

Selected references on PASS bioactivity predictions

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 phytochemicals 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 cure. 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 phytochemicals 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 phytochemicals 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 phytochemicals. 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.

Chauhan L.K., Chopra J., Vanangamudi M., et al. Hydroxytriazenes incorporating sulphonamide derivatives: evaluation of antidiabetic, antioxidant, anti-inflammatory activities, and computational study. *Mol. Divers.*, **2022** Apr 12. doi: 10.1007/s11030-022-10420-w. Epub ahead of print.

The existent investigation deals with synthesis, characterization, computational analysis, and biological activities of some hydroxytriazene derivatives containing sulphonamide moiety. The compounds were screened for antidiabetic, antioxidant, and anti-inflammatory activities. The antidiabetic activity was assessed using α -glucosidase and α -amylase inhibition assays with IC₅₀ values ranging from 32.0 to 759.13 μ g/mL and 157.77 to 340.47 μ g/mL while standard drug acarbose showed IC₅₀ values 12.21 and 69.74 μ g/mL, respectively. The antioxidant activity was evaluated using DPPH and ABTS radical scavenging assays with IC₅₀ value ranging from 54.01 to 912.66 μ g/mL and 33.22 to 128.11 μ g/mL, and standard drug ascorbic acid showed IC₅₀ values 29.12 μ g/mL and 69.13 μ g/mL, respectively. Anti-inflammatory activity was investigated using the carrageenan-induced paw edema method, where percentage inhibition was up to 93.0 and 98.57 for 2 h and 4 h, respectively, and all the compounds were found to exhibit excellent anti-inflammatory activity. Moreover, prediction of activity spectra for substance and molecular docking were also performed. The PASS prediction hypothesized the potential of the compounds for anti-inflammatory activity, and docking results suggested the best binding pose for compounds 1b and 2b with the least energy value from which compounds can be considered as potent COX-2 inhibitors. Furthermore, possible interactions between hydroxytriazene analogues and the targets of antioxidant NADPH oxidase and antidiabetic human maltase-glucoamylase enzyme have been identified. The HOMO and LUMO analysis revealed charge transfer within the compounds. These findings suggested that the synthesized compounds can be potential agents for the treatment of diabetes and inflammation.

Medvedeva S.M., Shikhaliev K.S., Geronikaki A.A., et al. Computer-aided discovery of pleiotropic effects: Anti-inflammatory action of dithioloquinolinethiones as a case study. *SAR QSAR Environ. Res.*, **2022**, 33(4): 273-287.

Most of pharmaceutical agents exhibit several or even many biological activities. It is clear that testing even one compound for thousands of biological activities is a practically not feasible task. Therefore, computer-aided prediction is the method-of-the-choice to select the most promising bioassays for particular compounds. Using PASS Online software, we determined the likely anti-inflammatory action of the 13 dithioloquinolinethione derivatives with antimicrobial activities. Chemical similarity search in the Cortellis Drug Discovery Intelligence database did not reveal close structural analogues with anti-inflammatory action. Experimental testing of anti-inflammatory activity of the synthesized compounds in carrageenan-induced inflammation mouse model confirmed the computational predictions. The anti-inflammatory activity of the studied compounds was comparable with or higher than the reference drug Indomethacin. Thus, based on the in silico predictions, novel class of the anti-inflammatory agents was discovered.

Linani A., Benarous K., Bou-Salah L., Yousfi M. The inhibitory kinetics of vitamins B9, C, E, and D3 on bovine xanthine oxidase: Gout treatment. *Chem. Biol. Interact.*, **2022**, 359: 109922.

Background: Over-consumption of foods high in purines like seafood, red meat, and alcoholic beverages leads to hyperuricemia causing gout attacks. Xanthine oxidase was reported responsible for the overproduction of uric acid.

Material and methods: We intend to test in silico and in vitro, the inhibition effect of four vitamins against bovine milk xanthine oxidase (BXO). We performed Molecular docking with GOLD v4.0, and the biological activity prediction with the PASS server. The best-selected vitamins were chosen based on their best PLPchem score. The BXO constant K_m and V_{max} were determined in vitro, and then the vitamins were tested for their inhibition effect to BXO. Furthermore, the inhibition constant K_i of each inhibitor were determined using Dixon method, the vitamins chosen were vitamin E, vitamin B9, vitamin D3, and vitamin C.

Results: The in silico results show that the tested vitamins were the best inhibitors model with PLPchem scores up to 70 comparing to the control. The in vitro results show that BXO have a K_m value of 163.55 μM with V_{max} of 37 U, vitamins B9, E, C, and D3 were potent inhibitors to BXO with an IC_{50} of 34.10 ± 0.21 , 36.68 ± 1.50 , 39.01 ± 0.02 , and 100.28 ± 0.33 μM , respectively comparing to the control (32.03 ± 0.73 μM). The kinetic study shows that all tested vitamins were Non-competitive inhibitors, the K_i values were 15 ± 1.76 μM , 29 ± 1.06 μM , 12 ± 1.41 μM , and 20 ± 0.71 μM , for respectively vitamins B9, E, C, and D3.

Conclusion: The obtained results promise an excellent strategy using vitamins to enhance immunity, treat hyperuricemia, and minimize the usual drug side effects.

Foudah A.I., Alqarni M.H., Alam A., et al. Phytochemical Screening, In Vitro and In Silico Studies of Volatile Compounds from *Petroselinum crispum* (Mill) Leaves Grown in Saudi Arabia. *Molecules*, **2022**, 27(3): 934.

The herbal plant *Petroselinum crispum* (*P. crispum*) (Mill) is commonly available around the world. In this study, the leaves of the herbal plant *P. crispum* were collected from the central region of Al-Kharj, Saudi Arabia, to explore their in vitro pharmacological activity. Essential oil from the leaves of *P. crispum* was isolated using the hydrodistillation method. The composition of *P. crispum* essential oil (PCEO) was determined using Gas chromatography-mass spectrometry (GC-MS). A total of 67 components were identified, representing approximately 96.02% of the total volatile composition. Myristicin was identified as the principal constituent (41.45%). The in vitro biological activity was assessed to evaluate the antioxidant, antimicrobial, and anti-inflammatory potential of PCEO. PCEO showed the highest antimicrobial activity against *Candida albicans* and *Staphylococcus aureus* among all the evaluated microbial species. In vitro anti-inflammatory evaluation using albumin and trypsin assays showed the excellent anti-inflammatory potential of PCEO compared to the standard drugs. An in silico study of the primary PCEO compound was conducted using online tools such as PASS, Swiss ADME, and Molecular docking. In silico PASS prediction results supported our in vitro findings. Swiss ADME revealed the drug likeness and safety properties of the major metabolites present in PCEO. Molecular docking results were obtained by studying the interaction of Myristicin with an antifungal (PDB: 1IYL and 3LD6), antibacterial (PDB: 1AJ6 and 1JIJ), antioxidant (PDB: 3NM8 and 1HD2), and anti-inflammatory (3N8Y and 3LN1) receptors supported the in vitro results. Therefore, PCEO or Myristicin might be valuable for developing anti-inflammatory and antimicrobial drugs.

Cruz-Salomón K.D.C., Cruz-Rodríguez R.I., Espinosa-Juárez J.V., et al. In Vivo and In Silico Study of the Antinociceptive and Toxicological Effect of the Extracts of *Petiveria alliacea* L. Leaves. *Pharmaceuticals (Basel)*, **2022**, 15(8): 943.

Petiveria alliacea L. is an herb used in traditional medicine in Mexico and its roots have been studied to treat pain. However, until now, the antinociceptive properties of the leaves have not been investigated, being the main section used empirically for the treatment of diseases. For this reason, this study aimed to evaluate the antinociceptive and toxicological activity of various extracts (aqueous, hexanic, and methanolic) from *P. alliacea* L. leaves in NIH mice and to perform an in silico analysis of the phytochemical compounds. Firstly, the antinociceptive effect was analyzed using the formalin model and the different doses of each of the extracts that were administered orally to obtain the dose-response curves. In addition, acute toxicity was determined by the up and down method and serum biochemical analysis. Later, the phytochemical study of extracts was carried out by thin layer chromatography (TLC) and visible light spectroscopy, and the volatile chemical components were analyzed by gas chromatography-mass spectrometry (GC/MS). Moreover, the most abundant compounds identified in the phytochemical study were analyzed in silico to predict their biological activity (PASSonline) and toxicology (OSIRIS Property Explorer). As a result, it was known that all extracts at doses from 10 to 316 mg/kg significantly reduced the pain response in both phases of the formalin model, with values of 50-60% for the inflammatory response. The toxicological studies (DL50) exhibited that all extracts did not cause any mortality up to the 2000 mg/kg dose level. This was corroborated by the values in the normal range of the biochemical parameters in the serum. Finally, the phytochemical screening of the presence of phenolic structures (coumarins, flavonoids) and terpenes (saponins and terpenes) was verified, and the highest content was of a lipid nature, 1.65 ± 0.54 meq diosgenin/mL in the methanolic extract. A total of 54 components were identified, 11 were the most abundant, and only four (Eicosane, Methyl oleate, 4-bis(1-phenylethyl) phenol, and Ethyl linolenate) of them showed a probability towards active antinociceptive activity in silico greater than 0.5. These results showed that the *P. alliacea* L. leaf extract possesses molecules with antinociceptive activity.

Shah S.T., Chowdhury Z.Z., Johan M.R., et al. Design and Synthesis of Multipotent Antioxidants for Functionalization of Iron Oxide Nanoparticles. *Coatings*. **2022**, 12(4): 517.

Multipotent antioxidants (MPAO) were synthesized and characterized by FTIR, NMR. The functionalized nanoparticles (IONP@AO) were characterized by FTIR, XRD, Raman, HRTEM, FESEM, VSM, and EDX. IONP@AO1 and IONP@AO2 have average particles size of 10 nm and 11 nm, respectively. The functionalized IONP@AO has a superparamagnetic nature, with saturation magnetization of $45 \text{ emu} \cdot \text{g}^{-1}$. Structure-based virtual screening of the designed MPAO was performed by PASS analysis and ADMET studies to discover and predict the molecule's potential bioactivities and safety profile before the synthesis procedure. The half-maximal inhibitory concentration (IC_{50}) of DPPH analysis results showed a four-fold decrease in radical scavenging by IONP@AO compared to IONP. In addition to antioxidant activity, IONP@AO showed suitable antimicrobial activities when tested on various bacterial and fungal strains. The advantage of the developed nanoantioxidants is that they have a strong affinity towards biomolecules such as enzymes, proteins,

amino acids, and DNA. Thus, synthesized nanoantioxidants can be used to develop biomedicines that can act as antioxidant, antimicrobial, and anticancer agents.

Nasrin S., Islam M.N., Tayab M.A., et al. Chemical profiles and pharmacological insights of *Anisomeles indica* Kuntze: An experimental chemico-biological interaction. *Biomed. Pharmacother.*, **2022**, 149: 112842.

Anisomeles indica (L.) Kuntze is an ethnomedicinally important plant that has long been used in traditional medicine to treat a variety of ailments, including dyspepsia, abdominal pain, colic, allergies, inflammation, and rheumatic arthritis. However, the scientific framework underlying these medicinal properties is not well known. This study aimed to investigate the antidepressive, antidiarrheal, thrombolytic, and anti-inflammatory potential of a methanol extract of *A. indica* (MeOH-AI). The potential bioactive compounds in the MeOH-AI were identified using gas chromatography-mass spectrometry (GC-MS), and antidepressant activities were evaluated using the tail suspension test (TST) and forced swim test (FST). Antidiarrheal effects were also assayed in castor oil-induced diarrhea and gastrointestinal motility studies. The anti-inflammatory activities were explored by examining the effects on protein inhibition and denaturation in heat- and hypotonic solution-induced hemolysis assays. The thrombolytic activity was evaluated using the clot lysis test in human blood. BIOVIA and Schrödinger Maestro (v11.1) were applied for docking analysis to determine binding interactions, and the absorption, distribution, metabolisms, excretion/toxicity (ADME/T) properties of bioactive compounds were explored using a web-based method. The GC-MS analysis of MeOH-AI revealed the presence of several bioactive compounds. MeOH-AI administration resulted in significant ($p < 0.01$) reductions in the immobility times for both the FST and TST compared with those in the control group. MeOH-AI also induced significant ($p < 0.01$) reductions in castor oil-induced diarrhea severity and gastrointestinal motility in a mouse model. In addition, the in vitro anti-inflammatory and thrombolytic activity studies produced remarkable responses. The binding assay showed that 4-dehydroxy-N-(4,5-methylenedioxy-2-nitrobenzylidene) tyramine interacts favorably with monoamine oxidase and serotonin and M3 muscarinic acetylcholine receptors, displaying good pharmacokinetic properties, which may mediate the effects of MeOH-AI on depression and diarrhea. Overall, the research findings indicated that MeOH-AI has significant antidepressant, antidiarrheal, and anti-inflammatory effects and may represent an alternative source of novel therapeutic factors.

Alghamdi S.S., Suliman R.S., Alsaeed A.S., et al. Novel Anti-Tubulin Compounds from *Trigonella foenum-graecum* Seeds; Insights into In-vitro and Molecular Docking Studies. *Drug Des. Devel. Ther.*, **2021**, 15: 4195-4211.

Background: Fenugreek, also known as *Trigonella foenum-graecum* L, is a natural plant that belongs to the Fabaceae family and has been known as a promising source of bioactive compounds. It has been widely used as traditional medicine since it has shown to lower blood glucose, manage cholesterol levels and further aid in the prevention and treatment of cancer. Herein, we aim to evaluate the anticancer activity of methanolic fenugreek seed extract against several cancer cell lines.

Methods: We sought to investigate the phytochemical classes present in multiple fenugreek seeds extracts using HPLC-DAD followed by LC/MS, predict and investigate anticancer activity using PASS online webserver, the CellTiter-Glo assay, evaluate ADME properties, and perform molecular docking for all bioactive compounds via Maestro software.

Results: Multiple extracts exhibited distinct phytochemical classes that demonstrated different biological activities. Fenugreek methanolic extract contains flavonoid chemical class, which showed the highest anticancer activity against the HCT8 cell line of colorectal cancer (IC₅₀ of 8.83 µg/mL), followed by KAIMRC1 breast cancer cell line (IC₅₀ of 35.06 µg/mL), HL60 leukemia cell line (37.80 µg/mL), MDA-MB-231 breast cancer cell line (38.51 µg/mL), and lastly, HCT116 colorectal cancer cell line with IC₅₀ of 56.03 µg/mL. In contrast, the chloroform extract was inactive. The molecular docking study for all the bioactive compounds suggested that flavonoids F6 (-9.713 and -12.132), F7 (-10.166 and -12.411), and F11 (-10.084 and -13.516) possess the highest docking scores through SP and XP scores, respectively.

Conclusion: The obtained results confirm that the bioactive compounds present in fenugreek seeds exhibit anticancer activity against several cancer cells that can mediate via tubulin polymerization inhibition. Although our study has evaluated the anticancer potential of *Trigonella foenum-graecum* as a promising natural source for new anticancer agents, fenugreek biological activity needs further research and investigations on their mechanism of action and toxicity profile.

Iskusnykh I.Y., Kryl'skii E.D., Brazhnikova D.A., et al. Novel Antioxidant, Deethylated Ethoxyquin, Protects against Carbon Tetrachloride Induced Hepatotoxicity in Rats by Inhibiting NLRP3 Inflammasome Activation and Apoptosis. *Antioxidants (Basel)*, **2021**, 10(1): 122.

Inflammation and an increase in antioxidant responses mediated by oxidative stress play an important role in the pathogenesis of acute liver injury (ALI). We utilized in silico prediction of biological activity spectra for substances (PASS) analysis to estimate the potential biological activity profile of deethylated ethoxyquin (DEQ) and hypothesized that DEQ exhibits antioxidant and anti-inflammatory effects in a rat model of carbon tetrachloride (CCl₄)-induced ALI. Our results demonstrate that DEQ improved liver function which was indicated by the reduction of histopathological liver changes. Treatment with DEQ reduced CCl₄-induced elevation of gene expression, and the activity of antioxidant enzymes (AEs), as well as the expression of transcription factors Nfe2l2 and Nfkb2. Furthermore, DEQ treatment inhibited apoptosis, downregulated gene expression of pro-inflammatory cytokines (Tnf and Il6), cyclooxygenase 2 (Ptgs2), decreased glutathione (GSH) level and myeloperoxidase (MPO) activity in rats with ALI. Notably, DEQ treatment led to an inhibition of CCl₄-induced NLRP3-inflammasome activation which was indicated by the reduced protein expression of IL-1β, caspase-1, and NLRP3 in the liver. Our data suggest that DEQ has a hepatoprotective effect mediated by redox-homeostasis regulation, NLRP3 inflammasome, and apoptosis inhibition, which makes that compound a promising candidate for future clinical studies.

Tratrat C., Haroun M., Papisva A., et al. New Substituted 5-Benzylideno-2-Adamantylthiazol[3,2-b][1,2,4]Triazol-6(5H)ones as Possible Anti-Inflammatory Agents. *Molecules*, **2021**, 26(3): 659.

Background: Inflammation is a complex response to noxious stimuli promoted by the release of chemical mediators from the damaged

cells. Metabolic products of arachidonic acid, produced by the action of cyclooxygenase and lipoxygenase, play important roles in this process. Several non-steroidal anti-inflammatory drugs act as cyclooxygenase inhibitors. However, almost all of them have undesired side effects.

Methods: Prediction of the anti-inflammatory action of the compounds was performed using PASS Program. The anti-inflammatory activity was evaluated by the carrageenan paw edema test. COX and LOX inhibitory actions were tested using ovine COX-1, human recombinant COX-2 and soybean LOX-1, respectively. Docking analysis was performed using Autodock.

Results: All designed derivatives had good prediction results according to PASS and were synthesized and experimentally evaluated. The compounds exhibited *in vivo* anti-inflammatory action with eleven being equal or better than indomethacin. Although, some of them had no or low inhibitory effect on COX-1/2 or LOX, certain compounds exhibited COX-1 inhibition much higher than naproxen and COX-2 inhibition, well explained by Docking analysis.

Conclusions: A number of compounds with good anti-inflammatory action were obtained. Although, some exhibited remarkable COX inhibitory action this activity did not follow the anti-inflammatory results, indicating the implication of other mechanisms.

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. *Molecular Informatics*, **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.

Emon N.U., Alam S., Rudra S., et al. Antidepressant, anxiolytic, antipyretic, and thrombolytic profiling of methanol extract of the aerial part of *Piper nigrum*: In vivo, in vitro, and in silico approaches. *Food Sci. Nutr.*, **2021**, 9(2): 833-846.

Piper nigrum L. also called black pepper is popular for its numerous uses. The present research is designed to investigate the pharmacological potential of methanol extract of *Piper nigrum* (MEPN). The antidepressant investigation was performed by using both *in vivo* forced swimming test (FST) and tail suspension test (TST) methods while the anxiolytic research by hole-board test (HBT) method. Again, the antipyretic analysis was conducted through yeast-induced pyrexia method, whereas clot lysis activity was employed by the thrombolytic method. Furthermore, *in silico* studies followed by molecular docking analysis of several secondary metabolites, pass prediction, and ADME/T were evaluated with AutoDock Vina, Discovery Studio 2020, UCSF Chimera software PASS online, and ADME/T online tools. The plant extract demonstrated dose-dependent potentiality in antidepressant, anxiolytic, antipyretic, and thrombolytic activities. Induction of MEPN produced a significant ($p < .5$, $p < .001$) increase of mobility in FST and TST, and increased the head dipping and decreased the latency of time ($p < .01$, $p < .001$) in HBT. MEPN 400 (mg/kg; b.w.; p.o.) lowered the rectal temperature of yeast-induced pyrexia substantially ($p < .001$). Besides, MEPN produced promising ($p < .001$) clot lysis activity. In the computational approach, among all the proteins, a docking score was found ranging from -1.0 to -7.90 kcal/mol. Besides, all the compounds were found safe in ADME/T study. The results of our scientific research validate the suitability of this plant as an alternative source of novel therapeutics.

Sarapultsev A., Vassiliev P., Grinchii D., et al. Combined In Silico, Ex Vivo, and In Vivo Assessment of L-17, a Thiadiazine Derivative with Putative Neuro- and Cardioprotective and Antidepressant Effects. *Int. J. Mol. Sci.*, **2021**, 22(24): 13626.

Depression associated with poor general medical condition, such as post-stroke (PSD) or post-myocardial infarction (PMID) depression, is characterized by resistance to classical antidepressants. Special treatment strategies should thus be developed for these conditions. Our study aims to investigate the mechanism of action of 2-morpholino-5-phenyl-6H-1,3,4-thiadiazine, hydrobromide (L-17), a recently designed thiadiazine derivative with putative neuro- and cardioprotective and antidepressant-like effects, using combined *in silico* (for prediction of the molecular binding mechanisms), *ex vivo* (for assessment of the neural excitability using c-Fos immunocytochemistry), and *in vivo* (for direct examination of the neuronal excitability) methodological approaches. We found that the predicted binding affinities of L-17 to serotonin (5-HT) transporter (SERT) and 5-HT₃ and 5-HT_{1A} receptors are compatible with selective 5-HT serotonin reuptake inhibitors (SSRIs) and antagonists of 5-HT₃ and 5-HT_{1A} receptors, respectively. L-17 robustly increased c-Fos immunoreactivity in the amygdala and decreased it in the hippocampus. L-17 dose-dependently inhibited 5-HT neurons of the dorsal raphe nucleus; this inhibition was partially reversed by the 5-HT_{1A} antagonist WAY100135. We suggest that L-17 is a potent 5-HT reuptake inhibitor and partial antagonist of 5-HT₃ and 5-HT_{1A} receptors; the effects of L-17 on amygdaloid and hippocampal excitability might be mediated via 5-HT, and putatively mediate the antidepressant-like effects of this drug. Since L-17 also possesses neuro- and cardioprotective properties, it can be beneficial in PSD and PMID. Combined *in silico* predictions with *ex vivo* neurochemical and *in vivo* electrophysiological assessments might be a useful strategy for early assessment of the efficacy and neural mechanism of action of novel CNS drugs.

Muratov E.N., Bajorath J., Sheridan R.P., Tetko I.V., Filimonov D., Poroikov V., Oprea T.I., Baskin I.I., Varnek A., Roitberg A., Isayev O., Curtarolo S., Fourches D., Cohen Y., Aspuru-Guzik A., Winkler D.A., Agrafiotis D., Cherkasov A., Tropsha A. QSAR without borders. *Chemical Society Reviews*, **2020**, 49, 3525-3564.

Multi-target profiling of compounds has led to the concept of the biological activity spectrum, defined as the set of different biological activities resulting from the compound interaction with different biological systems. It therefore represents an “intrinsic” property of the compound that depends only on its chemical structure. Several approaches for multi-target modeling have been proposed. One of the earliest developments in this area was the computer program PASS (prediction of activity spectra for substances) reported by Filimonov et al. almost 30 years ago. PASS employs a uniform set of multilevel neighborhoods of atoms (MNA) molecular descriptors and a Naive Bayes classifier to model structure–activity relationships across a wide variety of biological assays. This approach allows the prediction of a wide range of biological activities at molecular, cellular, organ/tissue and organism levels. It can predict pharmacotherapeutic effects, mechanisms of action, specific toxicities, terms related to drug metabolism, gene expression, etc. The current version of PASS predicts several thousand biological activities based on the analysis of structure–activity relationships in the training set of over one million biologically active compounds.

Bender A., Cortés-Ciriano I. Artificial intelligence in drug discovery: what is realistic, what are illusions? Part 1: Ways to make an impact, and why we are not there yet. *Drug Discovery Today*, **2020**, 26 (2), 511-524.

In silico target prediction have been active areas of interest for decades, starting with Prediction of Activity Spectra for Substances (PASS).

Amiranashvili L., Nadaraia N., Merlani M., et al. Antimicrobial Activity of Nitrogen-Containing 5-Alpha-androstane Derivatives: In Silico and Experimental Studies. *Antibiotics (Basel)*, **2020**, 9(5): 224.

We evaluated the antimicrobial activity of thirty-one nitrogen-containing 5-alpha-androstane derivatives in silico using computer program PASS (Prediction of Activity Spectra for Substances) and freely available PASS-based web applications (www.way2drug.com). Antibacterial activity was predicted for 27 out of 31 molecules; antifungal activity was predicted for 25 out of 31 compounds. The results of experiments, which we conducted to study the antimicrobial activity, are in agreement with the predictions. All compounds were found to be active with MIC (Minimum Inhibitory Concentration) and MBC (Minimum Bactericidal Concentration) values in the range of 0.0005-0.6 mg/mL. The activity of all studied 5-alpha-androstane derivatives exceeded or was equal to those of Streptomycin and, except for the 3β-hydroxy-17α-aza-d-homo-5α-androstane-17-one, all molecules were more active than Ampicillin. Activity against the resistant strains of *E. coli*, *P. aeruginosa*, and methicillin-resistant *Staphylococcus aureus* was also shown in experiments. Antifungal activity was determined with MIC and MFC (Minimum Fungicidal Concentration) values varying from 0.007 to 0.6 mg/mL. Most of the compounds were found to be more potent than the reference drugs Bifonazole and Ketoconazole. According to the results of docking studies, the putative targets for antibacterial and antifungal activity are UDP-N-acetylenolpyruvoylglucosamine reductase and 14-alpha demethylase, respectively. In silico assessments of the acute rodent toxicity and cytotoxicity obtained using GUSAR (General Unrestricted Structure-Activity Relationships) and CLC-Pred (Cell Line Cytotoxicity Predictor) web-services were low for the majority of compounds under study, which contributes to the chances for those compounds to advance in the development.

Lloyd K., Papoutsopoulou S., Smith E., et al. Using systems medicine to identify a therapeutic agent with potential for repurposing in inflammatory bowel disease. *Dis. Model. Mech.*, **2020**, 13(11): dmm044040.

Inflammatory bowel diseases (IBDs) cause significant morbidity and mortality. Aberrant NF-κB signalling is strongly associated with these conditions, and several established drugs influence the NF-κB signalling network to exert their effect. This study aimed to identify drugs that alter NF-κB signalling and could be repositioned for use in IBD. The SysmedIBD Consortium established a novel drug-repurposing pipeline based on a combination of in silico drug discovery and biological assays targeted at demonstrating an impact on NF-κB signalling, and a murine model of IBD. The drug discovery algorithm identified several drugs already established in IBD, including corticosteroids. The highest-ranked drug was the macrolide antibiotic clarithromycin, which has previously been reported to have anti-inflammatory effects in aseptic conditions. The effects of clarithromycin effects were validated in several experiments: it influenced NF-κB-mediated transcription in murine peritoneal macrophages and intestinal enteroids; it suppressed NF-κB protein shuttling in murine reporter enteroids; it suppressed NF-κB (p65) DNA binding in the small intestine of mice exposed to lipopolysaccharide; and it reduced the severity of dextran sulphate sodium-induced colitis in C57BL/6 mice. Clarithromycin also suppressed NF-κB (p65) nuclear translocation in human intestinal enteroids. These findings demonstrate that in silico drug repositioning algorithms can viably be allied to laboratory validation assays in the context of IBD, and that further clinical assessment of clarithromycin in the management of IBD is required. This article has an associated First Person interview with the joint first authors of the paper.

Abozeid M. A. , El-Sawi A. A. , Abdelmoteleb M., et al. Synthesis of novel naphthalene-heterocycle hybrids with potent antitumor, anti-inflammatory and antituberculosis activities. *RSC Adv.*, **2020**, 10(70): 42998–43009. Multitarget-directed drugs (hybrid drugs) constitute an efficient avenue for the treatment of multifactorial diseases. In this work, novel naphthalene hybrids with different heterocyclic scaffolds such as nicotinonitrile, pyran, pyranopyrazole, pyrazole, pyrazolopyridine, and azepine were efficiently synthesized via tandem reactions of 3-formyl-4H-benzo[h]chromen-4-one 1 with different nucleophilic reagents. Analysis of these hybrids using PASS online software indicated different predicted biological activities such as anticancer, antimicrobial, antiviral, antiprotozoal, anti-inflammatory, etc. By focusing on antitumor, anti-inflammatory, and antituberculosis activities, many compounds revealed remarkable activities. While 3c, 3e, and 3h were more potent than doxorubicin in the case of HepG-2 cell lines, 3a–e, 3i, 6, 8, 10, 11, and 12b were more potent in the case of MCF-7. Moreover, compounds 3c, 3h, 8, 10, 3d, and 12b manifested superior

activity and COX-2 selectivity to the reference anti-inflammatory Celecoxib. Regarding antituberculosis activity, 3c, 3d, and 3i were found to be the most promising with MIC less than 1 µg mL⁻¹. The molecular docking studies showed strong polar and hydrophobic interactions with the novel naphthalene-heterocycle hybrids that were compatible with experimental evaluations to a great extent.

Petrou A., Eleftheriou P., Geronikaki A., et al. Novel Thiazolidin-4-ones as Potential Non-nucleoside Inhibitors of HIV-1 Reverse Transcriptase. *Molecules*, **2019**, 24(21): 3821.

Background: HIV is the causative agent of Acquired Immunodeficiency Syndrome (AIDS), an infectious disease with increasing incidence worldwide. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) play an important role in the treatment of AIDS. Although, many compounds are already being used as anti-HIV drugs, research for the development of new inhibitors continues as the virus develops resistant strains.

Methods: The best features of available NNRTIs were taken into account for the design of novel inhibitors. PASS (Prediction of activity spectra for substances) prediction program and molecular docking studies for the selection of designed compounds were used for the synthesis. Compounds were synthesized using conventional and microwave irradiation methods and HIV RT inhibitory action was evaluated by colorimetric photometric immunoassay.

Results: The evaluation of HIV-1 RT inhibitory activity revealed that seven compounds have significantly lower IC₅₀ values than nevirapine (0.3 µM). It was observed that the activity of compounds depends not only on the nature of substituent and its position in benzothiazole ring but also on the nature and position of substituents in benzene ring.

Conclusion: Twenty four of the tested compounds exhibited inhibitory action lower than 4 µM. Seven of them showed better activity than nevirapine, while three of the compounds exhibited IC₅₀ values lower than 5 nM. Two compounds 9 and 10 exhibited very good inhibitory activity with IC₅₀ 1 nM.

Tratrat C. Novel Thiazole-Based Thiazolidinones as Potent Anti-infective Agents: *In silico* PASS and Toxicity Prediction, Synthesis, Biological Evaluation and Molecular Modelling. *Comb. Chem. High Throughput Screen.*, **2020**, 23(2): 126-140.

Aims and objective: The infectious disease treatment remains a challenging concern owing to the increasing number of pathogenic microorganisms associated with resistance to multiple drugs. A promising approach for combating microbial infection is to combine two or more known bioactive heterocyclic pharmacophores in one molecular platform. Herein, the synthesis and biological evaluation of novel thiazole-thiazolidinone hybrids as potential antimicrobial agents were dissimulated.

Materials and methods: The preparation of the substituted 5-benzylidene-2-thiazolyimino-4- thiazolidinones was achieved in three steps from 2-amino-5-methylthiazoline. All the compounds have been screened in PASS antibacterial activity prediction and in a panel of bacteria and fungi strains. Minimum inhibitory concentration and minimum bacterial concentration were both determined by microdilution assays. Molecular modeling was conducted using Accelrys Discovery Studio 4.0 client. ToxPredict (OPEN TOX) and ProTox were used to estimate the toxicity of the title compounds.

Results: PASS prediction revealed the potential antibacterial property of the designed thiazolethiazolidinone hybrids. All tested compounds were found to kill and to inhibit the growth of a vast variety of bacteria and fungi, and were more potent than the commercial drugs, streptomycin, ampicillin, bifomazole and ketoconazole. Further, *in silico* study was carried out for prospective molecular target identification and revealed favorable interaction with the target enzymes E. coli MurB and CYP51B of *Aspergillus fumigatus*. Toxicity prediction revealed that none of the active compounds was found toxic.

Conclusion: Substituted 5-benzylidene-2-thiazolyimino-4-thiazolidinones, endowing remarkable antibacterial and antifungal properties, were identified as a novel class of antimicrobial agents and may find a potential therapeutic use to eradicate infectious diseases.

Joshi S.V., Patel E.P., Vyas B.A., et al. Repurposing of Iloperidone: Antihypertensive and ocular hypotensive activity in animals. *Eur. J. Pharm. Sci.*, **2020**, 143: 105173.

Purpose: Iloperidone, second generation antipsychotic drug, reported in clinical trial to produce orthostatic hypotension as side effect. It was claimed to be antagonistic at alpha adrenergic receptor in central nervous system. We evaluated effect of Iloperidone on peripheral alpha 1 adrenoceptor by *in silico* and *in vitro* methods while *in vivo* hypotensive, antihypertensive and ocular hypotensive activity was evaluated in animals.

Methods: Pharmacological activity prediction of Iloperidone was done using PASSOnline and SwissTargetPrediction softwares and molecular docking with Alpha 1A adrenoceptor using AutoDock Vina. Hypotensive activity in normotensive and antihypertensive activity against DOCA-salt induced hypertension in rats were evaluated at doses 0.03 mg/Kg and 0.1 mg/Kg, *i.p.* of Iloperidone. Blood pressure was measured by invasive blood pressure measurement technique using PowerLab 4/30 and intraocular pressure was measured using digital tonometer.

Results: Iloperidone (0.1 mg/Kg) showed significant decrease in blood pressure (38.96 ± 1.1%) in normotensive rats, while in DOCA salt induced hypertensive rats, systolic blood pressure was found to be decreased by 29.04 ± 1.45% and 31.43 ± 1.21% in 0.03 mg/Kg and 0.1 mg/Kg treated rats respectively. Iloperidone prevented rise in systolic BP with adrenaline. Intraocular pressure was found to be decreased by 36.66 ± 3.15% in rabbits after 1 h of instillation of 0.1% Iloperidone.

Conclusion: Iloperidone exerted hypotensive and/or anti-hypertensive activity in rats and ocular hypotensive activity in rabbits.

Al-Madhagi W.M., Hashim N.M., Awadh Ali N.A., et al. Bioassay-Guided Isolation and *In Silico* Study of Antibacterial Compounds From Petroleum Ether Extract of *Peperomia blanda* (Jacq.) Kunth. *J. Chem Inf. Model.*, **2019**, 59(5): 1858-1872.

Bioassay-guided isolation protocol was performed on petroleum ether extract of *Peperomia blanda* (Jacq.) Kunth using column chromatographic techniques. Five compounds were isolated and their structures were elucidated via one-dimensional (1D) and two-dimensional (2D) NMR, gas chromatography mass spectrometry (GCMS), liquid chromatography mass spectrometry (LCMS), and

ultraviolet (UV) and infrared (IR) analyses. Dindygulerione E (a new compound), and two compounds isolated from *P. blanda* for the first time—namely, dindygulerione A and flavokawain A—are reported herein. Antimicrobial activity was screened against selected pathogenic microbes, and minimum inhibitory concentrations (MIC) were recorded within the range of 62–250 µg/mL. Assessment of the pharmacotherapeutic potential has also been done for the isolated compounds, using the Prediction of Activity spectra for Substances (PASS) software, and different activities of compounds were predicted. Molecular docking, molecular dynamics simulation and molecular mechanics/Poisson-Boltzmann Surface Area (MM-PBSA) calculations have proposed the binding affinity of these compounds toward methylthioadenosine phosphorylase enzyme, which may explain their inhibitory actions.

Paronikyan EG, Petrou A, Fesatidou M, et al. Derivatives of a new heterocyclic system - pyrano[3,4-c][1,2,4]triazolo[4,3-a]pyridines: synthesis, docking analysis and neurotropic activity. *MedChemComm.*, **2019**, 10(8): 1399-1411.

8-Hydrazino derivatives of pyrano[3,4-c]pyridines and derivatives of the new heterocyclic system 3-thioxopyrano[3,4-c][1,2,4]triazolo[4,3-a]pyridines on the basis of methanesulfonates of pyrano[3,4-c]pyridinium were synthesized by optimization of a previously used method. Derivatives of alkylsulfonyl pyrano[3,4-c][1,2,4]triazolo[4,3-a]pyridines were also synthesized. All compounds were evaluated for their neurotropic activity. Among all the compounds tested for anticonvulsant activity by pentylenetetrazole and maximal electric shock seizure (MES) tests, six compounds (5a, 5b, 5e, 5g, 5j, and 5p) appeared to be active. These compounds were also evaluated for their anxiolytic as well as antidepressant activities using "open field", "elevated plus maze" (EPM), and "forced swimming" tests, respectively. It should be mentioned that compounds tested by the "rotating rod" method did not affect neuromuscular coordination. The most active compound appeared to be 5g in all tests. Docking studies of the most active compounds were performed on the GABAA receptor, SERT and 5-HT1A receptor.

Sethi P., Bansal Y., Bansal G. Synthesis and PASS-assisted evaluation of coumarin–benzimidazole derivatives as potential anti-inflammatory and anthelmintic agents. *Medicinal Chemistry Research*, **2018**, 27: 61-71.

Two series of novel derivatives have been designed by coupling medicinally important coumarin and benzimidazole nuclei through different linkers. These compounds have been predicted to be potent anti-inflammatory and anthelmintic by in silico studies using PASS (prediction of activity spectra for substances) software. The compounds are synthesized and evaluated for the predicted activities as well as for their in vitro antioxidant potential. Compounds of first series (4a–4f) are found good to moderate anti-inflammatory agents. Among these, compounds 4b and 4f exhibited maximum anti-inflammatory activity (45% inhibition), which is equivalent to the activity of indomethacin (48% inhibition) after 3 h (peak inflammatory response time). Compounds of second series (5a–5f) exhibit anthelmintic activity. Amongst these, compound 5f has mortality activity marginally higher than albendazole (10–11 s). Compound 5e is found to be the most potent antioxidant with remarkable EC50 value (0.08 µM/mL), which is though a little less than that of ascorbic acid (0.03 µM/mL). In addition, a comparative analysis of calculated Lipinski's parameters reveals that all test compounds have the propensity to be orally bioavailable. Based on these findings, compounds 4b, 4f, 5e, and 5f are identified as new leads to develop potent anti-inflammatory, anthelmintic, and antioxidant compounds.

Murtazaliev K.A., Druzhilovskiy D.S., Goel R.K., et al. How good are publicly available web services that predict bioactivity profiles for drug repurposing? *SAR and QSAR in Environmental Research*, **2017**, 28 (10), 843-862.

Drug repurposing provides a non-laborious and less expensive way for finding new human medicines. Computational assessment of bioactivity profiles shed light on the hidden pharmacological potential of the launched drugs. Currently, several freely available computational tools are available via the Internet, which predict multitarget profiles of drug-like compounds. They are based on chemical similarity assessment (ChemProt, SuperPred, SEA, SwissTargetPrediction and TargetHunter) or machine learning methods (ChemProt and PASS). To compare their performance, this study has created two evaluation sets, consisting of (1) 50 well-known repositioned drugs and (2) 12 drugs recently patented for new indications. In the first set, sensitivity values varied from 0.64 (TarPred) to 1.00 (PASS Online) for the initial indications and from 0.64 (TarPred) to 0.98 (PASS Online) for the repurposed indications. In the second set, sensitivity values varied from 0.08 (SuperPred) to 1.00 (PASS Online) for the initial indications and from 0.00 (SuperPred) to 1.00 (PASS Online) for the repurposed indications. Thus, this analysis demonstrated that the performance of machine learning methods surpassed those of chemical similarity assessments, particularly in the case of novel repurposed indications.

Yildirim H., Bayrak N., Tuyun A.F. et al. 2,3-Disubstituted-1,4-naphthoquinones containing an arylamine with trifluoromethyl group: synthesis, biological evaluation, and computational study. *RSC Advances*, **2017**, 7: 25753-25764.

Antibacterial and antifungal organic compounds are becoming increasingly important for biomedical applications. This study deals with the synthesis, characterization of structures, in silico PASS prediction, and the discovery of antibacterial and antifungal properties based on new sulfanyl-1,4-naphthoquinone derivatives containing an arylamine with a trifluoromethyl group at different positions, which can be further applied in drug discovery and development. The in vitro antimicrobial potential of the newly synthesized compounds was evaluated in a panel of seven bacterial strains (three Gram-positive and four Gram-negative bacteria) and one yeast, with an additional study on antibiofilm activities. The compounds (5b and 5e) were identified as having strong antibacterial efficiency against the human-originated pathogen *S. epidermidis*, with minimal inhibitory concentration values (4.88 and 2.44 µg mL⁻¹, respectively). The toxicity of both compounds (5b and 5e) was studied in detail to compare these compounds with Cefuroxime (a clinically proven drug). The antibacterial activity of the compound 5f was equal to that of Cefuroxime. Moreover, three compounds (5b, 5e, and 5f) exhibited excellent antibacterial activity, and 5b and 5e were two and four times more active than the reference antimicrobial compound

(Cefuroxime), respectively. For this reason, these three compounds (5b, 5e, and 5f) are being considered as promising antibacterial agents. In addition, docking studies were used to better rationalize the action and prediction of the binding modes of these compounds.

Stasevych M., Zvarych V., Lunin V., et al. Computer-aided prediction and experimental testing of the dithiocarbamate derivatives of 9,10-anthracenedione as anticancer agents. *SAR and QSAR in Environmental Research*, **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 GI₅₀ values of 1.40 μM and 1.52 μM, whereas the GI₅₀ 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.

Jamkhande P.G., Pathan S.K., Wadher S.J. In silico PASS analysis and determination of antimycobacterial, antifungal, and antioxidant efficacies of maslinic acid in an extract rich in pentacyclic triterpenoids. *Int. J. Mycobacteriol.*, **2016**, 5(4): 417-425.

Objective/background: Microbial infections such as tuberculosis is a major cause of mortality worldwide. Plant-derived phytochemicals have a long history of providing much-needed novel therapeutics. Triterpenoids are among the prominent phytochemicals that possess numerous biological activities. Among them is maslinic acid (MA), a biologically active olean-type pentacyclic triterpenoid. In search of a novel antimicrobial agent, we aimed to evaluate the antimicrobial potential of MA.

Methods: Antibacterial and antifungal activity was evaluated through the agar well diffusion method. Antitubercular activity was analysed through the agar well diffusion and disc diffusion methods, respectively. Antioxidant capacity was determined through assays for total antioxidant capacity, 2,2-diphenyl-1-picrylhydrazyl radical scavenging, hydrogen peroxide radical scavenging, and Fe³⁺ reducing power. The program Prediction of Activity Spectra for Substances was used to calculate the possible biological activity of MA.

Results: MA showed dose-dependent antioxidant activity similar to that of ascorbic acid. It had no inhibitory effect on bacterial strains, but it had moderate activity against the fungi *Aspergillus flavus* and *Ustilago maydis*, with *Aspergillus niger* being the most sensitive to MA. MA also exhibited strong antimycobacterial activity. Probable antioxidant, antibacterial, and antifungal activity of MA based on software calculations are 0.479, 0.363 and 0.589 respectively.

Conclusion: This work provides scientific evidence of the antioxidant, antifungal, and antimycobacterial activities of MA, showing its potential application in the development of natural antioxidants and antimicrobial agents for the agro-food and pharmaceutical industries.

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 anti-amnesic 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.

Agarwal S., Baroliya P.K., Bhargava A., et al. Synthesis, characterization, theoretical prediction of activities and evaluation of biological activities of some sulfacetamide based hydroxytriazenes. *Bioorg. Med. Chem. Lett.*, **2016**, 26(12): 2870-2873.

Six new N [(4-aminophenyl)sulfonyl]acetamide based hydroxytriazenes have been synthesized and characterized using elemental analysis, IR, ¹H NMR, ¹³C NMR and MASS spectral analysis. Further, their theoretical predictions for probable activities have been taken using PASS (Prediction of Activity Spectra for Substance). Although a number of activities have been predicted but specifically anti-inflammatory, antiradical, anti-diabetic activities have been experimentally validated which proves that theoretical predictions agree with the experimental results.

Patil K.R., Mohapatra P., Patel H.M., et al. Pentacyclic Triterpenoids Inhibit IKKβ Mediated Activation of NF-κB Pathway: In Silico and In Vitro Evidences. *PLoS One*, **2015**, 10(5): e0125709.

Pentacyclic Triterpenoids (PTs) and their analogues as well as derivatives are emerging as important drug leads for various diseases. They act through a variety of mechanisms and a majority of them inhibit the nuclear factor kappa-beta (NF-κB) signaling pathway. In this study, we examined the effects of the naturally occurring PTs on IκB kinase-β (IKKβ), which has great scientific relevance in the

NF- κ B signaling pathway. On virtual screening, 109 PTs were screened through the PASS (prediction of activity spectra of substances) software for prediction of NF- κ B inhibitory activity followed by docking on the NEMO/IKK β association complex (PDB: 3BRV) and testing for compliance with the softened Lipinski's Rule of Five using Schrodinger (LLC, New York, USA). Out of the projected 45 druggable PTs, Corosolic Acid (CA), Asiatic Acid (AA) and Ursolic Acid (UA) were assayed for IKK β kinase activity in the cell free medium. The UA exhibited a potent IKK β inhibitory effect on the hotspot kinase assay with IC₅₀ of 69 μ M. Whereas, CA at 50 μ M concentration markedly reduced the NF- κ B luciferase activity and phospho-IKK β protein expressions. The PTs tested, attenuated the expression of the NF- κ B cascade proteins in the LPS-stimulated RAW 264.7 cells, prevented the phosphorylation of the IKK α/β and blocked the activation of the Interferon-gamma (IFN- γ). The results suggest that the IKK β inhibition is the major mechanism of the PTs-induced NF- κ B inhibition. PASS predictions along with in-silico docking against the NEMO/IKK β can be successfully applied in the selection of the prospective NF- κ B inhibitory downregulators of IKK β phosphorylation.

Jamuna S., Karthika K., Paulsamy S., et al. Confertin and scopoletin from leaf and root extracts of *Hypochaeris radicata* have anti-inflammatory and antioxidant activities. *Industrial Crops and Products*, **2015**, 70: 221-230.

Hypochaeris radicata is being prescribed by the local healers and Thoda tribals of Nilgiris, the Western Ghats, India for the treatment of inflammation and various other ailments. This study was designed to explore the anti-inflammatory and antioxidant effects of crude extracts, and the two isolated compounds, confertin and scopoletin from methanolic leaf and root extracts respectively in order to confirm the folkloric claim. Their effects were studied using carrageenan induced acute inflammation in rats. Indomethacin was used as the standard drug for comparison. Cytokine assay to measure the levels of proinflammatory mediators, TNF- α , IL-1 β and IL-6 in serum was made. Histopathological and in vivo antioxidant studies were carried out using standard procedures. Therapeutic potential of the isolated compounds was further studied using PASS software. In acute inflammation, the isolated compounds showed more potent activity by inhibiting the paw oedema than the respective crude extracts. Furthermore, the compounds, confertin and scopoletin (10 mg/kg b.w.) suppressed the production of proinflammatory cytokines such as TNF- α , IL-1 β and IL-6 and enhanced more prominent antioxidant activity, which was supported by histopathological observations. The obtained results, therefore, suggest that the compounds, confertin and scopoletin are prominent constituents of this species and they may be used as a remedy for inflammatory disorders.

Gillbro J.M., Lundahl M., Westman M., et al. Structural activity relationship analysis (SAR) and in vitro testing reveal the anti-ageing potential activity of acetyl aspartic acid. *International Journal of Cosmetic Science*, **2015**, 37 (Suppl. 1): 15–20.

BACKGROUND: Acetyl aspartic acid (A-A-A) was discovered through gene array analysis with corresponding connectivity mapping (Cmap), aiming for identification of new compounds with anti-ageing properties.

OBJECTIVE: The aim of this study was to use structural activity relationship (SAR) analysis to identify a predictive mechanism of action of A-A-A. The findings from SAR will be further characterized by in vitro activity testing. Furthermore, we aimed to investigate the role of polymerized filamentous F-actin in ageing fibroblasts and to evaluate the effect of A-A-A on this model.

METHODS: To predict the mode of action of A-A-A, we used the PASS computer program as a SAR model. In vitro, scratch motility tests with immortalized keratinocytes were used as a model for wound healing potential. Matrix metalloproteinase 1-3 (MMP 1-3) was analysed using multiplex protein assays (Luminex), and polymerized actin was detected by phalloidin staining in dermal fibroblasts (HDF).

RESULTS: SAR analysis predicted that A-A-A would possess both epidermal and dermal activities with identification of wound healing and MMP inhibition potential. Further in vitro studies confirmed the wound healing potential using keratinocyte scratch motility assays. We were also able to confirm the dermal activities predicted by inhibition of MMP (MMP 1–3) in HDF by A-A-A. In addition, we found a positive relationship between age and F-actin expression. We also discovered that stimulation of HDF with A-A-A for 72 h significantly reduced the polymerized cytoskeletal network as visualized by inhibition of F-actin expression. In fact, A-A-A leveraged the expression of F-actin in middle-aged female fibroblasts (50 years of age) to the level of young female fibroblasts (30 years of age), corresponding to a 40% reduction in F-actin expression.

CONCLUSION: Using an in silico and in vitro approach, we were able to demonstrate that A-A-A has the capacity to target different compartments of the skin through keratinocyte regeneration, MMP inhibition and relief in fibroblasts stiffness by reduction of F-actin cytoskeletal network in HDF.

Filimonov D.A., Lagunin A.A., Glorizova T.A., et al. Prediction of the biological activity spectra of organic compounds using the PASS online web resource. *Chemistry of Heterocyclic Compounds*, **2014**, 50 (3), 444-457.

The freely accessible web resource PASS Online is presented. This resource is designed for the prediction of the biological activity spectra of organic compounds based on their structural formulas for more than 4000 types of biological activity with average accuracy above 95% (<http://www.way2drug.com/passonline>). The prediction is based on an analysis of the structure-activity relationships in the training set containing information on the structure and biological activity of more than 300000 organic compounds. The possibilities and limitations of this approach are described. Recommendations are given for interpreting the prediction results. Examples are given for the practical use of the PASS Online web resource in order to establish priorities for chemical synthesis and biological testing of substances on the basis of prediction results. The further trends are considered for the using PASS Online as an Internet platform for joint projects of academic researchers for the search and development of new pharmaceutical agents.

Ariffin A., Rahman N.A., Yehye W.A., et al. PASS-assisted design, synthesis and antioxidant evaluation of new butylated hydroxytoluene derivatives. *Eur. J. Med. Chem.*, **2014**, 87: 564-577.

New multipotent antioxidants (MPAOs), namely 1,3,4-thiadiazoles and 1,2,4-triazoles bearing the well-known free radical scavenger butylated hydroxytoluene (BHT), were designed and synthesized using an acid-(base-) catalyzed intramolecular dehydrative cyclization reaction of the corresponding 1-acylthiosemicarbazides. The structure-activity relationship (SAR) of the designed antioxidants was performed along with the prediction of activity spectra for substances (PASS) training set. Experimental studies based on antioxidant activity using DPPH and lipid peroxidation assays verified the predictions obtained by the PASS-assisted design strategy. Compounds 4a-b, 5a-b and 6a-b showed an inhibition of stable DPPH free radicals at a 10^{-4} M more than the well-known standard antioxidant BHT. Compounds with p-methoxy substituents (4b, 5b and 6b) were more active than o-methoxy substituents (4a, 5a and 6a). With an IC_{50} of $2.85 \pm 1.09 \mu\text{M}$, compound 6b exhibited the most promising in vitro inhibition of lipid peroxidation, inhibiting $\text{Fe}(2^+)$ -induced lipid peroxidation of essential oils derived from the egg yolk-based lipid-rich medium by 86.4%. The parameters for the drug-likeness of these BHT derivatives were also evaluated according to Lipinski's 'rule-of-five'. All of the BHT derivatives were found to violate one of Lipinski's parameters ($\text{Log } P \geq 5$) even though they have been found to be soluble in protic solvents. The predictive TPSA and %ABS data allow for the conclusion that these compounds could have a good capacity for penetrating cell membranes. Therefore, these novel MPAOs containing lipophilic and hydrophilic groups can be proposed as potential antioxidants for tackling oxidative stress and lipid peroxidation processes.

Kale M.A., Shelke R., Nawale R.B. Zinc-aceclofenac complex: synthesis, hydrolysis study and antiinflammatory studies. *Antiinflamm. Antiallergy Agents. Med. Chem.*, **2014**, 13(1): 36-44.

Aceclofenac, a nonsteroidal anti-inflammatory drug, has a propensity to cause gastric ulcers, while zinc ions are known to possess anti-ulcer and anti-inflammatory activities. With a view to reduce the gastroenteropathies associated with aceclofenac, its zinc complex was prepared and characterized using spectroscopy and differential scanning calorimetry. In vitro hydrolysis study showed that zinc complex of aceclofenac is more stable in HCl buffer (pH 1.2) than in phosphate buffer (pH 7.4) indicating the stability of the complex in stomach. In silico testing of the aceclofenac and its complex using PASS (Prediction of activity spectra of substances) software revealed that the complex might possess antiinflammatory activity which was confirmed by carrageenan-induced rat paw edema test. It has been found that antiinflammatory activity of this complex is comparable with that of parent drug along with reduction in ulcer index. Thus, the use of complex is suggested to be more preferable than aceclofenac alone.

Kadir F.A., Kassim N.M., Abdulla M.A., Yehye W.A. PASS-predicted Vitex negundo activity: antioxidant and antiproliferative properties on human hepatoma cells--an in vitro study. *BMC Complement. Altern. Med.*, **2013**, 13: 343.

Background: Hepatocellular carcinoma is a common type of tumour worldwide with a high mortality rate and with low response to current cytotoxic and chemotherapeutic drugs. The prediction of activity spectra for the substances (PASS) software, which predicted that more than 300 pharmacological effects, biological and biochemical mechanisms based on the structural formula of the substance was efficiently used in this study to reveal new multitargeted actions for Vitex negundo (VN) constituents.

Methods: Experimental studies based on antioxidant and antiproliferative assays verified the predictions obtained by the PASS-predicted design strategy. Antioxidant activity of VN extract was studied using 1,1-diphenyl-2-picrylhydrazyl (DPPH) and Ferric reducing or antioxidant power (FRAP) assays. The antiproliferative activity of VN extract against WRL68 and HepG2 was investigated based on methylthiazol tetrazolium (MTT) spectrophotometric assay.

Results: VN extract showed 79.43% inhibition of DPPH stable radical with IC_{50} $13.31 \pm 0.18 \mu\text{g/ml}$. This inhibition was too closed to butylated hydroxyl toluene (BHT) 82.53% (IC_{50} 13.8 ± 0.14) and gallic acid 89.51% (IC_{50} 3.1 ± 0.08). VN extract exhibited the strongest free radical scavenging power compared with two commercial antioxidants, BHT and ascorbic acid. VN increased the activities of antioxidant enzymes in normal embryonic liver cells (WRL68) including, superoxide dismutase (SOD) and glutathione peroxidase (GPX) compared with H_2O_2 group. The ethanolic extract of VN showed cytotoxicity to HepG2 cells in a dose and time-dependent manner with IC_{50} $66.46 \mu\text{g/ml}$, $57.36 \mu\text{g/ml}$ and $65.12 \mu\text{g/ml}$ at 24, 48, and 72-hours incubation respectively, with no sensitivity in WRL68 cells. This was associated with significant elevation in lactate dehydrogenase (LDH) release in HepG2 cells. In addition, the activation of caspase-3 enzyme suggesting that the observed cytotoxicity was mediated via an intrinsic apoptosis pathway.

Conclusions: PASS-predicted plant activity could efficiently help in selecting a promising pharmaceutical leads with high accuracy and required antioxidant and antiproliferative properties. This is the first report on PASS-predicted VN 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.

Khurana N., Ishar M.P., Gajbhiye A., Goel R.K. PASS assisted prediction and pharmacological evaluation of novel nicotinic analogs for nootropic activity in mice. *Eur. J. Pharmacol.*, **2011**, 662(1-3): 22-30.

The aim of present study is to predict the probable nootropic activity of novel nicotine analogues with the help of computer program, PASS (prediction of activity spectra for substances) and evaluate the same. Two compounds from differently substituted pyridines were selected for synthesis and evaluation of nootropic activity based on their high probable activity (Pa) value predicted by PASS computer program. Evaluation of nootropic activity of compounds after acute and chronic treatment was done with transfer latency (TL) and step down latency (SDL) methods which showed significant nootropic activity. The effect on scopolamine induced amnesia was also observed

along with their acetylcholine esterase inhibitory activity which also showed positive results which strengthened their efficacy as nootropic agents through involvement of cholinergic system. This nootropic effect was similar to the effect of nicotine and donepezil used as standard drugs. Muscle coordination and locomotor activity along with their addiction liability, safety and tolerability studies were also evaluated. These studies showed that these compounds are well tolerable and safe over a wide range of doses tested along with the absence of withdrawal effect which is present in nicotine due to its addiction liability. The study showed that these compounds are true nicotine analogs with desirable efficacy and safety profile for their use as effective nootropic agents.

Basanagouda M., Jadhav V. B., Kulkarni M. V., and R. Nagendra Rao. Computer Aided Prediction of Biological Activity Spectra: Study of Correlation between Predicted and Observed Activities for Coumarin-4-Acetic Acids. *Indian J. Pharm. Sci.*, **2011**, 73(1): 88–92.

Coumarin-4-acetic acids have been synthesized from various phenols and citric acid under Pechmann cyclisation conditions. All the compounds have been evaluated for antiinflammatory and analgesic activity in acute models. Compounds have also been evaluated for their ulcerogenic potential. Using the computer program, prediction of activity spectra for substances, prediction results and their Pharma Expert software, we have found a correlation between the observed and predicted antiinflammatory activity.

Navarrete-Vazquez G., Hidalgo-Figueroa S., Torres-Piedra M., et al. Synthesis, vasorelaxant activity and antihypertensive effect of benzo[d]imidazole derivatives. *Bioorg. & Med. Chem.*, **2010**, 18(11): 3985–3991.

Fifteen benzo[d]imidazole derivatives have been designed, synthesized and tested as vasorelaxant agents in order to obtain potential antihypertensive compounds. Vasodilatory and phosphodiesterase inhibiting actions for the designed compounds have been predicted by PASS with probability “to be active” P_a ranged from 0.5 to 0.8, which is close to the known vasoactive drugs. Vasodilatory activity of the synthesized compounds has been confirmed by the experiment (*ex vivo* relaxant response in intact aortic rings); the most potent effect has been observed for all the nitro derivatives. 2-Methoxy-4-[5-nitro-1H-benzo[d]imidazol-2-yl]phenol (compound 13) was the most potent derivative of the series, showing an EC₅₀ value of 1.81 μ M and Emax of 91.7% for *ex vivo* relaxant response in intact aortic rings, resulting in a 2.5-fold higher activity compared to the reference drug Pimobendan. The antihypertensive activity of compound 13 was evaluated at doses of 25, 50 and 100 mg kg⁻¹, using spontaneously hypertensive rats (SHR), showing a statistically significant dose-dependent effect.

Torres-Piedra M., Ortiz-Andrade R., Villalobos-Molina R., et al. A comparative study of flavonoid analogues on streptozotocin/nicotinamide induced diabetic rats: Quercetin as a potential antidiabetic agent acting via 11 β -Hydroxysteroid dehydrogenase type 1 inhibition. *European Journal of Medicinal Chemistry*, **2010**, 45: 2606-2612.

The oral antidiabetic activity of six structurally related flavonoids has been investigated. They include flavone (**1**), 3-hydroxyflavone (**2**), 6-hydroxyflavone (**3**), 7-hydroxyflavone (**4**), chrysin (**5**) and quercetin (**6**). Before the establishment of an *in vivo* antidiabetic assay, PASS predictions have been obtained for flavonoids 1-6. PASS estimates for probability to be active P_a for the studied compounds were less than 0.5. It means that the structures of flavonoids 1-5 are not close to the flavonoids 1-5; therefore if the presence of this activity is confirmed experimentally, compounds might be new biologically active chemical entities. Normoglycemic and STZ-nicotinamide diabetic rats were treated with these flavonoids (50 mg/kg) and the hypoglycemic and antidiabetic effects in acute and sub-acute (five days of treatment) experiments were determined. Compounds **1**, **5** and **6** were found most active in both experiments in comparison with control group ($p < 0.05$).

Benchabane Y., Di Giorgio C., Boyer G., et al. Photo-inducible cytotoxic and clastogenic activities of 3,6-di-substituted acridines obtained by acylation of proflavine. *European Journal of Medicinal Chemistry*, **2009**, 44: 2459-2467.

The cytotoxicity and photo-enhanced cytotoxicity of a series of 18 3,6-di-substituted acridines were evaluated on both tumour CHO cells and human normal keratinocytes, and compared to their corresponding clastogenicity as assessed by the micronucleus assay.

Compounds 2f tert-butyl N-[(6-tert-butoxycarbonylamino)acridin-3-yl]carbamate and 2d N-[6-(pivalamino)acridin-3-yl]pivalamide displayed a specific cytotoxicity on CHO cells. These results suggested that the two derivatives could be considered as interesting candidates for anticancer chemotherapy and hypothesized that the presence of 1,1-dimethylethyl substituents was responsible for a strong nonclastogenic cytotoxicity. Compounds 2b and 2c, on the contrary, displayed a strong clastogenicity. They indicated that the presence of nonbranched aliphatic chains on positions 3 and 6 of the acridine rings tended to induce a significant clastogenic effect. Finally, they established that most of the acridine compounds could be photo-activated by UVA-visible rays and focussed on the significant role of light irradiation on their biological properties.

A series of 18 3,6-di-substituted acridines were synthesized and assessed for their photo-enhanced cytotoxic and clastogenic activities. Compounds 2f tert-butyl N-[(6-tert-butoxycarbonylamino)acridin-3-yl]carbamate, 2d (N-[6-(pivalamino)acridin-3-yl]pivalamide) and 4b (N-(3-(furan-2-carboxamido)acridin-6-yl)furan-2-carboxamide) displayed a specific cytotoxicity on tumour cells. The presence of a 1,1-dimethylethyl substituent was responsible for a nonclastogenic cytotoxicity, whereas nonramified aliphatic chains on positions 3 and 6 of the acridine rings tended to induce a significant clastogenic effect. Most of the acridine compounds could be photo-activated by UVA-visible rays.

Hernandez-Nunez E., Tlahuext H., Moo-Puc R., et al. Synthesis and in vitro trichomonocidal, giardicidal and amebicidal activity of N-acetamide(sulfonamide)-2-methyl-4-nitro-1H-imidazoles. *European Journal of Medicinal Chemistry*, **2009**, 44(7): 2975-2984.

Two new series of imidazole derivatives (acetamides: 1–8 and sulfonamides: 9–15) were synthesized using a short synthetic route. Compound 1 as well as the intermediate 16g were characterized by X-ray crystallography. Imidazole derivatives 1–15 were tested in vitro against three unicellular parasites (*Giardia intestinalis*, *Trichomonas vaginalis* and *Entamoeba histolytica*) in comparison with benznidazole (Bzn) and metronidazole. Compound 1 [N-benzyl-2-(2-methyl-4-nitro-1H-imidazol-1-yl)acetamide] was 2 times more active than Bzn against *T. vaginalis* and *G. intestinalis* and it was as active as Bzn against *E. histolytica*. Sulfonamides showed selective toxicity against *E. histolytica* over the other parasites. Toxicity assay showed that all compounds are non-cytotoxic against MDCK cell line. The results revealed that compounds 1–15 have antiparasitic bioactivity in the micromolar range against the parasites tested, and could be considered as benznidazole bioisosteres.

Compound 1 [N-benzyl-2-(2-methyl-4-nitro-1H-imidazol-1-yl)acetamide] was 2 times more active than benznidazole (Bzn) against *T. vaginalis* and *G. intestinalis* and it was as active as Bzn against *E. histolytica*. The results revealed that synthesized compounds have antiparasitic bioactivity in the micromolar range against the unicellular parasites tested. All compounds were non-cytotoxic against MDCK cell line, and could be considered as benznidazole bioisosteres.

Benchabane Y., Di Giorgio C., Boyer G., et al. Photo-inducible cytotoxic and clastogenic activities of 3,6-di-substituted acridines obtained by acylation of proflavine. *European Journal of Medicinal Chemistry*, **2009**, *44*: 2459–2467.

The cytotoxicity and photo-enhanced cytotoxicity of a series of 18 3,6-di-substituted acridines were evaluated on both tumor CHO cells and human normal keratinocytes, and compared to their corresponding clastogenicity as assessed by the micronucleus assay. The experimental data were compared with the antineoplastic, mutagenic and photosensitizer activities predicted by PASS. Predictive values for biological activities were obtained by comparing the chemical structure of each compound with structures of well-known biologically active substances. They were expressed as the probability Pa of each compound to be active and illustrated its degree of similarity with well-known antineoplastic compounds, mutagenic molecules, or photosensitizers. Pa > 0.7 indicated that the corresponding compound was very likely to reveal activity in experiments, 0.5 < Pa < 0.7 suggested that the compound was likely to reveal activity in experiments, while Pa < 0.5 implied that the compound was unlikely to reveal activity in experiments. All the predictive probabilities calculated for the antineoplastic activity were higher than 0.5: they implied that the 3,6-di-substituted proflavine derivatives were likely to exert cytotoxic activity against tumor cells. Among these compounds, four derivatives (**3h**, **3b**, **3a** and **3e**) showed Pa higher than 0.7. Concerning the mutagenic or the photosensitizing activities on the contrary, almost all the estimated Pa were lower than 0.3. They indicated that, according to the predictive model, the 3,6-di-substituted acridines were unlikely to exert mutagenicity or photo-inducible biologic activities. Comparisons between the experimental results and the biological properties calculated by predictive models showed that the cytotoxic and clastogenic activities of acridine compounds resulted from various complex mechanisms. They underlined the necessity of extended studies to better define their numerous cellular targets.

Carlsen L., Kenessov B., Batyrbekova S.Ye. A QSAR/QSTR study on the human health impact of the rocket fuel 1,1-dimethyl hydrazine and its transformation products: Multicriteria hazard ranking based on partial order methodologies. *Environmental Toxicology and Pharmacology*, **2009**, *27*(3): 415–423.

PASS (Prediction of Activity Spectra for Substances) has been used for estimating the probabilities for the substances to exhibit carcinogenic, mutagenic, teratogenic and/or embryotoxic effects for the rocket fuel 1,1-dimethylhydrazine (heptyl) and its transformation products as an illustrative example. It was shown that the combined computational approach is an attractive method to a preliminary assessment of the impact on environmental and human health by primary pollutants or possibly by a primary pollutant well as a possible suite of transformation subsequent products that may be both persistent in and bioaccumulating and toxic.

Musiol R., Jampilek J., Kralova K., et al. Investigating biological activity spectrum for novel quinoline analogues. *Bioorganic & Medicinal Chemistry*, **2007**, *15*(3): 1280–1288.

The lack of the wide spectrum of biological data is an important obstacle preventing the efficient molecular design. Quinoline derivatives are known to exhibit a variety of biological effects. In the current publication, we tested a series of novel quinoline analogues for their photosynthesis-inhibiting activity (the inhibition of photosynthetic electron transport in spinach chloroplasts (*Spinacia oleracea* L.) and the reduction of chlorophyll content in *Chlorella vulgaris* Beij.). Moreover, antiproliferative activity was measured using SK-N-MC neuroepithelioma cell line. We described the structure–activity relationships (SAR) between the chemical structure and biological effects of the synthesized compounds. We also measured the lipophilicity of the novel compounds by means of the RP-HPLC and illustrate the relationships between the RP-HPLC retention parameter log K (the logarithm of capacity factor K) and log P data calculated by available programs. Photosynthesis-inhibiting and antiproliferative activity for some compounds of the novel series of quinoline derivatives are comparable to those of the standards, DCMU and triapine.

Zotchev S.B., Stepanchikova A.V., Sergeyko A.P., et al. Rational design of macrolides by virtual screening of combinatorial libraries generated through in silico manipulation of polyketide synthases. *Journal of Medicinal Chemistry*, **2006**, *49*(6): 2077–2087.

Bacterial secondary metabolites display diverse biological activities, thus having potential as pharmacological agents. Although most of these compounds are discovered by random screening, it is possible to predict and re-design their structures based on the information on their biosynthetic pathways. Biosynthesis of macrolides, governed by modular polyketide synthases (PKS), obeys certain rules, which can be simulated in silico. PKS mode of action theoretically allows for a huge number of macrolides to be produced upon combinatorial manipulation. Since engineering of all possible PKS variants is practically unfeasible, we created Biogenerator software, which simulates manipulation of PKS and generates virtual libraries of macrolides. These libraries can be screened by computer-aided prediction of biological activities, as exemplified by analysis of erythromycin and macrolactin libraries. This approach allows rational selection of

macrolides with desired biological activities and provides instructions regarding the composition of the PKS gene clusters necessary for microbial production of such molecules.

Labanauskas L., Brukstus A., Udrenaitė E., et al. Synthesis and anti-inflammatory activity of 1-acylaminoalkyl-3,4-dialkoxybenzene derivatives. *Farmaco*, **2005**, 60: 203-207.

New 1-acylaminoalkyl-3,4-dialkoxybenzene derivatives 17–31 were synthesized by the acylation of amines 9–16 with acyl chlorides. Amines 9–16 were obtained from aryl ketones 1–8. Aryl ketones 1–8 were synthesized by the acylation of corresponding aromatic compounds. As it was preliminary predicted by PASS (Prediction of Activity Spectra for Substance) program, all 1-acylaminoalkyl-3,4-dimethoxy- and 3,4-diethoxybenzene derivatives possess anti-inflammatory activity. Activity of compounds 18, 19, 21, 24, 26, 27, 28, 29 was similar to that of acetylsalicylic acid or ibuprofen however their acute toxicity was less than that of mentioned anti-inflammatory drugs.

A series of 1-acylaminoalkyl-3,4-dimethoxybenzene, 1-acylaminoalkyl-3,4-diethoxybenzene and 6-acylaminoalkyl-2,3-dihydro-1,4-benzodioxine derivatives have been synthesized. These compounds possess moderate or strong anti-inflammatory activity and low toxicity.

Geronikaki A., Dearden J., Filimonov D., et al. Design of new cognition enhancers: from computer prediction to synthesis and biological evaluation. *Journal of Medicinal Chemistry*, **2004**, 47(11): 2870-2876.

To discover new cognition enhancers, a set of virtually designed synthesizable compounds from different chemical series was investigated using two computer-aided approaches. One of the approaches is prediction of biological activity spectra for substances (PASS) and the second is prediction of toxicity, mutagenicity, and carcinogenicity (DEREK). To increase the probability of finding new chemical entities, we investigated a heterogeneous set of highly diverse chemicals including different types of heterocycles: five-membered (thiophenes, thiazoles, imidazoles, oxazoles, pyrroles), six-membered (pyridines, pyrimidines), seven-membered (diazepines, triazepines), fused five+six-membered heterocycles (indoles, benzothiazoles, purines, indolizines, neutral, mesoionic, and cationic azolopyridines). A database including 5494 structures of compounds was created. On the basis of the PASS and DEREK prediction results, eight compounds with the highest probability of cognition-enhancing effect were selected. The cognition-enhancing activity testing showed that all of the selected compounds had a pronounced anti-amnesic effect and were found to reduce significantly scopolamine-induced amnesia of passive avoidance reflex (PAR). The action of compounds at doses of 1 and 10 mg/kg caused a statistically significant increase in latent time of reflex and in the number of animals, which did not enter the dark chamber when testing the PAR. Therefore, on the basis of computer prediction, new cognition-enhancing agents were discovered within the chemical series, in which this activity was not known previously.

Lagunin A.A., Gomazkov O.A., Filimonov D.A., et al. Computer-aided selection of potential antihypertensive compounds with dual mechanism of action. *J. Med. Chem.*, **2003**, 46(15): 3326-3332.

The prediction of biological activity spectra for substances as an approach for searching compounds with complex mechanisms of action was studied. New compounds with dual mechanisms of antihypertensive action were found by this approach. Biological activity spectra for substances were predicted on the basis of their structural formulas by the computer program PASS. Thirty molecular mechanisms of action of compounds from the MDDR 99.2 database, which cause the antihypertensive effect and can be predicted by PASS, have been identified. The analysis of predictions for compounds with 15 dual antihypertensive mechanisms of action from the MDDR 99.2 database has confirmed high accuracy of prediction. This approach was applied to databases of commercially available compounds (AsInEx and ChemBridge) and allowed us to select four substances that are potential inhibitors of angiotensin converting enzyme (ACE) and of neutral endopeptidase (NEP). At a later time, all these compounds were found to be the inhibitors of both ACE and NEP. The most potent compounds had IC₅₀ of 10(-7)-10(-9) M for ACE and 10(-5) M for NEP. New combinations of dual mechanisms of action never before found for antihypertensive compounds were predicted.

Di Giorgio C., Delmas F., Filloux N., et al. In vitro activities of 7-substituted 9-chloro and 9-amino-2-methoxyacridines and their bis- and tetra-acridine complexes against *Leishmania infantum*, *Antimicrobial Agents & Chemotherapy*, **2003**, 47: 174-180.

9-Chloro and 9-amino-2-methoxyacridines bearing different substituents in position 7, as well as their corresponding unsubstituted dimeric and tetrameric complexes, were investigated for in vitro antiproliferative properties against *Leishmania infantum* compared to toxicity towards human monocytes. The results clearly confirmed that several compounds of the 2-methoxyacridine series, together with their corresponding dimeric and tetrameric derivatives, had strong in vitro antiparasitic properties. Antileishmanial activity was shown to depend on the nature of both 7- and 9-substituted groups in monoacridines, while it varied according to the nature of the 9-substituted group and the length of the linker among bis- and tetra-acridines. The effects of acridine derivatives on DNA synthesis raised the hypothesis that DNA metabolism constituted their main target in *Leishmania promastigotes*; however, secondary effects on other biochemical pathways, including protein and lipid metabolism, were observed, suggesting that acridine compounds could be considered multitarget drugs.

Poroikov V.V., Filimonov D.A., Ihlenfeldt W.-D., et al. PASS Biological Activity Spectrum Predictions in the Enhanced Open NCI Database Browser. *Journal of Chemical Information and Computer Sciences*, **2003**, 43(1): 228-236.

The application of the program PASS (Prediction of Activity Spectra for Substances) to about 250 000 compounds of the NCI Open Database and the incorporation of over 64 million PASS predictions in the

Enhanced NCI Database Browser are described. A total of 565 different types of activity are included, encompassing general pharmacological effects, specific mechanisms of action, known toxicities, and others. Application of this Web-based service to prediction of activities of the kinds "Angiogenesis inhibitor," "Antiviral (HIV)", and a set of activities that can be associated with antineoplastic action are reported. For this latter data set, a very substantial enrichment over random selection was found in the PASS predictions. It is shown how the user can conduct complex searches by combining ranges of PASS-predicted probabilities of compounds to be active or to be inactive, respectively, with, e.g., value ranges of physicochemical parameters, presence or absence of particular substructural fragment, and other search criteria.

Anzali S., Barnickel G., Cezanne B., et al. Discriminating between drugs and nondrugs by Prediction of Activity Spectra for Substances (PASS). *Journal of Medicinal Chemistry*, **2001**, 44(15): 2432-2437.

Using the computer system PASS (prediction of activity spectra for substances), which predicts simultaneously several hundreds of biological activities, a training set for discriminating between drugs and nondrugs is created. For the training set, two subsets of databases of drugs and nondrugs (a subset of the World Drug Index, WDI, vs the Available Chemicals Directory, ACD) are used. The high value of prediction accuracy shows that the chemical descriptors and algorithms used in PASS provide highly robust structure-activity relationships and reliable predictions. Compared to other methods applied in this field, the direct benchmark undertaken with this paper showed that the results obtained with PASS are in good accordance with these approaches. In addition, it has been shown that the more specific drug information used in the training set of PASS, the more specific discrimination between drug and nondrug can be obtained.

Poroikov V., Akimov D., Shabelnikova E., Filimonov D. Top 200 medicines: can new actions be discovered through computer-aided prediction? *SAR QSAR Environ. Res.*, **2001**, 12(4): 327-344.

Computer-aided prediction of the biological activity spectra by the program PASS was applied to a set of 130 pharmaceuticals from the list of the Top 200 medicines. The known pharmacological effects were found in the predicted activity spectra in 93.2% of cases. Additionally, the probability of some supplementary effects was also predicted to be significant, including angiogenesis inhibition, bone formation stimulation, possible use in cognition disorders treatment, multiple sclerosis treatment, etc. These predictions, if confirmed experimentally, may become a cause for a new application of pharmaceuticals from the Top 200 list. Most of known side and toxic effects were also predicted by PASS. PASS predictions at earlier R & D stages may thus provide a basis for finding new "leads" among already launched drugs and may help direct more attention to those particular effects of pharmaceuticals in clinical use which become apparent only in a small part of the population and require additional precautions.

Poroikov V.V., Filimonov D.A., Borodina Yu. V., et al. Robustness of biological activity spectra predicting by computer program PASS for non-congeneric sets of chemical compounds. *J. Chem. Inform. Comput. Sci.*, **2000**, 40 (6), 1349-1355.

The computer system PASS provides simultaneous prediction of several hundreds of biological activity types for any drug-like compound. The prediction is based on the analysis of structure-activity relationships of the training set including more than 30000 known biologically active compounds. In this paper we investigate the influence on the accuracy of predicting the types of activity with PASS by (a) reduction of the number of structures in the training set and (b) reduction of the number of known activities in the training set. The compounds from the MDDR database are used to create heterogeneous training and evaluation sets. We demonstrate that predictions are robust despite the exclusion of up to 60% of information.

Lagunin A., Stepanchikova A., Filimonov D., Poroikov V. PASS: prediction of activity spectra for biologically active substances. *Bioinformatics*, **2000**, 16 (8), 747-748.

The concept of the biological activity spectrum was introduced to describe the properties of biologically active substances. The PASS (prediction of activity spectra for substances) software product, which predicts more than 300 pharmacological effects and biochemical mechanisms on the basis of the structural formula of a substance, may be efficiently used to find new targets (mechanisms) for some ligands and, conversely, to reveal new ligands for some biological targets. We have developed a WWW interface for the PASS software. A WWW server for the on-line prediction of the biological activity spectra of substances has been constructed.

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