Two ‘Golden Ratio’ indices in fragment-based drug discovery

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Fragment-based drug discovery (FBDD) is complementary to high-throughput screening. The approach has two key stages: identifying the starting fragment hit to be developed and generating the lead compound from the starting fragment hit. Here, we provide an overview of FBDD and introduce two indices originally developed at Astellas Pharma. The first is related to the size ratio of fragment hits to drug leads; this is useful for fragment-library design and the fragment-to-lead process. The second is related to maximum ligand efficiency; this is useful for fragment hit prioritization and the fragment-to-lead process. Both indices are based on the ‘Golden Ratio’.

Recent trends in fragment-based drug discovery (FBDD)

FBDD has emerged in the past decade and has proven to be a novel paradigm for drug discovery [1–3]. Significant efforts employing this technique by pharmaceutical companies (most notably Abbott) and biotechnology companies (such as Astex Therapeutics, SGX Pharmaceuticals, Plexxikon and Sunesis) in the 1990s and early 2000s have resulted in the development of >10 clinical candidates derived from FBDD technology [4]. These successes have, in turn, strongly stimulated the pharmaceutical community (both industrial and academic groups) to use a fragment-based approach in their lead-discovery campaigns over the past five years [3,5,6]. As a consequence, FBDD has become established as the principle alternative to traditional methods used for lead discovery, such as high-throughput screening (HTS) and virtual screening. There are two characteristic differences between FBDD and HTS. The first is the size of the chemical space. The number of ‘lead-like’ or ‘drug-like’ compounds is estimated to be $10^{60}$ [7], indicating that the chemical space of compounds for HTS is far too large to be sampled with a realistic library size. The size of the screening library decreases exponentially in accordance with the decreasing molecular size of compounds, and, for example, the number of compounds <160 Da is estimated at $10^7$ [8]. The number of compounds in a fragment library is typically reported to be several thousands and at most 20,000 [5,9,10], which would cover most of the chemical space of commercially available fragment-like compounds. The second is the compound complexity [11]. The complexity of fragment-sized compounds is low compared with those compounds usually examined by HTS, as theoretically formulated by Hann et al. [11]. Although FBDD hits have a lower affinity than those from HTS, because there are fewer interaction sites, they can interact with the ‘hot spot’ of the target protein with optimized binding mode, owing to their simple structure, without interference from less than optimized side chains [12,13]. As a result, hit rates for fragment screening are expected to be higher than those for HTS, and the ligand efficiencies [14] of fragment hits are expected to be higher than those of HTS hits. Several pharmaceutical companies have validated these concepts. The Abbott group analyzed 45 projects in-house, which underwent both FBDD and conventional HTS, and pointed out four topics of comparison [3]. First, fragment screening provides more hits against various protein targets; this phenomenon has also been demonstrated by a group at Novartis [15]. Second, the success rate of identifying inhibitors (IC$_{50}$ < 100 nM) from fragment hits is comparable with that from HTS hits. Third, fragment screening generally provides hits with higher-quality chemical properties than HTS owing to the lower rate of false positives. The Vertex group also mentioned that the hit rates of follow-up libraries based on fragment screening hits are much higher than those obtained by HTS [16]. Fourth, FBDD and HTS are complementary techniques. Unique chemotypes were generated by each method, in which potent inhibitors were obtained from both sources. In addition, in many cases potent inhibitors were obtained using either of the...
screening technologies alone. In regard to the last topic, it was suggested that FBDD might be an attractive approach for targets that are less amenable to HTS, such as protein–protein interactions [17]. This was demonstrated in the case of the Bcl-2 family, in which the fragment-derived compound ABT-263 is at the most advanced stage of development; this molecule disrupts Bcl-2 family protein–protein interaction and is currently in clinical trial [17–19]. BACE-1 also presents a challenging target for finding a non-peptidic inhibitor. AstraZeneca, in collaboration with Astex Therapeutics, identified a non-peptidic BACE-1 inhibitor with nanomolar potency using FBDD, despite the lack of success of traditional approaches carried out by AstraZeneca [20]. Therefore, FBDD has entered a new era: it has been proved to function, not only as a screening tool in biotechnology companies but also as a complementary and synergistic tool for HTS in pharmaceutical companies [5].

The process of FBDD

FBDD consists of two steps: the identification of fragment hits to be developed and the conversion of fragment hits to leads (Figure 1). The success of fragment-hit identification depends on the fragment-library design, fragment screening and the prioritization of fragment hits. As mentioned in many reviews [1,21,22], fragment-screening methods have advantages and disadvantages in terms of the sensitivity of detection, the throughput, the required instrumentation and the level of information generated. Although fragment screening per se was highly laborious in the early days of FBDD, significant developments, especially in X-ray crystallography and nuclear magnetic resonance (NMR), have resulted in higher throughput and resolution, and a lower requirement for protein preparation. Biophysical technologies (such as surface plasmon resonance, thermal shift assays and isothermal titration calorimetry) and high concentration biological assays have become available and are gaining popularity.

Another new trend is to use combinations of different types of technologies to eliminate the inherent false positives derived from each individual technology and to compensate the throughput. These developments in technology have made fragment screening more achievable and reliable. Therefore, fragment-library design and the prioritization of fragment hits have become increasingly important for success in fragment-hit identification.

There are many different approaches to convert fragment hits to leads, which are categorized into the following four types: fragment evolution, fragment linking, fragment optimization and fragment self-assembly [23]. Among them, fragment evolution has been the most applicable and successful method. Although structural information provides the medicinal and computational chemist with guidance on structurally validated design from fragment hits to leads in any approach, converting fragment hits to leads is still difficult and complicated, even with the huge amount of three-dimensional (3D)-structural data accumulated as a result of the recent rapid progress in structural biology.

In the following section, we mainly focus on the two important topics for success in FBDD, which are useful for fragment-library design, the prioritization of fragment hits and the fragment-to-lead process.

‘Golden Ratio’ in FBDD

Analysis of successful examples of FBDD

Many examples of FBDD have been published [1–3]. Not all of the cases were, however, successful in terms of the potential, and the drug-likeness or lead-likeness, of the drug leads obtained from the FBDD approach, and little has been reported about the relationship between fragment hits and drug leads in the case of the pharmacologically promising fragment-to-lead process. In order to achieve insight into successful results of FBDD, 30 examples were selected from three major reviews of FBDD.
reported by Erlanson et al. (Sunesis) [1], Alex et al. (Pfizer) [2] and Hajduk et al. (Abbott) [3] (Table 1 and Supplementary Data 1). These examples were selected from the viewpoint of the generality and wide applicability of the FBDD approach, using a filter that removed the compounds that did not meet the following requirements: first, the affinity (IC$_{50}$ or $K_i$) of both the fragment hit and the drug lead was described in the paper; second, the drug lead had high potency (IC$_{50}$ or $K_i$ value < 100 nM), there were no reactive groups (such as thiol groups) and its size was moderate (molecular weight [MW] < 600); third, the fragment hit did not have too great an affinity (IC$_{50}$ or $K_i$ value >1 μM) and had no reactive groups (such as thiol groups); and fourth, the fragment-to-lead process was not specialized and restrictive (the approaches of the dimerization of hit fragment [24] and the incorporation of the identified fragments into the original scaffold [25] were removed).

Analysis of successful examples in Table 1 revealed that the average number of non-hydrogen heavy atoms (HAs) of the drug leads was 28.933, while the average number of HAs of the scaffold part and the evolution part was 17.833 and 11.100, respectively (the scaffold part is defined as the larger part of the fragment-hit part and the remaining part of the drug lead, and the evolution part is defined as the smaller one, where the drug lead consists of these two parts).

The fact that the right-hand sides of Eqs. (1) and (2) were similar — namely, the average HA$_{lead}$/average HA$_{sca}$ value was almost equal to the average HA$_{sca}$/average HA$_{evo}$ value — suggested to us that the HA values of the drug lead, the scaffold part and the evolution part could be related by the Golden Ratio.

![Table 1](https://www.drugdiscoverytoday.com/323)

<table>
<thead>
<tr>
<th>Target</th>
<th>LE$_{frag}$</th>
<th>LE$_{lead}$</th>
<th>HA$_{lead}$</th>
<th>HA$_{sca}$</th>
<th>HA$_{evo}$</th>
<th>HA$<em>{lead}$/HA$</em>{sca}$</th>
<th>HA$<em>{sca}$/HA$</em>{evo}$</th>
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<td>CDK2</td>
<td>0.53</td>
<td>0.46</td>
<td>22</td>
<td>15</td>
<td>7</td>
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<td>31</td>
<td>16</td>
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<td>37</td>
<td>25</td>
<td>12</td>
<td>1.480</td>
<td>2.083</td>
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<td>Urokinase</td>
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<td>15</td>
<td>13</td>
<td>1.867</td>
<td>1.154</td>
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<td>19</td>
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<td>0.37</td>
<td>29</td>
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<td>1.417</td>
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<td>33</td>
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<td>1.357</td>
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<td>1.409</td>
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<td>19</td>
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<td>25</td>
<td>15</td>
<td>10</td>
<td>1.667</td>
<td>1.500</td>
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<tr>
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<td>0.49</td>
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<td>12</td>
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<td>1.750</td>
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<td>20</td>
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<td>1.600</td>
<td>1.667</td>
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<td>17</td>
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<td>1.647</td>
<td>1.545</td>
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<td>0.44</td>
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<td>1.545</td>
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<td>0.61</td>
<td>16</td>
<td>12</td>
<td>4</td>
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<td>0.25</td>
<td>40</td>
<td>22</td>
<td>18</td>
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<td>KDR</td>
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<td>37</td>
<td>20</td>
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<td>1.850</td>
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<td>0.41</td>
<td>31</td>
<td>20</td>
<td>11</td>
<td>1.550</td>
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<td>PDK1</td>
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<td>37</td>
<td>26</td>
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<td>1.423</td>
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<td>MMP</td>
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<td>0.35</td>
<td>35</td>
<td>22</td>
<td>13</td>
<td>1.591</td>
<td>1.692</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td><strong>0.404</strong></td>
<td><strong>0.379</strong></td>
<td><strong>28.933</strong></td>
<td><strong>17.833</strong></td>
<td><strong>11.100</strong></td>
<td><strong>1.631</strong></td>
<td><strong>1.725</strong></td>
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<td><strong>Standard Deviation</strong></td>
<td><strong>0.106</strong></td>
<td><strong>0.081</strong></td>
<td><strong>5.942</strong></td>
<td><strong>3.742</strong></td>
<td><strong>3.220</strong></td>
<td><strong>0.173</strong></td>
<td><strong>0.557</strong></td>
</tr>
</tbody>
</table>

*LE of fragment hit.

*LE of drug lead.

Average number of non-hydrogen HAs of scaffold part. The scaffold part is defined as the larger part of the fragment hit part and the remaining part of the drug lead, where the drug lead consists of these two parts.

The average number of non-hydrogen HAs of the evolution part. The evolution part is defined as the smaller part of the fragment hit part and the remaining part of the drug lead.
Golden Ratio

The Golden Ratio, usually denoted by the Greek letter Phi (φ), has fascinated many people over the years, and is an irrational number, the value of which is given by the proportion \( AC:AB = AB:BC \), where A and C are the endpoints of a line segment, and B is the point on the line segment between A and C such that \( AC:AB=AB:BC \) (Figure 3B). The Golden Ratio is approximately \( 1.6180339887 \) and it is so named because it is believed to represent a proportion of lengths that is aesthetically attractive to the human eye in art and design contexts. Because the HA shows the rough molecular size,
we suggest that our analysis indicates that ‘the size of the drug lead’ is to ‘the size of the scaffold part’, as ‘the size of the scaffold part’ is to ‘the size of evolution part’—namely, the ‘drug lead’ is divided into the ‘scaffold part’ by the Golden Ratio.

Next, we discuss the validity of our insight. Previously, Hopkins et al. proposed that the ligand efficiency (LE), the binding energy per HA, could be a useful parameter in the selection of a lead compound and in the optimization process [14]:

\[
\text{LE} = \frac{\Delta G}{\text{HA}}, \quad \Delta G = RT(pK_d)
\]  
(3)

Our analysis revealed that there is constancy in the LE value for a given series of molecules progressing from the fragment to the drug lead (the LE values of the fragment hit and the drug lead were 0.404 and 0.379, respectively; Table 1 and Supplementary Data 2-A), and the average pK_d values of the fragment hit and the drug lead were \(\approx 5\) and 8, respectively (4.68 and 7.77, respectively; Table 1 and Supplementary Data 1). Hajduk also reported similar results from an analysis of 18 in-house FBDD projects at Abbott (the average pK_d values of the fragment hit and the drug lead were 4.7 and 8.3, respectively). Therefore, as a general definition Eqs. (4) and (5) are as follows:

\[
\text{LE}_{\text{frag}} = \text{LE}_{\text{lead}} 
\]  
(4)

Here, \(\text{LE}_{\text{frag}}\) and \(\text{LE}_{\text{lead}}\) are the LEs of the fragment hit and the drug lead.

\[
(pK_d)_{\text{frag}} = 5, \quad (pK_d)_{\text{lead}} = 8 
\]  
(5)

Here \((pK_d)_{\text{frag}}\) and \((pK_d)_{\text{lead}}\) are the pK_d values of the fragment hit and the drug lead. Eq. (6) can be derived from Eq. (3):

\[
\text{LE}_{\text{frag}} = \frac{RT(pK_d)_{\text{frag}}}{\text{HA}_{\text{frag}}}, \quad \text{LE}_{\text{lead}} = \frac{RT(pK_d)_{\text{lead}}}{\text{HA}_{\text{lead}}}
\]  
(6)

Here, \(\text{HA}_{\text{frag}}\) and \(\text{HA}_{\text{lead}}\) are the HAs of the fragment hit and the drug lead. As a result Eq. (7) is obtained from Eqs. (4)–(6):

\[
\frac{\text{HA}_{\text{frag}}}{\text{HA}_{\text{lead}}} = \frac{8}{5} = 1.6 \approx \phi
\]  
(7)

In the Fibonacci number sequence, each member is simply the sum of the previous two numbers \((0, 1, 1, 2, 3, 5, 8, 13, 21, 34, 55... )\), and the ratio between any two successive Fibonacci numbers approaches the Golden Ratio as the numbers get larger. Because 5 and 8 in Eq. (7) are members of the Fibonacci sequence, it is obvious that the ratio of \(\text{HA}_{\text{lead}}\) and \(\text{HA}_{\text{frag}}\) is almost identical to the Golden Ratio. Therefore, our insight about the Golden Ratio in FBDD is thought to be reasonable.

Lipinski proposed the rule-of-five filter for drug-likeliness in which the MW is \(< 500\), the number of hydrogen-bond donors is \(< 5\), the number of hydrogen-bond acceptors is \(< 10\) and the ClogP is \(< 5\) [26]. Astex also suggested the rule-of-three filter for fragment hits in which the MW is \(< 300\), the number of hydrogen-bond donors is \(< 3\), the number of hydrogen-bond acceptors is \(< 3\) and the ClogP is \(< 3\) [27]. Interestingly, because both numbers (5 in the rule-of-five and 3 in the rule-of-three) are Fibonacci numbers, their ratio \((5/3)\) is almost identical to \(\phi\). The parameters in these two rules are also thought to support our proposed relation of the Golden Ratio between the fragment hit and the drug lead.

**Fragment-library design using the Golden Ratio**

There have been many reviews of fragment-library design [15,28,29], and key issues to be considered are as follows: the range of physicochemical properties; the desirable functional groups for interaction with the target protein; undesired chemical features; synthetic feasibility; molecular diversity; aqueous solubility; the number of fragments to be included; experimental constraints and, finally, generality and target-specificity. Some of these parameters are closely related to each other. It is also possible to design a fragment library using the Golden Ratio. If a natural ligand for a target protein, or a patent or compound published by other companies, is known, we suggest that a library with fragments with HA values near to the number in which the HA value of the known ligand or compound is divided by \(\phi\) should be used for the fragment screening. For example, Table 1 shows that the HA values of eight representative drug leads of ATP inhibitors of the kinase inhibitors (CDK2, ERK2, IKK, P38a, KDR, Akt, PDK1 and Syk) are in the range from 19 to 37. Therefore, when FBDD approaches to the identification of ATP inhibitors against such protein kinases are performed, those libraries containing fragments with HA values around the range from 12 (\(\approx 19/\phi\)) to 23 (\(\approx 37/\phi\)), with some tolerance, should be used for fragment screening. If there is no information about the inhibitors, because the HA value of ATP is 31, it can be recommended that the library with the fragments with HA values around 19 (\(\approx 31/\phi\)), with some tolerance, should be used. In the case of GPCR, it can be suggested that the fragment library should be changed according to the receptor class of GPCR using the available information about the HA values of known ligands and compounds, because it is known that the molecular size of ligands differs depending on the receptor class of GPCR. Many strategies of fragment-library design have been reported [15,28,29]. It is noteworthy that Vertex researchers proposed the idea of deconstructing known leads and drugs into fragments for screening [30]. To our knowledge, however, fragment-library design using the molecular size of known binding molecules is novel. As described above, we suggest that \(\phi\) is useful in fragment-library design, and can function as an index in the process of fragment-to-lead evolution, in order to speed up the drug-discovery effort.

**Prioritization of fragment hits using the LE value**

**Evolution of LE**

In the previous section, we analyzed successful examples of FBDD and proposed a novel concept that is useful for fragment-library design and the fragment-to-lead process. In this section, we turn to the prioritization of fragment hits, which is another crucial step for the success of FBDD. Several experimental methods are commonly used to set fragment priority, which have been well described in several excellent reviews [1,21,22]. Therefore, here we focus on the topic of the application of the LE value to the prioritization of fragment hits.

The LE concept is useful to compare hit fragments across different series and to set fragment priority. LE has been developed from the idea of maximal affinity of ligands, which Kuntz et al. proposed [31]. It represents the binding free energy per HA [Eq. (3)]. The concept of LE is frequently used in the field of FBDD. For example, Hajduk conducted a retrospective analysis of 18 highly optimized inhibitors [32]. In the Hajduk study, the highly optimized inhibitors were systematically reduced in size until the minimal fragment-like compounds could be identified. A remarkably linear relationship was found between potency and molecular
mass along this path of ideal optimization, which indicates that the LE values stay almost constant during the ideal fragment-to-lead process.

Up to now, several measures of LE have been proposed to quantitate the relative potency of HTS hits and/or fragment-screening hits. The group at Abbott proposed modified efficiency indices [33]. The percentage efficiency index (PEI) and the binding-efficiency index (BEI) are obtained by dividing the percentage inhibition at a given concentration and the pKi by the MW, respectively, as shown in Eqs. (8) and (9). The surface-binding efficiency index (SEI) is also obtained by dividing the pKi by the polar surface area (PSA) [Eq. (10)].

\[
\text{PEI} = \frac{pKi}{MW} \\
\text{BEI} = \frac{\%\text{inhibition}}{MW} \\
\text{SEI} = \frac{pKi}{PSA}
\]

Although the PEI is almost the same as the LE, there might be large differences in the case of iodinated and brominated compounds (whose mass values are 53 and 35, respectively). The BEI value is practical in the early stage, because the IC50 or pKi value is not needed. The SEI provides us with a new set of lenses with which to set the fragment priority, because the PSA value, which is included in Eq. (10), is one of the most important parameters in the optimization step. These modified LE values have been used not only in the conventional HTS approach but also in FBDD [32].

Like the SEI, the ligand-lipophilicity efficiency (LLE) has been proposed in order to assess ‘druggability’ [4]. Leeson and Springthorpe have shown that the increase of lipophilicity leads to an increase of risk in drug development owing to non-specific toxicity [34]. The LLE is defined as follows:

\[
\text{LLE} = pKi (\text{or } IC50) - c\text{LogP}
\]

Here, cLogP is an abbreviation of the ‘computed LogP’, which is a measure of differential solubility or rather hydrophobicity by the octanol/water partition coefficient. Because the cLogP value is one of the most important parameters in the optimization step, the LLE gives us important information for making our decision about not only the prioritization of fragment hits but also the fragment-to-lead process.

Furthermore, group efficiency (GE) has been proposed to estimate an individual group’s contribution towards the binding free energy [4,35,36]. In order to obtain the GE value, the relative binding free energy between matched pairs of compounds is needed.

\[
\text{GE} = \frac{\Delta AG}{HA_a} = \Delta AG = RT(pKi_{A+B} - pKi_{B})
\]

Here, HA is the number of non-hydrogen atoms in a particular group ‘A’. pKi_{B} and pKi_{A+B} are pKi values for the scaffold ‘B’ and the compound comprising scaffold ‘B’ and group ‘A’. This index enables us to assess the contribution to the binding free energy made by the particular group. Thus, it is useful in the optimization process.

Recently, the Johnson and Johnson group has proposed a new index, called the ‘Fit Quality Score’ [37,38]. This score has been developed from the empirical discovery that small ligands have an inherently greater LE value than large ligands. They suggested a Fit Quality Score that was normalized so that the most efficient binders in the IC50 data set were scaled to have a score of 1.0 across a wide range of molecular sizes.

\[
\text{LE}_\text{Scale} = 0.0715 + \frac{7.5328}{HA} + \frac{25.7079}{HA^2} + \frac{-361.47222}{HA^4}
\]

\[
\text{FQ} = \frac{\text{LE}}{\text{LE}_\text{Scale}}
\]

This index enables us to compare the efficiency between differently sized ligands and is especially useful for the analysis of HTS campaign results. Unfortunately, because the maximal LE in the Fit Quality Score is fitted as a cubic function of the number of HAs, it is underestimated when the ligand size is small (Figure 4). Therefore, this index is difficult to use in the process of the prioritization of fragment hits.

**Use of percentage LE at AstellasPharma**

To overcome the weakness of the Fit Quality Score, we explored a novel index for the prioritization of fragment hits. For this purpose, we paid attention to Kuntz’s data, which include a large number of the strongest-binding ligands [31], removing nontypical drug molecules such as heavy metals and carbon monoxide. Thus, we plotted the LE values of the strongest-binding ligands with HA (Figure 4). These represented the maximal LE values. As shown in Figure 4, we found a new rule that, when the HA decreases by half, the maximal LE increases by \( \pm 1.6 \)-fold. On the basis of this finding, the estimation of the maximal LE was established by curve fitting of Kuntz’s data and the %LE was defined as shown in Eqs. (15) and (16), respectively.

\[
\text{max LE} = 1.614^{\log_{10}(10/HA)} \approx 8^{\log_{10}(10/HA)}
\]

\[
\%\text{LE} = \left( \frac{\text{LE}}{\text{max LE}} \right) \times 100
\]

Here, HA is the number of HAs and %LE is the percentage LE. Figure 4 shows a comparison of the maximum LE value used in Astellas with that proposed by Johnson and Johnson researchers. Although they resemble each other, there are two important

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**FIGURE 4**

Relationship between the maximum LE and HA. The blue line and orange line indicate a fitting curve used in Astellas [Eq. (15)] and one proposed by Johnson and Johnson researchers [Eq. (13)], respectively. The blue diamonds indicate the LE values of highly optimized ligands studied by Kuntz et al. [31].
differences. First, the maximal LE is different when the HA is < 10; this is likely to be attributable to the overestimation of FQ. Second, the maximal LE proposed by us is larger than that proposed by the Johnson and Johnson group. This is because we used the data from the largest affinity ligands, while the Johnson and Johnson group used in-house HTS campaign data. As shown in Eq. (15), interestingly, the function of maximal LE proposed by us includes the number of the Golden Ratio (1.614), although we cannot clarify its meaning at present. The %LE can be a valuable index, which is easy to understand, because it shows the percentage of the LE of a compound to the strongest-binding ligand with the same number of HAs. Moreover, as shown in Supplementary Data 2-B, this index increases when fragments are successfully optimized to leads. This index is a good measure not only for the prioritization of fragment hits but also for the fragment-to-lead process.

Conclusions
This review has introduced two indices, which we believe may be useful, that are concerned with the Golden Ratio (ϕ ; 1.6180339887 . . .). First, we have shown that the size ratio of fragment hits to drug leads might be related to the Golden Ratio and have suggested a novel fragment-library design using this ratio to select compounds for screening against a particular target when something is known about a natural or synthetic ligand. Our strategy can be used in combination with previously reported strategies of fragment-library design [15, 28, 29], and we have also proposed that ϕ can function as an index in the process of fragment-to-lead evolution. Second, we have introduced the percentage LE as defined by the equation including the Golden Ratio. The percentage LE is useful, not only for the hit-prioritization processes in FBDD but also for the analysis of HTS hits. Moreover, because the percentage LE shows the percentage of the LE of a compound to the strongest-binding ligand with the same number of HAs, it is a valuable index that could also be used for the fragment-to-lead process. Why does the Golden Ratio appear in FBDD? This might be an artefact caused by human minds (medicinal chemists), to whom such a ratio is attractive. It is expected that arguments about the existence and usefulness of the Golden Ratio in the field of drug discovery will be advanced in future.

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Appendix A. Supplementary data

References