND FRAGMENT-BASED TECHNIQUES.
Vladimir A. Palyulin, Eugene V. Radchenko, Igor I. Baskin, Andrey A. Melnikov and Nikolay S. Zefirov.

MT-10 MOLECULAR ORBITAL CALCULATION FOR LARGE MOLECULE WITH SAKURAI-SUGIURA METHOD ON GRID COMPUTING ENVIRONMENT.
Umpei Nagashima, Yuichi Inadomi, Hiroaki Umeda, Toshio Watanabe, Takayoshi Ishimoto and Tetsuya Sakurai

Oral Communications

OC-1 INTEGRATING BACKGROUND KNOWLEDGE FROM INTERNET DATABASES INTO PREDICTIVE TOXICOLOGY MODELS.
Mira Edelstein, Fabian Buchwald, Lothar Richter and Stefan Kramer

OC-2 e-ENVIRONMENTAL POLLUTANT SHORT AND LONG TERM TOXICOLOGY EFFECT DATABASES.
Nathalie Marchand - Geneste and Julie Gonzalez

OC-3 A QSTR STUDY OF DYE ACUTE TOXICITY.
Simona Funar - Timofei and Walter M.F.Fabian

OC-4 PREDICTION OF ACUTE MAMMALIAN TOXICITY FROM QSARS AND INTERSPECIES CORRELATIONS.
J.Devillers and J.P.Doucet

OC-5 APPLICATION OF STRUCTURE - ACTIVITY RELATIONSHIPS IN THE CHEMICAL HAZARD ASSESSMENT.
Elena Fioravanzo and Arianna Bassan

OC-6 CEASAR MODELS FOR PREDICTION OF FIVE ENDPOINTS.
Marjan Vračko, Johannes J.M. van de Sandt, Quasim Chaudhry, Mark Cronin, Marco Pintore, Fran Lemke, Gerrit Schueuermann, Giuseppina Gini and Emilio Benfenati

OC-7 MODELING THE RELATIVE TOXICITY OF METALS ON RESPIRATION OF NITRIFIERS USING ION CHARACTERISTICS.
Melek Türker Şaçan, Ferhat Çeçen, M. Doğa Ertürk and Neslihan Semerci

OC-8 NEW PUBLIC QSAR MODEL FOR PREDICTION OF CARCINOGENICITY.
Natalja Fjodorova, Marjana Novič and Marjan Vračko

OC-9 MOLECULER MODELING OF STRUCTURAL AND ENERGETIC PROPERTIES OF CARCINOGEN DAMAGED DNA.
Julie Gonzalez and Nathalie Marchand - Geneste

OC-10 ANALYSIS OF HYDROPHOBIC ORGANISATION OF PROTEIN-LIGAND COMPLEXES: USING PLATINUM WEB-SERVER TO IMPROVE THE RESULTS OF MOLECULAR DOCKING.
Timothy V.Pyrkov, Anton O.Chugunov, Nikolay A.Krylov, Dmitry E. Nolde and Roman G. Efremov.

OC-11 CHEMOMETRICS EXPLORATION OF TRANS MEMBRANE PROTEINS AVALIABLE IN THE PUBLIC DATA BASES. FROM STATISTICAL MODELS TOWARDS STRUCTURE AND MECHANISM OF TRANSPORT.
Marjana Novič and Amrita Roy Choudhury

OC-12 LQTA-QSAR: A NEW 4D-QSAR METHODOLOGY.
João Paulo A. Martins, Euzébio G. Barbosa, Kerly F.M.Pasqualoto and Márcia M.C. Ferreira

OC-13 A QSAR STUDY ON PPAR -∝/γ GENE TRANSACTIVATION DATA USING MULTIVARIATE STATISTIC.
Theadosia Vallianatou, Costas Giaginis and Anna Tsantili- Kakoulidou

OC-14 A NEW METHOD TO ESTIMATE STABILITY OF CHELATE COMPLEXES AND ITS APPLICATION FOR HIV-1 INTEGRASE INHIBITOR DESIGN.
Anna Yu. Golovacheva, Fedor V. Grigoriev, Alexey N. Romanov, OLga A. Kondakova, Maxim A. Smolov, Marina B. Gottikh and Vladimir B. Sulimov

OC-15 GRID AIDED COMPUTER SYSTEM FOR ACCELERATED ANTI-CANCER DRUG DESIGN: CancerGrid.
György Dormán, Péter Kocsuk, József Kovács, István Baǵyi, Angelo Carotti, Orazio Nicolotti, Sandor Cseh, Simona Distinto, Amiram Goldblum, Johannes Kirchmair, David Marcus, Alfons Nonell-Canals, Jordi Mestres, Andre Lomaka, Miklos J. Szabó, Gábor Pőcze and Béla Bertók

OC-16 IN SILICO METHOD FOR IDENTIFICATION OF PRONISING ANTICANCER TARGETS.
O.N.Koborova, D.A. Filimonov, A.V.Zakharov, A.A.Lagunin, S.M.Ivanov, V.V.Poroikov and A.Kel

OC-17 CLASSIFICATION OF THE ESTROGEN RECEPTOR BINDING AFFINITY OF XENOBIOTICS FROM A MIXED 2D-SUBSTRUCTURAL AND 3D- PARAMETRIC APPROACH.
A.Panaye, J.P.Doucet and J.Devillers

OC-18 MECHANISTICALLY BASED CATEGORIZATION OF AROMATASE INHIBITORS.
Petro I. Petkov, Stanislav Temelkov, Daniel L.Villeneuve, Gerald T. Ankley and Ovanes Mekenyan

OC-19 QNA BASED "STAR TRACK" QSAR APPROACH.
Dmitry A.Filimonov, Alexey V.Zakharov, Alexey A.Lagunin and Vladimir V.Poroikov

OC-20 SERIOS ADVERSE DRUG EVENTS IN CURRENTLY MARKETED BIOTECHNOLOGY PRODUCTS.
Semra Şardaş

Poster Presentations

PO-1 MOLECULAR DYNAMICS STUDY OF PROLYL-OLIGOPEPTIDASE WITH INHIBITOR IN BINDING CAVITY.
K.Kaszuba, T. Rog, J.-F.St. Pierre, M.Karttunen and A.Bunker

PO-2 PREDICTION OF PROTEIN TRANSMEMBRANE REGIONS FROM SEQUENCE INFORMATION-A CHEMOMETRICS EXPLORATION OF TRANSMEMBRANE PROTEINS.
A. R. Choudhury and M. Novic

PO-3 GENOTOXICITY INDUCED BY TETDACHLOROETHYLENE IN DRY-CLEANING WORKERS IN EGYPT
A.M. Emara, M. M. Abo El Noor, N. I. Sarhan and M. A. Omara

PO-4 POTENTIAL HEPATOPROTEVTIVE EFFECTS OF VITAMIN E AND NIGELLA SATIVA OIL ON HEPATOTOXICITY INDUCED BY CHRONIC EXPOSURE MALATHION IN HUMAN AND MALE ALBINO RATS.
M. A. El-Gharieb, T.A. El- Marsry, A.M.Emara and M.A.Hashem

PO-5 2-HETEROARYLIMINO - 5 - BENZYLIDENE - 4 - THIAZOLIDINONES AS NEW INHIBITORS OF MATRIX METALLOPROTEINASE-13.
R.Messina, A. Geronikaki, A. Panico, M.Fragai and P.Vicini

PO-6 QSAR MODEL FOR PREDICTING THE POTENCY OF SUBSTITUTED FULLERENES AS HIV PROTEASE INHIBITORS.
D.Martin and M. Karelson

PO-7 MOLECULAR DESIGN OF THE ERYTHROPOIETIN RECEPTOR LIGANDS.
D.W.Oliver

PO-8 SYNTHESIS AND *IN SILICO* EVALUATION OF NOVEL 2-(2.6-DINALOSUBSTITUTED) -3-(SUBSTITUTED) BENZO (D) THIAZOLE-2-YL)-THIAZOLIDIN-4-ONES.
E.Pitta, A.Geronikaki and V. Poroikov

PO-9 A COMPRARISON OF VALIDATED QSTR MODELS BASED ON DESCRIPTORS FROM AM1PM3 HF AND DFT CALCULATIONS FOR ACUTE TOXICITY OF DIVERSE ORGANIC COMPOUNDS TO THE FATHEAD MINNOW.
S.Palaz, M.MYaşar, O.Oltulu and E.Eroğlu

PO-10 DESIGNING NEW POTENT SELECTIVE INHIBITORS FOR PDEIV *IN SILICO* THROUGH STRUCTURE - BASED DOCKING AND VIRTUAL SCREENING.
G. Çfitçi, D. Akten and V. Aviyente

PO-11 QSAR STUDY OF CYCLIC UREA TYPE HIV-1 PROTEASE INHIBITORS USING *AB INITIO* FRAGMENT MO CALCULATION OF THEIR COMPLEX STRUCTURES WİTH HIV-1 PROTEASE.
H. Chuman, T. Fujita and T. Yoshida

PO-12 NEW STATISTICAL TOOLS IN BACTEIRAL COMPARATIVE GENOMICS.
H. Devillers, M. El Karoui and S. Schbath

PO-13 DESIGN OF TYROSINE KINASE INHIBITORS USING *IN SILICO* HIGH-THROUGHPUT DOCKING.
J. Gonzales, N. Marchand- Geneste and M. Laguerre

PO-14 HIV-1 REVERSE TRANSCRIPTASE INHIBITORS: 2-AMINO-6-ARYLSULFONYLBENZONITRITES AND CONGENERS. 2D-QSAR AND 3D-QSAR USING MOLECULAR DOCKING.
R. Hu, F. Barbault, M. Delamar, R. Zhang and J-P. Doucet

PO-15 QSAR INVESTIGATION OF ANTI-INFLAMMATORY ACTIVITY OF A SERIES OF NON-SUBSTITUTED/ SUBSTITUTED (E)-1-(4-MENTYL-2(METHYLAMINO)THIAZOL-5-YL)-3-PHENYLPROP-2-EN-1-ONES.
K. Liaras, A. Geronikaki, D. Hajipavlou-Litina, J. C.Dearden and M. Hewitt

PO-16 2-OXO-2H-PYRAN-3-CARBOTHIOAMIDE DERIVATIVES: SYNTHESIS AND REACTION WITH HYDRAZINE HYDRATE.
M. Makhloufi-Chebli, M. Hamdi, A. M. S. Silva, P. Richommec, O. Duvalc and J. -J. Hélesbeuxc

PO-17 A RECEPTOR INDEPENDENT 4D-QSAR STUDY ON HIV-INTEGRASE INHIBITORS BY MEANS OF LQTA - QSAR SOFTWARE.
E. Borges de Melo and M. M. C. Ferreira

PO-18 ERROR BACK-PROPAGATION NEURAL NETWORK AS A QSAR MODEL FOR PREDICTION OF CARCINOGENICITY.
M. Tušar and M. Novič

PO-19 ASSESING THE REPRODUCTIVE TOXICITY OF SAME (CON)AZOLE FUNGICIDES USING STRUCTURE ACTIVITY RELATIONSHIP (SAR) APPROACH.
M. Bolčič Tavcăr and M. Vračko

PO-20 SYNTHESIS, EVALUATION OF PHARMACOLOGICAL ACTIVITIES AND QUANTITATIVE STRUCTURE - ACTIVITY RELATIONSHIP STUDIES OF A NOVEL GROUP OF BIS(4-NITROARYL-1.4-DIHYDROPYRIDINE).
R. Miri, K. Javidnia, B. Hemmateenejad, M. Tabarzad and M. Jafarpour

PO-21 TOXICITY OF BENZENE DERIVATIVES TO THE YEAST (*SACCHAROMYCES CEREVISAE*)
M. Türker Saçan, M. D. Ertürk and S. Erdem

PO-22 REMOVAL OF CORRELATED DESCRIPTORS DOES NOT NECESSARILY RESULT IN BETTER PREDICTION: QSAR STUDY OF CITOSTATIC ACTIVITY OF SELECTED HYDROXYUREA DERIVATIVES.
M. Bojić, Ž. Debeljak, M. Medić-Šarić and Z. Rajić

PO-23 COMPUTATIONAL STUDY OF CYCLOADDITION WITH DIFFERENT NANOTUBES.
M. Keshavarz and F. Mohhamadi

PO-24 *AB INITIO* STUDY OF HETERO DIELDS ALDER REACTION USING QUANTUM MECHANIC METHODS.
M. Keshavarz and M. Davoodifar

PO-25 HOMOLOGY MODELING AND DOCKING STUDIES ON HUMAN HISTAMINE H_1- RECEPTORS.
Mridula Saxena

PO-26 QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP STUDY ANTITUBERCULAR DRUGS FLUOROQUINOLONES.
N. Minovski, M. Vračko and T. Šolmajer

PO-27 STRUCTURAL AND SEMI-EMPIRICAL MOLECULAR DESCRIPTORS: APPLICATION IN PROPERTY CORRELATIONS OF POLYHALOGENATED DIPHENYL ETHERS.
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PO-31 DIPOLAR CYCLOADDITION REACTIONS: SYNTHESIS OF SEVERAL NEW PYRAZOLE DERIVATIVES OF PHARMACEUTICAL ACTIVITIES.
S. E. Abdou and S.M. Eldin

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S. Bouaziz- Terrachet and S. Tairi- Kellou

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A. Toumi-Maouche, S. Tairi-Kellou and B. Maouche

PO-34 MOLECULAR DOCKING OF NEW PYRAZOLINE DERIVATIVES TO THE ACTIVE SITE OF MONOANIME OXIDASE.
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PO-35 SYNTHESIS OF PYRROLINO (3.4 - *d*) PYRAZOLES, PYRAZOLES, PYRAZOLO(5.4 -*d*) PYRIMIDINES AND PYRAZOLO (3.4 - *d*) PYRIMIDINES FOR TOXICOLOGY STUDIES.
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PO-36 APPLICATION OF CoMFA/CoMSIA ANALYSIS TO HETEROCYCLIC AZO DYE AFFINITIES FOR CELLULOSE FIBRE.
S. Funar- Timofei, W. M. F. Fabian and L. Kurunczi

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T. Yoshida, Y. Munei and H. Chuman

PO-39 COMPUTER - ASSISTED PREDICTION OF BIOLOGICAL ACTIVITY IN A SEARCH FOR DRUGS AMONG NATURAL PRODUCTS.
T. A. Gloriozova, V. V. Poroikov and V. M. Dembitsky

PO-40 MOLECULAR DYNAMICS SIMULATIONS OF NEBIVOLOL COMPLEXED WITH B AND B ADRENERGIC RECEPTORS-SUBTYPE SPECIFICITY STUDIES.
K. Kaszuba, I. Vattulainen, M. Karttunen and T. Róg

PO-41 PHARMACOPHORE ANALYSIS ON SOME BENZOXAZOLES AGANIST DRUG-RESISTANT *ESCHERICHIA COLI.*
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PO-42 USING CONFORMATIONAL ENSEMBLES AS QUERIES IN BRUTUS SEARCHES: IS IT WORTH THE EXTRA EFFORT?
T. Kalliokoski and A. Poso

PO-43 QSAR DATA BANK FORMAT FOR ELECTRONIC ORGANIZATION AND ARCHIVING OF QSAR/QSPR MODEL INFORMATION.
S.Sild, V. Ruusman and U. Maran

PO-44 ANALYSIS OF HYDROPHOBIC ORGANISATION OF CPCR COMPLEXES WITH LIGANDS.
V. N. Novoseletsky, T. V. Pyrkov and R. G. Efremov

PO-45 MODELING THE HYDROPHILICITY AND LIPOPHILICITY OF WINE POLYPHENOLS USING DESCRIPTORS DERIVED FROM 3D STRUCTURES.
S. Nikolić and V. Rastija

ABSTRACT BOOK

Opening Lecture

ABSTRACT BOOK

LIGAND-BASED SAR-OMICS AS A PARADIGM FOR THE LEAD EVOLUTION IN DRUG DESIGN

Toshio Fujita

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Chemical structure of most synthetic bioactive compounds of practical use, whether they are medicinal or agrochemical, is mostly the one identified as a consequence of structure transformations originating from their respective lead compounds. The lead structure is often varied with more or less drastic skeletal transformations to "evolve" into the "next- generation" lead structures by crossing over barriers of pharmacological difference. The "lead evolution" process could be repeated to evolve even "higher generation" lead structures. In this presentation, structure evolution pathways starting from indole-3-acetic acid (IAA) and salicylic acid (SA), both of which are natural plant growth regulators (hormones), are traced to show that they eventually evolve into various pharmacologically important series such as auxin-type herbicides, plant defense activators, "fenac" and "profen" anti-inflammatory agents, "fibrate" hypolipidemic drugs, CRTh2 antagonizing antiasthma drugs, acetyl CoA carboxylase inhibiting herbicides, "glitazone" antidiabetics, topoisomerase inhibiting anticancer agents, and dual as well as pan PPAR agonists. The integration of relationships in structural features among original and newly evolved categories should be much informative in lead evolution phase of drug design. Structure-activity patterns within individual categories can be compared with each other and the possible relationships can be examined among them. Trans-categorical examinations among individual structure-activity relationships of various pharmacological series compounds could be called as SAR-ome analyses. SAR-ome is an acronym to mean a totality of structure-activity relationships. The outcome from SAR-ome analysis of existing series of bioactive compounds (ligands) can be extended to designing candidate bioanalogs belonging to different pharmacological categories. In this regard, compilation of lead evolution examples is regarded as a precious repository of information for synthetic chemists in medicinal as well as agrochemical field from which invaluable suggestions and ideas for designing "how to make structure modification in the next step for the evolution" can hopefully be retrieved.

ABSTRACT BOOK

Plenary Lectures

ABSTRACT BOOK

PUBCHEM: AN OPEN REPOSITORY FOR CHEMICAL STRUCTURE AND BIOACTIVITY INFORMATION

Stephen Bryant

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PubChem is an online public information resource from the National Center for Biotechnology Information (NCBI). The system provides information on the biological activities of chemical substances, linking together results from multiple sources on the basis of chemical structure and/or chemical structure similarity. Following the deposition model introduced by GenBank, PubChem's content is derived from user depositions of chemical structure and bioassay data, including high-throughput biological screening results from the NIH Molecular Libraries program. PubChem information retrieval provides basic searches by chemical names or structures as well as more complex structure-activity analysis within and among different bioassays. PubChem provides further information on biological activities via links to other NCBI information resources, such as the PubMed biomedical literature database and NCBI's protein 3D structure database, as well as via links to depositor web sites.

PL-2

STRUCTURE-BASED IN SILICO SCREENING COMPUTATIONS: FREE ACADEMIC AND CORPORATE SOFTWARE SOLUTIONS, FROM VISUALIZATION TO POST-PROCESSING

Bruno O. Villoutreix

Director Inserm-Paris 7 Unit U973, Bioinformatics-Chemoinformatics, Paris, France

Drug discovery is an interdisciplinary, expensive and time-consuming process. Advances in computational techniques, e.g., virtual screening, among others, help to speed-up modern hit identification and hit-to-lead optimization. These approaches can also be used for ADME/Tox prediction. Numerous tools are now freely available on the internet, from packages allowing visualization of molecules to docking/scoring and post-processing engines. This presentation summarizes some recently reported and freely available computer tools, attempts to highlight issues, challenges and future directions in the field of computational biology and chemistry.

COLLABORATIVE DEVELOPMENT OF PREDICTIVE TOXICOLOGY APPLICATIONS

Barry Hardy[*a], Christoph Helma[b], Nina Jeliazkova[c], Romualdo Benigni[d], Stefan Kramer[e], Andreas Karwath[f], Haralambos Sarimveis[g], David Gallagher[h], Vladimir Poroikov[i], Sunil Chawla[j], Sylvia Escher[k]*

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This lecture will provide a perspective on the growing significance of community and collaboration approaches in predictive toxicology. In part these challenges are technical and involve progressing issues related to cross-organisational, enterprise and application interoperability. Additional challenges include the development and application of best practices related to knowledge management, culture, organizational and industry development. The EC-funded FP7 project "OpenTox" (www.opentox.org) is developing an Open Source-based predictive toxicology framework that provides a unified access to toxicological data and (Quantitative) Structure-Activity Relationship i.e., (Q)SAR models. OpenTox provides tools for the integration of data, for the generation and validation of (Q)SAR models for toxic effects, libraries for the development and integration of (Q)SAR algorithms, and scientifically sound validation routines. OpenTox will support the development of applications for non-computational specialists in addition to interfaces for risk assessors, toxicological experts and model and algorithm developers.

OpenTox is relevant for the implementation of REACH as it allows risk assessors to access experimental data, (Q)SAR models and toxicological information from a unified interface that adheres to European and international regulatory requirements including OECD Guidelines for validation and reporting. The OpenTox framework is being populated initially with data and models for chronic, genotoxic and carcinogenic effects. These are the endpoints where computational methods promise the greatest potential reduction in animal testing required under REACH. Initial research has defined the essential components of the framework architecture, approach to data access, schema and management, use of controlled vocabularies and ontologies, web service and communications protocols, and selection and integration of algorithms for predictive modelling. The initial results of this research and next steps will be discussed.

OpenTox has been initiated as a collaborative project involving a combination of 11 different enterprise, university and government research groups to design and build the initial framework. Additionally numerous organizations with industry, regulatory or expert interests are being included from the start in providing guidance and direction. The goal is to expand OpenTox as a community project enabling additional expert and user participants to be involved in developments in as timely a manner as possible. To this end, our agreed upon intention is to carry out developments in an open and transparent manner from the early days of the project, and to open up discussions and development to the global community at large, who may either participate in developments or provide user perspectives. Cooperation on data standards, data integration, ontologies, integration of algorithm predictions from different methods, and testing and validation all have significant collaboration opportunities and benefits for the community. Additionally, practices for building effective collaborations from the OpenTox community approach will be discussed.

About OpenTox

OpenTox - An Open Source Predictive Toxicology Framework, www.opentox.org, is funded under the EU Seventh Framework Program: HEALTH-2007-1.3-3 Promotion, development, validation, acceptance and implementation of QSARs (Quantitative Structure-Activity Relationships) for toxicology, Project Reference Number Health-F5-2008-200787 (2008-2011).

Project Partners

Douglas Connect[a], In Silico Toxicology[b], Ideaconsult[c], Istituto Superiore di Sanita'[d], Technical University of Munich[e] Albert Ludwigs University Freiburg[f] , National Technical University of Athens[g], David Gallagher[h], Institute of Biomedical Chemistry of the Russian Academy of Medical Sciences[i] , Seascape Learning[j] and the Fraunhofer Institute for Toxicology & Experimental Medicine[k]

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CELLULAR AUTOMATA MODELING OF BIOMOLECULAR NETWORKS

Danail Bonchev

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The emergence of systems biology changed the strategy of drug design from a single target-single drug approach to a network-based one. Analyzing the intracellular gene regulatory, metabolic and protein-protein interaction networks it became possible to infer before clinical trials of new drugs the potential broad consequences of perturbing these highly connected networks. Yet, the highly sophisticated software for network analysis (such as Ingenuity, Pathway Studio and Cytoscape) does not provide information about the *dynamics* of intracellular processes. The traditional dynamic modeling by ordinary differential equations (ODE) is hindered by network complexity and the lack of experimental kinetic parameters. Cellular Automata (CA) modeling and its recent extension - the Agent-Based Modeling (ABM) - promises to fill the gap, although this promise still has long way to go. The presentation reviews the state of this emerging field of research. It starts with a brief historical introduction from the founding work of John von Neumann and Stanislaw Ulam in the 1940's up to the present day. The basics of cellular automata and agent-based modeling follow, illustrated by examples and extensive list of related software and websites. The applications of the CA technique to networks of biochemical reactions begin with the pioneering work on the modeling of a single enzymatic reaction. The case studies of the MAPK signaling pathway and the FAS- and BCL2-related apoptosis are presented in a variety of ways, including with accounting for the different apoptosis-related domains of the participating proteins. The potential of the CA method to model basic patterns of pathways is demonstrated, and ways to control pathway dynamics by selective enzyme inhibition and concentration variations are outlined. A different line of CA applications includes the search for the best performing network motifs, an analysis of importance for effective intracellular signaling and pathway cross-talk.

THE pKa DISTRIBUTION OF DRUGS - APPLICATION TO DRUG DISCOVERY

David Manallack

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Analyses of physicochemical properties relating to drug-like character have so far not fully explored the acid-base dissociation constant (pK_a) values of drugs. Our recent studies have sought to describe the proportion of drugs with ionizable functional groups as well as the distribution of the pK_a values themselves.

Three levels of analysis will be outlined focusing on a contemporary set of drugs. Firstly, the overall nature of the compounds will be described by simply highlighting those containing ionizable groups. These compounds will then be examined in isolation to look at the proportions of acid and base containing substances. Finally the pK_a distributions will be detailed for those compounds with a single acid or basic group. Further divisions will be shown for CNS, non-CNS and oral drugs1. The implications of this work are far reaching when considering the importance of pK_a values to drug research. Indeed, the pK_a parameter influences many biopharmaceutical characteristics. The findings of this study expand on current wisdom in the area and have implications for the pharmaceutical industry engaged in discovery research with regard to the composition of corporate databases and collections of screening compounds.

Reference

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Major Talks

ABSTRACT BOOK

INTERNET RESOURCES FOR AGENT-BASED MODELING

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The use of agent-based models (ABMs) for research and management is steadily increasing in all the fields including environmental chemistry and toxicology. This growth is mainly driven by their ability to address problems that conventional modeling techniques cannot, such as the change of scale or the emergence of unanticipated phenomena resulting from interactions between their constitutive goal-directed agents. Unfortunately, software availability remains an obstacle to the use of ABMs for many researchers, especially if they have limited programming skills. In this context, after a brief introduction on the basic principles of agent-based modeling, the main software resources available on the Internet will be presented. Attempt will be made to estimate the complexity of these tools versus their potentialities and flexibility.

Acknowledgement: The financial support from the French Ministry of Ecology and Sustainable Development is gratefully acknowledged (PNRPE program).

COMPUTATIONAL TOOLS AND DATABASES FOR TOXICOLOGY AND PHARMACOLOGY: IS THERE REAL INTEGRATION VIA THE INTERNET?

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In the 21st century, the Internet has become an absolutely necessary prerequisite for everyday's life. As a medium for global communication, the Internet provides access to numerous informational and computational resources. Various multidisciplinary databases and computational tools useful for pharmacologists and toxicologists are available directly to end-users.

Some examples of freely accessible data repositories are:
Chemical Structure Lookup Service (http://cactus.nci.nih.gov/lookup/),
PubChem (http://pubchem.ncbi.nlm.nih.gov/),
ChemBank (http://chembank.broad.harvard.edu/),
ChemSpider (http://www.chemspider.com/),
ChemIDplus (http://chem.sis.nlm.nih.gov/chemidplus),
Open NCI Database Browser (http://cactus.nci.nih.gov/ncidb2/),
NCI DIS 3D database (http://dtp.nci.nih.gov/docs/3d_database/dis3d.html),
Therapeutic Target Database (http://xin.cz3.nus.edu.sg/group/cjttd/ttd.asp),
Toxicological Databases (http://toxnet.nlm.nih.gov/, http://www.epa.gov/NCCT/dsstox/),
DrugBank (http://redpoll.pharmacy.ualberta.ca/drugbank/index.html),
Organic Synthesis Reactions (http://www.orgsyn.org/).

Most of the web sites from which these data are available use special database management systems (DBMS) that provide the informational retrieval. Different parameters can be used to construct the queries; in some cases the results of the search contain links to external information resources. In addition to the standard DBMS functions, some web sites offer computational tools, which estimates some physical-chemical properties, biological activities, polar surface area (PSA), Lipinski Rule of five, drug-likeness, etc. Some examples of such web services are:

PASS INet (http://www.ibmc.msk.ru/PASS),
Similarity Search (http://cheminformatics.org/simsearch/),
Molinspiration Galaxy 3D Structure Generator (http://www.molinspiration.com/cgi-bin/galaxy),
OSIRIS Property Explorer (http://www.chemexper.com/tools/propertyExplorer/main.html).

In addition to such individual informational resources and computational tools there are metasites and meta search engines providing access to a range of resources devoted to pharmacology and toxicology, WIKIS where information is created in collaborative efforts, RSS information feeds, etc. Special projects directed toward creation of a single framework for solving particular tasks are currently being developed (see, e.g. http://opentox.org). Current state and future trends in integration of databases and computational tools available via the Internet will be discussed.

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QSAR MODELLING OF TOXICITY ENDPOINTS OF EMERGING POLLUTANTS: FRAGRANCES AND PERFLUORINATED COMPOUNDS

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Fragrances and Perfluorinated compounds (PFCs) represent new classes of emerging pollutants. Fragrances are used in many consumer products as cleaning/washing agents and different personal care products [1]. PFCs are used in variety of industrial and commercial products as hydro-repellent, non adhesive materials and electronics because of their properties of thermal and chemical inertness [2]. They are often released directly to the environment during their usage, thus they act as source of both indoor and outdoor air pollutants. Their potential persistence in environmental media and their bio-accumulation presents risk for the ecosystem, wildlife and humans [1]. Fragrances are believed to have possible toxic effects on humans (asthma, allergies, headaches) and some PFCs are identified with reproductive and developmental toxicity in rats and mouse [2,3]. Unfortunately, little is known about the environmental fate and toxicity of these substances. Their potential effects on humans and aquatic ecosystems are not yet clearly understood. The use of predictive approaches such as Quantitative Structure Activity (Property) Relationships (QSA(P)R), can help in filling this data gap and in characterizing the environmental and toxicological profile of these substances. In the proposed study, Ordinary Least Squares (OLS) regression-based QSA(P)R models were developed for different toxicological and physico-chemical endpoints. Theoretical molecular descriptors were calculated by DRAGON software, the best modelling variables were selected by applying Genetic Algorithms (GA) and the models were validated also externally [4]. Data Sets: The experimental data related to toxicological and physico-chemical data were taken from literatures and available online databases. For Fragrances: Toxicological endpoints as Mouse Oral LD_{50}, inhibition of NADH-oxidase (EC_{50}NADH-Ox) and the effect on mitochondrial membrane potential ($EC_{50}\Delta\Psi m$) [1,2,5] were modeled. Physico-chemical properties as LogKow, Water Solubility and Vapor Pressure were also modeled. For Perfluorinated compounds Mouse and Rat Inhalation LC50 data were studied [6].
Conclusion: The developed predictive QSA(P)R models will be presented and discussed. The models were validated, internally by statistical cross-validation and also externally by splitting *a priori* the available data. Their applicability domain was also verified. The robust and predictive models could be particularly useful for characterization, screening and prioritization of widely used emerging pollutants, and also a priori in the design of new products as safer alternatives to the existing dangerous compounds.

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DEVELOPMENT THE METHOD FOR PRECITING METABOLITES BY USING CHEMOINFORMATICS METHODS

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Purpose

In drug discovery process, it is important to know physical properties of metabolites from the viewpoint of side effects prevention and so on, and therefore, the identification of metabolites is very important. If metabolites of a drug candidate turns out to have toxicity by clinic trial, the cost spent till then becomes useless. In order to avoid such cases, the technique for predicting metabolites beforehand is hoped. In this study, we aimed at development of a method for predicting metabolites by using chemoinformatics methods.

Methods

CYP450 is the group of enzymes that is deeply related to drug metabolizing. If we can know "Whether a drug candidate is metabolized or not by each CYP450 ?" i.e. isofrom specificity, and "Which site of the molecule is the site of metabolism ?", i.e. regioselectivity, to predict metabolites of each drug candidates is almost possible. Therefore, by using the chemoinformatics method, we aimed to construct two models, which are used to predict isoform specificity and regioselectivity, respectively. In order to build a isoform specificity model, we used Random Forest (RF) as a learning method and Dragon descriptors as explanatory variables. RF is one of the strongest machine learning method and Dragon is one of the most frequently used descriptor in QSAR studies. And in order to build a regioselectivity model, we also used RF as a learning method and three kinds of original descriptors as expalatory variables. The descriptors indicate activation energy, solvent accessible surface are, and pharmacophore of each sites of a molecule, respectively. The substrate and non-substrate of CYP3A4, which is the main drug-metabolizing enzyme, were used for data set.

Result

As for the isoform specificity model, the accuracy is over 70%. And as for the regioselectivity model, the model is succeeded to predict the site of metabolism precisely about over 80% of substrates.

Conclusion and References

In this study, we build two models by using chemoinformatics methods in order to predict a metabolite of a drug candidate. Accuracy of both models are also high, and therefore, we can identify metabolites quickly and precisely by using this method.

COMPUTER-AIDED DISCOVERY OF ANTI-INFLAMMATORY THIAZOLIDINONES WITH DUAL CYCLOOXYGENASE/LIPOXYGENASE INHIBITION

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Discovery of multi-targeted biologically active molecules can be performed either by rational design using combination of pharmacophores or by screening of compound libraries. Experimental evaluation of many molecules against multiple targets is rather expensive procedure, and therefore in silico screening is preferential. We have shown previously that prediction of biological activity spectra for substances on the basis of their structural formulas by the computer program PASS (Prediction of Activity Spectra for Substances) can be used in search for dual antihypertensive agents (angiotensin-converting enzyme and neutral endopeptidase inhibitors) [1]. The current version of PASS predicts more than 3300 types of biological activity including pharmacotherapeutic effects, mechanisms of action, interaction with drug-metabolizing enzymes, side effects, and toxicity. To analyze the PASS prediction results, taking into account the mechanism-effect relationships, and to search for compounds with the desirable profiles of biological activity, PharmaExpert [2] software was developed. New anti-inflammatory agents of general structure (Fig.1) possessing dual cyclooxygenase/lipoxygenase (COX/LOX) inhibitory action, were selected on the basis of computer-aided prediction of biological activity for 573 virtually designed chemical compounds. 2-(thiazole-2-ylamino)-5-phenylidene-4-thiazolidinone derivatives with high probability to reveal the required biological acitvities were synthesized and experimentally tested as potential COX/LOX inhibitors. Lipoxygenase inhibition was evaluated as reported in our previous publication [3]. The COX-1 and COX-2 activities of the compounds were measured using ovine COX-1 and human recombinant COX-2 enzymes included in the “COX Inhibitor Screening Assay” kit provided by Cayman (Cayman Chemical Co., Ann Arbor, MI).Many of the tested compounds exhibited anti-inflammatory activity in the carrageenin-induced paw edema. It was shown that about 78% of the selected compounds were LOX or/and COX inhibitors. Analysis of lipophilicity of the compounds showed a negative correlation with inhibition of edema formation. The binding modes of the most active compounds for COX-1, COX-2, and 15-LOX were proposed on the basis of docking studies.

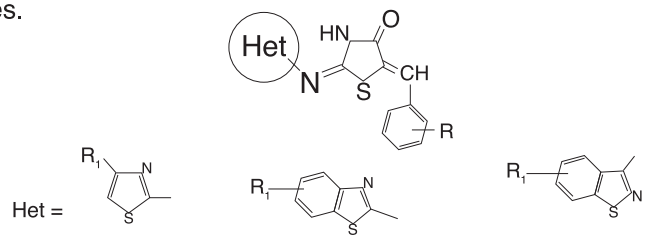

Figure 1. Structure of the synthesized compounds

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CRITICAL VALIDATION OF VIRTUAL SCREENING METHODS AGAINST THE MUV DATASET

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The validation is a vital prerequisite for any successful virtual screening campaign. Comparison studies of both structure and ligand-based tools are plenty. Common to all of them is a set of actives and decoys (inactives) and the objective to enrich the actives in the top of a list ranked by chemical similarity.

Validation can easily be misleading if the choice of actives and decoys is not done carefully. Clumping of actives and inadequate physicochemical resemblance of decoys to the actives can lead to overoptimistic conclusions on performance. To counter this bias, two publicly available standard benchmarking datasets have been developed, DUD[1] and MUV[2]

In the current work, we have measured the performance of five ligand-based tools and two pharmacophore-based tools into the MUV dataset. Initially, each active was used as template in the ligand-based tools and its score calculated against all the decoys and the actives in its target class (the dataset contains 17 target classes in total). From these scores, performance metrics including enrichment factors were calculated. We also studied the effect of data fusion on the results. With the pharmacophore tools, a set of actives were picked from each target class to build a pharmacophore model which was then used to screen the remaining compounds in the set.

Judging from the results, the MUV dataset is very demanding as the tools fail in most of the seventeen target classes. One interesting source of poor performance could be activity cliffs where small changes in ligand structure lead to dramatic changes in activity. We suggest the tools studied here are largely unable to identify these cliffs. As an additional finding, there was significant improvement in results when data fusion was applied.

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1 http://dud.docking.org/

2 http://www.pharmchem.tu-bs.de/lehre/baumann/MUV.html

MOLECULAR MODELING AND DOCKING STUDIES ON HSP90 INHIBITORS

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An ATP-dependent molecular chaperone Hsp90 is of current interest as a potential anticancer drug target. It has several oncogenic client proteins involved in signal transduction, cell cycle regulation, and apoptosis. In order to identify essential chemical functional features for HSP90 inhibition, a pharmacophore model consisting of one hydrogen bond donor, one hydrogen bond acceptor lipid and two hydrophobic features has been developed using HypoGen (Catalyst 4.7 software) on a total set of 104 inhibitors consisting of 16 and 88 compounds in training and test set respectively. The model shows good correlation coefficients for training (r^2=0.964) and test set [r^2_{pred} =0.654] respectively. In view of X-ray data structure of HSP90, GOLD 3.2 docking software was used to dock the 16 training set compounds. The good correlation (R^2=0.793) was observed between the experimental biological activity and the top ranked gold score. The analysis of conservation patterns across the hsp90 family using human Hsp90 X-ray structure as an alignment template led to the identification of important amino acids involved in the ligand binding interactions which were found similar to those observed in docking studies. Hence the model may be useful for designing new HSP90 inhibitors.

Keywords: Hypogen, Virtual screening, GOLD, Pharmacophore.

OZONE IN MEDICINAL RESEARCH AND APPLICATION

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Ozone (O_3) is a major air pollutant and is well-known for its very strong oxidative actions with beneficial effects in purifying various matrixes resulting in a variety of potential uses, in view of its antimicrobial and deodorising properties. We have previously shown that ozone firstly, induces a definite contraction of the isolated trachea immediately after exposure to ozone, and secondly, promotes a clearly visible and significant hyper responsiveness of the isolated trachea to irritants (methacholine in this case). Although ozone has a negative effect on the trachea, it was concluded that ozone has no adverse effect on muscarinic receptors. We found that ozone has a significant desensitizing effect on the pharmacological response of ß-sympathomimetics (anti-asthma drugs such as isoproterenol). While the biological effects of the gaseous ozone are associated with its toxicity, it has also been used for therapeutic purposes in alternative medicine and is currently applied in dentistry and various other medical conditions. However, the mechanisms involved in the actions of ozone, particular at molecular level, are not yet not fully understood. We have therefore investigated the effects of ozone in various biological systems in order to gain insight its actions. This presentation describes our *in vitro* findings using human epithelial HeLa cells.

HeLa cell viability was determined utilising the trypan blue or 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) tests, or by implementation of a DNA-fragmentation assay. Ozone exposures were also performed in the presence or absence of the selective enzyme inhibitors ME10092 (xanthine oxidase & NFκß inhibitor), Z-DQMD-FMK (caspase-3 and -6 inhibitor) and (-)-deguelin (Akt inhibitor). The gene modulating effects of ozone were determined with real-time PCR, for the expression of genes encoding for anti-apoptotic (Akt, Bcl2, Creb, NF-kappa B and BDNF) and pro-apoptotic (Bax, Caspase 3 and 8) proteins using single and repetitive ozone exposures of the HeLa cells.

The trypan blue test clearly indicated that acute O_3 exposure compromised cell membrane integrity, with significant damage visible from 25 min, and a maximum at 55 min. The MTT test, however, suggested only a slight reduction in cell viability at mitochondrial level. A single, short O_3 pre-exposure of HeLa cells did not affect the response of the cells during re-exposure, while multiple low-dose pre-exposures followed by a single high-dose exposure was associated with a protective adaptation, developing over a period of hours after the last exposure. This cellular adaptation was reversed by inhibition of Akt, caspase-3, xanthine oxidase and NFκß. Results from the investigations into DNA integrity and repair after O_3 pre-conditioning correlated well with results from the Trypan blue test. Treatment with ozone for 4 x 5 minutes + 25 minutes, induced an upregulation of Akt, and Creb at 8 hours. The current data suggest that *in vitro* O_3 exposure decreases HeLa cell viability by damaging cell membranes, with no significant effect on mitochondrial function. Importantly, multiple pre-exposure to O_3 induces an adaptive response in cellular membrane and DNA integrity, whereby cell plasticity is up-regulated.

In conclusion our data suggest that anti-apoptotic mechanisms may be involved in the adaptive effects following repetitive exposure to ozone. This adaptation may be preceded by the down-regulation of pro- and anti-apoptotic enzymes. These molecular actions of ozone may contribute to the beneficial effects observed during the application of ozone in the clinical setting.

EFFICIENT 2D APPROACHES TO VIRTUAL SCREENING: MFTA- AND FRAGMENT-BASED TECHNIQUES

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The classical and widely used approaches to virtual screening are primarily based on the docking of small molecules into the 3D structures of biotargets. However, 2D techniques could also be quite successful and efficient in this area.

One approach especially useful for the series of congeneric organic molecules whose activity is based on specific interactions with one or more biotarget proteins is the Molecular Field Topology Analysis (MFTA). It is based on the construction of a so-called molecular supergraph - a simple graph such that the molecular graphs of all training set structures can be represented as its subgraphs. It provides a common frame of reference for the local properties and thus a uniform descriptor set for the statistical analysis. Besides being a powerful tool for modelling and understanding of the structure-activity relationships, MFTA can be considered as an efficient technique for the virtual screening of new promising structures. The MFTA models of activity and selectivity serve as filters for a large set of structures allowing one to select the structures having high estimates of activity predicted with sufficient reliability. In spite of the 2D nature of this approach, the results are consistent with the molecular models of ligand-biotarget interactions and in many cases outperform the 3D QSAR approaches in terms of model quality, computational efficiency and chemical interpretability.

For more diverse structure sets the fragment-based techniques can be used in virtual screening. Here, the predictive non-linear activity/property models based on a set of fragments present in the structures serve as filters to identify the most promising structures.

As a source of structures for virtual screening, the databases of available compounds as well as the generated structure libraries can be used. For the latter case, efficient structure generators have been developed that take into account the features and constraints of an MFTA model as well as the fragmental composition of structures.

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MOLECULAR ORBITAL CALCULATION FOR LARGE MOLECULE WITH SAKURAI-SUGIURA METHOD ON GRID COMPUTING ENVIRONMENT

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We have been developing the computational tool to obtain the molecular orbitals for large molecules such as proteins and molecular clusters without excessive calculation costs. In our method, the entire Fock matrix is generated by the technique based on the fragment molecular orbital method [1], which is applicable to large systems and suitable for the parallel processing. To solve the large scale generalized eigenproblem, we use the Sakurai-Sugiura method [2]. Because this method solves several number of liner equation which has a large granularity and master-worker type of execution, the method is sufficient for parallel processing on the computers of the distributed memory parallel architecture. And the method is favorable to calculate only a small number of eigenvalues and corresponding eigenvectors of the large scale matrix. Our method has high parallelization efficiency and the communication cost is negligible to the total calculation costs. Thus, this is one of the right applications for using the Grid technology. Elapsed time of Hartree-Fock calculation of EGFR (Epidermal Growth Factor Receptor), which is a Target molecule for Anticancer agent (1,126 amino-acid residues, total 17,246atoms) with FMO/HF/STO-3G (96,234 basis functions) is listed in Table 1. Molecular structure of EGFR is depicted with HOMO (Higher right) and LUMO (Lower left) in Figure 1. Performance of the method was improved drastically by parallel processing.

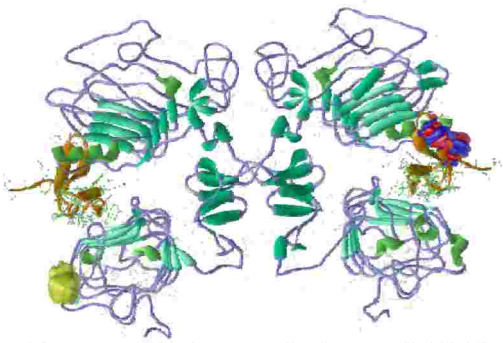

Figure 1. Position and shape of HOMO LUMO of EGFR

	Elapsed Time	#CPUs
FMO calculation	11.3 hr	512
Fock construction*2	49.1 hr	256
Eigen problem	10.0 min	256
Total	60.0 hr	

[a]Opteron: model 246, 2.0GHz,
[b]2.0GHz Xeon: 3.06 GHz

Table 1. E-time for FMO-MO calc. of EGFR

This work is supported by the research project, “Development of MO calculation system for large molecule on Grid”, CREST, JST. All numerical calculations were performed on the AIST super cluster at the National Institute of Advanced Industrial Science and Technology (AIST).

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Oral Communications

ABSTRACT BOOK

INTEGRATING BACKGROUND KNOWLEDGE FROM INTERNET DATABASES INTO PREDICTIVE TOXICOLOGY MODELS

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While data integration for data analysis has been investigated extensively in biological applications (see, e.g., [1, 2, 3]), it has not yet been so much the focus in computational chemistry and QSAR research. With the availability and growing number of chemical databases on the web, such data integration efforts become an intriguing possibility (and in fact, a necessity). In this paper, we take a first step towards the following vision and scenario for predictive toxicology applications: Given a new structure to be predicted, the first step would be to gather (integrate) all relevant information from internet databases for the structure itself, and all structures with available information for the endpoint of interest. In a second step, the collected information is combined statistically into a prediction of the new structure.

We simulated this scenario with three endpoints (datasets) from the DSSTox database [4], and collect information from three public chemical databases: PubChem, ChemBank and Sigma-Aldrich. In the experiments, we investigate whether the addition of background knowledge from the three databases can improve predictive performance (over using chemical structure alone) in a statistically significant way. To this purpose, we define groups of features (belonging together from an application point of view) from the three databases, and perform a variant of forward selection to include those feature groups into a prediction model. Our experiments show that the integration of background knowledge from internet databases can significantly improve prediction performance, in particular for regression tasks.

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e-ENVIRONMENTAL POLLUTANT SHORT AND LONG TERM TOXICOLOGICAL EFFECT DATABASES

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The rapid expansion of industrial progress has made a significant impact on the ecosystems related to the aquatic and terrestrial environments. Most of the environmental pollutants directly disrupt the metabolic biochemistry of organisms living in various ecosystems leading to short and long term toxicological effects. With REACH, alternative methods in toxicology such as *in vitro* tests and (Q)SAR models are encouraged. The advent of Internet has facilitated the public access to toxicological data and the data sharing in order to elaborate successful predictive SAR and QSAR models.

This review presents an overview of free Internet resources related to environmental short and long term toxicities. Toxicological data obtained from biological tests using sublethal effects such as abnormal development, growth, and reproduction, rather than solely lethality, as endpoints will be presented. Hence, our research was principally focused on toxicological databases collecting mutagenicity, reprotoxicity, teratogenicity, cancerogenicity test data for pollutants on aquatic and terrestrial environments. The addresses to retrieve quantitative toxicological data will be presented, the reliability of proposed data will be analysed. Some normalized *in vitro* tests for mammals will be presented and discussed.

A QSTR STUDY OF DYE ACUTE TOXICITY

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Most of dyes don't harm people and environment, generally having low acute toxicity. This does not exclude the possibility that the use of some products can be hazardous. In this study dye toxicity, expressed as rat oral LD_{50} values, was correlated with dye descriptors by the Partial Least Squares (PLS) method. Dye structures were modeled by density functional theory (DFT) calculations, with B3LYP as functional and 6-31G as basis set and 0D, 1D, 2D and 3D descriptors were derived from the optimized structures. Quantum chemical descriptors were, also, calculated from the dye conformations of minimum energy. A training set of 15 compounds was used to develop the PLS model, which was validated by a test set of 5 dyes. Despite the inhomogeneous series of compounds, an acceptable PLS model with predictive power (according to Tropsha's criterions [1]) was obtained (R^2 X(Cum) = 0.747, R^2 Y(cum) = 0.991, Q^2 (Cum) = 0.765). Specific dye structural features which influence the toxicity were derived. Dye substituents implied in intramolecular hydrogen bonding and having polar fragments including nitrogen and oxygen atoms, dye hydrophilicity and aromaticity decrease the dye toxicity. Increased molecular dimension, number of tertiary amino groups in the dye molecules and hydrophobicity favour higher toxicity.

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PREDICTION OF ACUTE MAMMALIAN TOXICITY FROM QSARS AND INTERSPECIES CORRELATIONS

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With the ever growing number of xenobiotics that can potentially contaminate the environment, the determination of their mammalian toxicity is of first importance. In this context, LD50 tests on rat and mouse have been used for a long time to express the relative hazard associated with the acute toxicity of inorganic and organic chemicals. However, these laboratory tests suffer from important hurdles. They are costly, time consuming, and actively fought by Animal Rightists. Moreover, new legislation policies, such as REACH (Registration, Evaluation, Authorization and Restriction of Chemicals) aim at reducing the use of toxicity tests on vertebrates. Consequently, there is a need to find alternative methods for estimating the acute mammalian toxicity of chemicals. The QSARs and interspecies correlations appear particularly suited to reach this goal. In this context, this study reviews more than 150 models aiming at predicting rat and mouse LD50 values from molecular descriptors or (and) ecotoxicity data. The advantages and limitations of these computational tools are discussed.

APPLICATION OF STRUCTURE-ACTIVITY RELATIONSHIPS IN THE CHEMICAL HAZARD ASSESSMENT

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There is a urgent need for valid, reliable and accurate ***in silico*** approaches for predicting ADME/Tox properties of chemicals in the regulatory framework of chemicals, where the use of non-testing data in the regulatory assessment of chemicals is openly supported by the REACH legislation. This new EU regulatory framework which came into force in Europe on 1st June 2007 aims at improving the protection of human health and environment through the better and earlier identification of the properties of chemical substances. This session focuses on the possible use of non-testing methods in the regulatory assessment of chemicals. The different techniques that are used to derive non-testing information include (quantitative) structure-activity relationship models, expert systems, and read-across/category approaches. To limit the cost and the number of animals used for testing, REACH explicitly encourages the use of computer-aided methods such as (Q)SAR methods and category/read-across approaches for filling in the enormous knowledge gap of chemical information. In order to be used in place of experimental data, REACH requires that the in silico methods meet certain conditions. For example, in the case of (Q)SARs, these requirements include:

1) the model has to be valid;
2) the substance has to fall within the applicability domain;
3) the prediction has to be adequate for the regulatory purpose;
4) the applied method has to be provided with adequate and reliable.

A structured workflow that assists users all the way through the generation of reliable non-testing data has been devised and will be presented together with a case study. Such a workflow includes a number of steps as for example:

1) Retrieving existing physicochemical properties and (eco)toxicological information for a given chemical;
2) Selecting relevant ***in silico*** approaches for predicting individual toxic endpoints;
3) Generating endpoint predictions;
4) Providing information on the reliability of the estimates;
5) Exploiting the capability of various ***in silico*** methodologies;
6) Integrating results;
7) Compiling robust summaries that document in a transparent way the use of the methods.

CAESAR MODELS FOR PREDICTION OF FIVE ENDPOINTS

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CAESAR is an EC funded project (Project no. 022674 - SSPI), which is specifically dedicated to develop QSAR models for the REACH legislation. Five endpoints are addressed within CAESAR: bioconcentration factor (BCF), skin sensitization, mutagenicity, carcinogenicity, developmental reprotoxicity (DR). The models have been assessed according to the OECD principles for validation of (Q)SAR models used for regulatory purposes (a defined endpoint, an unambiguous algorithm, a defined domain of applicability, appropriate measures of goodness-of-fit, robustness and predictivity, a mechanistic interpretation, if possible). We present a short description of models and some recent results.

The model for BCF is based on a dataset of 450 compounds with experiementally determined BCF values. The model is built using the Radial Basis Function Neural Networks developed with 8 descriptors. The model reached an R2 = 0.83 on the training set, and R2 = 0.80 on the test set.

This model for skin sensitization is based on a data set of 209 compounds. which were subdivided in two classes, sensitisers and non-sensitisers. The model was developed using the Adaptive Fuzzy Partition method with 8 descriptors from Dragon software.

The model for mutagenicity is based on a data set of 4225 compounds. For regulatory purposes, an integrated model was built combining the SVM algorithm with an expert facility based on known structural alerts.

The dataset used for the development model for carcinogenicity contains 805 chemicals extracted from CPDBAS with TD50 values for rat. A regression model based on TD50 and a classification model using the Counter-Propagation Artificial Neural Network were built. In the classification any compound with a finite TD50 dose was considered as carcinogenic. The specificity and sensitivity for test set were 65% and 70%, respectively.

The dataset for DR includes 292 compounds. Chemical compounds were categorized into toxicant or non toxicant according to FDA risk factors. Several models were developed using different methods: in one case the Waikato Environment for Knowledge Analysis software was used, in the second case the model was developed using the Adaptive Fuzzy Partitioning.

Reference

http://www.caesar-project.eu/

MODELING THE RELATIVE TOXICITY OF METALS ON RESPIRATION OF NITRIFIERS USING ION CHARACTERISTICS

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The effects of nine heavy metals (Ag, Cd, Co, Cu, Cr (III), Cr (VI), Hg, Ni and Zn) were studied in a nitrifying system where the main aim was to establish the relationship between ionic characteristics and their toxicity to nitrifiers. The Cumulative Oxygen Consumption and The Cumulative Carbon Dioxide Production were monitored throughout each respirometric batch run to determine the toxicity of studied metals to nitrifiers. The 50% reduction in oxygen consumption and 50% increase in carbon dioxide production were calculated for each metal and the corresponding IC_{50} values (in mmol/L) were converted to logarithmic toxicity units as pTO_2 and $pTCO_2$, respectively. Quantitative ion character-toxicity relationship (QiCTR) models were developed on the basis of these two different dependent variables.

The Energy of Polarized Solute-Solvent (E_{PSS}), The Energy of Metal in Water (EM_{aq}), The Water Binding Energy of Metal (E_{WB}), The Energy of the Lowest Unoccupied Molecular Orbital (E_{LUMO}) and The Energy of the Highest Occupied Molecular Orbital (E_{HOMO}) and The Electronic Spatial Extent (ESE) for metals were calculated using the Gaussian 03W software for all speciation -free and inorganic metal complexes- obtained by MINTEQA2 program. The Density Functional Theory (DFT) B3LYP - LANL2DZ basis set was used for all calculations. Apart from the descriptors obtained using the Gaussian 03W software, the following descriptors were retrieved from the literature to investigate the toxic effects of metals to nitrification: cationic charge (Z), electronegativity (X_m), atomic number (AN), Pauling ionic radius (r), ionization potentials (IP), the absolute difference in electrochemical potential between the ion and its first stable reduced state (ΔE_o), Covalent index ($X_m^2 r$) and the cation polarizing power (Z^2/r).

We obtained seven different one-descriptor model for $pTCO_2$ with the following descriptors and square of correlation coefficient values: $X_m^2 r$ (r^2=0.82), r (r^2=0.80), ESE (r^2=0.78), IP (r^2=0.58), E_{PSS}(r^2=0.53), E_{LUMA}(r^2=0.49) and E_{HOMO}(r^2=0.44). On the other hand ESE (r^2=0.76) was the only descriptor that significantly explained the variance in toxicity when pTO_2 was used as the dependent variable. The analysis of one descriptor models revealed the fact that endpoint preference had considerable effect on the significance of descriptors used to explain toxicity of metals on nitrification process. Cr^{+6}, which had significantly different ionic and structural values (E_{HOMO}-E_{LUMO} values, charge related descriptors like Z^2/r, Z, etc.) than the rest of the metals, was excluded for further analysis to be able to uncover any pattern that was previously clouded by the presence of Cr^{+6}.

For the two endpoints, new models were developed using 8 metals. The best one-variable model was obtained for $pTCO_2$ using IP (r^2=0.74). pTO_2 model also produced the same descriptor, IP, that was able to explain 85% of the variance in toxicity. Additionally, the energetic parameters that were calculated using the Gaussian 03W software, ESE and E_{PSS}, resulted in a two-descriptor model that significantly explained the toxicity for the two endpoints, with square of correlation coefficient values of 0.93 and 0.91 for pTO_2 and $pTCO_2$, respectively. These results show that ionic and structural parameters could be useful in modelling toxicity of the studied metals except Cr (VI) to nitrifiers.

NEW PUBLIC QSAR MODEL FOR PREDICTION OF CARCINOGENICITY

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One of the main goals of new chemical regulation REACH (Registration, Evaluation and Authorization of Chemicals) is to fulfil data gap in lack of data concerned with properties of chemicals effected human health. (Q)SAR models are accepted as a suitable source of information. Carcinogenicity is one of endpoints under the consideration.

Models for prediction of carcinogenic potency according to specific requirements of chemical regulation were developed. 805 noncongeneric chemicals extracted from Carcinogenic Potency Database (CPDBAS) were divided into the training (644compounds) and test sets (161 compounds). 2D descriptors calculated with MDL software program have been employed in present study.

The statistical performance of models was evaluated. The best carcinogenicity model was built using Counter Propagation Artificial Network (CPANN) method and yielded accuracy of training set 91% (internal performance) and accuracy of test set 73% (external performance). Sensitivity and specificity of obtained models are equal to 75% and 69% correspondingly.

The reported results were obtained within the framework of CAESAR project.

MOLECULAR MODELING OF STRUCTURAL AND ENERGETIC PROPERTIES OF CARCINOGEN DAMAGED DNA.

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Polycyclic aromatic hydrocarbons (HAP), such as benzo[a]pyrene (BaP), constitute a class of chemical mutagens/carcinogens produced by incomplete combustion, which are found ubiquitously in the environment. In cells, these compounds are metabolized into electrophilic diol-epoxydes that are able to be covalently bonded with the nucleophilic DNA bases leading to the formation of DNA adducts. The major mechanism for removing bulky DNA adducts is the nucleotide excision repair (NER). Unrepaired adducts can survive to cause mutations that initiate the carcinogenic process.

The goal of this study is to highlight the understanding of the NER process response, which could depend on the distortions and destabilization of the DNA due to the adduct inclusion. To achieve such task, molecular dynamics simulations were carried out to establish a relationship between the structural and energetic features of double-stranded DNA containing benzo[a]pyrene adducts and the susceptibility to NER activity. The DNA duplex 11-mer structural distorsion occured by four stereoisomeric benzo[a]pyrene adducts was revealed by 2ns dynamics simulations using AMBER10.0 and estimated with helicoidal parameters calculated with X3DNA. Energetic and geometrical features were analyzed and compared with the double-stranded DNA sequence without adduct and with different HAP metabolites.

ANALYSIS OF HYDROPHOBIC ORGANISATION OF PROTEIN-LIGAND COMPLEXES: USING PLATINUM WEB-SERVER TO IMPROVE THE RESULTS OF MOLECULAR DOCKING

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Molecular docking is a computational method to predict the conformation and orientation of a ligand in receptor binding site. It has become an integral part of biomolecular studies aimed at understanding the mechanism of enzyme functioning and drug discovery programmes. Improvement of methods to score the reliability of the ligand poses yielded by docking algorithm is an area of active research. One of the promising approaches is a consensus docking/scoring - re-scoring the docking poses with more efficient ranking criteria. Many popular scoring functions do not explicitly account for ligand-protein hydrophobic and stacking contacts. In our studies (Pyrkov et al., 2007, PROTEINS 66, 388-398; Pyrkov et al., 2008, SAR QSAR Environ Res 19, 91-99) we have demonstrated that taking these interactions into account can greatly improve the efficiency of scoring functions. To make this approach available to a broader community, we have designed web-server PLATINUM (Protein-Ligand ATtractions Investigation NUMerically). Given the 3D-coordinated of a molecular complex (ligand-protein, peptide-lipid bilayer, etc.) it provides an easy-to-use and customizable tool to estimate the hydrophobic/hydrophilic match or mismatch on the interface of two interacting molecules. This is done using the concept of Molecular Hydrophobicity Potential (MHP) based on empirical atomic constants derived from the water-octanol partition coefficients for organic compounds. Distribution of molecular hydrophobic/hydrophilic properties can also be visualized for the purposes of more thorough investigation either on-line or by downloading a data-file readable by molecular visualization software. Besides, hydrogen bonds, stacking, and cation-pi contacts are assessed in a quantitative manner.

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CHEMOMETRICS EXPLORATION OF TRANS MEMBRANE PROTEINS AVAILABLE IN THE PUBLIC DATA BASES. FROM STATISTICAL MODELS TOWARDS STRUCTURE AND MECHANISM OF TRANSPORT

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Biological membranes form the barrier through which both drugs and toxic molecules enter the organism. Despite the difficulties encountered in bio membrane research, membrane transport is the common step determining the effect of most drugs. The study and analysis of several sequences and structural properties of membrane proteins are of crucial importance in resolving their transport mechanism for molecules of diverse chemical structure. The aim of this research is to shed light onto the mechanism of transport and structural details of specific membrane proteins. The lack of knowledge of the secondary and tertiary structure, and of the position of membrane plane of majority of trans membrane proteins makes any explanation of the transport mechanism challenging. We report here on the first step in this research direction, which is the investigation of sequence-property relationship of protein trans membrane segments. The model for prediction of trans membrane segments is based on the graph-theoretical descriptors obtained from the information of membrane proteins of known 3D structure available in public databases (Protein Data Bank of Trans Membrane Proteins). Self organizing maps and consequent classification methods are applied to distinguish between the trans and non-trans membrane segments, and between the trans-membrane segments from different classes regarding protein families. Classification of the proteins is done manually according to the information from the TCDB (Phylogenetic and Functional Information) and Pfam (Protein families) data bases. Classification is done to 3 levels of hierarchy according to TCDB scheme.

LQTA-QSAR: A NEW 4D-QSAR METHODOLOGY

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The new 4D-QSAR approach presented and named LQTA-QSAR *(Laboratório de Quimiometria Teórica e Aplicada)*, is based on the generation of a conformational ensemble profile, CEP, for each compound, followed by the calculation of 3D descriptors. This new methodology explores jointly the main features of CoMFA and 4D-QSAR paradigms. GROMACS free package is used for molecular dynamics, MD, simulations and generating CEP. The module LQTAgrid calculates intermolecular interaction energies at each grid point considering different probes and all aligned conformations from MD simulations. These interaction energies are the descriptors employed in the QSAR analysis. The ordered predictor selection, OPS, algorithm2 recently developed in our laboratory, is applied as the variable selection method in the construction of the PLS models. OPS method has been proved to be fast and capable of providing suitable variables for the QSAR analysis. LQTA-QSAR models are thoroughly validated applying the leave-*N*-out cross-validation and y-randomization methods. The comparison of the proposed methodology to other 4D-QSAR and CoMFA formalisms was performed using a set of forty-seven glycogen phosphorylase b inhibitors (data set 1) and a set of forty-four MAP p38 kinase inhibitors (data set 2). The QSAR models were built using the OPS algorithm for variable selection. Model validation was carried out applying y-randomization and leave-*N*-out cross-validation in addition to the external validation. PLS models for data sets 1 and 2 provided the following statistics: $q^2 = 0.72$, $r^2 = 0.81$ for 12 variables selected and 2 latent variables; and, $q^2 = 0.82$, $r^2 = 0.90$ for 10 variables selected and 4 latent variables, respectively. Visualization of the descriptors in 3D space was successfully interpreted from the chemical point of view, supporting the applicability of this new approach in rational drug design.
LQTA-QSAR is available at http://lqta.iqm.unicamp.br

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A QSAR STUDY ON PPAR-α/γ GENE TRANSACTIVATION DATA USING MULTIVARIATE STATISTICS

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Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors and transcription factors that play a crucial role in the regulation of lipid and glucose metabolism. Among the three subtypes, the most investigated is the γ-subtype and currently PPAR-γ agonists (glitazones) are marketed as anti-diabetic agents. To overcome certain side effects, common in this type of drugs, research interest has recently been shifted towards dual agonists acting on both γ and α subtypes. In the present work, multivariate statistics was used to analyze PPAR-γ and α gene transactivation ($pEC_{50}\alpha$ and $pEC_{50}\gamma$) produced by several phenoxyacetic acids, meta-substituted phenyl propanoic acids and oxazole containing 1,3-dioxane-2-carboxylic acids, collected from ref. [1-3]. The pool of descriptors comprised physicochemical/molecular properties, 3-D descriptors, connectivity and electrotopological state indices. Compounds taken from ref. [1,2] (Subset I and II) and those taken from ref. [3] (Subset III) were treated separately due to small differences in the experimental protocols. Models were initially established for PPAR-α activity. For subset I and II (n= 21) a 2 component PLS model was obtained with R^2=0.89, Q^2=0.71, RMSEE=0.24. Among the most important descriptors χv^1, dipole moment at Z axis, ClogP, bulk descriptors of the non polar part of the molecules, hydrogen bond acceptors and electrophilicity exerted positive contribution, while χvc^4 and χvp^5 had a negative sign. Subset III (n=18) produced a 3 component PLS model with R^2 =0.95, Q^2=0.75, RMSEE=0.11. Bulk descriptors of the non polar part, ClogP and the E-state index on >CH contributed positively. Hydrogen bond donor and acceptor parameters and the E-state index on -OH had a significant negative effect. Inferior models were obtained for PPAR-γ activity. As a next step we attempted to create combined α/γ consensus models. Satisfactory α/γ models could be established for subset I and III with R^2=0.84, Q^2=0.64 and R^2=0.89, Q^2=0.70 respectively. In both models significant differences in the descriptor contributions to PPAR- α and γ activity were observed.

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A NEW METHOD TO ESTIMATE STABILITY OF CHELATE COMPLEXES AND ITS APPLICATION FOR HIV-1 INTEGRASE INHIBITOR DESIGN

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The ability of organic ligands to form chelate complexes with metal ions plays an essential role in binding of inhibitors with metalloproteins, such as HIV-1 integrase. Quantum chemistry calculations can quantify the contribution of chelation to HIV-1 integrase inhibition.

In this work a new method for predicting stability of Mg^{2+} chelate complexes in context of HIV-I integrase inhibitors design was developed. We adopted the two-stage scheme of complex formation, where the first stage comprises the ligand transfer from an arbitrary point of the solution to the second solvation shell of the Mg^{2+} ion. On the second stage, the formation of chelate complex of Mg^{2+} with ligand takes place. Quantum chemical calculations were performed in the frames of DFT methods with hybrid B3LYP functional and MP2 method with two basis sets: 6-31G** and cc-pVTZ and PCM solvation model. For all modeled complexes the reasonable agreement between calculated and experimental ΔG_b values was achieved. The main contributions to the free energy of the complex formation ΔG_b were resulted from breaking/creation of the coordination bonds around Mg^{2+}, solvation effects and the vibration degrees of freedom.

This method had been applied to estimate the relative stability of complexes formed by HIV-I integrase with inhibitors. Our model of the HIV-I integrase active site included only two Mg^{2+} ions , several water molecules and fragments of three aminoacid residues D116, E152 and D64. Calculated and experimental values of the integrase-ligand complex stability were found to correlate well, especially when the effect from the different pK_a values of ligands was taken into account.

GRID AIDED COMPUTER SYSTEM FOR ACCELERATED ANTI-CANCER DRUG DESIGN: CancerGrid

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CancerGrid, a three years' European research project aims to develop a system integrating novel computer technologies, chemistry and biology to facilitate the discovery of potential anti-cancer agents (http://www.cancergrid.eu/). The project includes model building for prediction of disease-related cytotoxicity using HTS results of 30,000 compounds (provided by AMRI and University of Bari) and for inhibition of cancer-associated targets; utilizing a purpose-built grid computing system which helps to accelerate and automate the in silico design of focused libraries.

The CancerGrid infrastructure consists of a DesktopGrid system to deliver computational resources, and Web-based portal to submit computations to the resources. SZTAKI Desktop Grid (SZDG), which is an extension of BOINC provides a framework to ease application development, porting and workunit creation, while a web-based portal called WS-PGRADE provides access to the applications, workflows and data for the users. Workflow processing, job distribution to resources and on-the-fly generated data maintenance are handled by the combination of WS-PGRADE portal and SZDG.

All related data like compounds, models, descriptors, properties, etc. are stored in a database that is accessible and manageable by the user through the portal. Compound computations are defined as workflows which provide various operations for the users like descriptor calculation, model building, property prediction or virtual screening. The portal also contains a workflow development module where the applications can be chained together to form a scientific workflow. The current DesktopGrid infrastructure is built by approximately 200 machines offered by the consortium members of the project. In the present stage the Grid is non-public in order to keep the data and results available only for the partners; however, in the future the system will be open to the public's contribution of computer source. During the testing phase the CancerGrid portal is mostly used for descriptor calculation and virtual screening where we estimated a processing power of 200,000 compounds per month. In the presentation the main features of the system will be described together with the results of the testing phase.

IN SILICO METHOD FOR IDENTIFICATION OF PROMISING ANTICANCER TARGETS

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Low efficacy of the current therapy is the reason for investigation of new anticancer drug targets. In recent years, accumulation of "Omics" data about topological and functional organization of regulatory networks in a cell provides possibility to identify the potential targets, involved in pathological processes and select the most promising targets for future drug development. We propose an algorithm for anticancer drug target identification, which is implemented in NetFlowEx program. The algorithm simulates a behavior of regulatory network on the basis of dichotomy model. The effect of pharmaceutical agents, which inhibit a particular protein or combination of proteins in the regulatory network, is simulated by blockade of single nodes in the network or their combinations [1, 2].

The method was applied to the three groups of breast cancer types: HER2/neu-positive breast carcinomas, invasive ductal carcinoma and ductal carcinoma in situ, invasive ductal carcinoma and/or a nodal metastasis and to the generalized breast cancer using fragment of the regulatory network, which contains proteins involved in cell cycle regulation, apoptosis, breast cancer progression and normal formation of breast. As a result, the promising specific molecular targets and their combinations were identified for the three types of breast cancer. Inhibitors of some identified targets are known as potential drugs for therapy of malignant diseases; for some other targets we identified hits in the commercially available samples databases.

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CLASSIFICATION OF THE ESTROGEN RECEPTOR BINDING AFFINITY OF XENOBIOTICS FROM A MIXED 2D-SUBSTRUCTURAL AND 3D-PARAMETRIC APPROACH

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A decision tree was used to classify 232 structurally diverse compounds according to their estrogen receptor binding affinity. Chemicals, which were described from CODESSA descriptors after energy minimization from Hyperchem, were categorized as active vs. inactive and then as strongly and moderately active vs. weakly active and inactive.

Decision tree analysis clearly confirmed the importance of the presence of an OH group in the molecules for explaining their estrogenic activity. Thus, the maximum Coulombic interaction for a H-O bond descriptor was able to correctly classify 85% of the chemicals. Examination of the misclassified compounds revealed the role of certain substructures inducing activity or inactivity, as well as the influence of the environment of the phenolic OH group for explaining the estrogenicity of chemicals. This prompted us to recompute a SAR model mainly based on 2D substructures. Use of about 10 structural descriptors and log P allowed a strong reduction of the 3D descriptors. The parameters being so identified, a support vector machine (SVM) was used as modeling tool for comparison purposes.

MECHANISTICALLY BASED CATEGORIZATION OF AROMATASE INHIBITORS

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Cytochrome P450 aromatase is a key steroidogenic enzyme that converts androgens to estrogens in vertebrates. There is much interest in aromatase inhibitors (AIs) both because of their use as pharmaceuticals in the treatment of estrogen-senstive breast cancers, and because a number of environmental contaminants can act as AIs, thereby disrupting endocrine function in humans and wildlife through suppression of circulating estrogen levels. The goal of the current work was to develop a mechanism-based structure-activity relationship (SAR) categorization framework highlighting the most important chemical structural features responsible for inhibition of aromatase activity. Two main interaction mechanisms were discerned: steroidal and non-steroidal. The steroidal scaffold is most pronounced when structure of the target chemical is similar to the natural substrates of aromatase - androstenedione and testosterone. Chemicals acting by non-steroidal mechanism(s) possess a heteroatom (N, O, S) able to coordinate heme iron of the cytochrome P450, and thus interfere with steroid hydroxylation. The specific structural boundaries controlling AI for both analyzed mechanisms were defined, and a software tool was developed allowing one to build a decision tree (profile) discriminating AIs by mechanism and potency. An input chemical follows a profiling path and the structure is examined at each step to decide whether it fulfils the structural boundaries implemented in the decision tree node. The system performance will be demonstrated and discussed. Such a system would aid drug discovery efforts, as well as provide a screening tool to detect environmental contaminants that could act as AIs.

QNA BASED "STAR TRACK" QSAR APPROACH

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In the existing QSAR methods any molecule is represented as a single point in many-dimensional space of molecular descriptors. We proposed a new "Star Track" QSAR approach based on Quantitative Neighbourhoods of Atoms (QNA) descriptors [1, 2], which characterize each atom of a molecule and depend on the whole molecule structure. In "Star Track" methodology any molecule is represented as a set of points in two-dimensional space of QNA descriptors. Substantially, we have proposed to use only two instead of more than three thousand molecular descriptors used in QSAR.

The estimate of target property of chemical compound is calculated in our new method as the average value of the function of QNA descriptors in the points of the atoms of a molecule ("stars" of "constellation") in QNA descriptors space.

We have developed computer program GUSAR on the basis of this approach and compared it with several widely used QSAR methods including CoMFA, CoMSIA, Golpe/GRID, HQSAR and others, using ten data sets representing various chemical series and diverse types of biological activity. It was shown that in the majority of cases the accuracy and predictivity of GUSAR models appeared to be better than for the reference QSAR methods.

Features of QNA descriptors space, applicability domain of new "Star Track" QSAR paradigm and new possibilities for targeted design of chemical compounds will be discussed.

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SERIOUS ADVERSE DRUG EVENTS IN CURRENTLY MARKETED BIOTECHNOLOGY PRODUCTS

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Safety issues arises throughout the life-history of a drug starting from the discovery stage through to preclinical screening, clinical trials and, importantly, after the drug is marketed and tested for the first time on large population. Serious adverse drug reactions (SADRs) can lead to drug withdrawals, and unfortunately, may not be recognized for years after a drug has been on the market. 51% of drugs have label changes because of major safety issues discovered after marketing, 14; 20% of drugs get box warnings after marketing; and 3% to 4% of drugs are ultimately withdrawn for safety reasons. SADRs are estimated to be the fourth leading cause of death in the world, not far behind cancer and heart diseases. The cost of SADR treatment to the healthcare systems are estimated approximately US$40 billion to $50 billion per year worldwide. From 1998 through 2005, reported serious adverse drug events to FDA increased 2.6-fold from 34 966 to 89 842, and fatal adverse drug events increased 2.7-fold from 5519 to 15 107. It has been recently reported that the increased use of biotechnology products, notably immunomodulators created through bioinformatics and molecular modeling techniques have an important impact on this increase. 13 biotechnology products of 3 types: anti-tumor necrosis factor immunomodulators, interferon alfa products, and interferon beta products and how the existing model for drug approval can be improved for safer drug development will be discussed during the course of the presentation.

Poster Presentations

MOLECULAR DYNAMICS STUDY OF PROLYL-OLIGOPEPTIDASE WITH INHIBITOR IN BINDING CAVITY.

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Prolyl oligopeptidases (POP) is a serine protease that cleaves small peptides (< 30 residues) at the C-side of an internal proline. In past work it has been demonstrated that POP may have a role in cell degeneration and apoptosis, and in clinical testing it has been determined that POP inhibition is purely beneficial with respect to memory stimulation. The structure of this protein has been determined from X-ray scattering, allowing for substantial progress in inhibitor design. POP has two domains, the peptidase domain and a Beta spiral staircase that enclose an internal cavity. The Beta spiral staircase controls access to the active site on the peptidase domain on the side of the internal cavity of the protein. Of particular interest is the crystal structure of POP with bound Z-Pro-Prolinal (ZPP) inhibitor[1] (PDB structure 1QFS).

We have performed an extensive molecular dynamics simulation (200 ns) of POP with ZPP inhibitor, refining all aspects of our understanding of the interaction between POP and the ZPP inhibitor, and gaining general insight into the mechanism of POP inhibition and the molecular properties required for POP inhibition. We identified residues involved in hydrogen bonding and nonpolar interactions between protein and ZPR, elucidating the role of water in these interactions as well as providing a dynamical description of these interactions.

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PREDICTION OF PROTEIN TRANSMEMBRANE REGIONS FROM SEQUENCE INFORMATION - A CHEMOMETRICS EXPLORATION OF TRANSMEMBRANE PROTEINS

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Although it is estimated that ~25% of proteins at a genomic scale are transmembrane proteins, they consist of only ~1.5% of the protein structures reported in Protein Data Bank (PDB) [1]. Even for those transmembrane proteins whose structures are predicted, the position of the membrane plane is not known, and hence the transmembrane regions are not defined. The transmembrane proteins play a vital role in transport of various molecules including drugs and toxins, act as receptors and help in cellular communications. They are also potential candidates of drug targets in pharmaceutical developments. Therefore, understanding their sequence and structural properties, as well as transport mechanism is of crucial importance. One of the initial steps towards this understanding is defining their transmembrane regions. The aim of this research is to develop a tool for predicting transmembrane regions of a sequence using neural network model. The information of transmembrane proteins is collected from public database PDBTM (Protein Data Bank of Transmembrane Proteins) and classified according to TCDB (phylogenetic and functional information) and Pfam (protein family information) databases. The transmembrane and non-transmembrane regions of these proteins are separated and graph-theoretical descriptors revealing their unique sequence characteristics are obtained. The model using self-organizing maps shows that it can distinguish between transmembrane and non-transmembrane regions and also group them according to the classification. Though the prediction model is based on sequence information alone, there is also scope of incorporating properties of amino acids in this model. This is a novel approach towards development of a transmembrane region prediction tool, and the model has the potential to predict the transmembrane regions of any new protein from sequence information alone.

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GENOTOXICITY INDUCED BY TETRACHLOROETHYLENE IN DRY-CLEANING WORKERS IN EGYPT

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Environmental exposures that increase the rate of damage above background levels increase the potential for un-repaired lesions to become permanent mutations. This concept has led to the use of oxidative DNA damage in the assessment of occupational and environmental exposures to chemicals that are capable of inducing an oxidative stress. The objective of the present study was to determine the possible tetrachloroethylene induced genotoxicity in Egyptian smoking and non smoking dry-cleaning workers. The study was carried out on eighty adult male workers. Subjects designated as controls (n=40) were healthy persons with no occupational exposure to tetrachloroethylene frequency-matched to exposed tetrachloroethylene dry-cleaning subjects (n=40) by age and lifestyle. The following parameters were measured blood Tetrachloroethylene, lymphocyte 8-OHdG, urinary 8-OHdG and chromosomal aberrations and damage. The average level of tetrachloroethylene in air was found to be ≤ 140 ppm for all workers from. The present study revealed that, tetrachloroethylene to induce oxidative DNA damage in Egyptian dry clean workers that was detectable as increased lymphocyte 8-OHdG/dG ratios and urinary excretion of 8-hydroxydeoxyguanosine (8-OHdG) in both smokers and non smokers. This is more evidenced by increase in the percentage of chromatid breaks in tetrachloroethylene exposed workers.

Keywords: Genotoxicity, Tetrachloroethylene, Dry-cleaning workers.

POTENTIAL HEPATOPROTECTIVE EFFECTS OF VITAMIN E AND NIGELLA SATIVA OIL ON HEPATOTOXICITY INDUCED BY CHRONIC EXPOSURE TO MALATHION IN HUMAN AND MALE ALBINO RATS

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Malathion is an organophosphorus insecticide and has a wide range of use in agriculture, veterinary medicine and public health. Malathion and other organophosphorus insecticides have hepatotoxic effect. The objective of the present study to investigate the protective effects of *Nigella sativa* oil and α-tocopherol (vitamin E) on the hepatotoxicity induced by malathion on workers involved in the formulation of pesticides, chronically exposed to malathion, and in male albino rats orally administrated malathion. This study was conducted on both human and experimental animals, the human study was conducted on 30 control subjects working as administrative and 45 subjects working in formulation of pesticides and exposed to malathion (≥ 3 years), all were males with age ranges from 30 to 60 years. The 45 males working in pesticides formulation were classified into 3 groups; (1) 15 workers exposed to pesticides (2) 15 workers exposed to pesticides and received vitamin (E), in a dose of 10 mg/kg/day orally for 60 days and (3) 15 workers exposed to pesticides and received 100 mg/kg/day of *Nigella sativa* oil for 60 days. The animal experiment was conducted on 40 adult male albino rats weighing 150-200 gram. They were divided into 4 groups (10 rats each group). First group served as the control group, the second group received malathion in a dose of 50 mg/kg orally per day for 60 days, the third group received malathione (in the same dose and route of administration) and vitamin E in a dose of 10 mg/kg/day orally for 60 days, the fourth group received malathione (in the same dose and route of administration) and *Nigella sativa* oil in a dose of 100 mg/kg/day orally for 60 days. Liver function tests (Alanine aminotransferase [ALT], Aspartate aminotransferase [AST], Serum alkaline phosphatase [ALP], Albumin, Globulin, Albumin/Globulin ratio, and Total proteins), antioxidant enzymes [Catalase (CAT), Superoxide dismutase (SOD) and Total glutathione peroxidase (GPx)] and lipid peroxidation [MDA] were analyzed in both human and animal experiments. The results of both human and animal study revealed that, exposure to malathion showed significant increases in AST, ALT and lipid peroxidation. There were significant decrease in Albumin, Albumin/Globulin ratio, total protein and antioxidant enzymes. It also showed no significant changes in alkaline phosphatase. In addition exposed workers showed significant decrease in serum globulin. *Nigella sativa* oil or vitamin E administration showed significant improvement of liver function tests, lipid peroxidation and antioxidant enzymes impairment induced by malathion. As such, as a dietary supplement, *Nigella sativa* oil or vitamin E could represent a potential therapeutic agent in reducing malathion-induced hepatotoxicity.

Key words: Hepatoprotective, Vitamin E, Nigella Sativa Oil, Malathion.

2-HETEROARYLIMINO-5-BENZYLIDENE-4-THIAZOLIDINONES AS NEW INHIBITORS OF MATRIX METALLOPROTEINASE-13

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Osteoarthritis (OA) is a degenerative process characterized by progressive destruction and erosion of cartilage. Numerous studies have demonstrated that matrix metalloproteinases (MMPs) are most frequently implicated in the destruction of articular cartilage in arthritic diseases. Moreover, the functional alteration of cartilage results also from the interaction of different mediators, such as cytokines, (e.g. interleukin-1ß), that induce high levels of nitric oxide (NO), inhibit collagen and proteoglycans synthesis, increase susceptibility to injury by other oxidants. Therefore, many efforts have been devoted to develop MMPs inhibitors able to block cartilage destruction during the inflammatory process. The inhibitory capability of a new class of 4-thiazolidinone derivatives towards MMP-13 has been investigated by evaluating their ability to prevent the hydrolysis of the fluorescent-quenched peptide substrate Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH_2 [1]. The inhibition constants (Ki) measured for the investigated compounds range from 18 to 142 μM.

In the present study the compounds selected for the investigation, 2-benzo[*d*]thiazolyl- and 2-benzo[*d*]isothiazolylimino-5-benzylidene-4-thiazolidinones, have been shown to possess anti-

inflammatory/chondroprotective activity *in vitro* in human chondrocyte cultures. These compounds also inhibit NO, MMP-3, GAGs, key molecules involved in matrix. degradation in OA disease. Our studies clearly demonstrate that 5-heteroarylimino-4-thiazolidinone can block cartilage destruction during the arthritic inflammatory process, as simulated in our experimental model.

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QSAR MODEL FOR PREDICTING THE POTENCY OF SUBSTITUTED FULLERENES AS HIV PROTEASE INHIBITORS

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One class of drugs that reduces HIV development is the one that inhibits the HIV aspartyl protease. HIV protease has a 10 Å inside channel lined mostly by hydrophobic amino acids and thus can accommodate the C_{60} fullerene molecule which has almost the same size and is also hydrophobic[1].

In this study, we propose a QSAR model based on the experimentally determined EC50 of 20 substituted fullerenes.[2] This model can be applied for the prediction of the inhibition potency of other potential substituted fullerenes against HIV protease.

The conformational analysis was made for all 20 substituted fullerenes and the lowest energy conformer was used for further calculations. The MOPAC calculations, descriptors extraction and calculation and Best Multiple Linear Regression (BMLR) analysis were performed using the QSAR Model[3] program. The model obtained has the following multi linear form:

$$-\log EC50 = -76.72 - 31.82*D1 + 11.19*D2 - 47.60*D3$$

with the following statistical parameters: R^2 =0.88 (Coefficient of determination), s^3 =0.12 (Standard error of the estimate) F=38.55 (Fisher function) and R_{cv}^2=0.76 (Leave one out cross validation coefficient) that indicate a good model.

The potency of the substituted fullerenes increases with the increase of the values of D2 which is the HOMO-LUMO energy gap. This descriptor shows that increases in the stability of the molecule also increase the potency of the substituted fullerenes.

The potency of a drug increases with the decrease of the value of descriptor D3 which is HA dependent HDCA-2/SQRT (TMSA) (Zefirov) and accounts for the hydrogen bonding ability of the molecule. The potency of the compounds increases with the decreasing of the hydrogen bonding ability as a consequence of the hydrophobicity of the inside channel of the HIV protease, the site for substitute fullerene binding.

The potency of the substituted fullerene also increases with the decreasing value of the descriptor D1 which is the Min net atomic charge (Zefirov) for any atom type. This is also due to the hydrophobicity of the inside channel of the protease which does not accommodate molecules with high values of atomic charges well. For validation purpose, the set of substituted fullerenes was separated into training and test sets and the predictive power of the obtained model was good.

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MOLECULAR DESIGN OF THE ERYTHROPOIETIN RECEPTOR LIGANDS

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Erythropoietin (EPO), a 166 amino acid hematopoietic hormone, is the major regulator of erythropoisis, which stimulates the growth and differentiation of hematopoietic cells through interaction with its class 1 cytokine erythropoietin receptor (EPO-R). It is believed that dimerization of the erythropoietin receptor (EPOR), in the presence of either natural (EPO) or synthetic (EPO-mimetic peptides, EMPs) ligands, is the principal extracellular event that leads to receptor activation. Recently, the X-ray crystal structures of the complexes a small peptide agonist (EMP1; PDB 1EBP) and an antagonist (EMP33; PDB 1EBA) with the extracellular domain of the EPO receptor have been reported. These structures revealed firstly, that the 20-residue cyclic peptidomimetic ligand, EMP1 induces an almost perfect twofold dimerization of the EPO receptor and secondly that the antagonist (EMP33) resulted in an altered orientation of the two EPO receptor molecules (although dimerization still occurs). These findings suggest that the extracellular domain orientation of the EPO receptor dimer is tightly coupled to the cytoplasmic signaling events and that the design of nonpeptidic small molecule mimetics for EPO and other cytokines may indeed be achievable.

These findings prompted us to explore the design possibilities of small molecule peptidomimetics for the twofold dimer of the EPO receptor, i.e. agonist ligand using computer molecular modeling drug design technologies. The Brookhaven Protein Databank X-ray crystal structure (PDB 1EBP) was used as starting structure for the molecular modelling of potential agonist ligands. The hydrophobic region of the dimeric interaction with the two erythropoietin receptors, consisting of the tryptophane and phenylalanine residues as well as the hydrogen bond between the hydroxyl groups of the two tyrosine residues from the small peptide, EMP1 and the serine backbone interaction of the EPO receptor, formed the basis of the molecular modelling strategy.

Novel structures were designed to address the symmetrical aspects found in the EPO receptor dimer. Novel symmetrical substituted polycyclic hydrocarbon compounds of the cubane and (D_3)-trishomocubane types were designed. These structures were investigated for their interactions with the EPO receptor dimer. The (D_3)-trishomocubane hydrocarbon structure was found to be the most promising scaffold for substitution to obtain an acceptable molecular interaction with the EPO receptor dimer.

SYNTHESIS AND *IN SILICO* EVALUATION OF NOVEL 2-(2,6-DIHALOSUBSTITUTED)-3-(SUBSTITUTED)BENZO[*d*]THIAZOLE-2-YL)-THIAZOLIDIN-4-ONES

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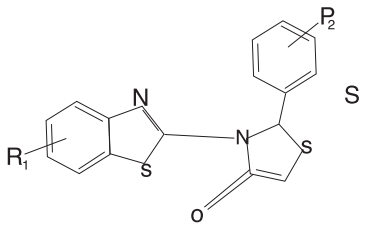
A series of twenty four 2-(2,6-dihalosubstituted)-3-(substituted)benzo[d]thiazole-2-yl)-thiazolidin-4-ones of general formula (1) were synthesized and characterized by elemental analysis, ^{1}H-NMR and HRMS.



R1: 6-OMe, R2: 2,6-Cl, 2,6-F, 2-Cl-6-F
R1: 6-OEt, R2: 2,6-Cl, 2,6-F, 2-Cl-6-F
R1: 4-OMe, R2: 2,6-Cl, 2,6-F, 2-Cl-6-F
R1: 6-Cl, R2: 2,6-Cl, 2,6-F, 2-Cl-6-F
R1: 6-F, R2: 2,6-Cl, 2,6-F, 2-Cl-6-F
R1: 4-Cl, R2: 2,6-Cl, 2,6-F, 2-Cl-6-F
R1: -H, R2: 2,6-F, 2-Cl-6-F

Formula (1)

Prediction of biological activity spectra was done using computer program PASS, which predicts 3300 kinds of biological activity (http://www.ibmc.msk.ru/PASS). As was shown by the analysis of predictions with computer program PharmaExpert, the most probable kinds of biological activity at Pa>50% are: Amyotrophic lateral sclerosis treatment, Follicle-stimulating hormone agonist, Antinephritic, HDL-cholesterol increasing, Hydrolase inhibitor, Muramoyltetrapeptide carboxypeptidase inhibitor, Vascular (peripheral) disease treatment, DNA directed RNA polymerase inhibitor, Platelet aggregation inhibitor.

By estimation of compounds' novelty using Chemical Lookup Service (CLS) (http://cactus.nci.nih.gov/cgi-bin/lookup/search), which contains the information about 46 mln unique chemical structures, it was found that the only synthesized compound corresponds to the molecule registered in CLS. Antitumor activity of this molecule (No. 364735) was tested in DTP/NCI *in vivo* anticancer drug screen (tumor model P388 Leukemia in CD2F1 mice, intraperitoneal), and it was found to be inactive. Since no antitumor activity is predicted by PASS for this molecule at Pa>20%, one may conclude that this prediction coincides with the experiment. Usability of available Internet resources for estimation of compounds' novelty and probable biological activities will be discussed.

A COMPARISON OF VALIDATED QSTR MODELS BASED ON DESCRIPTORS FROM AM1 PM3 HF AND DFT CALCULATIONS FOR ACUTE TOXICITY OF DIVERSE ORGANIC COMPOUNDS TO THE FATHEAD MINNOW

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To construct statically good quality predictive QSAR/QSTR models, one has a choice to try various types of descriptor such as quantum chemical, topological, constitutional and geometrical descriptors. Accuracy of these quantum chemical and geometrical descriptors for molecules is directly related to methods by which calculations of geometry optimization and many other properties as a descriptor can be accomplished. In this study, we were interested in to test performance of the descriptors obtained from AM1 PM3 HF and DFT calculation schemes for QSTR modeling of 117 diverse organic compounds to the fathead minnow with polar and non polar narcosis modes of action using Codessa Pro methodology. Multi linear regression technique was used to derive QSTR models. Initially, 117 compounds were split into training and test set using duplex method. Statistical quality of the best models obtained from each calculation schemes are very close each other; squared correlation coefficient, R^2, cross-validation correlation coefficient, q^2 and squared correlation coefficient for test, $R^2_{prediction}$ ranges from 0.813 to 0.874, from 0.784 to 0.847, from 0.715 to 0.825 respectively. Robustness of obtained models was confirmed by successful Y-randomization test. Predictive ability of all models satisfy the criteria of a predictive model (q^2 >0.5 and $R^2_{prediction}$ >0.6) given in [Golbraikh, A., Tropsha, A. Beware of q^2 ! J. Mol. Graphics Mod. 20, 269-276, (2002)].

Although the most of obtained models comprises the some types of molecular descriptors values of which are sensitive to QC calculation schemes, a comparison of all the regression models indicates that different QC calculation schemes have not influenced much of the statistical significance, predictive ability and robustness of obtained models.

DESIGNING NEW POTENT SELECTIVE INHIBITORS FOR PDEIV *IN SILICO* THROUGH STRUCTURE-BASED DOCKING AND VIRTUAL SCREENING

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The control of intracellular cAMP levels, a secondary messenger which mediates the actions of numerous cellular receptor, is accomplished by a balance of cAMP synthesis by adenylate cyclase, and its degradation by a variety of phosphodiesterases (PDEs).[1-3] The role of PDEIV in the inflammatory responses associated with asthma and chronic obstructive pulmonary disease has been widely studied. The potentially important clinical benefits of PDEIV inhibition, coupled with the limitations of current PDEIV inhibitors, highlight the need for novel, more potent and specific PDEIV inhibitor chemotypes with fewer side effects.[4] In this study, new potent inhibitors which inhibit the enzyme PDEIV are presented, a library of 2000 compounds generated via pharmacophore modeling is screened using a structure-based docking algorithm[5] and novel drug candidates selected based on their binding affinity to PDEIV are displayed.

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QSAR STUDY OF CYCLIC UREA TYPE HIV-1 PROTEASE INHIBITORS USING *AB INITIO* FRAGMENT MO CALCULATION OF THEIR COMPLEX STRUCTURES WITH HIV-1 PROTEASE

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Several classical QSAR studies as to HIV-1 protease (PR) inhibitors have been published. In these studies, parameters used in the QSAR equations have been derived only from chemical structures of inhibitors, but three-dimensional structural information on inhibitors and HIV-1 PR has not been considered explicitly. In the current work, we performed QSAR analyses on a series of cyclic urea type inhibitors (CUIs) using three-dimensional and electronic descriptors obtained from the molecular dynamics (MD) and *ab initio* fragment molecular orbital (FMO) calculations. Based on our newly proposed QSAR results, we discuss the binding mechanism of inhibitors with HIV-1 PR in detail.

Methods

Thirteen CUIs were selected from those used in the classical QSAR study reported by Garg *et al* [1]. Each complex structure of CUI with HIV-1 PR was constructed by using the MD calculation (AMBER). The change in water accessible surface area (Δ*ASA*) upon complex formation with HIV-1 PR was calculated. We also carried out FMO calculations (ABINIT-MP) of the complex structure of HIV-1 PR with each CUI (HF/6-31G level), and then the ligand binding energy (ΔE_{bind}) and inter-fragment interaction energy (IFIE) between CUI and each amino acid residue of the HIV-1 PR were estimated.

Results and Discussion

The structure-dependent descriptors obtained through the MD and FMO calculations were used to describe the variation of the inhibition constants (p*K*i). We formulated Eq. 1 as a linear combination of ΔE_{bind} and Δ*ASA* terms [2, 3].

$$pKi = -0.0445\ \Delta E_{bind} + 8.75\cdot10^{-3}\ \Delta ASA + 16.1,$$
$$0.555,\ F = 17.3 \qquad (1)$$

From the IFIE analysis, the major contributions to the stabilization of the total electronic interaction energy were found to be from Asp25/ 25', Asp30/ 30', and Ile 50/ 50' in that order. In fact, the sum of IFIEs with these six residues was nicely correlated with ΔE_{bind} ($r = 0.978$), and Eq. 1 can be transformed as the following Eq. 2.

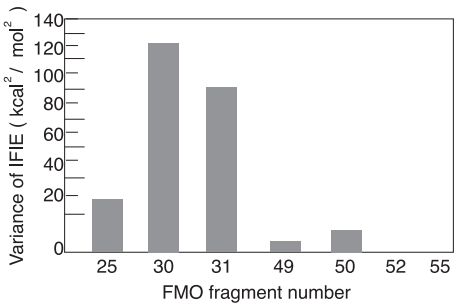

Figure 1. Variance of IFIE

$$pKi = -0.0377\ [IFIE(25) + IFIE(30) + IFIE(31) + IFIE(50)] + 9.50\cdot10^{-3}\ \Delta ASA + 16.2,$$
$$n = 12,\ r = 0.931,\ s = 0.446,\ F = 29.1 \qquad (2)$$

Among the all compounds, the variances of IFIE(30) and IFIE(31) which represent the interaction energy with Asp30/30' were found to be higher than those of the other residues (Fig. 1), indicating that the interaction with Asp30/30' which is in close vicinity to the substituted moiety in each CUI determine the variations in the inhibitory potency dominantly.

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NEW STATISTICAL TOOLS IN BACTERIAL COMPARATIVE GENOMICS

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During the last decade, the number of bacterial genomes completely sequenced has drastically increased. The sudden availability of this wealth of data has stimulated both the formulation of new biological questions about bacterial evolution and the development of new methods to investigate these data. Among them, approaches aiming at comparing directly the complete DNA sequences of bacterial genomes offer the opportunity to gain insights into the molecular mechanisms involved in the bacterial evolution such as DNA exchanges, regulatory motifs or origin of pathogenicity. There exist different software tools and methods dedicated to complete genome comparisons. They are mainly based on the determination of the conserved and the variable (specific) regions between the compared sequences. However, no statistical method still has been proposed to evaluate or to compare these different tools while the investigation of DNA molecular events requires accurate and robust techniques. In this context, two local scores to measure the robustness of bacterial genome comparisons were developed. In this work, computation procedures and illustrative examples are presented. The interest of the method is briefly discussed.

DESIGN OF TYROSINE KINASE INHIBITORS USING *IN SILICO* HIGH-THROUGHPUT DOCKING

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Over 80% of the oncogenes and proto-oncogenes involved in human cancers code for protein tyrosine kinases (PTK). PTK catalyze transfer of phosphate from adenosine tri-phosphate (ATP) to tyrosine residue of specific target proteins. This class of protein activates many processes involved in cell surviving such as cell growth, cell cycle, differentiation or gene expression. Aberrant activation of PTK, owing to mutation or overexpression, has been related to many proliferative diseases such as leukaemia, psoriasis and many cancers. Among the several investigated approaches to regulate or inhibit tyrosine kinase activity, low molecular weight compounds are found to be potent inhibitors as they compete with ATP binding to prevent target protein phosphorylation. *In silico* High-Throughput Screening (HTS) is an approach to drug discovery that has gained widespread popularity over the last years. The ambition of HTS is to accelerate drug discovery by screening large chemical libraries. This study is based on the use of *in silico* high-throughput screening and docking to design potent and selective inhibitors of EGFR tyrosine kinases. Chemical libraries, such as “chimiothèque nationale” or “National Cancer Institute Database”, provide a large amount of diverse chemicals, which are docked into the tyrosine kinase active site, whose structure was provided by crystallographic studies. The combination of docking tools and scoring functions allowed prioritizing chemicals having high affinity with the target. On the other hand, the PASS (Prediction of Activity Spectra of Substances) prediction available on the NCI Enhanced Database will be used to select numerous environmental compounds with potent biological tyrosine kinase activity, such as endocrine disrupters. Such procedure would provide information about the ability of existing environmental compounds to activate tyrosine kinases involved in cancer.

HIV-1 REVERSE TRANSCRIPTASE INHIBITORS: 2-AMINO-6-ARYLSULFONYLBENZONITRILES AND CONGENERS. 2D-QSAR AND 3D-QSAR USING MOLECULAR DOCKING

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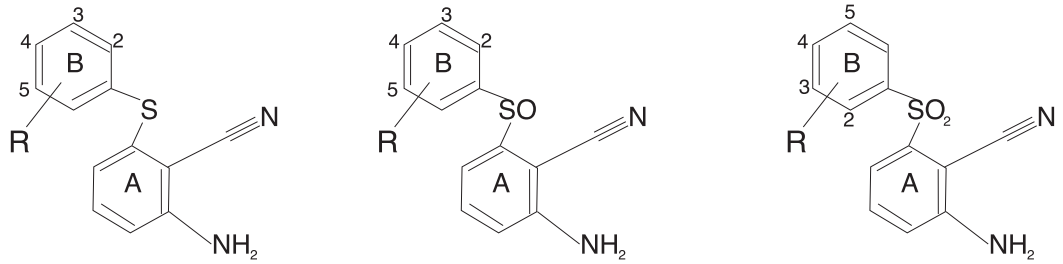

Fig. 2-Amino-6-arylsulfonylbenzonitriles and their thio and sulfinyl congeners [4]

2D QSAR of 2-amino-6-arylsulfonylbenzonitriles and their thio and sulfinyl congeners (Fig.) HIV-1 reverse transcriptase inhibitors is carried out using topological and geometrical, as well as quantum mechanical energy-related and charge distribution-related descriptors. We compare six techniques : multiple linear regression (MLR), multivariate adaptive regression splines (MARS), radial basis function neural networks (RBFNN), general regression neural networks (GRNN), projection pursuit regression (PPR) and support vector machine (SVM) to establish QSAR models for two data sets: anti-HIV-1 activity and HIV-1 reverse transcriptase binding affinity. Our results show that PPR and SVM models provide a powerful capacity of prediction[5].

This 2D-QSAR analysis is completed by a 3D-QSAR analysis[6], relying on molecular docking employed to position the inhibitors into the RT active site to determine the most probable binding mode and most reliable conformations. Comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) approaches, using a complex receptor-based and ligand-based alignment procedure and different alignment modes is performed to obtain highly reliable and predictive CoMFA and CoMSIA models with cross-validated q^2 value of 0.723 and 0.760, respectively. The CoMFA and CoMSIA contour maps with the 3D structure of the target (the binding site of RT) inlaid allow us to better understand the structural requirements for inhibitory activity against HIV-1. For instance, we show that for these inhibitors to have appreciable inhibitory activity, bulky and hydrophobic groups in 3- and 5-position of the B ring are required. Moreover, H-bond donor groups in 2-position of the A ring to build up H-bonding with the Lys101 residue of the RT protein are also favorable to activity.

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QSAR INVESTIGATION OF ANTI-INFLAMMATORY ACTIVITY OF A SERIES OF NON-SUBSTITUTED/SUBSTITUTED (E)-1-(4-METHYL-2(METHYLAMINO)THIAZOL-5-YL)-3-PHENYLPROP-2-EN-1-ONES

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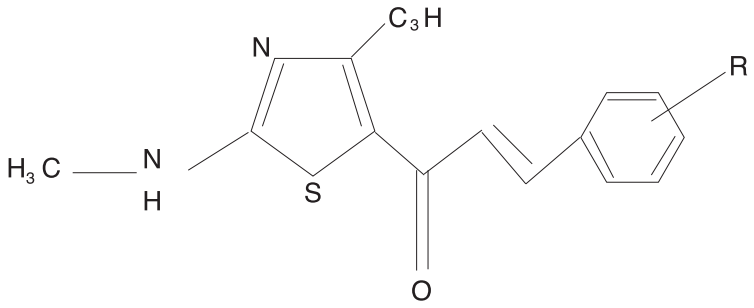
Inflammation is a natural protective reaction of human organism against tissue damage which is induced by physical injuries, chemical substances, pathogenic microorganisms and other factors. Taking into account that many chalcones as well as thiazole derivatives have shown anti-inflammatory activity, a number of chalcones with thiazolyl moiety were synthesized. Their possible anti-inflammatory activity was tested on mice, using the carrageenin induced mouse paw edema method. A series of 15 candidate non-steroidal anti-inflammatory compounds of general formula 1, were tested at a fixed dose of 0.01mg/kg in mice and QSAR studies were performed.



Formula 1

R= 1) H, 2) *p*-NO_2 3) m-NO_2, 4) *o*-Cl, 5) *p*-Cl, 6) *m*-Cl, 7) *p*-F, 8) *m*-F, 9) *m*-CH_3, 10) 2,6-Cl, 11) 2,3-Cl, 12) 2,4 Cl, 13) *m*-Br, 14) *o*-OCH_3, 15) *p*-OCH_3

QSAR descriptors were calculated using TSAR, HYBOT and DRAGON software. Minitab statistical software was used to select the best descriptors, and the following QSAR was obtained:

$$\log (\%AIA) = 1.22 - 1.38\ Mor14v - 2.52\ Mor27v - 0.277\ MATS8p$$

$$n = 15 \quad R^2 = 0.854 \quad Q^2 = 0.623 \quad s = 0.058 \quad F = 21.4$$

where %AIA is % anti-inflammatory activity, Mor14v and Mor27v are MoRSE signals weighted by van der Waals volume, MATS8p is the Moran 2D autocorrelation weighted by atomic polarisability , n is the number of compounds, R is the correlation coefficient, Q is the cross-validated correlation coefficient (leave-one-out procedure), s is the standard error of estimate, and *F* is the Fisher statistic. All p values are < 0.005.

The MoRSE descriptors reflect molecular size and branching, and the Moran descriptor is a topological descriptor encoding molecular structure and physico-chemical properties.

2-OXO-2H-PYRAN-3-CARBOTHIOAMIDE DERIVATIVES: SYNTHESIS AND REACTION WITH HYDRAZINE HYDRATE

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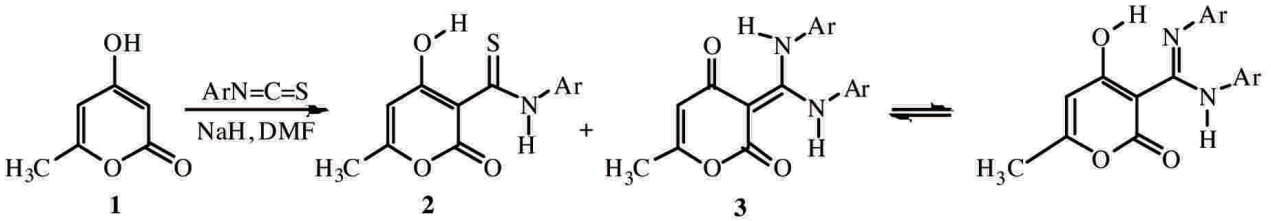
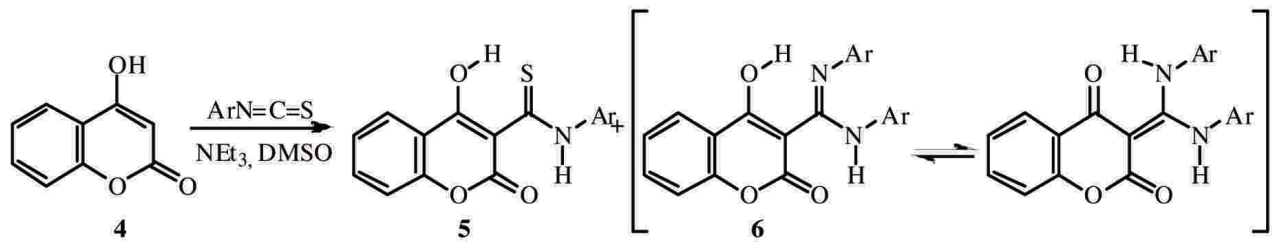
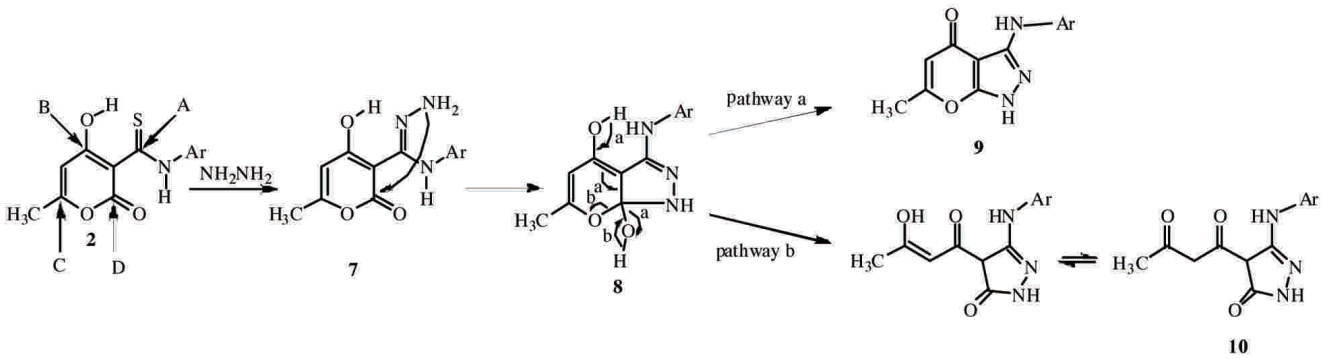
2-Pyrones and coumarins are two important groups of natural products isolated from different families of plants (Ranunculaceae and Asteraceae, Rutaceae, …) [1] and displaying significant biological activities. Some synthetic derivatives are also biologically active compounds, (e.g. potent HIV-1 protease and photosynthetic electron transport inhibitors; sedative, anti-convulsive, anaesthetic, and antifungal agents) [2-5].
Bearing in mind these properties and starting from 4-hydroxy-6-methyl-2-pyrone (triacetic acid lactone, TAL) 1 and 4-hydroxycoumarin 4 we developed a new synthesis of respectively *N*-aryl-4-hydroxy-6-methyl-2-oxo-2*H*-pyrano-3-carbothioamides 2 and N-aryl-4-hydroxy-2-oxo-2*H*-chromene-3-carbothioamides 5 with yields ranging from 35 to 75%. Along with the expected products, respectively new 3-[bis(arylamino)methylene]-6-methyl-2*H*,4*H*-pyran-2,4-diones 3 and N,N'-diaryl-4-hydroxycoumarin-3-carboximidamides 6 derivatives have also been isolated with yields ranging from 30 to 55%. In the present communication the synthesis of new 4-acetoacetyl-3-phenylamino-4,5-dihydro-5*H*-pyrazol-5-ones 10 is also described, using the reaction of *N*-aryl-4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-carbothiamides 2 with hydrazine hydrate.



a) Ar = C_6H_5
b) Ar = 4-BrC_6H_4
c) Ar = 2,5-$(CH_3O)_2C_6H_3$



a) Ar = C_6H_5;
b) Ar = 4-BrC_6H_4



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A RECEPTOR INDEPENDENT 4D-QSAR STUDY ON HIV-INTEGRASE INHIBITORS BY MEANS OF LQTA-QSAR SOFTWARE

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In spite of the implementation of HAART, there is a continuous need to search for new anti-HIV agents. The computer aided-drug design (CADD) related methods are the main approach used for the research of this class of drugs. In this work, the new 4D-QSAR methodology[1] , named LQTA-QSAR, is applied to a set of 85 HIV-IN inhibitors having the ß -diketo acid (DKA) pharmacophoric substructure in common. Geometry optimizations were carried out at B3LYP/6-31G** level and ChelpG charges calculated using Gaussian. Ionic states of compounds at pH 7.5 were determined by Marvin (74 anions and one cation), and several properties were calculated for all compounds. GROMACS software was used for molecular dynamics, MD, simulations and generating the conformational ensemble profile. LQTA-QSAR method was used for calculating intermolecular interaction energies at each grid point, using two different probes and all aligned conformations from MD simulations. The probes used were: Zn^{+2} to explore possible interactions with the metallic co-factor, and Ar(C-H) for hydrophobic interactions. The OPS method[2] was applied for variable selection in the construction of the PLS model. In addition to external validation, the QSAR model was validated by leave-*N*-out cross-validation and y-randomization. The best model (n=75; outliers: 10; R^2 = 0.83; SEC= 0.39; F(7,67)= 39.26; Q^2_{LOO} = 0.71; SEV = 0.47; R^2_{pred} = 0.74; SEP= 0.53; ARE_{pred} = 6.66%; k= 0.99; k'= 0.99; $|r^2_0 - r'^2_0|$= 0.19) was built with 15 descriptors. Visualization of descriptors in the 3D space indicates that they can be related with the metallic co-factors necessary for the enzymatic and inhibition activity, with possible interactions in the hydrophobic pocket and with some accessory interactions at the HIV-IN active site. The good statistics of the model, its robustness and relation with the inhibition mechanism, support the applicability of this model in the proposition of new active compounds.

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ERROR BACK-PROPAGATION NEURAL NETWORK AS A QSAR MODEL FOR PREDICTION OF CARCINOGENICITY

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In the framework of new chemical regulations REACH (Registration, Evaluation and Authorization of Chemicals) (Q)SAR models are accepted as a suitable source of information. As a crucial part of CAESAR project several models for prediction of carcinogenic potency according to specific requirements of chemical regulation were developed.
Structural descriptors calculated with MDL and DRAGON software program have been employed as factors in present study. 644 compounds were used as training and 161 compounds as test sets. First, Back-Propagation model was compared with the best carcinogenicity model [1], which is Counter Propagation Artificial Network (CPANN) model. Sensitivity and specificity of both types of NN models were similar. Second, Back-Propagation neural network employed as autoassociator [2, 3, 4], was used as a mapping device. The signals in the two hidden nodes were then taken as two coordinates for each input object acting as a 2D projection of samples into a map. The hidden nodes enabled us to cluster the compounds used for training the network.

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ASSESSING THE REPRODUCTIVE TOXICITY OF SOME (CON)AZOLE FUNGICIDES USING STRUCTURE-ACTIVITY RELATIONSHIP (SAR) APPROACH

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(Con)azoles are used as fungicides in agriculture for treatment of fruits, vegetables, cereals, and seeds, or as human antimycotic therapeutics. According to the regulations regulating the mentioned uses of (con)azoles, the active substances must undergo the reproductive toxicity testing. The reproductive toxicity is a complex biological endpoint, which includes many different biological processes and, therefore, it can be only in limited extend assessed by a single QSAR model. In our study, we focused on (con)azoles which are used as active substances in plant protection products. Most of them were peer reviewed by The European Food Safety Authority. The proposed SAR models have been built with unsupervised methods: hierarchical clustering, principal component analysis and Kohonen neural network, with the aim to study the similarity relationships among structures. The molecular structures have been represented with a set of topological and structural descriptors. The two closest neighbours identified in all three methods are two isomers dinicnazole and diniconazole-M. The proposed classification for these two is different, but there was a problem of lack of data for diniconazole for which the only available information was that no classification as reproductive toxicity is needed; we suggest a more detailed modelling has to be performed. Three substances (1,2,4-triazole, amitrole, triazole acetic acid) were always situated very close to each other in all three methods suggesting the same type of classification as substances which cause concern for humans owing to possible developmental toxic effects. In spite of a small dataset used, we believe the models showing clusters, closest neighbours, or outliers may support the categorization and the classification of (con)azoles as potential reproductive toxicants.

SYNTHESIS, EVALUATION OF PHARMACOLOGICAL ACTIVITIES AND QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP STUDIES OF A NOVEL GROUP OF BIS(4-NITROARYL-1,4-DIHYDROPYRIDINE)

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Voltage-dependent calcium channels are crucial targets for a wide range of clinically active pharmacological agents. From these agents, 1,4-dihydropyridines constitute a group of small organic compounds are based on a core pyridine structure which can both block and enhance calcium currents. They are considered specific for L-Type calcium channels; however, other channel types, and in particular certain T-Type channels, may show sensitivity to dihydropyridine compounds. In this study, we synthesized a novel group of *bis*-1,4-dihydropyridines using the procedure reported by Dagnino that involved the condensation of n-alkyl diacetoacetate (n = 2-7) with methyl-3-aminocrotonate and nitrophenylaldehyde. The synthesis was run under two conditions: (i) reflux and (ii) microwave.

Calcium channels antagonist activity were determined in vitro using guinea-pig ileum longitudinal smooth muscle assay. Synthesis of these compounds was confirmed with ^{1}H-NMR, IR and mass spectrometry. Then IC50 of them are calculated and compared with Nifedipine. Finally, the result of this pharmacological assay was used in quantitative structure-activity relationship studies utilizing multiple linear regression analysis. Most of these compounds are less active compared with Nifedipine. Decrease in activity is the result of increase in steric hindrance. The quantitative structure-activity relationship study indicates that the activity is related to the electrostatic and topological parameters and the distance between two C5-esteric groups of 1,4-dihydropyridine rings.

TOXICITY OF BENZENE DERIVATIVES TO THE YEAST (*SACCHAROMYCES CEREVISAE*)

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Yeast are found widely distributed in nature, playing important roles in many ecosystems and its cellular structure resembles that of higher organisms. In this study, we have modeled the non-specific 12h toxicity of 57 benzene derivatives to the yeast Saccharomyces cerevisae using several descriptors calculated by different commercially available software packages such as SPARTAN 06 and DRAGON 5.4. The Characteristic Root Index (CRI) which has been previously shown to correlate with many physicochemical and biological properties of organic compounds1,2,3 was also included as a descriptor in the model development.

Semi-emprical molecular descriptors calculated by SPARTAN 06 include the energy values of the highest unoccupied molecular orbital (E_{HOMO}), the energy values of the lowest unoccupied molecular orbital (E_{LUMO}) gas-phase energy (*E*), and Area (A) and Volume (V) obtained from CPK model (a molecular model in which atoms are represented by spheres, the radii of which correspond to van der Waals Radii), dipole moment (μ), aqueous-phase energy (*E*aq) and difference between gas phase and aqueous phase energies (*E*-*E*aq). Principal Component Analysis (PCA) was used as the data-preprocessing step to reduce the dimensionality of the data matrix. Multiple Linear Regression (MLR) analyses show that the best model for CRI-SPARTAN-based descriptors has the following statistical quality: n=53; r^2 =0.874; F (df 4, 48) = 83.43; s= 0.183 whereas the best model produced only for the DRAGON-based descriptors has the following quality: n=56; r^2=0.851; F (df 3, 52) =98.87; s= 0.210. An attempt to use combined set including both DRAGON-based descriptors and the CRI comes out with the following statistics: n=51; r^2=0.94; F(df 3, 47)=177.68; s=0.129. The model having the CRI together with SPARTAN and DRAGON-based descriptors excluded SPARTAN-based descriptors and gave a similar model to the latter one.

All these models were compared with the previously published three models in which they have also used the same toxicity data. It appears that the CRI descriptor when combined with SPARTAN and/or DRAGON-based descriptors has a significant potential in QSTR models.

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REMOVAL OF CORRELATED DESCRIPTORS DOES NOT NECESSARILY RESULT IN BETTER PREDICTION: QSAR STUDY OF CITOSTATIC ACTIVITY OF SELECTED HYDROXYUREA DERIVATIVES

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Purpose of the study: Hydroxyurea is citostatic agent used in treatment of leukemia and other malignant tumors, as well sickle cell anemia and virus infections. Thus amino acid derivates of hydroxyureas were synthesized.[1] The ratio between corresponding therapeutic and toxic effect was used as a dependant variable for QSAR analysis. This data set was used to asses how reduction of dimensionality of well correlated, redundant descriptors (Pearson coefficient of correlation greater than 0.9) influences the prediction based on random forest approach. Methods: 39 descriptors were generated using MOPAC 7 and ACD/ChemSketch freeware v10.02 on a PC computer. Correlation analysis was done in Statistica v7.1 while modeling based on random forests and leave-one-out external validation have been made within R environment v2.8.1.
Results obtained: Significant inter-correlation was established for 11 descriptors. Descriptors that were highly correlated with more than one parameter and correlated descriptors which interpretation is ambiguous were removed from the complete set f descriptors. Final set of descriptors was reduced to 28 elements. Due to this reduction prediction accuracy was decreased from 82% to 81%, but what is more important scattering of results was increased from 5% to 9% for non reduced and reduced dimensionality, respectively. *Conclusion:* Removal of highly-correlated descriptors decreased the quality of prediction and thus lowered the value of QSAR model of citostatic activity of amino acid derivates of hydroxyurea.

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COMPUTATIONAL STUDY OF CYCLOADDITION WITH DIFFERENT NANOTUBES

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Carbon Nanotubes (CNT) are probably the most studied nanomaterials in the last decade. Apart from being very interesting from a theoretical point of view, carbon nanostructures have a wide range of potential applications owing to their remarkable physical and chemical properties. In this research, the stability and the structures of the adducts obtained from the Cycloaddition derivatives to different Nanotubes have been studied. In addition, high-level *ab initio* and density functional calculations DFT are shown to provide strong evidence to evaluate the energies and geometries for [2+2], [2+4] and [4+2] Cycloaddition adducts. Our studies show that the [2+4] products are more strongly bound than the [4+2] ones. The geometries of the [2+2] and [2+4] products. For the [2+2] Cycloaddition HF benzene triple bond increase in length from 1.216Å to 1.322 A. For the [2+4] HF Cycloaddition benzene triple bond increase in length from 1.225Å to 1.445Å. Triple bond increases in length B3LYP from 1.25Å to 1.45Å.The bond connecting benzene [2+2] HF to CNT are 1.53Å. Mulliken population analysis shows a molest increase of negative charge at the CNT connection points from -0.21 to -0.52.

Keywords: Computational; Cycloaddition; Nanotubes; CNT; HF; DFT; B3LYP.

AB INITIO STUDY OF HETERO DIELDS ALDER REACTION USING QUANTUM MECHANIC METHODS

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The main purpose of this research is investigation of some hetero Dields Alder reactions using quantum mechanic methods. In this regard the structure of molecule was drawn in Hyper and after optimizing, it was entered to Gaussian and then using different methods such as B3LYP and HF, basis sets of 6-311++G** and 6-31G** and semi empirical methods of AM1, CNDO and MNDO, optimization was carried out. Using Gaussian software the parameters such as hardness (), polarizability (), electrophilicity () and zero point energy (E) were calculated and after obtaining their values, the stability of reactants and products were compared and the stable structures were specified. Results showed that B3LYP/6-31G** method is the most proper method for calculating the stability. In most cases, energy and electrophilicity showed that *Cis* isomer is more stable than Trans but hardness in most cases did not give the correct answer. According to obtained values of energy by different methods, the major product was 3C. In most cases electrophilicity did not predict the major product and also in most cases hardness did not present a correct prediction about stability of *Cis* and *Trans* and also about major product.

Keywords: Ab initio; Dields Alder reactions; Density functional method; Hardness; Polarizability; Electrophilicity; Zero point energy; Stability

HOMOLOGY MODELING AND DOCKING STUDIES ON HUMAN HISTAMINE H_1-RECEPTORS

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Histamine controls a multitude of physiological functions by activating specific receptors on target cells and acts as one of the major inflammatory mediators as well as a neurotransmitter in the central nervous system. It exerts its effects by binding to four different histamine receptors (H_1 -H_4), which all belong to the large family of G protein-coupled receptors (GPCR). These are integral membrane proteins on cell's surface that possess seven membrane-spanning domains or transmembrane helices. In mammalian smooth muscle, endothelial, and brain tissue, histamine activation of H_1 receptors predominantly triggers Gq/11 protein activation with subsequent stimulation of phospholipase (PL)C and formation of inositol phosphates (IP) and diacylglycerol. In the first half of last century, research in the histamine field completely focused on the role of histamine in allergy, resulting in the development of several potent “anti-histamines” for the treatment of allergy and related disorders. Research and development of H_1 ligand largely has focused on antagonists that are used for their anti-allergy effects in the periphery. Recent understanding of the clinical importance of H_1 receptors in brain, however, suggests the pharmacotherapeutic potential of H_1 agonists in neurodegenerative and neuropsychiatric disorders. Despite the therapeutic importance of the H_1 receptor for many years the molecular features of the H_1 receptor protein had been unknown except some efforts in the recent past. In view of it and in continuation of our work on the development of 3D-pharmacophore model on antihistamine H_1, the homology modeling and docking studies on the human H_1 receptor based on the X-ray structure of bovine rhodopsin have been carried out. The generated H_1 receptor model has been validated by docking studies where the model describes well the binding of the histamine H_1 ligands and the importance of the hydrogen bonding interactions with the amino acid Asp107.

QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP STUDY OF ANTITUBERCULAR DRUGS FLUOROQUINOLONES

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Quantitative structure-activity relationship (QSAR) study on three diverse sets of structurally-similar fluoroquinolones was performed using a comprehensive set of molecular descriptors. Multiple linear regression (MLR) technique was applied to generate linear models for predicting the biological activity in the series (Minimal Inhibitory Concentration (MIC (μg/mL), treated as negative decade logarithm, *p*MIC). Using the non-linear technique CP ANN, we obtained good predictive models. All models were validated using CV LOO procedure. The results (the best models: *Assay1, R* = 0.8108; *Assay2, R* = 0.8454 and *Assay3, R* = 0.9212) obtained on external, previously excluded test data sets show the ability of these models in providing SAR of fluoroquinolones. Thus, we demonstrated the advantage of non-linear approach in prediction of biological activity in this series. Furthermore, these validated models could be proficiently used for the design of novel structurally-similar fluoroquinolone analogues with potentially higher activity.

Key words: Tuberculosis, Fluoroquinolones, DNA gyrase, QSAR, CP ANN

STRUCTURAL AND SEMI-EMPIRICAL MOLECULAR DESCRIPTORS: APPLICATION IN PROPERTY CORRELATIONS OF POLYHALOGENATED DIPHENYL ETHERS

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Of the environmentally important chemicals brominated flame retardants (BFRs), and in particular polybrominated diphenyl ethers (PBDEs), are an emerging group of persistent organic pollutants (POPs), with a known endocrine disruption (ED) activity, which are widely used in a variety of consumer products. Polychlorinated diphenyl ethers (PCDEs) have also received increasing concerns as a group of ubiquitous POPs.

Physicochemical properties (e.g., *n*-octanol/water partition coefficient (log K_{ow}), Henry's Law Constant (log H) etc.) of pollutants play a major role in determining the distribution and fate of organic contaminants in the global environments and have been used for assessing environmental partition and transport of organic substances. Thus accurate estimation and/or prediction of their properties are essential for any reliable ecological model that describes the environmental fate of pollutants.

Structure-property, namely *n*-octanol/water partition coefficient and Henry's Law Constant were studied for polyhalogenated diphenyl ethers by means of multiple linear regression (MLR) analysis. Models based on the Characteristic Root Index (CRI) and semi-empirical molecular descriptors (the energy values of the highest unoccupied molecular orbital (E_{HOMO}), the energy values of the lowest unoccupied molecular orbital (E_{LUMO}), gas-phase energy (E), dipole moment (μ), aqueous-phase energy (Eaq), etc.) are obtained for log K_{ow} and log H for the two subsets containing 86 PCDE and 8 PBDE and a combined set of 94 polyhalogenated diphenyl ethers, and 87 PCDE and 5 PBDE and a combined set of 92 polyhalogenated diphenyl ethers, respectively. The best models were tested using external test set and jacknife test, respectively.

The model for log K_{ow} had a correlation coefficient r^2 = 0.953 and a standard error SE = 0.185 for the training set of 94 compounds, and r^2_{pred}= 0.928 and SE_{pred} = 0.228 for the prediction of set of 23 compounds. For log K_{ow} improved models were obtained for the subsets containing 87 PCDE and 10 PBDE, respectively.

The model for log H had a correlation coefficient r^2 = 0.735 and a standard error SE = 0.372 for the training set of 91 compounds, and r^2_{pred} = 0.791 and SE_{pred} = 0.405 for the prediction of set of 22 compounds.

Because of the relatively small number of molecules in the PBDE data set the models developed for log $K_{ow}$and log H were tested only using leave-one-out cross validation. The cross-validation set of PBDE had r^2_{cv} = 0.981; SE_{cv} = 0.144 and r^2_{cv} = 0.944; SE_{cv}= 0.198 for log $K_{ow}$and log H, respectively.

All these models were compared with the literature models in which they have also used the same experimental data. It appears that structural and semi-empirical descriptors have a potential in Quantitative Structure-Property Relationship (QSPR) models.

COMPUTER-AIDED DESIGN OF NEW ANTIPSYCHOTICS AND ANTICONVULSANTS USING FRAGMENT LIBRARIES

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Several new drugs with atypical antipsychotic activity have been discovered recently. Mainly these compounds are partial functional agonists of dopamine D_2 receptor. Some of them also have an agonistic effect on 5 HT_{1A} subtype of serotonin receptor (Lieberman et al., 2004). At the same time selective $5HT_{1A}$ ligands are known to be used as anticonvulsants (Bagdy et al., 2007).

The purpose of the study is the computer-aided design and comparative analysis of antipsychotic and anticonvulsant agents using fragment libraries.

Fragments, which may exhibit partial agonistic effect on dopamine D_2 and 5 HT_{1A} receptors, were identified using PASS approach (*http://www.ibmc.msk.ru/PASS*). The algorithm of prediction is based on representation of the chemical structure as a set of MNA (multilevel neighborhoods of atoms) descriptors (Filimonov D. et all., 1999). The probabilities of chemical compound to be active (P_a) or inactive (P_i) are estimated on the basis of Bayes method. In the proposed method fragments for new structures were generated in two manners: 1) fragment as a graphic representation of MNA-descriptor and 2) fragments were created from entire molecule using retrosynthetic rules.

New chemical structures, which consisted of 5-7 fragments, were generated using fragment libraries. The algorithm of generation is based on the comparison of two fragments and determining of common substructures. The new structures at every step of generation are obtained by addition new atoms that are diverse for two fragments. New bonds are formed after addition of the atoms.

The fragments with potential agonistic effect on dopamine D_2 and 5 HT_{1A} receptors simultaneously were selected from fragments corresponding to second and third levels of MNA descriptors, and from retrosynthetic fragment library. About 100000 structures were created from each fragment library. Some of new structures were selected as the antipsychotics and anticonvulsants agents on the basis of PASS prediction, and then were compared with $5HT_{1A}$ and dopamine D_2 receptor pharmacophores (Bojarski and Andrzej, 2006; Hackling et al., 2003). Pharmacophores, associated with 5 HT_{1A}, D_2 , $5HT_{1A}$&D_2 agonists are considered.

QSAR MODELLING OF THE ENDOCRINE DISRUPTION ACTIVITY OF BROMINATED FLAME RETARDANTS (BFRS)

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In the last decade, brominated flame retardants (BFRs) have been recognized as an emerging class organic pollutants. They are widely used in a variety of consumer products, such as electronic devices, building materials and textiles. Experimental evidences have shown the potential of these compounds to persist in the environment and to accumulate in biota as well as their endocrine-disrupting (ED) effects, especially on thyroid and sex-related hormones [1]. In the EU REACH regulation the crucial step of Authorisation is mandatory for chemicals with PBT and ED behaviour: the identification of safer alternatives to these chemicals is required.
Unfortunately, the available amount of experimental data is very small and is mainly related to already banned BFRs. According to REACH there is urgent need to maximize the value of existing data, also by using them to predict unknown activities for existing or even not yet synthesized chemicals. The development of QSAR models is among the successful strategies which can meet these needs.
In this study QSAR models were developed, according to the OECD principles, to predict endocrine disrupting potencies of BFRs. Two approaches are proposed: multiple linear regression, by Ordinary Least Squares (OLS), and classification, by K-NN method. Theoretical molecular descriptors were calculated by the DRAGON software and the best models were identified by selecting the available descriptors with the All Subset Method.
Data set: Experimental data were available for several PBDE and OH-BDE congeners, bromo(bis)phenols (246-TBP, TBBPA, TBBPA-DBPE), and HBCD [2-3].
Selected endpoints: T4-TTR relative competing potencies (IC_{50}T4-TTR_{T4}/IC_{50} T4-TTR_{BFR}) and estradiol sulfotransferase relative inhibiting potencies (IC_{50} $E2SULT_{PCP}$ /IC_{50} $E2SULT_{BFR}$).
All the responses were converted into logarithmic units.

Conclusions: The proposed models were developed taking into account the OECD principles for QSAR validation [4]: i) internal and external validation [5]; ii) analysis of the applicability domain (leverage approach (OLS) - descriptors range (KNN)). Both regression and classification models have good predictive power and applicability domain. These QSARs could be used to fill data gaps according to the new REACH regulation, and represent a simple tool for the screening and characterization of BFRs.

Financial support by the European Union through the project CADASTER (FP7-ENV-2007-1-212668) is gratefully acknowledged.

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PAY ATTENTION TO MOLECULAR STRUCTURES, ENDPOINTS' VALUES AND PREDICTIVITY PARAMETERS

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QSAR methodology aims to find out the relationship between molecular structures and endpoints. So the quality of structures and endpoints strongly influence the performance of QSAR models. Here we emphasize the importance of them by analyzing our own published work[1]. Meanwhile we compare different statistical parameters for external model validation[2].

Young[3] has proved that even structures contained in public databases have significant error rates, let alone other ways to get molecular structure. So people must pay more attention to structures. We have published a model[1] on endocrine disruptors using EDKB database[4], but we found some errors in the 3D conformations. Though the published model performs well, we decided to redevelop a model with corrected structures. And we got a model with better performance.

The model is used to predict 9 new compounds in EDKB, demonstrating better performance than the old one. We assessed the predictivity of the model by calculating Q^2 with different formulas: one is reported in the OECD principles (F1)[5], another one is suggested by Schüürmann (F2)[6]. But the two Q^2 are low. It seems that the model fails to predict their activities. However, analyzing the applicability domain (AD) and Williams plot, almost all the compounds are into the model AD and appear well predicted, which is contradictory to the parameter Q^2.

Then we calculated the RMSE for these data, the similar RMSE value to the training set confirming the predictivity of the model. We applied a new formula proposed by Consonni (F3)[7] to calculate the Q2F3. Unlike F1 and F2, the function F3 appears independent of the external object distribution and satisfies the ergodic property. The Q^2_{F3} value is very high, which means the prediction is good, consistent with the conclusion from regression line, AD and RMSE.

At the same time, we found another database METI[8] with classification assignments. The two databases have 108 common molecules. Comparing the endpoints we found that 17.6% of them (19/108) were opposite. We predicted these common samples as blind data by using our new model. Most of the predictions were consistent with METI. Then we built a classification model using the 89 consistent compounds to predict the 19 compounds, and most of them were also agreed with METI.

Financial support from PRIN 07 Program (2007R57KT7) is acknowledged.

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DIPOLAR CYCLOADDITION REACTIONS: SYNTHESIS OF SEVERAL NEW PYRAZOLE DERIVATIVES OF PHARMACEUTICAL ACTIVITIES

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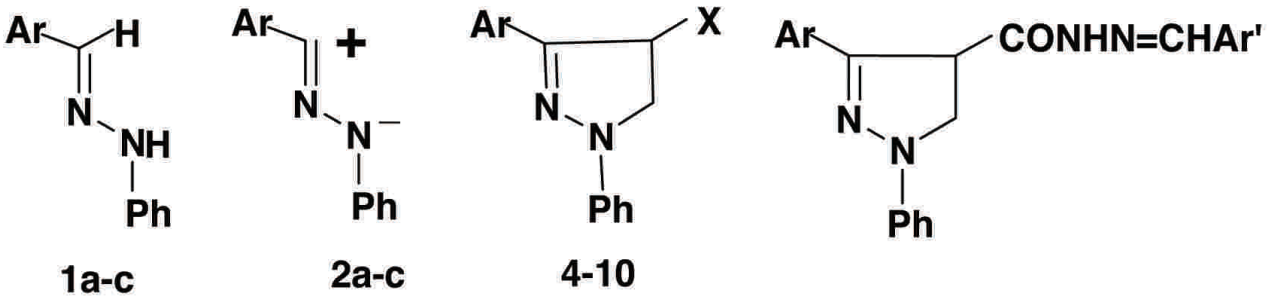
Some new 4-electron three atomic ceneters were prepared via the reaction of several arylhydrazones with N-chlorosuccinimide (NCS) and triethylamine (TEA). These compounds underwent dipolar cycloaddition reactions with different dipolarophiles to yield a vaste number of new pyrazoline and pyrazole derivatives of expected antimicrobial activity. Structures of the newly synthesised heterocyclic derivatives were established on the basis of elemental and spectral data studies.



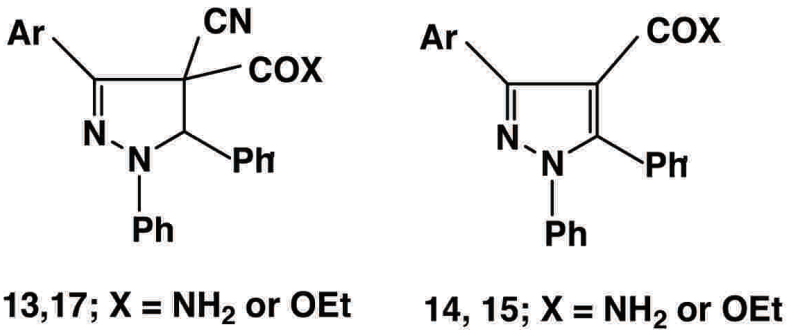
11a,b, Ar = C_6H_4-Cl-*p*

11a, Ar = C_6H_5

11b, Ar = C_6H_4-OCH_3-*p*

1-10a, Ar = C H : b,Ar = C_6H_5-Cl-*p*: c,Ar = C_6H_4-OCH_3-*p*

1-10, X= H, CN, COOEt, $CONH_2$, $CONHNH_2$



MODELING THE BINDING MODE OF STILBENES DERIVATIVES TO CYCLOOXYGENASE-2

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Cyclooxygenase-2 (COX-2) enzyme binds to arachidonic acid and releases metabolites that are used to induce pain and inflammation. COX-2 selective inhibitors are currently used to reduce inflammatory response. However, they lack anti-thrombotic activity and hence lead to cardiovascular and renal liabilities apart from gastrointestinal irritation. In view of the market withdrawal of rofecoxib and valdecoxib due to their adverse cardiovascular side effects there is need to develop alternative more potent COX-2 inhibitors with reduced side effects. To obtain inhibitors with higher selectivity it has become essential to gain additional insight into the details of the interactions between COX-2 and inhibitors experimentally known.

In the present work an automated flexible molecular docking procedure was applied in order to explore the binding mode of a series of stilbenes derivatives as COX-2 inhibitors.

The dataset used for this study contains 21 compounds which are selected with purpose of defining a manageable data set characterized by adequate biological and structural diversity [1,2]. The protein coordinates used are the X-ray structure of COX-2 with SC-558 (6cox.pdb).

The quality of the model of the receptor-ligand complexes was estimated on the basis of their binding energies and inhibition constant.

Our molecular docking studies undertaken to generate atomic models compatible with the experimental data available, provide new insights into a better understanding of the binding mode to COX-2 of these anti-inflammatory molecules.

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DOCKING AND QSAR STUDY ON SOME PYRIDOPYRIMIDINE-BASED CCK1 RECEPTOR ANTAGONISTS

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Cholecystokinin (CCK) is an important endogenous neuropeptide hormone involved in many biological actions, such as regulation of pancreatic enzyme secretions, gallbladder contraction, colonic motility and satiety control. The therapeutic potential of the transmembrane GPCR-subtype-1 receptor (CCK1R) of the cholecystokinin antagonists in treating CCK-related disorders has stimulated extensive research in this area. In this work we propose a quantitative structure-activity relationship (QSAR) study on a series of pyridopyrimidine-based analogues, which were found to be among the most highly potent and selective antagonists of the CCK1R, described to date both *in vitro* and *in vivo*. Molecules are represented by a large number of chemical molecular descriptors including topological, constitutional, geometrical, electrostatic, and quantum. The molecular descriptors have been calculated on the putative bioactive conformations into the binding site of the CCK1R, obtained by molecular docking [1]. This hybrid ligand-based/structure-based strategy could reproduce the real behaviour of this antagonist family into the protein binding pocket and allow us to provide an improved understanding of the main features that relates molecular properties of the compounds with their biological activity (log 1/IC50). As a result, predictive models were successfully obtained in the data set with significant correlations. Interestingly, pertinent descriptors related to hydrophobicity and flexibility of the molecule have been obtained.

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MOLECULAR DOCKING OF NEW PYRAZOLINE DERIVATIVES TO THE ACTIVE SITE OF MONOAMINE OXIDASE*

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Monoamine Oxidase (MAO, EC 1.4.3.4) is a flavoenzyme bound to the mitochondrial outer membranes of the cells and is responsible for the oxidative deamination of neurotransmitter and dietary amines. It has two distinct isozymic forms, designated MAO-A and MAO-B, each displaying different substrate and inhibitor specificities. They are the well-known target for antidepressant, Parkinson's disease and neuroprotective drugs. Since multiple factors contribute to the pathology of these disorders, compounds such as pyrazoles, which possess different biochemical and pharmacological actions give us hope to the possibility to treat these diseases. In the light of the previous findings[1,2], we aim to describe N-substituted pyrazoline derivatives as novel potential MAO inhibitory agents which might have promising features in the treatment of the mentioned diseases.

Elucidation of the x-ray crystal structure of MAO-A and MAO-B has opened the way for molecular modeling studies. In this research, 10 chiral pyrazoline derivatives, including their enantiomers, have been docked computationally to the active site of the MAO-B enzyme as potential MAO-B inhibitors. The structures of these ligands were initially optimized with Spartan 04 using PM3 method. Autodock 4.0.1 was employed to perform molecular docking. The results were compared with our previous docking studies on the known MAO inhibitors[3].

The result of docking studies generated the inhibitors thermodynamic properties such as free energy of bindings (ΔG_b) and inhibition constants (K_i). For majority of these pyrazolines, the inhibition constants were predicted to be in nanomolar range, suggesting that they are more effective than the well-known MAO inhibitors whose values are in micromolar range. Thus, pyrazolines are promising compounds as potent monoamine oxidase inhibitors. Moreover, 3D views of inhibitor-enzyme complexes afforded valuable data regarding the binding orientation of each inhibitor in the active site. The important features of these results will be presented.

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SYNTHESIS OF PYRROLINO[3,4-*d*]PYRAZOLES, PYRAZOLES, PYRAZOLO[5,4-*d*]PYRIMIDINES AND PYRAZOLO[3,4-*d*]PYRIMIDINES FOR TOXICOLOGY STUDIES

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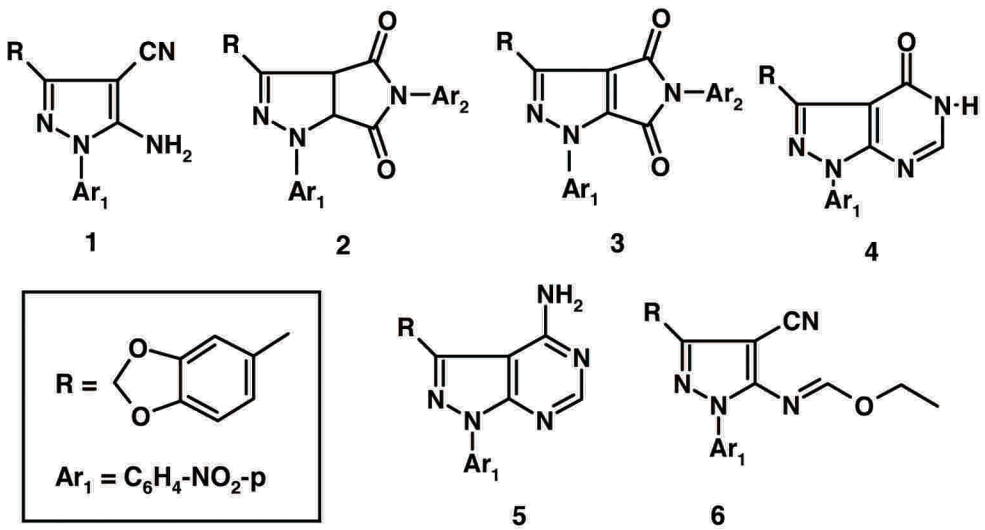
Pyrroles and pyrazoles are known for a long time to possess diverse biological activities. Among these activities may be mentioned their use as antiinflamatory[1,2],antibacterial[3] , antitumor[4] agents as well as antibiotics[5,6]. The reaction of hydrazonoyl halides with N-arylmaleimides and with malononitrile constituted an easy and logical route for the synthesis of several new pyrrolino[3,4-*d*]pyrazoles, pyrazoles and pyrazolopyrimidines of expected biological activities which are required for a medicinal and pharmaceutical chemistry programs.



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APPLICATION OF COMFA/COMSIA ANALYSIS TO HETEROCYCLIC AZO DYE AFFINITIES FOR CELLULOSE FIBRE

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Textile dyeing has economical and ecological implications. Our application of QSAR techniques to dye-cellulose binding is based on the hypothesis of specific dye-fiber interactions. As an alternative to classical QSAR studies, comparative molecular field analysis (CoMFA) was previously used to predict technical dye adsorption properties [1, 2]. This paper presents a structure-affinity study of heterocyclic azo dye adsorption on cellulose fibre by (CoMFA) and comparative molecular similarity index (CoMSIA) analysis. Dye structures obtained by the AM1 approach were aligned using atom per atom superposition of a common frame. The statistically significant models were established for 16 molecules, were validated by an external test set of 5 compounds, yielding the best predictive CoMFA model [r^2 (non-cross-validated square of correlation coefficient) = 0.919, with 2 components, r^2_{cv} (cross-validated r^2) = 0.796, *F* value = 73.52, sdep (standard error of prediction) = 2.55 and see (standard error of estimate) = 0.180]. The CoMSIA model yielded [r^2 = 0.937, with 2 components, = 0.843, *F* value = 96.60, sdep = 2.235 and see = 1.416]. The contour maps obtained from 3D-QSAR studies were appraised for affinity trends for the molecules analyzed. Results indicate that steric, electrostatic and hydrophobic interactions play a significant role in dye binding to cellulose. Hydrogen donor and acceptor substituents influence, also, the dye affinity. The data generated from the present study will further help design novel dye molecules with better affinity for cellulose.

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CHARACTERIZATION OF THE PON1 ACTIVE SITE USING MODELING SIMULATION, IN RELATION TO PON1 LACTONASE ACTIVITY

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Paraoxonase1 (PON1) is a HDL bound enzyme and many of the anti-atherogenic properties of HDL are attributed to PON1. A recent interest has focused on the possible protective role of PON1 in vascular disease as a result of its inhibitory effects on lipoprotein oxidation. PON1 hydrolyzes organophosphates, arylesters and lactones while the endogenous substrate remains elusive, whereas the lactonase activity is assumed as the physio/pathological one. Purpose of the study: The present study is aimed to predict the location of the PON1 active site within PON1 crystal structure, and the lactone structure suitability as PON1 ligand, by employing modeling techniques.

Methods: Ligand docking was carried out with AutoDock 3.0.5 and docking results were visualized and analyzed using ADT and Chimera software.

Results: Previous publication, predicted PON1 active site base on the elucidation of PON1 crystallographic structure.1 Using AutoDock3 software, performing superposition analysis, we were able to allocate the possible PON 1 active site and to partially approve the authors' assumptions. We suggest that indeed Asn168, Asn224, and to some extent, His115, form hydrogen bonds with the substrate and thus have a major role in the enzyme active site function. We have found also a strong correlation between the calculated docking energy of the substrate during their interaction with the enzyme active site and PON1 known rate of lactones hydrolysis (R2= 0.73, P<0.0001), and to the number of carbons constructing the adjacent chain of the _, or _ lactones (R2= 0.85, P<0.0001).

In conclusion, the present study characterized the PON1 possible active site and proposes a tool which may make it possible to envisage the structure of potential endogenous and exogenous lactones such as the PON1 ligand.

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COMPARATIVE QSAR ANALYSIS OF A SERIES OF BENZENE SULFONAMIDE INHIBITORS USING AB INITIO FRAGMENT MO CALCULATION OF THEIR COMPLEX STRUCTURES WITH CARBONIC ANHYDRASE

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Carbonic anhydrase (CA) is a zinc containing metalloprotein and catalyzes various chemical reactions such as acid-base equilibrium. Several classical QSAR studies of CA inhibitors have been published. In this study we discuss the detailed interaction mechanism between CA and a series of benzene sulfonamide (BSA) derivatives using fragment *ab initio* molecular orbital (FMO) calculations on their complex structures, in comparison with the classical QSAR result [1].

Methods

We constructed each BSA-CA complex structure with MD (AMBER) calculations starting from the crystallographic structure (PDB: 1V9I) and calculated ΔE_{bind} (= *E*(complex) - [*E*(CA) + *E*(BSA)]) using FMO calculations (ABINIT-MP, HF/6-31G) on its apo and complex structures (including 258 amino acid residues, Zinc atom, and inhibitor). Then, the total interaction energy (ΔE_{bind}) was further decomposed into the contribution from each amino acid residue fragment in CA with the Inter-Fragment Interaction Energy (IFIE) analysis.

Results and Discussion

The binding potency pKb (= log (1/Kb), Kb; binding equilibrium constant) was formulated as;

$pK_b = -0.106\ \Delta E_{bind} - 12.2$

$n = 11$, $r = 0.928$, $s = 0.462$, $F = 55.9$

ΔE_{bind} is nicely correlated with the Hammett ? value of a substituent in BSA derivatives ($r = 0.95$), resulting the significant correlation between pK_b and Hammett ??, originally reported by Hansch [1]. Figure 1 (a) shows the variance of IFIE of inhibitors ($n = 11$) with amino acid residues and

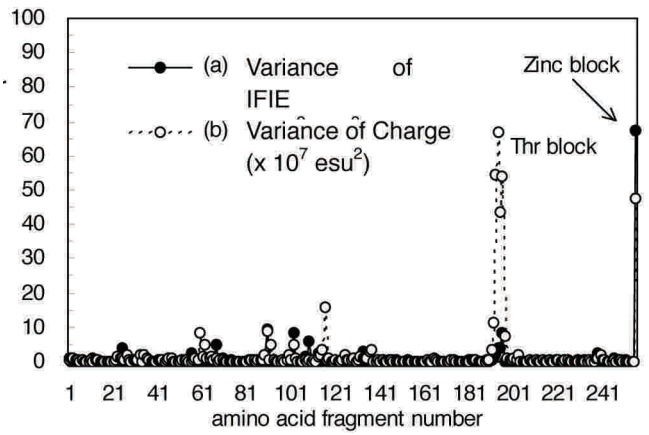

Figure 1. Variations of IFIE (a) and fragment charge (b)

Zinc- block (Zn, His95, His97, and His120) in CA; the variance of IFIE with Zinc-block predominantly determines that of total interaction energy (ΔE_{bind}). Figure 1 (b) shows the variance of fragment charges; variances of BSA and Zinc-block and Thr199, Thr200, Pro201, and Pro202 (Thr-block) are significantly large. These results clearly suggest that charge transfer and redistribution induced by the binding of BSA with residues located in the active pocket of CA (Zinc- and Thr- blocks) govern the variations in the binding potency.

This work was supported by the Japan Science and Technology Corporation (JST-CREST) and Grants-in-Aid for Scientific Research (No.18590034 and 20590036) from the Ministry of Education, Culture, Sports, Science and Technology.

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COMPUTER-ASSISTED PREDICTION OF BIOLOGICAL ACTIVITY IN A SEARCH FOR DRUGS AMONG NATURAL PRODUCTS

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Among thousands of modern drugs about 40% are of natural origin. Recently, we reported structures, origin, synthesis and biological activity of 122 natural peroxides, 92 marine sponge alkaloids and 233 acetylenic compounds as novel natural anticancer agents which isolated from terrestrial and marine sources: cyanobacteria, algae, fungi, invertebrates, plant and other sources [1-3]. Keeping in mind that reported data on biological activity of reviewed compounds and their analogues characterize only a small part of possible biological potential in these molecules, we tried to estimate their biological activity spectra by computer prediction. For this purpose we used computer program PASS (*Prediction of Activity Spectra for Substances*), which predicts about 3000 pharmacological effects, mechanisms of action, mutagenicity, carcinogenicity, teratogenicity and embryotoxicity on the basis of structural formulae of compounds. PASS predictions are based on structure-activity relationships (SAR) analysis of the training set consisting of more than 100,000 of drugs, drug-candidates and lead compounds. Algorithm of PASS predictions is described in detail in several publications [4-7]. Using the program PASS we have shown that many reported activities for natural peroxy compounds, marine sponge alkaloids and naturally occurring aquatic acetylenes have been confirmed and some additional activities were predicted, which point toward new possible applications of these compounds.

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MOLECULAR DYNAMICS SIMULATIONS OF NEBIVOLOL COMPLEXED WITH ß$_1$ AND ß$_2$ ADRENERGIC RECEPTORS - SUBTYPE SPECIFICITY STUDIES

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Beta-adrenergic antagonists (Beta blockers) are the class of drugs which play an important role in the treatment of various cardiovascular diseases including hypertension, cardiomyopathy and congestive heart failure. Beta antagonists interact with beta adrenergic receptors which are divided into a three subtypes: ß$_1$, ß$_2$ and ß$_3$ - respectively beta-adrenergic receptor of type 1, 2 and 3. By blocking or reversing the action of naturally occurring in our body catecholamines ß-blockers lower the heart rate and decrease heart muscle contractility. Thus the overall effects of their action lead to lowering of blood pressure.

The work discussed here constitutes a part of computational studies which address the problem of ß$_1$ selectivity which is of essential importance in treatment of hypertension. The specificity for subtype ß$_1$ is one the key properties which contributes to the anti-hypertensive profile of various Beta blockers. Here we are presenting the results which relate to nebivolol - the most ß$_1$selective agent among all available ß-blockers. By using several computational approaches (including quantum mechanics, molecular docking and classical molecular dynamics) we mapped the interactions between the ne-bivolol and receptor proteins. We found a binding pattern which explains a different specificity of nebivolol for ß$_1$ and ß$_2$ adrenergic receptors. Obtained data will help us to design a highly selective ß antagonist which could be used as an effective agent for management of cardiovascular diseases such as hypertension and heart failure.

PHARMACOPHORE ANALYSIS ON SOME BENZOXAZOLES AGAINST DRUG-RESISTANT *ESCHERICHIA COLI*

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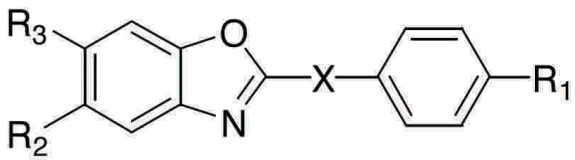
The dramatically rising prevalence of multi-drug resistant microbial infections in the past few decades has become a serious health care problem. In particular, the emergence of multi-drug resistant strains of Gram-positive bacterial pathogens such as methicillin-resistant *Staphylococcus aureus* and *S. epidermis* and vancomycin-resistant *Enterococcus* is a problem of ever-increasing significance.[1-3] In order to prevent this serious medical problem, the elaboration of the new types of the previously known drugs is a very actual task. The benzoxazoles have been the aim of many researches for many years; because they constitute an important class of heterocyclic compounds exhibiting substantial chemotherapeutic activities. In the last few years, we reported some derivatives of benzoxazoles, which exhibited antimicrobial, antiviral, multi-drug resistance cancer cell activities with inhibiting activity on eukaryotic topoisomerase II enzyme in cell-free system [4-9]. Inhibitor effects against drug-resistance *Escherichia coli* of some benzoxazole derivatives which have a nitro or amine group attached on position 5 or 6 of 2-(p-substitutedphenyl / benzyl)benzoxazoles binding them were investigated [9].

In this study, common-features hypotheses are generated by using Catalyst 4.9 [10] for finding the chemical features among a set of some amide derivatives given in Figure.



X = –, CH_2;
R_1 = H, F, Br, Cl, CH_3, C_2H_5, $C(CH_3)_3$;
R_2 = **R_3** = H, NO_2, NH_2

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USING CONFORMATIONAL ENSEMBLES AS QUERIES IN BRUTUS SEARCHES: IS IT WORTH THE EXTRA EFFORT?

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Three-dimensional ligand-based virtual screening (LBVS) is widely used methodology in the drug discovery process. One commonly used technique is to align a molecular database to query molecule and calculate similarity between the two molecules. Usually a single conformation (so-called "bioactive conformation") is used for the query molecule. However, the bioactive conformation(s) of compounds cannot be, generally speaking, be represented by a single conformer [1].

One way of dealing with the query molecule's flexibility is to pre-calculate several conformations and use each of them as a query. This does however significantly increase the computing time. In this study, we investigated if it's worth of the extra effort to use multiple conformations or is it enough to use just a single, low-energy conformer.

Ten data sets were taken from the literature and conformations were generated using CORINA/ROTATE. Query compounds were selected using ALMOND. Molecules in the data sets were aligned with BRUTUS and best ranking superposition for each compound was used in scoring.

From the results, it seems that using several conformations instead of a single low-energy conformation does not increase the quality of alignments significantly and therefore there would be only a marginal effect on the virtual screening performance. These findings with BRUTUS are in line with the previously published studies with other LBVS methods [2,3].

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QSAR DATA BANK FORMAT FOR ELECTRONIC ORGANIZATION AND ARCHIVING OF QSAR/QSPR MODEL INFORMATION

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QSAR/QSPR models are useful tools for *in silico* predictions in drug discovery, chemical industry applications, safety assessment of chemicals in environmental toxicology, etc. Although many QSAR/QSPR models have been proposed over the past decades, the sharing and application of models is often hard because different computational procedures have been used for the calculation of molecular descriptors and the models itself have different representations. In order to use models for reliable *in silico* predictions it is necessary to understand the applicability domain of the models and use the correct procedure for molecular descriptor calculation and QSAR/QSPR prediction. This requires the precise definition of the QSAR model, well defined and repeatable procedure for the calculation of molecular descriptor, training and validation set information. Currently there is no well established computer representation of QSAR/QSPR models.

The QSAR Data Bank (QDB) format is an open data representation for the electronic organization and archiving of QSAR/QSPR model information. The QDB format can be used for the representation of compounds, experimentally measured activities/properties, descriptors, QSAR/QSPR models, QSAR/QSPR predictions, and workflows. The specification for QDB format has been designed to be flexible and easily extendable. It tries to reuse existing data formats as much as possible. For example, chemical markup language for the representation of molecular structures, predictive model markup language for QSAR/QSPR models, BibTeXML for literature references, UnitsML for units specification. The workflows provide step-by-step instructions for producing predictions. As such it can be used as an executable format for QSAR/QSPR predictions.

Software for the authoring of QSAR/QSPR models in QDB format is open source. More information about the QDB format and its example applications are available at http://qsardb.com/

ANALYSIS OF HYDROPHOBIC ORGANISATION OF GPCR COMPLEXES WITH LIGANDS

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G-protein-coupled receptors (GPCR) play a key role in signal transduction in living cells, participate in regulation of numerous biological functions and, thus, are important therapeutic targets in a variety of disease states. Beta-adrenoreceptor antagonists are among the most widely used drugs in clinical practice. It has been shown earlier that antagonist binding is accompanied by a hydrophobic interaction between the receptor and the ligand (Contreras ML et al., 1986, J. Pharm. Exp. Ther. 237: 165). To further investigate this issue and arrive to numerical models, we used web-server PLATINUM (http://model.nmr.ru/platinum). It provides an easy-to-use and customizable tool to estimate the hydrophobic/hydrophilic match or mismatch at the interface of two interacting molecules based on the concept of the Molecular Hydrophobicity Potential (MHP), which utilizes empirical atomic hydrophobicity constants derived from the water-octanol partition coefficients for organic compounds. We present theoretical modeling approach to estimation of hydrophobic interactions between the beta2-adrenoreceptor and a set of antagonists with experimentally derived binding constants. Recently obtained spatial structure of adrenoreceptor (Cherezov V et al., 2007, Science, 318: 1258) was used to perform molecular docking of antagonist molecules. Resulting complexes were then optimized to satisfy experimentally derived spatial restraints. Strong correlation (R^2 = 0.8) between pKd and hydrophobic match was found. Therefore our method of estimating hydrophobic match can be further used to discover new potent inhibitors to beta2-adrenoreceptor.

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MODELING THE HYDROPHILICITY AND LIPOPHILICITY OF WINE POLYPHENOLS USING DESCRIPTORS DERIVED FROM 3D STRUCTURES

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Due to importance of three-dimensional (3D) shape of molecules for passive diffusion through the biological membranes, our attempt was to develop a quantitative structure-property relationship (QSPR) models that relates hydrophilicity (Hy) and lipophilicity (log *P*) of 19 polyphenols present in wine, with descriptors derived from an optimized 3D molecular structures. The aim of this study was also to correlate the experimentally determined log P values for polyphenols (taken from web database, http://chem.sis.nlm.nih.gov/chemidplus/) and values that are calculated using four different programs: HyperChem (log P_{Hyp}), MLOGP, ALOGP, and CLOGP. The 3D structures of 19 polyphenols were optimized applying the HyperChem 8.0 (Hypercube Inc.) using AM1 method. Several physico-chemical parameters were calculated with HyperChem: the energy of the highest occupied (E_{HOMO}) and lowest unoccupied molecular orbital (E_{LUMO}), difference between E_{HOMO} and E_{LUMO} (GAP), the heat of formation (H_f), and hydration energy (E_{HYDR}). Applying the Dragon program, different group of molecular descriptors have been calculated: geometrical, 3D-MoRSE, Randic molecular profiles, GETAWAY, RDF, WHIM, and BCUT descriptors. Selection of descriptors based on best-subset method and multiple regression analysis was performed using the program Statistica 7.0 (StatSoft, Inc.). The generated QSPR models were validated by leave-one-out cross-validation procedure using the CROMRsel (Rugjer Boskovic Institute, Zagreb). The best model for hydrophilicity contains the two 3D-MoRSE descriptors: *Mor*13*e* and *Mor*13*e*. The best agreement with experimentally observed log P values was obtained with CLOGP values. However, the most appropriate model was achieved for the ALOGP using two variables: *BELe1* (BCUT) and *RTm* (GETAWAY). Obtained models imply that lipophilicity and hydrophilicity of polyphenols is mainly influenced by the presence of different substitutions on the basic structure of phenolic acids and flavonoids.

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ABSTRACT BOOK

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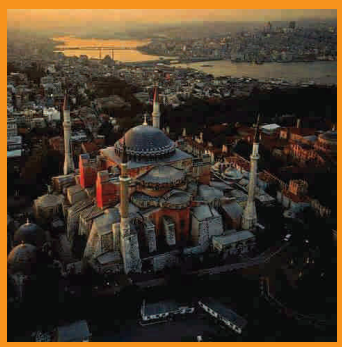




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