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PASS APPLICATION IN R&D OF NEW PHARMACEUTICALS

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Abstract: A systematic approach through computer assisted design to identify novel pharmaceutical for research and development has been discussed in the present paper.

Introduction:

There are dozen thousands chemicals in use today and many more being synthesized. It is necessary to have the efficient methods for assessment of action of these compounds in the environment and human health. Experimental testing is both time-consuming and expensive. Thus, there is a pressing requirement for accurate *in silico* methods to predict the carcinogenicity. In this investigation, we studied how accuracy of rodent carcinogens estimation may be improved by using two different computer programs on the basis of their structural formulae.

Result and discussions

Usually, research and development of new pharmaceuticals are carried out step-by-step:

1. Disease identification.
2. Target choice.
3. Assay development.
4. Ligand design (hits).
5. Chemical synthesis and/or purchase of samples for biological testing.
6. Ligand finding (leads): in vitro testing of the required specific biological activity.
7. Ligand optimization (drug-candidates): *in vivo* confirmation of the required specific biological activity; investigation of general pharmacological/toxicological profile (no adverse/toxic effects at the appropriate doses) of the selected substances; investigation of pharmacokinetics of the selected substances (favourable absorption, distribution, metabolism and excretion characteristics).
8. Submitting IND to get a permission of Drug Authority for clinical trials.
9. Clinical trials, final proof of the concept.

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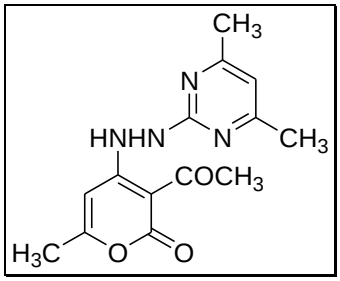
10. Submitting NDA to get an approval of Drug Authority for medical application of the drug-candidate.

At any stage, project may failure due to different reasons. More than 30% of failures in pharmaceutical R & D projects are due to the adverse/toxic effects, which are found at the later stages of the project when a lot of time and money are already spent (for nothing). Typically, any chemical compound exhibits several or many kinds of biological activity, and the final goal of R&D is to select the compounds with the required pharmacological action but without unwanted adverse/toxic effects. The whole complex of biological activities that might be revealed by chemical compound during its interaction with the human organism is called biological activity spectrum. It is not possible to test experimentally millions of available compounds against thousands known kinds of biological activity.

For example PASS prediction data of **1a**:



1a

Activity Prediction
35 Substructure descriptors; 2 new.
268 Possible activities at Pa > Pi

Pa	Pi	for Activity:
0.813	0.037	Membrane integrity agonist
0.619	0.008	5 Hydroxytryptamine release inhibitor
0.632	0.074	Steroid 21-monooxygenase inhibitor
0.538	0.035	Allergic conjunctivitis treatment
0.521	0.037	Nucleotide metabolism regulator
0.471	0.015	Maillard reaction inhibitor
0.467	0.021	Antiurolithic
0.478	0.033	Phosphopantothenoylcysteine decarboxylase inhibitor
0.527	0.086	Antianemic
0.453	0.054	Histamine release inhibitor
0.419	0.026	Carcinogenic, female mice

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0.424	0.034	Tyrosine 3 hydroxylase inhibitor
0.459	0.074	Aminobutyraldehyde dehydrogenase inhibitor
0.481	0.109	Taurine dehydrogenase inhibitor
0.463	0.097	Complement factor D inhibitor
0.416	0.055	Mediator release inhibitor
0.428	0.069	Aspartate-phenylpyruvate transaminase inhibitor
0.455	0.110	Ribonuclease T1 inhibitor
0.392	0.055	Vasodilator, coronary
0.491	0.154	15-Oxoprostaglandin 13-reductase inhibitor
0.341	0.005	CDK2/cyclin A inhibitor
0.445	0.112	Leukotriene C4 antagonist
0.421	0.092	Antiinflammatory
0.418	0.108	Glutaminyl-peptide cyclotransferase inhibitor
0.380	0.074	Amine dehydrogenase inhibitor
0.485	0.180	Ankylosing spondylitis treatment
0.349	0.058	Diamine N-acetyltransferase inhibitor
0.343	0.052	Corticosteroid side-chain-isomerase inhibitor
0.419	0.129	H+-exporting ATPase inhibitor
0.328	0.039	Paraoxonase substrate
0.367	0.079	Gamma-guanidinobutyraldehyde dehydrogenase inhibitor
0.414	0.128	Phosphatase inhibitor
0.404	0.121	Cyclic AMP antagonist
0.295	0.015	Liver fibrosis treatment

Conclusion:

Computer programme PASS can be used for:

(i) Finding of compound with required properties and without undesirable side effect.

(ii) Revealing of new effects and mechanism of action for known substances from corporate and personal databases.

(iii) Determining of more relevant screens for particular compound.

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