Advances in Pharmacology and Pharmacy 10(4): 234-246, 2022 http://www.hrpub.org
DOI: 10.13189/app.2022.100402

Drug Likeness Screening and Evaluation of Physicochemical Properties of Selected Medicinal Agents by Computer Aided Drug Design Tools

Ganesh Sampat[1], Shailendra S. Suryawanshi[1,*], Mahesh S. Palled[1], Archana S. Patil[2], Pukar Khanal[3], Abhijeet S. Salokhe[2]

[1]Department of Pharmaceutical Chemistry, KLE College of Pharmacy, Belagavi, KLE Academy of Higher Education and Research, Belagavi, Karnataka, India
[2]Department of Pharmaceutics, KLE College of Pharmacy, Belagavi, KLE Academy of Higher Education and Research, Belagavi, Karnataka, India
[3]Department of Pharmacology, KLE College of Pharmacy, Belagavi, KLE Academy of Higher Education and Research, Belagavi, Karnataka, India

Received February 8, 2022; Revised April 28, 2022; Accepted June 21, 2022

Cite This Paper in the following Citation Styles

(a): *[1] Ganesh Sampat, Shailendra S. Suryawanshi, Mahesh S. Palled, Archana S. Patil, Pukar Khanal, Abhijeet S. Salokhe , "Drug Likeness Screening and Evaluation of Physicochemical Properties of Selected Medicinal Agents by Computer Aided Drug Design Tools," Advances in Pharmacology and Pharmacy, Vol. 10, No. 4, pp. 234 - 246, 2022. DOI: 10.13189/app.2022.100402.*

(b): *Ganesh Sampat, Shailendra S. Suryawanshi, Mahesh S. Palled, Archana S. Patil, Pukar Khanal, Abhijeet S. Salokhe (2022). Drug Likeness Screening and Evaluation of Physicochemical Properties of Selected Medicinal Agents by Computer Aided Drug Design Tools. Advances in Pharmacology and Pharmacy, 10(4), 234 - 246. DOI: 10.13189/app.2022.100402.*

Copyright©2022 by authors, all rights reserved. Authors agree that this article remains permanently open access under the terms of the Creative Commons Attribution License 4.0 International License

Abstract The current drug research techniques, combinatorial synthesis and high throughput screening, help in obtaining and pre-evaluating thousands of compounds in a short duration of time. Among the selected compounds, the best hit molecule becomes the lead, and the drug likeness property helps to optimize the selection. Lipinski's Rule of five is the most widely used filter in pre-evaluation of compounds, according to Lipinski's Rule of five the molecule with poor oral absorption and low permeation has the molecular weight >500, Clog*P* >5, hydrogen bond acceptor more than 10 and hydrogen bond donor more than 5. To evaluate the Rule of Five, the top selling drugs of 2018-19 were selected. Among the selected 56 drugs, 12 drugs (tenofovir disoproxil, sofosbuvir and ledipasvir, sofosbuvir/velpatasvir, trastuzumab, glecaprevir, pegtilgrastion, Lumacaftor/ ivacaftor, fluticasone propionate and salmetarol, elbasvir, darunavir ethanolate, Linagliptin, metformin, fluticasone furoate and vilanterol) did not fulfill the rule. The rule is very useful in selecting the better compound in chemolibraries, but should be used carefully and with certain criterion due to possible exclusion of promising compounds.

Keywords Computer Aided Screening, Molsoft, Blockbuster Drugs, Lipinski's Rule of Five, Metformin, Chemolibraries

1. Introduction

The beginning of Medicinal chemistry in 1930 helped in the development of most of the synthetic drugs, till 1930 the drug research was mainly focused on the investigation of natural products. Nowadays, there are a number of diseases which can be treated using synthetic drugs, so the development of technique for synthesis and purification of large amount of new compound in a short time is very much essential [1]. Due to the development of Bioisosterism in 1950-80's, the drug development process changed drastically. Molecular modification was used intensively, starting with Structure-Activity Relationship

studies (SAR). In the 80's, the biochemical aspect that was related with pathological conditions contributed to the target-based drug design approach [2]. In order to minimize the time required for synthesis and purification of a large amount of new compound, pharmaceutical companies have developed the combinatorial synthesis strategy, which enables the rapid acquisition of combinatorial libraries. This also leads to the development of High-Throughput Screening [HTS] methods using these compounds could be evaluated quickly [3]. It is possible to synthesize thousands of compounds using combinatorial techniques [4]. Despite of lots of efforts in identifying the best lead molecule and to obtain better results, most of the compounds were reproved during clinical trials due to their pharmacokinetic problems and toxicity [5]. The current research approach is to find the key points in pharmacokinetic and pharmacodynamic properties that can be set as standards in drug design. With these research techniques, the nature of the drug and the search for them become remarkable. This process is also referred to as Drug-likeness or drug-like molecule recognition [6].

Various rules were tried to facilitate the recognition of the promising molecules. The most common and widely used, is Lipinski's Rule of Five (Ro5), developed by the Pfizer's medicinal chemist Christopher. The rule of five is widely applied to filter the potentially active compounds from the combinatorial libraries that could have good oral absorption and/or permeation [7]. The Ro5 states that the drugs which are poorly absorbed by intestinal walls show two or more following characteristics: Molecular weight more than 500, Partition coefficient more than 5, Hydrogen bond donor group more than 5 and Hydrogen bond acceptor group more than 10. Since, each threshold in the rule is multiple of 5, the rule was called Ro5. Biomacromolecules, natural products are excluded from this analysis as they generally do not fit in Ro5 [8].

Literature search revealed that till date the lack of computational studies has been reported on computer based screening on Blockbuster drugs, to investigate its drug likeness properties. Hence in the present investigation, an attempt has been made to study drug likeness properties, of selected Blockbuster drugs, using computer applications and servers. The main aim of the pharmaceutical companies is the production of promising marketing drugs and also called "BLOCKBUSTERS", oral route of administration is the most preferred route of administration because of its great economy and therapeutic advantages, therefore, prediction of promising compounds that could be used orally in combinatorial libraries, it is always considered in search of leading molecules. The main objective of this study is to analyze the top selling drugs of 2018-19 (list published in TRUE COST OF HEALTH CARE by David Belk M.D. Pharma's Best Sellers) and to evaluate if they fulfill the Ro5.

2. Materials and Methods

Server used: PubChem database, Molsoft.

Blockbuster drugs used: To realization of the study, a table published by TRUE COST OF HEALTH CARE as "Pharma's 50 best sellers" was used, where most widely selling drugs in US and worldwide were found and listed in Table 1. And the structure of the selected drugs is shown in Table 2. The structure of the selected drugs was obtained using "PUBCHEM" data bank. Only the molecules which have small molecular size were analyzed and biomacromolecules such as Ibrutinib, Lenalidomide, Elvitegravir, Tenofovir disoproxil, Sofosbuvir and ledipasvir, Sofosbuvir/velpatasvir, Sitagliptin, Trastuzumab, Apixaban, Dasatinib, Pregabaline, Palbociclib, Glecaprevir, Abiraterone acetate, Paliperidone, Rivaroxaban, Pegfilgrastion, Osimertinib, Dimethyl fumarate, Lumacaftor and ivacaftor, Pemetrexed, Abacavir, Fluticasone propionate and Salmeterol, Fingolimod, Tadalafil, Budesonide, Elbasvir, Pomalidomide, Darunavir ethanolate, Teriflunomide, Enzalutamide, Dolutegravir, Ruxolitinib, Empagliflozin, Linagliptin and Metformin, Fluticasone furoate and Vilanterol were excluded from analysis.

Table 1. List of published by TRUE COST OF HEALTH CARE of Top selling drugs

Sl. No.	Trade Name	Generic Name
1	Humira	Adalimumab*
2	Imbruvica	Ibrutinib
3	Revlimid	Lenalidomide
4	Genvoya	Elvitegravir
5	Truvada	Tenofovirdisoproxil
6	Harvoni	Sofosbuvir and Ledipasvir
7	Epclusa	Sofosbuvir/velpatasvir
8	Keytruda	Pembrolizumab*
9	Januvia/Janumet	Sitagliptin
10	Herceptin	Trastuzumab

Table 1. Continued

11	Avastin	Bevacizumab*
12	MabThera/Rituxan	Rituximab*
13	Perjeta	Pretuzumab*
14	Opdivo	Nivolumab*
15	Eliquis	Apixaban
16	Orencia	Abatacept*
17	Sprycel	Dasatinib
18	Lyrica	Pregabalin
19	Ibrance	Palbociclib
20	Simponi	Golimumab*
21	Mavyret	Glecaprevir
22	Stelara	Ustekinumab*
23	Zytiga	Abiraterone acetate
24	Invega Sustena	Paliperidone
25	Xarelto	Rivaroxaban
26	Enbrel	Etanercept*
27	Neulasta	Pegfilgrastim
28	Tagrisso	Osimertinib
29	Tecfidera	Dimethyl fumarate
30	Eylea	Aflibercept*
31	Orkambi	Lumacaftor and ivacaftor
32	Victoza	Liraglutide*
33	Botox	Onabotulinumtoxin*
34	Alimta	Pemetrexed
35	Soliris	Eculizumab*
36	Triumeq	Abacavir
37	Seretide/Adavir	Fluticasone propionate and Salmetarol
38	Gilenya	Fingolimod
39	Cosentyx	Seuainmab*
40	Trulicity	Dulaglutide*
41	Cialis	Tadalafil
42	Humalog	Insulin lispro
43	Symbicort	Budesonide
44	Zepatier	Elbasvir
45	Pomalyst/imnovid	Pomalidomide
46	Darzalex	Daratumumab*
47	Prezista	Darunavir ethanolate
48	Prolia/Xgeva	Denosumab*
49	Aubagio	Teriflunomide
50	Ocrevus	Ocrelizumab*
51	Xtandi	Enzalutamide
52	Tivicay	Dolutegravir
53	Jakafi/Jakavi	Ruxolitinib
54	Jardiance	Empagliflozin
55	Trajenta/Jentadueto	Linagliptin and Metformin
56	Relvar/Breo	Fluticasone furoate and Vilanterol

*Drugs that were not analysed because they are biomacromolecules

Table 2. Structures of some selected blockbuster drugs

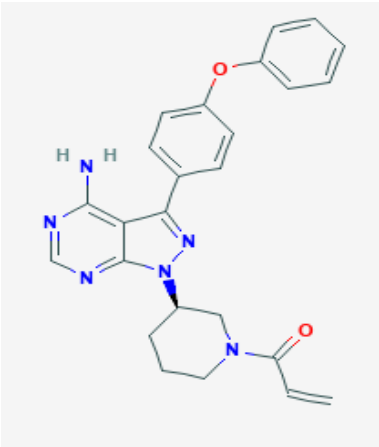
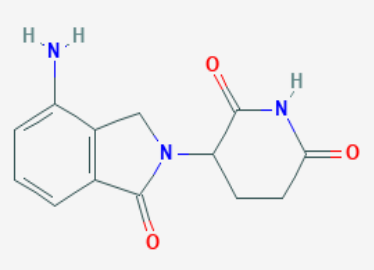
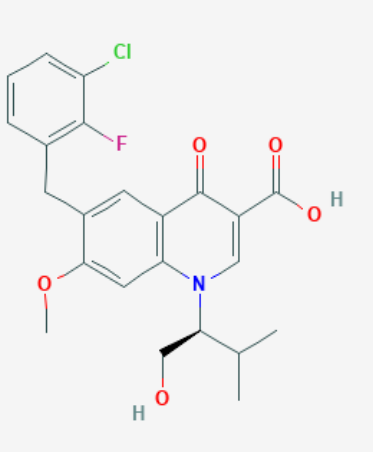
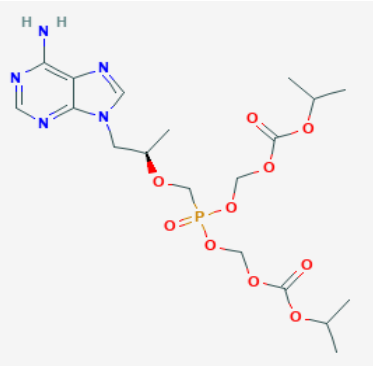
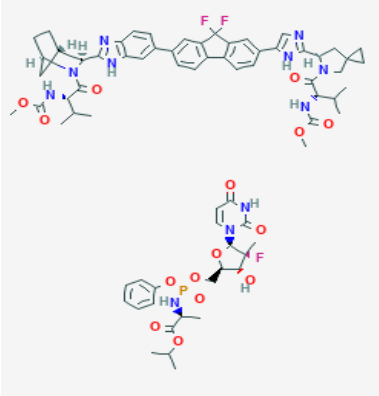
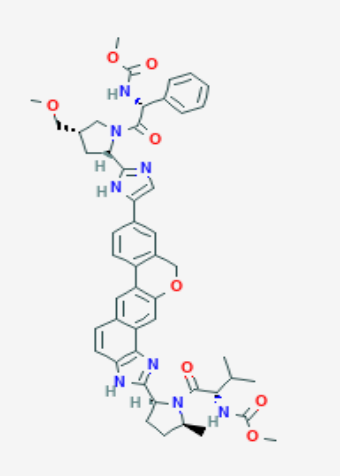
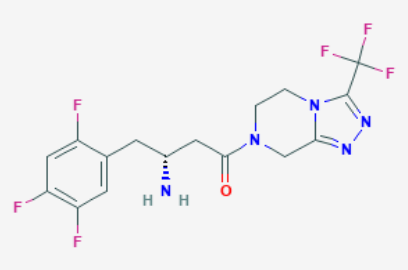
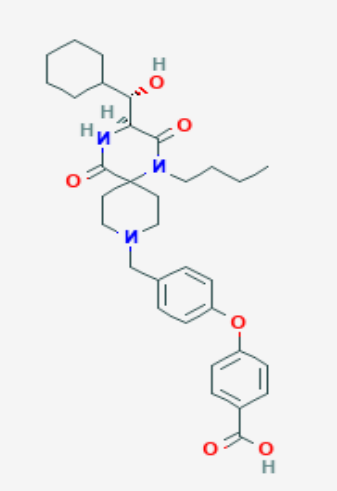
Irutinib 	Lenalidomide 	Elvitegravir 	Tenofovir disproxil 
Harvoni 	Velpatasvir 	Sitagliptin 	Trastuzumab 

Table 2. Continued

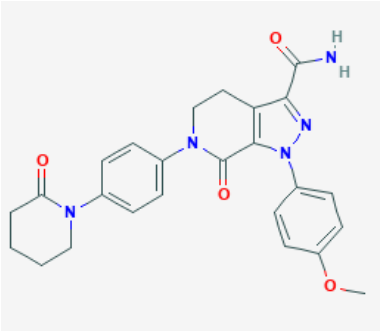
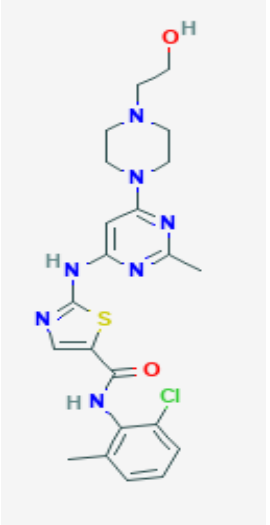
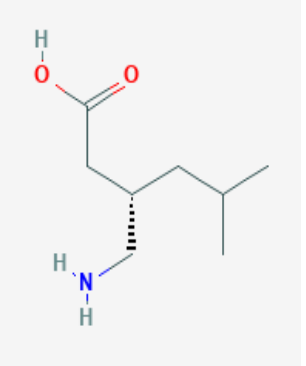
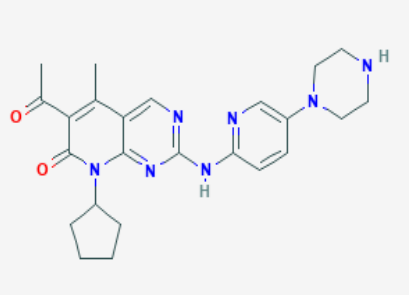
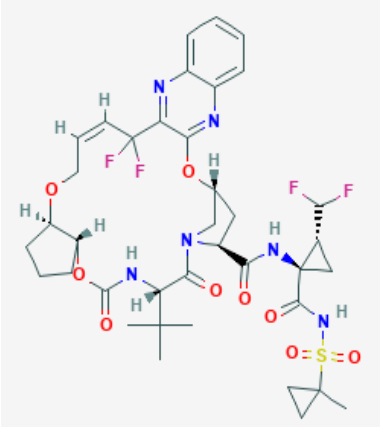
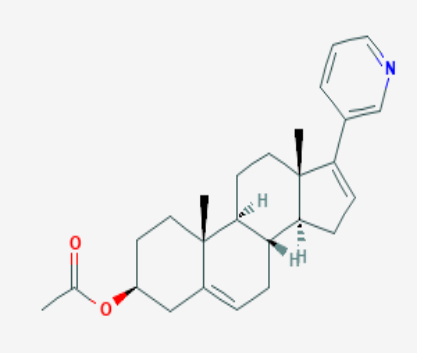
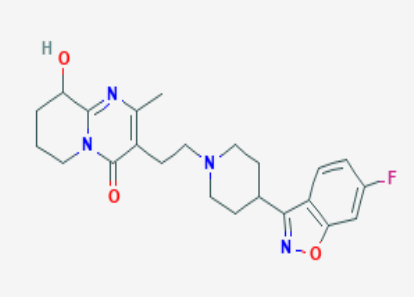
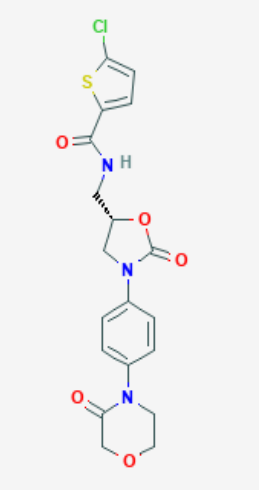
Apixaban 	Dasatinib 	Pregabalin 	Palbociclib 
Glecaprevir 	Abiraterone acetate 	Paliperidon 	Rivaroxaban 

Table 2. Continued

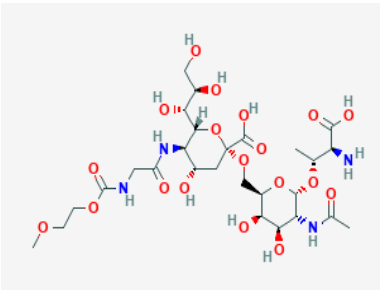
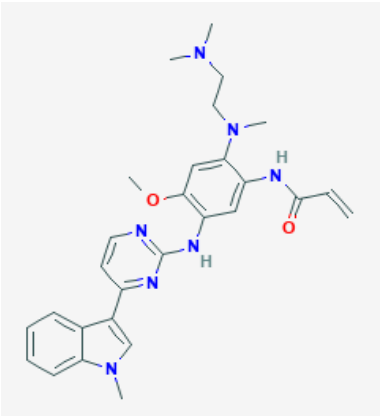
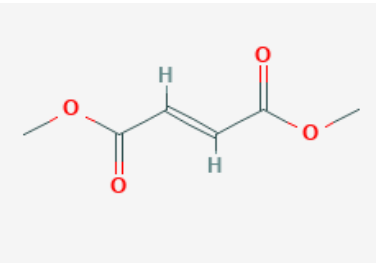
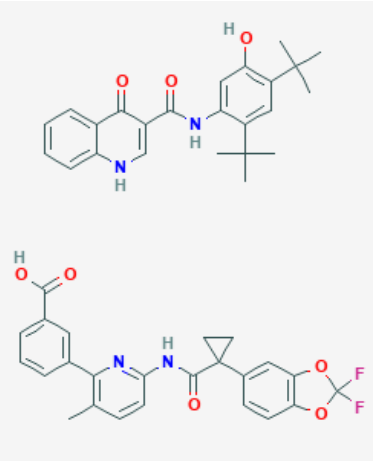
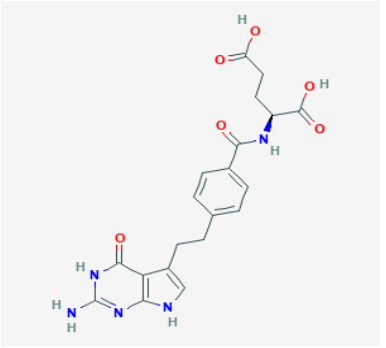
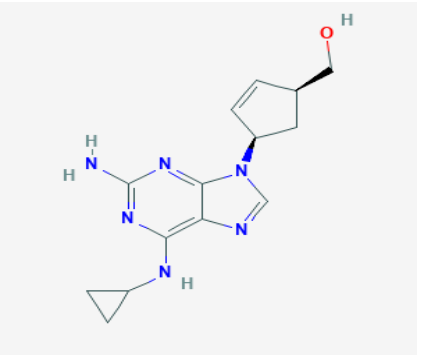
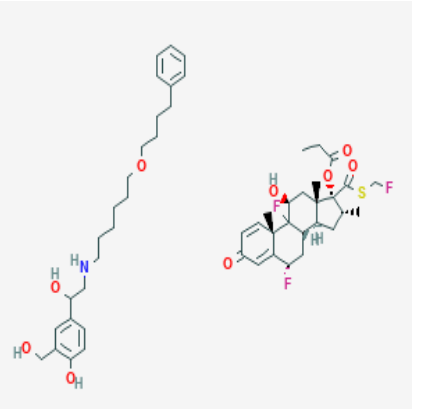
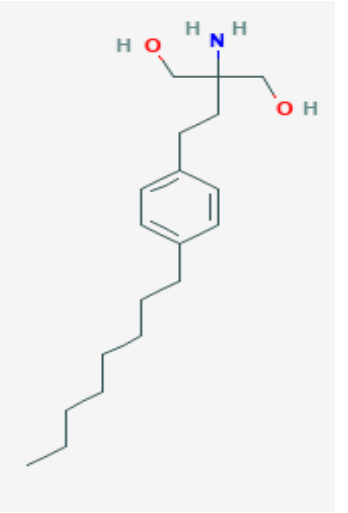
Pegfilgrastion 	Osimertinib 	Dimethyl fumarate 	Lmacaftor and ivacaftor 
Pemetrexed 	Abacavir 	Seretide 	Fingolimod 

Table 2. Continued

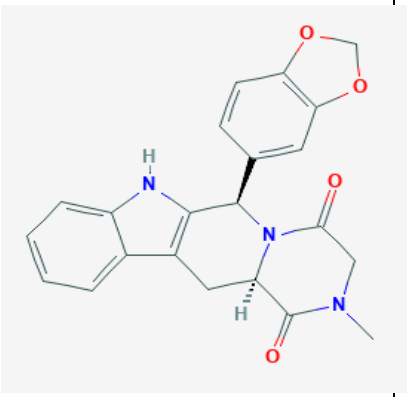
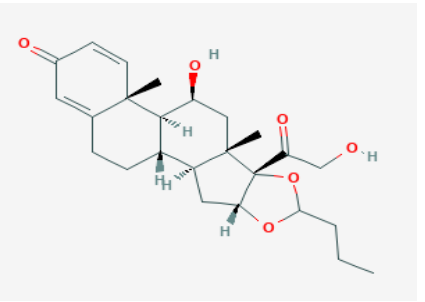
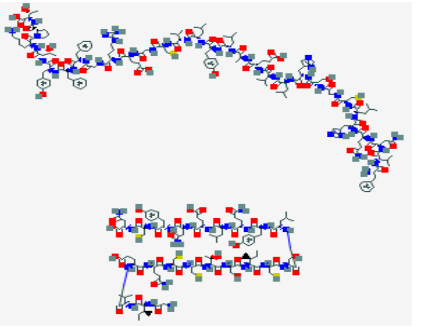
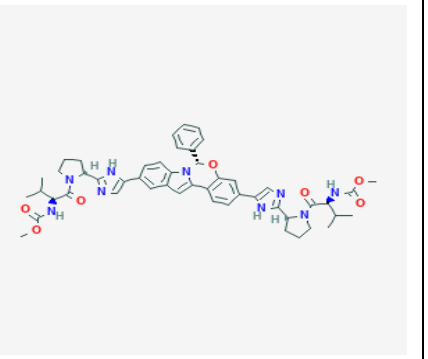
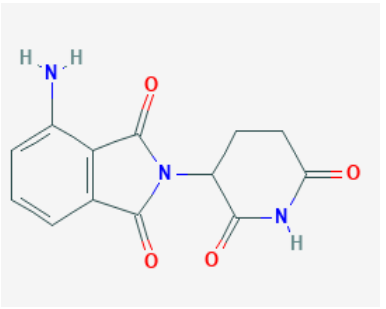
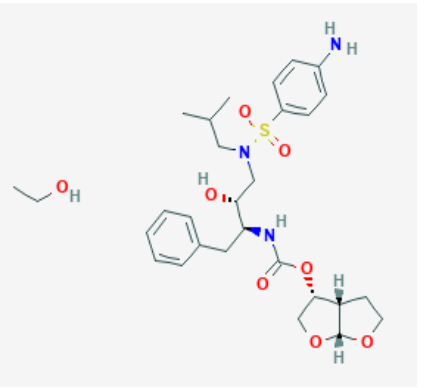
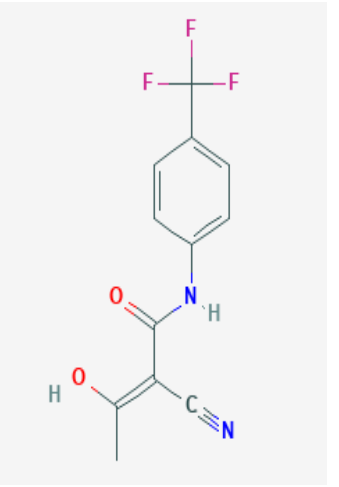
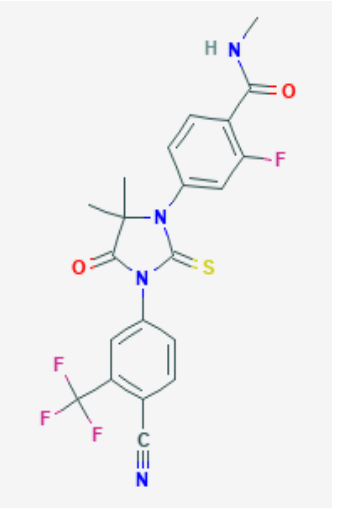
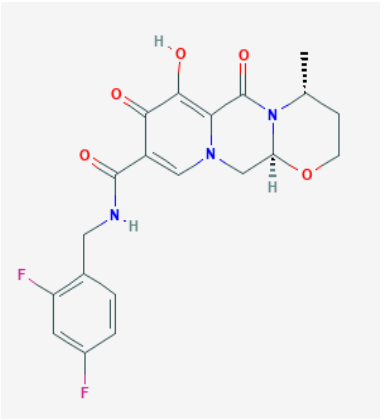
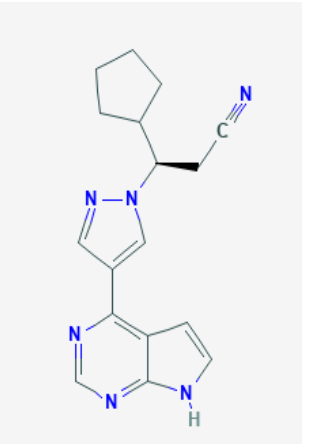
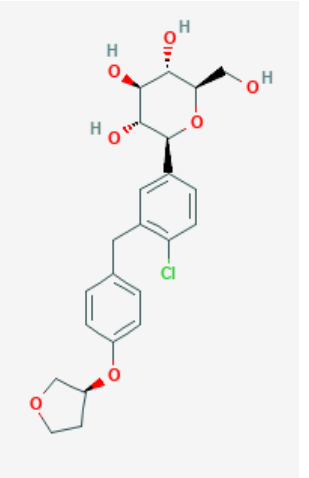
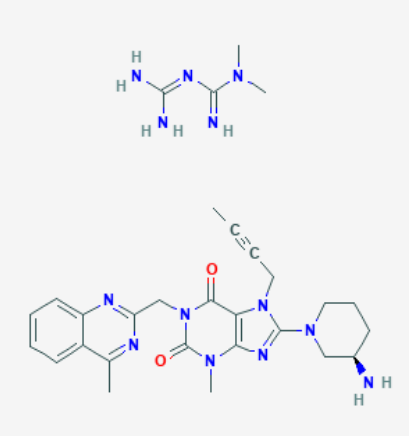
Tadalafil 	Budesonide 	Insulin lispro 	Elbasvir 
Pomalidomide 	Darunavir ethanolate 	Teriflunomide 	Enzalutamide 

Table 2. Continued

Dolutegravir 	Ruxolitinib 	Empagliflozin 	Linagliptin and metformin 

Investigation of Drug Likeness Score and Physicochemical Properties

In the present study we have identified and taken some Blockbuster drugs, for determining drug likeness score according to Lipinski's Ro5. Lipinski's rule of five was followed so as to find out drug likeness property of each of the selected drugs. The data about drug likeness was complied with adherence of Lipinski's rule. The canonical SMILES (Simplified Molecular Line Entry System) were obtained from PubChem and applied in Molsoft software to collect the data, to calculate the descriptions, "MOLSOFT" was used which is on line available (www://molsoft.com/mprop/) Obtained descriptor was tabulated and compared with Ro5 which is shown in Table 3 [9-12].

Table 3. Selected blockbuster drugs and Molecular Properties Prediction by Molsoft Analysis, Biomacromolecules are excluded

Drug	MW	Clog *P*	HBA	HBD	DLS
Ibrutinib	440.20	3.47	5	2	0.96
Lenalidomide	256.10	-0.44	3	3	0.26
Elvitegravir	447.12	3.71	5	2	1.05
Tenofovir disoproxil	519.17	-0.51	13	2	0.99
Sofosbuvir and ledipasvir	529.16	0.81	10	3	0.10
Sofosbuvir/velpatasvir	868.39	5.73	10	5	0.10
Sitagliptin	407.12	1.34	4	2	0.52
Trastuzumab	577.32	5.63	7	3	1.96
Apixaban	459.19	2.25	5	2	0.44
Dasatinib	487.16	3.86	7	3	2.39
Pregabaline	159.136	0.11	3	3	-1.10
Palbociclib	447.24	2.52	6	2	0.62
Glecaprevir	838.9	3.66	11	3	-0.03
Abiraterone acetate	391.25	4.97	3	0	1.10
Paliperidone	426.21	2.48	6	1	1.16
Rivaroxaban	435.07	1.63	6	1	0.80
Pegfilgrastion	730.28	-7.67	20	13	-0.07
Osimertinib	499.27	3.98	5	2	0.46
Dimethyl fumarate	144.04	0.59	4	0	-1.80
Lumacaftor and ivacaftor	844.33	11.35	9	5	0.36
Pemetrexed	427.15	-0.76	7	7	1.00
Abacavir	286.15	1.04	4	4	1.03
Fluticasone propionate and salmetarol	915.46	6.16	11	5	1.51
Fingolimod	307.25	5.06	3	4	-0.97
Tadalafil	389.14	2.54	4	1	0.04
Budesonide	430.24	3.22	6	2	1.39
Elbasvir	881.42	6.61	9	4	0.10
Pomalidomide	273.07	-0.78	4	3	-0.33
Darunavir ethanolate	593.28	2.34	9	5	0.59
Teriflunomide	270.06	2.37	3	2	-0.71
Enzalutamide	464.09	2.75	4	1	-0.73
Dolutegravir	419.13	0.96	5	2	0.98
Ruxolitinib	306.16	1.92	4	1	-0.30
Empagliflozin	450.14	1.88	7	4	0.49
Linagliptin and metformin	601.33	0.95	8	7	1.52
Fluticasone furoate and vilanterol	1023.34	5.82	13	5	1.69

3. Results

The descriptors Clog*P*, Molecular weight, HB acceptor, HB donor groups counts were used as proposed by Lipinski. The value of Clog*P*, molecular weight HB acceptor, donor was calculated using "PUBCHEM AND MOLSOFT" software shown in Table 3. Compounds that overcame two or more thresholds were considered as non-drug like compounds. The compounds that overcame two or more thresholds were Tenofovir disoproxil, Sofosbuvir/velpatasvir, Trastuzumab, Gelcaprevir, Pegtilgrastion, Lumacaftor/ivacaftor, Fluticasone propionate and salmetarol, Elbasvir, Linagliptin and metformin, Fluticasone furoate and vilanterol. Pharmaceutical companies spend lots of money on drug research and development. It is estimated the total cost of inserting a new drug in therapeutics is more than 1billion US$ [13]. The modern drug research is based on HTS and other modified techniques which can evaluate thousands of compounds in less time, out of the thousand compounds the best hit becomes the lead compound and finally a successful drug. Inspite of lots of efforts, most of the lead molecules fail in pre-clinical or in clinical research, moment when much of the money is already spent. During such scenario the drug like characteristics serve as a parameter in choosing a more promising compound as a lead from the extensive combinatorial libraries. It is estimated that the chance of hit compound to reach the market is one in a million [14].

One of the most widely used selection factor is Ro5. The Ro5 is used as a filter to separate the compounds that could have good oral bioavailability and permeability and better pharmaceutical characteristics. The Ro5 being most widely used filter but has to be used with some criteria as some companies themselves observed that antibiotics, antifungal, cardiac glycosides, vitamins, naturally occurring substance and biomacromolecules did not fulfill the Ro5. Some published work revealed that Ro5 has limitations.

In the present work the worldwide best-selling drugs in 2018-19 were evaluated using the Ro5. Among the selected 56 drugs, 10 (17.8%) did not fulfill the Ro5 in two or more thresholds, and were considered as non-drug-like compound and 2 (3.5%) compounds overcame one threshold. The compounds which are classified as non-drugs are: Tenofovir disoproxil, Sofosbuvir/velpatasvir, Trastuzumab, Gelcaprevir, Pegtilgrastion, Lumacaftor/ivacaftor, Fluticasone propionate and salmetarol, Elbasvir, Linagliptin and metformin, Fluticasone furoate and vilanterol. Two compounds: Sofosbuvir and ledipasvir, and Darunavir ethanolate did not fit in only one criterion. Adalimumab is the most widely selling drug but does not fit inRo5, if Adalimumab was evaluated under the Ro5, probably it would have not reached into the market, hence, Ro5 must be used carefully.

The Molecular weight describes the molecular size, Bigger the molecule, greater the difficulty for absorption, because the passage of these large molecules through the biological membrane is unfavorable. The compounds that did not pass these criteria were Tenofovir disoproxil, Sofosbuvir and ledipasvir, Sofosbuvir/velpatasvir, Trastuzumab, Glecaprevir, Pegtilgrastion, Lumacaftor/ivacaftor, Fluticasone propionate and salmetarol, Elbasvir, Darunavir ethanolate, Linagliptin and Metformin, Fluticasone furoate and Vilanterol. Bigger molecules have lower promiscuity i.e the molecules have less interaction with a greater number of targets which decrease the druggable target. Also, it is observed that the molecular weight of the drug increases during the passage through clinical phases which is clearly shown in Figure 1 [15].

The Clog*P* is one of the most important descriptions in evaluating the oral bioavailability as it indicates the lipophilicity and hydrophilicity of the compound [16]. The greater the lipophilicity of the compound is, the better its capacity to cross the lipid-bilayer of the cellular membrane is, and consequently the higher the bioavailability will be. The problem is that the compound with greater lipophilicity is difficult to dissolve in aqueous part of organism, and then, it will not be absorbed. The compounds that overcame Clog*P* threshold value were Sofosbuvir /valpatasvir, Trastuzumab, Lumacaftor/ivacaftor, Fluticasone propionate and Salmetarol, Fingolimod, Elbasvir, Fluticasone furorate and Vilanterol. Despite this, most of the drugs are administered orally, among them, Lumacaftor/Ivacaftor, Sofosbuvir, Fingolimod have good bioavailability (greater than 50%), which is shown in Figure 2 [17].

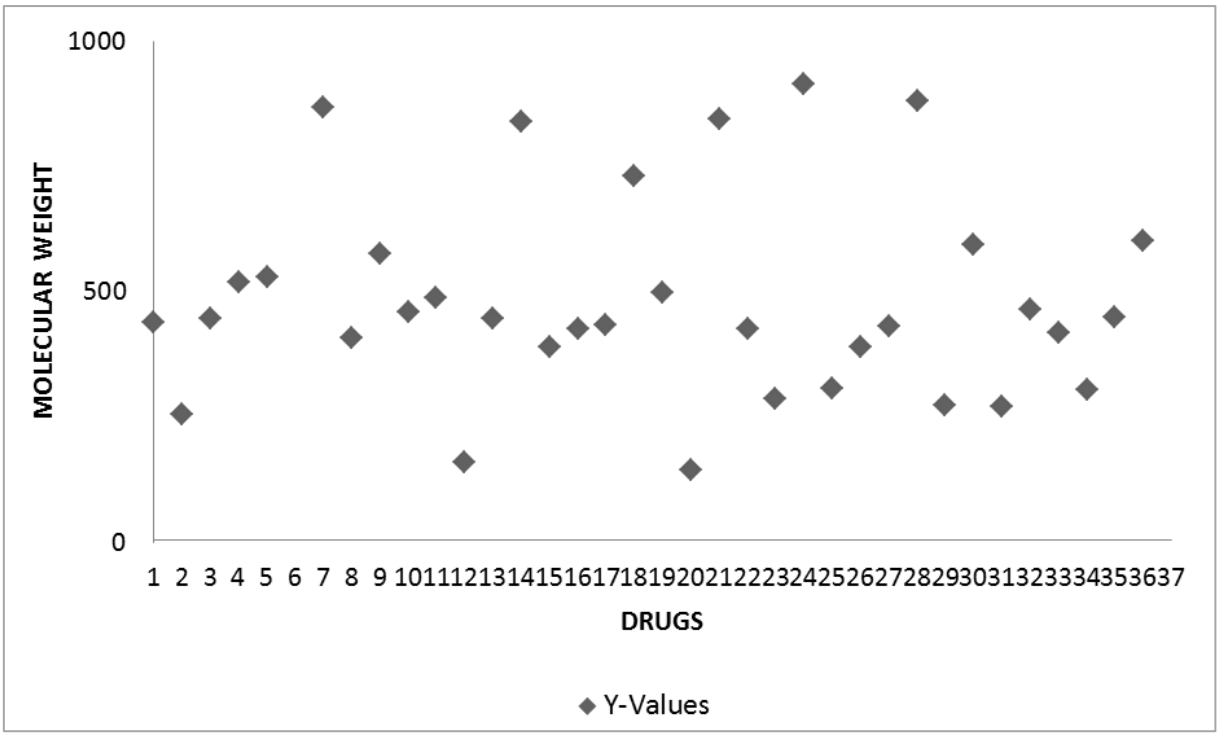


Figure 1. Plot of Molecular weight of selected drug molecules

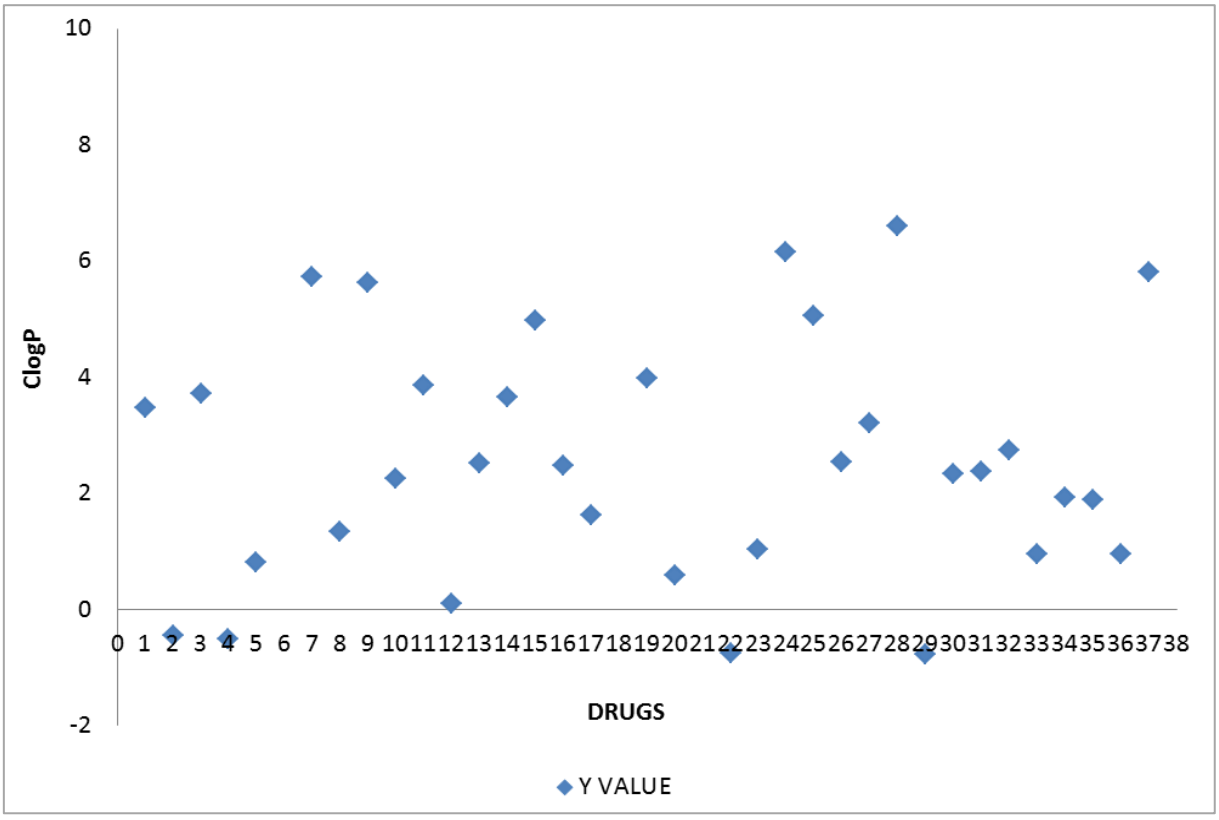


Figure 2. Plot of ClogP value of selected drug molecules

The HB acceptor and donor groups indicate the capacity of intermolecular interactions, mainly with water molecules. The passage of the compound through cellular membrane becomes thermodynamically unfavorable with the increase in HB counts groups because desolvatation is required to enter the lipophilic environment [18]. Thus, the

HB count is limited in Ro5. The compounds that overcame these criteria were Tenofovir, Glecaprevir Pegfilgrastion, Pemetrexed, Linagliptin and metformin, Fluticasone furoate and Vilanterol. As said before, the Ro5 excludes the analysis of biomacromolecules. As can be seen in Table 1, many biomacromolecules are in the list of successful pharmaceutical products. These compounds can be seen as non-drug-like when selected from combinatorial libraries, but are very lucrative drugs to the company. Generally, biomacromolecules will not have good oral bioavailability, but a successful drug can be administered through any other route. Researchers have discussed the overemphasis given to drugs like characteristics and to the oral administration and the purpose that Parenteral drugs could be "Blocker Busters" too (examples are provided in Table 1) [19-21].

4. Conclusions

The Ro5 is a simple and useful method to pre-filter the candidate compounds for drug with good oral bioavailability. It was verified that more than 80% of successful drugs fulfill the threshold of the Ro5 but it is important to highlight that it has its own limitations. Moreover, it may cause mistakes in the evaluation of compounds that could be well absorbed drugs, or compounds that fit in the rule, but have poor absorption. In summary, the Ro5 must be improved to decrease the number of its limitation, as has been claimed and purposed in some research and review papers.

List of Abbreviations

DLS- Drug Likeness Score
HBA- Hydrogen Bond Acceptor
HBD- Hydrogen Bond Donor
HTS- High Throughput Screening
MW- Molecular Weight
Ro5- Rule of Five
SAR- Structure-Activity Relationship
SMILES- Simplified Molecular Line Entry System

Declarations Section

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and materials: The research work has been carried out by us, and we assure you that it can be provided to you whenever required.

Competing interests: Not applicable.

Funding: Not applicable.

Acknowledgements

The Authors are thankful to Dr. Sunil S. Jalalpure, PRINCIPAL KLE College of Pharmacy, Belagavi for providing support, motivation and guidance to complete present study and investigation.

REFERENCES

[1] Lima LM (2007). Qu ímica Medicinal Moderna: Desafio e Contribui ção Brasileira. Quim Nova 30: 1456 – 1468

[2] Lima LM, Barreiro EJ (2005). Bioisosterism: a useful strategy for molecular modification and drug design. Curr Med Chem 12: 23 – 49.

[3] Gershell LJ, Atkins JH (2003). A brief history of novel drug discovery technologies. Nat Rev Drug Discov 2: 321 – 327.

[4] Walters WP, Ajay A, Murcko MA (1999) Recognizing molecules with drug-like properties. CurrOpin Chem Biol 3: 384 – 387.

[5] Keller TH, Pichota A, Yin Z (2006). A practical view of 'druggability'. CurrOpin Chem Biol 10: 357 – 361.

[6] Vistoli G, Pedretti A, Testa B (2008). Assessing drug-likeness – what are we missing? Drug Discov Today 13: 285 – 294.

[7] Biswas D, Roy S, Sen S (2006). A simple approach for indexing the oral druglikeness of a compound: discriminating druglike compounds from nondruglike ones. J Chem Inf Model 46: 1394 – 1401.

[8] Lipinski CA, Lombardo F, Dominy BW, Feeney PJ (1997). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev 23: 3 – 25.

[9] Patil R S, Khatib N A, Patil V S, Suryawanshi S S. Cholonergic acid may be a potent inhibitor of dimeric SARS-CoV-2 main protease 3CLpro: an in silico study. Traditional Medicinal Research.2020;1-14.

[10] Suryawanshi SS, Jayannache PB, Patil RS, Palled MS, SG A. Molecular Docking Studies on Screening and Assessment of Selected Bioflavonoids as Potential Inhibitors of COVID-19 Main Protease. Asian Journal of Pharmaceutical and Clinical Research. 2020;31:174-8.

[11] Suryawanshi SS, Maruche S, Patil P, Palled MS, Pancham Y. Comparative *in-vitro* antioxidant activity of fruit extracts of *Embelica officinalis* Gaertn and drug likeness profile of selected phytoconstituents. International Journal of Botany Studies. 2020: 5(6):704-9

[12] Sampat G, Suryawanshi SS, Sawant R, Khanal P, Palled MS, Alegaon SG, Kavalapure R. Molecular docking studies and antibacterial activity of leaves of *Tabernamontana divaricate*. Journal of Global Trends in Pharmaceutical Sciences. 2020;11(2):7818-24.

[13] Henry DR (2004). Combinatorial chemistry. In: Block JH, Beale JM Jr (eds.) Wilson and Gisvold's textbook of organic medicinal and pharmaceutical chemistry,

Philadephia, p. 43 – 64.

[14] DiMasi JA (1995). Success rates for new drugs entering clinical testing in the United States. Clin Pharmacol Ther 58: 1 – 14.

[15] Navia MA, Chaturvedi PR (1996). Design principles for orally bioavailable drugs. Drug Dev Today 1: 179 – 189.

[16] Leeson PD, Springthorpe B (2007). The influence of drug-like concepts on decision-making in medicinal chemistry. Nat Rev Drug Discov 6: 881 – 890.

[17] Hansch C, Leo A, Hoekman D (1995). Exploring QSAR: hydrophobic, electronic and steric constants, Washington.

[18] Sweetman SC (2007). Matindale: the complete drug reference. 35th ed., London.

[19] Clark DE (1999). Rapid calculation of polar molecular surface area and its application to the prediction of transport phenomena. 2. Prediction of blood-brain barrier penetration. J Pharm Sci 88: 807 – 814. Veber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD (2002) Molecular properties that influence the oral bioavailability of drug candidates. J Med Chem 45: 2615 – 2623.

[20] Zhang M, Wilkinson B (2008). Drug discovery beyond the 'rule-of-five'. CurrOpin Biotech 18: 478 – 488

[21] Ghose AK, Viswanadhan VN, Wendoloski JJ (1999). 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 – 68.