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Design and synthesis of a fragment set based on twisted bicyclic lactams

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ABSTRACT

Current fragment sets tend to be dominated by flatter molecules, and their shape diversity does not reflect that of the fragments that are theoretically possible. The design and synthesis of a set of bridged fragments containing a bridgehead nitrogen is described. Many of these fragments contain twisted lactams whose modulated electronic properties may present unusual opportunities for interaction with target proteins. The demonstrated novelty, three-dimensionality and molecular properties of the set of 22 fragments may provide valuable, and highly distinctive, starting points for fragment-based drug discovery.

1. Introduction

Over the last 15–20 years, fragment-based discovery has become a mainstream approach in medicinal chemistry.[1] Consequently, guidelines have been formulated to facilitate the assembly of fragment sets that target diverse relevant chemical space.[2] However, current fragment sets tend[3] to be dominated by flatter (generally heteroaromatic) molecules whose shape diversity is not representative of the fragments that are theoretically possible.[4] As a result, significant effort has been invested in the design of fragment sets with higher shape diversity.[3a,d] More three dimensional (3D) fragments have inherently higher molecular complexity which has been argued[5] to result in lower hit rates in fragment screens.[6] Yet, such fragments are likely to offer distinctive opportunities for subsequent growth along specific vectors.

Here, we describe the design and synthesis of a fragment set that is based on a number of bicyclic ring systems containing a bridgehead nitrogen atom. Such ring systems are substructures within the frameworks of a diverse range of alkaloid natural products (see Fig. 1 for examples[7]) which can serve as an inspiration for drug discovery.[8] The geometric constraints imposed by these ring systems can perturb functional group properties and characteristics by restricting or preventing the overlap of the bridgehead nitrogen lone pair with an adjacent π-system, and in the case of twisted amides, parameters have been developed to describe the extent of deformation.[9,10] In extremely twisted amides, for example, the electronic properties of the functional group are more reminiscent of those of unconjugated amino ketones (for examples, see Fig. 2): this is reflected in the electrophilic reactivity of the carbonyl group[10,11] and in the full[12] or partial[13] *N*-protonation of the amide in contrast to the *O*-protonation observed with non-twisted amides. Despite the unusual and distinctive hydrogen-bonding opportunities offered by such motifs, bicyclic lactams have barely been explored in a medicinal chemistry context, and may therefore provide new opportunities in drug discovery.[14]

2. Results and discussion

Our synthetic approach to bridged bicyclic fragments is shown in Scheme 1. Thus, 3-(ω-carboxylate)-substituted piperidines **1** would be lactamised to yield a range of bridged lactams **2** (with variable n and R). It was envisaged that, with appropriate choice of substituent, addition of ring(s) (→ **3**) or functionalisation of the twisted amide (→ **4**) might be possible to yield related scaffolds. Finally, decoration would yield corresponding fragments for addition to a screening set.

2.1. Synthesis of bridged bicyclic lactams

Initially, a range of 3-(ω-carboxylate)-substituted piperidine substrates **7** was prepared (Scheme 2 and Table 1). The reductive aminations between the piperidin-3-one **5** and the amino esters **6a–d** gave the corresponding 3-amino piperidines **7a–d**. Alternatively, condensation of the piperidin-4-one **9** with pyrrolidine gave an enamine that was reacted directly with ethyl acrylate to give

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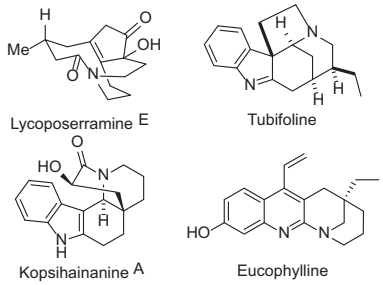


Fig. 1. Ring systems with bridgehead nitrogens embedded in alkaloids.

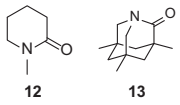
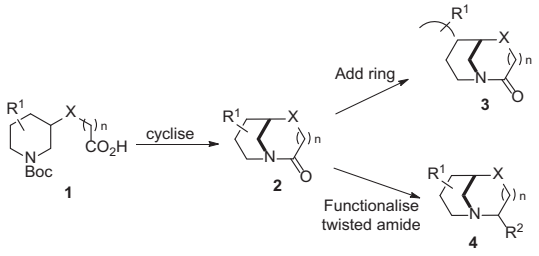
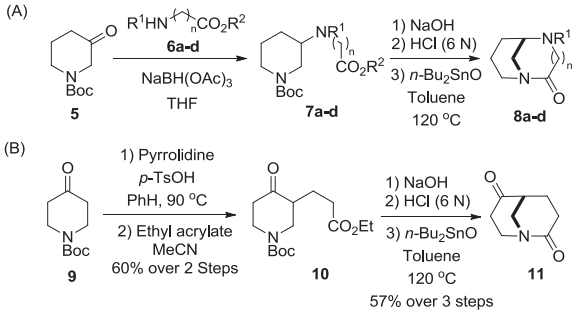


Fig. 2. Unstrained amide **12** and Kirby's most twisted amide **13**.



Scheme 1. Envisaged synthetic approach to bridged bicyclic fragments.



Scheme 2. Synthesis of bridged bicylic lactams (see Table 1).

the 3-substituted piperidin-4-one **10**. Boc deprotection of **7a–d** and **10**, and ester hydrolysis, was followed by Bu_2SnO-mediated cyclisation to give the corresponding lactams **8a–d** and **11**.[15] The approach enabled the synthesis of both bicyclo[3.3.1]nonane and bicyclo[4.3.1]decane bicyclic ring systems in moderate yield. Unfortunately, the approach did not enable the synthesis of the alternate bicyclo[3.2.2]nonane, bicyclo[4.2.2]decane and bicyclo[4.1.1]octane ring systems, presumably owing to increased ring strain in these species. Furthermore, deprotection of benzyl-protected **8a** and **8c** and Cbz-protected **8d** was not successful under a range of hydrogenation conditions (see Fig 3).

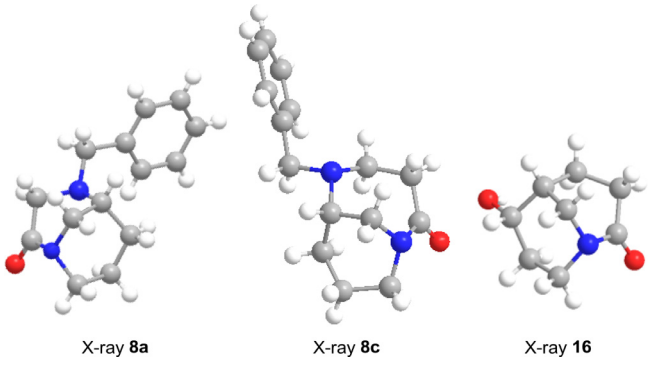


Fig. 3. X-ray crystal structures of **8a**, **8c** and **16**.

The distortion[10] of the bridged bicyclic lactams **8a–d** and **11**, and their derivatives (see below), was assessed. ^{13}C NMR spectroscopy is a valuable technique for investigating amide distortion, with the chemical shift of the carbonyl carbon serving as a sensitive probe of strain (see Fig. 2; unstrained δ-lactam **12**, δ_C: 165 ppm; Kirby's most twisted amide **13**, δ_C: 200 ppm).[11,16] The lactams based on bicyclo[3.3.1]nonane ring systems (e.g. **8a**, **8b** and **11**; amide carbonyl δ_C: 181–185 ppm) were markedly more strained than those (e.g. **8c** and **8d**; amide carbonyl δ_C: 174–177 ppm) based on bicyclo[4.3.1]decane ring systems.

Strain was also assessed by analysis of the X-ray crystal structures of **8a** and **8c** and a derivative of **11** (lactam **16**, see below), and determination of standard amide distortion parameters (Supporting Information). For example the sum of the bond angles around the amide nitrogen (Θ) deviated further from 360° in the bicyclo[3.3.1]nonanes (**8a**: Θ = 337°; **16**: Θ = 341°) than in the bicyclo[4.3.1]decane ring system **8c** (Θ = 349°).

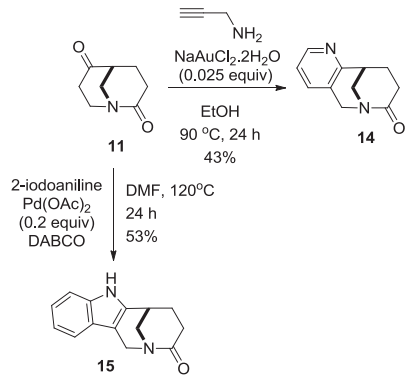
2.2. Synthesis of hetaryl-annulated scaffolds

The potential to access alternative scaffolds by annulation of heteroaromatic rings by exploiting the ketone in bicyclic lactam **11** was then explored (Scheme 3). Thus, reaction of the ketone **11** and propargylamine, catalyzed by 2.5 mol% $NaAuCl_4$,[17] gave the related pyrido-fused lactam **14** in 43% yield. In a similar vein, reaction of **11** with 2-iodoaniline, catalyzed by 20 mol% $Pd(OAc)_2$, gave the indolo-fused lactam **15** in 53% yield.

Table 1
Synthesis of bridged bicyclic lactams (see Scheme 2).

	Intermediate synthesis		Lactam synthesis		
Substrates	Product	Yield,%	Product	Yield[b]%	δ_C[c]
5, **6a** (n = 1; R^1 = Bn; R^2 = Et)	**7a** (n = 1; R^1 = Bn; R^2 = Et)	68	**8a** (n = 1; R^1 = Bn)	46	182.9
5, **6b** (n = 1; R^1 = Me; R^2 = Me)	**7b** (n = 1; R^1 = Me; R^2 = Me)	57	**8b** (n = 1; R^1 = Me)	45	182.6
5, **6c** (n = 2; R^1 = Bn; R^2 = Et)	**7c** (n = 2; R^1 = Bn; R^2 = Et)	72	**8c** (n = 2; R^1 = Bn)	59	176.2
5, **6d** (n = 2; R^1 = H; R^2 = Et)	**7d** (n = 2; R^1 = Cbz; R^2 = Et)	74[a]	**8d** (n = 2; R^1 = Cbz)	52	176.7
9, ethyl acrylate	**10**	60	**11**	57	182.4

[a] Isolated after Cbz protection: CbzCl (1.1 eq.), $NaHCO_3$ (6.0 eq.) in CH_2Cl_2.
[b] Yield over 3 steps.
[c] Lactam carbonyl.



Scheme 3. Synthesis of hetaryl-annulated ring systems.

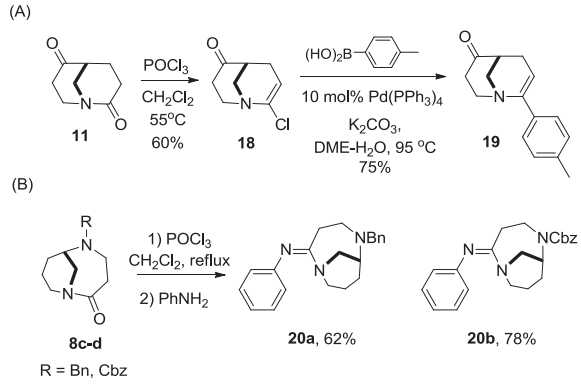
2.3. Synthesis of a diverse fragment set

A range of approaches was exploited to enable decoration at different positions within the bicyclic scaffolds. It was decided to focus on the synthesis of a diverse set of fragments with 17 or fewer heavy atoms and with clogP < 2.5.

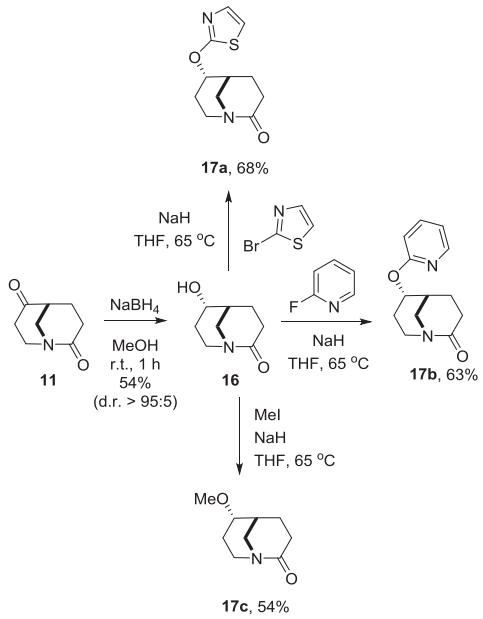
First, we investigated *O*-functionalisation of the alcohol **16** derived from the bicyclic keto lactam **11** (Scheme 4). Treatment of **11** with $NaBH_4$ resulted in attack onto the less hindered face of the ketone to yield the secondary alcohol **16** with >95:<5 diastereoselectivity. Treatment of **16** with NaH, followed by reaction with 2-bromothiazole, 2-fluoropyridine or methyl iodide gave the ethers **17a**, **17b** and **17c** respectively.

Second, we showed that the twisted amide of **11** could also be functionalised (Scheme 5, Panel A). Thus, treatment of **11** with $POCl_3$ gave the stable and isolable chloroenamine **18**. Subsequent Suzuki coupling of the chloroenamine **18** with *p*-tolyl boronic acid gave the enamine **19**.[18] Notably, reaction of the less strained bicyclic lactams **8c** and **8d** with $POCl_3$ did not yield isolable chloroenamine products; presumably, the twisted nature of **11** increases its reactivity by disrupting conjugation of the nitrogen lone pair and the alkene. Instead, the bicyclic lactams **8c** and **8d** were converted into related bicyclic amidines (Scheme 5, Panel B). Thus, treatment of **8c** and **8d** with $POCl_3$, and direct reaction with aniline, gave the amidines **20a** and **20b** in good yield (for another example, see Supporting Information). The amidines **20a**–**b** were shown to be stable, being unchanged after heating at 65 °C in DMSO for 3 days.

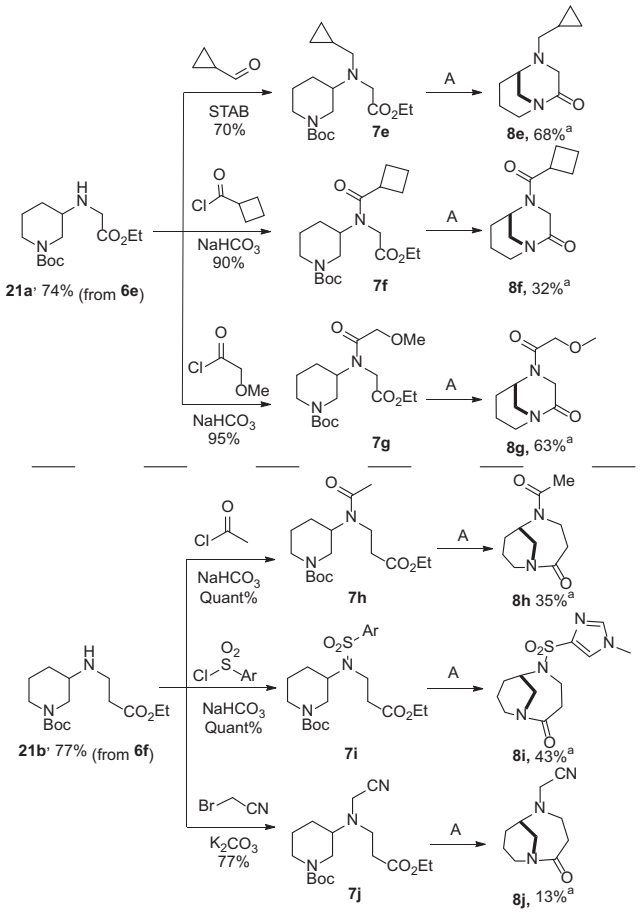
Third, we prepared fragments in which the amino group within the bicyclic amino lactam had been decorated (Scheme 6). Because *N*-benzyl and *N*-Cbz deprotection had proved difficult, we investigated the cyclisation of precursors with an unprotected secondary amine. $NaBH(OAc)_3$-mediated reductive amination of *N*-Boc piperidin-3-one with the hydrochloride salts of glycine ethyl ester **6e**



Scheme 5. Twisted lactam functionalization. Panel A: Chloroenamine formation and Suzuki reaction. Panel B: Synthesis of bicyclic amidines.



Scheme 4. Reduction of the bicyclic keto lactam **11**, and *O*-functionalization of the resulting alcohol.



Scheme 6. Synthesis of bicyclic lactams functionalised at a remote nitrogen atom. Method A: (1) NaOH (1.1 equiv), 1:1 H_2O-MeOH, 70 °C. (2) 6 N HCl. (3) Bu_2SnO, PhMe, 120 °C. [a]Yield over 3 steps.

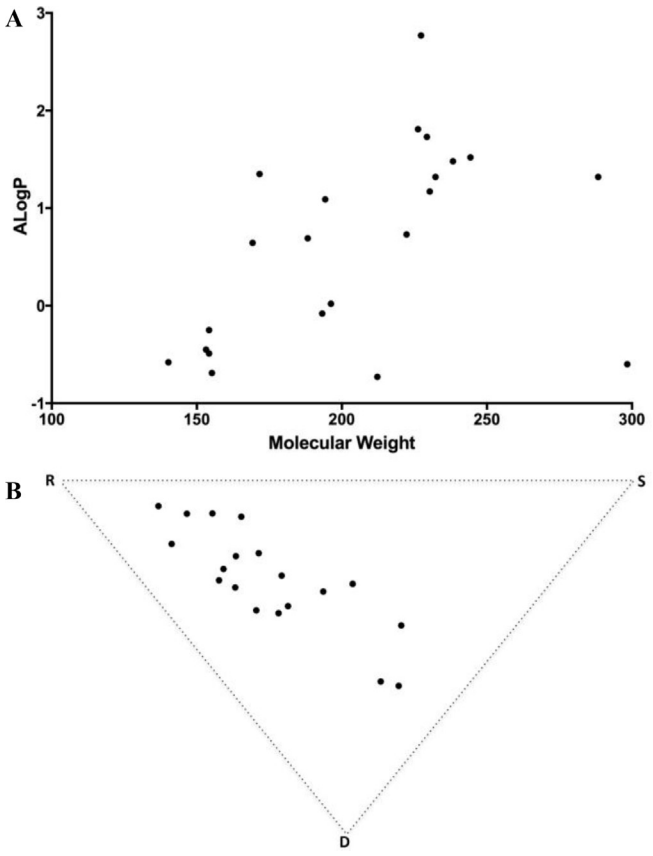


Fig. 4. Properties and diversity of the 22 synthesised fragments. Panel A: Molecular properties. Panel B: Shape diversity. D, disk; R, rod; S, sphere.

and β-alanine ethyl ester **6f** gave the corresponding secondary amines **21a** and **21b** in 74% and 77% yield respectively. Unfortunately, after Boc deprotection and ester hydrolysis, Bu_2SnO-mediated cyclisation was not successful in either case; perhaps the presence of a free secondary amine enabled competing polymerisation of the substrate. Therefore, the secondary amines **21a** and **21b** were decorated by alkylation, acylation or sulfonylation to yield the intermediates **7e**–**j**; Boc deprotection, ester hydrolysis, and Bu_2SnO-mediated cyclisation[15] then gave the corresponding decorated lactams **8a**–**f**.

2.4. Analysis of shape diversity and molecular properties

The molecular properties and shape diversity of the fragment set was analysed using LLAMA (Lead-Likeness And Molecular Analysis; llama.leeds.ac.uk), an open-access computational tool that we have developed (Figure 4).[19] The 22 synthesised fragments had molecular properties that were appropriate for fragment-based drug discovery. Furthermore, the fragments were highly distinctive from existing fragment sets. None of the Murcko frameworks[20] of the fragments were found as a substructure in a random 2% sample of the ZINC database[21] of commercially-available compounds. Furthermore, the bridged scaffolds were shown to result in a fragment set that was highly three-dimensional.

3. Conclusion

A set of 22 fragments was prepared that was based on some bridged scaffolds containing a bridgehead nitrogen atom. The key step was Bu_2SnO-mediated amide formation, which enabled the synthesis of alternative heteroatom-substituted bicyclo[3.3.1]nonane and bicyclo[4.3.1]decane ring systems. In addition to having appropriate molecular properties, the fragment set may offer distinctive opportunities for fragment-based drug discovery. The fragments were shown to be highly three-dimensional, and thus are complementary to existing fragment sets. Furthermore, the strained nature of the bicyclic frameworks will perturb the electronic properties of the embedded functional groups, presenting unusual opportunities for interaction with target proteins. The fragment set will be exploited in screens against a range of protein targets, and the results of these investigations will be reported in due course.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.bmc.2018.02.027.

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