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using the extremely powerful technology of RNA interference (RNAi) to examine the role of individual proteins in cellular functioning, and reported the production of an RNAi library to knockout all known human mRNA transcripts (to date, approximately a third of the project has been completed). The use of such technology enables us to increase our knowledge of biological processes and identify novel therapeutic targets. Plant discussed the need to think of the cell as a whole and not just a series of independent processes, commenting that the way in which each process interacts with others is central to determining the overall response to a drug; these interactions must be understood before responses can be accurately predicted. The interaction of nuclear receptors in determining drug-mediated increases in CYP expression was used to illustrate this argument.

Conclusion

Conferences on *in vitro* technologies are common, but the data presented at this meeting showed why – the rapid progress in this field requires constant updating of the scientist to keep them abreast of the field, from the validation of cell systems to the development of cell toxicity microchips, which are the weapons in the arsenal of researchers. Although I feel that we are not yet in a position to extrapolate rapidly, and accurately, from *in vitro* to *in vivo*, we are at least moving towards the elusive crystal ball.

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Ligand efficiency indices as guideposts for drug discovery

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Successful drug discovery involves the optimization of many variables, such as compound potency, selectivity, cellular activity, solubility, metabolic stability, bioavailability and acceptable toxicity. It is a tortuous path beginning with lead selection and continuing through to preclinical testing in animal models. Efficient navigation through this hyper-variable space should be possible by reducing the number of variables to expedite the optimization process from lead discovery to evaluation in the clinic. Recently, the concept of ligand efficiency as a measure for lead selection was suggested. Here, a more comprehensive analysis of ligand efficiency indices is presented, including the introduction of three new indices: percentage efficiency; binding efficiency; and surface efficiency. These indices reduce the number of variables by combining potency with molecular weight and polar surface area. It is suggested that these indices, either individually or in combination, are useful markers for effective and efficient drug discovery, and might provide the basis for a mathematically robust optimization of the drug discovery process.

The complexity of the drug discovery process is well recognized. Crucial issues along the discovery path are lead selection and validation, followed by optimization strategies to achieve high potency and specificity at later stages. Discovery and optimization strategies often include structure-based technologies. An increasing volume of chemical, biochemical and clinical data support the concept that the intrinsic physicochemical parameters of putative pharmacological entities play a crucial role in their pharmacokinetic (PK) properties and therefore in their ultimate success as marketed drugs [1–3]. Wenlock *et al.* [3] documented a consistent increase in molecular weight (MW) at the clinical candidate stage, which was subsequently found to be counter-balanced by a trend towards lower MW and more acceptable pharmacological entities in marketable and successful drugs [3,4]. Other methods designed to aid in the identification of drugs from organic molecules have been considered, including: characterization of molecular scaffolds and substituents [5,6]; statistical analysis of different drug databases [7]; the use of neural networks [8–10]; analysis of property

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BOX 1

Names, definitions and idealized reference values for ligand efficiency indices

Reference values are calculated for each index using the following idealized values and the equations given in Table I:

- percentage inhibition of 50.0% (on a 0–1 scale) is equal to 0.50 at a given screening concentration of the compound;
- MW is equal to 0.333 kDa;
- K_i, K_d or IC_{50} value of 1.0 nM;
- pK_i of 9.00;
- van der Waals PSA is 50 Å^2 (normalized to 100 Å^2);
- compound (inhibitor) concentration (e.g. 10 μM).

These indices can be defined at any screening concentration. However, even after approximate scaling, direct comparison of the PEI values obtained at different screening concentrations (10 μM versus 100 μM) is not recommended.

TABLE I

Calculation of PEI, BEI and SEI

Index	Calculation	Reference value
PEI	$\frac{\%\ \text{inhibition at a given [compound]}}{\text{MW}}$	1.5
BEI	$\frac{pK_i,\ pK_d \text{ or } pIC_{50}}{\text{MW}}$	27.0
SEI	$\frac{pK_i,\ pK_d \text{ or } pIC_{50}}{\text{PSA}}$	18.0

distributions [7,11]; and the introduction of drug-like indices to classify different compounds [12]. Currently, it is accepted that potent compounds do not necessarily result in good drugs and that crucial parameters along the discovery process are MW and other physicochemical properties related to optimal pharmacological properties. The phenomenological Lipinski's 'Rule of Five' [1] and others are used as guides in this process more as rules-of-thumb than as rigorous mathematical frameworks to optimize the drug discovery process.

Rationale for the approach

There is need for a more effective way of guiding the optimization of the drug discovery process from lead selection to successful clinical candidates. The concept of 'efficient' compounds or chemical entities should be incorporated into the drug discovery process at all stages. Hopkins *et al.* [13] and Rees *et al.* [14] have briefly discussed the use of ligand efficiency as a measure to select leads or fragments for further development. Although the application of ligand efficiency, which can be calculated using Equation 1, is an important concept, it does have limitations. The number of non-hydrogen atoms can be used as a normalizing factor to define efficiency.

$$\Delta g = \frac{\Delta G}{N} \qquad \text{[Eqn 1]}$$

where $\Delta G = -RTlnK_d$ and N is the number of non-hydrogen atoms [13].

However, it is simpler and more straightforward to calculate total MW or obtain this value from chemical database software. In addition, total MW is superior in dealing with the contribution of heteroatoms from different rows of the periodic table (e.g. fluorine versus iodine). Thus, we suggest two modified ligand binding efficiency indices, percentage efficiency index (PEI) and binding efficiency index (BEI), based on a MW scale that provides an easy and effective ranking, not only of the leads but also of the successive compounds on their route to optimization.

Today, HTS plays a crucial role in the early stages of drug discovery. As indicated by Hopkins *et al.* [13] and Rees *et al.* [14], potency is probably the predominant criterion used in assessing leads in the early stages. A simple efficiency index, PEI, derived from the currently used measure of percentage inhibition at a specific concentration can be introduced to guide the selection of the best initial leads for further development. An analogous efficiency index, BEI, based on the measured binding affinity in secondary assays and related to the MW of the compound, is also suggested as a guide in the optimization process.

In addition, a parameter that was not emphasized in the brief communication by Hopkins *et al.* [13] as crucial in the process of lead selection or optimization was van der Waals polar surface area (PSA). The importance of PSA to intestinal permeability and oral bioavailability has been described in several publications [15–17]. MW and PSA are physicochemical properties that dominate the optimization of many drugs. The creation of molecules with adequate efficiency indices that include these two crucial parameters on a similar increasing scale could drive the lead optimization process in a more rigorous and efficient manner.

Definition of efficiency indices

As well as PEI and BEI, we also define a third parameter – surface-binding efficiency index (SEI) – on a per PSA basis: the complete definitions and reference values for PEI, BEI and SEI are listed in Box 1.

In the HTS phase of drug discovery, compound activity is often obtained by measurement of percentage target inhibition at a single concentration (typically 1–30 μM). We define PEI as percentage inhibition under standard conditions (e.g. 10 μM) per MW (in kDa). The PEI value for an HTS hit with a MW of 0.333 kDa, exhibiting 50% inhibition at 10 μM will be 1.50. An HTS hit with a MW of 0.600 kDa exhibiting 50% inhibition at 10 μM has a PEI value of 0.83. Hence, HTS hits tested at the same concentration with PEI values of ~1.5 or greater have a good quotient of potency per MW and should be prioritized for lead optimization. We have chosen an idealized MW reference value of 0.333 kDa because it is near the mean value of marketed oral drugs described by Wenlock *et al.* [3] and Vieth *et al.* [4] and makes the calculations easy. It should be clear that PEI values could be calculated at different screening concentrations, although

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comparisons between PEI values for compounds must be made at the same assay concentration. Comparison and scaling of the PEI values obtained at different concentrations (e.g. 10 μM versus 100 μM) is not straightforward and can lead to erroneous conclusions.

Kuntz *et al.* [18] found that there is a negligible increase in the free-energy of binding for those ligands containing >15 non-hydrogen atoms. This result, coupled with the MW limitations described by Wenlock *et al.* [3] and Vieth *et al.* [4], has motivated us to combine binding affinity and MW into a BEI, which is defined as pK_i, pK_d or pIC_{50} per kDa. An idealized compound with K_i or IC_{50} of 1 nM and MW of 0.333 kDa has a BEI value of 27. We realize that K_i, K_d and IC_{50} values are not strictly interchangeable, but, for the purpose of the indices described here, we do not make a rigorous distinction because we expect comparisons to be made using similar measurements. BEI values could shift by several units for different series as represented by two different chemical scaffolds (Figure 1).

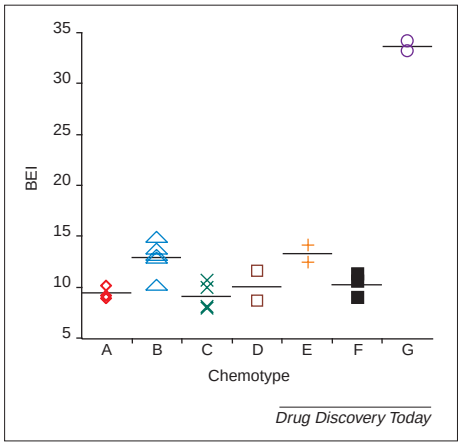

FIGURE 1

Binding efficiency indices for different chemotypes in the structure-based optimization of a target. Retrospective analysis of the BEI for several chemotypes during a drug discovery project involving human protein tyrosine phosphatase 1B (hPTP1B) [21,22]. On the x-axis, representatives of different chemotypes are plotted in an arbitrary order, with a line showing the mean BEI value of the group. Successive compounds within each series show increased efficiency along the vertical axis. The artifact compounds (Chemotype G, BEI ~33) represent true outliers even after improvement of each different class. Chemotypes are: A, difluorophosphonates; B, 1-site napthyl oxamates; C, 2-site oxamate amino acid; D, 2-site oxamate salicylate; E, 2-site isoxazole salicylate; F, 1-site oxamate; and G, isoquinoline diols.

We define SEI as the pK_i, pK_d, or pIC_{50} per PSA (where 100 Å^2 is used as a normalizing factor for PSA values). A compound with an affinity of 1 nM and a PSA of 50 Å^2 will have a SEI of 18. The choice of 100 Å^2 PSA as a normalizing factor was based on the results of Palm *et al.* [16] who found a sharp change in oral bioavailability for compounds with PSAs near 100 Å^2. Different series or chemical scaffolds could shift the SEI values by several units. It should be noted that BEI and SEI rank compounds on a logarithmic scale, thus, an increase or decrease of one unit implies a corresponding 10-fold change of potency per MW (for BEI) or per PSA (for SEI). In addition, this numerical framework for SEI and BEI provides similar increasing scales for the optimization of both quantities simultaneously.

The PEI at the HTS stage of discovery

Compounds with high PEI values in the early stages of lead validation should be scrutinized carefully because they are often related to assay artifacts and/or irreversible damage to the target enzyme. The histogram of PEI values for 252 compounds at a screening concentration of 100 μM against a protein kinase target has been plotted in Figure 2. The histogram can be broadly divided into three different PEI regions or values: (i) low; (ii) medium; and (iii) high. The first set clusters the compounds with the lowest efficiency with corresponding errors associated with the measurements (approximately a Gaussian distribution centered at ~1.2). The 'high' section could contain the most suitable compounds,

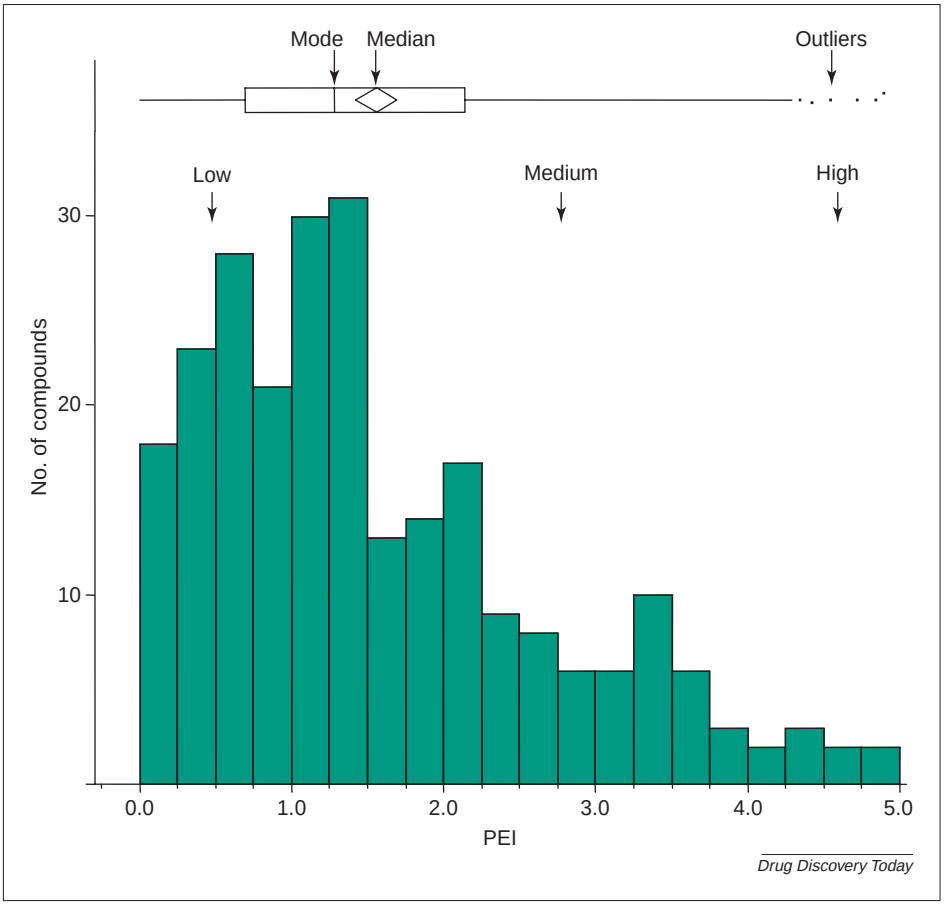

FIGURE 2

Histogram of the values of the efficiency index PEI for the results of a single-point inhibition assay. Distribution of the PEI values at 100 μM for 252 compounds tested against a protein kinase target are shown. The rectangle above the histogram shows levels of distribution. Outliers are shown as dots beyond the horizontal line that extends to the right of the rectangle. The statistical analysis and the plot were created using JMP version 5.1.1 (SAS Institute 1989–2004). Outlier compounds on the edge of the distribution are often associated with artifacts of the assay or nuisance compounds (e.g. oxidants). The most efficient lead compounds are typically found on the upper ranges of the medium section or the lower values of the high section. PEI values obtained at a different concentration (e.g. 10 μM) should be considered in a separate analysis.

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but based on our experience it often contains most of the 'nuisance' compounds with artificially high PEI values (>5.5). The majority of these nuisance compounds have activities in the low μM range (>90% inhibition) and have low MWs (<0.180 kDa). In particular cases, some of the potential leads with high PEI values correspond to artifacts or compounds that modify the enzyme target irreversibly (i.e. oxidants).

The medium section (PEI ~3.0) contains the majority of the compounds that are most likely to yield good hits, although they are not the most potent (e.g. 50% inhibition at 100 μM, with an approximate MW of 0.160 kDa). This is the point made by Rees *et al.* [14] in their discussion of fragment-based lead discovery. It is in the upper portion of the medium section that the most efficient hits can be found. In some cases, it might be possible to find excellent leads in the lower range of the high portion that are bona fide efficient compounds. To extract a robust reversible inhibitor from a single point assay, it is wise to examine the distribution of PEI values as opposed to looking only to the potency (or percentage inhibition of activity) of the compounds in a particular assay. In this example, the distribution of the percentage inhibition alone (not shown) is more compressed and does not reveal the outlier status of the nuisance compounds.

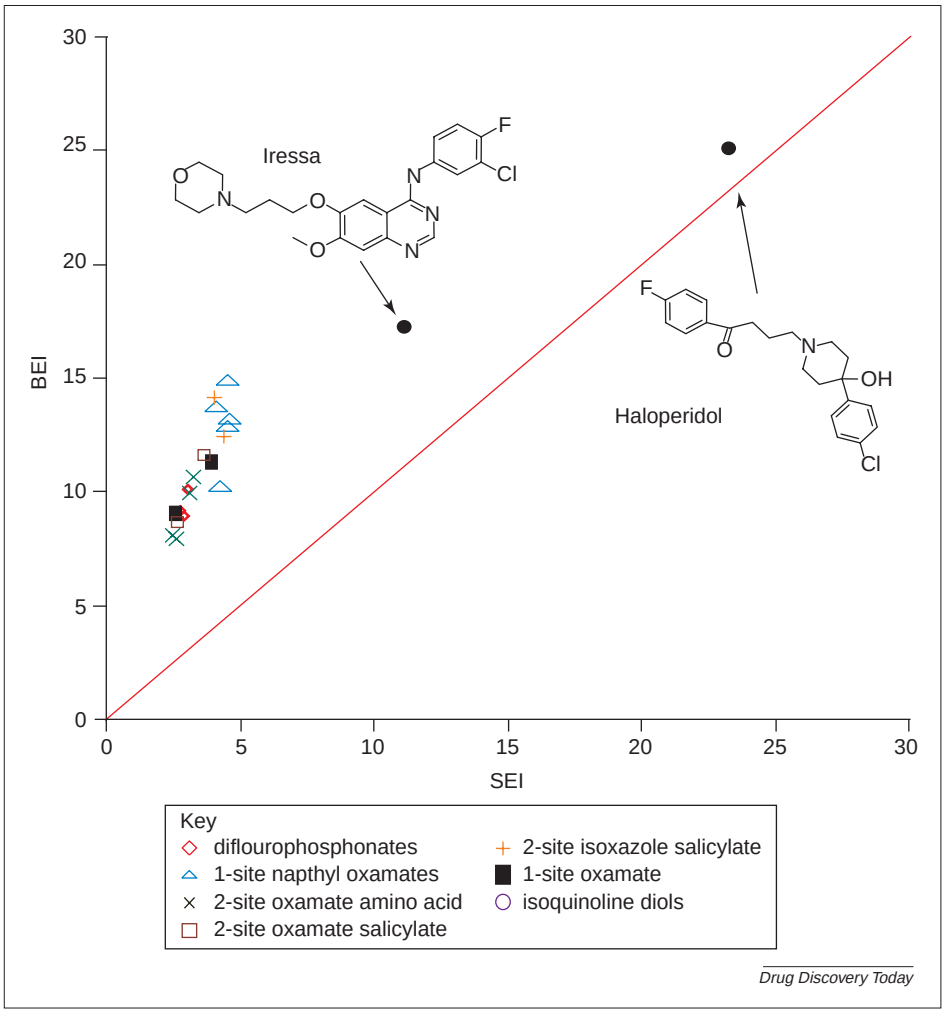

FIGURE 3

Mapping of surface-binding and binding efficiency indices in the SEI–BEI optimization plane for various compounds. Retrospective analysis of the efficiency indices of the representatives of the different chemotypes (A–F) [21,22] presented in Figure 1 is shown. The successive chemotypes of the project were progressively more efficient along the BEI axis, but their SEI values did not increase accordingly and never reached a value greater than 6.0. Only one compound from the series, represented by chemotype E, was found to have some activity in cell assays [22]. This finding is in agreement with the low SEI values of the compounds represented. For comparison, the positions in the SEI–BEI plane for two known drugs, Iressa® and Haloperidol®, are also shown. The SEI has been plotted along the x-axis using PSA values calculated by the method described by Ertl *et al.* [17]. The ordinate corresponds to the same values plotted on Figure 1. It should be noted that although the two variables represent different properties related to potency, the scales of both axes are somewhat similar, which facilitates the comparison of the values and their relative optimization. The diagonal of the SEI–BEI plane is also shown for reference. Chemotype G (isoquinoline diols, oxidants) will map outside of the range and has been excluded. The artifact compounds (Chemotype G, BEI ~33) represent true outliers even after improvement of each different class. Chemotypes are: A, difluorophosphonates; B, 1-site napthyl oxamates; C, 2-site oxamate amino acid; D, 2-site oxamate salicylate; E, 2-site isoxazole salicylate; F, 1-site oxamate; and G, isoquinoline diols.

Combined use of BEI and SEI during ligand optimization

During the optimization process, it is useful to examine the BEI and SEI simultaneously. In addition to providing useful and comparable numerical scales, these indices combine three crucial variables (potency, MW and PSA) in an optimization plane (Figure 3). A ratio of potency and MW are combined in BEI and potency and PSA are combined in SEI. Thus, three variables are reduced to two and placed on similar increasing scales so that simultaneous optimization is more straightforward. After the initial hit selection for each series, the drug discovery process should strive to optimize BEI and SEI simultaneously (Figure 3). BEI monitors the potency per additional kDa and SEI ensures that the potency per exposed PSA is maximized. Compounds with a high affinity per kDa (independent of their exposed surface area) are located on the upper portion of the diagonal on the SEI–BEI plane, whereas compounds with high affinity per unit of PSA are on the lower section of the diagram. Experience suggests that compounds with the highest probability of having favorable PK properties (consistent with Lipinski's rules) will have SEI–BEI pair wise-values in the upper ranges (lower PSA per MW <0.5 kDa).

In general, irrespective of the target, various chemical series should strive to move the physicochemical properties of a compound towards the diagonal in the SEI–BEI plane, where SEI and BEI are maximized

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simultaneously. In the example presented in Figures 1 and 3, different chemotypes progressed along the binding efficiency direction but exhibited a large PSA, which keeps the SEI values low (<6.0). Eventually, only specific compounds of the 2-site isoxazole salicylate series (Figures 1 and 3) had any measurable cellular activity, although the various series were progressively more efficient on a per kDa basis: the SEI–BEI values for two known drugs have also been plotted for comparison.

Based on our limited data thus far, we suggest that the use of these indices, either individually or in combination, can be useful guideposts along the process of lead selection, validation and optimization. In addition, we have found them particularly useful at highlighting compounds with unusually good efficiency. Indeed, we have observed a situation where compounds with comparatively high BEI values turned out to be artifacts (oxidants) rather than bona fide inhibitors (Figure 1, open circles). As the medicinal chemistry effort develops, the indices can be used to monitor the relative efficiency of different chemotypes and the progress towards compounds that will probably have desirable PK properties (lower MW and PSA) (Figures 1 and 3). Depending on synthetic feasibility or accessibility, an efficient drug-design effort can be envisioned as a series of successive 'tacks' along the approximate SEI and BEI directions towards regions of the SEI–BEI plane with optimum PK properties for each specific target.

Different optimum efficiency indices for different targets

Although we suggest some idealized reference values (independent of the target) for PEI, BEI and SEI in Box 1, it should be noted that different therapeutic targets will probably have different optimum efficiency indices, reflecting a combination of active or receptor site characteristics and PK properties. Furthermore, there could be significant differences in the progression of the optimization process on the SEI–BEI plane, depending on the structural parameters (total volume and polar or hydrophobic character) of the pocket to be fitted. For example, Iressa®, an anticancer agent targeting epidermal growth factor receptor kinase, has a reported IC_{50} of 20.00 nM, a MW of 0.447 kDa and a PSA of 68.7 Å^2 resulting in a BEI of 17.0 and a SEI of 11.2. By contrast, Haloperidol®, an antipsychotic agent targeting CNS dopamine 2 receptors, has a K_d of 0.35 nM, a MW of 0.376 kDa and a PSA of 40.5 Å^2 yielding a relatively higher BEI of 25.0 and a SEI of 23.3. The relative positions of these known agents in the SEI–BEI optimization plane are shown in Figure 3 in relation to several sub-optimal series, as illustrated in Figure 1.

An initial mapping in the SEI–BEI plane of the location of 122 marketed drugs discussed by Andrews *et al.* [19] is presented in Figure 4. The centroid of the distribution has mean values of 17.9 (SD 15.7) for SEI and 28.0 (SD 11.5) for BEI. It is interesting to note that the majority of the drugs cluster towards the optimum values of SEI and BEI near the diagonal line and that few examples are mapped far below this line. This is consistent with the concepts and ideas regarding the optimization process during drug–design projects and the difficulty of optimizing polar surface properties.

Sakaeda *et al.* [20] analyzed the molecular and PK properties of 222 commercially available oral drugs in humans and described different averages of properties for CNS, anti-inflammatory, antimicrobial and renal and cardiovascular drugs. Further analysis of the positions of these oral drugs on the SEI–BEI plane should provide additional information about the utility of these concepts for the future optimization of drug discovery.

A robust mathematical and statistical framework is needed

Successful drug design is a multidimensional optimization process. Putting known phenomenological rules (e.g. Lipinski's rules) into a consistent and robust numerical

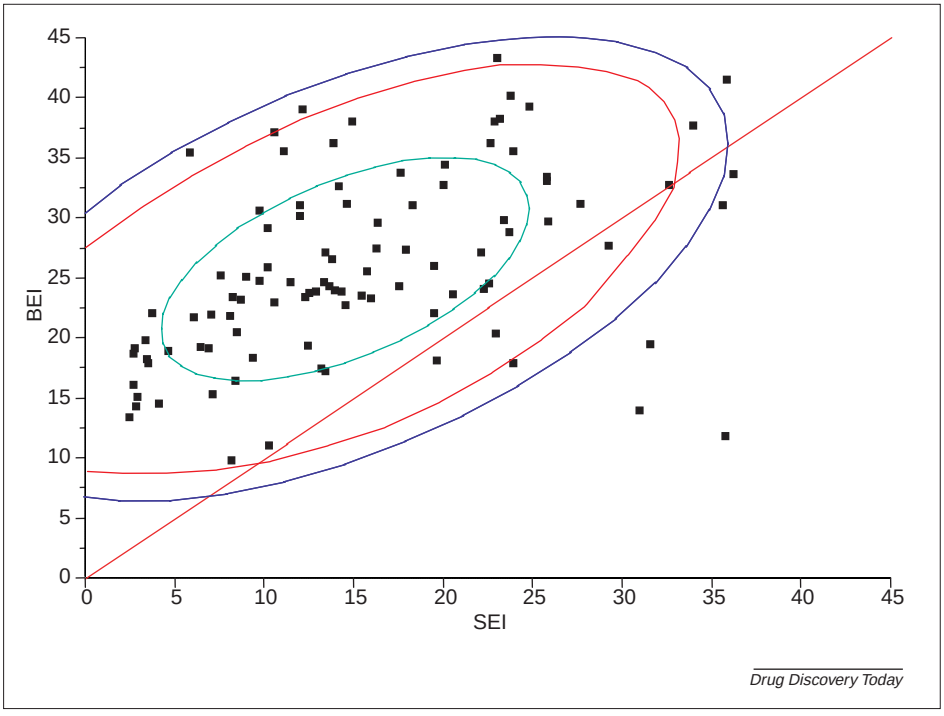

FIGURE 4

Mapping of the surface-binding and binding efficiency indices for a sample of marketed drugs. The SEI–BEI values for the 92 examples of marketed drugs (a subset of the sample discussed by Andrews *et al.* [19]) with values between 0 and 50 SEI–BEI have been plotted together with the ellipsoids including 50% (green), 90% (red) and 95% (blue) of the sample. Examples with extreme values [SEI and BEI >50 (30 cases)] have been excluded. The centroid of the distribution for the entire sample (122) is 17.9 SEI and 28.0 BEI and near the reference values presented in Box 1. The centroid for the subset is 14.5 and 25.8 (SD of 8.7 and 7.9, respectively). The vast majority of marketed oral drugs map near and above the diagonal line, reflecting a reasonable optimization of both BEI (MW) and SEI (PSA). Note the distance between the sub-optimal series for the target presented in Figure 3 (centered around an SEI of 5 and a BEI of 12) and the sample of marketed drugs presented. The diagonal line has been plotted for reference. The statistical analysis and the plot were carried out using JMP version 5.1.1 (SAS Institute 1989–2004). Data provided by Tudor Oprea as private communication to Yvonne Martin.

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framework will aid in directing the drug design process. However, it should be understood that numerical rules or guidelines fail in some cases. For example, two well-known drugs, Lipitor® and Crestor®, do not meet Lipinski's Rules of Five criteria. Therefore, an evaluation of the utility of efficiency indices should also consider the probability of false-positives and false-negatives in the statistical decision process. Furthermore, the reliability of a decision criterion should increase if it is based on a collection of many relevant and predictive properties of compounds (i.e. a multivariate approach) and is based on a robust model for estimating the probability of success of compounds having these properties. This might prove particularly useful if the number of active and truly independent variables is substantially reduced.

Irrespective of their mathematical formulation, a question that must be answered is whether efficiency indices will be simply numerical rules-of-thumb or whether they will become the foundations for the complex optimization process of drug design by reducing the number of variables and facilitating a more adequate mathematical and statistical treatment of drug discovery in the future. Questions such as 'what is the probability that an anticancer compound with a BEI of 17 and a SEI of 22 will become a clinical candidate?' or 'what is the statistical likelihood that a compound with a BEI below 25 that targets the CNS will succeed beyond Phase II?' might be answered in the future with a high degree of statistical confidence.

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