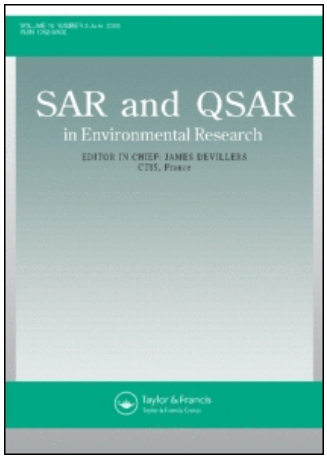

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Computer-aided prediction for medicinal chemistry via the Internet

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Computer-aided prediction for medicinal chemistry via the Internet[1]

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Some computational tools for medicinal chemistry freely available on the Internet were compared to examine whether the results of prediction obtained with different methods coincided or not. It was shown that the correlation coefficients varied from 0.65 to 0.90 for log P (seven methods), from 0.01 to 0.73 for aqueous solubility (four methods), and from 0.19 to 0.73 for drug-likeness (three methods). While for log P estimates, reasonable average pairwise correlation was found, for aqueous solubility and drug-likeness it was rather poor. Therefore, using computational tools freely available via the Internet, medicinal chemists should evaluate their accuracy versus experimental data for particular series of compounds. In contrast to prediction of above mentioned properties, which can be done with several Internet tools, wide profiling of biological activity can be obtained only with PASS Inet (http://www.ibmc.msk.ru/PASS). PASS Inet was tested by a dozen medicinal chemists for compounds from different chemical series with various kinds of biological activity, and in the majority of cases the results of prediction coincided with the experiments. New anxiolytics, antiarrhythmics, antileishmanials, and other biologically active agents have been identified on this basis. The advantages and limitations of computer-aided predictions for medicinal chemistry via the Internet are discussed.

Keywords: medicinal chemistry; internet prediction; lipophylicity; aqueous solubility; drug-likeness; biological activity; validation

1. Introduction

Chemical compounds synthesized in the framework of academic research are considered as a valuable source for discovery of new leads [1]. To increase the hits rate, medicinal chemists should apply rational approaches at the earliest stages of the studies, ideally during the planning of the synthesis. Computer-aided methods are widely used for this purpose, providing estimation of physical-chemical properties, biological activity, toxicity, etc. In addition to the numerous commercially-available computer programs, there are computational tools freely available via the Internet. Among them, the programs for prediction of melting point, boiling point, critical temperature, critical pressure and

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other physicochemical properties [2], solubility, lipophylicity and pKa [3], some kinds of biological activity (GPCR ligands, ion channel modulators, kinase inhibitors, nuclear receptor ligands) [4], irritancy, mutagenicity, carcinogenicity and reproductive effects [5], drug-likeness [6], etc. About 2500 pharmacotherapeutic effects, molecular mechanisms of action, adverse and toxic effects, and metabolic terms can be predicted with PASS Inet [7].

Currently, these computational tools are widely used by medicinal chemists for estimation of physical-chemical properties, biological activity, and (Q)SAR/(Q)SPR analysis [8–15]. However, in the majority of publications related to the medicinal chemistry there is no clear argumentation why this or that particular computational tool has been selected to obtain the computer-aided estimations. Usually, researchers, who are not specialized in (Q)SAR/(Q)SPR analysis, do not examine if a specific tool is applicable to molecules from the particular chemical series. Also, the validation of particular methods has been mostly provided by these authors; despite the importance of this problem [16], in many cases no independent comparative analysis of the prediction accuracy for different tools has been performed.

The purpose of this study was to survey some computational tools for medicinal chemistry freely available on the Internet in order to compare the prediction results provided by different tools for the same property, and to consider the advantages and drawbacks of computational predictions via the Internet for medicinal chemists.

2. Methods

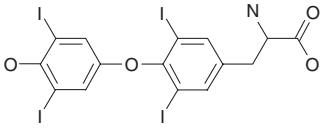
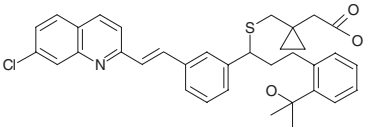
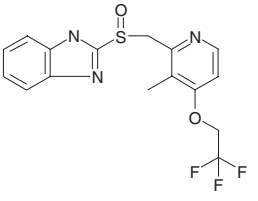
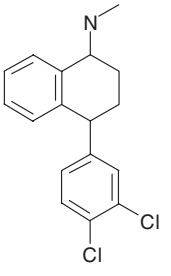
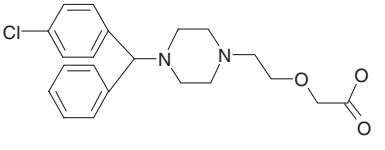
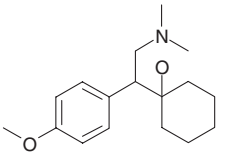
For the comparative study, several freely available Internet computational tools were selected. They predicted lipophylicity (log P) [3, 5, 6, 17], aqueous solubility [3, 5, 6, 17], and drug-likeness [5–7]. PASS Inet, which predicts about 2500 pharmacotherapeutic effects, molecular mechanisms of action, adverse and toxic effects, metabolic terms, is rather unique and there is no other freely available computational tool offering these functionalities. The methods of calculation are described in detail in the appropriate web-sites [3–7, 17] and/or in the publications, references on which can be found in these web-sites.

The criteria for selecting the computational tools applied in this work included: (1) possibility to obtain predictions with the real not with demo version of the program; (2) availability of detailed description of the appropriate algorithm; (3) usage of the representative training set as the basis for the prediction (more than 10,000 molecules for log P prediction, more than 1200 molecules for solubility prediction, more than 60,000 molecules for biological activity predictions).

Structural formula of compounds presented as a MOL-file or SMILES code can be used as input for some computational tools [3, 17], while for the others, structural formula is prepared using special web interface [5, 6]. Both options are possible for PASS Inet [7].

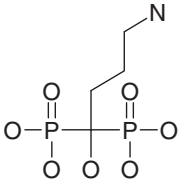
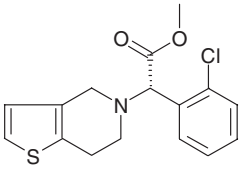
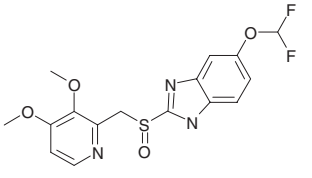
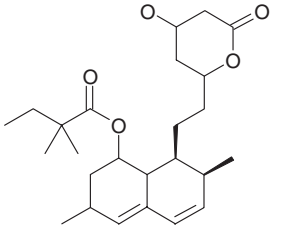
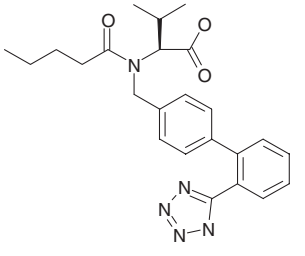
To compare the prediction results for the same properties obtained with different computational tools via the Internet, Top 20 mono-component drugs were selected among the Top 200 by prescription dispensed drugs [18]. The list of these drugs, their structural formulae, major pharmacotherapeutic effects, and mechanisms of action are given in Table 1. It is obvious from the data presented in Table 1 that the Top 20 set is rather diverse, both in chemical structure and biological activity.

Table 1. List of Top 20 mono-component drugs.

No.	*Drug name and structural formula*	*Pharmacotherapeutic action*
1	Synthroid (Lebothyroxine sodium) 	Thyroid hormone agonist
2	Singulair (Montelukast sodium) 	Leukotriene receptor antagonist
3	Prevacid (Lansoprasole) 	Antiulcerative Anti-Helicobacter pylori H +/K + -transporting ATPase inhibitor
4	Zoloft (Sertraline hydrochloride) 	Antidepressant 5 Hydroxytryptamine uptake inhibitor
5	Zyrtec (Cetirizine hydrochloride) 	Antiallergic Antihistaminic Histamine H1 receptor antagonist
6	Effexor XR (Venlafaxine hydrochloride) 	Antidepressant 5-Hydroxytryptamine uptake inhibitor Adrenaline uptake inhibitor Dopamine uptake inhibitor

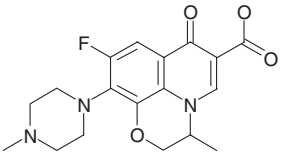
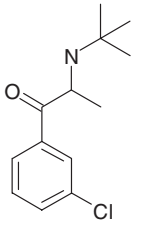
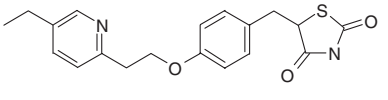
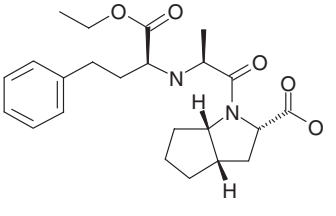
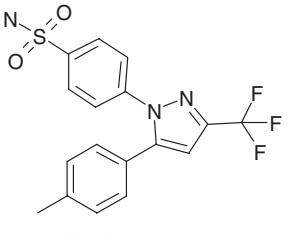
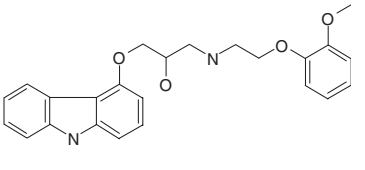
(*Continued*)

Table 1. Continued.

No.	*Drug name and structural formula*	*Pharmacotherapeutic action*
7	Fosamax (Alendronate sodium) 	Antiosteoporotic Bone formation stimulant Bisphosphonate
8	Plavix (Clopidogrel bisulfate) 	Platelet aggregation inhibitor
9	Protonix (Pantoprazole sodium) 	Gastric antisecretory H+/K+-transporting ATPase inhibitor
10	Zocor (Simvastatine) 	Atherosclerosis treatment Antihypercholesterolemic
11	Diovan (Valsartan) 	Antihypertensive Angiotensin II receptor antagonist Angiotensin AT1 receptor antagonist

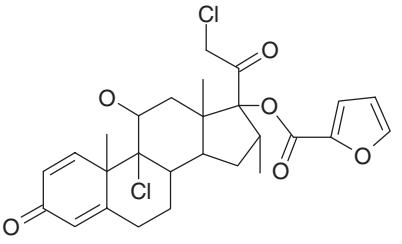
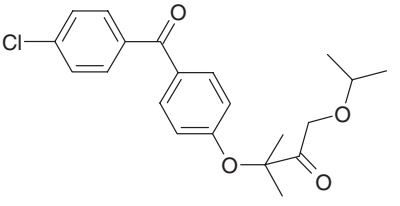
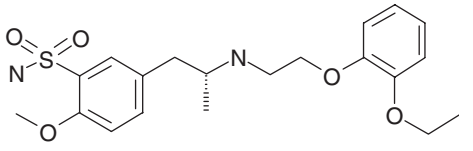
(*Continued*)

Table 1. Continued.

No.	*Drug name and structural formula*	*Pharmacotherapeutic action*
12	Levaquin (Levofloxacine) 	Antibacterial Topoisomerase II inhibitor
13	Wellbutrin XL (Bupropion hydrochloride) 	Antidepressant Noradrenaline uptake inhibitor Dopamine uptake inhibitor
14	Actos (Pioglytazone hydrochloride) 	Antidiabetic Peroxisome proliferator-activated receptor (PPAR) gamma agonist
15	Altace (Ramipril) 	Antihypertensive Angiotensin converting enzyme inhibitor
16	Celebrex (Celecoxib) 	Non-steroidal anti-inflammatory Analgesic Antipyretic Cyclooxygenase 2 inhibitor
17	Coreg (Carvedilol) 	Heart failure treatment Beta adrenoreceptor antagonist Alpha 1 adrenoreceptor antagonist

(*Continued*)

Table 1. Continued.

No.	*Drug name and structural formula*	*Pharmacotherapeutic action*
18	Nasonex (Mometasone fluorate monohydrate) 	Antiinflammatory steroid, glucocorticoid
19	Tricor (Fenofibrate) 	Atherosclerosis treatment Antihypercholesterolemic
20	Flomax (Tamsulosine hydrochloride) 	Benign prostatic hyperplasia treatment Alpha 1 adrenoreceptor antagonist

The Pearson correlation coefficient values were calculated as a measure of pairwise correlation of prediction results obtained by the different methods.

3. Results and discussion

3.1 *Lipophylicity estimation*

Seven different methods were used for estimation of the log P of the Top 20 drugs, including: A – ALOGPs [3], B – XLOGP [3], C – miLOGP [3], D – KOWWIN [3], E – IA_Log P [17], F – Log P [6], and G – Log P [5]. The two last computational tools presented at the web-sites [5] and [6] are called by the same names. Pairwise correlation coefficients between the prediction results acquired with different methods are presented in Table 2.

As shown in Table 2, the values of correlation coefficients vary from 0.65 (A and D) to 0.90 (B and G). In general, the results of prediction obtained with different methods looks similar that corresponds to the earlier conclusions [19]. Since the importance of lipophylicity for drug design and (Q)SAR is recognized more than forty years ago, the methods of log P calculation were extensively developed and improved during the past forty years. Thus, medicinal chemist can choose any of tools freely available via Internet for log P calculations.

Table 2. Correlation coefficients for log P values predicted by seven different methods.

Method	*A*	*B*	*C*	*D**	*E*	*F*	*G*
A	1.00	0.71	0.74	0.65	0.90	0.81	0.67
B		1.00	0.90	0.72	0.76	0.85	0.90
C			1.00	0.72	0.77	0.83	0.88
D*				1.00	0.62	0.69	0.65
E					1.00	0.77	0.66
F						1.00	0.84
G							1.00

*Estimations of log P values by KOWWIN method were obtained for 17 drugs. Prevacid, Celebrex and Flomax contain the sulphur, and KOWWIN cannot do predictions for such molecules.

3.2 *Solubility estimation*

Four different methods were used for the aqueous solubility estimation of the Top 20 drugs. They included: H – ALOGpS [3], I – Log W [17], J – Log S [6], and K – Log S [5]. Two computational tools presented at web-sites [5] and [6] are based on different methods but their authors use the same name for them. Pairwise correlation coefficients between the prediction results acquired with different methods are presented in Table 3.

As one may see from the data presented in Table 3, in general there is no significant pairwise correlation between the values of solubility obtained with different computational tools except those for H and J. Since there is no objective criterion to determine *a priori* which method of solubility estimation is "the best", the choice of medicinal chemist may be either based on her/his confidence to particular authors or recommendations of colleagues. Both rationales for the choice are rather arbitrary, and do not provide the guaranty for a high quality of the obtained results.

3.3 *Drug-likeness estimation*

The three following different methods were used for the estimation of drug-likeness of the Top 20: L [6], M [5], N [7]. Pairwise correlation coefficients between the prediction results acquired with different methods are presented in Table 4.

As it is shown in Table 4, the correlation coefficient between the results obtained with methods L and N equals to 0.73; while for two other pair correlations, they are less than 0.3. Thus, the conclusion is quite similar to the one made in paragraph 3.2: it is not possible to select "the best" method for drug-likeness estimation on the basis of objective criteria.

3.4 *Biological activity estimation*

In contrast to lipophylicity, solubility, and drug-likeness, which can be predicted with several methods, there are not so many computational tools for prediction of biological activity which are freely available via Internet. We were able to identify two resources for prediction of a few kinds of biological activity [4, 5] and PASS Inet that predicts about 2500 kinds of biological activities [7]. These computational resources are quite different in coverage of biological activities; therefore the direct comparison of their results does not

Table 3. Correlation coefficients for aqueous solubility values predicted by four different methods.

Method	*H*	*I*	*J*	*K*
H	1.00	0.19	0.73	0.13
I		1.00	0.27	0.01
J			1.00	0.40
K				1.00

Table 4. Correlation coefficients for drug-likeness values predicted by three different methods.

Method	*L*	*M*	*N*
L	1.00	0.19	0.73
M		1.00	0.27
N			1.00

give statistically significant estimations. PASS Inet [20, 21] is a rather unique service that can be used by medicinal chemists for evaluation of general biological potential of molecules under study.

Despite the extensive validation of PASS performed by the authors (see, e.g., [22–24]), where ~90% accuracy of prediction has been demonstrated, independent estimations of its prediction accuracy might be valuable. As PASS Inet service is available from 2000, it is reasonable to suggest that PASS predictions have been further tested experimentally and at least some results are published. Such publications [8, 10, 11, 25–36] were identified by special information search in bibliographic databases and in the Internet. The results of PASS predictions testing presented in these publications are summarized in Table 5.

From these data it is clear that in the past seven years, PASS predictions have been tested for chemical compounds from different chemical series with various kinds of biological activity by a dozen of medicinal chemists from several countries. As a result, it was concluded that predictions coincided well with the experiments, thus providing the independent validation of PASS approach.

3.5 *Advantages and limitations of computer-aided predictions via the Internet*

The main advantage of computer-aided predictions of physical-chemical properties, drug-likeness, and biological activity, using the Internet tools, is their free availability. This is particularly important for medicinal chemists from academy, because (1) researchers from academy are rather limited in resources for the purchase of expensive licenses on commercially available software; (2) researchers from industry cannot send the molecules under study via the Internet due to the confidentiality of their data.

However, as we shown in this study, because of the poor correlation between the results of prediction of aqueous solubility and drug-likeness, obtained with different methods, it is necessary to perform independent evaluations of the prediction accuracy of the selected methods for each particular case.

Table 5. PASS predictions of biological activity confirmed by further experiments.

Chemical class	*Biological activity*	*References*
7-Substituted 9-Chloro and 9-Amino-2-Methoxyacridines	Antileishmanial	[8]
Quinazolines	Anxiolytic, GABA-ergic	[10]
1-Acylaminoalkyl-3,4-dialkoxybenzene derivatives	Antiinflammatory	[11]
Substituted amides and hydrazides of dicarboxylic acids	Antibacterial Antiinflammatory	[25] [26]
2 Substitution-Bearing 6-Nitro- and 6-Amino-Benzothiazoles	Antileishmanial, Antitrichomonal	[27]
Harmane, harmine, and harmaline (beta-carboline alkaloids)	Antileishmanial	[28]
Violacein (violet pigment produced by *Chromobacterium violaceum*)	Antlieishmanial, Antiviral	[29]
Azetidin-2-ones	CNS-modulating activity	[30]
2-Diethylamino-2, 6 dimethylphenylacetamide derivatives	Antiarrhythmic	[31]
2-(substituted phenyl)-1H-benzimidazoles	Antihypertensive	[32]
Polyketides (from the marine-derived fungus *Ascochyta salicorniae*)	Phosphatase inhibitor	[33]
Ninhydrin–phenol adducts	Antioxidant, Analgesic, Antinflammatory	[34]
Cyclic nitrones	Nootropic	[35]
Gem-diphosphono substituted-thiazoles	Antiinflamatory, Antiresorptive	[36]

Even in the case of log P predictions, for which the estimates obtained with different methods have the best coincidence each to the others, it is necessary to keep in mind that the average number of outliers, for which this property cannot be predicted by the "traditional" methods, is about 12% [19]. In some cases the molecule under study may appear to be one of such outliers, therefore prior to the prediction for new molecules medicinal chemist should evaluate the accuracy of the used method versus the experimental data obtained for her/his particular series of compounds. However, correspondence between the calculated and experimental data significantly varies for both different methods and the range of log *P* values, thus further studies are still required [37].

In contrast to the prediction of physical-chemical properties, where several tools can be compared, PASS Inet is the only computer tool freely available via the Internet, which predicts about 2500 kinds of biological activities. Therefore, it is impossible to compare the quality of PASS predictions with any other method freely available via the Internet. Fortunately, as surveyed in this work, PASS Inet service has been independently evaluated by many medicinal chemists from different countries, who demonstrated that the majority of PASS predictions were confirmed by the experiment (Table 5).

The main drawback of PASS Inet service is unfeasibility to submit for prediction many molecules simultaneously presented as SDF file. Secondly, PASS Inet provides prediction for less number of biological activities in comparison with the local version of the program. At third, PASS Professional allows addition of new data about

biologically active compounds to the training set with further re-training of PASS, which might significantly increase the accuracy of prediction in the framework of particular projects.

This was clearly demonstrated by our joint project supported by INTAS, in the framework of which new anxiolytics and cognition enhancers were discovered [38, 39].

4. Conclusions

Different computational tools for medicinal chemistry available freely on the Internet were considered. By comparison of the prediction results for the same properties provided by different tools (lipophylicity, solubility and drug-likeness) it was shown that these data may vary significantly, and in general there is no objective criteria for selecting "the best" method. Therefore, the validation of computational approaches can be performed only by comparison of predicted properties with the results of experimental studies. Such validation was done by a dozen independent teams for PASS and in the majority of cases the results of prediction were confirmed by the experiments.

Acknowledgements

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