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ARTICLE

in silico Analysis of 4-((1-(3-Nitrophenyl)-5-oxo-3-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)methyl)benzoic Acid: An Emerging 3-CLpro Non-peptidic Inhibitors for COVID-19

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ABSTRACT

Existing study involves effort to forecast absorption, distribution, metabolism, excretion, toxicity and polypharmacological profile of 4-((1-(3-nitrophenyl)-5-oxo-3-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)-methyl)benzoic acid (NPOPPBA), a 3CLpro non-peptidic inhibitors with the aid of by means of *in silico* methods. In the beginning, PASS online computational software's utilized to investigate pharmacological action of NPOPPBA. Followed by, Swiss ADME online tool utilized to estimate of physical parameters, chemical properties, log P, solubility, absorption, distribution, metabolism, excretion, drug like property and medicinal chemistry. Lastly, XUNDRUG eMolTox online tool utilized to forecast toxicity. End result of PASS online prediction tool confirmed that NPOPPBA may be used as Fusarinine-C ornithinesterase inhibitor, which may be beneficial in most cancers treatment; Swiss ADME end outcome confirmed molecule may orally absorbable but not able to pass lipophilic membrane of brain and hence will not able to show undesirable effect centrally. Observations of bioavailability study shows NPOPPBA may be taken into consideration as a drug like because it shows all parameters falls inside red location of graph. The log P become observed about 3.7 signifying NPOPPBA may absorb on oral administration, solubility in water was found to be poor demonstrating need of attempts to enhance it in formulation development. This molecule can also additionally inhibits CYP2C19 which performs an essential function in metabolism of drugs live omeprazole, which are utilized to cure of gastrointestinal disorder and need to take precaution in the course of use of proton pump inhibitors. It is also CYP2C9 inhibitor therefore due care need to be taken for drugs undergoing phase I metabolism. XUNDRUG online resource outcomes confirmed hepatic and nephron toxicity possibility of NPOPPBA. Here from this existing analysis, it may be confirmed that the beneficial absorption, distribution, metabolism, excretion, drug like property and easy in synthesis of current molecule recommended that NPOPPBA may be an amazing medicinal agent in upcoming COVID-19 treatment.

KEYWORDS

COVID-19, Drug likeness, 3CLpro non-peptidic inhibitors.

INTRODUCTION

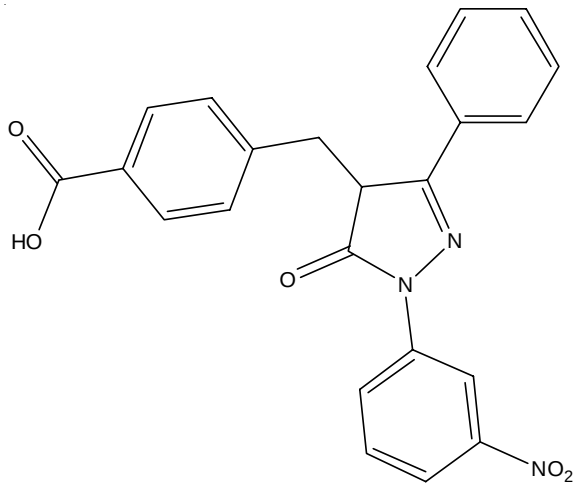
The novel corona virus sickness "COVID-19" began in Republic of China and unexpectedly contaminated to different nations; because of speedy international contamination, the most of the nations has stated COVID-19 as a worldwide

disaster. Currently no particular drug approved to deal with this virus, the searching for an appropriate therapeutics amongst present drugs appears to be valuable. Researchers are trying to find useful medicines towards corona virus. Corona virus has a cysteine protease referred to as 3-chymotrypsin like protease [3CLpro] is needed to novel corona virus to grow and spread. Since 3CLpro plays essential role these viral proteins are taken into consideration and became an important candidate to develop of antiviral compounds towards COVID-19. The 3CLpro non-peptidic inhibitors as rising small-molecule therapeutics alternatives for COVID-19 [1]. Undesirable absorption, distribution, metabolism and excretion emerged as primary reasons of the withdrawal of molecules at one or another stage of clinical trial. Subsequently the idea of drug like molecule become major suggestion, turn out to be an essential consideration with inside the choice of molecules with suitable properties throughout the initial steps of drug design and discovery [2]. Development of these inhibitors for COVID-19 essential to investigate for their pharmacokinetic things earlier than going for *in vivo* testing.

In recent times drug removal rate is increasing the financial stress on pharma enterprise as initial stages of drug discovery are expensive and difficult. Hence, computational strategies had been extensively utilized to assess those properties. Computational estimation has the capability to lessen the number of compounds to be synthesized with insufficient desirable drug properties. Animal are being used presently for figuring out the feasible toxic impact of drug candidates and cosmetics. Computational prediction techniques constitute an opportunity strategies and intention to rationalize the preclinical drug improvement [3-7].

EXPERIMENTAL

4-((1-(3-Nitrophenyl)-5-oxo-3-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)methyl)benzoic acid (NPOPPBA) structure were sketched by using Chemsketch software and converted to SMILES file format by Open Babel software and utilized for investigations (Fig. 1).



N1=C(C(C(=O)N1c1cccc(c1)[N+](=O)[O-])
Cc1ccc(cc1)C(=O)O)c1ccccc1

Fig. 1. 2D Chemical and SMILES structures of NPOPPBA (canonical)

Method used for calculation of ADME properties: Online server Swiss ADME was used to analyze absorption, distribution, metabolism, excretion properties of 4-((1-(3-nitrophenyl)-5-oxo-3-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)-methyl)benzoic acid (NPOPPBA) [8].

Bioavailability radar was used for a quick calculation of drug like property. Resulted diagram graphically describes relationship within the physical and chemical properties of molecule (Table-1). When above physico-chemical properties of molecule fall in to pink area that molecule can be considered as a drug like molecule. The physico-chemical properties of compound always used for quick estimation pharmacokinetic were calculated in which weight of molecular in Dalton, HBD, HBA, PSA, number of rotatable bonds and molecular refractivity were also preferably determined.

TABLE-1
RESULTS OF PHYSICO-CHEMICAL PROPERTIES OF MOLECULE NPOPPBA (PREDICTED)

Properties	Results	Ref.
m.f.	$C_{23}H_{17}N_3O_5$	
m.w. (g/mol)	415.40	
Heavy atoms	31	
Rotatable bonds	6	[8]
HBD	1	
HBA	6	
Molar refractivity (MR)	123.05	
TPSA (topological polar surface area)	115.79 Å²	[9]

Log P a lipophilicity indicator were predicted by freely accessible models like XLOGP3, WLOGP, MLOGP, SILICOS-IT and iLOGP and results of these models in terms of partition coefficient and arithmetic mean were recorded (Table-2). Water solubility of molecule was determined by ESOL calculation model (Table-3). For prediction of pharmacokinetic parameters of molecule BOILED-Egg calculation mode and multiple linear regression mode were used (Table-4).

TABLE-2
RESULTS OF log P OF MOLECULE NPOPPBA (PREDICTED)

log P	Results	Ref.
iLOGP	2.75	[9]
XLOGP3	4.27	[10]
WLOGP	3.14	[11]
MLOGP	2.76	[12]
SILICOS-IT	1.98	[13]
log Po/w	2.98	Average

TABLE-3
RESULTS OF WATER SOLUBILITY OF MOLECULE NPOPPBA (PREDICTED)

Solubility in water	Results	Ref.
log S (ESOL) obtained by directly from molecular structure	-5.14	[14]
Class of solubility	Moderate	
log S (Ali) obtained by QSPR models	-6.41	[15]
Class of solubility	Poor	
log S (SILICOS-IT) obtained from SILICOS-IT program	-6.36	[16]
Class of solubility	Poor	

log S scale: (insoluble < -10, poorly soluble < -6, moderately soluble < -4, soluble < -2, very soluble < 0 < highly soluble).

TABLE-4
RESULTS OF PHARMACOKINETICS PROPERTIES OF MOLECULE NPOPPBA (PREDICTED)

Properties	Results	Ref.
Gastro intestinal absorption	High	[17]
Permeation through blood brain barrier	No	
Substrate for *p*-glycoprotein	No	[18]
Inhibitor CYP1A2 enzyme	No	
Inhibitor CYP2C19 enzyme	Yes	
Inhibitor CYP2C9 enzyme	Yes	
Inhibitor CYP2D6 enzyme	No	
Inhibitor CYP3A4 enzyme	No	

Drug-likeness of molecule were determined by different filters specifically the Lipinski rule of 5 (Table-5), the Ghose Filter and other Pan Assay Interference compounds interface were determined which may support medicinal chemists in drug discovery process (Table-6). Swiss Target Prediction tool was utilized for guessing of possible protein targets for molecule under investigation (Table-7).

Prediction of polypharmacological activity: PASS online a web interface for assessing the pharmacological probabilities of molecule PASS results provides score as probability to be active (Pa) and probability to be active (Pi) (Table-8).

TABLE-8
RESULTS OF MULTIPLE PHARMACOLOGICAL ACTIONS

Pa score	Pi score	Predicted targets
0.806	0.006	Fusarinine-C ornithinesterase inhibitor
0.792	0.004	Arylalkylacylamidase inhibitor
0.789	0.004	Aldehyde dehydrogenase (pyrroloquinoline-quinone) inhibitor
0.771	0.005	L-Glutamate oxidase inhibitor
0.757	0.008	Fibrinolytic
0.757	0.009	Bisphosphoglycerate phosphatase inhibitor
0.759	0.012	Glucan endo-1,6-β-glucosidase inhibitor
0.727	0.004	Hyponitrite reductase inhibitor
0.734	0.014	Arylacetonitrilase inhibitor
0.722	0.016	Acute neurologic disorders treatment

Process for forecast of ADME by using XUNDRUG eMolTox online tool: Tools, which can forecasts toxicity of molecules by studying and analyzing structure was utilized for prediction of Hepato, Nephro, Cardio, CNS, Geno, respiratory, reproductive and cytotoxicty (Table-9).

RESULTS AND DISCUSSION

Results of prediction of absorption, distribution, metabolism, excretion by using Swiss ADME online prediction computational tool: Bioavailability radar of molecule (Fig. 2)

TABLE-5
RESULTS OF DRUG LIKENESS OF MOLECULE NPOPPBA (PREDICTED)

Filters	Results	Ref.
Lipinski's rule of 5	Yes; 0 violation	[19,20]
Ghose filter (knowledge based approach)	Yes; 0 violation	[21]
Veber filter (based on molecular properties)	Yes; 0 violation	[22]
Egan filter (based on multivariate statistics approach)	Yes; 0 violation	[23]
Bioavailability score	0.56	[24]

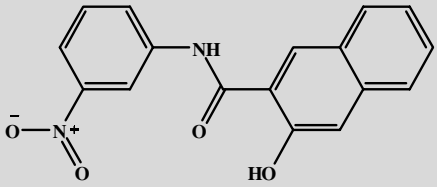
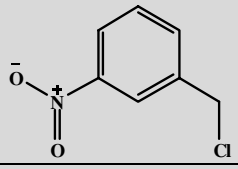
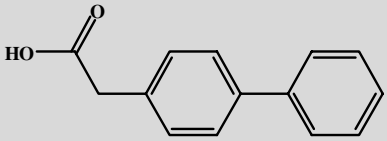
TABLE-6
RESULTS OF MEDICINAL CHEMISTRY OF NPOPPBA (PREDICTED)

Filter	Results	Ref.
Pan assay interferance structures	0 alert	[25]
Brenk filter	2 alerts: nitro group, oxygen-nitrogen	[26]
Lead likeness filter	No; 2 violations: MW>350, XLOGP3>3.5	[27]
Synthetic accessibility score (Based on molecular complexity and fragment contributions)	3.86	[28]

TABLE-7
RESULTS OF SWISS TARGET PREDICTION ONLINE TOOL

Rank	Target	Target class
1	LK tyrosine kinase receptor	Kinase
2	Thromboxane A2 receptor	Family A G protein-coupled receptor
3	Leukocyte adhesion glycoprotein LFA-1 alpha	Adhesion
4	Cholecystokinin B receptor	Family A G protein-coupled receptor
5	Apoptosis regulator Bcl-X	Other ion channel
6	Transient receptor potential cation channel subfamily M member 8	Voltage-gated ion channel
7	Hematopoietic cell protein-tyrosine phosphatase 70Z-PEP	Phosphatase
8	Protein-tyrosine phosphatase 1B	Phosphatase
9	Matrix metalloproteinase 8	Protease
10	Serine/threonine-protein kinase TNNI3K	Kinase
11	Endothelin receptor ET-A (by homology)	Family A G protein-coupled receptor
12	Glycogen synthase kinase-3 alpha	Kinase
13	Cyclin-dependent kinase 2/cyclin A	Other cytosolic protein
14	G protein-coupled receptor 44	Family A G protein-coupled receptor
15	Anandamideamidohydrolase	Enzyme

TABLE-9
PROBABILITY OF TOXICACTION OF MOLECULE BY USING XUNDRUG *in silico* ONLINE TOOL

Act as	Damage	Confidence interval	Analogous compounds
Hepatotoxicity			
Antagonist of the farnesoid-X-receptor (FXR) signaling pathway	Liver	0.984	
Agonist of the antioxidant response element (ARE) signaling pathway	Liver	0.983	
Nephrotoxicity			
Agonist of the peroxisome proliferator-activated receptor gamma (PPARg) signaling pathway	Kidney, Heart, immune	0.98	

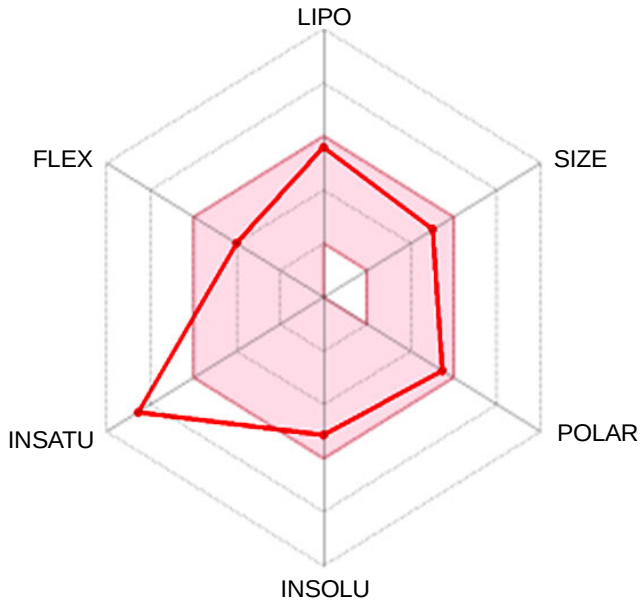


Fig. 2. Bioavailability radar for molecule NPOPPBA

under investigation shows all properties of molecule came in the colour region demonstrating that molecule can be active when given by oral route.

Log P value of NPOPPBA molecule is less than 5, representing this molecule can be orally active. NPOPPBA molecule displays reasonable to low water solubility demonstrating solubility enhancement tactics need to be used in formulation and development stage. Gastric absorption of NPOPPBA was discovered to be excessive without ability to pass through tight highly lipophilic membrane of brain demonstrating this molecule may be taken orally with high absorption rate from gut without difficulty. Further, this molecule cannot show any unwanted effect on brain part because it cannot passes lipophilic membrane. NPOPPBA won't be removed by efflux mechanism from gut because it isn't a targeted by P-glycoprotein. The data regarding role of molecules with CYP offers evidence of these enzymes which performs central function in drug removal *via* metabolism. It is consequently of exceptional significance get information of enzyme inhibition. NPOPPBA have interaction with cytochrome P450 and act as CYP2C19 and CYP2C9 inhibitor, signifying this can be concerned in biotransformation of various molecules.

Bioavailability score of NPOPPBA molecule was found to be 0.56 and molecule not breech filters used signifying that this molecule can be a drug might be synthesized and endorsed in next stage of a drug design, development and discovery. Foretold results showed that NPOPPBA can be targeted for LK tyrosine kinase receptor. NPOPPBA can interact well with different Thromboxane A2 receptor (Fig. 3) [29]. Results of expected pharmacological actions of NPOPPBA molecule disclose that NPOPPBA is a possible anti-neoplastic candidate [30], however, may cause hepatic injury due to presence of nitro and carboxylic acid group [30].

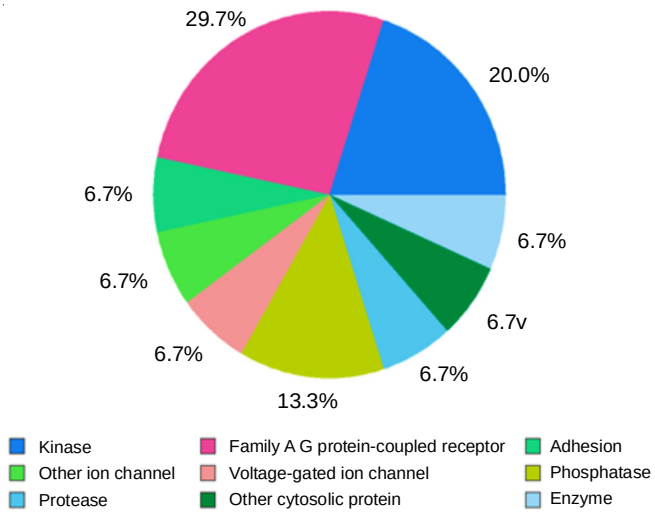


Fig. 3. Summary of target classes for NPOPPBA molecule

Conclusion

Development of antiviral compounds towards COVID-19 mainly 3CLpro non-peptidic inhibitors as an rising small-molecule therapeutics alternatives for COVID-19 is tough one. In this study Mainly, PASS online pharmacological activity analyzing web application had been used to forecast multiple pharmacological actions of NPOPPBA and effects confirmed Fusarinine-C ornithinesterase inhibitor activity. Succeeding, SWISS ADMET end result confirmed that Gastric absorption of NPOPPBA was discovered to be excessive without ability to pass through tight highly lipophilic membrane of brain demonstrating this molecule may be taken orally with high absorption rate from gut without difficulty. Lastly, XUNDRUG online web application device used to forecast toxicity and NPOPPBA confirmed with hepatic and nephron toxicity. These all prediction can be beneficial for the further development 4-((1-(3-nitrophenyl)-5-oxo-3-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)methyl) benzoic acid as a 3CLpro non-peptidic Inhibitors for Covid-19 as a drug candidate.

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REFERENCES

1. D. Tian, Y. Liu, C. Liang, L. Xin, X. Xie, D. Zhang, M. Wan, H. Li, X. Fu, H. Liu and W. Cao, An Update Review of Emerging Small-Molecule Therapeutic Options for COVID-19, *Biomed. Pharmacother.*, **137**, 111313 (2021); https://doi.org/10.1016/j.biopha.2021.111313
2. C.Y. Jia, J.Y. Li, G.F. Hao and G.F. Yang, A Drug-likeness Toolbox Facilitates ADMET Study in Drug Discovery, *Drug Discov. Today*, **25**, 248 (2020); https://doi.org/10.1016/j.drudis.2019.10.014
3. R. Ramajayam, K.-P. Tan, H.-G. Liu and P.-H. Liang, Synthesis and Evaluation of Pyrazolone Compounds as SARS-Coronavirus 3C-Like Lrotease Inhibitors, *Bioorg. Med. Chem.*, **18**, 7849 (2010); https://doi.org/10.1016/j.bmc.2010.09.050
4. J. Jacobs, V. Grum-Tokars, Y. Zhou, M. Turlington, S.A. Saldanha, P. Chase, A. Eggler, E.S. Dawson, Y.M. Baez-Santos, S. Tomar, A.M. Mielech, S.C. Baker, C.W. Lindsley, P. Hodder, A. Mesecar and S.R. Stauffer, Discovery, Synthesis, And Structure-Based Optimization of a Series of N-(*tert*-Butyl)-2-(N-arylamido)-2-(pyridin-3-yl) Acetamides (ML188) as Potent Noncovalent Small Molecule Inhibitors of the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) 3CL Protease, *J. Med. Chem.*, **56**, 534 (2013); https://doi.org/10.1021/jm301580n
5. P. Wei, K. Fan, H. Chen, L. Ma, C. Huang, L. Tan, D. Xi, C. Li, Y. Liu, A. Cao and L. Lai, The N-Terminal Octapeptide Acts as a Dimerization Inhibitor of SARS Coronavirus 3C-like Proteinase, *Biochem. Biophys. Res. Commun.*, **339**, 865 (2006); https://doi.org/10.1016/j.bbrc.2005.11.102
6. H.J. Thibaut, A.M. De Palma and J. Neyts, Combating Enterovirus Replication: State-of-the-Art On Antiviral Research, *Biochem. Pharmacol.*, **83**, 185 (2012); https://doi.org/10.1016/j.bcp.2011.08.016
7. M. Turlington, A. Chun, S. Tomar, A. Eggler, V. Grum-Tokars, J. Jacobs, J.S. Daniels, E. Dawson, A. Saldanha, P. Chase, Y.M. Baez-Santos, C.W. Lindsley, P. Hodder, A.D. Mesecar and S.R. Stauffer, Discovery of N-(Benzo[1,2,3]triazol-1-yl)-*N*-(benzyl)acetamido)phenyl) Carboxamides as Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) 3CLpro Inhibitors: Identification of ML300 and Noncovalent Nanomolar Inhibitors with an Induced-Fit Binding, *Bioorg. Med. Chem. Lett.*, **23**, 6172 (2013); https://doi.org/10.1016/j.bmcl.2013.08.112
8. A. Daina, O. Michielin and V. Zoete, SwissADME: A Free Web Tool to Evaluate Pharmacokinetics, Drug-likeness and Medicinal Chemistry Friendliness of Small Molecules, *Sci. Rep.*, **7**, 42717 (2017); https://doi.org/10.1038/srep42717
9. P. Ertl, B. Rohde and P. Selzer, Fast Calculation of Molecular Polar Surface Area as a Sum of Fragment-Based Contributions and Its Application to the Prediction of Drug Transport Properties, *J. Med. Chem.*, **43**, 3714 (2000); https://doi.org/10.1021/jm000942e
10. T. Cheng, Y. Zhao, X. Li, F. Lin, Y. Xu, X. Zhang, Y. Li, R. Wang and L. Lai, Computation of Octanol-Water Partition Coefficients by Guiding an Additive Model with Knowledge, *J. Chem. Inf. Model.*, **47**, 2140 (2007); https://doi.org/10.1021/ci700257y
11. S.A. Wildman and G.M. Crippen, Prediction of Physicochemical Parameters by Atomic Contributions, *J. Chem. Inf. Comput. Sci.*, **39**, 868 (1999); https://doi.org/10.1021/ci990307l
12. I. Moriguchi, S. Hirono, Q. Liu, I. Nakagome and Y. Matsushita, Simple Method of Calculating Octanol/Water Partition Coefficient, *Chem. Pharm. Bull. (Tokyo)*, **40**, 127 (1992); https://doi.org/10.1248/cpb.40.127
13. Silicos-it.be.s3-website-eu-west-1.amazonaws.com, (2019). Silicos-it | Filter-it™. [online] Available at: http://silicos-it.be.s3-website-eu-west-1.amazonaws.com/software/filter-it/1.0.2/filter- it.html [Accessed 20 Feb. 2022].
14. J.S. Delaney, ESOL: Estimating Aqueous Solubility Directly from Molecular Structure, *J. Chem. Inf. Comput. Sci.*, **44**, 1000 (2004); https://doi.org/10.1021/ci034243x
15. J. Ali, P. Camilleri, M.B. Brown, A.J. Hutt and S.B. Kirton, In Silico Prediction of Aqueous Solubility Using Simple QSPR Models: The Importance of Phenol and Phenol-like Moieties, *J. Chem. Inf. Model.*, **52**, 2950 (2012); https://doi.org/10.1021/ci300447c
16. A. Daina and V. Zoete, A BOILED-Egg To Predict Gastrointestinal Absorption and Brain Penetration of Small Molecules, *ChemMedChem*, **11**, 1117 (2016); https://doi.org/10.1002/cmdc.201600182
17. T. Eitrich, A. Kless, C. Druska, W. Meyer and J. Grotendorst, Classification of Highly Unbalanced CYP450 Data of Drugs Using Cost Sensitive Machine Learning Techniques, *J. Chem. Inf. Model.*, **47**, 92 (2007); https://doi.org/10.1021/ci6002619
18. R.O. Potts and R.H. Guy, Predicting Skin Permeability, *Pharm. Res.*, **9**, 663 (1992); https://doi.org/10.1023/A:1015810312465
19. C.A. Lipinski, F. Lombardo, B.W. Dominy and P.J. Feeney, Experimental and Computational Approaches to Estimate Solubility and Permeability in Drug Discovery and Development Settings, *Adv. Drug Deliv. Rev.*, **23**, 3 (1997); https://doi.org/10.1016/S0169-409X(96)00423-1
20. A.K. Ghose, V.N. Viswanadhan and J.J. Wendoloski, A Knowledge-Based Approach in Designing Combinatorial or Medicinal Chemistry Libraries for Drug Discovery. 1. A Qualitative and Quantitative Characterization of Known Drug Databases, *J. Comb. Chem.*, **1**, 55 (1999); https://doi.org/10.1021/cc9800071
21. D.F. Veber, S.R. Johnson, H.Y. Cheng, B.R. Smith, K.W. Ward and K.D. Kopple, Molecular Properties that Influence the Oral Bioavailability of Drug Candidates, *J. Med. Chem.*, **45**, 2615 (2002); https://doi.org/10.1021/jm020017n
22. W.J. Egan, K.M. Merz and J.J. Baldwin, Prediction of Drug Absorption Using Multivariate Statistics, *J. Med. Chem.*, **43**, 3867 (2000); https://doi.org/10.1021/jm000292e
23. Y.C. Martin, A Bioavailability Score, *J. Med. Chem.*, **48**, 3164 (2005); https://doi.org/10.1021/jm0492002
24. J.B. Baell and G.A. Holloway, New Substructure Filters for Removal of Pan Assay Interference Compounds (PAINS) from Screening Libraries and for Their Exclusion in Bioassays, *J. Med. Chem.*, **53**, 2719 (2010); https://doi.org/10.1021/jm901137j

25. R. Brenk, A. Schipani, D. James, A. Krasowski, I.H. Gilbert, J. Frearson and P.G. Wyatt, Lessons Learnt from Assembling Screening Libraries for Drug Discovery for Neglected Diseases, *ChemMedChem*, **3**, 435 (2008); https://doi.org/10.1002/cmdc.200700139
26. S.J. Teague, A.M. Davis, P.D. Leeson and T. Oprea, The Design of Leadlike Combinatorial Libraries, *Angew. Chem. Int. Ed.*, **38**, 3743 (1999); https://doi.org/10.1002/(SICI)1521-3773(19991216)38:24<3743::AID-ANIE3743>3.0.CO;2-U
27. P. Ertl and A. Schuffenhauer, Estimation of Synthetic Accessibility Score of Drug-like Molecules Based on Molecular Complexity and Fragment Contributions, *J. Cheminform.*, **1**, 8 (2009); https://doi.org/10.1186/1758-2946-1-8
28. A. Daina, O. Michielin and V. Zoete, Swiss Target Prediction: Updated Data and New Features for Efficient Prediction of Protein Targets of Small Molecules, *Nucleic Acids Res.*, **47(W1)**, W357 (2019); https://doi.org/10.1093/nar/gkz382
29. Xundrug.cn, (2018). eMolTox. [online] Available at: http://xundrug.cn/moltox [Accessed 20 Feb. 2022].
30. Pharmaexpert.ru, (2018). [online] Available at: http://www.pharmaexpert.ru/passonline/predict.php [Accessed 20 Feb. 2022].