PhD STUDIES COURSE UNIT DESCRIPTION

Name of subject	Field of science, code	Faculty / Center	Department
Drug Design	Chemistry N 003	Life Sciences Center	Institute of Biotechnology
Student's workload	**Credits**	**Student's workload**	**Credits**
Lectures	0	Consultations	1
Independent study	5	Seminars	1

Course annotation

Human being- diseases- drugs. The relationship between chemistry and medicine.
Drug binding. Covalent binding, targeted covalent binding, electrostatic or ionic bonds, hydrogen bonds, hydrophobic interaction, Van der Walls interaction, dipole-dipole and ion-dipole interaction, cation- π interaction, π - π interaction, the role of water in interactions.
Drug target- proteins. Enzymes, receptors, transport proteins.
Enzymes. Interaction models: lock and key model, induced fit, conformational selection. Types of inhibitors: reversible- competitive, noncompetitive, uncompetitive, irreversible (e.g. suicide inhibitors), alosteric. Enzyme kinetics V_{max}, k_{cat}, K_M. Binding affinity. The strength of the interaction (K_b, K_d, ΔG_b). Enzymatic Activity Inhibition Assay. The potency of inhibitor (K_i, IC_{50}). Isozymes.
Receptors as drug targets. Types of receptors. Agonists, antagonists, alosteric antagonists, partial agonists, inverse agonists. The strategies for design of agonists and antagonists. Sensitization and desensitization. Affinity, efficacy, and potency.
Nucleic acids as drug targets. DNA as drug target, classification of active compounds. RNA as drug target, agents that bind to ribosomes, antisense therapy.
Miscellaneous drug targets- lipids, carbohydrates.
Bioassay. *In vivo*, *ex vivo*, *in vitro*, *in silico* tests.
The search of lead compound. Hit. From hit to lead. Screening. HTS- high-throughput screening. Fragment screening. Screening methods: biophysical approaches, mass spectrometry, nuclear magnetic resonance (NMR) spectroscopy, crystallographic screening. Virtual screening. Early tests for potential toxicity. The strategies of the search of lead compound (e.g. screening of natural sources, combinatorial synthesis, etc.).
Lead compound optimization. *Improvement of target interactions*. The role of functional groups (e.g. amines, carboxylic acids, etc.) in optimization. Indentification of pharmacophore. Lead compound optimization strategies (e.g. ring variations, variation of substituents on aromatic or heteroaromatic rings, etc.). Isosteres and bioisosteres. Chirality. *Improvement of access to the target*. Optimization of ADME properties. Druglikeness. Lipinski's rule of five. Veber's rules Optimizing hydrophilic/hydrophobic properties. Making drugs more resistant to chemical and enzymatic degradation. Strategies for reduction of toxicity. Prodrugs and their aplication (e.g. improvement of membrane permeability, prolongation of drug activity, etc.).
Pharmacokinetics. Absorption, distribution, metabolism, and excretion (ADME). The first pass effect-first-pass metabolism. Orally active drugs. Drug distribution. Pharmacokinetic parameters (e.g. clearance (Cl), half-life, bioavailability (F), etc.) Blood brain barrier. Drug metabolism (phase I, phase II). Phase I- oxidative reactions catalysed by cytochrome P450 enzymes on saturated carbon centres, amines, ethers, hetroatoms and unsaturated centres. Other important oxidative enzymes**-** alcohol dehydrogenases, aldehyde dehydrogenases, esterases, peptidases. Phase II (e.g. glucuronic acid conjugation, sulphate conjugation, methylation, etc.). Metabolic stability.
Computers in drug design. Docking. *De Novo* drug design. QSAR- quantitative structure-activity relationship. Physicochemical descriptors- hydrophobicity- the partition coefficient (P), the substituent hydrophobicity constant (π). Electronic descriptors- Hammett constant. Steric descriptors- Taft's steric constant. Free-Wilson model. Hansch model. The Craig plot. The Topliss scheme. 3D QSAR.
Combinatorial and parallel synthesis.
Getting the drug to market. Patenting. Chemical development. Regulatory affairs. Fast tracking drugs. Orphan drugs. Preclinical trials. Toxicity testing. *In Vivo* toxicity testing. Metabolic stability testing. Clinical trials. Phase I. Phase II. Phase III. Phase IV.

Reading list

Graham L. Patrick An Introduction to Medicinal Chemistry.
Robert M. Rydzewski Real World Drug Discovery
C. Wermuth, D. Aldous, P. Raboisson, D. Rognan The Practice of Medicinal Chemistry
J. Holenz Lead Generation
Li Di and E. H. Kerns Drug-Like Properties: Concepts, Structure Design, and Methods

The names of consulting teachers	Science degree	Main scientific works published in a scientific field in last 5 year period
Virginija Dudutienė	Dr.	**Dudutienė, V**., Zubrienė, A., Kairys, V., Smirnov, A., Smirnovienė, J., Leitans, J., Kazaks, A., Tars, K., Manakova, L., Gražulis, S., and Matulis D. 2020. Isoform-Selective Enzyme Inhibitors by Exploring Pocket Size According to the Lock-and-Key Principle. *Biophysical Journal,* 119, 1513–1524. 10.1016/j.bpj.2020.08.037. **Dudutienė V.**, Matulis D. 2019. Organic Synthesis of Substituted Fluorinated Benzensulfonamides as Selective Inhibitors of CAIX and Other Isoforms. In: Matulis D. editor „Carbonic Anhydrase as Drug Target: Thermodynamics and Structure of Inhibitor Binding“. Cham, Switzerland: Springer International Publishing, 153–161. DOI: 10.1007/978-3-030-12780-0. Kazokaitė J., Niemans N., **Dudutienė V.**, Becker H., Leitans J., Zubrienė A., Baranauskienė L., Gondi G., Zeidler R., Matulienė J., Tars K., Yaromina A., Lambin P., Dubois L.J., Matulis D. 2018. Novel fluorinated carbonic anhydrase IX inhibitors reduce hypoxia-induced acidification and clonogenic survival of cancer cells. *Oncotarget*, **9**(42): 26800-26816. Zubrienė, A., Smirnov, A., **Dudutienė, V**., Timm, D. D., Matulienė, J., Michailovienė, V., Zakšauskas, A., Manakova, E., Gražulis, S., Matulis, D. 2017.Intrinsic Thermodynamics and Structures of 2,4- and 3,4-Substituted Fluorinated Benzenesulfonamides Binding to Carbonic Anhydrases. *ChemMedChem.* **12**(2): 161-176. **Dudutienė, V.,** Zubrienė, A., Smirnov, A., Timm, D.D., Smirnovienė, J., Kazokaitė, J., Michailovienė, V., Zakšauskas, A., Manakova, E., Gražulis, S., Matulis, D. 2015. Functionalization of fluorinated benzenesulfonamides and their inhibitory properties toward carbonic anhydrases. *ChemMedChem*. **10**: 662-687. Matulis, D., **Dudutienė V**., Zubrienė, A Fluorinated benzenesulfonamides as inhibitors of Carbonic Anhydrase. US9725467 (B2)- 2017-08-08, US2015266900 (A1) – 2015-09-24, EP2914583 (A1) — 2015-09-09, EP2914583 (B1) — 2019-02-27.

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