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Natural products as lead structures: chemical transformations to create lead-like libraries

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In this review, we analyze and illustrate the variation of the two main lead-like descriptors [molecular weight (MW) and the partition coefficient (logP)] in the generation of libraries in which a natural product (NP) is used as the guiding structure. Despite the different approaches used to create NP-like libraries, controlling these descriptors during the synthetic process is important to generate lead-like libraries. From this analysis, we present a schematic approach to the generation of lead-like libraries that can be applied to any starting NP.

Since ancient times, NPs have been a significant source for the treatment of diseases and illnesses. Analysis of NPs over the past 30 years revealed that approximately 40% of the developed therapeutics drugs approved by the US Food and Drug Administration (FDA) were NPs, NP derivatives, or synthetic mimetics related to NPs [1]. Investigation of structural differences between NPs, drug substances and other chemicals, found that NPs interrogate a different and wider chemical space compared with synthetic derivatives [2–5]. Furthermore, it has been showed that 83% of core ring scaffolds present in NPs were absent from commercially available molecules and screening libraries [6]. It was concluded that including molecules with a NP-like scaffold into the screening library would increase hit rates [6].

With their highly and sophisticated biological and chemical diversity, NPs and their derivatives have been used to explore biologically relevant space [7,8]. The significant impact of NPs on the discovery of therapeutic agents is based on their embedded biosynthetic molecular recognition [9]. Despite the pivotal role of NPs in drug discovery [10–12], their use over the past two decades has decreased in the pharmaceutical industry [1]. This unfortunate downturn is mainly attributed to the availability of the materials, and the time and cost of isolating and identifying active NPs from extracts [10,11,13]. However, these limitations inspired the design of NP-like libraries based on small molecules with improved stability and bioavailability.

To capture NP-like characteristics, the generation of a library can be planned following four main approaches: (i) target-oriented synthesis (TOS) [14,15]; (ii) diversity-oriented synthesis (DOS) [14,16]; (iii) biology-oriented synthesis (BIOS) [17,18]; and (iv) functional-oriented synthesis (FOS) [19]. Although in-depth discussion of these strategies is beyond the scope of this review, two points are worth noting: (i) a library collection that is diverse in chemical space is generally used to explore a wide spectrum of biological targets; and vice versa (ii) a less chemically diverse or focused library is mostly used to explore a smaller biological target area.

Analysis of libraries using concepts of lead-likeness

In 1997, Lipinsky proposed a set of four simple physicochemical properties (rule of five, Ro5) that were common to 90% of more than 2000 drugs and candidate drugs at or beyond phase II clinical trials [20]. In essence, to be drug-like, a candidate molecule should have less than five hydrogen bond donors (HBD $\leq$ 5), less than ten hydrogen bond acceptors (HBA $\leq$ 10), a MW $\leq$ 500 Da and a logP $\leq$ 5 [20]. All these parameters help to identify potential bioavailability issues if two or more violations occur [20].

TABLE 1

Selected examples of natural product-like libraries

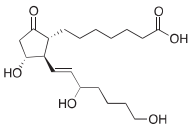
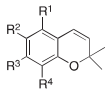
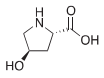
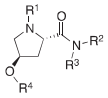
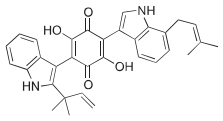
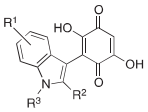
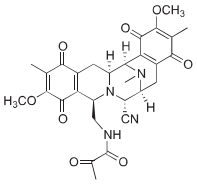
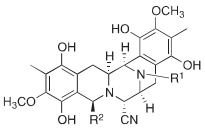
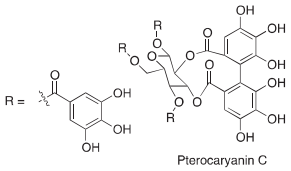
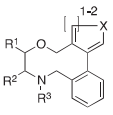
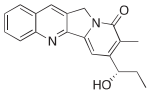
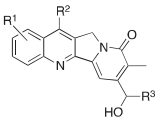
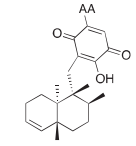
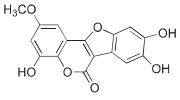
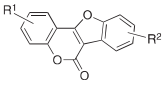
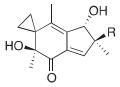
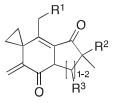
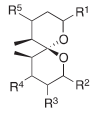
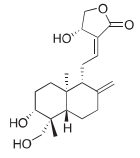
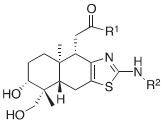
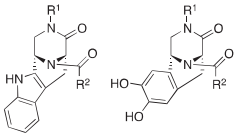
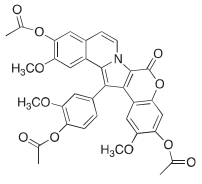
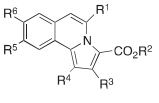
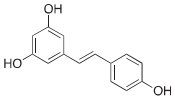
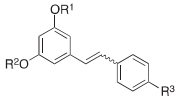
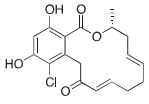
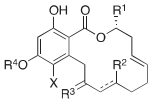
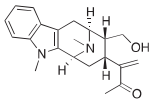
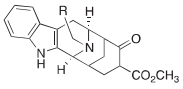
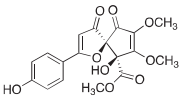
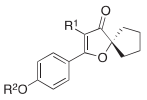
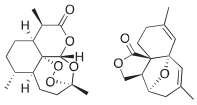
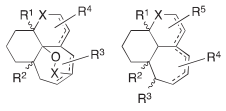
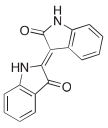
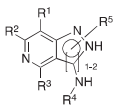
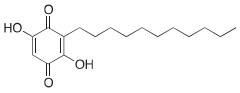
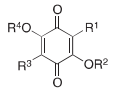
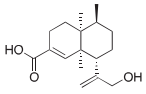
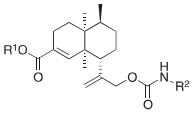
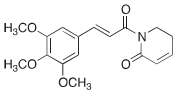
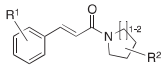
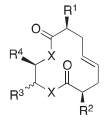
Leading NP	NP-like library	Leading NP	NP-like library
 Prostaglandin E1	Library 1 [37]  Ellman and co-workers (1999)	 2,2-dimethyl-2H-benzopyran	Library 2[a] [38]  Nicolaou *et al.* (2000)
 L-Hydroxyproline	Library 3 [39]  Boldi *et al.* (2001)	 Demethylasterriquinone B1	Library 4 [40]  Pirrung *et al.* (2002)
 (–)-Saframycin A	Library 5 [41]  Myers *et al.* (2002)	 Pterocaryanin C	Library 6 [42]  Schreiber and co-workers (2002)
 (S)-Mappicine	Library 7 [43]  Zhang et al. (2002)	 Nakijiquinone A, AA = Gly Nakijiquinone B, AA = L-Val Nakijiquinone C, AA = L-Ser Nakijiquinone D, AA = L-Thr	Library 8 [44]  Giannis, Waldmann and co-workers (2003)
 Wedelolactone	Library 9 [45]  Yang and co-workers (2003)	 Illudin S, R = CH_2OH Illudin M, R = CH_3	Library 10 [46]  Pirrung *et al.* (2003)
Okadaic acid Integramycin Tautomycin	Library 11[b] [47]  Waldmann and co-workers (2005)	 Andrographolide	Library 12 [48]  Mang *et al.* (2006)
ET-743 Cribrostatin IV Phthalascidin Saframycin A and B	Library 13[b] [49]  Park and co-workers (2006)	 Lamellarin D triacetate	Library 14 [50]  Porco and co-workers (2007)
 Resveratrol	Library 15 [51]  Rimando and co-workers (2008)	 Pochonin D	Library 16 [52]  Winssinger and co-workers (2008)

TABLE 1 (*Continued*)

Leading NP	NP-like library	Leading NP	NP-like library
 Macroline	Library 17[c] [53]  Waldmann, Kaiser and co-workers (2008)	 Limnophilaspiroketone	Library 18 [54]  Amslinger *et al.* (2011)
 Artemisinin Anthecularin	Library 19 [55]  Oguri *et al.* (2011)	 Indirubin	Library 20 [56]  Collins and co-workers (2011)
 Embellin	Library 21 [57]  Gree and co-workers (2011)	 14-hydroxy-6,12-muuroloadien-15-oic acid	Library 22 [58]  Davis and co-workers
 Piplartine	Library 23 [59]  Rao, Reddy and co-workers (2012)	Picromycin Erythromycin Enterobactin FK506	Library 24[b] [60]  Dockendorff *et al.* (2012)

[a] A privileged scaffold is represented instead of the leading NP.
[b] Listed are the most representative NPs used in the library design.
[c] Although the library was generated focusing on the macroline family, the guiding natural product is reported here.

Hopkins and co-workers recently proposed a measure of drug-likeness based on the concept of desirability called the 'quantitative estimate of drug-likeness' (QED) [21]. This new concept was introduced because they observed that Lipinsky's rule could sometimes be misleading [21]. For example, undesirable compounds can satisfy the Ro5 and, therefore, pass the drug-likeness criteria, whereas more appropriate compounds can fail because of the violation of one or more cut-offs. QED is an integrated function of eight desirability functions calculated for each physicochemical properties: MW, logP, HBD, HBA, polar surface area, rotatable bonds (RTB), aromatic ring count (RNG) and number of alerts. Moreover, each molecular descriptor is weighted by its relative significance in the contribution to drug-likeness. As Leeson pointed out [22], QED is not the final word in understanding the features of drug-likeness, but provides a richer and more balanced view on this concept compared to Ro5. Therefore, this new parameter could be used in the lead optimization process or potentially for the generation of libraries with lead-like properties.

Contrary to drug-like properties, which are still mostly represented by Ro5, lead-like properties are more restricted. This is because the identification of lead compounds is the starting point for further development in drug design [23]. A lead is a less complex compound with defined physicochemical properties, suitable for further manipulation and optimization to generate a drug-like compound. Lead-likeness was first introduced by Opera in 1999, who suggested that lead-like compounds should have the following requirements: MW $\leq$ 350 Da and logP $\geq$ 3 [24]. This concept was then further elaborated by taking into consideration other physical properties, such as HBA, HBD, RTB, RNG and its aqueous solubility (LogS). More importantly, the range of MW was extended to 460 Da and the logP values to between -4 and 4.2 [25,26]. Meanwhile, an analysis by Leeson and Davis [27] of 864 drugs approved before 1983 compared with 329 drugs approved between 1983 and 2002 showed that the logP values remained consistent over time, with minor changes compared with the other physicochemical properties. Since the first guidelines of lead-likeness were established, several publications over the past decade have reported variations of this concept, either introducing new physicochemical properties or slightly modifying the existing range values [28–33].

In this review, we analyze and illustrate the variation of the two main lead-like descriptors (MW and logP) in the generation of NP-like libraries in which a NP is used as the guiding structure. For each library, an analysis of four physicochemical properties (HBD, HBA, RTB and RNG) is presented.

To provide a more comprehensive analysis, 24 libraries (Table 1) were selected based on different features. (i) Origin of the library. Two major categories of library were selected: NP-derived and NP-inspired libraries. Molecules in which the scaffold is identical to the scaffold of a leading NP belong to the first category, whereas compounds in which the scaffold is closely related to the guiding NP fall into the second category. In this collection, most libraries are based on one NP representative. However, in a few examples, more than one NP was taken as the guiding structure. Library 8 was created considering four NPs that were based on the same quinone moiety. Library 19 was based on two sesquiterpenes, artemisinin and anthecularin, bearing a peroxide bridge and a diene, respectively. In our selection, we also included NP-like libraries based on a common structural motif. In this category, we included library 2, which was generated around the privileged scaffold 2,2-dimethyl-2H-benzopyran, and libraries 11, 13 and 24 based on spiroketal, diaza-bridge and macrolactone scaffolds, respectively; (ii) MW: a wide range in MW of the representative NPs was chosen (from 130 Da to 940 Da); (iii) Library size; small libraries of 10–15

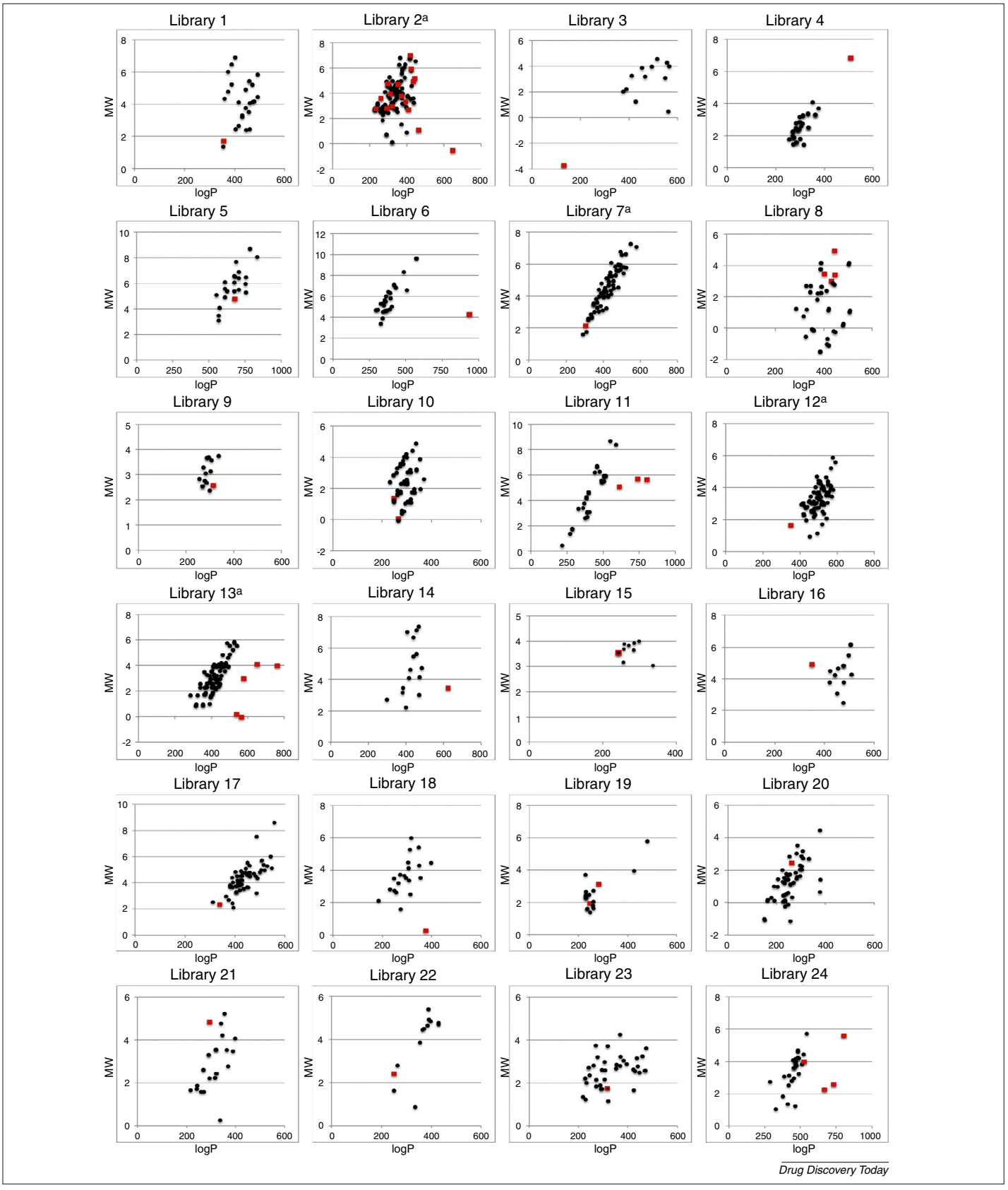


FIGURE 1

Analysis of 24 natural product (NP)-like libraries based on two physicochemical properties: molecular weight (MW) in Dalton (*x*) and the partition coefficient (logP) (*y*). In each chart, values are plotted of the guiding NP(s) in red and the library of the compound in black. [a]Libraries with >100 compounds were filtered to generate smaller libraries with similar chemical diversity.

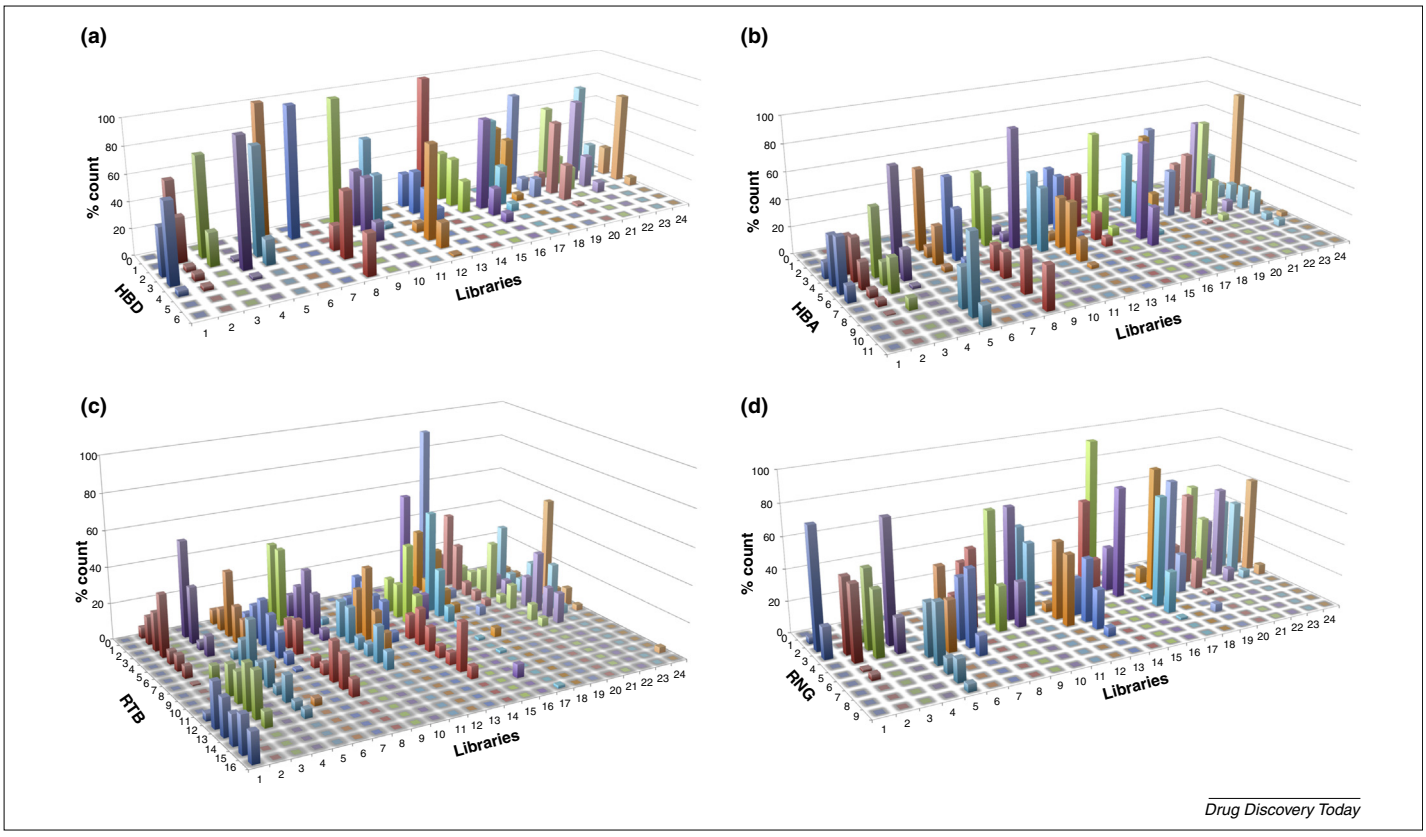


FIGURE 2

Summary of calculated physicochemical properties for 24 libraries: (a) hydrogen bond donors (HBD); (b) hydrogen bond acceptors (HBA); (c) rotatable bonds (RTB); and (d) ring count (RNG).

entities to large libraries of >2000 entities were analyzed.

The initial analysis of the 24 libraries was carried out by generating scatterplots using MW and logP as the two variables. From the data sets summarized in Fig. 1, three major distribution trends were identified, as discussed below.

Rising libraries

Rising libraries contained compound collections with higher MWs than the guiding NP. In most cases, logP values rose in direct proportion to MW (libraries 1, 3, 7, 10, 12 and 17). In two cases (libraries 1 and 10), the distribution values were not as compact as in the other examples and different linearity sets can be observed within the same library. However, an increase of MW did not always lead to a rise in logP, as shown for libraries 15, 16 and 22. In these three plots, the logP vales of the libraries are both below and above the guiding NP.

Falling libraries

This second trend of distribution is characterized by libraries with a MW lower than the guiding NP. By decreasing the MW, two different sets were identified: libraries with LogP values lower than the guiding NP, in which the logP decreased directly proportional to the MW (libraries 4 and 8); and libraries with logP values predominantly above the guiding NP (libraries 6, 9, 14 and 18). In this trend, we also included libraries 11, 13 and 24. As expected, because these three libraries were generated using the common structural motif approach, a decrease in MW compared with the guiding NPs was detected. In the first two examples, a linear decrease of logP values was observed, whereas library 24 showed a more scattered distribution of values.

Uncorrelated libraries

This class was characterized by libraries having both lower and higher MW compounds compared with the guiding NP. In two examples (libraries 5 and 23), most compounds in the library had logP values above the guiding NP. However, the opposite distribution, in which a predominant part of the library entities have logP values below the guiding NP (libraries 19, 20 and 21), was also observed. Given that library 2 was generated using a privileged scaffold approach, only selected examples of benzopyran-containing NP were plotted. In this case, we observed a library built with similar physicochemical properties as the guiding NPs.

As mentioned above, a more complete analysis of lead-likeness should include additional physicochemical properties, such as HBD, HBA, RNG and RTB. The analysis of individual properties is summarized in Fig. 2 expressed as percentages. The histogram of the HBDs (Fig. 2a) shows a predominant distribution that peaks at 1–3, and values >5 are rarely reached. In a few examples (libraries 4, 6, 9 and 14), there was a lack of HBD distribution, showing predominately just one value of HBD within the library. The histogram in Fig. 2b, which indicates HBA distribution, shows values for most of the libraries, with a maximum at 4–7 HBA. Despite the first two distributions, in which we were able to define a range of maximum values for HBD and HBA, the histogram representing the number of RTB (Fig. 2c) showed more scattered values. However, approximately 75% of the libraries fell into the lead-likeness cut-off value (RTB $\leq$ 9). Furthermore, RNG was calculated and the values for each library are summarized in Fig. 2d. For this property, a major distribution is observed, with peak values of between 3 and 5 RNG.

Although the 24 selected libraries were created using different synthetic strategies and not necessary with the ultimate goal to generate a

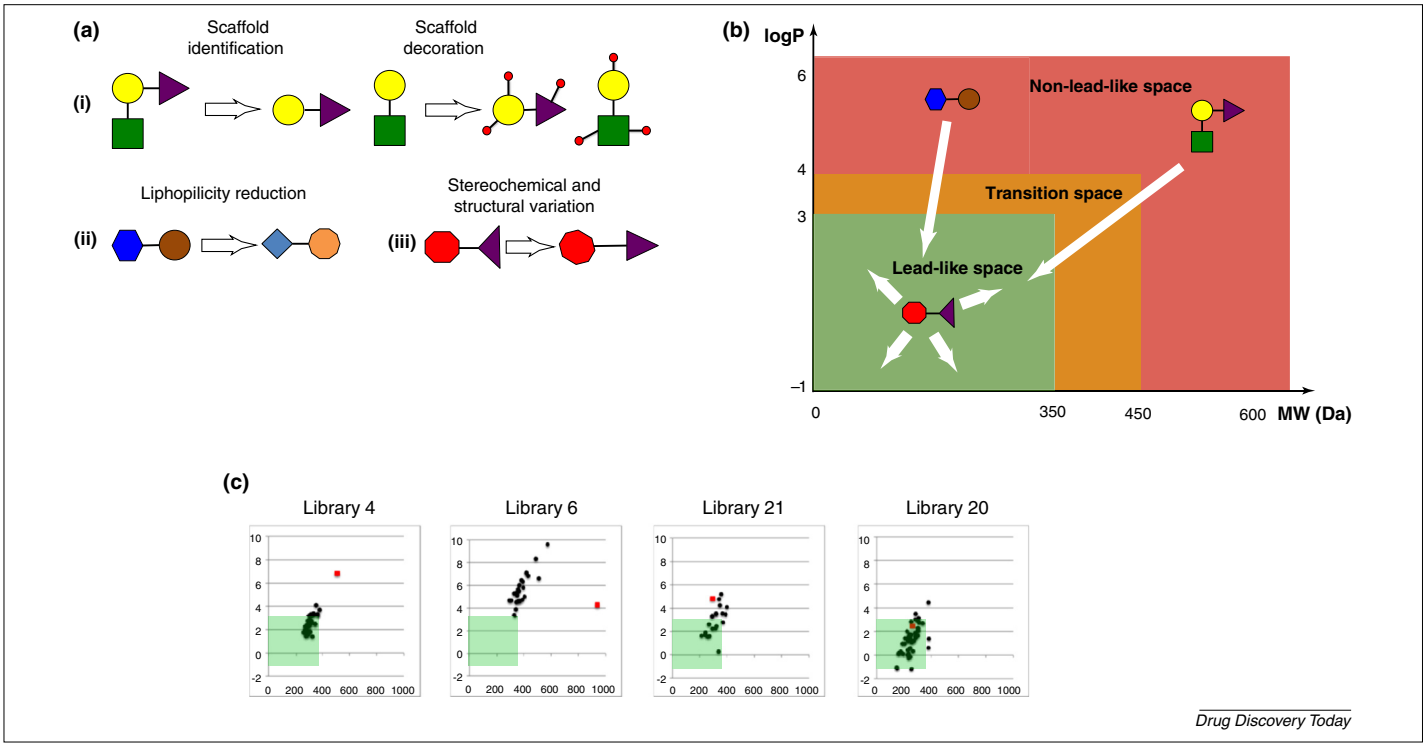


FIGURE 3

Schematic approaches (a and b) to the generation of lead-like libraries. Representation of the lead-like region (green) of four libraries selected from Fig. 1 (c). *Abbreviations*: logP: partition coefficient; MW: molecular weight.

lead compound, we wanted to illustrate with our analysis the impact of chemical transformations on physiochemical properties in the generation of libraries using NPs as a guiding structure.

Chemical transformations to create lead-like libraries

From this analysis, we present a schematic approach to the generation of lead-like libraries that can be applied to any starting NP. Given that, during the lead-optimization process, an increase in MW and logP is generally observed [24,34], we believe that the optimum property cut-off values to identify NP lead-like libraries should be as follows: MW $\leq$ 350 Da and $-1 \leq \text{logP} \leq 3$. The initial step to generate potential leads is to define the guiding NP with relevant biological activity. Next, the NP-like library can be created following three different approaches, as simplified in Fig. 3: (i) if the guiding NP has a MW $\geq$ 350 Da, it is necessary to reduce the structural complexity. This can be achieved through the identification of scaffolds. The synthetic process to produce attractive scaffolds should take in consideration the insertion of several functional groups, which could then be elaborated [35,36]. This is a crucial point in the generation of potential leads because functionalization of these molecules should provide a library with appropriate logP values ($-1 \leq \text{logP} \leq 3$) and, at the same time, with chemical diversity. As we observed in our previous analysis in Fig. 1, a reduction in structural complexity can lead to a library with optimal logP values, as in library 4, and to a library with logP values in the non-lead-like region, as in library 6 (Fig. 3). Therefore, the challenge will be to create small molecule libraries within the lead-like region starting from NP scaffolds in which the main features of the guiding NP are retained; (ii) if the guiding NP has a MW $\leq$ 350 and logP $\geq$ 3, is it necessary to reduce lipophilicity. Library 21 (Fig. 3) is a typical example of this situation. Moreover, to provide chemical diversity within the library, the presence of several functional groups is necessary; and (iii) if the guiding NP falls in the lead-like region, as in library 20 (Fig. 3), this can be used as a starting point for the preparation of a library with skeletal and stereochemical variations with the condition to generate molecules in the lead-like region.

Concluding remarks

In conclusion, despite the different approaches used to create NP-like libraries, we believe that controlling the two main descriptors (MW and logP) during the synthetic process would facilitate the generation of lead-like libraries. Therefore, the use of *in silico* analysis in scaffold identification and elaboration will avoid the generation of unwanted entities with resulting improvement in the quality of the library.

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