Centro Universitário São Camilo[1], São Paulo; Universidade do Grande ABC[2], Santo André, SP, Brazil

Evaluation of blockbuster drugs under the Rule-of-five

B. G. Giménez[1], M. S. Santos[1], M. Ferrarini[2], J. P. S. Fernandes[1,2]

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Prof. João Paulo dos Santos Fernandes, Centro Universitário São Camilo, Av. Nazaré 1501, 04263-200 São Paulo, SP, Brazil
jpsfer@usp.br

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The current drug research techniques, combinatorial synthesis and high throughput screening, enabled the obtaining and pre-evaluation of thousands of compounds in short time. In order to chose the best hits to become leads, observation of drug-likeness tries to optimize this selection. Probably, the most widely used filter is Lipinski's Rule-of-five, which proposes that molecules with poor permeation and oral absorption have molecular weight > 500, Clog *P* > 5, hydrogen-bond donor > 5 and hydrogen-bond acceptor > 10. In order to evaluate the Rule-of-five, the top pharmaceutical products in 2007 were analyzed. Among 60 drugs, 7 (atorvastatin, montelukast, docetaxel, telmisartan, tacrolimus, leuprolide and olmesartan) did not fit the rule, and 5 failed only one of the threshold values. It was possible to conclude that the rule is very useful to select better compounds in chemolibraries, but it must be used carefully and with criteria, to avoid a possible exclusion of promising compounds.

1. Introduction

For many years, drug research was centered in the investigation of vegetal natural products. The medicinal chemistry age started in the 1930's with the synthesis and utilization of antibacterial sulfonamides. In the meantime, limitations to synthesize and purify a large amount of new compounds in short time became an evident bottleneck (Lima 2007).

During the 1950's until the 80's, the drug design process changed drastically. The molecular modification approach was intensively used due to the development of bioisosterism (Lima and Barreiro 2005), starting the structure-activity relationships studies. After the advance of molecular biology techniques in the 1980's, the biochemical aspects related with the physiopathology contributed to the target-based drug design approach (Lima 2007).

In order to optimize the time-production relationship, pharmaceutical companies developed the combinatorial synthesis strategy, enabling the rapid acquisition of large combinatorial libraries. Adding this to the development of high-throughput screening (HTS) methods (Gershell and Atkins 2003), these compounds could be quickly evaluated, obtaining compounds called "hits". The size of these combinatorial libraries to be evaluated (also called chemolibraries) can beyond one million of compounds. In one year, it is possible synthesize thousands of compounds using combinatorial techniques (Walters et al. 1999).

Despite of efforts to increase the number of compounds in chemolibraries to obtain better results on search for hits, most of the compounds are reproved during clinical trials due to pharmacokinetic problems, thus being discarded in clinical phase II, where efficacy and toxicity are evaluated (Keller et al. 2006).

The current research approach is to find in previously described compounds what are the key points in its pharmacokinetic and pharmacodynamic properties that can be set as standards to drug design (Vistoli et al. 2008). These strategies set a new pace for drug design and synthesis. These processes are, sometimes, referred as drug-likeness or drug-like molecules recognition (Walters et al. 1999; Vistoli et al. 2008).

Basically, the drug-likeness concept involves molecular features compatible with biological activity, including desirable pharmacokinetic (absorption, distribution and excretion) and pharmacodynamic properties. These features are physicochemical properties that complement pharmacophoric sites without affecting its chemical functions, giving them the potential to an adequate pharmacology (Vistoli et al. 2008).

Several "rules" appeared attempting to facilitate the recognition of promising molecules. The most important, and probably the most applied, is Lipinski's Rule-of-Five (Ro5) (Lipinski et al. 1997), developed by the Pfizer's medicinal chemist Christopher A. Lipinski. This rule is widely applied to filter compounds potentially active from combinatorial libraries that could have good oral absorption and/or permeation (Biswas et al. 2006). The Ro5 advocates that poorly absorbed molecules by intestinal wall present two or more of these characteristics: molecular weight over than 500, the calculated logarithm of *n*-octanol/water partition coefficient (Clog*P*) over than 5 (or Mlog*P* lower than 4.15), more than 5 hydrogen-bond (HB) donor groups (expressed as the sum of OHs and NHs groups) and more than 10 HB acceptor groups (expressed as the sum of Os and Ns atoms). Because each threshold is a multiple of 5, the rule was called Ro5. However, biomacromolecules are excluded of the analysis for their sizes, and natural products or substrates of naturally transporters generally not fit in the Ro5 (Lipinski et al. 1997).

Starting on the premise that the pharmaceutical companies aim promising marketing drugs (also called "blockbusters"), oral administration is the preferred one, once they present great economic and therapeutic advantages. Therefore, prediction of compounds that could be used orally in combinatorial libraries

Table 1: List published by IMS-Health Institute of top pharmaceutical products in 2007

Trade name	Generic name
1. Lipitor®	Atorvastatin
2. Plavix®	Clopidogrel
3. Ad Vair®	Fluticasone
	Salmeterol
4. Enbrel®	Etanercept*
5. Nexium®	Esomeprazole
6. Diovan®	Valsartan
7. Remicade®	Infliximab*
8. Zyprexa®	Olanzapine
9. Risperdal®	Risperidone
10. Rituxan®	Rituximab*
11. Singulair®	Montelukast
12. Herceptin®	Transtuzumab*
13. Seroquel®	Quetiapine
14. Lovenox®	Enoxaparin
15. Effexor®	Venlafaxine
16. Aranesp®	a-Darbepoetin*
17. Norvasc®	Amlodipine
18. Avastin®	Bevacizumab*
19. Cozaar®	Losartan
20. Atacand®	Candesartan
21. AcipHex®	Rabeprazole
22. Lantus®	Insulin glargine*
23. Humira®	Adalimumab*
24. Fosamax®	Alendronate
25. Gleevec®	Imatinib
26. Lexapro®	Escitalopram
27. Neulasta®	Pegfilgrastim*
28. Actos®	Pioglitazone
29. Procrit®	Epoietin*
30. Taxotere®	Docetaxel
31. Prevacid®	Lansoprazole
32. Avapro®	Irbesartan
33. Vytorin®	Ezetimibe
	Simvastatin
34. Crestor®	Rosuvastatin
35. Epogen®	Epoietin*
36. Spiriva®	Tiotropium
37. Topamax®	Topiramate
38. Avandia®	Rosiglitazone
39. Prevnar®	Antipneumococcical vaccine*
40. Zetia®	Ezetimibe
41. Eloxatin®	Oxaliplatin
42. Celebrex®	Celecoxib
43. Zyrtec®	Cetirizine
44. Lamictal®	Lamotrigine
45. Aricept®	Donepezil
46. Micardis®	Telmisartan
47. Cymbalta®	Duloxetin
48. Levaquin®	Levofloxacin
49. Protonix®	Pantoprazole
50. Ambien®	Zolpidem
51. Prograf®	Tacrolimus
52. Avonex®	Interferon β-1a*
53. Valtrex®	Valacyclovir
54. TriCor®	Fenofibrate
55. Viagra®	Sildenafil
56. Epogin®	Epoietin*
57. Tamiflu®	Oseltamivir
58. Arimidex®	Anastrozole
59. Copaxone®	Glatiramer acetate*
60. Rebif®	Interferon β-1a*
61. Abilify®	Aripiprazole
62. Xalatan®	Latanoprost
63. Gemzar®	Gemcitabine
64. Truvada®	Tenofovir
	Emtricitabine
65. Lupron®	Leuprolide
66. Depakote®	Valproate
67. Symbicort®	Budesonide
	Formoterol
68. Humalog®	Insulin lispro*
69. Pulmicort®	Budesonide
70. Toprol®	Metoprolol
71. Cialis®	Tadalafil
72. Betaseron®	Interferon β-1b*
73. Flomax®	Tansulosin
74. Imitrex®	Sumatriptan
75. Pegasys®	Interferon α-2a*
76. Benicar®	Olmesartan
77. Erbitux®	Cetuximab*
78. Casodex®	Bicalutamide
79. Zometa®	Zoledronate
80. Neupogen®	Pegfilgrastim*
81. Flovent®	Fluticasone
82. Botox®	Botulinum toxin*

* biomacromolecules

is usually considered for promising leads. This study has as objective to analyze the top pharmaceutical products in 2007 (IMS Health Institute 2008) to evaluate if they fulfill the Ro5, and identify possible outliers based in the Ro5.

2. Investigations and results

2.1. Database

The data presented by the IMS-Health Institute (IMS Health Institute 2008) having the best selling drugs in 2007, reproduced in Table 1, were the source data for the present study.

2.2. Computational

The structures of the drugs included in Table 1 were obtained in .mol format via the available download from the DrugBank molecule databank (Wishart et al. 2008). The structures not available were built in the MarvinSketch software (MarvinSketch 2007). Only compounds that are small molecules were analyzed.

To calculate the descriptors, the MarvinSketch software (ChemAxon, Inc.) was used in its on-line available version (MarvinSketch 2007). Obtained descriptors were tabulated and compared with those from the Ro5. The descriptors calculated were molecular weight, HB donor and acceptor groups and the logarithm of *n*-octanol/water partition coefficient (Clog*P*).

2.3. Results

Obtained values are shown in Table 2.

3. Discussion

A large budget is being spent by the pharmaceutical sector in drug research and development. It is estimated that the costs to

Table 2: Results obtained for selected drugs. Repeated drugs and biomacromolecules were excluded

Drug	Clog *P*	Molecular weight	HB donor	HB acceptor
Atorvastatin	5.39	558.64	4	6
Clopidogrel	4.03	321.82	0	4
Fluticasone	2.58	444.51	2	8
Salmeterol	3.1	415.57	4	5
Esomeprazole	2.43	345.42	1	5
Valsartan	4.51	435.52	2	6
Olanzapine	3.39	312.43	1	5
Risperidone	2.1	412.5	0	6
Montelukast	7.8	588.2	2	6
Quetiapine	2.81	383.51	1	6
Venlafaxine	4.31	275.43	0	2
Amlodipine	1.64	408.88	2	6
Losartan	5.08	422.91	2	6
Candesartan	5.21	438.48	1	6
Rabeprazole	2.09	359.44	1	5
Alendronate	−4.1	249.1	6	8
Imatinib	4.38	493.6	2	7
Escitalopram	3.76	324.39	0	4
Pioglitazone	2.69	356.44	1	6
Docetaxel	2.92	807.88	5	11
Lansoprazole	3.03	369.36	1	7
Irbesartan	5.5	428.53	1	5
Ezetimibe	4.56	409.53	2	5
Simvastatin	4.46	418.57	1	3
Rosuvastatin	1.92	481.54	3	9
Tiotropium	−1.76	472.42	1	5
Topiramate	0.13	339.36	1	8
Rosiglitazone	1.86	357.43	1	7
Oxaliplatin	−0.01	397.29	2	2
Celecoxib	4.01	381.37	1	6
Cetirizine	0.34	388.89	1	6
Lamotrigine	1.93	256.09	2	7
Donepezil	4.21	379.49	0	4
Telmisartan	5.14	514.62	1	4
Duloxetin	4.2	297.42	1	3
Levofloxacin	0.65	361.37	1	8
Pantoprazole	2.18	383.37	1	8
Zolpidem	3.02	307.39	0	3
Tacrolimus	5.59	804.02	3	11
Valacyclovir	−0.46	324.34	3	8
Fenofibrate	5.28	360.83	0	4
Sildenafil	1.87	474.58	1	8
Oseltamivir	1.16	312.4	2	4
Anastrozole	3.03	293.37	0	4
Aripiprazole	4.9	448.38	1	6
Latanoprost	3.98	432.59	3	4
Gemcitabine	−1.47	263.2	3	8
Tenofovir	−0.9	287.21	3	8
Emtricitabine	−3.96	247.25	2	7
Leuprolide	−3.79	1209.4	15	16
Valproate	2.78	144.2	1	2
Budesonide	2.73	430.53	2	6
Formoterol	0.83	344.4	4	5
Metoprolol	1.76	267.36	2	4
Tadalafil	1.64	389.4	1	4
Tamsulosin	1.78	408.51	2	6
Sumatriptan	0.74	295.4	2	3
Olmesartan	5.55	558.59	2	8
Bicalutamide	2.71	430.37	2	9
Zoledronate	−3.87	272.09	5	8

introduce a new drug in therapeutics are over than US$ 1 billion (Henry 2004). To reduce these expenses modern drug research is pointing towards the HTS technique to quickly evaluate thousands of hit compounds to select the most promising as lead compounds (Gershell and Atkins 2003; Henry 2004). However, the majority of candidates fail in pre-clinical or clinical phases of research when a lot of money was already wasted.

To cut this scenario drug-like characteristics serve an additional parameter that medicinal chemists use as a selection factor to pinch more promising compounds as leads from extensive combinatorial libraries (Lipinski et al. 1997). It is estimated (DiMasi 1995) that the chance of a hit compound to reach the market is one in a million (as search a needle in a haystack). It should be added that patients are more comfortable with oral treatments, once they are cheaper, easy to take and painless (Boxton 2006). Drugs that produce billions of dollars to the companies are commonly called as "blockbusters".

One of the most widely used selection factor is the Ro5. The Ro5 is used as a filter to compounds that could have good oral bioavailability and permeability (Lipinski et al. 1997), and then, better pharmaceutical characteristics. Ro5, however, can fail and thus it must be used with criterion. Among the authors' comments in these regards, it is included that senior managers in some companies did not accept a highly promising compound because it did not fit the Ro5 (Zhang and Wilkinson 2008). Lipinski et al. (1997) observed that antibiotics, antifungals, vitamins and cardiac glycosides felt outside their rule, and justified that these compounds are substrates of naturally occurring transporters. Other investigations revealed the Ro5 has limitations (Lu et al. 2004; Vieth and Sutherland 2006).

In this work, among the 60 compounds evaluated, 7 (11.7%) did not fit the Ro5 in two or more thresholds, and were classified as non-drug-like compounds, and 5 compounds (8.3%) failed only one threshold. The compounds classified as non-drug-like were atorvastatin, montelukast, docetaxel, telmisartan, tacrolimus, leuprolide and olmesartan. Compounds like losartan, candesartan, alendronate, irbesartan and fenofibrate did not fit in only one criterion.

Atorvastatin (Lipitor®) is the number one drug in published ranking. If atorvastatin was pre-evaluated as a hit under the Ro5, probably it would not reach the market. This is the best example why the Ro5 must be used carefully. Montelukast (Singulair®) and the angiotensin-II receptor antagonists telmisartan, olmesartan, losartan, candesartan and irbesartan are other examples that did not fulfill the Ro5. In a recent work, 1204 US FDA-approved small-molecule drugs revealed that only 885 drugs (73%) passed by the Ro5 criteria, of which 619 drugs (70%) are used orally (Overington et al. 2006). It means that only about half of the FDA-approved drugs are both orally administered and fulfill Ro5. The reasons for this outcome is briefly rationalized below.

The Clog*P* value is one of the most important descriptors to evaluate oral bioavailability because indicates the lipophilicity and hydrosolubility of a compound (Hansch et al. 1995). The more lipophilic the compound is, the better is the capacity to cross the lipidic-bilayer of the cellular membrane, and consequently, the higher the bioavailability will be. The problem is that excessively lipophilic compounds have difficulty to dissolve in the water of the organism, and then, will not be absorbed. The compounds that surpass the Clog*P* threshold value were atorvastatin, montelukast, losartan, candesartan, irbesartan, telmisartan, tacrolimus, fenofibrate and olmesartan (respectively, compounds 1, 9, 13, 14, 22, 34, 39, 41 and 58 in Fig. 1). Despite this, all of these compounds are available for oral administration, but among them, only irbesartan and montelukast show good oral bioavailability (more than 50%) (Sweetman 2007). Although the Clog*P* implemented in this

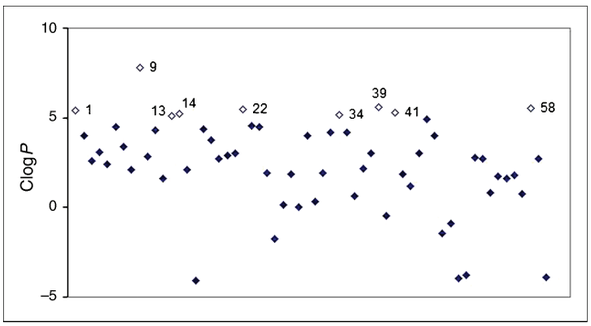

Fig. 1: Plot of Clog*P* value to the 60 compounds. The filled lozenges are compounds with Clog*P* < 5, and the unfilled lozenges compounds with Clog*P* > 5

work is calculated by a method different from that used by Lipinski et al. (1997), the global values obtained are slightly higher than those obtained with Mlog*P*.

The molecular weight describes the molecular size. Big molecules will have difficulties to be absorbed, because the passage through biological membranes is unfavorable (Navia and Chaturvedi 1996). The compounds that not passed this criterion were atorvastatin, montelukast, docetaxel, telmisartan, tacrolimus, leuprolide and olmesartan (respectively, compounds 1, 9, 20, 34, 39, 50 and 58 in Fig. 2). Docetaxel and leuprolide are good examples of the effect of molecular weight in oral bioavailability: none of them are orally absorbed (Sweetman 2007). Leeson and Springthorpe (2007) showed that during the years the molecular weight and the Clog*P* of the approved drugs became higher. The researchers justify that the number of druggable targets have been reduced, forcing the design of bigger and more lipophilic molecules. Bigger molecules have lower promiscuity, i.e. bigger molecules interact with less macromolecular targets. Also, it was observed that the molecular weight of drugs increases during the passage through clinical phases (Leeson and Springthorpe 2007).

The HB donor and acceptor groups correlate to the capacity of intermolecular interactions, mainly with water molecules. The passage through cellular membranes becomes thermodynamically unfavorable with the increase of HB groups because desolvatation is needed to enter the lipidic environment (Clark 1999; Veber et al. 2002). Thus, the HB number is limited in Ro5. The drugs that overcame this criterion were alendronate, docetaxel, tacrolimus and leuprolide. All of them are poorly absorbed following oral administration (Sweetman 2007). Although the criterion to select the groups is different from those used by Lipinski et al. (1997), the meaning of them is the same and does not affect the result.

As said before, the Ro5 excludes biomacromolecules of the analysis. As can be seen in Table 1, many biomacromolecules

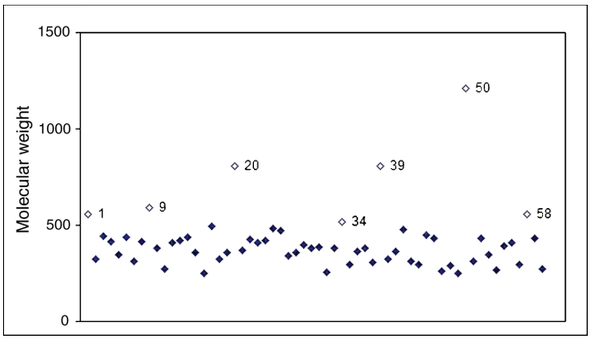

Fig. 2: Plot of the molecular weight for the compounds in Table 2. Unfilled lozenges are drugs with molecular weight > 500

are in the list of successful pharmaceutical products. Then, these compounds can be seen as non-drug-like when selected from combinatorial libraries, but are very lucrative drugs to the companies. Obviously, biomacromolecules will not have good oral bioavailability, but a successful drug can also be administered parenterally. Zhang and Wilkinson (2008) discuss the overemphasis given to the drug-like characteristics and to the oral administration, and propose that parenteral drugs can be "blockbusters" too, and the examples presented in Table 1 prove it.

Some compounds have not a good oral bioavailability in spite of fulfilling the Ro5 thresholds. These compounds are fluticasone, valsartan, rosuvastatin, tiotropium, oxaliplatin, sildenafil, gemcitabine, tenofovir, budesonide, sumatriptan and zolendronate. In fact, few of these compounds are available for oral administration. Some of these compounds have its oral bioavailability influenced by first-pass metabolism, as fluticasone, budesonide and sumatriptan (Sweetman 2007), while the remaining are affected by other factors, such low solubility or very low lipophilicity. This manner, the prediction of drug first-pass metabolism is as important as the prediction of good absorption or permeation. Not any biological transporter that could affect the oral bioavailability of these compounds was found in the literature. Currently, great efforts have been made to predict the pharmacokinetic behavior of a compound *in silico*, mainly the biotransformation. This has been the bottleneck in actual search for new drugs. In the future, the prediction of pharmacokinetics may help, and certainly will be useful in early stages of drug design.

In conclusion, the Ro5 is a simple and useful method to pre-filter candidate compounds for drugs with good oral bioavailability. The present study shows that some drugs approved in the Ro5 test exhibit low bioavailability, whereas others not approved are doing well in the market. It was verified that about 89% of successful drugs fulfill the thresholds of the Ro5, but is important to highlight that it has limitations. Moreover, it may induce mistakes in the evaluation of compounds that could be a well-absorbed drug, or in compounds that fit the rule, but have poor absorption. In summary, the Ro5 must be improved to decrease the number of outliers, as have been claimed and proposed in some papers and reviews (Ghose et al. 1999; Oprea et al. 2007; Oprea et al. 2001; Veber et al. 2002; Vistoli et al. 2008).

4. Experimental

4.1. Descriptor calculations

The descriptors Clog*P*, molecular weight, HB donor and acceptor groups count were used as proposed by Lipinski et al. (1997). Compounds that overcame two or more threshold values were considered non-drug-like.

The Clog*P* value was calculated using the method described by Viswanadhan et al. (1989). These calculations are fragment-based and are implemented in the software. The program MarvinSketch allow the user to weight the calculation, extended by the methods of Klopman et al. (1994) and PhysProp database (Syracuse Research Corporation 1994), that were 1 for all of them. The stipulated Na^+, K^+ and Cl^- concentrations used to the calculation were 0.1 M.

The HB donor groups were taken as any heteroatom with at least one bonded hydrogen, and the HB acceptor groups were taken as any heteroatom without a formal positive charge, excluding pyrrole and tertiary amide nitrogen, heteroaromatic and ester oxygen and non-aromatic sulfur. These groups were determined by MarvinSketch software, that calculates the HB donor and acceptor inclination.

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