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feature

Towards the realisation of lead-oriented synthesis

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Sourcing large numbers of lead-like molecules – compounds that would serve as good starting points for drug discovery programmes – is currently very challenging. The concept of lead-oriented synthesis has recently been articulated to capture the specific problem of preparing diverse small molecules with lead-like molecular properties. In this Feature, some methods that might be used to prepare lead-like molecular scaffolds are described, and presented in the context of diversity-oriented synthetic strategies that allow wide variation in molecular scaffold. It is concluded that the development of a wider toolkit of reactions that is reliable with more polar substrates will be required to allow genuine combination of molecular scaffold within lead-like chemical space.

Lead-oriented synthesis: a major challenge for synthetic chemists

There is a strong link between the molecular properties of clinical candidates and the probability of successful development to yield marketed drugs [1]. Molecular properties that correlate with success in the development process include molecular size and lipophilicity (*clogP*) [2], the fraction of sp3-hybridised carbon atoms (Fsp^3) [3] and the number of aromatic rings (*n*Ar) [4]. Lead optimisation almost inevitably leads to increases in molecular weight and lipophilicity, and therefore tight control over the properties of initial lead molecules is advisable [5,6].

The concept of lead-oriented synthesis has recently been introduced to capture the specific problem of preparing diverse small molecules with lead-like molecular properties (Table 1) [7] (i.e. compounds that would serve as good starting points for lead optimisation). A recent study [7] found that >99% of commercially available compounds are not lead-like. This study also found the vast majority of compounds that are reported in synthetic methodology papers are not lead-like either. The scale of the problem is further compounded by historically uneven and unsystematic exploration of chemical space: around half of all known compounds are based on just 0.25% of the known small molecule scaffolds [8]. This uneven exploration is reflected in the (lack of) diversity of small molecule screening collections [9,10]. How, then, might large numbers of diverse, lead-like compounds be sourced to allow high-quality screening collections to be built and maintained?

The realisation of lead-oriented synthesis will require the development of new synthetic methods and approaches that can deliver large numbers of diverse, lead-like small molecules. Indeed, the poor availability of diverse, lead-like small molecules might stem, in part, from the limited toolkit that is generally used to support drug discovery [11,12]. The challenge of realising lead-oriented synthesis should serve as a clarion call to the synthetic chemistry community; (for example, see [13]).

Learning from diversity-oriented synthesis

We describe synthetic approaches that can assist the realisation of lead-oriented synthesis. We focus on approaches that could enable the synthesis of lead-like molecular scaffolds (i.e. scaffolds that can be decorated to yield large numbers of compounds that have lead-like molecular properties: such scaffolds need to be rather small, with up to ~16 heavy atoms, so that lead-like properties are retained after decoration).

Synthetic approaches that enable the combinatorial variation of the molecular scaffold will have particular value in lead-oriented synthesis. Although many diversity-oriented syntheses have tended to yield scaffolds that lie well outside lead-like chemical space, the underlying

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TABLE 1

Molecular properties and features proposed for lead-like small molecules [7]

Molecular property and/or feature	Preferred values
Molecular size	$14 \leq$ heavy atoms ≤ 26[a]
Lipophilicity	$-1 < \mathit{clogP} < 3$
Aromatic rings	$n\mathrm{Ar} \leq 3$
Shape	More 3D shape[b]
Substructures	Absence of chemically reactive or redox-active groups

[a] Molecular weight ~ 200–350 Da.[b]Fsp^3 can be a useful parameter for assessing three-dimensionality.

synthetic strategies [14–17] might nonetheless also be exploited in lead-oriented synthesis. Indeed, diversity-oriented approaches have already been exploited in the synthesis of diverse central nervous system (CNS)-focused scaffolds [18] and in the synthesis of 3D fragments [19]. Fig. 1 illustrates three syntheses that exploit three important strategies for diversity-oriented synthesis. All three of these syntheses can be considered to exemplify the

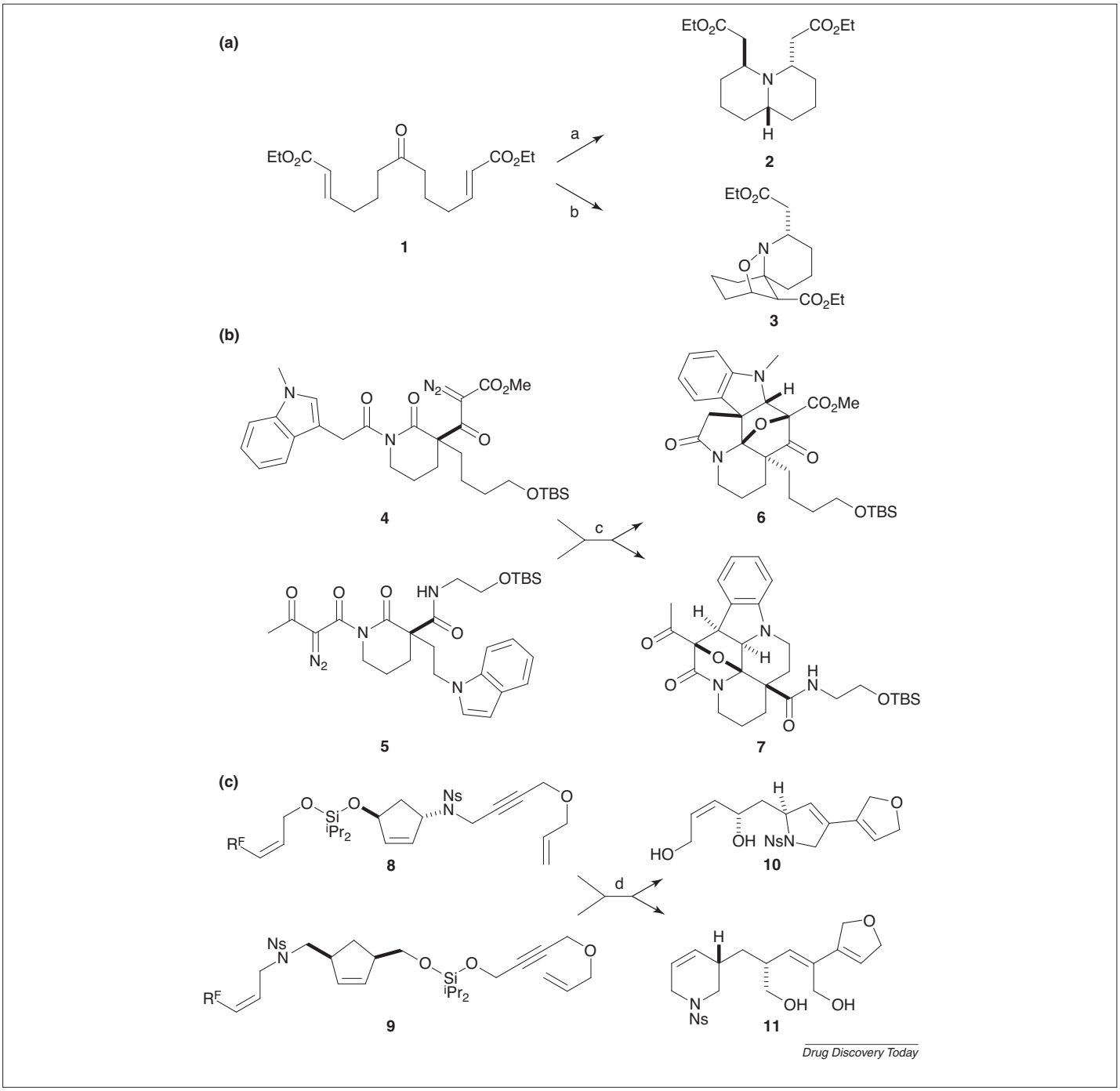

FIGURE 1

Alternative diversity-oriented synthetic approaches. **(a)** An example of a branching pathway. **(b)** An example of a folding pathway. **(c)** An oligomer-based approach. (a) (i) NH_3, $NaBH_4$, $Ti(OEt)_4$, EtOH; (ii) AcOH; (b) (i) $NH_2OH{\cdot}HCl$, NaOAc, MeCN; (ii) toluene, 140 °C; (c) $Rh_2(O_2CC_7H_{15})_4$, benzene, 50 °C; (d) metathesis. R^F denotes a fluorous-tagged linker.