Selected references on PASS bioactivity predictions


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


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 μg/mL and 157.77 to 340.47 μg/mL while standard drug acarbose showed IC50 values 12.21 and 69.74 μg/mL, respectively. The antioxidant activity was evaluated using DPPH and ABTS radical scavenging assays with IC50 value ranging from 54.01 to 912.66 μg/mL and 33.22 to 128.11 μg/mL, and standard drug ascorbic acid showed IC50 values 29.12 and 69.74 μg/mL, respectively. The 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-glucosidase 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.


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 dithiolooquinolinethione 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.

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 163.35 μM with $V_{max}$ of 37 U, vitamins B9, E, C, and D3 were potent inhibitors to BXO with an IC50 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.


Anisomeles indica (L.) Kunzte 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, anti diarrheal, thrombotic, 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). Anti diarrheal 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 thrombotic 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, metabolism, excretion and toxicity (ADMET) 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 thrombotic 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, anti diarrheal, and anti-inflammatory effects and may represent an alternative source of novel therapeutic factors.


**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, evaluate ADMET 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.


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) and perform molecular docking for all bioactive compounds via Maestro software. 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.


**Background:** Inflammation is a complex response to noxious stimuli promoted by the release of chemical mediators from the damaged amino acids, and DNA. Thus, synthesized nanoantioxidants can be used to develop biomedicines that can act as antioxidant, antimicrobial, and anti cancer agents.
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.

**Conclusion:** 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.


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 (AHiH). Effects of Panax japonicus and Tribulus terrestris preparations exceeded the activity of the reference drug Mexidol in the AHiH 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.


*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 -7.9 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.


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-thiaizidine, hydrobromide (L-17), a recently designed thiaizidine 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-HT1A receptors are compatible with selective 5-HT serotonin reuptake inhibitors (SSRIs) and antagonists of 5-HT3 and 5-HT1A 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-HT1A antagonist WAY100135. We suggest that L-17 is a potent 5-HT reuptake inhibitor and partial antagonist of 5-HT3 and 5-HT1A 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.
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 Naïve Bayesian 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.


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


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-17u-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-acetylenopyruvoylglucosamine 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.


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-kB signalling network to exert their effect. This study aimed to identify drugs that alter NF-kB 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-kB 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-kB-mediated transcription in murine peritoneal macrophages and intestinal enteroids; it suppressed NF-kB protein shuttling in murine reporter enteroids; it suppressed NF-kB (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-kB (p65) nuclear translocation in human intestinal enteroids. These findings demonstrate that in silico drug repositioning algorithms can viably be laboratory validated 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.


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, 3ae, 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.


**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 it 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.


**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 dissimilated.

**Materials and methods:** The preparation of the substituted 5-benzylidene-2-thiazolimino-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 potentiality antibacterial property of the designed thiazoletiazolidinone 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-thiazolimino-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.


**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.


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 spectroscopy (LCMS), and
ultraviolet (UV) and infrared (IR) analyses. Dindygulerone E (a new compound), and two compounds isolated from P. blanda for the first time—namely, dindygulerone A and flavokawain A—are reported herein. Antimicrobial activity was screened against selected pathogenic microbes, and minimum inhibition 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.


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.


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 anti-inflammatory 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.


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 patented for new indications 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 0.00 (SuperPred) to 1.00 (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.


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
The Liliaceae family is cultivated mainly in Asian countries. Among them is maslinic acid (MA), a biologically active oleanane-type pentacyclic triterpenoid. In search of a novel antimicrobial agent, we aimed to evaluate the antimicrobial potential of MA.

**Anticancer 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 Fe²⁺ 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.


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.

Asparagus adscendens Roxb. commonly known as safed musli is a traditional medicine in Asia. In this study, we examined the effects of the naturally occurring PTs on scopolamine-induced amnesia and scopolamine-induced amnesia model. To elucidate the mechanism of nootropic activity, the effect of 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.


Six new N-[(4-aminophenyl)sulfonyl]acetamide based hydroxypyrazines 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.


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 IKKβ kinase-β (IKKβ), which has great scientific relevance in the field of cancer research and drug discovery.
NF-κB signaling pathway. On virtual screening, 109 PTs were screened through the PASS (prediction of activity spectra of substances) software for prediction of NF-κB inhibitory activity followed by docking on the NEMO/IKKβ 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 IKKβ kinase activity in the cell free medium. The UA exhibited a potent IKKβ inhibitory effect on the hotspot kinase assay with IC50 of 69 μM. Whereas, CA at 50 μM concentration markedly reduced the NF-κB luciferase activity and phospho-IKKβ protein expressions. The PTs tested, attenuated the expression of the NF-κB cascade proteins in the LPS-stimulated RAW 264.7 cells, prevented the phosphorylation of the IKKα/β and blocked the activation of the Interferon-gamma (IFN-γ). The results suggest that the IKKβ inhibition is the major mechanism of the PTs-induced NF-κB inhibition. PASS predictions along with in-silico docking against the NEMO/IKKβ can be successfully applied in the selection of the prospective NF-κB inhibitory downregulators of IKKβ phosphorylation.

**Jamuna S., Karthika K., Paulsamy S., et al.** Confertin and scopecolin 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 scopecolin from melatonin 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-1β 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 scopecolin (10 mg/kg b.w.) suppressed the production of proinflammatory cytokines such as TNF-α, IL-1β 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 scopecolin are prominent constituents of these species and they may be used as a remedy for inflammatory disorders.


**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.


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.

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 IC50 of 2.85 ± 1.09 μM, compound 6b exhibited the most promising in vitro inhibition of lipid peroxidation, inhibiting 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 (Log P ≥ 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.


Acetofenac, 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 acetofenac, its zinc complex was prepared and characterized using spectroscopy and differential scanning calorimetry. In vitro hydrolysis study showed that zinc complex of acetofenac 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 acetofenac 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 acetofenac alone.


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 multitaled 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 IC50 13.31 ± 0.18 μg/ml. This inhibition was too closed to butylated hydroxytoluene (BHT) 82.53% (IC50 13.8 ± 0.14) and gallic acid 89.51% (IC50 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 H2O2 group. The ethanolic extract of VN showed cytotoxicity against HepG2 cells in a dose and time-dependent manner with IC50 66.46 μg/ml, 57.36 μg/ml and 65.12 μg/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.


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, 4i, 4j, 6b, 6e, 6g showed excellent analgesic activity compared with standard drug Diclofenac sodium.


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 nortopic activity. The effect on scopolamine induced amnesia was also observed.
along with their acetycholine 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.


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 ulcrogenic 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.


Fifteen benzodimidazole 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” Pa 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 aortal 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 µM and Emax of 91.7% for *ex vivo* relaxant response in intact aortal 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.


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 Pa 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).


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-butoxycarbonyl)amino]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 activity. 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-butoxycarbonyl)amino]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 clastogenicity on tumour cells. The presence of a 1,1-dimethylethyl substituent was responsible for a nonclastogenic cytotoxicity, whereas nonamified 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.

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.


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 antiparasitic, 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 antiparasitic 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 photosensitising 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.


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.


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.


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.


New 1-acylaminoaalkyl-3,4-dialkoxynbenzene 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 preliminarily predicted by PASS (Prediction of Activity Spectra for Substance) program, all 1-acylaminoaalkyl-3,4-dimethoxy- and 3,4-dietethoxybenzene derivatives possess anti-inflammatory activity. Activity of compounds 18, 19, 21, 24, 26, 27, 28, 29 was similar to that of acetyl salicylic acid or ibuprofen however their acute toxicity was less than that of mentioned anti-inflammatory drugs.

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


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, pyroles), six-membered (pyridines, pyrimidines), seven-membered (diazepines, triazepines), fused five+six-membered heterocycles (indoles, benzothiazoles, purines, indolizines, neutral, mesionic, 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 antiamnesic 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.


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 (AssInEx 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 IC(50) 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.


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 raise the hypothesis that DNA metabolism constitute 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.


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.


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.


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.


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.


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.


Burov Yu.V., Poroikov V.V., Korolchenko L.V. National system for registration and biological testing of chemical compounds: facilities for new drugs search. *Bulletin of the National Center for Biologically Active Compounds (Rus)*, 1990, No. 1, 4-25.

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