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How good are publicly available web services that predict bioactivity profiles for drug repurposing?[$]

K. A. Murtazalieva[a,b], D. S. Druzhilovskiy[a], R. K. Goel[c], G. N. Sastry[d] and V. V. Poroikov[a]

[a]Institute of Biomedical Chemistry, Moscow, Russia; [b]Pirogov Russian National Research Medical University, Moscow, Russia; [c]Punjabi University, Patiala, Punjab, India; [d]CSIR-Indian Institute of Chemical Technology, Hyderabad, India

ABSTRACT

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

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Drug repurposing; bioactivity profile prediction; similarity assessment; machine learning; web services; performance evaluation

Introduction

The increased interest in drug repurposing in recent years is caused by the significant advantages provided through exploitation of such an approach to society, which include possibilities of finding new therapies for unmet medical needs, discovery of more efficacious treatments, replacing expensive with cheaper drugs and substituting drugs with unwanted side-effects with safer medications [1–4]. Successfully repositioned drugs enter the market 3–5 years faster, their development is less expensive and the success rate is higher in comparison with the pharmaceutical research and development carried out *de novo* [1, 5, 6]. Due to the substantial reduction of cost, such studies could be performed by the academic

CONTACT V. V. Poroikov vladimir.poroikov@ibmc.msk.ru

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researchers with a limited budget, which might be particularly useful in the discovery of new medicines for the neglected diseases [7–11]. Earlier, novel indications for the majority of repositioned drugs were found either due to serendipity or by utilization of the side-effects observed in clinical practice [1, 12]. Currently, more systematic efforts to identify new indications for old drugs are being performed through the detection of new drug-target interactions, determining new roles of existing targets, finding new disease pathways and revealing compounds that modulate specific disease phenotypes [13–17]. Experimental profiling of multitargeted drug action is shown to be useful; however, it requires considerable investment into the appropriate infrastructure and covers only a limited part of the general pharmacological field. *In silico* methods provide the opportunity of finding novel drug-target-disease associations that might substantially diminish the number of experimental and clinical studies due to the reduction in size of the chemical-biological space [4, 18–21].

In recent years some freely available via the Internet ligand-based computational tools for prediction of biological activity profiles of drug-like compounds have appeared [22–28]. These tools have been retrospectively validated by their authors [29–40] and they could be potentially useful for executing drug repositioning projects performed by academic researchers [41–45]. Performance of some predictive web services was compared in computational experiments earlier [46–48]. However, no systematic assessment of their accuracy and applicability for the drug repurposing task has been performed yet. Here we present the results of a computational evaluation of the comparative strength and weakness of seven ligand-based computational web services freely available via the Internet. Analysis of the obtained results will help researchers to make a reasonable choice of the most appropriate computational approaches directed to drug repurposing.

Freely available web services for predicting bioactivity profiles

The studied web services may be broadly classified in accordance with the methods used for estimating the biological activity profiles. They are based either on chemical similarity assessment (ChemProt, SuperPred, SEA, SwissTargetPrediction, and TargetHunter) or on machine learning classification methods (ChemProt, PASS).

A brief description of the web services evaluated in our work is given below.

SuperPred

SuperPred [24, 31, 38] provides two methods of prediction: (1) drug classification according to the ATC (Anatomic-Therapeutic-Chemical) taxonomy based on analysis of a dataset containing 2650 drugs; and (2) target prediction based on 665,000 known compound-target interactions for 1800 mammal proteins and 341,000 compounds.

The first method takes into account 2D fragment similarity and a method for 3D superposition of small molecules. The second method considers the similarity distribution among ligands, to estimate the individual thresholds for the particular target, thus reducing the probability of false positive predictions. The input information is the compound's structural formula, which may be uploaded as either MOL file or SMILES. Also, a PubChem name search may be performed or the user may draw a structural formula with ChemDoodle editor.

The output in both cases includes the structural formula, some calculated structural and physical-chemical properties of the input compound. In addition, the output contains the

predicted ATC groups with the calculated value of Tanimoto Coefficient (drug classification) or list of predicted targets with the calculated E-values (target prediction). The estimated accuracy of prediction for drug classification is 75.1% and for target prediction is 94.1% [38].

SwissTargetPrediction

SwissTargetPrediction [35] estimates the 2D- and 3D-similarity of the studied compound with 280,381 known ligands of 2686 targets, with the majority of targets (66%) represented by human proteins. The input information is the compound's structural formula, which may be either uploaded as SMILES or drawn with ChemAxon's (http://www.chemaxon.com) chemical editor. The user has to select the organism for which the prediction will be performed (human, mouse, rat, cow or horse). By default, the prediction is performed for human proteins. The output presents the list of the predicted targets' names ranked according to their score concerning the studied compound. In addition, the links to GeneCards [49], UniProt [50] and ChEMBL [51] databases are provided (if available). Validation of the different methods applied in SwissTargetPrediction by leave-one-out cross-validation gave area under the curve (AUC) values in the range 0.894–0.994 [34]. Suggesting that such estimates may suffer from internal biases in the training data, validation using the external set has been performed. AUC values obtained in such a validation are equal to 0.87 for both positive and negative interactions [35].

TargetHunter

TargetHunter [40] estimates the similarity of the query molecule with 117,535 known ligands of 794 targets using TAMOSIC (Targets Associated with its MOst SImilar Counterparts) method. This method determines the most similar compounds from the training set based on ESFP6/ESFP4/FP2 fingerprints. If the Tanimoto Coefficients (TC) reflecting the similarity of the studied compound and more than N compounds from the training set interacting with a given target exceeded a certain threshold, one might suggest that the studied compound may also interact with this target. The higher value of the threshold should correspond to less probability of the false positive results. By default, the web service works with TC > 0.6. The input information is the compound's structural formula, which may be uploaded as a MOL or SDF file, or to be drawn by the user with the embedded JSME Molecule Editor [52]. The output contains information about structural formula, associated protein targets, bioactivity information and references for the most similar compounds in the ChEMBL database estimated based on TC values. The average accuracy of 7-fold cross-validations of this method is 90.9% when the top 3 predictions are taken into account.

SEA

SEA (Similarity Ensemble Approach) [30] predicts the targets for the studied compound based on similarity assessment with known ligands of those targets. The similarity is estimated by calculating the Tanimoto Coefficient values using Daylight fingerprints. If the TC > 0.57, the studied compound is considered as probably having affinity to the appropriate target. Input information is the structural formula of the studied compound, presented as SMILES. The user should also select the database of compounds with which the similarity

will be estimated. The list of available databases includes ChEMBL v.16 or v.12, MDDR, WOMBAT, KEGG and StarLite. The output contains the structural formula of the query molecule and the list of predicted targets arranged in descending order of the maximum TC values. Besides, E-values are presented for each predicted target. It is possible to view the structural formulae of the similar molecules, based on which the prediction for particular targets has been performed. We did not find any data about the average accuracy of this web service in the paper [30]; instead, the website [23] contains the disclaimer: 'SEA is provided free-of-charge in the hope that it will be useful, but you must use it at your own risk'. In our study, we used ChEMBL v.16 with the cut-off for active compounds binding corresponding to 10 uM.

ChemProt

ChemProt 3.0 [39] estimates the chemical similarity of the studied compound with about 1.7 million known ligands of more than 20,000 protein targets. The 2D similarity is estimated based on the SEA method (see above): if the TC value exceeded 0.85, the compounds were predicted to have common targets. To increase the accuracy of prediction, the interaction of the studied compound with 850 human proteins may be predicted by pre-calculated QSAR models developed with a Bayesian classifier. Input information is the common name or the structural formula of the studied compound presented as SMILES. The structural formula may also be drawn with the JSME chemical editor. The output presents a heatmap that provides the options for the visualization and selection of chemicals that share similar structural properties as well as analyses the associations with targets, pathways, diseases and clinical effects. Validation of the predictive methods was carried out using the independent test set of 2090 chemical compounds interacting with 143 proteins responsible for the development of adverse effects. QSAR models were found to provide significantly better accuracy compared to the similarity assessment with the SEA: Mathew coefficient values were 0.288,056 and 0.151,965, respectively. In our study, we uploaded the SMILES with the structural formula of the drug and used the default value of the Tanimoto coefficient equals to 0.85.

PASS online

PASS (Prediction of Activity Spectra for Substances) estimates probabilities of belonging to the classes of 'actives' (Pa) and 'inactives' (Pi) for over 4000 biological activities from structure-activity relationships' analysis for the training set, including more than 300,000 biologically active compounds. The machine learning method implemented in PASS is based on the Bayesian algorithm and Multilevel Neighbourhoods of Atoms (MNA) descriptors. There are three options to input the structural formula of the studied compound to this web service: upload SMILES or MOL files or draw the structure using Marvin JS chemical editor [53]. As an output, the user obtains the list of probable activities with the estimated Pa and Pi values, which is arranged in the descending order of Pa to Pi. PASS validation by leave-one-out and 20-fold cross-validation gave an average accuracy of prediction of about 95% [36].

To avoid the overfitting, all information about the substance from PASS training set, which is equivalent to the substance under prediction, is excluded from SAR Base during the training procedure, which are equivalent to the substance under prediction. The chemical

structures are considered equivalent in PASS if their molecular structures have the same set of MNA descriptors. Thus, if PASS Online input contains the structure of the drug, which is included in the PASS training set, during the prediction all information about this drug is excluded and prediction is performed based on the remaining part of the PASS knowledge base.

TarPred

TarPred [32, 33] estimates the similarity of the query molecule with 179,807 known ligands of 533 individual targets using *K* Nearest Neighbour (*K*NN) method. The similarity is measured by the Tanimoto coefficient. *K*NN score is the average similarity of *K* most similar ligands of the target to the query molecule based on ECFP4 fingerprints. The input information is the compound's structural formula, which may be either uploaded as SMILES or drawn with Marvin JS chemical editor [53]. The output presents the list containing the top 30 of the predicted targets' names ranked according to their *K*NN score for the studied compound. For each target, detailed information about its Binding DB and DrugBank names, Gene IDs, predicted diseases and the pictures of three nearest compound neighbours to the query compound in the target ligand set are available. Validation of the method applied in TarPred by 10-fold cross-validation gave the uninterpolated precision (PR') value as 0.95. PR' is given by the averaged precision values PRi from the ranking places 1 to *m*, which corresponds to the number of true targets of the ligand from the reference set. In the validation, the overall reference set was randomly split into 10 parts. For the ligands of each part, their targets were predicted using the ligands and the targets information of the remaining nine parts.

Preparation of the evaluation sets

The set of well-known repositioned drugs

Despite the existence of numerous reviews [1, 2, 4–6, 12] and specialized web-resources [54–56] dedicated to the problem of drug repurposing, creating an accurate evaluation set for validation of predictive tools required the particular efforts. As was noted in a recently published paper: 'No common definition of drug repositioning or indeed for other similar terms has been found in the literature. Moreover, the definitions differed significantly in their wording used for the features, often leading to essential differences in their meaning' [57].

Moreover, we found that sometimes the information in the literature regarding the drug repurposing mentioned in earlier publications was not confirmed by the subsequent clinical trials. For example, the antibacterial drug Ceftriaxone was suggested to be repurposed for treatment of Amyotrophic lateral sclerosis [58]. However, the clinical efficacy of Ceftriaxone in the therapy of amyotrophic lateral sclerosis was not shown at stage III of clinical trials [59]. Despite that, in the subsequent review [60], Ceftriaxone was mentioned 'as a repurposed treatment for amyotrophic lateral sclerosis'.

Therefore, we have carefully examined each case of drug repurposing based on the official information presented in the FDA Label database [61, 62] and analysis of the original publications, not relying only on the information presented in the databases and reviews. To find the relevant information about the original publications we used the freely available informational systems PubMed [63] and DrugBank [64] as well as the commercially available

specialized drug information portal Clarivate Analytics (former Thomson Reuters) Integrity [65]. In some cases, the Google search engine was exploited to find the relevant information. For the evaluation set, we selected mostly those drugs which were approved for use in medical practice for both initial and repurposed indication. We also included in the set several drugs with the repurposed indication, which are currently under registration or in phase III clinical trials.

The list of drugs included in the first evaluation set with the information about their initial and repurposed indications as well as about the appropriate molecular mechanisms of action and the corresponding references are given in Tables 1 and 2.

The first evaluation set of 50 drugs represents organic molecules from different chemical classes and covers broad pharmacotherapeutic fields, which allows its utilization for comparative evaluation of various web services predicted biological activity profiles. Information about structural formulae of the active pharmaceutical ingredients (APIs) of these 50 drugs was exported from the Integrity database [65] and subjected to curation following the recent recommendations [96, 97].

The set of recently patented repositioned drugs

The majority of the analysed web services are based on a similarity assessment. If the knowledge base of the particular computational tool contains the information about initial and repurposed indications, such indications must be easily identified. However, such good performance of any similarity-based tool for the well-known repositioned drugs does not guarantee its reasonable predictive accuracy in the case of novel drug molecules. To check the predictive accuracy of the seven web services under consideration, we created a second evaluation set, consisting of 12 drugs patented for their repositioned indication from April 2016 to March 2017 [98–101]. The list of drugs included in the second evaluation set with the information about their initial and repurposed indications as well as about the appropriate molecular mechanisms of action and the corresponding references is given in Tables 3 and 4. This set also covers several pharmacotherapeutic fields and includes pharmaceutical substances belonging to different chemical classes.

Since the information about the repurposed indications of these drugs is likely not included in the knowledge bases of the analysed web services, appraisal of performance using this evaluation set provides more unbiased estimates of their predictivity.

The procedure of preparation of the evaluation set based on the information from the patents was completely the same as described above for the first evaluation set.

Results

Bioactivity profile predictions for drugs from the first evaluation set

The comparative performance of the seven analysed web services is characterized by the sensitivity (*S*) values, which are calculated as a ratio of the number of correctly predicted biological activities to the total number of known biological activities.

The prediction was considered as correct if the predicted pharmacotherapeutic effect or molecular mechanism of action (or both) correspond to those associated with the initial or repurposed indications for a particular drug.

Table 1. List of the initial indications of drugs included in the first evaluation set.

Drug	*Indication(s)/year*	*Target(s)/MOA(s)*
Alfentanil hydrochloride	Anaesthesia (1986)	Mu-type opioid receptor agonist
Alprostadil	Hypotension and peripheral obstructive vascular disease (1979)	Prostaglandin E2 receptor agonist
Amantadine hydrochloride	Influenza A virus infection (1966)	Matrix protein 2 (Influenza virus A) inhibitor
Amitriptyline hydrochloride	Depression (1962)	Norepinephrine and 5-HT reuptake inhibitor
Apomorphine hydrochloride	Parkinson's disease (1968)	Dopamine D2 agonist
Acetylsalicylic acid	Inflammation, Pain (1899)	Cyclooxygenase inhibitor
Baclofen	Spasticity (1974)	GABA(B) receptor agonist
Bethanidine sulphate	Hypertension (1976)	Alpha-2a adrenergic receptors agonist
Bosentan	Pulmonary hypertension (2001)	Endothelin (ETA/ETB) receptor antagonist
Buprenorphine hydrochloride	Pain (1982)	Mu-type opioid receptor agonist
Celecoxib	Arthritis Osteoarthritis Polyposis coli (1999)	Cyclooxygenase 2 inhibitor
Chloroquine phosphate	Malaria (1949)	Haem polymerase inhibitor
Chlorpromazine	Antipsychotic (1959)	Dopamine D2 antagonists
Digitoxin	Heart failure Arrhythmia (1937)	Sodium-potassium ATPase inhibitor
Doxepin hydrochloride	Depression (1971)	5HT and norepinephrine reuptake inhibitor
Duloxetine hydrochloride	Depression (2004)	5HT, norepinephrine and dopamine reuptake inhibitor
Eflornithine hydrochloride	African trypanosomiasis (sleeping sickness) (1991)	Ornithine decarboxylase inhibitor
Erlotinib hydrochloride	Non-small cell lung cancer (2004)	Epidermal growth factor receptor (EGFR) inhibitor
Everolimus	Transplant rejection (2004)	FK506-binding protein 12 inhibitor mTOR inhibitor
Finasteride	Benign prostatic hyperplasia (1992)	Steroid 5alpha reductase inhibitor Androgen receptor antagonist
Galantamine hydrobromide	Polio, Paralysis, Anaesthesia (1961)	Acetyl-cholinesterase inhibitor
Gemcitabine hydrochloride	Antiviral (1980)	Ribonucleoside-diphosphate reductase inhibitor
Guanfacine hydrochloride	Hypertension (1981)	Alpha-2 adrenergic receptor agonist
Ibuprofen	Inflammation (1969)	Prostaglandin G/H synthase 1, 2 inhibitor
Imatinib	Chronic myelogenous leukaemia (2001)	Proto-oncogene tyrosine-protein kinase ABL inhibitor
Iproniazid	Tuberculosis (1953)	Generation of reactive metabolites inhibiting Biosynthetic enzymes of M. tuberculosis inhibitor
Itraconazole	Antifungal agent (1988)	Lanosterol 14-alpha demethylase inhibitor
Ketoconazole	Antifungal (1981)	Fungal Cytochrome P450 51 inhibitor
Lidocaine	Local anaesthesia (1994)	Sodium channels (voltage-gated) blocker
Memantine hydrochloride	Antiviral (1981)	NMDA receptor antagonists
Metformin hydrochloride	Diabetic (1959)	AMP-activated protein kinase (AMPK) activator
Methotrexate	Cancers (breast, metastatic head and neck cancer, leukaemia) Rheumatoid arthritis (1954)	Dihydrofolate reductase inhibitor
Milnacipran	Depression (1995)	5-HT and norepinephrine reuptake inhibitor
Miltefosine	Cancer (1993)	Akt/PKB inhibitor
Minocycline hydrochloride	Antibacterial Acne treatment (1971)	30S ribosomal protein inhibitor

(*Continued*)

Table 1. (*Continued*).

Drug	*Indication(s)/year*	*Target(s)/MOA(s)*
Nelfinavir mesilate	HIV (Human immuno-deficiency virus) infection (1997)	HIV-1 (Human immuno-deficiency virus, type 1) protease inhibitor
Nilotinib hydrochloride monohydrate	Chronic myeloid leukaemia (2007)	Bcr-Abl kinase inhibitor
Nitisinone	Hereditary tyrosinemia type I (2002)	4-hydroxy-phenylpyruvate dioxygenase inhibitor
Paclitaxel	Cancers (breast, ovary, lung non-small cell, AIDS-related Kaposi's sarcoma, stomach, endometrium, angiosarcoma, cervix, head and neck, oesophageal carcinoma, germ cells) (1993)	Tubulin beta modulator (microtubule-stabilizing agent)
Phentolamine mesilate	Erectile dysfunction (1998)	Alpha-adrenoceptor antagonist
Raloxifene hydrochloride	Osteoporosis (1998)	Oestrogen receptor agonist
Ropinirole	Parkinson's disease (1996)	Dopamine D2 and D3 receptor agonist
Sildenafil citrate	Erectile dysfunction (1998)	Phospho-diesterase (PDE5A) inhibitors
Simvastatin	Hypercholesterolemia (1988)	3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor
Targretin	T-cell lymphoma (2000)	Retinoid X receptor (RXR) agonist
Tetrabenazine	Huntington's disease (1971)	Vesicular monoamine transporter 2 (VMAT2) inhibitor
Thalidomide	Sedative Nausea preventing (1957)	—
Topiramate	Epilepsy (1995)	Kainate receptor antagonist, AMPA receptor antagonist, Carbonic anhydrase type II inhibitor, Sodium channel blocker
Toremifene	Breast cancer (1988)	Selective oestrogen receptor modulator
Vorinostat	Cutaneous T-cell lymphoma (2006)	Histone deacetylase 6, 2, 1, 3 inhibitor

Table 2. List of the repurposed indications of drugs included in the first evaluation set.

Drug	*Indication(s)/year*	*Target(s)/MOA(s)*	*Refs*
Alfentanil hydrochloride	Acute pain (phase II/III)	Mu-type opioid receptor agonist	[62, 65, 66]
Alprostadil	Erectile dysfunction (1994)	Prostaglandin E2 receptor agonist	[62, 65]
Amantadine hydrochloride	Parkinson's disease (1966)	Dopamine receptor agonists NMDA receptor antagonists	[62, 65]
Amitriptyline hydrochloride	Fibromyalgia (phase III) Peripheral neuropathy (phase III)	Sodium channel blocker	[62, 65]
Apomorphine hydrochloride	Erectile dysfunction (phase II)	Dopamine D4 agonist	[62, 65, 67]
Acetylsalicylic acid	Thrombosis (2009)	Cyclooxygenase inhibitor	[62, 65]
Baclofen	Alcoholism (phase III)	GABA(B) receptor agonist	[68]
Bethanidine sulphate	Ventricular fibrillation suppression (1982)	Potassium channel blocker	[69, 70]
Bosentan	Digital ulcers in systemic sclerosis (2008)	Endothelin (ETA/ETB) receptor antagonist	[62, 65, 71]
Buprenorphine hydrochloride	Opioid dependency (1995)	Mu-type opioid receptor agonist	[62, 65]
Celecoxib	Pain Dysmenorrhea (2002) Ankylosing spondylitis (2005)	Cyclooxygenase 2 inhibitor	[62, 65]
Chloroquine phosphate	Glioma Glioblastoma multiforme (phase III)	TGF beta suppression	[62,65,72,73]
Chlorpromazine	Colorectal cancer (phase II)	Sirtuin 1 inhibitor	[62, 65, 74]
Digitoxin	Cystic fibrosis (phase II)	TNF-α/NF-κb signalling pathway inhibitor	[75]
Doxepin hydrochloride	Pruritis (1998) Insomnia (2010)	H1 and H2 histamine receptor blocker	[62, 65, 76]
Duloxetine hydrochloride	Urinary incontinence Generalized anxiety disorder (2007) Neuropathic pain (2010)	5HT, norepinephrine and dopamine reuptake inhibitor	[62, 65]
Eflornithine hydrochloride	Hair growth abnormality (2000) Cancer (phase II/III)	Ornithine decarboxylase inhibitor	[62, 65]
Erlotinib hydrochloride	Pancreatic and pancreatic metastatic cancer, Ependymoma, Mouth cancer, Head and neck cancer (2007)	Epidermal growth factor receptor (EGFR) inhibitor	[62, 65]
Everolimus	Cancers (2009)	FK506-binding protein 12 inhibitor mTOR inhibitor	[62, 65]
Finasteride	Hair loss (1998)	Steroid 5alpha reductase inhibitor Androgen receptor antagonist	[62, 65]
Galantamine hydrobromide	Alzheimer's type dementia (1995)	Acetyl-cholinesterase inhibitor	[62, 64, 65]
Gemcitabine hydrochloride	Cancers (NSCLC, pancreas, breast, biliary, ovary, bladder, breast, lymphoma) (1995)	Ribonucleoside-diphosphate reductase inhibitor	[62, 65, 77]
Guanfacine hydrochloride	Attention-deficit/Hyperactivity disorder (2009)	Alpha-2 adrenergic receptor agonist	[62, 65]
Ibuprofen	Patent ductus arteriosus (2004)	Prostaglandin G/H synthase 1, 2 inhibitor	[62, 65, 78]
Imatinib	Gastrointestinal stromal tumour (2003) Fibrosarcoma Hypereosinophilic syndrome Acute lymphocytic leukaemia Myeloproliferative diseases and systemic mastocytosis (2006)	Platelet-derived growth factor receptors (PDGFR) inhibitor, Stem cell factor (SCF) and Proto-oncogene c-Kit inhibitor	[62, 65]
Iproniazid	Depression (1990)	Monoamine oxidase inhibitor	[62, 65, 79–81]
Itraconazole	Non-small cell lung cancer (phase II)	Smoothened homologue inhibitor, Lanosterol 14-alpha demethylase inhibitor	[1, 2, 82, 83]
Ketoconazole	Seborrheic dermatitis (2006) Cushing syndrome (2015)	Cytochrome P450 aromatase (CYP19A1) inhibitor	[62, 65]
Lidocaine	Eye disorders (1999) Arrhythmia (2010) Pain (2013)	—	[62, 65]
Memantine hydrochloride	Spasticity Alzheimer's type dementia Non-alcoholic steatohepatitis (2002)	NMDA receptor antagonists	[62, 65, 84, 85]

(*Continued*)

Table 2. (*Continued*).

Drug	*Indication(s)/year*	*Target(s)/MOA(s)*	*Refs*
Metformin hydrochloride	Breast cancer prostate cancer (phase III)	AMP-activated protein kinase (AMPK) activator	[1, 2, 86–88]
Methotrexate	Cancers (gestational choriocarcinoma chorioadenoma destruens, cutaneous T cell lymphoma, lung cancer, non-Hodgkin's lymphomas) Polyarticular juvenile arthritis psoriasis (2014)	Dihydrofolate reductase inhibitor	[62, 65]
Milnacipran	Fibromyalgia (2009)	5-HT and norepinephrine reuptake inhibitor	[62, 65]
Miltefosine	Leishmaniasis (2003)	Phosphatidyl-choline biosynthesis inhibitor	[62, 65, 89]
Minocycline hydrochloride	Amyotrophic lateral sclerosis (phase III) Huntington's disease (phase II/III)	iNOS inhibitor, p38 mitogen-activated protein kinase (MAPK) inhibitor, Cytochrome c release inhibitor (down-regulation caspase-1 and caspase-3)	[62, 65, 90–92]
Nelfinavir mesilate	Cancers (liposarcoma, glioblastoma multiforme, advanced hematologic cancer, refractory or recurrent solid tumours) (phase II)	Proteasome inhibitor (caspase 9 activator, PPARgamma affinity)	[62, 65]
Nilotinib hydrochloride monohydrate	Glioma, Melanoma (phase II)	Platelet-derived growth factor receptors (PDGFR) inhibitor Proto-oncogene c-Kit inhibitor	[62, 65]
Nitisinone	Alkaptonuria (phase II/III)	4-hydroxy-phenylpyruvate dioxygenase inhibitor	[62, 65]
Paclitaxel	Restenosis (2000)	Tubulin beta modulator (microtubule-stabilizing agent)	[62, 65, 93]
Phentolamine mesilate	Reversal of soft-tissue (dental) anaesthesia (2009)	Alpha-adrenoceptor antagonist	[62, 65]
Raloxifene hydrochloride	Invasive breast cancer (2007)	Oestrogen receptor antagonist	[62, 65]
Ropinirole	Restless legs syndrome (2005)	Dopamine D2 and D3 receptor agonist	[62, 65]
Sildenafil citrate	Hypertension pulmonary arterial (2005)	Phospho-diesterase (PDE5A) inhibitors	[62, 65]
Simvastatin	Colorectal cancer (phase II)	3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor	[62, 65, 94]
Targretin	Alzheimer's type dementia (phase II)	Retinoid X receptor (RXR) agonist, ATP-binding cassette transporter (ABCA1), Expression enhancers extracellular-regulated kinase (ERK) inhibitor, SAPK1 (JNK) inhibitor	[62, 65]
Tetrabenazine	Extrapyramidal disorders (2006) Tardive dyskinesia (2007)	Vesicular monoamine transporter 2 (VMAT2) inhibitor	[62, 65]
Thalidomide	Leprosy (1998) Multiple myeloma (2003)	TNF-alpha production inhibitor Cereblon (CRBN) inhibitor	[62, 65, 95]
Topiramate	Migraine (2004) Alcoholism (phase III)	Kainate receptor antagonist, AMPA receptor antagonists, Carbonic anhydrase type II inhibitor, Sodium channel blocker	[62, 65]
Toremifene	Osteoporosis (2008)	Selective oestrogen receptor modulator	[62, 65]
Vorinostat	Multiple myeloma (phase II/III)	Histone deacetylase 6, 2, 1, 3 inhibitor	[62, 65]

Table 3. List of the initial indications of drugs included in the second evaluation set.

Drug	*Indication(s)/year*	*Target(s)/MOA(s)*
Apremilast	Psoriatic arthritis (Launched 2014)	Phosphodiesterase IV (PDE4) (non-specified sub-type) inhibitor
Canagliflozin	Diabetes type 2 (Launched 2013)	Sodium-glucose co-transporter type 2 (SGLT-2) inhibitor
Clemizole	Allergies	H1 histamine receptor antagonist
Desloratadine	Rhinitis, allergic (Launched 2001)	H1 histamine receptor antagonist
Dipyramidole	Hypertension pulmonary arterial (Launched 1960)	cGMP-specific 3',5'-cyclic phosphodiesterase (PDE5) inhibitor
Fenofibrate	Hyperlipidaemia (Launched 1980)	Apolipoprotein A-I gene expression inhibitor Peroxisome proliferator-activated receptor alpha activator
Hydroxychloroquine	Malaria (Launched 1956)	Toll-like receptor 7/9 inhibitor
Irbesartan	Hypertension (Launched 1997)	Angiotensin II receptor type 1 blocking
Mefloquine	Malaria (Launched 1985)	Haemoglobin sub-unit alpha binding
Metformin	Type 2 diabetes (Launched 1989)	Lysosomal alpha-glucosidase inhibitor
Moxifloxacin	Infection, respiratory tract (Launched 1999)	Topoisomerase II inhibitor
Silmitasertib	Cholangiocarcinoma (Phase I/II)	Casein kinase II (CK2) inhibitor

Table 4. List of the repurposed indications of drugs included in the second evaluation set.

Drug	*Indication(s)/year*	*Target(s)/MOA(s)*
Apremilast	Antiviral (Influenza A) (International Patent Application WO/2015/0697112015)	Multidrug resistance protein 1 (MDR-1) (isoform 3) inhibitor Phosphodiesterase IV (PDE4) (non-specified sub-type) inhibitor Tumour necrosis factor (TNF-alpha) inhibitor
Canagliflozin	Cancer (International Patent Application WO/2016/134486)	AMP-activated protein kinase (AMPK) inhibitor
Clemizole	Epilepsy (International Patent Application WO/2015/026849)	H1 histamine receptor antagonist
Desloratadine	Breast Cancer (International Patent Application WO/2016/116438 A1)	H1 histamine receptor antagonist
Dipyramidole	Chronic kidney diseases (International Patent Application WO/2017/007120)	cGMP-specific 3',5'-cyclic phosphodiesterase (PDE5) inhibitor
Fenofibrate	Inflammation (International Patent Application WO/2015/042286)	Peroxisome proliferator-activated receptor-gamma coactivator 1 alpha inhibitor
Hydroxychloroquine	Sinus tachycardia (International Patent Application WO/2015/004470)	—
Irbesartan	Cancer (International Patent Application WO/2016/141476)	Peroxisome proliferator-activated receptor gamma inhibitor
Mefloquine	Neuropathic pain (International Patent Application WO/2014/187225 & WO/2014/187226)	Adenosine A2a-receptor antagonists
Metformin	Autoimmune diseases (International Patent Application WO/2015/046857)	ATP-binding cassette sub-family G member 2 (isoform 1) inhibitor cGMP-specific 3',5'-cyclic phosphodiesterase (PDE5) inhibitor Dipeptidyl peptidase 4 inhibitor Tumour necrosis factor ligand superfamily member 6 inhibitor Hydroxymethylglutaryl-CoA reductase (NADPH) (isoform 1) inhibitor Multidrug resistance protein 1 (MDR-1) (isoform 3) inhibitor
Moxifloxacin	Alzheimer's disease (International Patent Application WO/2015/120280A1)	Topoisomerase II inhibitor
Silmitasertib	Fatty liver disease (International Patent Application WO/2015/053452)	Casein kinase II (CK2) inhibitor

All predictions obtained using the studied web services are given in the Supplementary materials.

The obtained results are summarized in Figure 1. As one may see from the data presented in Figure 1, according to the *S* values for the predictions of initial indications, the web services are ranked in the following descending order: PASS (1.00), ChP (0.82), TH (0.82), SEA (0.80), SP (0.76), STP (0.72), TP (0.64). For the repurposed indications, the S values and order are somewhat different: PASS (0.98), ChP (0.84), TH (0.82), SEA (0.78), STP (0.72), SP (0.64), TP (0.64). On average, predictions of the initial indications ($S = 0.794$) are slightly better than predictions of the repurposed indications ($S = 0.774$). For different web services, S values vary from 0.64 obtained with TarPred to 1.00 obtained with PASS Online.

Bioactivity profile predictions for drugs from the second evaluation set

The same numerical parameter *S* was used to compare the performance of the seven analysed web services. The results are summarized in Figure 2.

As one may see from data presented in Figure 2(a), according to the S values for the predictions of initial indications, the web services are ranked in the following descending order: PASS (1.00), ChP (0.75), TH (0.67), SEA (0.67), STP (0.33), SP (0.08). For the repurposed indications, the S values and order are somewhat different: PASS (1.00), SEA (0.83), TH (0.75), ChP (0.67), STP (0.42), SP (0.00). On average, predictions of the initial indications ($S = 0.583$) are slightly worse than predictions of the repurposed indications ($S = 0.611$), which differs

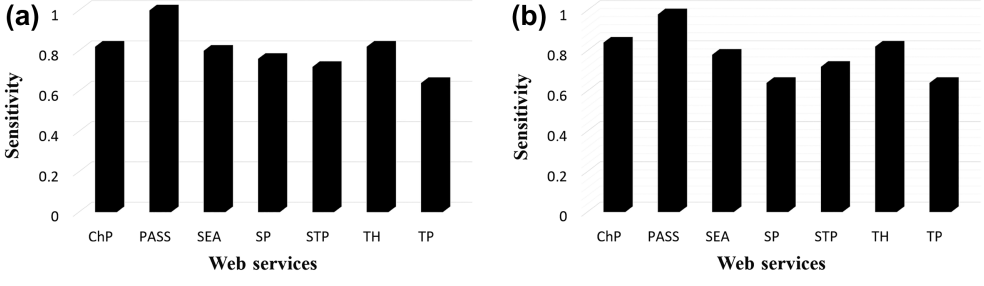

Figure 1. Comparative performance of the analysed web services for the initial (a) and repositioned (b) indications of well-known drugs. ChemProt (ChP), PASS Online (PASS), Similarity Ensemble Approach (SEA), SuperPred (SP), SwissTargetPrediction (STP), TargetHunter (TH), TarPred (TP).

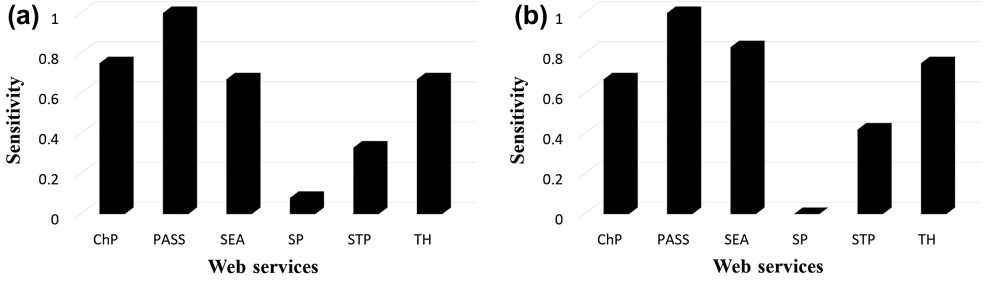

Figure 2. Comparative performance of the analysed web services for the initial (a) and repositioned (b) indications of recently patented repurposed drugs. All abbreviations correspond to those in Figure 1.

from the results obtained for the first evaluation set (*S* equal to 0.794 and 0.774, respectively).

When we performed computations for the second evaluation set, web service TarPred was not accessible (it was also not available at the time when the paper was prepared for publication, 25 October 2017).

Discussion

Using two evaluation sets of repurposed drugs, we compared the performance of seven freely available web services, with predictions carried out by ligand-based drug design approaches. For the set of well-known repurposed drugs, sensitivity values exceeded those obtained for the set of recently patented repurposed pharmaceuticals.

On average, predictions obtained using the web services based on machine learning methods were significantly better than with web services based on similarity assessment, particularly for the second evaluation set. This appears reasonable because similarity estimations do not always extract the molecular features, which are responsible for drug-target interactions. In the landmark paper of Martin et al. [102], it was demonstrated that there exists only a 30% chance of finding the same biological activity of chemical compounds that have structural similarity with a Tanimoto coefficient higher than 85%. Thus, similarity methods performed well for indications, both initial and repurposed, if the information about the respective pharmacotherapeutic effects and mechanisms of action was already included in the knowledge base. However, they may exhibit worse or even poor performance if such information is not included in their knowledge base.

It is necessary to mention that the activity profiles estimated with different web services contained several or even many biological activities. The activity associated with the known initial or repurposed indication was not always found in the top position. To confirm the computational prediction of the known biological activity by the experiment, one should study all activities that are observed above the known activity in the list of predicted activities.

The average number of tests that should be performed with this purpose varies significantly (see Table 5). In the case of the initial indications, this varies from 25 (ChemProt) to 1 (TarPred); in the case of the repurposed indications, it varies from 57 (PASS Online) to 25 (SuperPred). On average, it is necessary to perform twice as many experiments to confirm the known activity in cases of repurposed indications than in cases of initial indications (~16 and ~8 tests, respectively).

As one may see from the data presented in Figure 1 and Table 2, the higher sensitivity values obtained with the predictive web services based on the machine learning methods

Table 5. The average number of tests needed to confirm the known biological activity predicted by different web services.

Web services	*Initial indication*	*Repurposed indication*
ChemProt 3.0	25	27
SuperPred	21	2
PASS	14	57
TargetHunter	6	13
SEA	4	5
SwissTargetPrediction	4	4
TarPred	1	3

(PASS Online, ChemProt) corresponds to a higher number of tests, which should be performed to confirm the known activity by the experiment. Contrarily, for the web services based on the similarity assessment (TarPred, SuperPred, etc.) the lower number of tests, which should be performed to confirm the known activity by the experiment, corresponds to a lower number of the sensitivity of prediction.

One of the purposes of our study was to estimate if it is possible to increase the efficacy of drug repurposing using predictions of several web services in combination, applying so-called consensus prediction. For the first evaluation set consensus prediction improves the performance in some cases. For example, consensus prediction by ChemProt and TarPred gives $S = 0.94$ instead of $S = 0.84$ (max); by SwissTargetPrediction and TarPred gives $S = 0.90$ instead of $S = 0.72$ (max), etc. However, consensus prediction combining PASS Online with any other web service does not improve the performance because for both evaluation sets PASS provides almost 100% accuracy (in three cases $S = 1.00$ and only for the repurposed indications of drugs from the first evaluation set $S = 0.98$).

It is also necessary to emphasize that application of consensus prediction may significantly increase the number of experimental tests needed for proving the predictions because the overlap of biological activities predicted by two (or more) methods is rather small.

Conclusions

Since drug repurposing caused significant interest in recent years, the attempt to apply the computational methods for identification of new pharmacotherapeutic effects and mechanisms of action for the launched pharmaceuticals looks reasonable. Access to the information about the biological activity of drug-like substances from several publicly available repositories including ChEMBL, PubChem, DrugBank, etc. allowed the creation of several web resources predicting biological activity profiles based on structural formulae of organic compounds. These web-resources differ in the applied (Q)SAR methods, used training sets, and the lists of biological activities that may be predicted.

Taking into account that currently drug repurposing is suggested as a very promising way of novel pharmaceutical discoveries, it is important to estimate how accurate the predictions of the initial and repurposed drug indications provided by the computational tools are. We created two evaluation sets, including 50 well-known and 12 recently patented repurposed drugs belonging to the diverse chemical classes and exhibiting broad spectra of biological activities.

The sensitivity is the only characteristic that could be used for estimation of the predictive performance of different web services because of the incompleteness of the information about biological activity profiles of pharmaceuticals included into the test set (no one drug was tested against all known kinds of biological activity).

It was found that web services based on machine learning methods (PASS and ChemProt) supersedes those based on similarity assessment (TarPred, SuperPred, etc.) in sensitivity, but conceded in the number of tests that should be performed to confirm the known biological activities by the experiment. This may be explained by the difference in the approaches: actually, a similarity assessment might give 100% for sensitivity provided all information about initial and repurposed indications is contained in the appropriate training sets.

In general, some of the analysed web services exhibited a reasonable quality of prediction for both initial and repurposed indications. Thus, we found that those web services may be used for prediction of novel indications for the launched drugs.

Our own experience has shown that the published computational predictions have a good chance of being confirmed by further experimental studies. For instance, in 2001 we published predictions of new pharmacotherapeutic effects for eight medicines from the list of Top 200 Drugs [103]. In particular, we predicted that Sertraline could be applied for cocaine dependency treatment, Amlodipine could be an anti-neoplastic enhancer, Oxaprozin could be an interleukin 1 antagonist and Ramipril could exhibit an anti-arthritic action. Recent analysis of the published literature has shown that all these predictions have been confirmed, either by experiment or by clinical studies [104–107].

Later [108], we predicted that some anti-hypertensive drugs, angiotensin-converting enzyme inhibitors (Captopril, Enalapril, Ramipril, etc.) may have a nootropic action. In pharmacological studies it was shown that Perindopril in a dose of 1 mg/kg and Quinapril and Monopril in doses of 10 mg/kg improved the patrolling behaviour in the cross-maze, like Piracetam and Meclofenoxate (in doses of 300 and 120 mg/kg, respectively) [108]. This result was further confirmed in clinical trials [109].

Of course, the optimistic conclusions about applicability of freely available web services predicted the biological activity profiles to drug repurposing may be considered as 'good will'. Keeping in mind the incompleteness of any training set and possibility of activity cliffs, any prediction should be experimentally validated in each particular case.

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Disclosure statement

The authors confirm that this article content has no conflict of interest. The results presented in the Supplementary material correspond to the current version of the program(s), which may alter in future as the webservers and methods are under constant development.

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ORCID

K. A. Murtazalieva http://orcid.org/0000-0003-3344-8365
D. S. Druzhilovskiy http://orcid.org/0000-0001-9024-1331
R. K. Goel http://orcid.org/0000-0003-1408-4295
G. N. Sastry http://orcid.org/0000-0003-3181-7673
V. V. Poroikov http://orcid.org/0000-0001-7937-2621

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