International Journal for Parasitology: Drugs and Drug Resistance 7 (2017) 248–249

Contents lists available at ScienceDirect

International Journal for Parasitology: Drugs and Drug Resistance

journal homepage: www.elsevier.com/locate/ijpddr

Invited article

The rule of five should not impede anti-parasitic drug development

James H. McKerrow*, Christopher A. Lipinski, Ph.D., LLC

Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego, United States

ARTICLE INFO

Article history:
Received 19 May 2017
Received in revised form
24 May 2017
Accepted 25 May 2017
Available online 27 May 2017

ABSTRACT

The "rule of 5" has become a mainstay of decision-making in the pharmaceutical industry as well as in nonindustrial (academic and institutional) drug development. However the authors of the original paper never intended for "double cutoffs" to preclude development of new drug leads for parasitic diseases.

In 1997, Lipinski and co-workers published an article in Advanced Drug Delivery Reviews entitled "Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings" (Lipinski et al., 1997). The purpose of the review was to present distinctly different, but complementary, experimental and computational approaches to facilitate medicinal chemistry efforts. The major conclusions presented in this review have become known as "the rule of five". In short, the rule of five predicts that poor absorption or drug permeability is more likely when there are more than 5 H-bond donors, 10 H-bond acceptors, a molecular weight greater than 500, and a calculated Log P greater than 5. The term "rule of five" refers to the fact that each of these conclusions is either 5 or a multiple of 5.

The motivation behind the review was the fact that, in prior years, the sources of drug leads in the pharmaceutical industry had changed significantly. Large empirically-based screening programs became less and less important in the drug industry as the knowledge base grew for "rational drug design". With the advent of combinatorial chemistry, the automated synthesis of massive numbers of compounds for screening became a reality. This resulted in "HTS" or high throughput screens. The screening of such large numbers of compounds in turn necessitated a radical departure from the traditional methods of predicting drug solubility and permeability. Because drug development became a very expensive process, it was important that poorly behaving compounds could be weeded out early. The authors therefore used the United States Adopted Name (USAN) or International Nonproprietary Name (INN) to identify compounds that survived.

Having identified a library of drugs selected by the economics of entry into the Phase II process, the authors identified calculable parameters for the library that were likely related to absorption or permeability. The goal was to set up an absorption-permeability alert procedure to guide medicinal chemists. This is how the authors identified molecular weight, lipophilicity, hydrogen bond donor groups, and hydrogen bond acceptor groups as predictive parameters. When they examined the USAN data set, they found that combinations of any two parameters outside the desirable range did not exceed 10%.

The "rule of 5" has become a mainstay of decision-making both within the pharmaceutical industry as well as in nonindustrial drug screening efforts. However, when drug development efforts began to focus on new drugs for infectious diseases, and in particular parasitic diseases, an important question arose as to whether the "rule of 5" should be applied to Go/No Go decision making. Lipinski and authors never intended such an application. In fact they stated in the review "the only orally active compounds outside the double cutoffs were seven antibiotics. Fungicides-protozoacides also fall outside the rule".

It has come to our attention that, despite this stated exception, many potential anti-parasitic drugs leads have unfortunately been cast aside, or deprioritized, because they fail two or more "rules". This has been the case even if the original hits were discovered in phenotypic screens versus helminthes or protozoa. This was not the intent of the original review, nor does it make pharmacological sense. If the original screen was mechanism-based or biochemical then of course a confirmatory screen against the parasite itself is required (Payne et al., 2007; Mugumbate and Overington, 2015). Even with this cautionary note, as stated in the original review (Lipinski et al., 1997), several very effective and widely used antibiotics fail at least two of the "rules" (Pawlowski et al., 2016).

Given the fact that anti-parasitic drug development is woefully under-populated and underfunded, we need less stringent, not more stringent, criteria for advancement. As noted above, less

* Corresponding author.
E-mail address: jmckerrow@ucsd.edu (J.H. McKerrow).

http://dx.doi.org/10.1016/j.ijpddr.2017.05.003

stringent criteria would allow more lead compounds to be advanced in a field where there are few leads.

Conflict of interest

None.

Funding

None.

References

Lipinski, C.A., Lombardo, F., Dominy, B.W., Feeney, P.J., 1997. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv. Drug Deliv. Rev. 23, 3–25.

Mugumbate, G., Overington, J.P., 2015. The relationship between target-class and the physicochemical properties of antibacterial drugs. Bioorg. Med. Chem. 23, 5218–5224.

Pawlowski, A.C., Johnson, J.W., Wright, G.D., 2016. Evolving medicinal chemistry strategies in antibiotic discovery. Curr. Opin. Biotechnol. 42, 108–117.

Payne, D.J., Gwynn, M.N., Holmes, D.J., Pompliano, D.L., 2007. Drugs for bad bugs: confronting the challenges of antibacterial discovery. Nat. Rev. Drug Discov. 6, 29–40.