# Identification and Evaluation of Molecular Properties Related to Preclinical Optimization and Clinical Fate

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Abstract: The economic case for fundamental changes that are required to ensure long term viability of the pharmaceutical industry demands a close look at which compounds are advanced into clinical development. This perspective will cover recent efforts that have had the greatest influence on defining the optimal range of physical properties of compounds that are intended to act as human therapeutic agents. Our focus will be on models and properties that are most amenable to change *via* synthetic design, are potentially fixable in the lead optimization process, and have the greatest impact on overall attrition in clinical development. In particular, we will examine the optimal physicochemical properties for oral absorption based on solubility, permeability, and a few easily computed parameters. Additionally, the fate of compounds that have entered clinical trials provides a compelling case for adhering to the defined properties ranges. Finally, emerging data suggests that there has been a shift in the leading causes of compound attrition, and attention should now be focused on building toxicological models to guide drug discovery efforts.

## THE CASE FOR STUDYING DRUG-LIKE PROPERTIES

A contemporary review of compound attrition rates in the development of human therapeutic agents paints a sobering picture of the overall health, and future, of the pharmaceutical industry [1]. As Kola and Landis report [1], the average success rate during the ten year period from 1991-2000 for first-in-man to registration is *ca.* 11% for all compounds (roughly 1 in 9 succeed). The success rate varies widely among the different therapeutic areas, from cardiovascular at *ca.* 20% survival to oncology with an aggregate 5% success rate. Perhaps most surprising is the relatively high rate of attrition for NDAs (New Drug Applications) of 23%, which is particularly problematic given that the bulk of the estimated $800 million USD required to produce an NDA has generally been incurred [2]. Against the backdrop of overall productivity in the pharmaceutical industry are the expectation of future earnings growth from investors, and the loss of revenue owing to patent expirations. For a company with $30 billion in 2002 sales, and a modest 5% annual growth rate, a minimum of 50-60 NCEs (New Chemical Entities) would need to be produced over the following decade, with sustained output of nearly 6-7 NCEs per year in 2012 and thereafter to meet these financial expectations [1]. Given that on average only four new-in-class drugs are launched each year against three novel targets (during the period from 1991-2001) for the entire pharmaceutical industry [4], the challenges that are faced seem enormous. Compounding this picture is the often overlooked factor that on average, only three of ten compounds that gain FDA approval generate sufficient revenue to recuperate their research and development costs [3]. Milne underscores many of these points in an article on productivity in the pharmaceutical industry, and the imperative to improve productivity in preclinical drug discovery [5]. As illustrated in Fig. (**1**), one must consider overall attrition, including preclinical discovery, when discussing productivity. From an analysis of drug discovery programs at Pfizer Inc over a 10 year period, nearly 100 small-molecule discovery programs need to be initiated to result in the identification of an NCE.

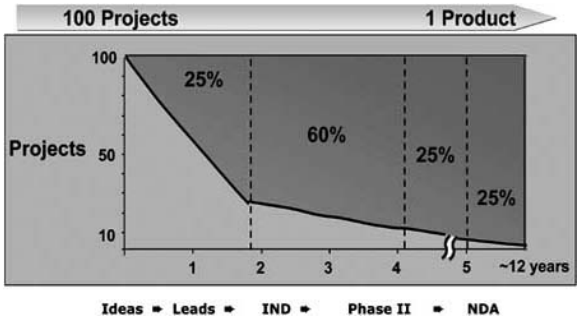


**Fig. (1).** Adapted from Reference 5. Attrition curve that incorporates the preclinical discovery phase into the overall number of projects required to produce an NDA. Percentages indicate the number of compounds that survive from the preceding phase.

The analysis by Milne suggests that, on average, in only 25% of cases does the process of "lead-seeking" result in the identification of candidate quality leads (*i.e.,* suitable for clinical development). As Milne writes, "However, by far the largest routine hit to survival (75%) comes because we have simply selected a chemical or chemical series that is not truly drugable". From the above discussion, it is clear that identification of quality lead compounds is critical to success in drug discovery. The often asked question regarding clinical attrition is: From where do these attrition problems originate?

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Are they present in the lead, or did they get optimized into the candidate during the discovery phase? Further, how can we improve our chances of identifying and optimizing the best leads?

In many drug discovery programs, the medicinal chemist often has the freedom to manipulate several variables that influence various physicochemical properties, size, and structural content. This perspective will focus on advances made in understanding the types of compounds that should be pursued, and the relationships those compounds have to survival in clinical development.

## DEFINING THE OPTIMAL PHYSICOCHEMICAL PROPERTIES OF DRUG-LIKE COMPOUNDS

Experience has shown that obtaining good oral bioavailability for a potent compound can be the most time consuming and labor intensive aspect of a preclinical drug discovery effort. Lipinski has suggested that these difficulties in lead optimization and development can be attributed to the pursuit of hits and leads with poorer physicochemical properties [6]. This observation led Lipinski to create the "Rule-of-5", which was the first attempt at defining acceptable ranges for various physicochemical properties, and was based on mining relevant databases, to uncover differences between classes of compounds [7]. The Rule-of-5 sets an upper limit of 500 AMU and a calculated log*P* of 5 as acceptable (in addition to counts of nitrogen, oxygen, and H-bond donors). These parameters are believed to be related specifically to the permeability and solubility of drug-like compounds that play a critical role in determining the oral absorption characteristics of therapeutic agents. The linking of these two properties is embodied by the so-called absorption potential (AP) of a compound. Dressman *et al.* [8] have related this dependence *via* the following relationship:

$$\mathrm{AP} = \log (P \cdot F_{\mathrm{non}} \cdot S_{\mathrm{o}} \cdot V_{\mathrm{L}} \cdot X_{\mathrm{o}}^{-1}) \qquad (1)$$

Where $P$ is the octanol–water partition coefficient, $F_{\mathrm{non}}$ is the fraction in nonionized form at *p*H 6.5, $S_{\mathrm{o}}$ is the intrinsic solubility, $V_{\mathrm{L}}$ is the volume of the lumenal contents, and $X_{\mathrm{o}}$ is the dose administered. Johnson and Swindell [9] extended this concept to include the permeability explicitly, by introducing the maximum absorbable dose (MAD) of a compound. In their formalism, the MAD is given by:

$$\mathrm{MAD} = K_{\mathrm{a}} \cdot S \cdot SIWV \cdot SITT \qquad (2)$$

In this form, $K_{\mathrm{a}}$ is the measured rat intestinal perfusion rate, $S$ is the aqueous solubility at *p*H 6.5, and *SIWV* and *SITT* are the small intestine (SI) water volume and residency time. The previous two equations describe the quantity of drug that could be absorbed under ideal conditions, assuming no influence from transporters. Fig. (**2**) illustrates this relationship for a few target doses (0.1 mg/kg, 1 mg/kg, and 10 mg/kg) and permeability ranges [6]. From Fig. (**2**), one can see that for a projected dose of 1 mg/kg a compound with "average" permeability [9] would need to achieve at least 52 μg/ml aqueous solubility in order for there to be complete absorption. Defining the limits of acceptable solubility provides important guidance, however, the above relationships require synthesis of the compounds, and testing in relatively time-consuming assays. The desire to avoid this scenario has led to the search for computational alternatives.

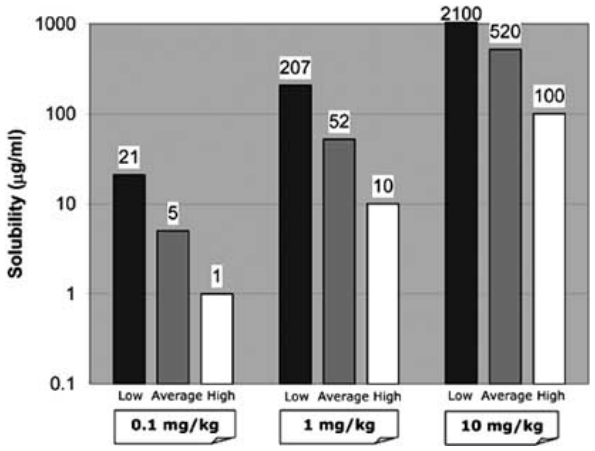


**Fig. (2).** Parameters derived from Reference 6. Each group of three bars presents the minimum aqueous solubility computed from Equation 2 for high, average, and low permeability compounds at the projected dose. For an "average" permeability compound at a 1 mg/kg dose, a minimum of 52 mg/ml aqueous solubility is needed to ensure complete absorption.

The necessity to improve the chances of developing novel therapeutic agents has spawned a number of excellent studies aimed at quantifying the properties associated with successful compounds. In one such study, Veber and colleagues assembled a database of *ca.* 1100 drug candidates with extensive animal data such as rat oral bioavailability and clearance, and *in vitro* data including artificial membrane permeation rates [10]. From an extensive list of easily computed molecular properties such as rotatable bond and H-bond acceptor/donor counts, log*P,* molecular weight, *etc.*, the authors found that reducing the number of rotatable bonds had the largest impact on determining a compound's oral bioavailability in the rat. The authors of that study suggest that compounds with 10 or fewer rotatable bonds and a polar surface area below 140 Å$^2$ will have a higher chance of displaying good bioavailability. Interestingly, molecular weight was not found to correlate with poor oral bioavailability. A recent effort aimed at quantifying the differences between not only drugs and related compounds, but also differing routes of administration, was conducted by Vieth *et al*. [11]. The ultimate goal of their effort was to uncover optimal physicochemical parameters associated with compounds that are presumed to have good pharmacokinetic properties (PK) *vs*. those assumed to have poorer PK properties (*i.e.*, injectable, absorbent, and topical drugs). From a large database of 1729 marketed drugs, compounds in clinical development, and related molecules known to possess biological activity, they found that on average intravenous drugs have significantly higher MW, greater numbers of H-bond acceptors/donors, rotatable bonds, and rings. Consistent with an intravenous route of administration, they also found these compounds tended to possess much lower Clog*P* when compared to oral drugs (presumably due to the increased solubility requirements *vs*. oral drugs). The authors also computed the time-averaged property distributions, and found the properties of oral drugs to remain fairly constant, suggesting that successful drug candidates share common physicochemical characteristics. The preceding

studies have defined not only the distinguishing properties of drugs, but also the acceptable ranges for each of the physicochemical properties.

## ADJUSTING THE STARTING POINT: LEAD-LIKENESS IN DRUG DISCOVERY

If Milne's assertion is correct and nearly 75% of the clinical failures can be traced to selecting a lead, or a series, that is not truly drugable, then studying not only drug-like properties, but also the leads from which they were derived, is necessary. One of the first systematic evaluations of lead-drug pairings was conducted by Oprea and colleagues, wherein the computed properties of 96 pairs of compounds were compared [12]. The authors demonstrated that the process of optimizing a lead into a drug generally results in noticeable increases in molecular weight, log*P*, and other important physicochemical properties. In particular, lead-to-drug optimization results in a median molecular weight increase of *ca.* 69 AMU, a Clog*P* increase of 0.43 units, the addition of two rotatable bonds, and the addition of one ring and one H-bond acceptor. While these increases are significant, they also highlight how closely related the final development compounds are to their corresponding leads. This observation is confirmed *via* a recent analysis of drugs launched during 2000 and their corresponding lead structures [13]. For the 29 series of compounds in that study, the lead-drugs pairs had molecular weight differences within 25% of one another, and one log*P* unit. Additionally, there was a very high degree of structural similarity between the pairs of molecules. Nearly all of this similarity can be traced to the origin of the leads, which in most cases were derived from known drugs or literature compounds. High quality lead structures are very closely related to the final development compound and tend to be 'drug-like'. The average property changes from the above, and other studies [14], are summarized in Table **1**. An updated review by Hann and Oprea details the efforts on defining the "leadlikeness" of compounds [15]. The implicit assumption is that lead-like compounds should have their computed properties adjusted in anticipation of increases that are likely during lead-optimization efforts. These studies have had significant impact on the design of lead-like screening sets and combinatorial libraries, where smaller size, reduced complexity, and stringent property ranges drive the final composition.

**Table 1. Average Property Increases from Lead-to-Drug Optimization**

| Property | Increase |
|---|---|
| Clog*P* | 0.4 - 1.0 |
| Molecular Weight | 40 – 100 |
| Rotatable Bonds | 1 – 2 |
| H-Bond Acceptor | 1 |
| Number of Rings | 1 |
| Andrews' Binding Energy (kcal/mol) | 2 - 3 |

## CLINICAL FATE AND COMPUTED PROPERTY PROFILES: IMPLICATIONS

In the development of Lipinski's "Rule-of-5", the authors made a clear distinction between compounds that were expected to possess well-behaved physicochemical properties (Phase II compounds with INN and USAN designations) *vs*. compounds found in the Available Chemicals Directory (ACD). The logic for the selection of those compounds believed to be in phase II, was as follows [7]:

> "Drug development is expensive and the most poorly behaved compounds are weeded out early. Our hypothesis was that poorer physicochemical properties would predominate in the many compounds that enter into and fail to survive preclinical stages and Phase I safety evaluation. We expected that the most insoluble and poorly permeable compounds would have been eliminated in those compounds that survived to enter Phase II efficacy studies".

This seemingly innocent distinction raises the following question, namely, does progress through clinical development from Preclinical toxicology studies to NDA select for compounds with better physical properties? In particular, is the above expectation from Lipinski correct, and do Preclinical and Phase I studies eliminate compounds with poorer ADME characteristics? Clinical development is the ultimate judge of appropriate properties.

The optimal experiment would entail tracking individual compounds as they progress through clinical development. Given an average time of 12 years from Preclinical to approval, this isn't a feasible approach if a research organization needs to act to reduce attrition now. An alternate methodology would be to examine compounds that are, or have been, in clinical trials and compute their properties relative to the stage of development, which represents more of a "snapshot". Clearly compounds will attrite during clinical development for any number of reasons, such as failure to show efficacy, toxicity, confidence in rationale, competition, marketability, *etc.* [16]. However, for the purposes of guiding preclinical drug discovery, it would be valuable to identify those properties or features that may be linked to an increased risk of clinical failure.

Three recently published articles considered the computed property distributions of compounds at various stages of clinical development [17, 18, 19]. The papers by Blake [18] and others [17, 19] tracked the changes that occur in computed property profiles (molecular weight, Clog*P*, polar surface area, *etc*.) relative to the stage of clinical development. Clinical stages (Preclinical, Phase I, II, III, *etc*.) provide well-defined points from which to make comparisons. Additionally, the decision to progress a compound from one stage of clinical development to another is most likely similar across different therapeutic areas and organizations. The results of these studies found that as the stage of development progresses (Preclinical, Phase I, Phase II, Phase III, and Launched), compounds that are advanced have lower molecular weight, Clog*P*, and polar surface area, Table **2**. What was most compelling was that the property distributions

**Table 2. Computed Properties for Compounds in Clinical Development**

| Property | Preclinical | Phase I | Phase II | Phase III | Launched | Change |
|---|---|---|---|---|---|---|
| **Entries** | 4195 | 466 | 700 | 229 | 884 | |
| **ClogP** | 3.2 | 3.0 | 3.2 | 2.6 | 2.5 | -23% |
| **% ClogP>5** | 22 | 19 | 21 | 17 | 14 | -38% |
| **Polar Surface Area (Å$^2$)** | 137 | 139 | 129 | 130 | 122 | -11% |
| **% PSA>200 Å$^2$** | 24 | 23 | 20 | 22 | 19 | -23% |
| **Molecular Weight** | 393 | 387 | 382 | 361 | 338 | -14% |
| **% MW>500** | 23 | 18 | 19 | 15 | 11 | -51% |
| **% Rule-of-5 Violations** | 20 | 14 | 18 | 16 | 10 | -47% |
| **No. H-Bond Acceptor** | 4 | 4 | 4 | 4 | 4 | 0% |
| **No. H-Bond Donor** | 2 | 2 | 2 | 2 | 1 | -50% |
| **Rotatable Bonds** | 7 | 7 | 6 | 6 | 6 | -14% |
| **% Rotatable Bonds>10** | 24 | 23 | 21 | 20 | 16 | -33% |
| **Andrews' BE (kcal/mol)** | 13 | 12 | 13 | 11 | 11 | -16% |

Median values are listed for each property. Values were computed as detailed in Reference 18. Change is computed from the Preclinical and Launched categories.

tended to show these effects beyond Phase II, when compared to Preclinical and Phase I stages. Blake also found that the fate of compounds with excessive molecular weight (>500) or Clog*P* (>5) tended to be heavily disfavored in the latter stages of clinical development (illustrated in Fig. (**3**)).

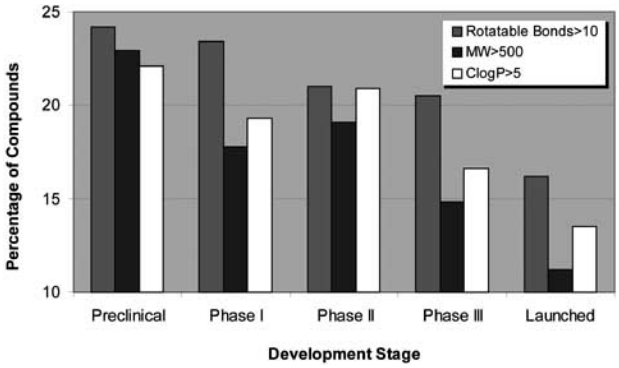


**Fig. (3).** For each stage of clinical development, the percentages of compounds that exceed the indicated cut-off values are illustrated, data is from Table **2**.

As indicated above, these studies involve a static picture of compounds in development, many of which entered clinical trials some time ago. Historically, how much would the Rule-of-5 affect the results if we only progressed Rule-of-5 compliant compounds? Clearly, compounds that lack Rule-of-5 compliance have low chances of survival based on the 47% decrease in representation from Preclinical to Launched classifications in Table **2**. A total of 1144 compounds in the current data set are not Rule-of-5 compliant (*i.e.* two or more parameters are out of range). Elimination of these compounds from further study followed by regeneration of the statistics yields the results presented in Table **3**. When compounds with Rule-of-5 violations are eliminated from the study, the same trend toward improved computed physical properties is observed.

One question remains, namely, why aren't the Preclinical and Phase I studies eliminating compounds with "poorer" physical properties? Why this selection process tends to occur from Phase II to Phase III may be based on the cost differential between the various stages. Illustrated in Fig. (**4**) are the mean and median out-of-pocket costs associated with each phase of development [2], in addition to the probability of filing an NDA. Based on these estimates from DiMasi, the decision to advance a compound from Phase II to Phase III leads too much higher costs. Phase III trials have seen rapidly rising costs due to more sophisticated studies and larger clinical trial size. As discussed in the paper by DiMasi, part of this rise in cost can be attributed to an increase in the number of competitive studies against known therapies in addition to placebo controls. Additionally, an increase in the number of compounds that target chronic and degenerative diseases require more careful patient monitoring and care. By inspection of Fig. (**4**), one can conclude that the "best" compounds are advancing into late stage clinical trials. The success rate in filing an NDA for Phase III compounds is 69%, which is more than a doubling in the rate over Phase II compounds (30%). Clearly, the correct decisions to advance a given compound are being made. One could speculate that Phase I studies may not eliminate compounds with poor properties due in part to the desire to test efficacy in Phase II studies, even with "marginal" compounds. Based on the costs for a Phase II study, which are not significantly higher than a Phase I study, this would

**Table 3. Computed Properties for Rule-of-5 Compliant Clinical Compounds**

| Property | Preclinical | Phase I | Phase II | Phase III | Launched | Change |
|---|---|---|---|---|---|---|
| **Entries** | 3369 | 399 | 577 | 193 | 792 | |
| **ClogP** | 3.1 | 2.9 | 3.0 | 2.4 | 2.5 | -18% |
| **% ClogP>5** | 16 | 15 | 14 | 12 | 12 | -23% |
| **Polar Surface Area (Å$^2$)** | 124 | 132 | 116 | 123 | 115 | -7% |
| **% PSA>200 Å$^2$** | 17 | 17 | 15 | 17 | 14 | -21% |
| **Molecular Weight** | 362 | 366 | 357 | 346 | 325 | -10% |
| **% MW>500** | 5 | 5 | 4 | 1 | 2 | -65% |
| **No. H-Bond Acceptor** | 4 | 4 | 4 | 4 | 3 | -25% |
| **No. H-Bond Donor** | 2 | 2 | 1 | 1 | 1 | -50% |
| **Rotatable Bonds** | 6 | 6 | 6 | 5 | 6 | 0% |
| **% Rotatable Bonds>10** | 13 | 14 | 11 | 10 | 10 | -24% |
| **Andrews' BE (kcal/mol)** | 10 | 10 | 10 | 9 | 9 | -7% |

Median values are listed for each property. Values were computed as detailed in Reference 18. Change is computed from the Preclinical and Launched categories.

seem to be a reasonable strategy if a proof-of-concept is required to validate a particular therapeutic target.

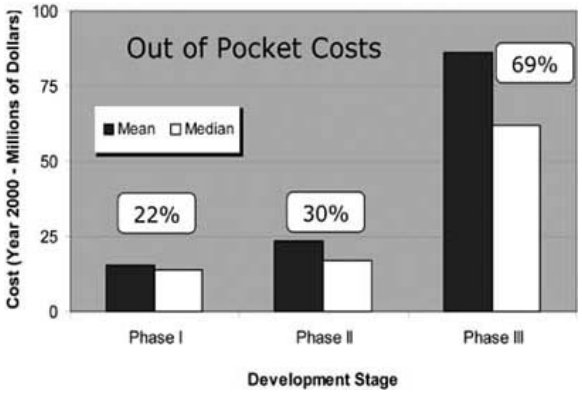


**Fig. (4).** Direct out of pocket costs associated with each phase of clinical development from Reference 2. The probability of filing an NDA from each phase is also shown [2].

## FUNCTIONAL GROUPS LINKED TO PROBLEMATIC PERFORMANCE

An often-cited statistic in reported causes of attrition is the overwhelming contribution of bioavailability and poor pharmacokinetics (*ca.* 40%) to total attrition [20]. This value was based on data gathered for the twenty-year period from 1964-1985 from seven large pharmaceutical companies [21]. As discussed above, both solubility and permeability are intimately connected with this key parameter, and lack of attention to this factor during preclinical discovery has serious consequences during clinical development. During the 1990s emphasis shifted to ensuring that predictive assays were in place during the discovery phase to impact this parameter early in the discovery cycle. A more recent survey (2000 metrics) of a number of large pharmaceutical companies suggests that this factor in attrition has been drastically reduced [22]. In this benchmarking survey of 537 drug discovery programs, statistics from the respondents indicated that only *ca.* 11% of clinical attrition is currently attributed to poor pharmacokinetics. The three leading causes of attrition in drug discovery are now lack of efficacy (30%), safety and toxicology (33%), and commercial reasons (20%). The shift away from poor pharmacokinetics suggests that careful attention, coupled with relevant assays, can be used to address these issues early in the discovery phase. For the purposes of the current discussion, one may assume that "commercial reasons" is largely an economic, rather than scientific, issue, and that "lack of efficacy" is primarily related to the choice of the therapeutic target. If we focus our attention on the "safety and toxicity" classifications, the challenge is to develop both assays and predictive models that can be deployed to medicinal chemists. A recurring question in compound design concerns the idiosyncratic toxicity of certain chemical functionalities. Based on extensive practical experience major categories would include reactive groups and compounds or functionalities that have been show to be mutagenic or carcinogenic. Rishton has cataloged many of these reactive functional groups, which also tend to give false-positives in high-throughput screens, illustrated in Fig. (**5**) [23]. In a series of papers spanning many years, Ashby and Tennant have conducted an extensive evaluation of rodent carcinogenicity and Salmonella mutagenicity data compiled by the United States National Toxicology Program (NTP) [24, 25, 26, 27]. Their research has focused on identifying chemical functionality (structural alerts) that correlates with positive mutagenic and carcinogenic results. The structures in Fig. (**6**) depict those groups that are most likely responsible for the

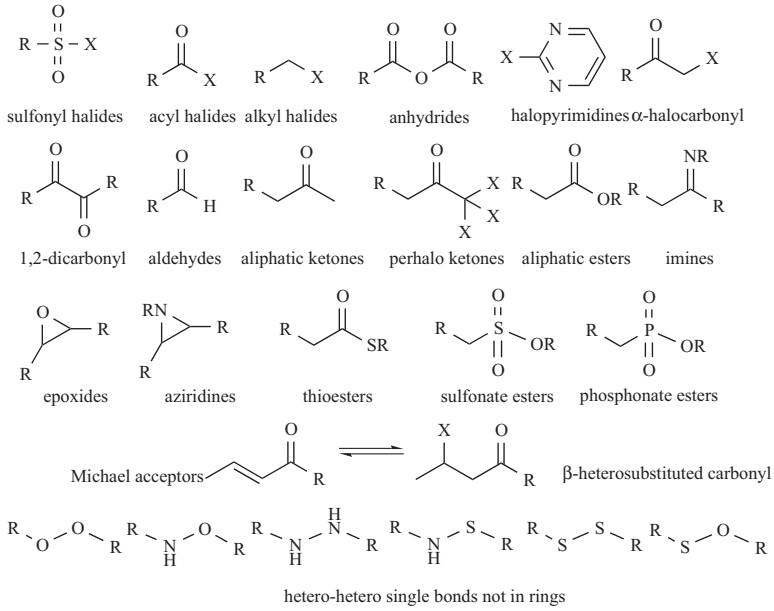


**Fig. (5).** Examples of reactive functionalities that should be avoided, if possible, in the design of novel chemical matter intended to be pursued as leads (adapted from Reference 23).

observed positive results in the mutagenic and carcinogenic assays [25]. The question then becomes, that, as with computed physical properties, is there an attrition trend for these so-called "problematic" functional groups? Using the clinical dataset from Reference 18, each compound was processed [28] to check for the presence of any structural alert. The results of this study are summarized in Fig. (**7**). As seen with the computed physical properties, there is a 23% decrease from the Preclinical to Launched classifications in the number of compounds that generate an alert. In this study, the decrease in altering structures tends to occur earlier, prior to Phase II. These results suggest that, in this case, Phase I studies do eliminate many of the compounds with toxicity issues (as intended), and this is captured in the flagging of problematic groups. While avoiding problematic functional groups in preclinical discovery doesn't guarantee success, including them increases the chances of problems later in clinical development and beyond. Extensions of this research will investigate the degree to which different functional groups fail in clinical development to aid in the refinement of these rules.

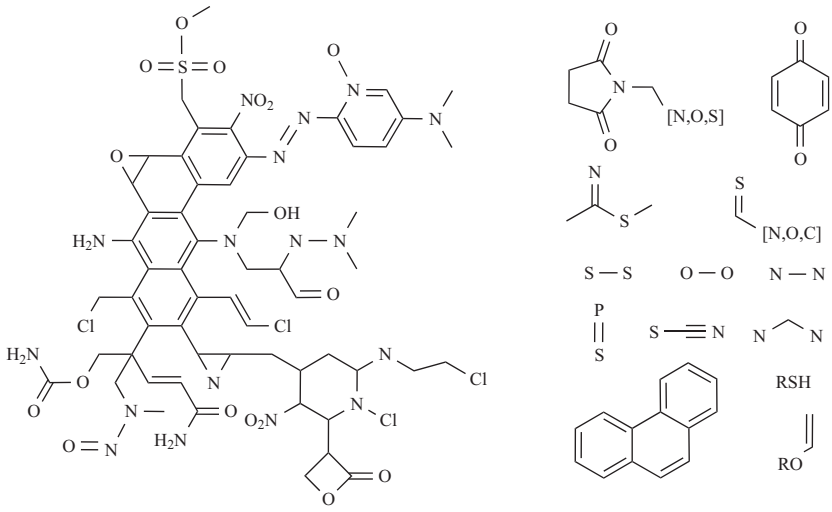


**Fig. (6).** The structure on the left is adapted from Tennant and Ashby [25]. Together with the groups listed in Fig. (**5**), the chemical functionalities represent the so-called "lint" rules of functional groups to avoid [28].

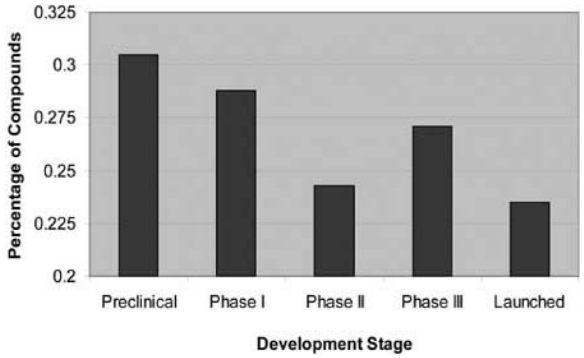


**Fig. (7).** Percentage of compounds from the clinical database [18] that generate a structural alert based on the "lint" rules, computed for each phase of clinical development.

## CONCLUSIONS

The challenges that are faced in improving the productivity of drug discovery programs are formidable. From the economic imperative, it is clear that fundamental changes are required to ensure a vibrant industry that is capable of providing innovative treatments for serious diseases. The significant decrease during the last decade in the percentage of compounds that fail owing to poor pharmacokinetic parameters provides hope that additional studies can lead to similar decreases in other problematic areas of attrition, such as safety and toxicology. A key element of this change should involve the selection and refinement of the best leads. For chemists engaged in preclinical drug discovery, the above studies provide important guidance for what is considered to be optimal property space for the discovery of human therapeutic agents. Good leads have low MW and log*P*, which enables both potency and selectivity to be increased during the lead optimization phase without compromising essential drug properties. Valuable leads also possess chemical features that are amenable to optimization, are not overly complex, and are devoid of problematic functional groups. From analysis of historical clinical data, clear risks are associated with selecting compounds for development that possess poorer physicochemical properties. Using available filters and predictive models, coupled with focused experimental assays, we can improve our chances of advancing the best compounds for clinical development.

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## REFERENCES

[1] Kola, I.; Landis, J. *Nature Rev. Drug Discov*., **2004**, *3*, 711-715.
[2] DiMasi, J.A.; Hansen, R.W.; Grabowski, H.G. *J. Health Econ.*, **2003**, *22*, 151-185.
[3] Grabowski, H.G.; Vernon, J.; DiMasi, J.A. *Pharmacoeconomics*, **2002**, *20*, 11–29.
[4] Hopkins, A.L.; Groom, C.R. *Nature Rev. Drug Discov.,* **2002**, *1*, 727-730.
[5] Milne Jr., G.M. *Ann. Rep. Med. Chem.,* **2003**, *38*, 383-396.
[6] Lipinski, C.A. *J. Pharmacol. Toxicol. Method,* **2000**, *44*, 235-249.
[7] Lipinski, C.A.; Lombardo, F.; Dominy, B.W.; Feeney, P.J. *Adv. Drug Delivery Rev.,* **1997**, *23*, 3-25.
[8] Dressman, J.B.; Amidon, G.F.; Fleisher, D. *J. Pharm. Sci.,* **1985**, *74*, 588-589.
[9] Johnson, K.; Swindell, A. *Pharm. Res.,***1996**, *13*, 1795-1798.
[10] Veber, D.F.; Johnson; S.R.; Cheng, H-Y.; Smith, B.R.; Ward, K.W.; Kopple, K.D. *J. Med. Chem.,* **2002**, *45,* 2615-2623.
[11] Vieth, M.; Siegel M.G.; Higgs, R.E.; Watson, I.A.; Robertson, D.H.; Savin, K.A.; Durst G.L.; Hipskind, P.A. *J. Med. Chem.,* **2004**, *47*, 224-232.
[12] Oprea, T.I., Davis, A.M.; Teague, S.J.; Leeson, P.D. *J. Chem. Inf. Comput. Sci.*, **2001**, *41*, 1308-1315.
[13] Proudfoot, J.R. *Bioor. Med. Chem. Lett.,* **2002**, *12*, 1647–1650.
[14] Hann, M.M.; Leach, A.R.; Harper, G. *J. Chem. Inf. Comput. Sci.,* **2001**, *41*, 856-864.
[15] Hann, M.M.; Oprea, T.I. *Curr. Opin. Chem. Biol.,* **2004**, *8*, 255-263.
[16] Venkatesh, S.; Lipper, R.A. *J. Pharm. Sci.,* **2000**, *89*, 145-154.
[17] Oprea, T.I. *J. Comput.-Aided Mol. Des.,* **2002**, *16*, 325-334.
[18] Blake, J.F. *BioTechniques*, **2003**, *34*, S16-S20.
[19] Wenlock, M.C.; Austin, R.P.; Barton, P.; Davis, A.M.; Leeson, P.D. *J. Med. Chem.,* **2003**, *46*, 1250-1256.
[20] Blake, J.F. *Curr. Opin. Biotech.*, **2000**, *11*, 104-107.
[21] Prentis, R.A.; Lis, Y.; Walker, S.R. *Br. J. Clin. Pharmacol.,* **1988**, *25*, 387-396.
[22] KMR Group, Pharmaceutical R&D Benchmarking Forum, General Metrics 2001, Chicago, Illinois 60606.
[23] Rishton, G.M. *Drug Discov. Today,* **1997**, *2*, 382-384.
[24] Ashby, J.; Tennant, R.W.; Zeiger, E.; Stasiewicz, S. *Mutat. Res.,* **1989**, *223*, 73-103.
[25] Ashby, J.; Tennant, R.W. *Mutat. Res.,* **1991**, *257*, 209-227.
[26] Ashby, J.; Tennant, R.W. *Mutat. Res.,* **1991**, *257*, 229-306.
[27] Ashby, J.; Tennant, R.W. *Mutat. Res.,* **1993**, *286*, 3-74.
[28] Blake, J.F. Lint: A Computational Procedure for Removing Problematic Functionality. Tripos Inc Sybyl Users Meeting, Princeton, NJ; May **1995**.