ELSEVIER

feature

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

Mauro Pascolutti and Ronald J. Quinn*, r.quinn@griffith.edu.au

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.

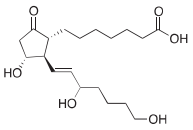
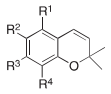
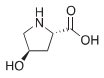
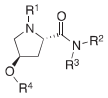
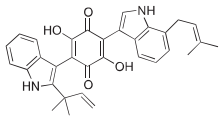
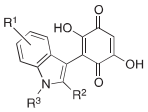
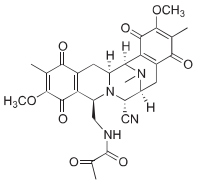
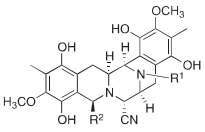
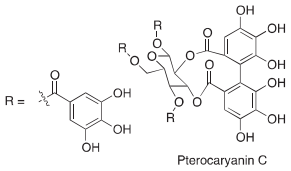
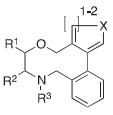
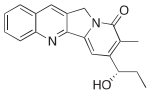
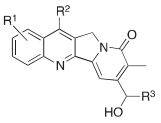
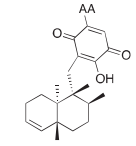
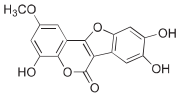
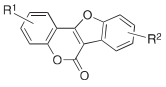
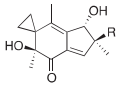
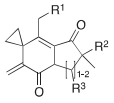
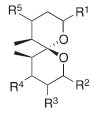
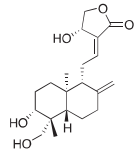
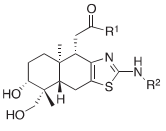
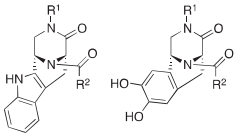
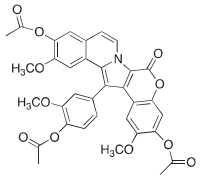
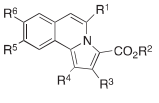
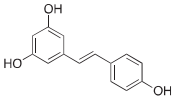
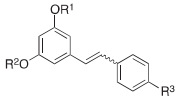
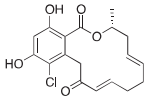
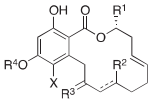
To capture NP-like characteristics, the generation of a library can be planned following four main approaches: (i) target-oriented synthesis (TOS) [14,15]; (ii) diversity-oriented synthesis (DOS) [14,16]; (iii) biology-oriented synthesis (BIOS) [17,18]; and (iv) functional-oriented synthesis (FOS) [19]. 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)