Diastereoselective Synthesis of Highly Substituted, Amino- and Pyrrolidino-Tetrahydrofurans as Lead-like Molecular Scaffolds

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Abstract. A series of highly substituted tetrahydrofurans (THFs), decorated with modifiable 2-aryl, 3-carboxy and 4-amino substituents, has been prepared for biological evaluation within the European Lead Factory. Diastereoselective reductive amination of pre-functionalised 4-oxofurans, readily prepared from cinnamate esters via oxa-Michael/Dieckmann annulation, provided the requisite THF cores on gram scale with three contiguous stereocentres, including full substitution at C-3. In a second series, a pyrrolidine ring was fused to the same oxofuran scaffold via an intramolecular reductive amination, inverting the configuration at C-4 relative to the other ring substituents. The resulting compounds, which displayed desirable physical properties as lead-like scaffolds, were derivatised into a small library of 24 compounds, demonstrating their ability to serve as starting points for drug discovery. Ultimately, this chemistry enabled the preparation of 1948 THF-containing compounds for inclusion in the Joint European Compound Library.

Introduction

The search for new bioactive small molecules lies at the heart of modern drug discovery programmes. In addition, such molecules serve as useful probes for, and modulators of, the activity of a range of proteins. In the quest for these high value small molecules as potential medicines or biological tools,[1–3] natural products often play a key role. For example, in the 30 years

to 2010, an estimated 26% of new medicines were either natural products or derivatives thereof, with a further 13% possessing a natural product-like pharmacophore.[4] Natural products have also inspired a number of approaches to replicate the key structural features of these often densely functionalised small bioactive molecules, and this has been aided by analysis and charting of the chemical space populated by medicinally active natural products.[5,6] In attempting to define "natural product likeness" the analysis identified oxygen-containing heterocycles as a major contributor to chemical space for drug discovery.[5,6]

Within the large family of oxygen heterocycle-containing natural products that occupy biologically relevant chemical space,[5] the tetrahydrofuran (THF) ring system assumes an important place. It is found in myriad natural products,[7] biologically active small molecules[8] and FDA-approved drugs.[9] The significance of the THF moiety in medicinal chemistry continues to inspire the development of methods for the *de novo* synthesis of functionalised variants and THF-containing natural products,[10,11] as well as methods for selective C–H functionalisation of the ring itself.[12]

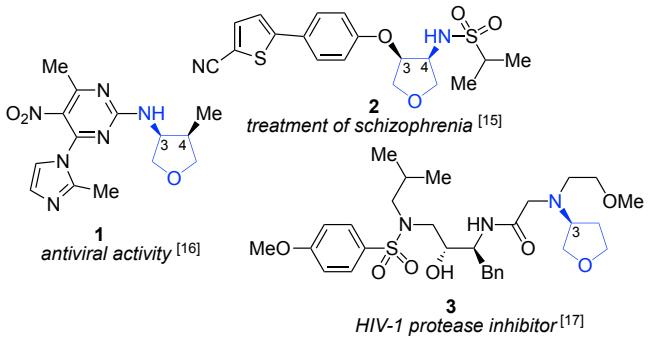
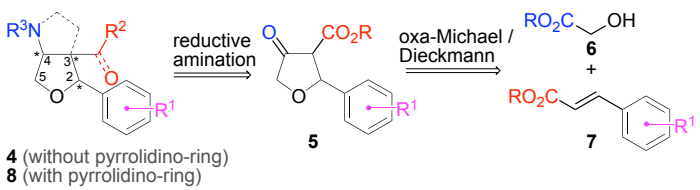


Figure 1. Exemplar amino-substituted THFs with biological activity.[15–17]

As part of our contributions[13] to the European Lead Factory (ELF) drug discovery initiative,[14] we were interested in the design and synthesis of new THF scaffolds bearing an amino substituent on the heterocycle backbone (i.e., at C-3 or C-4). In addition to serving as a convenient template for library synthesis, the biological activity of amino-THFs is well precedented (e.g., compounds **1**–**3**,

Figure 1).[15–17] In the design of a lead-like scaffold[18] incorporating this structural feature that fulfilled the requirements of the ELF,[14] we identified THF **4** as our principal target (Scheme 1). In addition to the key amino group at C-4, a carboxylic acid or derived functionality (e.g., amide or hydroxymethyl) was proposed at C-3 as a second major point for orthogonal diversification. Notably, despite the intense general interest in THF-based amino acids,[19] THFs containing an embedded β-amino acid (or derivative) of equivalent constitution to compound **4** remain underrepresented in the literature.[20] To complete our scaffold design, an aryl group was incorporated at C-2 to increase the lead-likeness,[21] stereochemical complexity[22] and diversity potential of the scaffold.

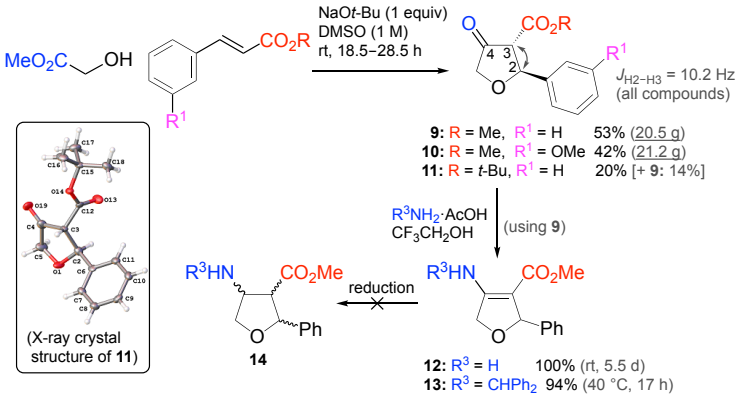
Given that THF **4** is a purely synthetic scaffold intended for high-throughput screening, we did not target a specific stereoisomer at the outset. However, to ensure synthetic tractability, it remained of prime importance to establish a synthetic pathway capable of controlling the relative stereochemistry at three contiguous centres (C-2, C-3, C-4) with high fidelity, in favour of one of the four possible diastereomers. To gain access to our primary target, we envisioned a reductive amination using 4-oxofuran **5**, which itself could arise from a tandem oxa-Michael/Dieckmann condensation using readily available starting materials, namely glycolate **6** and cinnamate **7** (Scheme 1). The β-keto ester functionality embedded in 4-oxofuran **5** was also expected to endow flexibility to produce C-3 fully-substituted derivatives via alkylation,[23] including introduction of an aminoethyl tether, allowing reductive cyclisation to give our second THF-containing target - the pyrrolidino-fused bicycle **8**, thereby creating molecular complexity from simple starting materials in a few steps.



Scheme 1. General synthetic strategy to target THF scaffolds.

Results and Discussion

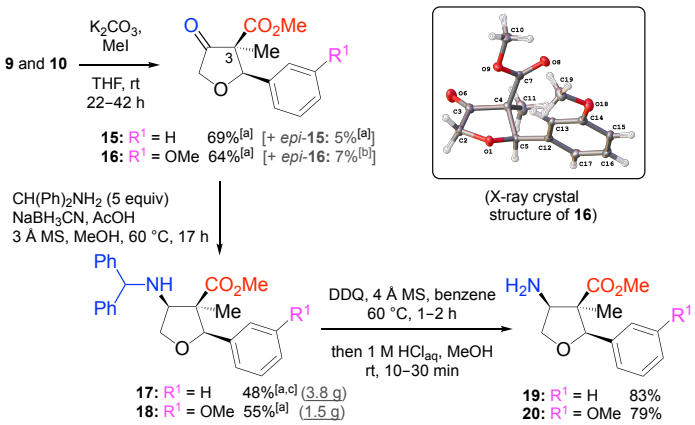
The oxa-Michael/Dieckmann annulation of the type shown in Scheme 1 is well established using acrylate esters or β-alkyl-acrylate esters as Michael acceptors,[24[but there is little precedent for the use of less electrophilic cinnamate esters[25] in such a process to provide an aryl group at C-2.[26] After considerable optimisation (base/solvent/temperature/time/R group in Scheme 2), we arrived at a practical procedure to obtain the required oxo-furans **9** and **10** on decagram scales in reasonable yields (Scheme 2). Our choice to prepare the *meta*-methoxy derivative **10** was based on the installation of an activating/directing group to enable potential late-stage electrophilic aromatic substitution, while avoiding compromising the stability of the embedded benzylic ether in THF **4** through mesomeric effects. During reaction optimisation, a mixed ester reactant combination[24b] of *tert*-butyl cinnamate and methyl glycolate was also investigated, which gave a low yield of THF **11** (20%) amidst complications from partial product transesterification to methyl ester **9** (Scheme 2). Nonetheless, an X-ray structure of the crystalline *tert*-butyl ester **11** enabled assignment of the *trans* stereochemistry to all annulation products by comparison of the J_{H2-H3} coupling constant (10.2 Hz for compounds **9**–**11**).



Scheme 2. Synthesis of key intermediates **9** and **10** and attempted elaboration of **9** to β-amino ester **14**.

Installation of the requisite C-4-amino group was investigated via stepwise formation of a β-enamino ester and subsequent reduction (Scheme 2). Our initial attempt to prepare an enamine from β-ketoester **9** was carried out with ammonium acetate in methanol, giving a 19% yield of

enamine **12** due to predominant C-3–C-4 bond cleavage by methanol-mediated retro-Dieckmann reaction (Scheme S1, SI). This competing side reaction was completely suppressed by switching to the less nucleophilic trifluoroethanol as solvent, giving a quantitative yield of enamine **12** and, under similar conditions, a 94% yield of benzhydryl-protected analogue **13** (Scheme 2). These compounds were obtained in high purity after a simple aqueous work-up and were indefinitely stable to room temperature storage. Under analogous conditions, three additional enamines were prepared from β-ketoester **9** using functionalised amines, all in excellent yields (Scheme S2, SI). Despite having efficient access to enamines **12** and **13**, we were, however, unable to affect their reduction to the corresponding β-amino esters **14** under standard protocols (Scheme 2),[27] resulting in decomposition and/or complex mixtures that did not contain the desired products (for specific conditions attempted, see Table S1, SI). We thus turned our attention to alkylation of β-ketoesters **9** and **10** with the aim of preparing C-3 fully-substituted derivatives. Although this would increase the steric encumbrance of the ketone, we envisioned that removing (enamine) conjugation with the ester would increase the reactivity of a derived imine towards protonation and reduction. Accordingly, 3-methyl derivatives **15** and **16** were prepared by treatment of β-ketoester **9** and **10** with iodomethane in the presence of potassium carbonate (Scheme 3). This alkylation showed reasonable diastereoselectivity (*ca.* 7:1 ratio of diastereomers after work-up) with preference for methylation *trans* to the aryl group. In both cases the major diastereomer was efficiently separated from the minor epimer by flash chromatography and all four compounds (**15**, **16** and *epi*-**15**/**16** – epimeric at C-3) were fully characterised. The relative stereochemistry of THF **16** was determined at this stage by X-ray crystallography.

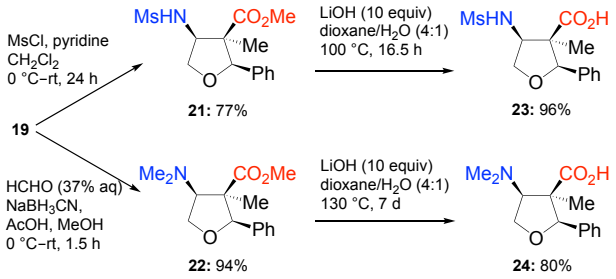


Scheme 3. Synthesis of β-amino esters **19** and **20**. [a] Isolated dr = >20:1. [b] Isolated dr = 8:1. [c] Excess $CH(Ph)_2NH_2$ was recovered as the hydrochloride salt (3.9 equiv recovered out of 5.0 equiv used).

Ketones **15** and **16** proved to be challenging substrates for the key reductive amination step and most known methods attempted were unsuccessful in forming the desired products (e.g., 4-methoxybenzylamine with $NaBH(OAc)_3$/1,2-dichloroethane[28], benzhydrylamine with $NaBH_4$/trifluoroethanol[29] or $NaBH_4$/Ti(O*i*-Pr)$_4$/THF[30]). Ultimately, by heating the ketones and an excess of benzhydrylamine (5 equiv) in methanol under acidic conditions with sodium cyanoborohydride as reductant, amines **17** and **18** were obtained in acceptable yields of 48% and 55%, respectively (Scheme 3).[31] The excess benzhydrylamine could be conveniently recovered as the hydrochloride salt if desired, as demonstrated in the former case (3.9 equiv recovered). Most importantly, this amination protocol was amenable to multigram scale and occurred with complete diastereoselectivity for both examples to give the all-*cis* relationship between the three contiguous stereocentres. In order to avoid potential chemoselectivity issues arising from the embedded benzylic ether, we avoided the use of hydrogenolysis or strongly acidic conditions for removal of the benzhydryl group. Thus, oxidative removal of the benzhydryl group proceeded smoothly with DDQ,[32] providing amines **19** and **20** in 83% and 79% yields, respectively (Scheme 3).

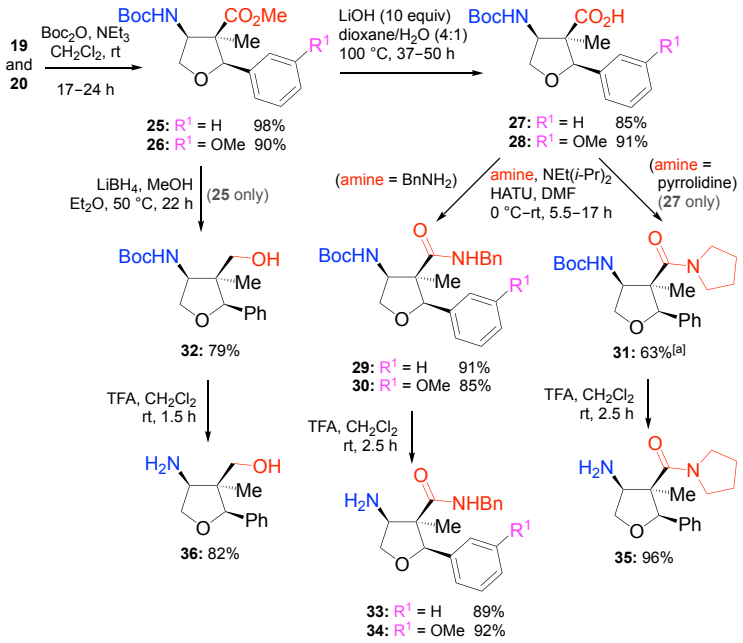
With gram quantities of the amino esters **19** and **20** in hand, the synthesis of our first set of core scaffolds (represented by THF **4** in Scheme 1) was undertaken. Firstly, the divergent preparation of carboxylic acids was examined via sequential *N*-functionalisation and ester saponification (Scheme

4). Thus, amine **19** was treated with methanesulfonyl chloride and separately, with formaldehyde in a double reductive methylation, giving sulfonamide **21** and tertiary amine **22** in 77% and 94% yields, respectively. Subsequent saponification of the sterically hindered esters was not trivial, but was achieved with excess lithium hydroxide at elevated temperatures, without notable decomposition. Under these conditions, carboxylic acid **23** was obtained in 96% yield after heating for 16.5 h. Ester **22** was more resilient to hydrolysis, likely due to inductive carbonyl deactivation by the basic amino group. Nonetheless, the zwitterionic amino acid **24** was isolated in good yield (80%) after prolonged heating.



Scheme 4. Synthesis of carboxylic acids **23** and **24**.

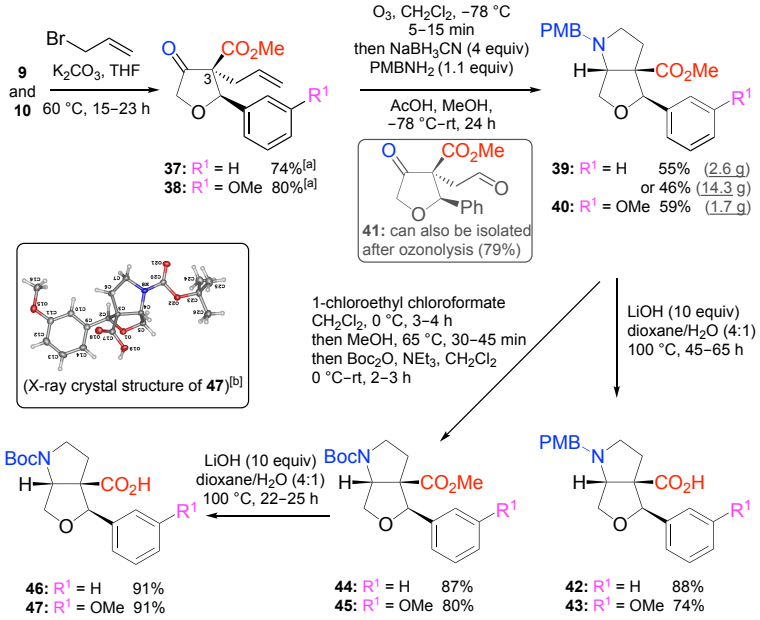
To retain the primary amino group in a complementary set of scaffolds, amino esters **19** and **20** were Boc-protected to enable manipulation of the ester moiety (Scheme 5). Thus, the protected derivatives **25** and **26** were saponified under the previously developed conditions to give carboxylic acids **27** and **28**, which were coupled with benzylamine and pyrrolidine as representative amines under the action of HATU. Notably, these reactions proceeded at room temperature and afforded good–excellent yields of amides **29**–**31**, despite the sterically encumbered nature of the acid. Separately, alcohol **32** was produced (79% yield) by reduction of ester **25** with lithium borohydride. Deprotection of penultimate compounds **29**–**32** with TFA proceeded smoothly in all cases, giving amines **33**–**36** in 82–96% yields.



Scheme 5. Synthesis of amines **33**–**36**. [a] The azabenzotriazolyl ester was also isolated in 7% yield.

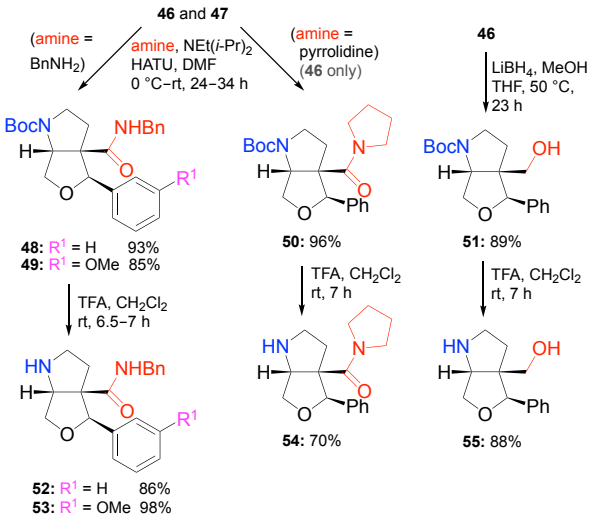
As discussed earlier, our proposed synthetic approach to pyrrolidino-fused analogues **8** relied on the previously prepared oxo-furans (**9** and **10**) as common precursors, to enable annulation of the second ring via intramolecular reductive amination (Scheme 1). To build-in the required tether, C-3-allylation of β-ketoesters **9** and **10** was carried out with allyl bromide under analogous conditions to methylation (K_2CO_3, THF, Scheme 6). Although heating was required to ensure adequate reaction rates, the desired products **37** and **38** were formed in good yields and excellent diastereoselectivity (dr = ≥20:1 after work-up), with the same stereochemical preference as observed in the methylation, as confirmed through X-ray crystal structures of downstream derivatives **47** (Scheme 6) and **58** (Scheme 8). Using these terminal alkenes (**37** and **38**), a one-pot tandem ozonolysis/double reductive amination procedure was developed using 4-methoxybenzylamine and sodium cyanoborohydride as reductant,[33] enabling the preparation of multigram quantities of pyrrolidino-THFs **39** and **40** in rapid fashion with modest yields (55 and 59%). In this case, the requirement for a *cis*-fused pyrrolidine ring in the 5,5-bicycle overrides the previous stereochemical preference for hydride delivery *trans* to the ester in the intermolecular case (see amine products **17** and **18**, Scheme 3).[34] The highly functionalised, stable aldehyde **41** could also be isolated (79%)

after a modified reductive work-up with triphenylphosphine (see the SI), however, for our purposes, the one-pot reductive amination method proved more practical and gave slightly higher overall yields than a stepwise procedure.



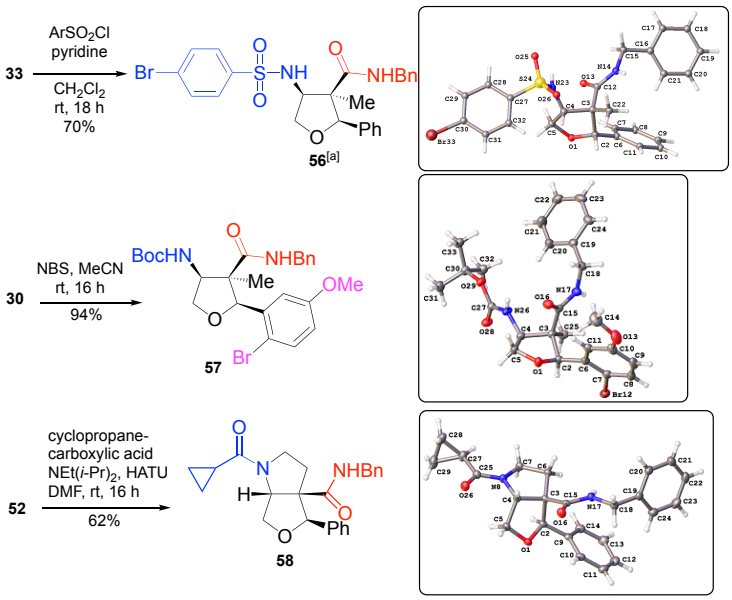
Scheme 6. Synthesis of pyrrolidino-THFs. [a] Product dr (before and after chromatographic purification) = ≥20:1. [b] Depicted as the opposite enantiomer to drawn.

The embedded functional array in the bicyclic products was, by design, analogous to the original THF scaffolds, allowing further manipulations to be performed in a similar manner to previously described as outlined in Schemes 6 and 7. The ester was hydrolysed to zwitterionic amino acids **42** and **43**, which were isolated in 88% and 74% yields, respectively, after precipitation from water at pH 5 (Scheme 6). Alternatively, exchange of the *para*-methoxybenzyl (PMB) group with the Boc group[35] using 1-chloroethyl chloroformate,[36] allowed preparation of Boc-protected amino acids **46** and **47** (Scheme 6), which were readily amenable to amide coupling reactions or reduction with lithium borohydride (Scheme 7). The obtained amides **48–50** and alcohol **51** were cleanly deprotected with TFA to give an additional set of scaffolds **52–55** with an unmasked pyrrolidine nitrogen (Scheme 7).



Scheme 7. Synthesis of amines **52**–**55**.

The relative orientation of the three stereocentres in the monocyclic and bicyclic THF scaffolds was confirmed through X-ray crystal structures of derivatives **56**–**58**, prepared via *N*-sulfonylation, aryl bromination and *N*-acylation, respectively (Scheme 8). Notably, the *cis*-relationship between the amino group and the amide in the monocyclic THF system (i.e., **56** and **57**) compared to the *trans*-arrangement in the bicyclic scaffold (**58**), allows the occupation of distinct chemical space from the N-substituent between the two systems. Further, the facile, regioselective bromination[37] of THF **30** demonstrates the potential of the methoxy group to enable chemoselective late-stage functionalisation of the aryl ring, as mentioned earlier. This halogen could potentially be used in future studies as a handle to explore an additional vector proximal to the THF core via cross-coupling reactions.



Scheme 8. Synthesis and X-ray crystal structures of derivatives **56–58**. [a] The X-ray crystal structure of **56** is depicted as the opposite enantiomer to drawn.

The chemical space distribution of the 12 prepared THF scaffolds relative to molecular weight and AlogP was formulated using the computational model LLAMA[21] (Figure 2; physical properties for each compound are fully documented in Table S2, SI). Each of these core scaffolds retains either a nucleophilic amino group or a carboxylic acid functionality, offering potential to create compound libraries through further derivatisation. As shown in Figure 2, all examples fall within or close to lead-like territory[18] (molecular weight <350, AlogP <3), enabling significant flexibility for derivatisation within Lipinski space (molecular weight <500, AlogP <5). A balanced pharmacokinetic profile is predicted by an average AlogP of 1.7 and topological polar surface area (TPSA) of 59.3 Å^2 (Table S2, SI), suggesting good oral bioavailability[38] while preserving capacity to penetrate cell membranes, including the blood-brain barrier for central nervous system (CNS) targets.[39]

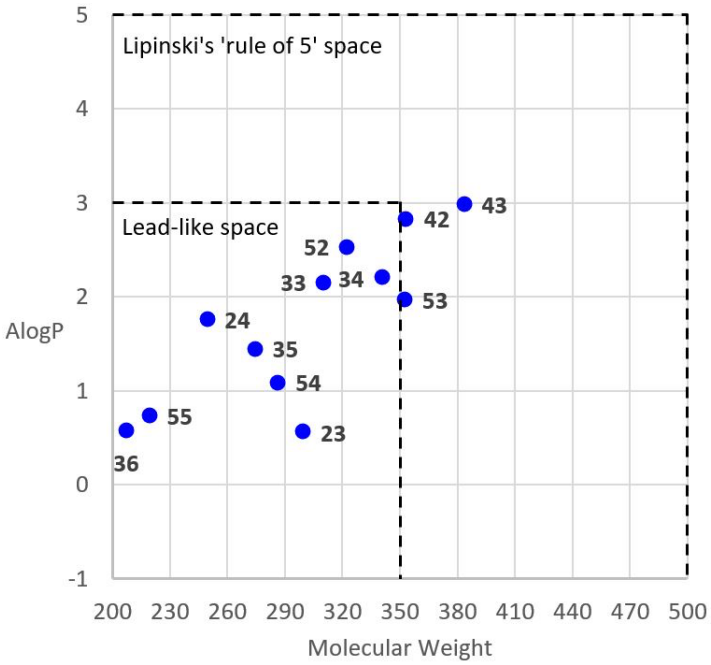


Figure 2. Chemical space distribution of the prepared scaffolds relative to molecular weight and AlogP, generated using LLAMA.[21] Data points are labelled with the corresponding compound numbers.

The principal moments of inertia (PMI)[40] plot of the 12 compounds (Figure 3, generated using LLAMA[21]) shows a good degree of shape coverage with reasonable spherical character, moving away from the predominant rod- or disc-like character observed in commercial fragment libraries[41] and known bioactive compounds.[42] The three-dimensional nature of the THF scaffolds[43] is further supported by an average plane-of-best-fit (PBF)[44] deviation of 1.0 Å (Table S2, SI), which compares favourably with that of the ChEMBL database[45] of published bioactive compounds (average PBF for ChEMBL compounds = 0.6 Å).[42]

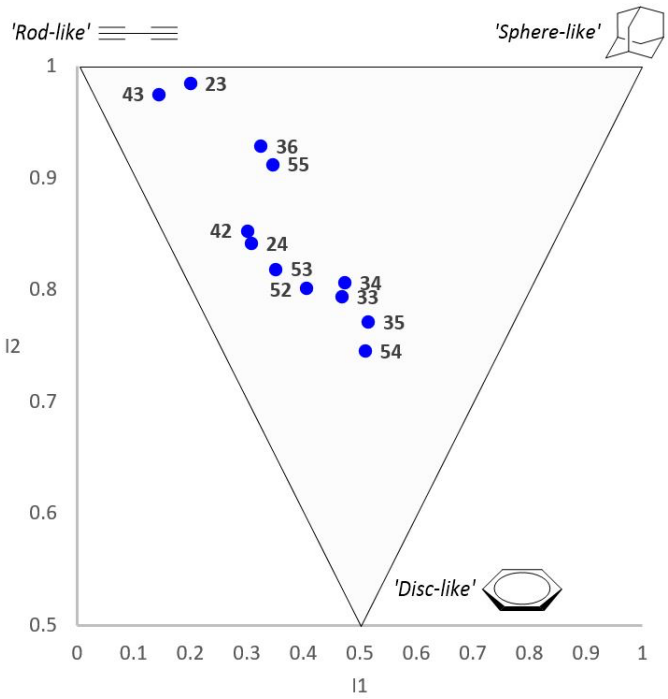


Figure 3. Principal moments of inertia (PMI) plot of the prepared scaffolds, generated using LLAMA.[21] Data points are labelled with the corresponding compound numbers.

To demonstrate the ability to derivatise these THF scaffolds, a small library of 24 compounds (**59**–**82**) was prepared and fully characterised (Figure 4; full details are given in the SI). Standard transformations were utilised including *N*-acylation, *N*-reductive alkylation, *N*-sulfonylation and carboxylic acid-amide couplings. Outside of this compound set (Figure 4), an additional 1948 compounds were prepared and submitted to the Joint European Compound Library (JECL),[46] consisting of 923 derivatives of **4** with an average molecular weight of 403 and an average clogP of 2.0 and 1025 derivatives of **8** with an average molecular weight of 448 and an average clogP of 2.5 (see the SI for further details). These compounds are freely available for target screening to both academic and private researchers through the ELF initiative.[14]

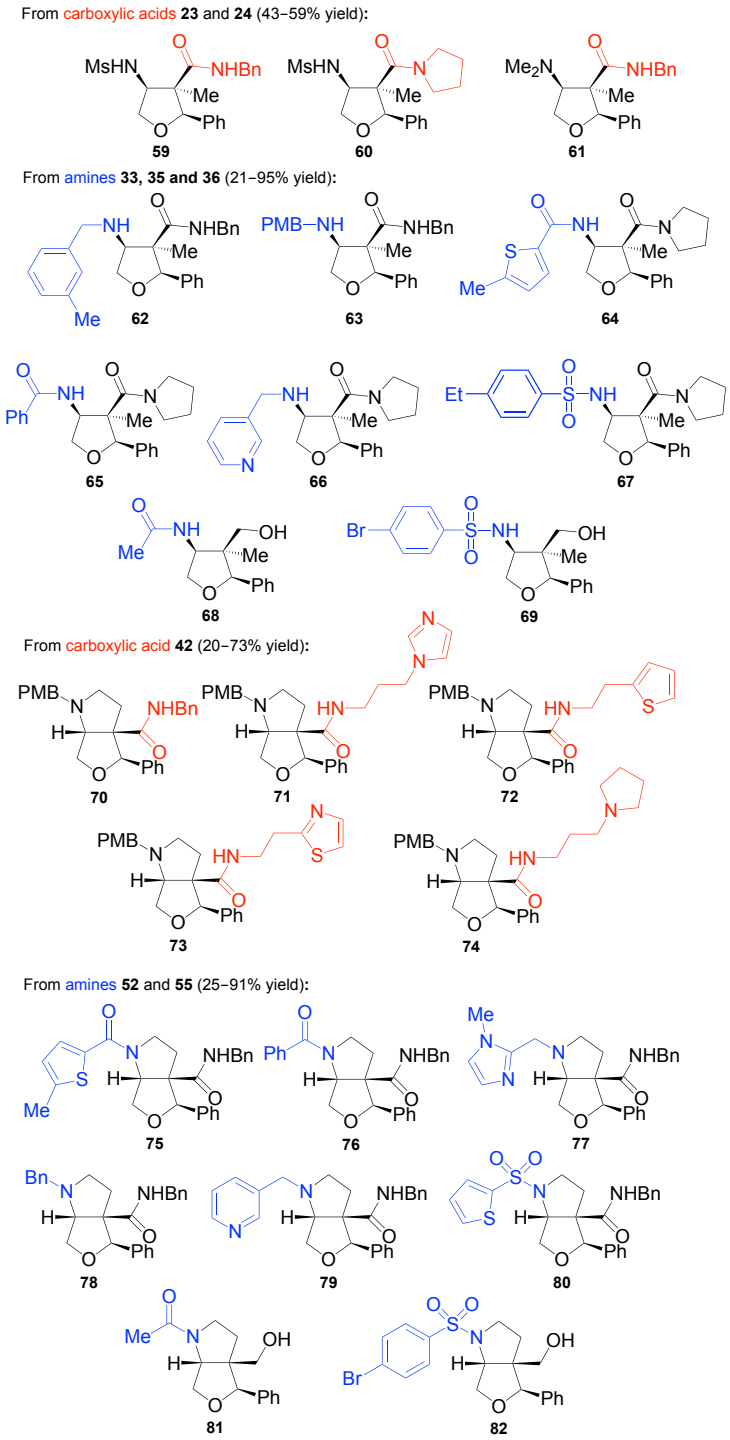


Figure 4. Representative synthetic library prepared from the amine and carboxylic acid THF scaffolds. See the SI for full details.

Conclusions

A series of highly substituted THFs and pyrrolidino-THFs embedded with modifiable 2-aryl, 3-carboxy and 4-amino functionalities has been prepared. Divergent synthetic routes were developed

to access the desired mono- and bicyclic scaffolds via a common 4-oxofuran intermediate, from which inter- and intramolecular reductive aminations, respectively, enabled diastereoselective formation of the key C-4–N bond. These scaffolds were designed with careful consideration of novelty, stereochemical complexity, synthetic tractability and diversity potential, and show promise in drug discovery, as demonstrated by their desirable physical properties and ease of elaboration to diverse compound libraries.

Experimental Section

Full experimental details are given in the SI.

Acknowledgements

The research leading to these results was done within the European Lead Factory and has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no. 115489, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007–2013) and EFPIA companies' in-kind contribution.

Conflict of interest

SMW, WL and CJM declare no conflict of interest. EGM, HVA, CAP, IRS and DH are employees of Sygnature Discovery Ltd.

Keywords: tetrahydrofurans • pyrrolidines • heterocycles • drug discovery • lead-oriented synthesis

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