

Experimental confirmations of predictions made with PASS

Prasad Y.R., Rajasekhar K.K., Shankarananth V., Pradeepkumar G.S.S., Surya Teja S.P., Rajeev Reddy B. (2010). *In silico* biological activity evaluation of some 3-substituted-4-hydroxy-6-methyl-2Hpyran-2-ones. *Journal of Pharmacy Research*, **3** (10): 2470-2472.

The objective of the present work was to estimate mechanism of action, pharmacological activity and toxic or side effects of some 3-substituted-4-hydroxy-6-methyl-2H-Pyran-2-ones. Prediction of activity spectra for substances (PASS) is the computer program used in this work. Anti-inflammatory activity predicted by PASS was confirmed by experimental evaluation (Rat paw edema method) and the results are promising.

Ferdosiyani M., Sardari S. (2010). *In silico* design and selection of anti-fungal AmB-polyene-analog lead molecules by virtual screening method. *Avicenna J. Med. Biotech.*, **2** (3): 137-143.

Screening of various compounds from the Enhanced NCI database against ergosterol and cholesterol as receptors is reported. Biological activities of about 250,000 compounds in the Enhanced NCI Database are predicted by PASS prediction, which predicts biological activity spectrum of compound based on its structural formula. The strategy employed is divided into two categories, screening and docking, respectively. Screening was performed using structure search based on AmB and molecular constraints to filter compounds with physico-chemical properties similar to the polyene macrolid antibiotics. The selected compounds were docked and scored to identify structurally novel ligands that make similar interactions to AmB. Our screening approach identified several molecules with high ranking criteria mentioned above. PASS predicts the antifungal activity with probability to be active P_a ranged from 0.241 to 0.637. Two compounds, NSC 177379 ($P_a=0.549$) and NSC 174187 ($P_a=0.637$), were previously studied on antifungal activities and proved to be active; that further validated the proposed approach in finding the bioactive hits. Two other molecules, NSC 89270 ($P_a=0.413$) and NSC 62792 ($P_a=0.322$) were tested in this study for their bioactivity against three fungal strains using broth microdilution assay. It was shown that both compounds have a moderate antifungal activity against the tested fungi. Thus, they could be possible lead compounds that grant further research on them to improve their potency and compare their mechanism of action in comparison to AmB.

Navarrete-Vazquez G., Hidalgo-Figueroa S., Torres-Piedra M., et al. (2010). Synthesis, vasorelaxant activity and antihypertensive effect of benzo[d]imidazole derivatives. *Bioorganic & Medicinal Chemistry*, **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 EC_{50} value of 1.81 μM and E_{max} 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.

Da Silva C.H., Da Silva V.B., Resende J., et al. (2010). Computer-aided drug design and ADMET predictions for identification and evaluation of novel potential farnesyltransferase inhibitors in cancer therapy. *Journal of Molecular Graphics and Modeling*, **28** (6): 513–523.

PASS predictions have been applied to design of new potent farnesyltransferase inhibitors among the Tipifarnib derivatives as potential anticancer drugs. Pa value estimated for compound 1, which has a cyanide group in substitution to the chlorine in the chloro-benzene ring, as well as an isosteric replacement of the quinolinone ring by a quinoline moiety, which contains a methyl group in substitution to the oxygen atom, equals to 0.934. Pa value estimated for compound 2, which has a cyanide group in substitution to the chlorine in the chloro-benzene ring, as well as an isosteric replacement of the quinolinone ring by a methylnaphthalene moiety, equals to 0.980. In contrast, similar prediction performed for Tipifarnib reveals lower Pa value of 0.840 for this activity. Drug-likeness values estimated for both designed compounds have indicated them as promising farnesyltransferase inhibitors in comparison with Tipifarnib and Lonafarnib, two reference pharmaceuticals.

Mustafayeva K., Di Giorgio C., Elias R., et al. (2010). DNA-Damaging, mutagenic, and clastogenic activities of gentiopicroside isolated from *Cephalaria kotschyi* roots. *Journal of Natural Products*, **73** (2): 99–103.

PASS INet prediction obtained for Gentiopicroside, the major secoiridoid glucoside constituent of *Cephalaria kotschyi* roots, revealed a weak structural similarity to established genotoxic and mutagenic agents*. The mutagenicity, DNA damaging capacities, and clastogenicity of this molecule were evaluated by the *Salmonella typhimurium* mutagenicity assay (Ames test) on tester strains TA97a, TA98, TA100, and TA102, the alkaline comet assay, and the micronucleus assay on CHO cells. All tests were performed with and without the metabolism mixture, S9 mix. In the Ames test, the mutagenicity of Gentiopicroside was limited to TA102 without S9 mix (2.3 rev μg^{-1}). The genotoxicity was more evident without S9 mix (0.78 OTM χ 2 units μg^{-1} mL) than with the metabolic mixture (0.16 OTM χ 2 units μg^{-1} mL) with the comet assay. Similarly, the clastogenicity without S9 mix was 0.99 MNC μg^{-1} mL and 0.38 MNC μg^{-1} mL with S9 mix in the micronucleus assay. However, the specific positive response obtained with the TA102 tester strain suggested the involvement of oxidative DNA lesions, probably due to the presence of hydroxy groups, which produce oxygen singlets that may cause oxidative DNA lesions.

*Commercially available PASS 10.1 predicts Gentiopicroside as Carcinogenic, group 2A (substance that according to IARC classification is probably carcinogenic to humans) with Pa=0.361 and Carcinogenic, group 1 substance that according to IARC classification is carcinogenic to humans) with Pa=0.307.

Raja A.K., Vimalanathan A.B., Raj S.V., et al. (2010). Indispensable chemical genomic approaches in novel systemic targeted drug discovery. *Biology and Medicine*, **2** (3): 26-37.

Data mining in annotated chemical database is useful for predicting targets for small molecules. Multi-dimensional models resulting from data mining differ from similarity searching because the information from multiple ligands can be considered in parallel to make target suggestions. PASS (Prediction of Activity Spectra for Substances) is one of the first such applications (ref. on: Poroikov et al., 2000).

Torres-Piedra M., Ortiz-Andrade R., Villalobos-Molina R., et al. (2010). A comparative study of flavonoid analogues on streptozotocin-induced diabetic rats: Quercetin as a potential antidiabetic agent acting via 11 β -Hydroxysteroid dehydrogenase type 1 inhibition. *European Journal of Medicinal Chemistry*, **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. (2009). Photo-inducible cytotoxic and clastogenic activities of 3,6-di-substituted acridines obtained by acylation of proflavine. *European Journal of Medicinal Chemistry*, **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 P_a of each compound to be active and illustrated its degree of similarity with well-known antineoplastic compounds, mutagenic molecules, or photosensitizers. $P_a > 0.7$ indicated that the corresponding compound was very likely to reveal activity in experiments, $0.5 < P_a < 0.7$ suggested that the compound was likely to reveal activity in experiments, while $P_a < 0.5$ 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 P_a higher than 0.7. Concerning the mutagenic or the photosensitising activities on the contrary, almost all the estimated P_a 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.

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

PASS (Prediction of Activity Spectra for Substances) estimations have been used for design of new antiparasitic compounds in imidazole series. Predictive antiparasitic values for the designed compounds 1–8 (acetamides) were higher than 0.6 for all structures, which indicated that these compounds could be likely to reveal this activity in experiments. For sulfonamides series 9–15, P_a values were also in the range of 0.5–0.6; hence, the structures are likely to reveal antiparasitic activity in experiments. Since the estimated P_a values were less than 0.7, it could be interpreted as rather small similarity of the studied compounds to the structures of known antiparasitic drugs. Experimental testing of biological activity against these three unicellular parasites has shown that compounds 1–8 (acetamide derivatives) exhibited mainly trichomonocidal and giardicidal properties, whereas compounds 9–15 (sulfonamide derivatives) exhibited antiamoebic activity.

Babaev E.V. (2009). Combinatorial chemistry at the university: ten years experience of research, educational and organizational projects. *Russian Chemical Journal*, **53** (5), 140-152.

1. PASS predicted the probable antimicrobial action for combinatorial libraries of 1-amino-4-(1,3-azoly-2)butadienes-1,3 derivatives. Studies of compounds' action against both gram-positive (*St. Aureus*) and gram-negative (*E. Coli*) bacteria have shown that for all synthesized compounds the predicted activity was confirmed by the experiment.
2. For novel 5-aminoindolysine derivatives beta-adrenergic activity has been predicted by PASS. Based on this prediction, these compounds have been tested on binding with the receptors from rats' brain synaptosomes. For the most potent compound the binding to beta-adrenoreceptors in percent to the control was equal to 89.7% in concentration 10 μ M, and 97.0% in concentration 100 μ M.
3. Based on PASS predictions, a few compounds has been selected for synthesis and experimental testing as potential anxiolytics among the five thousands structures of virtually designed combinatorial library. All the selected compounds exhibited the predicted activity in the experiment.
4. For series of new 2-imidazole derivatives antileishmanial activity has been predicted by PASS. Experimental testing of these compounds in University of Karachi (Pakistan) has demonstrated that their antileishmanial activity is comparable with the reference drug Amphotericin, which is known to be rather toxic.

Riju A., Sithara K., Suja S.N., et al. (2009). *In Silico* Screening Major Spice Phytochemicals for their Novel Biological Activity and Pharmacological Fitness. *Journal of Bioequivalence and Availability*, **1** (2): 063-073.

In silico screening of biological activity has been performed for 328 compounds present in five major spices namely, cinnamon (*Cinnamomum verum*), nutmeg (*Myristica fragrans*), garcinia (*Garcinia cambogia*), allspice (*Pimenta dioica*) and black pepper (*Piper nigrum* L.). Out of 328 compounds analyzed, ascorbic acid, nonaldehyde, delphinidin, malabaricone-B, malabaricone-C, isoquercitrin, quercitrin, α -bisabolol, cis-nerolidol, γ -eudesmol, hexan-1-ol and n-octanal were predicted as noncarcinogenic and non-mutagenic phytochemicals. Biological activity such as antiinflammatory, antioxidant, antiviral (HIV), antitoxic, free radical scavenging, cardioprotectant, hepatoprotectant, antitussive, antihemorrhagic etc. were predicted for these compounds; therefore they can be considered as promising pharmacotherapeutic agents.

Ghadimi S., Ebrahimi-Valmoozi A.A. (2009). Lipophilicity, electronic, steric and topological effects of some phosphoramidates on acetylcholinesterase inhibitory property. *J. Iran. Chem. Soc.*, **6** (4): 838-848.

Acetylcholinesterase (AChE) inhibitory activity has been predicted for phosphoramidates with the general formula $[(CH_3)_2N]P(O)[p-NHC_6H_4-X]_2$, where, X = F (1), Cl (2), Br (3), I (4), and $[(CH_3)_2N]P(O)X[p-OC_6H_4-CH_3]$, where, X = *o*-NHC₆H₄-CH₃ (5), *m*-NHC₆H₄-CH₃ (6), *p*-NHC₆H₄-CH₃ (7) using PASS program. The compounds have been synthesized and tested on human AChE activity using a modified Ellman's method, and spectrophotometric measurements. The IC₅₀ values for compounds 1-7 were found to be 0.19, 0.35, 0.50, 0.63, 2.70, 2.44 and 1.50 mM, respectively. The conclusions have been made about a stronger agreement between the computational evaluation and the experimental results.

Gregirchak N.M., Kosyanchuk Ya.S. (2009). Studies of biological activity of newly synthesized compounds. *Proceedings of the National University of Food Technologies*, No.28, 27-30.

PASS predictions have been obtained for 9809 chemical compounds synthesized at the Organic Chemistry Department of the National University of Food Technologies. 576 compounds predicted with $P_a > 0.5$ as antibacterial and/or antifungal agents with five probable mechanisms of action (2,3 Oxidosqualene lanosterol cyclase inhibitor, Anti-Helicobacter pylori, Antimycobacterial, Topoisomerase inhibitor, Membrane integrity antagonist) were selected. 22 chemical compounds were synthesized and tested on antibacterial (*Bacillus subtilis*, *Staphylococcus aureus* and

Escherichia coli) and antifungal (*Penicillium chrysogenum*, *Rhizopus nigricans*, *Fusarium*) activities. The most potent antimicrobial compounds contain the fragment 1-(1-phenylethyl)-pyrrolo[2,3-b]quinaxoline in their structure. As was shown by the sub-structural search in the available MDL databases, antibacterial and antifungal activity for compounds has not been ever described for this chemical series.

Carlsen L., Kenessov B., Batyrbekova S.Ye. (2009). 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*, **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.

Gholivand K., Orouzadeh N., Erben M.F., Della Vedova C.O. (2009). Synthesis, spectroscopy, computational study and prospective biological activity of two novel cyclic N-carbonyl phospholidines XP(O)(HNC(O)C(O)NH), X = Cl, C₆H₅CH₂NH, *Polyhedron*, **28** (3): 541-547.

Two new 1,3,2-diazaphospholidine-2,4,5-trione derivatives including 2-chloro-1,3,2-diazaphospholidine-2,4,5-trione (compound **1**) and 2-benzylamino-1,3,2-diazaphospholidine-2,4,5-trione (compound **2**) have been synthesized. A biological activity prediction using the PASS software has demonstrated that compound **1** with high probability exhibits anti-HIV activity, whereas compound **2** can be classified as a potential antineoplastic.

Mirzabekova N.S., Kuz'mina N.E., Lukashova O.I., et al. (2009). Synthesis and biological activity of permethrin analogs containing various substituents in position 2 of the cyclopropane ring. *Rus. J. Org. Chem.*, **45** (3), 355–359.

A number of permethrin derivatives having various substituents (Me, Et, Pr, Ph, PhCH₂, PhCH₂CH₂) in position 2 of the cyclopropane ring were synthesized and assayed for insecticidal activity against typhoid flies, rice weevils, and black bean aphid and juvenile hormone activity against flour beetle chrysalises. The examined compounds showed a weak insecticidal activity. Using PASS software the general pharmacological potential of the newly synthesized permethrin analogs was analyzed. It was found with a probability Pa>50% that some of the obtained compounds possessing no appreciable insecticidal activity (toxicity) may act as fibrinogen receptor antagonists, agents for the treatment of Alzheimer disease, inhibitors of cholesterol synthesis, stimulators of acetylcholine synthesis, and exhibit estrogenic and antiestrogenic activity.