Selected references on PharmaExpert

Bocharova O.A., Ionov N.S., Kazeev I.V., et al. Computer-Aided Evaluation of Polyvalent Medications' Pharmacological Potential. Multiphytoadaptogen as a Case Study. *Molecular Informatics*, **2022** Sep 8. doi: 10.1002/minf.202200176. Epub ahead of print.

Multiphytoadaptogen (MPhA) containing 70 major phytocomponents of different chemical classes from 40 medicinal plant extracts has been studied in vitro, in vivo and in clinical researches. Antiproliferative and anti-tumor activities have been shown against some tumors as well as evidence-based therapeutic effects against age-related pathologies. In addition, the neuroprotective, antioxidant, antimutagenic, radioprotective, and immunomodulatory effects of MPhA were confirmed. Many human diseases including cancer, degenerative and autoimmune disorders, diabetes and others are multifactorial. Pharmaceutical agents acting on a single target do not provide their efficient curation. Multitargeted drugs exhibiting pleiotropic pharmacological effects have certain advantages due to the normalization of the complex pathological processes of different etiology. Extracts of medicinal plants (EMP) containing multiple phytocomponents are widely used in traditional medicines for multifactorial disorders' treatment. Experimental studies of pharmacological potential for multicomponent compositions are quite expensive and time-consuming. In silico evaluation of EMP the pharmacological potential may provide the basis for selecting the most promising directions of testing and for identifying potential additive/synergistic effects. Analysis of the PASS profiles of the biological activity of MPhA phytocomponents showed that most of the predicted anti-tumor and anti-metastatic effects were consistent with the results of laboratory and clinical studies. Antimutagenic, immunomodulatory, radioprotective, neuroprotective and anti-Parkinsonian effects were also predicted for most of the phytocomponents. Effects associated with positive effects on the male and female reproductive systems have been identified too. Thus, PASS and PharmaExpert can be used to evaluate the pharmacological potential of complex pharmaceutical compositions containing natural products.

Brkich G., Pyatigorskaya N., Zyryanov O., et al. In silico profiling of the new allosteric modulator of AMPA receptors. *Georgian Med. News*, **2022**, 323:151-156.

The aim of this study is to investigate the computer-aided prediction of pharmacological activity and mechanisms of action of 6-[4-methoxy-3-(1H-pyrazol-1-ylmethyl)benzyl]-1,11-dimethyl-3,6,9-triazatricyclo[7.3.1.1]tetradecane-4,8,12-trione (TCT-9). The compound was designed for modulation of ionotropic glutamate AMPA receptors, and its affinity for the receptor has been earlier proven experimentally. A cognitive stimulating effect of TCT-9 has been shown using a model of freezing behavior in mice. The drug candidate TCT-9 is now under the development process: it is intended for the treatment of cognitive impairments in case of brain injury. Following the existing requirements, the present study was carried out in the framework of secondary pharmacodynamic studies to determine possible off-target effects and interaction of the compound with regulatory signaling and metabolic networks/pathways. In silico study of the TCT-9 binding to pharmacologically significant targets and the new AMPA receptor modulator's effects on signaling pathways was carried out by the analysis of structure-activity relationships. Prediction of biological activity spectra was performed using PASS (Prediction of Activity Spectra for Substances), which estimates the probabilities for more than five thousand biological activities. The PharmaExpert program assessed information on the belonging of the targets predicted by the PASS program to the signaling and metabolic pathways. The prediction results are the basis for the experimental verification of the binding of the TCT-9 to the steroid hormone receptor ERR1 and further studies of the drug activity in animal models of diseases.

Ionov N.S., Baryshnikova M.A., Bocharov E.V., et al. Possibilities of in silico estimations for the development of pharmaceutical composition phytoladaptogene cytotoxic for bladder cancer cells. *Biomed. Khim.*, **2021**, 67(3):278-288.

Based on the prediction of biological activity spectra for several secondary metabolites of medicinal plants using the PASS computer program and validation in vitro of the predictions results the priority direction of the pharmaceutical composition Phytoladaptogene (PLA) development was determined. PLA is a complex of structurally diverse small organic compounds including biologically active substances of phytoadaptogenes (ginsenosides from Panax ginseng, rhodionin from Rhodiola rosea and others) compiled considering previously developed pharmaceutical compositions. Two variants of the pharmaceutical composition were studied: - the major and minor variants included 22 and 13 compounds, respectively. The probability of activity exceeds the probability of inactivity for 1400 out of 1945 pharmacological effects and mechanisms predicted by PASS for the major variant of PLA. The wide range of predicted activities is mainly due to the low structural similarity of constituent compounds. An in silico prediction indicates the possibilities of antitumor properties against bladder, stomach, colon, ovarian and cervical cancers both for minor and major PLA compositions. It was found that the highest probability values of activity were predicted for three mechanisms: apoptosis agonist, caspase-3 stimulant, and transcription factor NF-κB inhibitor. According to the PharmaExpert program they are associated with the antitumor effect against bladder cancer. Experimental validation was using the human bladder cancer cell line RT-112. The results of the MTT test have shown that the cytotoxicity of the major PLA variant is higher than that of the minor PLA variant. In vitro experiments performed using two methods (double staining with annexin V and propidium iodide and detection of active caspase-3 in cells) confirmed that the death of bladder cancer cells occurred via the apoptotic mechanism. The data obtained correspond to the results of the prediction and indicate advantages of the major PLA composition. Thus, PLA can become the basis for the development of a drug with the antitumor activity against bladder cancer. The antitumor activity predicted by PASS for other cancers may be the subject of further studies.

Lagunin A., Povydysh M., Ivkin D., et al. Antihypoxic Action of Panax Japonicus, Tribulus Terrestris and Dioscorea Deltoidea Cell Cultures: In Silico and Animal Studies. *Mol. Inform.*, **2020**, 39(11): e2000093.

Chemical diversity of secondary metabolites provides a considerable variety of pharmacological actions with a significant extension due to their combinations in plant extracts. Production of plant-derived medicinal products in cell cultures has advantages because of the efficient use of different biotic and abiotic elicitors and better control of the developmental processes. Using PASS software, we predicted biological activity spectra for phytoconstituents identified in cell cultures of Panax japonicus (12 molecules), Tribulus terrestris (4 molecules), and Dioscorea deltoidea (3 molecules). Mechanisms of action associated with the antihypoxic effect were predicted for the majority of molecules. PharmaExpert software allowed analyzing possible synergistic or additive effects of the combinations of phytoconstituents associated with the antihypoxic action. Experimental studies of the antihypoxic effect of the plants' extracts in water and ethanol have been performed in 3 animal models: Acute asphyctic hypoxia (AAH), Acute haemic hypoxia (AHeH), and Acute histotoxic hypoxia (AHtH). Effects of Panax japonicus and Tribulus terrestris preparations exceeded the activity of the reference drug Mexidol in the AHtH model. In the AHeH model, all preparations demonstrated moderate activity; the most potent has been observed for Dioscorea deltoidea. Thus, we found that experimental studies in animal models have confirmed the in silico prediction.

Goel R.K., Gawande D.Y., Lagunin A.A., Poroikov V.V. Pharmacological repositioning of Achyranthes aspera as an antidepressant using pharmacoinformatic tools PASS and PharmaExpert: a case study with wet lab validation. *SAR QSAR Environ. Res.*, **2018**, 29(1): 69-81.

Traditional knowledge guides the use of plants for restricted therapeutic indications, but their pharmacological actions may be found beyond their ethnic therapeutic indications employing emerging computational tools. In this context, the present study was envisaged to explore the novel pharmacological effect of Achyranthes aspera (A. aspera) using PASS and PharmaExpert software tools. Based on the predicted mechanisms of the antidepressant effect for all analysed phytoconstituents of A. aspera, one may suggest its significant antidepressant action. The possible mechanism of this novel pharmacological effect is the enhancement of serotonin release, in particular caused by hexatriacontane. Therefore, pharmacological validation of the methanolic extract, hexatriacontane rich (HRF) and hexatriacontane lacking fraction (HLF) of A. aspera was carried out using the Forced Swimming Test and Tail suspension test in mice. The cortical and hippocampal monoamine and their metabolite levels were measured using high performance liquid chromatography (HPLC). A. aspera methanolic extract, HRF treatments showed a significant antidepressant effect comparable to imipramine. Further, the corresponding surge in cortical and hippocampal monoamine and their metabolite levels was also observed with these treatments. In conclusion, A. aspera has shown a significant antidepressant effect, possibly due to hexatriacontane, by raising monoamine levels.

Sarapultsev A.P., Vassiliev P.M., Sarapultsev P.A., et al. Immunomodulatory Action of Substituted 1,3,4-Thiadiazines on the Course of Myocardial Infarction. *Molecules*, **2018**, 23(7): 1611.

This review focuses on the biological action of the compounds from the group of substituted 1,3,4-thiadiazines on stress response and myocardial infarction. The aim of this review is to propose the possible mechanisms of action of 1,3,4-thiadiazines and offer prospectives in the development of new derivatives as therapeutic agents. It is known, that compounds that have biological effects similar to those used as antidepressants can down-regulate the secretion of proinflammatory cytokines, up-regulate the release of anti-inflammatory ones and affect cell recruitment, which allows them to be considered immunomodulators as well. The results of pharmacological evaluation, in silico studies, and in vivo experiments of several compounds from the group of substituted 1,3,4-thiadiazines with antidepressant properties are presented. It is proposed that the cardioprotective effects of substituted 1,3,4-thiadiazines might be explained by the peculiarities of their multi-target action: the ability of the compounds to interact with various types of receptors and transporters of dopaminergic, serotonergic and acetylcholinergic systems and to block the kinase signal pathway PI3K-AKT. The described effects of substituted 1,3,4-thiadiazines suggest that it is necessary to search for a new agents for limiting the peripheral inflammatory/ischemic damage through the entral mechanisms of stress reaction and modifying pro-inflammatory cytokine signaling pathways in the brain.

Stasevych M., Zvarych V., Lunin V., et al. Computer-aided prediction and cytotoxicity evaluation of dithiocarbamates of 9,10-anthracenedione as new anticancer agents. *SAR QSAR Environ. Res.*, **2017**, 28(5): 355-366.

Anticancer activity as an associated action for a series of dithiocarbamates of 9,10-anthracenedione was predicted using the PASS computer program and analysed with PharmaExpert software. The predicted cytotoxic activity of the dithiocarbamate derivatives of 9,10-anthracenedione was evaluated in vitro on cancer cells of the human lung (A549), prostate (PC3), colon (HT29) and human breast (MCF7) using the sulforhodamine B (SRB) cell viability assay. Among these compounds, 9,10-dioxo-9,10-dihydroanthracen-1-yl pyrrolidin-1-carbodithioate and 9,10-dioxo-9,10-dihydroanthracen-2-yl pyrrolidin-1-carbodithioate were identified as the most potent anticancer agents with cytotoxic activity against the MCF-7 human breast cell line with GI_{50} values of 1.40 μM and 1.52 μM, whereas the GI_{50} value for the reference anticancer drug mitoxantrone was 3.93 μM. Thus, anticancer activity predicted by PASS with a probability Pa > 30% was confirmed by the experiment. Relatively small Pa values estimated by PASS indicated the novelty of the considered derivatives comparing to the compounds from the PASS training set.

Zakharov A.V., Varlamova E.V., Lagunin A.A., et al. QSAR Modeling and Prediction of Drug-Drug Interactions. *Mol. Pharm.*, **2016**, 13(2):545-556.

Severe adverse drug reactions (ADRs) are the fourth leading cause of fatality in the U.S. with more than 100,000 deaths per year. As up to 30% of all ADRs are believed to be caused by drug-drug interactions (DDIs), typically mediated by cytochrome P450s, possibilities to predict DDIs from existing knowledge are important. We collected data from public sources on 1485, 2628, 4371, and 27,966 possible

DDIs mediated by four cytochrome P450 isoforms 1A2, 2C9, 2D6, and 3A4 for 55, 73, 94, and 237 drugs, respectively. For each of these data sets, we developed and validated QSAR models for the prediction of DDIs. As a unique feature of our approach, the interacting drug pairs were represented as binary chemical mixtures in a 1:1 ratio. We used two types of chemical descriptors: quantitative neighborhoods of atoms (QNA) and simplex descriptors. Radial basis functions with self-consistent regression (RBF-SCR) and random forest (RF) were utilized to build QSAR models predicting the likelihood of DDIs for any pair of drug molecules. Our models showed balanced accuracy of 72-79% for the external test sets with a coverage of 81.36-100% when a conservative threshold for the model's applicability domain was applied. We generated virtually all possible binary combinations of marketed drugs and employed our models to identify drug pairs predicted to be instances of DDI. More than 4500 of these predicted DDIs that were not found in our training sets were confirmed by data from the DrugBank database.

Ivanov S.M., Lagunin A.A., Poroikov V.V. In silico assessment of adverse drug reactions and associated mechanisms. *Drug Discovery Today*, **2016**, 21 (1), 58-71.

During recent years, various in silico approaches have been developed to estimate chemical and biological drug features, for example chemical fragments, protein targets, pathways, among others, that correlate with adverse drug reactions (ADRs) and explain the associated mechanisms. These features have also been used for the creation of predictive models that enable estimation of ADRs during the early stages of drug development. In this review, we discuss various in silico approaches to predict these features for a certain drug, estimate correlations with ADRs, establish causal relationships between selected features and ADR mechanisms and create corresponding predictive models.

Lagunin A.A., Druzhilovsky D.S., Rudik A.V., et al. Capacities of computer evaluation of hidden potential of phytochemicals of medicinal plants of the traditional Indian Ayurvedic medicine. *Biochemistry (Moscow) Supplement Series B: Biomedical Chemistry*, **2016**, 10 (1), 43–54.

Applicability of our computer programs PASS and PharmaExpert to prediction of biological activity spectra of rather complex and structurally diverse phytocomponents of medicinal plants, both separately and in combinations has been evaluated. The web-resource on phytochemicals of 50 medicinal plants used in Ayurveda was created for the study of hidden therapeutic potential of Traditional Indian Medicine (TIM) (http://ayurveda.pharmaexpert.ru). It contains information on 50 medicinal plants, their using in TIM and their pharmacology activities, also as 1906 phytocomponents. PASS training set was updated by addition of information about 946 natural compounds; then the training procedure and validation were performed, to estimate the quality of PASS prediction. It was shown that the difference between the average accuracy of prediction obtained in leave-5%-out cross-validation (94,467%) and in leave-one-out cross-validation (94,605%) is very small. These results showed high predictive ability of the program. Results of biological activity spectra prediction for all phytocomponents included in our database are in good correspondence with the experimental data. Additional kinds of biological activity predicted with high probability provide the information about most promising directions of further studies. The analysis of prediction results of sets of phytocomponents in each of 50 medicinal plants was made by PharmaExpert software. Based on this analysis, we found that the combination of phytocomponents from Passiflora incarnata may exhibit nootropic, anticonvulsant and antidepressant effects. Experiments carried out in mice models confirmed the predicted effects of Passiflora incarnata extracts.

Pahwa P., Goel R.K. Asparagus adscendens root extract enhances cognition and protects against scopolamine induced amnesia: An in-silico and in-vivo studies. *Chem. Biol. Interact.*, **2016**, 260: 208-218.

Asparagus adscendens Roxb. commonly known as safed musli and belonging to the Liliaceae family is cultivated mainly in Asian countries. In traditional medicine, safed musli is recommended as nerve tonic and remedy for memory impairment. The present study was aimed to evaluate nootropic and antiamnesic activities of Asparagus adscendens extract (AAE) using in silico and in vivo approach. Phytoconstituents of A. adscendens root reported in literature were subjected to in silico prediction using PASS and Pharmaexpert. The radial arm maze and passive shock avoidance paradigm were employed to evaluate nootropic activity. Subsequently, the anti-amnesic activity was evaluated in scopolamine induced amnesia model. To elucidate the mechanism of nootropic activity, the effect of AAE on the activities of acetylcholinesterase and antioxidant enzymes in the cortex and hippocampus of mice were also evaluated. In silico activity spectrum for all of A. adscendens phytoconstituents exhibited excellent prediction score for nootropic activity. Pretreatment with AAE (50, 100 & 200 mg/kg, i.p.) for 15 days showed significant decrease in working memory error, reference memory error and retrieval latency in radial arm maze and decrease in step down latency in passive shock avoidance paradigm were observed. Further, AAE significantly reduced acetylcholinesterase and oxidative stress parameters in cortex and hippocampus of mice. Thus, in silico and in vivo results suggest that A. adscendens root may exert its nootropic activity through both anti-acetylcholinesterase and antioxidant activities.

Gawande D.Y., Goel R.K. Pharmacological validation of in-silico guided novel nootropic potential of Achyranthes aspera L. *J. Ethnopharmacol.*, **2015**, 175: 324-334.

Ethnopharmacological relevance: Achyranthes aspera (A. aspera) has been used as a brain tonic in folk medicine. Although, ethnic use of medicinal plant has been basis for drug discovery from medicinal plants, but the available in-silico tools can be useful to find novel pharmacological uses of medicinal plants beyond their ethnic use.

Aim of the study: To validate in-silico prediction for novel nootropic effect of A. aspera by employing battery of tests in mice.

Material and methods: Phytoconstituents of A. aspera reported in Dictionary of Natural Product were subjected to in-silico prediction using PASS and Pharmaexpert. The nootropic activity predicted for A. aspera was assessed using radial arm maze, passive shock avoidance and novel object recognition tests in mice. After behavioral evaluation animals were decapitated and their brains were collected and stored for estimation of glutamate levels and acetylcholinesterase activity.

Results: In-silico activity spectrum for majority of A. aspera phytoconstituents exhibited excellent prediction score for nootropic activity of this plant. A. aspera extract treatment significantly improved the learning and memory as evident by decreased working memory

errors, reference memory errors and latency time in radial arm maze, step through latency in passive shock avoidance and increased recognition index in novel object recognition were observed, moreover significantly enhanced glutamate levels and reduced acetylcholinesterase activity in hippocampus and cortex were observed as compared to the saline treated group.
Conclusion: In-silico and in-vivo results suggest that A. aspera plant may improve the learning and memory by modulating the brain glutamatergic and cholinergic neurotransmission.

Goel R.K., Gawande D., Lagunin A., et al. Revealing Medicinal Plants That Are Useful for the Comprehensive Management of Epilepsy and Associated Comorbidities through In Silico Mining of Their Phytochemical Diversity. *Planta Med.*, **2015**, 81(6): 495-506.
In silico techniques in drug discovery may rationalise and speed up the identification of lead molecules from nature. Drug discovery from medicinal plants has mostly been confined to indications in accordance with their ethnical use only. However, the availability of multiple phytoconstituents in medicinal plants suggests that these may be much more useful beyond their traditional uses and in the management of chronic diseases, along with their comorbidities. In this study, the computer programmes PASS and PharmaExpert were used to reveal the medicinal plants useful in the comprehensive management of epilepsy and associated psychiatric disorders based on the pleiotropic effects predicted for their phytoconstituents. In silico analysis revealed that seven of 50 medicinal plants from traditional Indian medicine possessed the desired pleiotropic effect, i.e., anticonvulsant, antidepressant, and nootropic activities. The majority of phytoconstituents from Passiflora incarnata were concurrently predicted to have the desired pleiotropic effects. Therefore, P. incarnata was pharmacologically validated using the pentylenetetrazole kindling mouse model. Behavioural and neurochemical evaluations confirmed the ameliorative role of P. incarnata in epilepsy and the associated depression and memory deficit. The pharmacological findings from this study propose that PASS and PharmaExpert may serve as good tools for the optimisation of the selection of plants based on their phytoconstituents for the treatment of different ailments, even beyond their traditional use.

Lagunin A.A., Goel R.K., Gawande D.Y., et al. Chemo- and bioinformatics resources for in silico drug discovery from medicinal plants beyond their traditional use: a critical review. *Natural Product Reports*, **2014**, 31(11), 1585-1611.
In silico approaches have been widely recognised to be useful for drug discovery. Here, we consider the significance of available databases of medicinal plants and chemo- and bioinformatics tools for in silico drug discovery beyond the traditional use of folk medicines. This review contains a practical example of the application of combined chemo- and bioinformatics methods to study pleiotropic therapeutic effects (known and novel) of 50 medicinal plants from Traditional Indian Medicine.

Corominas-Faja B., Santangelo E., Cuyàs E., et al. Computer-aided discovery of biological activity spectra for anti-aging and anti-cancer olive oil oleuropeins. *Aging (Albany NY)*, **2014**, 6(9):731-741.
Aging is associated with common conditions, including cancer, diabetes, cardiovascular disease, and Alzheimer's disease. The type of multi-targeted pharmacological approach necessary to address a complex multifaceted disease such as aging might take advantage of pleiotropic natural polyphenols affecting a wide variety of biological processes. We have recently postulated that the secoiridoids oleuropein aglycone (OA) and decarboxymethyl oleuropein aglycone (DOA), two complex polyphenols present in health-promoting extra virgin olive oil (EVOO), might constitute a new family of plant-produced gerosuppressant agents. This paper describes an analysis of the biological activity spectra (BAS) of OA and DOA using PASS (Prediction of Activity Spectra for Substances) software. PASS can predict thousands of biological activities, as the BAS of a compound is an intrinsic property that is largely dependent on the compound's structure and reflects pharmacological effects, physiological and biochemical mechanisms of action, and specific toxicities. Using Pharmaexpert, a tool that analyzes the PASS-predicted BAS of substances based on thousands of "mechanism-effect" and "effect-mechanism" relationships, we illuminate hypothesis-generating pharmacological effects, mechanisms of action, and targets that might underlie the anti-aging/anti-cancer activities of the gerosuppressant EVOO oleuropeins.

Choudhary K.M., Mishra A., Poroikov V.V., Goel R.K. Ameliorative effect of Curcumin on seizure severity, depression like behavior, learning and memory deficit in post-pentylenetetrazole-kindled mice. *Eur. J. Pharmacol.*, **2013**, 704 (1-3), 33-40.
Epilepsy is a chronic neurological disorder and generally associated with certain psychiatric comorbidities. Among several comorbidities depressive behavior and cognitive impairment has been reported to be most debilitating comorbidity associated with epilepsy. This study was envisaged to evaluate the ameliorative effect of Curcumin on depression like behavior and cognitive impairment observed in pentylenetetrazole kindled animals. Male Swiss Albino mice were kindled with subconvulsive dose of pentylenetetrazole (35 mg/kg, i.p.). Successfully kindled animals were used in the study to observe the effect of different treatments. Treatment groups received phenytoin (30 mg/kg) and Curcumin (50, 100 and 200mg/kg) for 15 days. The animals were challenged with pentylenetetrazole (35 mg/kg, i.p.) on day 5, 10 and 15 and seizure severity score, immobility period, number of mistakes and step down latency were recorded. On 15th day, all the animals were sacrificed after behavioral evaluations and their brain was isolated and homogenized to estimate brain norepinephrine, serotonin, total nitrite level and acetylcholinesterase activity. Phenytoin treatment significantly improved the depressive like behavior along with its anticonvulsant effect, however was unable to improve memory impairment. Curcumin significantly attenuated seizure severity, depression like behavior and memory impairment in kindled animals, in dose dependent manner. These results were supported by the biochemical modulation of brain monoamine, nitrosative stress level and acetylcholinesterase activity. Thus present study concluded that Curcumin has the ameliorative effect on seizure severity, depression like behavior and memory impairment in pentylenetetrazole kindled mice, possibly via central monoaminergic modulation and inhibitory effect on nitrosative stress and acetylcholinesterase activity.

Kumar A., Lohan P., Aneja D.K., et al. Design, synthesis, computational and biological evaluation of some new hydrazino derivatives of DHA and pyranopyrazoles. *Eur. J. Med. Chem*., **2012**, 50: 81-89.
Two series of compounds namely, 4-aryl/heteroaryl hydrazino-3-acetyl-6-methyl-2H-pyran-2-ones (4a-4j) and pyrano[4,3-c]pyrazoles (6a-6e and 6g) were synthesized starting from 3-acetyl-4-chloro-6-methyl-2H-pyran-2-one (2). Estimation of pharmacotherapeutic potential, possible molecular mechanism of action, toxic/side effects and interaction with drug-metabolizing enzymes were made for the synthesized compounds on the basis of prediction of activity spectra for substances (PASS) prediction results and their analysis by PharmaExpert software. COX inhibition predicted by PASS was confirmed by experimental evaluation and validated via docking studies. Out of all the compounds, compounds 4h, 4j, 6e, 6g exhibited good anti-inflammatory activity, whereas compounds 4b, 4c, 4h, 4i, 4j, 6b, 6e, 6g showed excellent analgesic activity compared with standard drug Diclofenac sodium.

Lagunin A., Filimonov D., Poroikov V. Multi-targeted natural products evaluation based on biological activity prediction with PASS. *Curr. Pharm. Des*., **2010**, 16(15): 1703-1717.
Natural products found a wide use in folk medicine. Presently, when routine development of new drugs faced a considerable challenge, they become an inspiration and valuable source in drugs discovery. Rather complex and diverse chemical structures of natural compounds provide a basis for modulation of different biological targets. Natural compounds exhibit a multitargeted action that may lead to additive/synergistic or antagonistic effects. Rational design of more safe and potent pharmaceuticals requires an estimation of probable multiple actions of natural products. Our software PASS can perform such estimation. It predicts with reasonable accuracy over 3500 pharmacotherapeutic effects, mechanisms of action, interaction with the metabolic system, and specific toxicity for drug-like molecules on the basis of their structural formulae. We analyzed PASS predictions utilizing PharmaExpert, which performs selection of compounds with multiple mechanisms of action, analysis of activity-activity relationships and drug-drug interactions. The paper describes an application of PASS and PharmaExpert to the evaluation of biological activity of natural compounds including marine sponge alkaloids, triterpenoids of lupane group, and their derivatives. Proposed computer-aided methods can generate combinatorial libraries of macrolides. They help to select the most promising pharmaceutical leads with the required properties. Case study, based on the analysis of biological activity spectra predicted for St John's Wort constituents, clearly demonstrates capabilities of computational methods in the evaluation of multitargeted actions, additive/synergistic and/or antagonistic effects of natural products.

Geronikaki A.A., Lagunin A.A., Hadjipavlou-Litina D.I., et al. Computer-aided discovery of anti-inflammatory thiazolidinones with dual cyclooxygenase/lipoxygenase inhibition. *J. Med. Chem*., **2008**, 51(6): 1601-1609.
New anti-inflammatory agents possessing dual cyclooxygenase/lipoxygenase (COX/LOX) inhibition were discovered by computer-aided prediction of biological activity for 573 virtually designed chemical compounds. Prediction of biological activity was performed by PASS, and prediction results were analyzed with PharmaExpert software. Nine 2-(thiazole-2-ylamino)-5-phenylidene-4-thiazolidinone derivatives differing by the phenyl group substitution were selected for synthesis and experimental testing as potential COX/LOX inhibitors. Eight tested compounds exhibited anti-inflammatory activity in the carrageenin-induced paw edema. It was shown that seven tested compounds (77.8%) were LOX inhibitors, seven compounds were COX inhibitors (77.8%), and six tested compounds (66.7%) were dual COX/LOX inhibitors. Analysis of lipophilicity of the compounds showed a negative correlation with inhibition of edema formation. The binding modes of the most active compounds of this series (2-(thiazole-2-ylamino)-5-(m-chlorophenylidene)-4-thiazolidinone for COX-1 and COX-2, and 2-(thiazole-2-ylamino)-5-(m-nitrophenylidene)-4-thiazolidinone for 15-LOX) were proposed on the basis of docking studies.

Filz O., Lagunin A., Filimonov D., Poroikov V. Computer-aided prediction of QT-prolongation. *SAR QSAR Environ. Res*., **2008**, 19(1-2): 81-90.
Drug-induced cardiac arrhythmia is acknowledged as a serious obstacle in successful development of new drugs. Several methods for in silico prediction of acquired long QT syndrome (LQTS) caused by the pharmacological blockade of human hERG K+ channels are discussed in literature. We propose to use the computer program PASS, which estimates the probabilities of about 3000 biological activities, not only for prediction of hERG blockade and QT-prolongation but also for the analysis of indirect mechanisms of these actions. After addition in the PASS training set of 163 compounds with data on QT-Prolongation and re-training, it was shown that accuracy of prediction was 87.1% and 81.8% for hERG blockade and QT-prolongation, respectively. Using computer program PharmaExpert we found that in the predicted biological activity spectra there was a certain correlation between the hERG blockade and some other molecular mechanisms of action. Possible role of 1-phosphatidylinositol-4-phospate 5-kinase, dimethylargininase and progesterone 11 alpha-monooxygenase inhibition in hERG blockade was discussed.

Benaamane N., Nedjar-Kolli B., Bentarzi Y., et al. Synthesis and in silico biological activity evaluation of new N-substituted pyrazolo-oxazin-2-one systems. *Bioorg. Med. Chem*., **2008**, 16(6):3059-3066.
Cyclisation of pyrazolo-beta-enaminones 3 readily obtained from 4-aceto acetyl pyrazol 2 with triphosgene led to the formation of N-substituted pyrazolo-1,3-oxazin-2-ones 4 in good yields. Estimation of pharmacotherapeutic potential, possible molecule mechanisms of action, toxic/side effects and interaction with drug-metabolizing enzymes were made for synthesised compounds on the basis of prediction of activity spectra for substances (PASS) prediction results and their analysis by PharmaExpert software. COX inhibition predicted by PASS was confirmed by experimental evaluation.

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