Design, synthesis and decoration of molecular scaffolds for exploitation in the production of alkaloid-like libraries


A R T I C L E   I N F O

Article history:
Received 14 November 2014
Revised 16 December 2014
Accepted 18 December 2014
Available online 29 December 2014

Keywords:
Alkaloid
Small molecule libraries
Aminoarylation
Cycloaddition

A B S T R A C T

The design, synthesis and decoration of six small molecule libraries is described. Each library was inspired by structures embedded in the framework of specific alkaloid natural products. The development of optimised syntheses of the required molecular scaffolds is described, in which reactions including Pd-catalysed aminoarylation and diplolar cycloadditions have been exploited as key steps. The synthesis of selected exemplar screening compounds is also described. In five cases, libraries were subsequently nominated for production on the basis of the scope and limitations of the validation work, as well as predicted molecular properties. In total, the research has led to the successful synthesis of >2500 novel alkaloid-like compounds for addition to the screening collection (the Joint European Compound Library, JECL) of the European Lead Factory.

1. Introduction

A key challenge in both medicinal chemistry and chemical biology is to design compound libraries that target biologically-relevant chemical space. Natural products arise through the evolution of biosynthetic pathways, driven by functional benefit to the host organism. The biological relevance of natural products is thus pre-validated, and their structures continue to provide tremendous inspiration in both medicinal chemistry and chemical biology.

The field of biology-oriented synthesis exploits structures embedded in natural product frameworks to inform the design of productive small molecule libraries. The approach enables diversity to be focused around a biologically-relevant starting point within chemical space. An hierarchical approach has been developed that can facilitate navigation between frameworks found in, and inspired by, natural products. This approach can help prioritise simplified scaffolds that are most related to those of natural products, although, in many cases, other simplified scaffolds can also be envisaged. Library design can thereby focus on scaffolds related to natural product frameworks, and can enable the discovery of novel bioactive chemotypes. For example, it has previously been demonstrated that simplification of the frameworks of alkaloids (e.g., morphine) can be a productive strategy in medicinal chemistry.

In this paper, we discuss the design of six small molecule libraries that were inspired by alkaloid natural products (Fig. 1). In some cases, the scaffolds were simplified analogues of alkaloid frameworks; whereas in other cases, the scaffolds were related to ring systems embedded in a natural product framework. In each case, we describe the synthesis of the required scaffold(s), and generally demonstrate that decoration is possible to yield exemplar screening compounds.
The rationale for library design is summarised in Figure 2. The library 1 was inspired both by the 2-(3-pyridyl)-pyrrolidine framework of nicotine and the 2-arylmethyl-substituted pyrrolidine that is embedded in lycorine (Fig. 2), anisomycin and aphanorphine.12 The 2-arylmethyl-substituted pyrrolidine ring system also inspired the library 2. The framework of martinellic acid A inspired the design of the library 3, which retains a tricyclic framework similar to that of the natural product.13 The library 4 is based on a fused bicyclic pyrrolidine/cyclopentane ring system which is embedded in many natural products including meloscine.14 The library 5 was based on a scaffold which is a substructure in a range of spirocyclic natural products including rhynchophylline and horsfiline.15 Finally, the library 6 was inspired by the more complex framework of daphnezomine M.16

2. Synthesis and decoration of scaffolds prepared using Pd-catalysed aminoarylation reactions

It was proposed that the scaffolds required for the libraries 1, 2 and 4 would be prepared using Pd-catalysed aminoarylation reactions (Scheme 1). Each scaffold would thus be prepared from a N-Boc pentenamine 7 and a (het)aryl bromide 8. Aminoarylation18–21 would result in pyrrolidine formation and concomitant (het)arylation to yield a product scaffold (e.g., 7 + 8 → 9). It has previously been shown that aminoarylation reactions of acyclic pentenamine derivatives yield 2,5-disubstituted pyrrolidines with high cis diastereoselectivity, whereas 2,4-disubstituted pyrrolidines are generally formed with poorer diastereoselectivity.18 It was therefore decided to focus on the synthesis of scaffolds 9 in

Scheme 1. Envisaged synthesis of scaffolds from N-Boc pent-4-enamines 7 (het)aryl bromides 8. New bonds are shown in bold. Ar is a variable het(aryl) substituent.

Scheme 2. Synthesis of cyclisation precursors. DIAD = diisopropyl azodicarboxylate, LiHMDS = lithium hexamethyldisilazide.

Figure 2. Rationale for the design of libraries inspired by alkaloids. The arrows show which natural product(s) inspired the design of the required scaffolds.
Crucially, it was expected that this approach would allow wide variation of the carbon-based substituent, Ar.

The syntheses of substrates for the aminoarylation reactions are shown in Scheme 2. The aldehyde 10 was treated with but-3-enyl magnesium bromide to give the alcohol 11 in 87% yield. The conversion of the alcohol 11 into the N-Boc-protected amine 13 exploited the N-Boc oxalyl amide 12 which can serve as an ammonia equivalent in Mitsunobu reactions. Treatment of the alcohol 11 with 12, DIAD and triphenylphosphine resulted in clean substitution; subsequent reaction with lithium hydroxide resulted in

which R² = R.³ Crucially, it was expected that this approach would allow wide variation of the carbon-based substituent, Ar.

The syntheses of substrates for the aminoarylation reactions are shown in Scheme 2. The aldehyde 10 was treated with but-3-enyl magnesium bromide to give the alcohol 11 in 87% yield. The conversion of the alcohol 11 into the N-Boc-protected amine 13 exploited the N-Boc oxalyl amide 12 which can serve as an ammonia equivalent in Mitsunobu reactions. Treatment of the alcohol 11 with 12, DIAD and triphenylphosphine resulted in clean substitution; subsequent reaction with lithium hydroxide resulted in

which R² = R.³ Crucially, it was expected that this approach would allow wide variation of the carbon-based substituent, Ar.

The syntheses of substrates for the aminoarylation reactions are shown in Scheme 2. The aldehyde 10 was treated with but-3-enyl magnesium bromide to give the alcohol 11 in 87% yield. The conversion of the alcohol 11 into the N-Boc-protected amine 13 exploited the N-Boc oxalyl amide 12 which can serve as an ammonia equivalent in Mitsunobu reactions. Treatment of the alcohol 11 with 12, DIAD and triphenylphosphine resulted in clean substitution; subsequent reaction with lithium hydroxide resulted in
hydrolysis of the oxalyl amide to yield the N-Boc-protected pent-4-enamine derivative 13.

The N-Boc-protected pent-4-enamines 16, 19 and 22, chosen to incorporate an extra heteroatom without introducing diastereoselectivity issues, were prepared by alkylation of the corresponding nitriles. Initially, the piperidine 14 and the azetidine 17 were benzoylated; subsequently, treatment with LiHMDS at 0 °C in THF, and reaction with allyl bromide, yielded the γ,δ-unsaturated nitriles 15 and 18. Treatment of 15 and 18 with lithium aluminium hydride resulted in reduction of both the nitrile and benzamide groups to yield, after Boc protection, the N-Boc pent-4-enamines 16 and 19. In a similar vein, the nitrile 20 was allylated to yield the γ,δ-unsaturated nitrile 21 which was then reduced and Boc-protected to yield the N-Boc pent-4-enamine 22.

Finally, the N-Boc-protected cyclopentylamine 25 was prepared from methyl 2-oxocyclopentanecarboxylate 23 using a three step sequence. The β-ketoester 23 was allylated to furnish the β-ketoester 24. Subsequent reductive amination of 24 with ammonium acetate and sodium cyanoborohydride, followed by Boc protection, enabled diastereoselective formation of the N-Boc-protected cyclopentylamine 25. The relative configuration of 25 was determined by X-ray crystallography (Fig. 3).

A range of scaffolds was synthesised from combinations of N-Boc pent-4-enamines (13, 16, 19, 22 and 25) and a variety of (het)aryl bromides (Table 1). In each case, the reactants were treated with 5 mol % Pd(OAc)$_2$, 10 mol % DPEPhos and cesium carbonate in dioxane at 110 °C; in two cases, the cyclised products were immediately deprotected by treatment with 9:1 CH$_2$Cl$_2$–TFA (entries 1 and 3).

The synthetic approach enabled the synthesis of a range of scaffolds in good yield. Pleasingly, provided that an electron-deficient aryl bromide was used, wide variation of the carbon-based (het)aryl substituent was possible (Table 1 and Supplementary information).

Finally, it was demonstrated that scaffold decoration was possible (see Scheme 3 for selected examples). Thus the Boc-deprotection of the scaffolds 26 and 29 could be followed by sulfonylation (e.g., →35 or 38) or reductive amination (e.g., →36). Alternatively, transfer hydrogenation resulted in benzyl deprotection of the scaffold 31; sulfonylation then yielded the exemplar screening compound 37. These exemplar compounds, together with those described elsewhere in this paper, were purified by mass-directed HPLC; this approach facilitated the subsequent production of large numbers of screening compounds.
Scheme 7. Synthesis of a spirocyclic lactam scaffold and subsequent functionalization. LiHMDS = lithium hexamethyldisilazide, DMEDA = N,N-dimethylmethylenediamine. DMA = dimethylacetamide, DIPEA = diisopropylethylamine.

Scheme 8. Presumed mechanism of a cascade of three Diels–Alder reactions.

3. Synthesis and decoration of scaffolds prepared using cycloaddition reactions

3.1. Synthesis and decoration of tricyclic scaffold inspired by martinellic acid

It was envisaged that the tricyclic scaffold 3 would be prepared using the intramolecular cycloaddition of an azomethine ylide derived from an O-allylated salicaldehyde and a suitably protected glycine ester. The cycloaddition would form both the central dihydropyrany ring and the pyrroline ring in a single step. It was planned to exploit N-benzyl glycine ethyl ester to enable, after deprotection, subsequent deprotection and diversification of the nitrogen atom.

Initially, the commercially-available salicaldehydes (39–41) were allylated by treatment with K₂CO₃ and allyl bromide in DMF to deliver the required O-allylated salicaldehydes (42–44) (Scheme 4).

The key condensation-cycloaddition cascade was successfully accomplished through treatment of the O-allylated salicaldehydes 42–44 with N-benzyl glycine ethyl ester in refluxing toluene. Pleasingly, high (>95:<5) diastereoselectivity was observed in each case which compared favourably with the 90:10 diastereoselectivity previously observed in a similar system. The relative configuration of the cycloadducts was determined by correlation of key coupling constants observed in closely-related systems.

The methoxy-substituted scaffold 45 was deprotected under transfer hydrogenation conditions (48; Scheme 4). Unfortunately, deprotection of both the chloro- and diethylamino-substituted scaffolds (46 and 47) was unsuccessful; hydrogenation of 47 resulted in hydrogenolysis of the benzyl C–N bond within the tricyclic scaffold, whilst reaction of 46 resulted in dechlorination (Supporting information). To circumvent these problems, 2,4-dimethoxybenzyl-protected (DMB-protected) glycine ethyl ester was exploited in the cycloaddition step to yield the DMB-protected scaffolds 49 and 50. Subsequent deprotection of the DMB group was achieved through treatment with TFA in refluxing CH₂Cl₂ (Scheme 5).


Scheme 10. Synthesis of exemplar screening compounds by scaffold decoration. DMA = dimethylacetamide, TBTU = O-(benzotriazol-1-yl)-N,N,N’-tetramethyluronium tetrafluoroborate.
3.2. Synthesis and decoration of a spirocyclic scaffold

It was envisaged that the spirocyclic scaffold 5 would be prepared using a [3+2] cycloaddition reaction. The required substrate was prepared by treatment of N-Boc pyrrolidinone 60 with LiHMDS, and reaction of the resulting lithium enolate with Eschenmoser's salt (59); subsequent elimination gave the required α,β-unsaturated amide 61 in an overall yield of 63% over two steps (Scheme 7). A cycloaddition reaction between the α,β-unsaturated amide 61 and an unstabilised azomethine ylide, generated from N-(methoxymethyl)-N-(trimethylsilylmethyl)benzylamine in presence of TFA, provided the protected spirocyclic lactam 62 (remarkably, without loss of the Boc group). Subsequently, Boc-deprotection and functionalisation of the resulting lactam by copper-mediated arylation, provided the N-aryl lactams 63 and 64 in good yield.

The decoration of the spirocyclic scaffold 63 was demonstrated (see Scheme 7 for selected examples). Benzyl deprotection under catalytic transfer hydrogenation conditions could be followed by either reductive amination or urea formation to give exemplar screening compounds (e.g., 65 and 66).
3.3. Synthesis and decoration of scaffolds prepared using a cascade of three Diels–Alder reactions

It was envisaged that the synthesis of the scaffold 6 would exploit a triple Diels–Alder, multicomponent cascade reaction, first developed by Taylor and further adapted in our laboratory.30,31 The approach would involve the multi-component reaction of a triazine (67), an allylamine (68) and an aldehyde (69) to give, ultimately, the required caged scaffold 70: in this sequence, it is presumed that enamine formation (→71) is followed by electron demand Diels–Alder reaction (→72), expulsion of \( \text{N}_2 \) by retro-Diels–Alder reaction (→73), and finally intramolecular Diels–Alder reaction of the pendant allyl group (Scheme 8).

Although it has previously been shown that substitution of the caged scaffold can be widely varied,31 it was decided to vary only the triazine component 67. Two exemplar triazines were prepared bearing either a 4-trifluoromethylphenyl (74) or a 4-pyridyl (75) substituent. Pleasingly, both triazines delivered the corresponding caged scaffolds (76 and 77), albeit in a moderate yield (Scheme 9).

We had initially planned to decorate the scaffolds using three-component Ugi reactions;31 however, whilst such Ugi reactions were generally successful, the resulting products were difficult to purify by mass-directed HPLC. As an alternative, the imine scaffold 76 was reduced using NaBH\(_4\) and the crude amine product (78) was directly decorated by reductive amination, urea formation and amide formation to yield exemplar screening compounds (e.g., 79–81) (Scheme 10).

4. Discussion

In this paper, some of the research undertaken to validate six alkaloid-like libraries has been described. The development of viable scaffold syntheses was essential which often required adaption of the proposed synthetic route and, in some cases, revision of the library design. Subsequently, the potential for scaffold decoration was demonstrated through the synthesis of a range of exemplar screening compounds (for which selected examples have been described).

The validation work defined the scope and limitations of the developed chemistry for exploitation in library synthesis. In five cases, a library was subsequently nominated for production on the basis of the validation work (including the success of decoration reactions used in the synthesis of exemplar screening compounds) and the predicted molecular properties of the virtual compounds (Fig. 4).32 The nominated libraries were selected to target drug-like space in accordance with the overall objectives of the ELF consortium.33 In one case, the mass-directed HPLC of more polar compounds had proved problematic during the validation work, which was fed into the design of the library nominated for production (Fig. 3, Panel E). For each of the five libraries, between 300 and 750 screening compounds were successfully produced (with a success rate of between 58% and 84%), leading to a total of >2500 novel alkaloid-like compounds.

5. Conclusion

In this paper, the design and experimental validation of six libraries inspired by alkaloid natural products has been described. In five cases, the validation work has informed the design of a library that has been nominated for production, leading to the successful synthesis of >2500 novel alkaloid-like compounds. These compounds will be added to the screening collection (the Joint European Compound Library, JECL) of the European Lead Factory.

Acknowledgments

We acknowledge support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n° 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. We thank Anthony Wil-lamae and Carine Roche (Edelris) for production of the compound libraries and Chris Pask (University of Leeds) for X-ray crystallography.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcc.2014.12.048.

References and notes