A modular lead-oriented synthesis of diverse piperazine, 1,4-diazepane and 1,5-diazocane scaffolds

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Piperazines are found widely in commercially-available compounds and bioactive molecules (including many drugs). However, in the vast majority of these molecules, the piperazine ring is isolated (i.e. not fused to another ring) and is not substituted on any of its carbon atoms. A modular synthetic approach is described in which combinations of cyclic sulfamidate and hydroxy sulfonamide building blocks may be converted into piperazines and related 1,4-diazepine and 1,5-diazocane scaffolds. By variation of the combinations of building blocks used, it was possible to vary the ring size, substitution and configuration of the resulting heterocyclic scaffolds. The approach was exemplified in the synthesis of a range of heterocyclic scaffolds that, on decoration, would target lead-like chemical space. It was demonstrated that lead-like small molecules based on these scaffolds would likely complement those found in large compound collections.

Dedicated to J. Andrew Grant who initiated this project.

Introduction

The development of the field of lead-oriented synthesis, in which diverse compounds with lead-like molecular properties are prepared, has recently been framed as a major challenge for synthetic chemists.[1] The molecular properties of clinical candidates[2-5] – particularly molecular size and lipophilicity[5] – are strongly linked to the probability of successful negotiation of the development process. Optimisation almost inevitably leads to increases in both molecular weight and lipophilicity, making it essential to control the properties of lead compounds.[6,7] The significant challenges associated with preparing diverse lead-like small molecules – i.e. molecules that would be good starting points for lead optimisation – have recently been articulated.[1]

Sourcing large numbers of lead-like small molecules is a major challenge in maintaining large, high quality screening collections.[1] The vast majority of commercially-available screening compounds – as well as compounds reported in the synthetic chemistry literature – do not have lead-like properties.¶ In addition, chemists have historically explored chemical space rather unsystematically.[8] The challenge is thus further exacerbated when diversity considerations are also introduced.

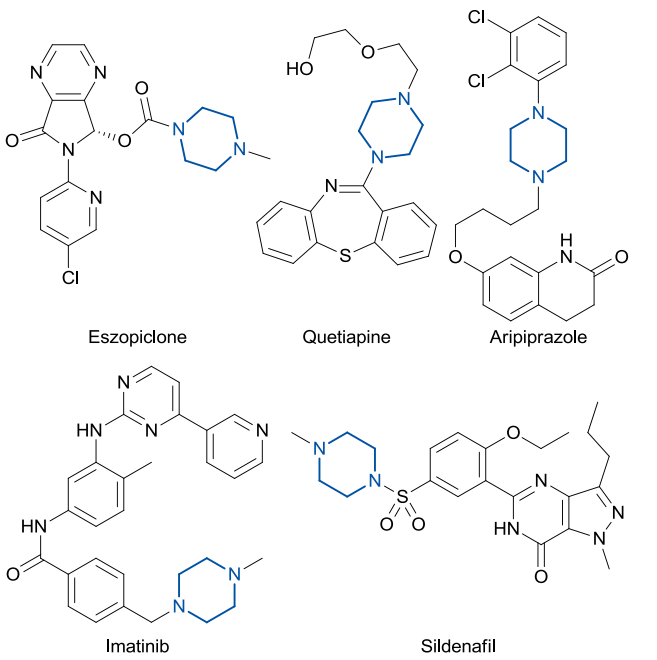
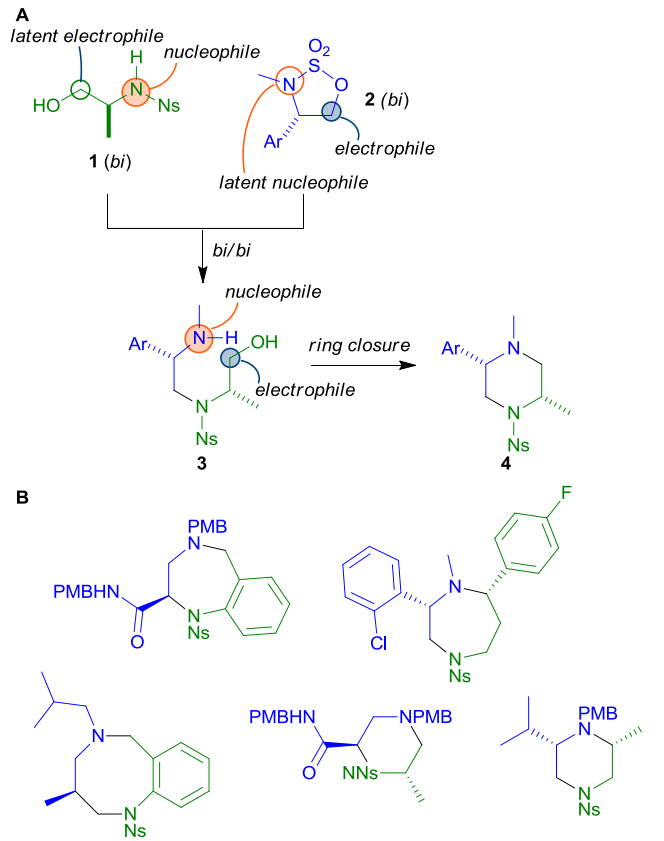


Figure 1 Examples of best-selling drugs that contain a piperazine ring system



Scheme 1 Overview of the proposed modular approach to diverse lead-like heterocycles. The provenance of atoms from building blocks is indicated using colour, and new bonds are shown in black. Panel A: Combination of two bi-connective building blocks – for example the hydroxy sulfonamide **1** and the cyclic sulfamidate **2** – would yield the piperazine **4**. Panel B: Examples of additional scaffolds that might also be prepared using the approach.

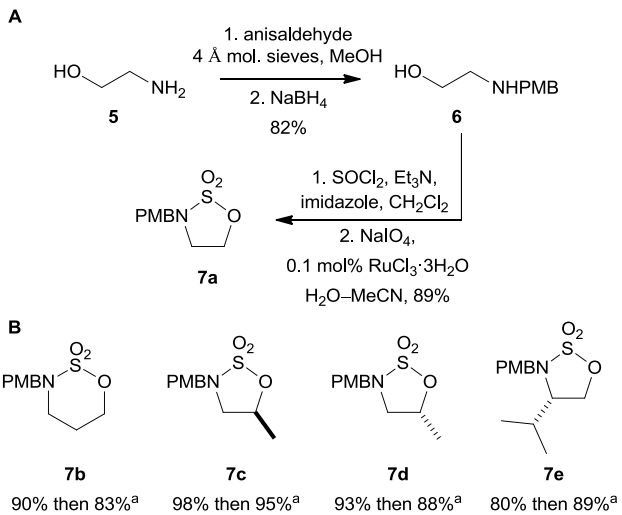
In this paper, a modular approach to diverse heterocyclic scaffolds, including those based on piperazines, 1,4-diazepanes and 1,5-diazocanes, is described. Piperazines are found widely in commercially-available compounds (in around 5.4% of compounds in the ZINC database) and bioactive molecules (in around 7.7% of compounds in the ChEMBL database). Indeed, 13 of the 200 best-selling small molecule drugs in 2012 contain a piperazine ring (for examples, see Figure 1).[9] However, in the vast majority of these molecules, the piperazine ring is isolated (i.e. not fused to another ring) and is not substituted on any of its carbon atoms.[10] Significant chemical space that is closely related to that known to be biologically-relevant therefore remains underexplored.

An overview of the proposed modular synthetic approach is shown in Scheme 1. It was proposed that bi-connective[11] building blocks would be prepared from readily available amino alcohols (Panel A). Thus, ring-opening of a cyclic sulfamidate[12] (e.g. **2**) with a hydroxy sulfonamide (e.g. **1**) would yield an intermediate (e.g. **3**) in which the functionality needed for cyclisation had been revealed. Finally, cyclisation would yield a specific heterocyclic scaffold (e.g. **4**). It was envisaged that, by varying the building blocks used, it would be possible to vary both the size of the new heterocyclic ring, and the substituents on specific carbon atoms. The overall synthesis – from the bi-connective building blocks (e.g. **1** and **2**) to the product scaffold (e.g. **4**) – may be classified as a *bi/bi* process[11] or as an ambiphile pairing[13] process.

Results and Discussion

Development of a modular synthesis of diverse heterocyclic scaffolds

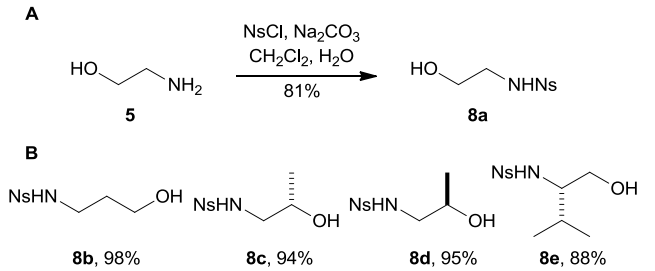
Initially, a modular synthesis of diverse heterocyclic scaffolds was developed. Specifically, it was decided to investigate the effect of both the ring size and substitution of the product scaffold. A range of cyclic sulfamidates was prepared by reductive amination of the corresponding amino alcohol (e.g. **5** → **6**), followed by cyclic sulfamidite formation and ruthenium-catalysed oxidation (e.g. → **7a**) (Scheme 2). In addition, a range of hydroxy sulfonamides was prepared by sulfonylation of the corresponding hydroxy alcohols (Scheme 3).



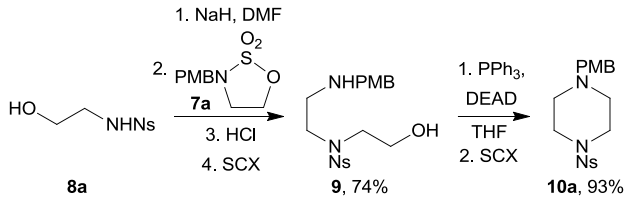
Scheme 2 Synthesis of cyclic sulfamidate building blocks **7**. PMB: *p*-methoxybenzyl. Panel A: Synthesis of the building block **7a**. Panel B: Additional building blocks prepared using the same approach. [a]Yields for reductive amination and cyclic sulfamidate formation respectively.

Initial work focused on the combination of the hydroxy sulfonamide **8a** and the cyclic sulfamidate **7a** (Scheme 4). It was decided that the ideal method would minimise the need for purification of the intermediate **9** and the product **10a** using silica gel column chromatography. The hydroxy sulfonamide **8a** was treated with sodium hydride in DMF, reacted with the cyclic sulfamidate **7a** at room temperature and finally treated with aqueous acid; after work-up, and strong ion exchange chromatography (SCX), the ring-opened intermediate **9** was obtained in 74% yield. The successful purification of **9** using SCX stems from the basicity of **9** (but not **7a** or **8a**). Treatment of **9** with triphenylphosphine (1.4 eq.) and DEAD (1.4 eq.) triggered cyclisation[14] to give the piperazine **10a**; here, SCX was used successfully to facilitate the purification of the (basic) product **10a** from the by-products of the reaction. The use of

hydrogen-borrowing chemistry to promote the cyclisation of intermediates such as **9** was also investigated, but without success.



Scheme 3 Synthesis of hydroxy sulfonamide building blocks **8**. Ns: *o*-nitrophenylsulfonyl. Panel A: Synthesis of the building block **8a**. Panel B: Additional building blocks prepared using the same approach.

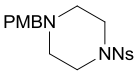
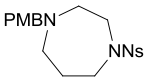
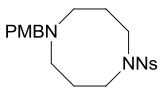
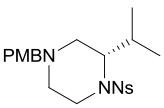
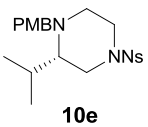
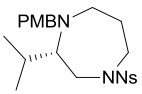
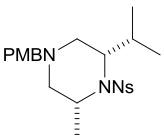
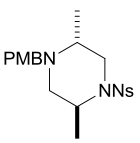
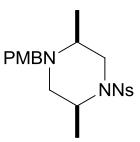
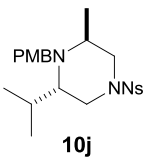
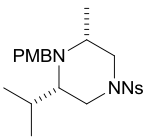


Scheme 4 Modular synthesis of the piperazine **10a**

The scope and limitations of the modular synthetic approach were investigated (Table 1). Initially, the effect of the ring-size of the product scaffold was investigated (compare entries 1-3). Remarkably, the yields of the 1,4-diazepane **10b** (entry 2) and the 1,5-diazocane **10c** (entry 3) were only marginally lower than that of the piperazine **10a** (entry 1). It should be noted, however, that ring opening of the six-membered cyclic sulfamidate **7b** required heating (70 °C).[15]

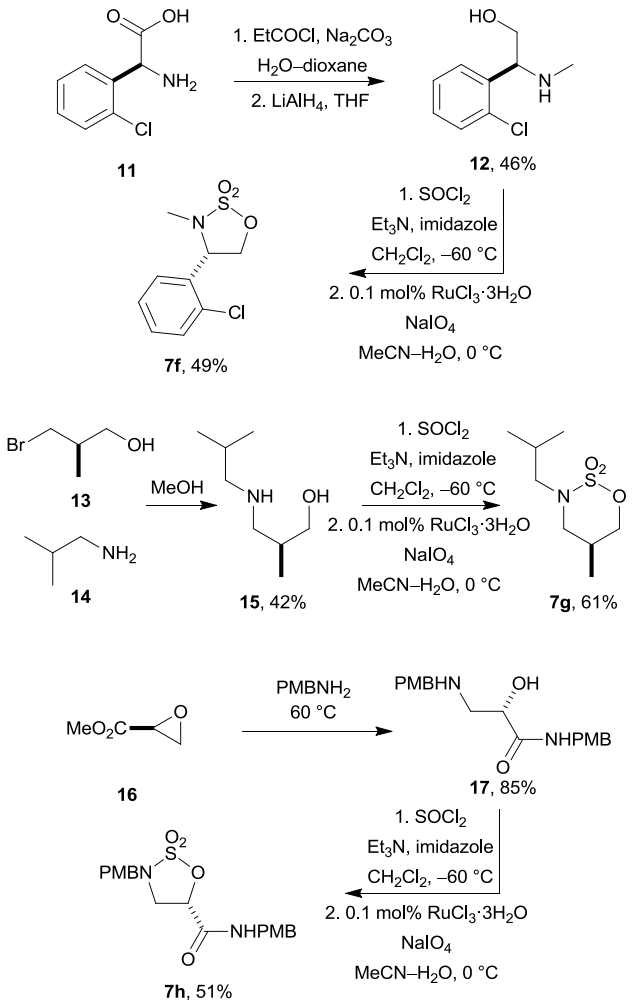
The effect of substitution on the yield of the product scaffold was investigated using the valinol-derived building blocks **7e** and **8e** (Table 1; entries 4-6). The effect of a single *iso*-propyl substituent on the yield of the product scaffold was small, both in the synthesis of piperazines (compare entry 4 and 5 with entry 1) and 1,4-diazepanes **10f** (compare entry 6 with entry 4). However, with the hindered hydroxy sulfonamide **8e**, no product was obtained with either 4- or 5-substituted cyclic sulfamidates (**7c**, **7d** or **7e**) (entry 7). Here, the specific combination of a hindered electrophile and a hindered nucleophile prevented efficient ring-opening of the cyclic sulfamidate.

Table 1 Investigation into the effect of product ring size and substitution on the efficiency of heterocycle synthesis

Entry	Building blocks	Product[a]	Yield[b] / %
1	**7a**, **8a**[c]	 **10a**	69
2	**7b**, **8a**	 **10b**	40[d]
3	**7b**, **8b**	 **10c**	60[d]
4	**7a**, **8e**	 **10d**	68
5	**7e**, **8a**	 **10e**	72
6	**7e**, **8b**	 **10f**	44
7	**7c**, **8e**	 **10g**	0[e]
8	**7d**, **8c**	 **10h**	41 (33[f])
9	**7d**, **8d**	 **10i**	36 (29[f])
10	**7e**, **8d**	 **10j**	40
11	**7e**, **8c**	 **10k**	40

[a]See Scheme 4 for the method used. [b]Yield of product over 2 steps. [c]See Scheme 4 for this specific combination of building blocks. [d]Opening of cyclic sulfamidate **7b** were performed at 70 °C. [e]The required product was also not obtained when the building block **8e** was combined with either **7d** or **7e**. [f]Yield of the enantiomeric product prepared from the enantiomeric building blocks.

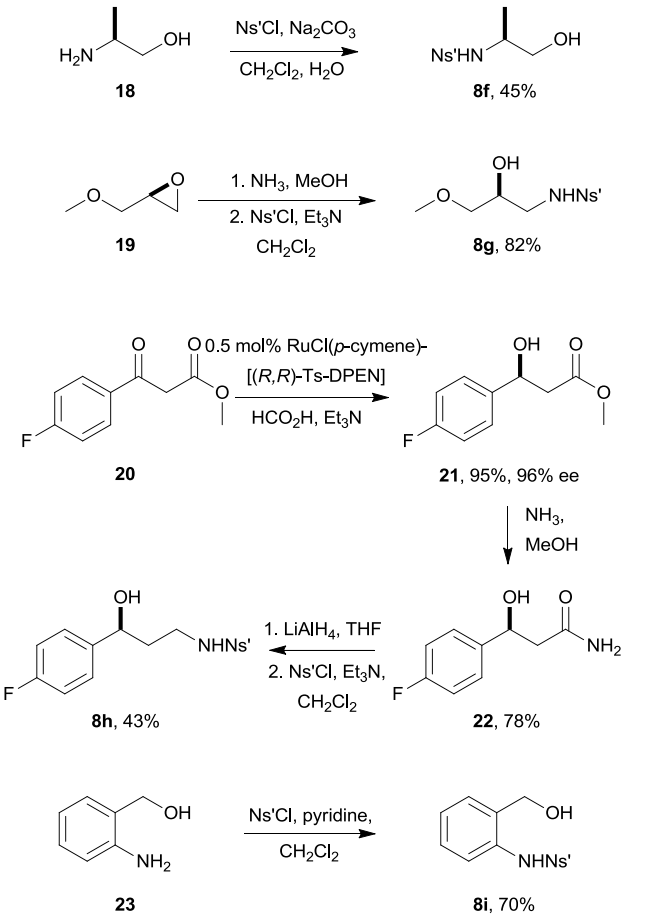
Finally, the possibility of matched-mismatched[16] effects was investigated in the synthesis of diastereomeric piperazines (Table 1; entries 8-11). Remarkably, the yields of diastereomeric pairs of piperazines (**10h**/**10i** and **10j**/**10k**; compare entries 8-9 and entries 10-11) were broadly similar. In each of these cases, a single diasteromeric product was obtained, demonstrating that both the ring-opening and cyclisation steps were stereospecific.



Scheme 5 Synthesis of cyclic sulfamidate building blocks.

Exemplification in the synthesis of lead-like scaffolds

The modular synthetic approach was exemplified through the synthesis of a range of molecular scaffolds. The required building blocks were selected carefully such that diverse scaffolds might be prepared which, on derivatisation, would yield molecules with lead-like molecular properties. Crucially, different combinations of the building blocks would yield scaffolds (a) in which the size of the new heterocycle was varied; (b) with contrasting carbon-based substituents; and, (c) in which, in some cases, the new heterocycle was fused to another ring.

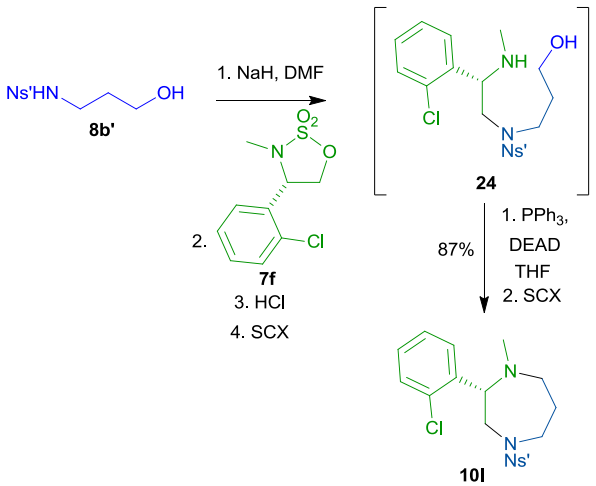


Scheme 6 Synthesis of hydroxy sulfonamide building blocks. Ns': *p*-nitrophenylsulfonyl.

The required building blocks were prepared from readily-available starting materials (Schemes 5 and 6). The amino alcohols **12**, **15** and **17** were prepared respectively by reduction of the amino acid **11** (→ **12**), by substitution of the bromo alcohol **13** (→ **15**), and by ring-opening[17] of the epoxide **16** (→ **17**) (Scheme 5). In each case, the amino alcohols were converted into the corresponding cyclic sulfamidites which were then oxidised to give the required cyclic sulfamidates **7**. The hydroxy sulfonamide building blocks **8f**-**8i** were prepared by sulfonylation of the corresponding amino alcohols (Scheme 6).

Pairs of building blocks were combined to yield a range of lead-like molecular scaffolds (see Scheme 7 and Table 2). In each case, a hydroxy sulfonamide building block **8** was treated with sodium hydride in DMF, reacted with a cyclic sulfamidate **7** and, finally, treated with aqueous acid; after work-up, SCX yielded the crude ring-opened intermediate. Subsequently, the ring-opened intermediates were treated with triphenylphosphine (1.2 eq.) and DEAD (1.1 eq.). A wide range of molecular

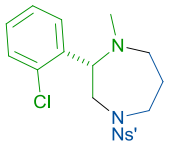
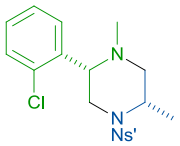
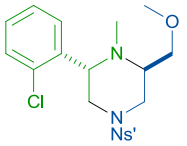
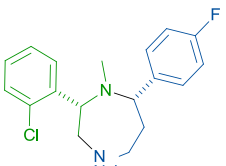
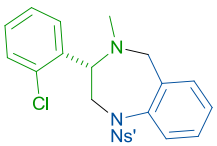
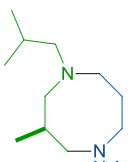
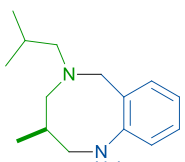
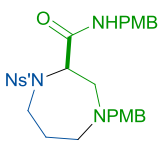
scaffolds was obtained that display significant structural diversity. The new heterocyclic rings were six-, seven- or eight-membered; and substituents were introduced on contrasting carbons on the new ring. In addition, in some cases, the new heterocyclic ring was benzo-fused.

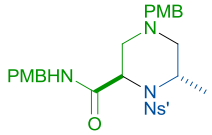
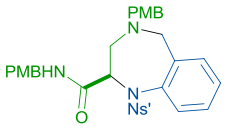


Scheme 7 Modular synthesis of the lead-like scaffold **10l**. Ns: *o*-nitrophenylsulfonyl. Ns': *p*-nitrophenylsulfonyl.

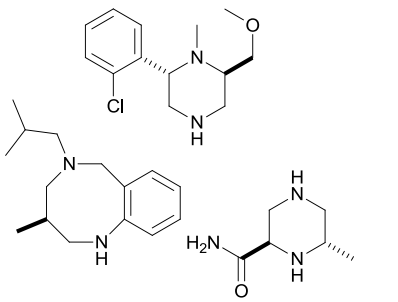
The efficiency of the modular approach depended on the specific building blocks used (Table 2). Diverse molecular scaffolds were prepared efficiently from the 5-substituted cyclic sulfamidate **7f**: 2-substituted and 2,7-disubstituted 1,4-diazepanes (**10l** and **10o** respectively; entries 1 and 4), and 2,5- and 2,6-disubstituted piperazines (**10m** and **10n** respectively; entries 2-3). However, the benzo-fused 1,4-diazepane **10p** was obtained in low yield (entry 5). With the 6-membered cyclic sulfamidate building block **7g**, low yields of the 1,5-diazocanes **10q** and **10r** were obtained (entries 6-7). With the 4-substituted cyclic sulfamidate **7h**, the success of the approach depended on the specific hydroxy sulfonamide building block used; as had previously been observed with a 4-substituted substituted cyclic sulfamidate (see entry 7, Table 1), the approach was less successful when more hindered hydroxy sulfonamides were used (compare entries 8-10, Table 2).

Table 2 Synthesis of diverse lead-like molecular scaffolds

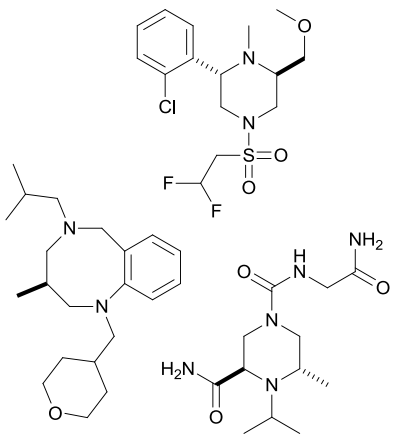
Entry	Building blocks	Product[a]	Yield[b] / %
1	**7f**, **8b'**[c]	 **10l**	87
2	**7f**, **8f**	 **10m**	44
3	**7f**, **8g**	 **10n**	55
4	**7f**, **8h**	 **10o**	80
5	**7f**, **8i**	 **10p**	11
6	**7g**, **8b'**	 **10q**	13
7	**7g**, **8i**	 **10r**	14
8	**7h**, **8h**	 **10s**	38

9	**7h**, **8f**	 **10t**	8
10	**7h**, **8i**	 **10u**	28

[a]See Scheme 7 for the method used. [b]Yield of product over 2 steps. [c]See Scheme 7 for this specific combination of building blocks. Ns': *p*-nitrophenylsulfonyl.



Virtual decoration



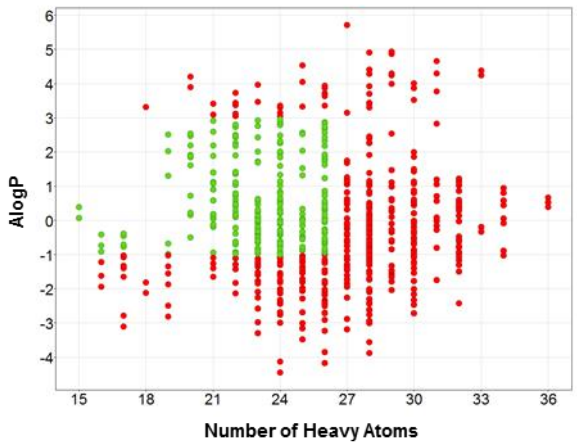
Scheme 8 Enumeration of a virtual library of likely synthetically-accessible small molecules based on the molecular scaffolds **10l-u**.

Assessment of the value of the molecular scaffolds

A virtual library of compounds was enumerated from combinations of the deprotected scaffolds (derived from **10l-u**) and a range of exemplar medicinal chemistry reagents for amine decoration (see Scheme 8 and Supporting Information). The resulting library comprised 977 likely synthetically-accessible small molecules. The value of the scaffolds was assessed by analysis of this virtual library.

First, the lead-likeness of the members of the virtual library was assessed. For each compound, the number of heavy atoms (*n*HA), lipophilicity (AlogP) and number of aromatic rings (*n*Ar) were determined (Figure 2). With these properties determined, the lead-likeness of the compounds was assessed. Remarkably, this analysis showed that 338 (~34%) of the compounds in the virtual library had lead-like molecular properties ($14 \leq n\text{HA} \leq 26$; $-1 \leq \text{AlogP} \leq 3$; $n\text{Ar} \leq 3$).

A



B

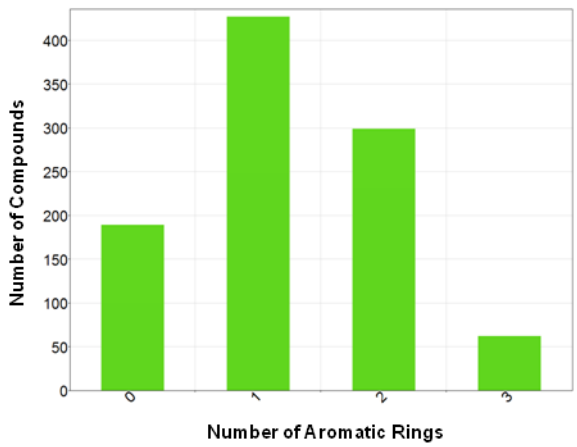


Figure 2 Lead-likeness of a virtual library of compounds derived from the scaffolds **10l-u** (see Scheme 8). Data for compounds with lead-like properties is highlighted in green. Panel A: Distribution of the number of heavy atoms (*n*HA) and the lipophilicity (AlogP). Panel B: Distribution of the number of aromatic rings (*n*Ar).

Second, the shape diversity of the 338 lead-like compounds from the virtual library was assessed using two alternative methods. In order to compare these compounds with compounds of a similar size, ~100,000 compounds with 14-26 heavy atoms were randomly selected from the ZINC[18] database.

To allow shape analysis, low-energy conformations were determined for all compounds using CORINA.

Initially, the three principal moments of inertia (PMI) were determined each compound, which were then used to calculate two normalised PMI values.[19] These data are presented in the form of a triangular plot (Figure 3) in which the vertices are defined by rod, disk and spherical shapes. The analysis showed that the virtual library derived from the scaffolds **10l-u** was significantly more three-dimensional than most of the commercially-available compounds selected from the ZINC database.

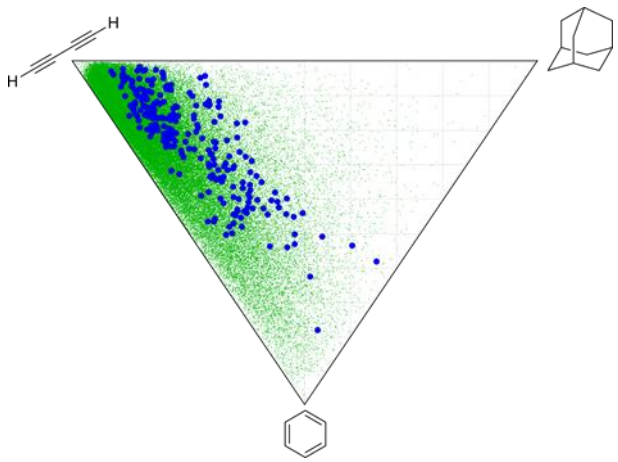
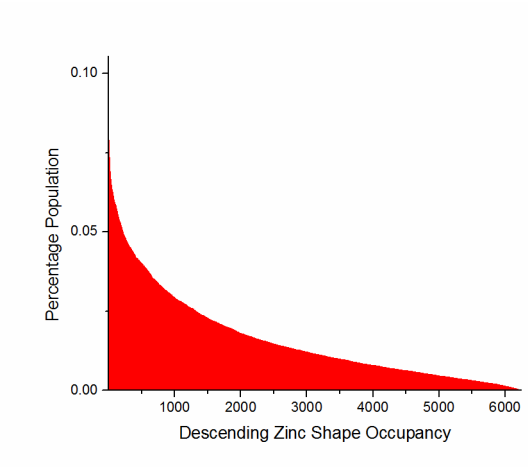


Figure 3 Principal moment of inertia analysis of small molecules. The two normalised PMI values are shown, both for the 338 lead-like compounds derived from the scaffolds **10l-u** (see Scheme 8) (blue, enlarged for clarity) and ~100,000 compounds derived from the ZINC database (green).

A



B

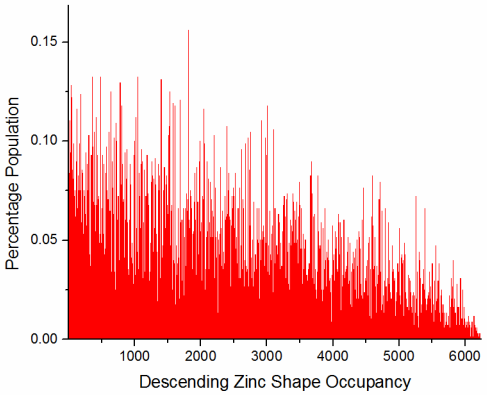


Figure 4 Shape-diversity of lead-like small molecules. The proportion of compounds that have similar shape to each reference shape is shown. The reference shapes are ordered by the proportion of the ~100,000 compounds from the ZINC database that map onto each shape. Panel A: Mapping of ~100,000 compounds from the ZINC database. Panel B: Mapping of 338 lead-like compounds derived from the scaffolds **10l-u**.

Secondly, a more sophisticated shape analysis was undertaken using the ROCS (Rapid Overlay of Chemical Shapes) tool. Here, each compound was compared with a set of reference shapes. The set of reference shapes, generated using an established procedure,[20] describes the shape diversity of both the 338 lead-like compounds within the virtual library and the ~100,000 compounds within the ZINC database.** The shape of each compound was then compared to that of each reference shape and, using a shape Tanimoto cut-off of 0.7, the number of compounds that match each reference shape recorded (Figure 4). Crucially, the 338 lead-like compounds based on the scaffolds **10l-u** target a large number of the reference shapes, including many that are targeted poorly by the ~100,000 compounds from the ZINC database (compare Panels A and B). The shapes of compounds based on the scaffolds **10l-u** are therefore diverse, and complement those of commercially-available compounds of similar size.

Conclusions

In summary, an approach to the synthesis of diverse heterocyclic scaffolds has been developed and exemplified. The modular approach involved ring-opening of cyclic sulfamidates with hydroxy sulfonamides, followed by cyclisation. Crucially, by variation of the combinations of building blocks used, it was possible to vary the ring size, substitution and configuration of the resulting heterocyclic scaffold.

The synthetic approach was exemplified in the synthesis of a range of heterocyclic scaffolds (**10l-u**). The scaffolds were carefully designed such that, after decoration, many small molecules with lead-like molecular properties could be obtained. A virtual library of small molecules was enumerated

from combinations of the deprotected scaffolds and a range of exemplar medicinal chemistry reagents for amine decoration. Remarkably, ~34% of the resulting virtual compounds had lead-like molecular properties. These lead-like compounds were shown to complement the three-dimensional shape of commercially-available compounds of similar size. Thus, the modular synthetic approach was exemplified in the synthesis of lead-like molecular scaffolds. Lead-like small molecules based on these scaffolds would likely complement those found in extisting small molecule screening collections.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

‡ Deceased.

¶ In a recent survey, the vast majority of 4.9M commercially-available compounds (>99%) and compounds reported in the synthetic chemistry literature (~98%) failed at least one of the following filters: $-1 < \text{clogP} < 3$; $14 \leq$ heavy atoms ≤ 26; number of aromatic rings, *n*Ar, ≤ 3; absence of specific chemically-reactive and redox-active groups (ref. 1).

‖ Determined by substructure searches of the ZINC and ChEMBL databases using Pipeline Pilot version 8.5 (Accelrys).

** Each pair of reference shapes has a distinct shape with shape Tanimoto similarity score < 0.8 (calculated using ROCS).

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