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Modular synthesis of thirty lead-like scaffolds suitable for CNS drug discovery†

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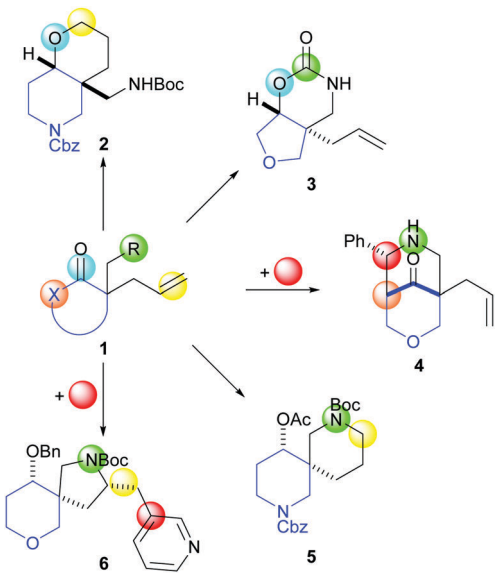
A modular synthetic approach was developed that yielded thirty diverse lead-like scaffolds suitable for CNS drug discovery.

Controlling molecular properties is a challenge that is intrinsic to drug discovery.[1] The challenge is intensified in central nervous system (CNS) programmes in order that CNS drugs are able to cross the blood–brain barrier.[2] The properties of drugs differ from those of high-quality lead molecules since molecular weight, lipophilicity and complexity tend to increase during optimisation.[3] Sourcing large numbers of lead-like screening compounds[4] is, however, a significant challenge that is heightened by the limited scaffold diversity of historically explored chemical space.[5] To address this challenge, the development of new synthetic methods to support discovery applications is being increasingly informed by prospective molecular property, diversity and novelty analyses.[6,7] To facilitate the exploration of lead-like space for CNS drug discovery,[8] we recently adapted a multi-parameter optimisation (MPO) system[8b] for scoring CNS drugs.[9] We have now exploited our MPO scoring system to guide the development and exemplification of a unified synthetic approach to diverse sp^3-rich[10] lead-like scaffolds suitable for CNS drug discovery.[11] In addition, the approach was designed to yield scaffolds adhering to accepted CNS design principles: small and rigid scaffolds[8a] that could yield screening compounds lacking functionality that could contribute to poor permeability and high efflux (*e.g.* carboxylate and sulfonyl groups and multiple amides, basic centres and hydrogen bond donors).[8e]



Scheme 1 Envisaged approach for the synthesis of diverse lead-like scaffolds.

These characteristics were largely captured in our filtering and scoring process.

Our synthetic approach (Scheme 1) exploits cyclisation precursors **1** with an embedded ring system (blue) and up to four functional group handles (green, light blue, beige and yellow blobs). It was envisaged that product scaffolds would be formed by reaction between pairs of functional groups, in some cases in conjunction with an external reactant (red). Crucially, the approach should result in significant product scaffold diversity including fused (light blue to yellow *e.g.* **2**; light blue to green *e.g.* **3**), bridged (green to beige *e.g.* **4**) and spirocyclic (green to yellow *e.g.* **5** and **6**) ring systems.

A range of cyclisation precursors **1** was prepared (Scheme 2). For example, reaction of the lithium enolate of **7** with the carbonyl imidazole **8** (→ **9**),[12] and base-catalysed reaction with the α-NHBoc sulfone **10**, gave the β-keto ester **11**; Pd-catalysed

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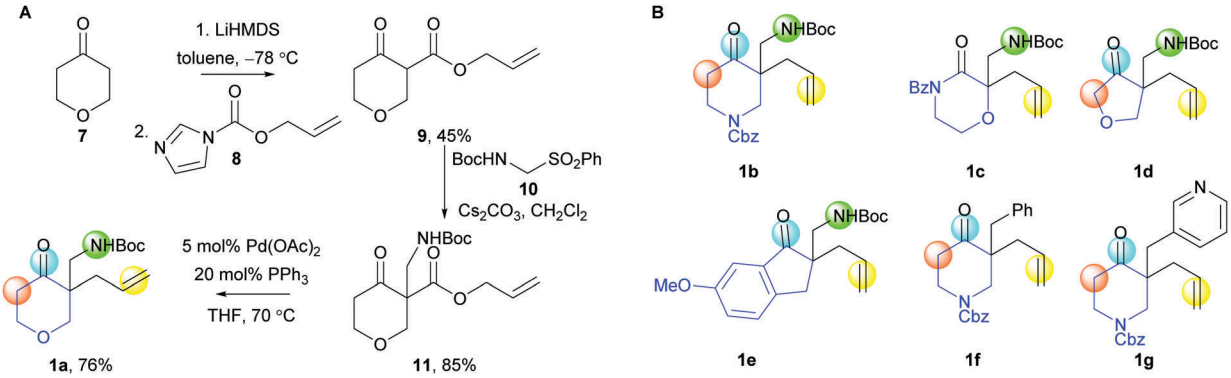
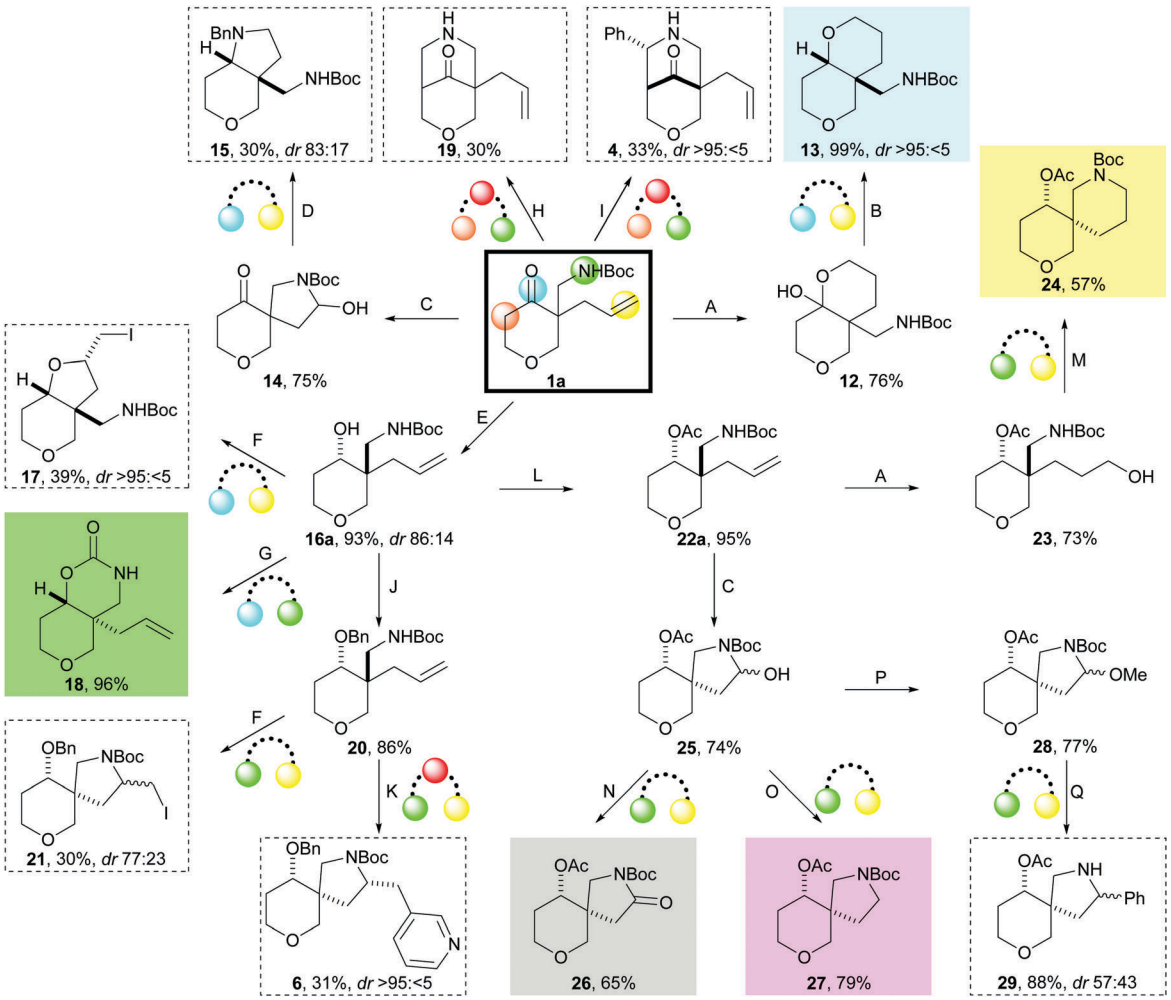


Scheme 2 Synthesis of the cyclisation precursors **1**. Panel A: Synthesis of **1a**. Panel B: Other cyclisation precursors prepared (see ESI†).

decarboxylative allylation[13] then gave the exemplar cyclisation precursor **1a** (panel A).

A toolkit of cyclisations was developed using the exemplar substrate **1a** (Scheme 3). Initially, cyclisations to give fused

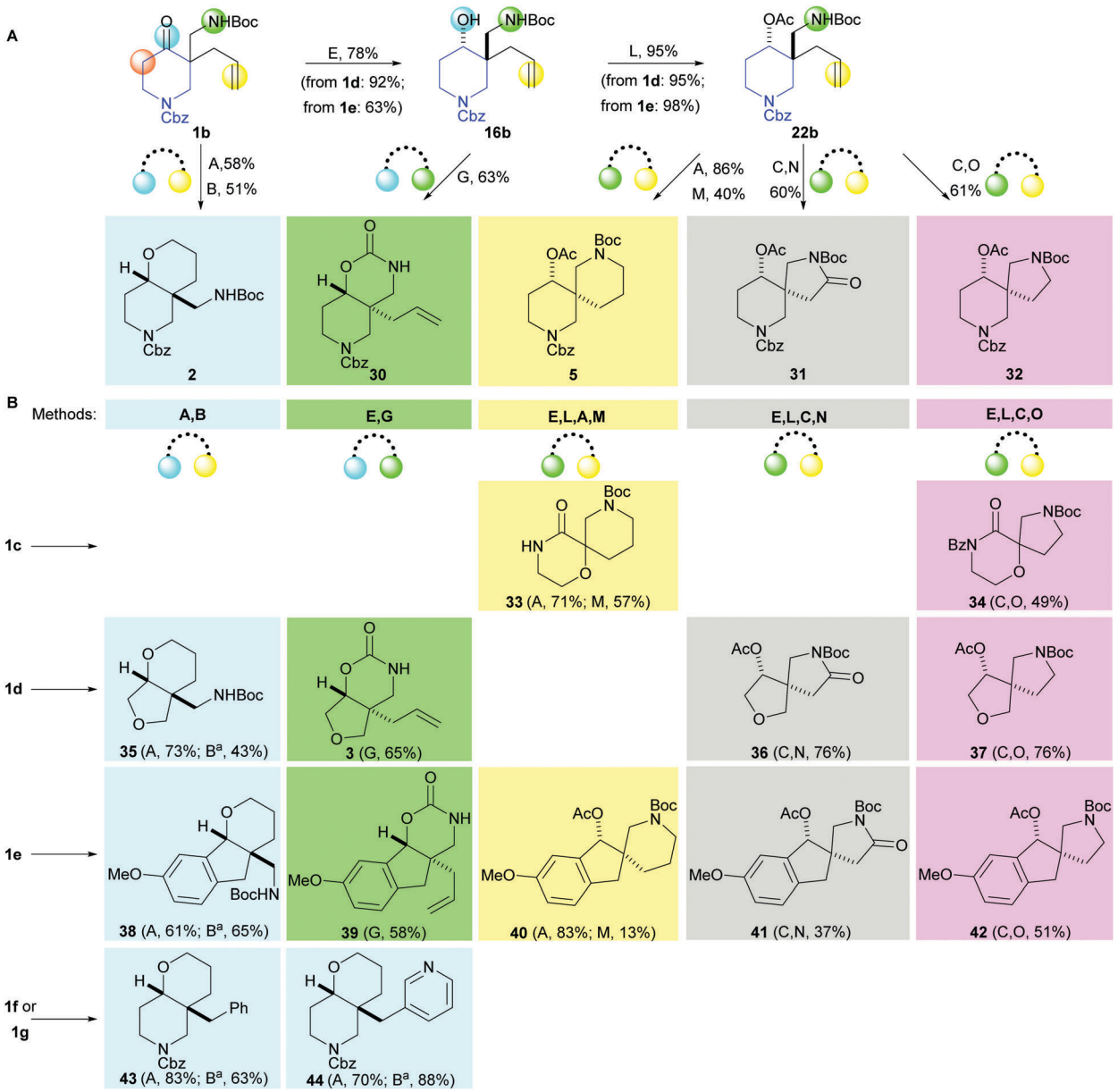


Scheme 3 Identification of cyclisations for the synthesis of lead-like scaffolds using the precursor **1a** (bold box). Scaffolds prepared using prioritised (coloured background; see Scheme 4) and other (dashed boxes) methods are shown. The functional groups that react to form rings are denoted by colour. Methods: A: disiamylborane, THF, 0 °C then $NaBO_3{\cdot}4H_2O$, THF–H_2O; B: Et_3SiH, TFA, CH_2Cl_2 then Boc_2O, Et_3N, CH_2Cl_2; C: O_3, CH_2Cl_2, –78 °C then Me_2S, CH_2Cl_2; D: $BnNH_2$, $NaBH(OAc)_3$, CH_2Cl_2; E: $^iBu_2AlH$, CH_2Cl_2, –78 °C; F: I_2, $NaHCO_3$, MeCN; G: ^tBuOK, THF, 0 °C; H: paraformaldehyde, TFA, MeOH, 65 °C; I: PhCHO, TFA, MeOH, 65 °C; J: NaH, BnBr, cat. Bu_4NI, THF, 0 °C; K: 3-bromopyridine, 5 mol% $Pd(OAc)_2$, 10 mol% DPE-Phos, Cs_2CO_3, dioxane, 105 °C; L: Ac_2O, pyridine; M: MsCl, Et_3N, CH_2Cl_2 then TFA, CH_2Cl_2 then Et_3N, CH_2Cl_2 then Boc_2O, Et_3N, CH_2Cl_2; N: PDC, celite, CH_2Cl_2; O: $NaBH(OAc)_3$, AcOH; P: cat. TsOH, MeOH; Q: PhMgBr, CuBr·Me_2S, $Et_2O{\cdot}BF_3$, Et_2O, 0 °C.

scaffolds were investigated that involved the ketone (light blue) and either the alkene (yellow) or the Boc-protected amine (green) in the cyclisation precursor **1a**. Hydroboration–oxidation of **1a** gave the hemiacetal **12** which was reduced (Et_3SiH, TFA) to give, after reprotection, **13** as a single diastereomer. Ozonolysis of **1a** gave the hemiaminals **14** which, on treatment with benzylamine and $NaBH(OAc)_3$, underwent double reductive amination to yield **15** as a 83 : 17 mixture of diastereomers. Alternatively, reduction of the ketone **1a** with $^{i}Bu_2AlH$ gave the corresponding secondary alcohol **16a** which iodocyclised to give **17** with high diastereoselectivity. Finally, treatment of the alcohol **16a** with ^{t}BuOK gave the fused bicyclic carbamate **18**.

Cyclisations between the distal α carbon (beige) and the Boc-protected amine (green) yielded bridged scaffolds. Thus, intramolecular Mannich reaction[14] with either formaldehyde (→ **19**) or benzaldehyde (→ **4**) gave the bridged scaffolds.

Finally, cyclisations between the Boc-protected amine (green) and the alkene (yellow) in **1a** gave spirocyclic scaffolds. Iodocyclisation of benzyl-protected **20** gave **21** (dias: 77 : 23), whilst Pd-catalysed aminoarylation[15] with 3-bromopyridine gave the spirocycle **6**. Alternatively, hydroboration–oxidation of acetyl-protected **22a**, followed by sulfonylation and cyclisation, gave, after reprotection, the spirocycle **24** in 57% overall yield. Finally, ozonolysis of **22a** gave a mixture of hemiaminals **25** that



Scheme 4 Eighteen additional scaffolds prepared using the prioritised cyclisation toolkit. Standard methods: A: disiamylborane, THF, 0 °C then $NaBO_3{\cdot}4H_2O$, THF–H_2O; B: Et_3SiH, TFA, CH_2Cl_2 then Boc_2O, Et_3N, CH_2Cl_2; C: O_3, CH_2Cl_2, −78 °C then Me_2S, CH_2Cl_2; E: $^{i}Bu_2AlH$, CH_2Cl_2, −78 °C; G: ^{t}BuOK, THF, 0 °C; L: Ac_2O, pyridine; M: MsCl, Et_3N, CH_2Cl_2 then TFA, CH_2Cl_2 then Et_3N, CH_2Cl_2 then Boc_2O, Et_3N, CH_2Cl_2; N: PDC, celite, CH_2Cl_2; O: $NaBH(OAc)_3$, AcOH. See ESI† for diastereoselectivities. [a] See ESI† for details of method variations.

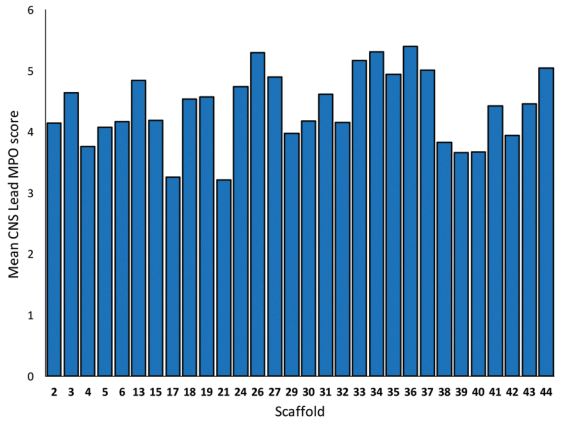


Fig. 1 Mean CNS lead MPO scores of virtual compounds generated from the thirty prepared scaffolds and one or two decorations with exemplar medicinal chemistry capping groups (see ref. 9 and ESI† for details). Individual compounds received an MPO score for CNS lead-likeness on a 0.3–6 scale (see text).

could be converted into three different spirocyclic scaffolds: oxidation with PDC gave the γ-lactam **26**; reduction with $NaBH(OAc)_3$ in AcOH gave **27**; and conversion into the aminals **28** and treatment with PhMgBr and $CuBr{\cdot}Me_2S$ gave **29**.

In total, twelve scaffolds[16] were prepared from the precursor **1a** using the toolkit of cyclisation reactions. High scaffold diversity was possible, with product scaffolds based on fused, spiro and bridged bicyclic ring systems.

The toolkit of cyclisations was exploited in the synthesis of additional scaffolds by changing the precursor **1** (Scheme 4). Product scaffolds were selected on the basis of the potential of their derivatives to serve as high-quality leads for CNS drug discovery.[9] Thus, potential scaffolds were decorated once or twice with exemplar capping groups, and the CNS lead-likeness of the resulting virtual compounds scored (see ref. 9 and ESI†). Thus, desirability scores (0.05–1) were determined for six properties (clog*P*; clog*D* at pH 7.4; pK_a; number of H bond donors; molecular weight; and topological polar surface area), and summed to give a CNS Lead MPO score (0.3–6) (Fig. 1). Lead-like scaffolds for CNS drug discovery would have many derivatives with high ($> \sim 4$) CNS Lead MPO scores. In addition, the five cyclisations that had proceeded in high yield and diastereoselectivity with **1a** were prioritised (see Scheme 3).

Remarkably, our synthetic approach was highly modular. By varying both the precursor (**1a–g**) and the cyclisation, it was possible to vary independently the rings in product scaffolds.[17] The approach was also highly efficient, delivering 30 scaffolds in a total of 51 steps from the precursors **1a–g**.[18] We note that, in addition to specific application in CNS drug discovery, simple derivatives of scaffolds would be highly distinctive fragments with suitable properties for fragment-based discovery.[19]

In conclusion, a highly modular and efficient approach for the synthesis of structurally diverse molecular scaffolds was developed. Crucially, it was demonstrated that independent variation of the rings within the scaffolds was possible, enabling the synthesis of thirty diverse and lead-like molecular scaffolds suitable for CNS drug discovery programmes. We thank Takeda, the University of Leeds and EPSRC (EP/N025652/1) for funding, and Dr Andrew Ayscough for discussions.

Conflicts of interest

There are no conflicts to declare.

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