Title

A novel complexity-to-diversity strategy for the diversity-oriented synthesis of structurally diverse and complex macrocycles from quinine

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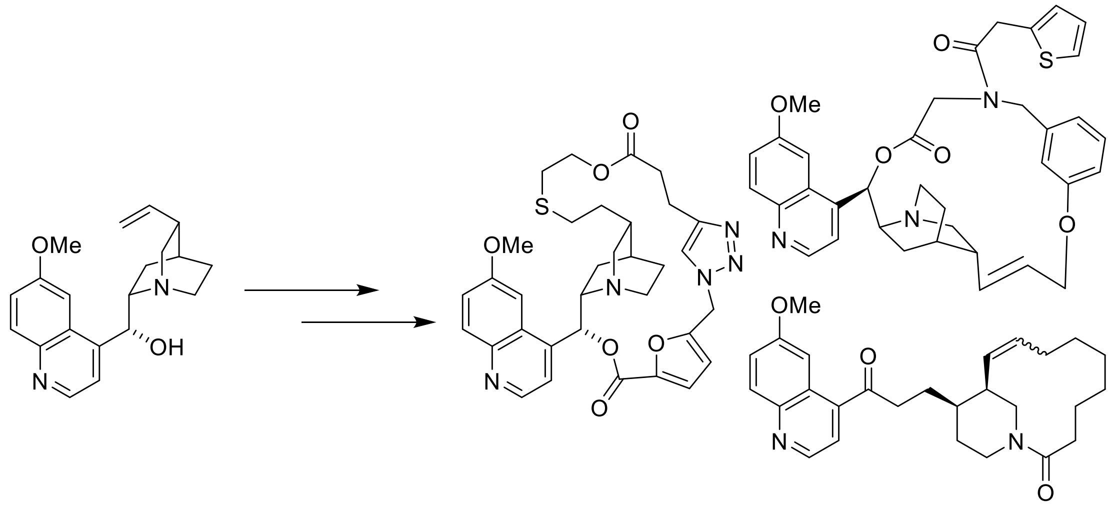
Abstract

Recent years have witnessed a global decline in the productivity and advancement of the pharmaceutical industry. A major contributing factor to this is the downturn in drug discovery successes. This can be attributed to the lack of structural (particularly scaffold) diversity and structural complexity exhibited by current small molecule screening collections.

Macrocycles have been shown to exhibit a diverse range of biological properties, with over 100 natural product-derived examples currently marketed as FDA-approved drugs. Despite this, synthetic macrocycles are widely considered to be a poorly explored structural class within drug discovery, which can be attributed to their synthetic intractability.

Herein we describe a novel complexity-to-diversity strategy for the diversity-oriented synthesis of novel, structurally complex and diverse macrocyclic scaffolds from natural product starting materials. This approach exploits the inherent structural (including functional) and stereochemical complexity of natural products in order to rapidly generate diversity and complexity. Readily-accessible natural product-derived intermediates serve as structural templates which can be divergently functionalized with different building blocks to generate a diverse range of acyclic precursors. Subsequent macrocyclisation then furnishes compounds that are each based around a distinct molecular scaffold. Thus, high levels of library scaffold diversity can be rapidly achieved. In this proof-of-concept study, the natural product quinine was used as the foundation for library synthesis, and six novel structurally diverse, highly complex and functionalized macrocycles were generated.

Graphical Abstract



Abbreviations

ADMET, adsorption, distribution, metabolism, excretion and toxicity; CtD, complexity-to-diversity; DCC, *N,N'*-dicyclohexylcarbodiimide; DCE, 1,2-dichloroethane; DIPEA, *N,N'*-diisopropylethylamine; DMAP, 4-dimethylaminopyridine; DMF, *N,N'*-dimethylformamide; DMSO, dimethyl sulfoxide; DOS, diversity-oriented synthesis; EDC, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimine; FDA, US food and drugs administrations; HATU, 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate; HTS, high-throughput screening; NCE, new chemical entities; PMI, principal moments of inertia; PPI, protein-protein interaction; PTSA, *para*-toluene sulfonic acid; TEA, triethylamine; THF, tetrahydrofuran.

Keywords

Natural products; macrocycles; diversity-oriented synthesis; complexity-to-diversity; library synthesis; scaffold; chemical space

1 Introduction

1.1 History

In the 1990s, with the advent of high-throughput screening and combinatorial chemistry, the drug discovery industry moved towards the rapid and efficient synthesis of large collections of compounds.[1] It was hoped that by screening thousands (and even millions) of compounds, multiple novel therapeutic leads would be identified. Unfortunately, this expected surge in productivity did not materialise.[2] This disappointing degree of productivity has been primarily attributed to the relative lack of structural diversity within the libraries.

Typically, such libraries were comprised of flat, sp^2 rich and structurally similar compounds.[2-4] As a result, there has been a drive in recent years to develop robust methodologies that allow for the rapid generation of compounds possessing more complex and diverse sp^3-rich architectures.

1.2 Natural Products

Natural products represent a highly diverse and structurally innovative compound class. They possess significant sp^3 character, chirality, diverse core scaffolds, differing ratios of hetero to non-hetero atoms and, computationally, occupy a larger fraction of chemical space than typical combinatorial libraries.[5-8] As such, natural products play a crucial role in the discovery of drugs. Despite the number of new chemical entities (NCEs) having fallen in recent years, the number of natural product and natural product-derived NCEs has remained relatively high; they are responsible for approximately 33% of all small molecule drugs approved from 1981 to 2014.[5,9-17]

Despite their key role in drug development, natural products are underrepresented in compound screening collections. This is attributed to the challenges associated with their identification, isolation and synthesis. In recent years, a variety of strategies have been reported to tackle this issue and deliver libraries of natural product-like compounds, including utilisation of simplified core motifs, diverted total synthesis[18,19] and diversity-oriented synthesis (DOS).[5,7,20-28] However, whilst natural products and their derivatives have featured as the end-goal in many drug discovery programs (both DOS-focused and otherwise), their use as starting materials in the manufacture of compound libraries remains relatively rare. Recent years have witnessed a growing interest in the development of strategies for the synthesis of complex and diverse compounds from natural products.[29-31]

One such approach pioneered by Hergenrother and co-workers, is referred to as "complexity-to-diversity (CtD)"; this involves the production of complex natural product-like libraries via the controlled application of ring distortion reactions on readily available natural products.[12,21,30-36] The CtD approach, which was inspired by nature's proclivity to manufacture complex natural products from common intermediates, enables natural products which are already inherently structurally complex, to be rapidly converted into markedly different core scaffolds. The CtD strategy has been successfully applied to several readily available natural products, including gibberellic acid, adrenosterone, quinine, abietic acid and fumagillol.[21,30-32]

1.3 Macrocycles

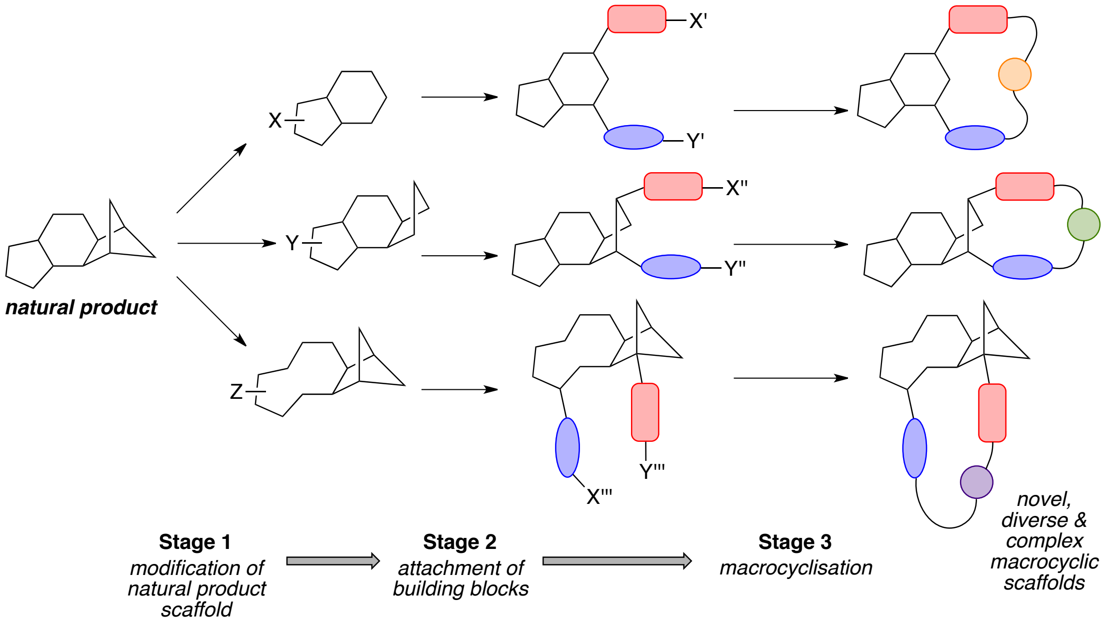
Macrocycles (compounds containing a ring size of 12 atoms or more) have been shown to exhibit a diverse range of biological activities and feature in a variety of marketed drugs.[37-39] More specifically, natural-product derived macrocycles, of which over 100 are found as FDA-approved drugs, have demonstrated excellent efficacy as antibiotics and anticancer drugs.[40-45] They have been shown to exhibit good physiochemical and pharmacokinetic properties, binding with high affinity and selectivity to targets.[42,46]

Macrocycles possess unique structural properties that separate them from their acyclic small molecule counterparts and to which much of their useful biological activity is attributed. In particular, their potency is credited to their structural pre-organisation and ability to interact with multiple binding sites across a large area.[46] In addition, acyclic compounds suffer major entropic loss upon binding to proteins due to the restriction of their conformational degrees-of-freedom. This effect is less prominent during macrocycle binding, due to a higher level of pre-organisation.[44,47-49] Even with a restricted number of conformations, macrocycles still possess sufficient flexibility to allow them to mould to a protein surface.[42,50] As such, they represent excellent synthetic targets and show great potential in succeeding where small molecules have previously failed, especially in the modulation of PPIs.[51,52]

Their lack of compliance with Lipinski's "rule of five" bears some of the responsibility for the slow uptake of macrocycles in medicinal chemistry and HTS campaigns.[44] Furthermore their perceived synthetic intractability alongside a lack of understanding of their ADMET properties has led to concern over their suitability as pharmaceutical leads.[50] Despite the advantages illustrated above, macrocyclic compounds are severely under-represented and under-exploited within the drug discovery industry.[42] As of 2008, almost half of all new small molecule drugs are generated synthetically whilst almost all of their macrocyclic counterparts are derived from natural products with minimal decoration to their structures.[46] As such, there is an unmet need for a robust methodology for the production of structurally diverse macrocycles.

1.4 Summary

Herein, we report the development of a novel complexity-to-diversity (CtD) approach for the synthesis of libraries of novel, structurally complex and diverse macrocyclic scaffolds from natural product starting materials (Scheme 1). This approach exploits the inherent structural and stereochemical complexity in natural products in order to rapidly generate diversity and complexity through the use of simple chemistry. In this proof-of-concept study, the natural product quinine was used as the foundation for the library synthesis and six novel, structurally diverse, highly complex and functionalised macrocycles were generated.



Scheme 1: Schematic outline of the CtD approach towards macrocycles from natural product starting materials. Readily accessible natural products are converted into functionalised intermediates (stage 1) which serve as structural templates that can be divergently functionalised with different building blocks to generate a diverse range of acyclic precursors (stage 2). Subsequent macrocyclisation then furnishes compounds that are each based around a distinct molecular scaffold (stage 3). In addition, the natural product starting material itself could act as a template for macrocycle construction (i.e. direct functionalisation of the natural product with suitable building blocks followed by macrocyclisation).

2 Results and Discussion

2.1 Aims

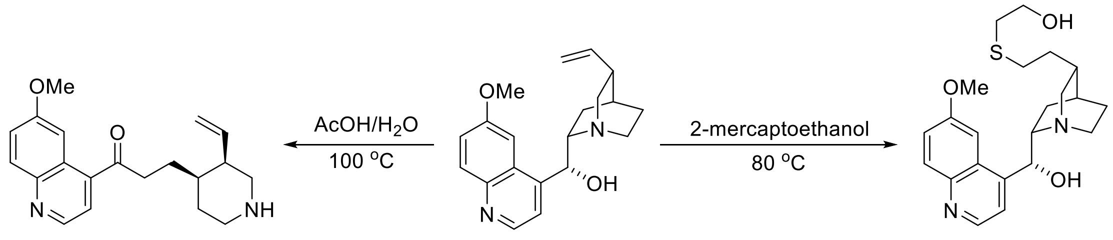
We considered that the natural product starting materials to be used in the CtD strategy should ideally be inexpensive, readily available, structurally interesting and feature a selection of chemically distinct functional groups that would act as handles for diversification. Based upon these criteria, we selected the alkaloid quinine for initial proof-of-concept studies. Furthermore, its historical use as an antimalarial drug suggests that its inherent complexity is sufficient to achieve biological selectivity, and with its two discrete quinoline and quinuclidine cage ring systems, quinine possesses excellent structural complexity.

2.2 Strategy

Of the variety of known synthetic transformations of quinine,[30,53-60] we identified two key conversions that would help in demonstrating our strategy.

Firstly, work carried out by Huigens III et al.*[30]* demonstrated the successful Hoffmann degradation of quinine into quinotoxine- a promising transformation for this project. Not only would it yield a much more synthetically amenable secondary amine, but it would furnish another structural template for macrocycle construction.[30] Secondly, work by Zhang et al.*[55]* illustrated a successful thio-ene reaction upon quinine, allowing a facile means for functionalisation of the pendant alkene.[55]

Construction of these two additional core templates began with the boiling of quinine **(1)** in an aqueous acetic acid solution, which promoted acid-catalysed degradation to afford quinotoxine **2**. To form the final core scaffold, quinine **(1)** was heated overnight at 80 °C in neat mercaptoethanol to deliver diol **3** (Scheme 2).



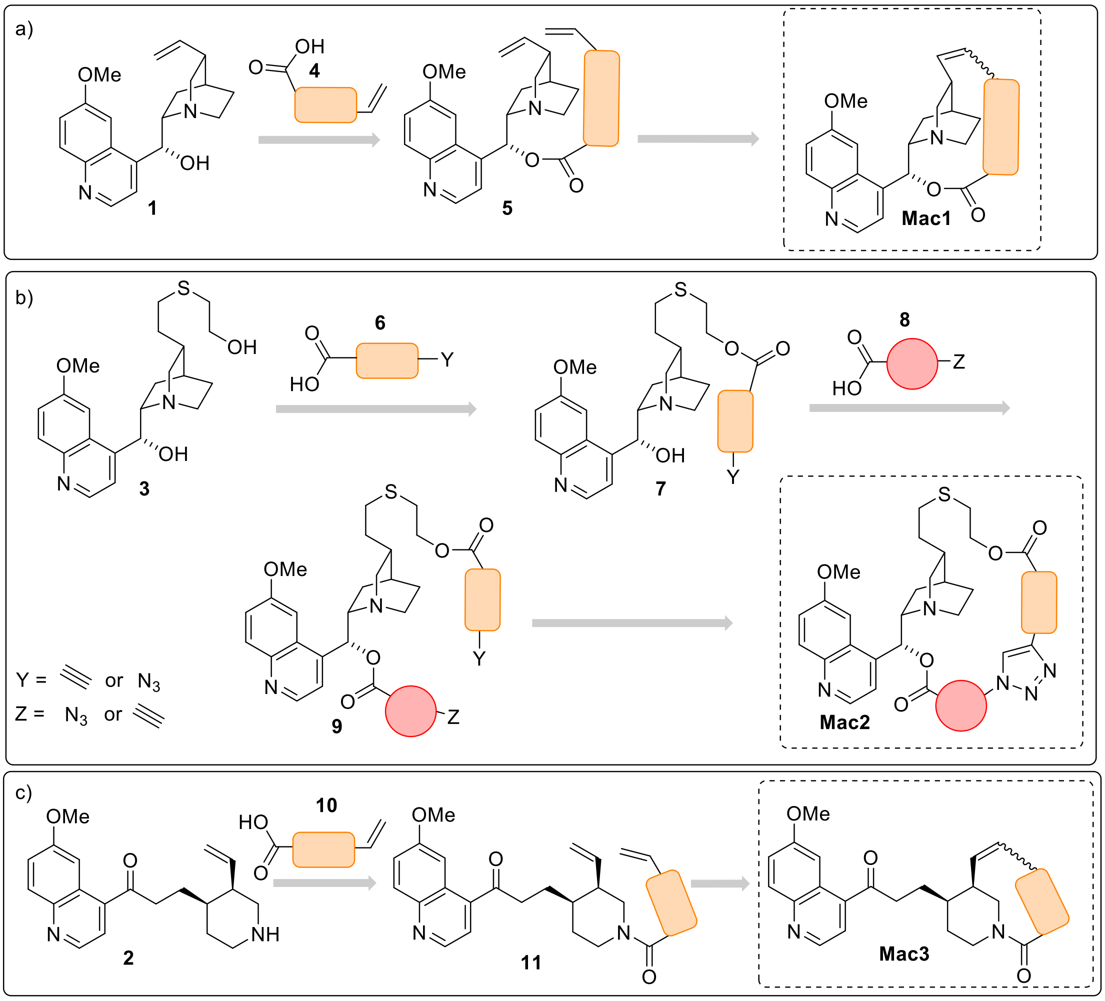
2, 94 % **1** **3**, 43%

Scheme 2: Synthesis of quinotoxine **2** and diol **3** from quinine **1**. The yield for **2** is the crude yield, since this was sufficiently pure.

With these three core templates in hand, we anticipated that we could construct three different structural types of macrocycle (Scheme 3a). It was hoped that the first class of macrocycles (Mac1) could be constructed by esterifying general building blocks **4** to the pendant hydroxyl of quinine **(1)** to afford linear precursors of the form **5**. Subsequent treatment with Grubbs' II catalyst would then initiate ring-closing metathesis to yield scaffolds of the form Mac1.

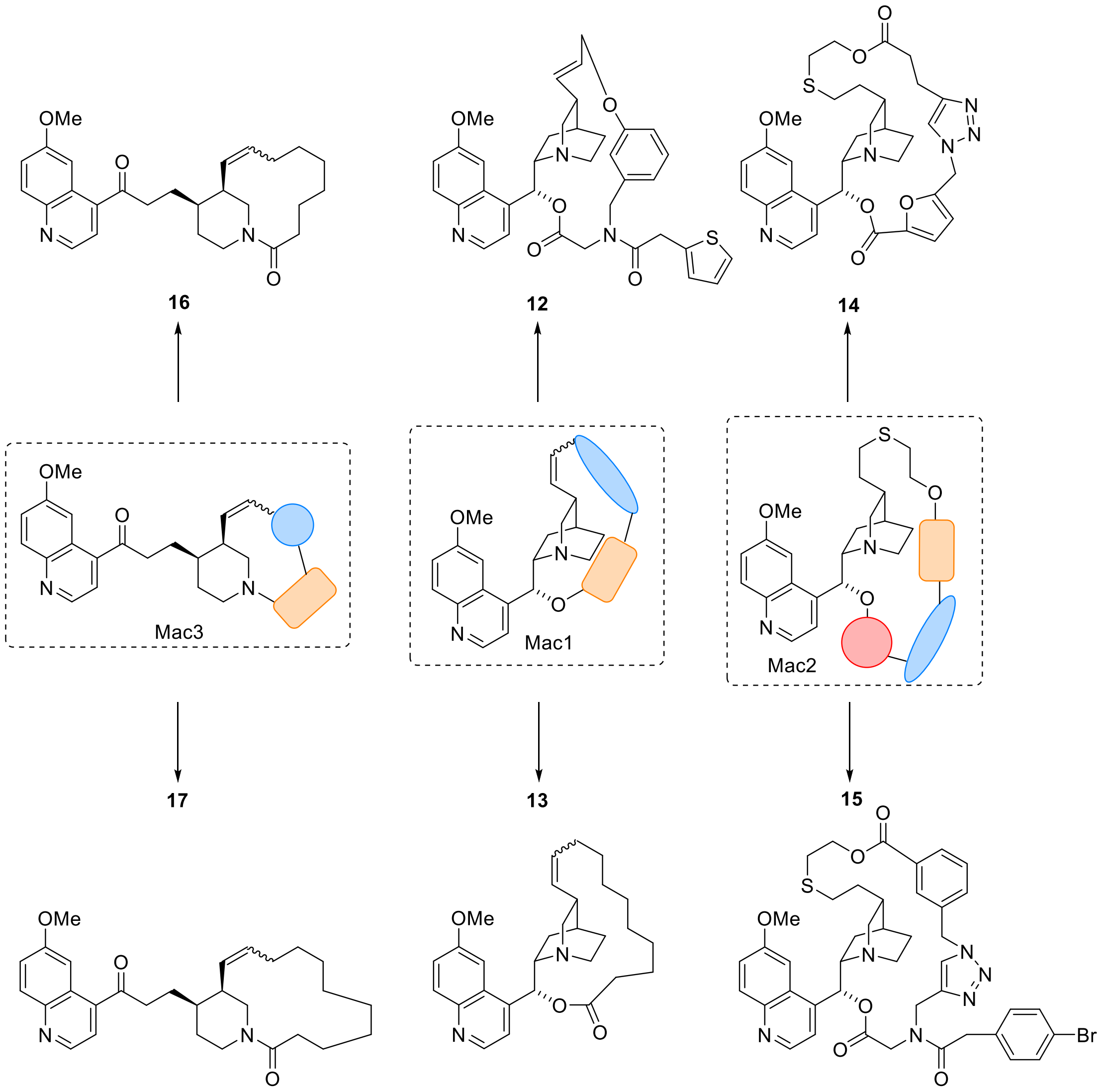
Starting in a similar manner, the second class of macrocycles (Mac2) would begin with the chemoselective esterification of building blocks **6** to diol **3**, followed by the coupling of building blocks **8** to the secondary alcohol to generate linear precursors **9** (Scheme 3b). These azido-alkyne intermediates would then undergo copper-mediated click-type 1,3-dipolar cycloadditions to afford macrocyclic scaffolds of the form Mac2 .

Finally, it was envisaged that we could deliver macrocycles of structural form Mac3 by a two-step sequence from quinotoxine **2** (Scheme 3c). Initially, quinotoxine **2** would be treated with a selection of acids **10** to construct amides **11**. Exposure of these amides to the appropriate cyclisation conditions for olefin metathesis, it was hoped, would promote formation of the desired macrocycles (Mac3).



Scheme 3: General strategies for the synthesis of macrocycles Mac1, Mac2 and Mac3 from the natural product core, quinine **(1).**

To test the hypothesis suggested above, we proposed to construct six macrocyclic scaffolds, two based on each structural class (Scheme 4). However, the modular nature of this strategy provides the opportunity for substituting both the building blocks and the natural product core. Thus there is great scope for expanding the breadth of chemical space interrogated by these diverse libraries.

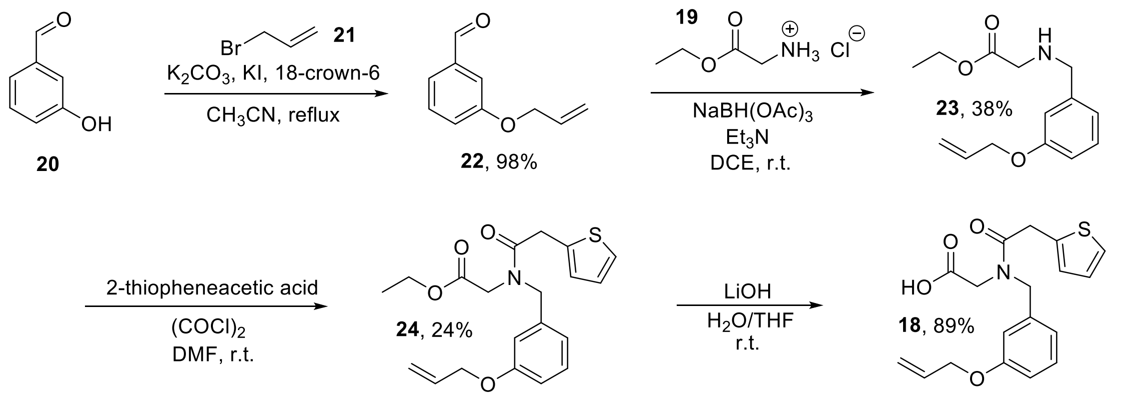


Scheme 4: Proof-of-concept target macrocycles based on the three macrocyclic structural classes, Mac1, Mac2 and Mac3

2.3 Building Blocks

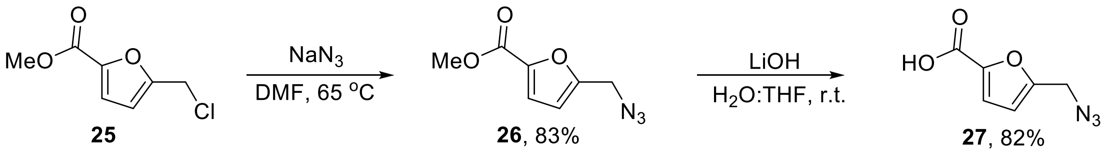
Whilst some building blocks were commercially available, others required a short sequence of steps to synthesise.

Formation of acid **18** was achieved in a four-step sequence from commercially available ethyl glycinate hydrochloride **19** and 3-hydroxybenzaldehyde. The sequence was initiated by the alkylation of 3-hydroxybenzaldehyde with allyl bromide to yield ether **22**. Subsequent reductive amination with the hydrochloride **19** furnished amine **23**.[61] 2-Thiopheneacetic acid was treated with oxalyl chloride and catalytic DMF to generate the corresponding acid chloride. The freshly prepared acid chloride was quenched with amine **23** to deliver amide **24**. Saponification of the amide with LiOH afforded the desired acid **18** (Scheme 5).



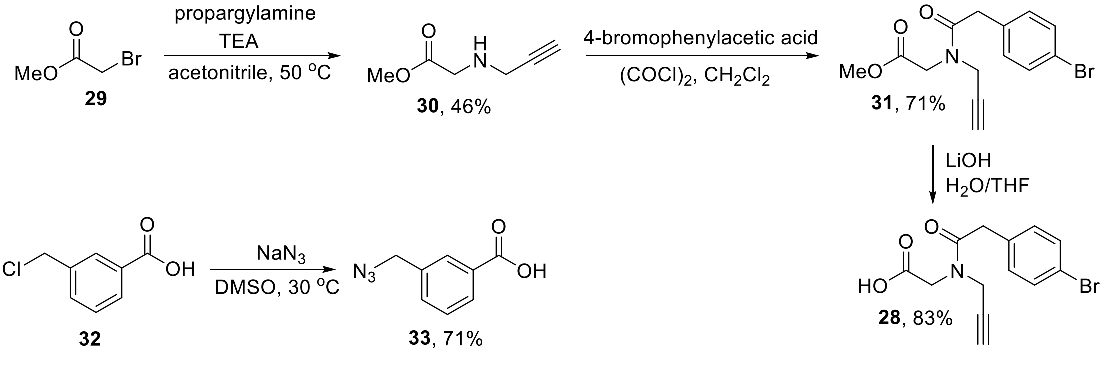
Scheme 5: Synthesis of building block **18**

Treatment of methyl 5-(chloromethyl)-2-furoate **25** with NaN_3, in line with the procedure detailed by Beckmann et al.,[62] afforded azido compound **26**, after which a subsequent LiOH- mediated saponification furnished the desired carboxylic acid **27** (Scheme 6).[62]



Scheme 6: Synthesis of building block **27**

We hoped to furnish acid **28** in a three-step sequence from readily available methyl bromoacetate **29**. Exposure of the methyl ester **29** to propargylamine and TEA yielded amine **30**. Treatment of 4-bromophenylacetic acid with oxalyl chloride generated the corresponding acid chloride, which was subsequently quenched with amine **30** to deliver amide **31**. LiOH mediated hydrolysis conditions furnished the desired building block acid **28**. Following the protocol outlined by Beckmann et al.,[62] treatment of benzyl chloride **32** with NaN_3 in DMSO successfully delivered the second building block acid **33** (Scheme 7).

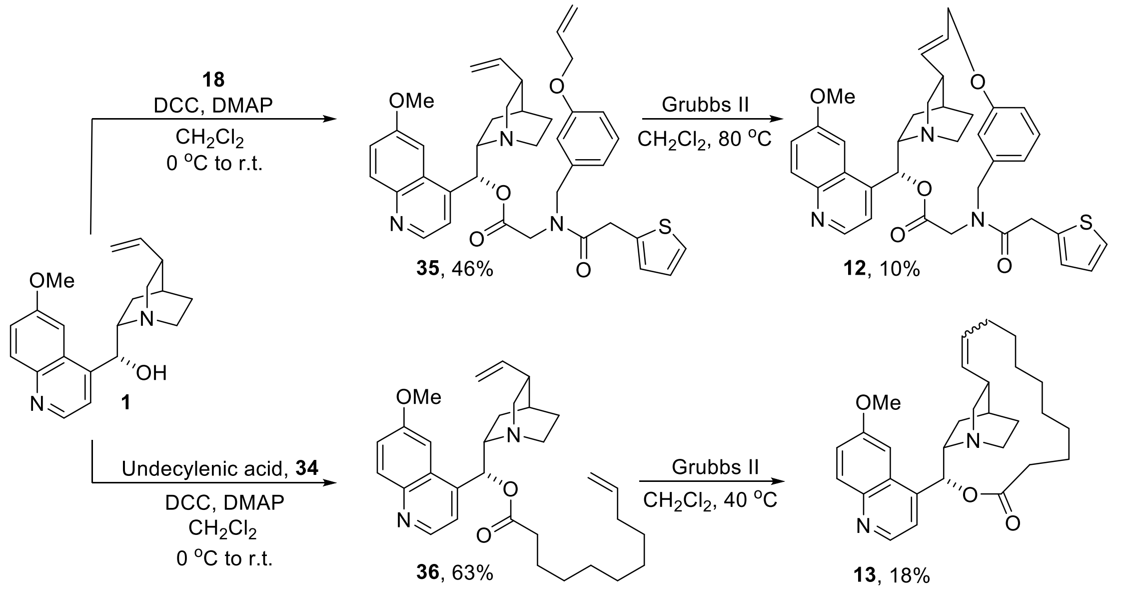


Scheme 7: Synthesis of building blocks **28** and **33**

2.4 Macrocycles of the structural class Mac1

It was anticipated that macrocycles **12** and **13** could be constructed in two steps from quinine **(1)**. Synthesis began with the DCC-mediated esterification of quinine **(1)** with acids **18** and **34** to furnish linear precursors **35** and **36** respectively. Subsequent treatment of these intermediates with the Grubbs II catalyst afforded macrocycles **12** and

13 (Scheme 8). Whilst it was not possible to determine the stereochemistry of the resulting alkene in macrocycle **12**, the alkene in macrocycle **13** was determined to have cis geometry from two-dimensional NMR data.

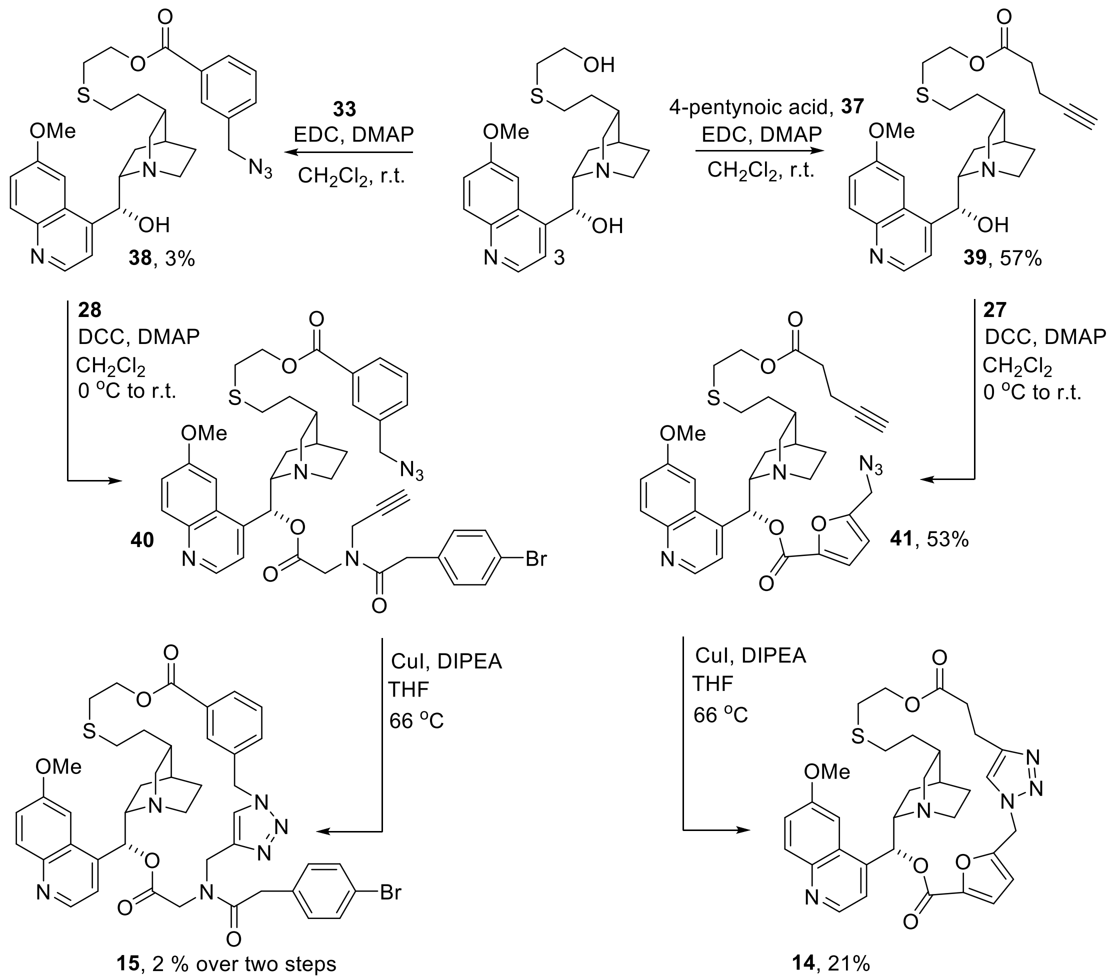


Scheme 8: Synthesis of macrocycles **12** and **13**

2.5 Macrocycles of the structural class Mac2

It was envisaged that macrocycles **14** and **15** could be furnished in a three-step sequence from diol **3** (Scheme 9). Synthesis began with the coupling of acids onto the primary hydroxyl of compound **3**. EDC-mediated esterification of the core compound with acid **33** afforded intermediate **38**, whilst the same conditions effected intermediate **39** from 4-pentynoic acid **37**.

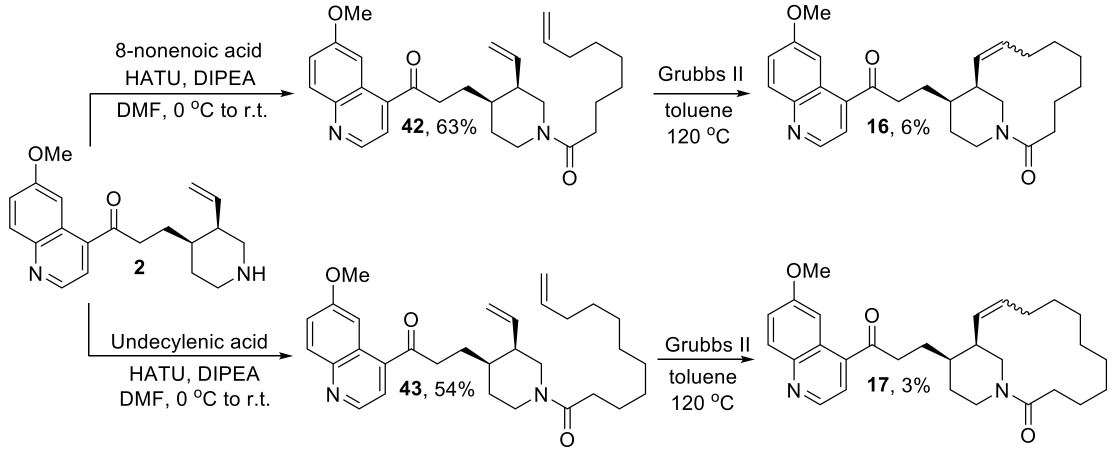
Subsequently, we attempted the esterification of **38** with acid **28** to afford linear precursor **40**. Whilst LCMS data indicated formation of **40** in the reaction mixture, it was not possible to obtain a spectroscopically pure sample before the material completely degraded. So the material was carried through without purification. The furnishing of linear precursor **41** was achieved by the DCC-mediated esterification of intermediate **39** with acid **27**. Treatment of both linear precursors with CuI promoted the desired click cycloaddition step and afforded macrocycles **15** and **14**, respectively (Scheme 9).



Scheme 9: Synthesis of macrocycles **14** and **15**

2.6 Macrocycles of the structural class Mac3

Macrocycles **16** and **17** were synthesized via a two-step sequences from quinotoxine. Synthesis began with HATU-mediated amide coupling of quinotoxine **2** and the acids 8-nonenoic acid and undecylenic acid to furnish linear precursors **42** and **43** respectively. Exposure of these alkene-containing intermediates to Grubbs II triggered ring-closing metathesis and delivered two macrocyclic scaffolds: **16** and **17** respectively (Scheme 10). Both macrocycles were isolated as single isomers but in both cases the double bond geometry could not be determined.



Scheme 10: Synthesis of macrocycles **16** and **17**

Molecular Shape Analysis

It has been argued that the overall molecular shape diversity of a compound library is the most fundamental indicator of overall biological (functional) diversity.[63,64] To assess the 3D shape diversity of the six macrocycles, we carried out a principal moments of inertia (PMI) analysis. PMI plots are often used to visually represent the shape diversity of compounds of a collection in "molecular shape space" spanned by the three basic extreme shape types: "rod-like" (e.g., acetylene), "disk-like" (e.g., benzene) and "spherical" (e.g., adamantine). After an initial conformational search and energy minimisation on the DOS library, we selected the lowest energy conformations for each compound and calculated their principal moments of inertia (full details of the PMI analysis can be found in Section 4.3). We also computed the PMIs for 40 top-selling drugs, 60 natural products and 36 macrocycles in clinical development so that we could compare the shape diversity between these collections and our library. The PMI plot produced is shown below (Figure 1a).

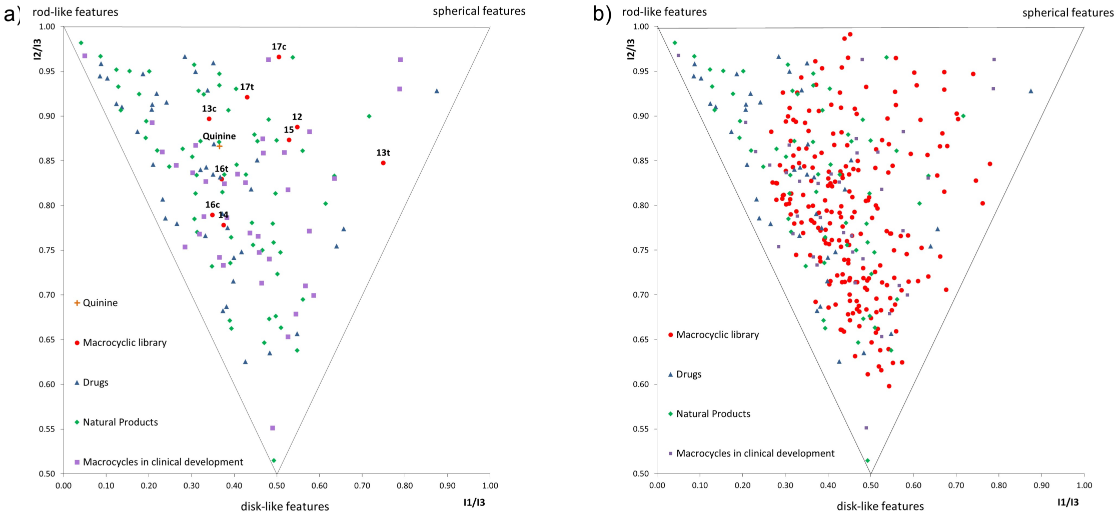


Figure 1: a) Principal moments of inertia plot illustrating the shape diversity of our proof-of-concept library, including both cis (c) and trans (t) isomers for the macrocycles for which the alkene geometry could not be determined, and 3 reference sets. The red marks represent our collection, with the orange marker highlighting the position of quinine. b) PMI plot for Isidro Llobet's library.[44,62]

The collection of 40 top-selling drugs are mainly one- and two- dimensional, with very little three-dimensionality observed. In contrast, the natural product, macrocyclic compound collection and our proof-of-concept library demonstrate much more three dimensional "spherical" character. It is pleasing to see that our small proof-of-concept library mimics the shape diversity of the natural product and macrocycle collections. Furthermore, we have included on the plot the natural product core, quinine, to demonstrate the breadth of shape diversity generated from a single compound. Taking this further, if we compare our PMI plot to a similar one constructed to assess Isidro-Llobet's macrocycle library[47,65] (against the same reference set), we can see that both DOS libraries exhibit similar levels of shape diversity (Figure 1b). This result is particularly pleasing, given that our collection is significantly smaller.

Conclusions

Herein we have reported a complexity-to-diversity (CtD) strategy for the diversity-oriented synthesis of structurally complex and diverse macrocycles from natural product starting materials. In this proof-of-concept study, quinine was used as the foundation for library synthesis and six novel, structurally diverse, highly complex and functionalised macrocycles were generated, each of which is based around a distinct molecular scaffold.

Our library showed excellent shape diversity in the PMI analysis, rivaling that of the natural product and macrocycles in clinical development reference sets. It also shows excellent shape diversity compared to a diverse macrocyclic library over thirty times its size. In principle, a wider range of building blocks could be employed in the routes described above in order to access additional macrocyclic compounds from quinine. This modular nature of the strategy should allow for easy substitution of building blocks and possibility or localised SAR studies upon hit identification. It is anticipated that our general CtD approach will prove applicable to a wider range of natural products and therefore represent a useful strategic method for the synthesis of complex and diverse macrocyclic scaffolds.

4 Materials and Methods

4.1 General Experimental

All non-aqueous reactions were performed in dry glassware under an atmosphere of N_2 using anhydrous solvents. Tetrahydrofuran was dried over sodium wire and distilled from a mixture of lithium aluminium hydride and calcium hydride with triphenyl methane as the indicator. CH_2Cl_2, toluene, methanol and acetonitrile were distilled from calcium hydride. Chemicals were purchased from commercial sources and used as received unless otherwise stated. Reactions were carried out at room temperature unless otherwise stated. Reactions at 0 ^{o}C were maintained using an ice/water bath and reactions at -78 ^{o}C were maintained using an acetone/dry ice bath.

Thin layer chromatography, used to analyse and monitor reaction progress, was carried out on Merck Kieselgel 60 F_{254} plates with visualisation by UV fluorescence (λ_{max} = 254 nm) or by staining with potassium permanganate. R_f values are quoted to the nearest 0.01. Flash column chromatography was performed using slurry-packed SiO_2 (Merck Grade 9385, 230-400 mesh) under positive pressure of compressed air. Automated chromatography was carried out using a Teledyne ISCO Combiflash® chromatography system.

Preparative HPLC purification was performed on an Agilent 1260 Infinity system fitted with a Supelcosil ABZ+Plus column (250 mm x 21.2 mm, 5 μm) using linear gradient systems (solvent A: 0.1% (v/v) TFA in water, solvent B: 0.05% (v/v) TFA in acetonitrile) at a flow rate of 20 mL min^{-1}.

Analytical HPLC analysis was performed on an Agilent 1260 Infinity system fitted with a Supelcosil ABZ+Plus column (150 mm x 4.6 mm, 3 μm) using linear gradient systems (solvent A: 0.05% (v/v) TFA in water, solvent B: 0.05% (v/v) TFA in acetonitrile) over 15 min at a flow rate of 1 mL min^{-1}. Retention times (tr) are reported to the nearest 0.01 min.

Infrared spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}) and assigned as either: weak (w), medium (m), strong (s) or broad (br).

Melting points were obtained on a Buchi B-545 melting point apparatus and are uncorrected.
Optical rotations were recorded on an Anton-Paar MCP polarimeter. α_D^{20} values are reported in 10^{-1} deg cm^2 g^{-1} at 598 nm, concentration (c) is given in g(100 mL)$^{-1}$.

Proton nuclear magnetic resonance (^1H NMR) were recorded on the following instruments: Bruker DPX-400 (400 MHz), Bruker Avance 400 QNP (400 MHz), Bruker BB 500 (500 MHz) and Bruker Avance 500 Cryo Ultrashield (500 MHz). They were recorded at room temperature unless otherwise stated. Chemical shifts are referenced to the residual non-deuterated solvent peak and quoted in parts per million to the nearest 0.01. Coupling constants are quoted in Hertz to the nearest 0.1 Hz and the data is reported as follows: chemical shift, integration, multiplicity (s, singlet; d, doublet; t, triplet; dd, doublet of doublets; m, multiplet; br, broad), coupling constant(s) and assignment. Assignments are supported by either chemical shift, coupling constants, 2D experiments (COSY, HMQC, HMBC and NOESY) or by comparison with similar, fully characterised compounds.

Carbon nuclear magnetic resonance (^{13}C NMR) were recorded on the following instruments: Bruker DPX-400 (101 MHz), Bruker Avance 400 QNP (101 MHz), Bruker BB 500 (126 MHz) and Bruker Avance 500 Cryo Ultrashield (126 MHz). Chemical shifts are referenced to the residual non-deuterated solvent peak and quoted in parts per million to the nearest 0.1 ppm. Assignments are supported by either chemical shift, APT/DEPT, 2D experiments (HMQC and HMBC) or by comparison with similar, fully characterised compounds.

The numbering of molecules used for ^{13}C and ^1H NMR assignments does not conform to IUPAC standards.

Diastereotopic protons are identified as Hxa and Hxb (or Cxa and Cxb) where "x" is the numerical assignment and Hxa represents the higher shift. Terminal alkene protons are identified as
Hxc and Hxt where "x" is the numerical assignment, "c" indicates a cis coupling constant has been observed and "t" indicates a trans coupling constant has been observed.

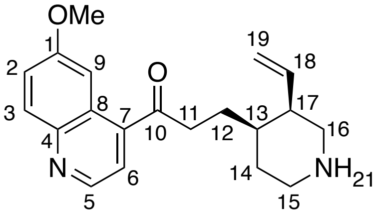
Low-resolution mass spectra (ESI) were recorded using an LCMS system (Agilent 1200 series LC with an ESCi Multi-Mode IonizationWaters ZQ spectrometer using MassLynx 4.0 software).

High-resolution mass spectrometry (HRMS) was carried out on a Micromass LCT Premier spectrometer using electron spray ionisation (ESI) or electron impact (EI) techniques. Masses are quoted within the 5ppm error limit.

4.2 Methods

4.2.1 Cores

4.2.1.1 Quinotoxine (2)



Quinine (20.0 g, 61.6 mmol) was dissolved in H_2O (600 mL) and AcOH (50 mL) and heated at reflux for 118 h. The reaction mixture was quenched with an aqueous NaOH solution (25% by weight) and extracted with EtOAc (3 x 600 mL). The organic extracts were combined, washed with H_2O (500 mL), brine (400 mL) and dried ($MgSO_4$). The solution was filtered and the solvent removed under reduced pressure to yield the title compound as a crude brown oil, which was used without further purification (18.8 g, 57.9 mmol, 94 %).

R$_f$ = 0.30 (10% methanol in CH_2Cl_2, TEA-deactivated SiO_2).

α_D^{20}= -17.8 (c = 0.18 in $CHCl_3$).

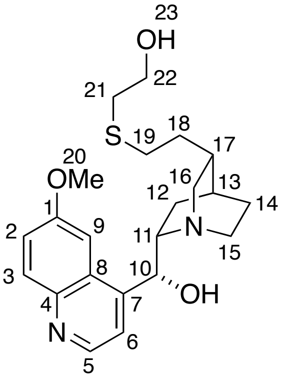
IR: λ$_{max}$ = 2924 (m, C–H), 1689 (m, C=O), 1617 (s, C=C), 1580 (w, C=C), 1506 (s, C=C).

^{1}H NMR (500 MHz, d$_6$-DMSO): δ_H = 8.88 (1H, d, *J* = 4.6 Hz, H5), 8.01 (1H, d, *J* = 9.2 Hz, H3), 7.90 (1H, d, *J* = 4.3 Hz, H6), 7.69 (1H, d, *J* = 2.8 Hz, H9), 7.48 (1H, dd, *J* = 9.2, 2.8 Hz, H2), 6.17 – 6.09 (1H, m, H18), 5.11 (1H, dd, *J* = 17.1, 2.1 Hz, H19t), 5.07 (1H, dd, 10.4, 2.4 Hz, H19c), 3.88 (3H, s, H20), 3.11 (2H, t, *J* = 7.5 Hz, H11), 2.96 (1H, d, *J* = 9.8 Hz, H15a), 2.85 (1H, d, *J* = 10.7 Hz, H16a), 2.74 (1H, d, *J* = 11.9 Hz, H16b), 2.58 – 2.52 (1H, m, H15b), 2.30 (1H, br s, H17), 1.66 – 1.40 (4H, m, H12, H13, H14a), 1.37 - 1.30 (1H, m, H14b).

^{13}C NMR (126 MHz, d$_6$-DMSO): δ_C = 204.9 (C10), 158.9 (C1), 148.1 (C5), 145.2 (*sp*^{2}-C), 141.1 (*sp*^{2}-C), 136.5 (C18), 131.6 (C3), 124.8 (*sp*^{2}-C), 122.5 (C2), 121.1 (C6), 116.5 (C19), 103.7 (C9), 55.9 (C20), 51.2 (C16), 45.9 (C15), 42.3 (C17), 39.4 (C11), 38.0 (C13), 28.4 (C14), 27.6 (C12).

HRMS (ESI+): *m/z* found $[M+H]^+$ 325.1916, $C_{20}H_{25}O_2N_2$ required 325.1911.
Literature procedure followed.[30]

4.2.1.2 Diol (3)



A stirred solution of quinine (10.0 g, 30.8 mmol) in 2-mercaptoethanol (30 mL) was refluxed at 80 °C for 72 h after which the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on TEA-deactivated silica, eluting with a gradient from 0% to 20% MeOH in CH_2Cl_2 to yield the title compound as a pale yellow foam (5.30 g, 13.2 mmol, 43%).

R$_f$ = 0.13 (40% EtOAc in petroleum ether 40–60, TEA-deactivated SiO_2).

α_D^{20} = -136 (c = 0.17 in MeOH).

IR: λ$_{max}$ = 3151 (br, O–H), 2913 (w, C–H), 1620 (s, C=C), 1591 (w, C=C), 1506 (s, C=C).

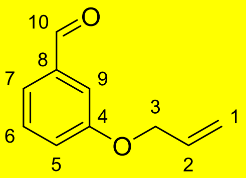
^{1}H NMR (500 MHz, d$_4$-MeOH): δ_H =8.68 (1H, d, *J* = 4.6 Hz, H5), 7.97 (1H, d, *J* = 9.5 Hz, H3), 7.70 (1H, d, *J* = 4.6 Hz H6), 7.46 – 7.43 (2H, m, H2, H9), 5.59 (1H, d, *J* = 3.4 Hz, H10), 4.00 (3H, s, H20), 3.72 – 3.66 (1H, m, H15a), 3.62 (2H, t, *J* = 6.7 Hz, H22), 3.17 – 3.11 (2H, m, H11, H16a), 2.75 – 2.68 (1H, m, H15b), 2.58 (2H, t, *J* = 6.7 Hz, H21), 2.50 (2H, t, *J* = 7.3 Hz, H19), 2.48 – 2.43 (1H, m, H16b), 1.96 – 1.86 (2H, m, H12a, H14a), 1.80 (2H, br s, H13, H17), 1.58 – 1.42 (4H, m, H12b, H14b, H18).

^{13}C NMR (126 MHz, d$_4$-MeOH): δ_C = 159.9 (C1), 150.8 (*sp*^{2}-C), 148.3 (C5), 144.9 (*sp*^{2}-C), 131.5 (C3), 128.3 (*sp*^{2}-C), 123.5 (C2/C9), 120.3 (C6), 102.7 (C2/C9), 72.4 (C10), 62.6 (C22), 61.1 (C11), 59.2 (C16), 56.6 (C20), 44.3 (C15), 35.8 (C18), 35.7 (C17), 35.4 (C21), 31.0 (C19), 28.8 (C14), 27.1 (C13), 21.7 (C12).

HRMS (ESI+): *m/z* found $[M+H]^+$ 403.2038, $C_{22}H_{31}O_3N_2S$ required 403.2050.
Literature procedure followed.[55]

4.2.2 Building Blocks

4.2.2.1 3-(allyloxy)benzaldehyde (22)



To a stirred solution of 3-hydroxybenzaldehyde (8.0 g, 65.6 mmol) in acetonitrile (80 mL) was added allylbromide (11.0 mL, 131 mmol), KI (1.09 g, 6.56 mmol), 18-crown-6 (864 mg, 3.26 mmol) and K_2CO_3 (26.4 g, 191 mmol) at rt, after which the solution was refluxed at 75 °C for 18 h. The K_2CO_3 was filtered off and the solvent was removed under reduced pressure. H_2O (100 mL) was added and the aqueous layer extracted with EtOAc (2 x 100 mL). The organic layer was separated, washed with brine (50 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure to yield the title compound as an orange oil, which was used without further purification (10.5 g, 64.4 mmol, 98%).

R_f = 0.38 (5% EtOAc in hexane).

IR: λ_{max} = 2861 (w, C–H), 1681 (s, C=O), 1598 (s, C=C), 1483 (m, C=C), 1457 (m, C=C).

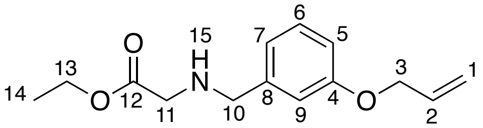
^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 9.92 (1H, s, H10), 7.37 - 7.44 (2H, m, H6 & H7), 7.36 (1H, dd, *J*=2.0, 1.0 Hz, H9), 7.15 (1H, dt, *J*=7.2, 2.4 Hz, H5), 5.96 - 6.09 (1H, ddt, *J*=17.2, 10.5, 5.2 Hz, H2), 5.40 (1H, dq, *J*=17.3, 1.5 Hz, H1t), 5.28 (1H, dq, *J*=10.6, 1.4 Hz, H1c), 4.55 (2H, dt, *J*=5.3, 1.4 Hz, H3)

^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 192.0 (C10), 159.1 (C4), 137.8 (C8), 132.7 (C2), 130.1 (C6), 123.5 (C7), 122.0 (C5), 118.0 (C1), 113.1 (C9), 68.9 (C3)

HRMS (ESI+): *m/z* found $[M+H]^+$ 163.0751, $C_{10}H_{11}O_2$ required 163.0754.

Modified from an unpublished procedure.[66] Data consistent with that reported in the literature.[67]

4.2.2.2 ethyl (3-(allyloxy)benzyl)glycinate (23)



To a stirred solution of **22** (774 mg, 4.77 mmol) and ethyl glycine hydrochloride (1.00 g, 7.16 mmol) in DCE (30 mL), TEA (1.33 mL, 9.54 mmol) and 4Å molecular sieves were added. After 2 h, 50% of the required $NaBH(OAc)_3$ (1.42 g, 6.68 mmol) was added and the final 50% added after an additional 20 min. The reaction was allowed to stir at rt for 12 h, after which it was quenched with saturated aqueous Na_2CO_3 solution (30 mL) and subsequently extracted with CH_2Cl_2 (3 x 30 mL). The organic extracts were combined, washed with brine (50 mL) and dried ($MgSO_4$). The solution was filtered and solvent removed under reduced pressure. The crude product was purified by flash column chromatography (CombiFlash Companion), eluting with a gradient from 0% to 100% EtOAc in petroleum ether 40–60 to yield the title compound as a colourless oil (456 mg, 1.83 mmol, 38%).

R_f =0.16 (40% EtOAc in petroleum ether 40–60).

IR: λ_{max} = 2983 (w, C–H), 1734 (s, C=O), 1598 (m, C=C), 1585 (m, C=C).

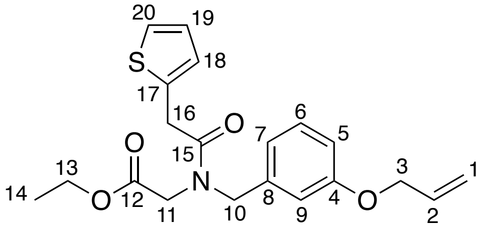
^{1}H NMR (500 MHz, $CDCl_3$): δ_H =7.25 (1H, t, *J* = 7.9 Hz, H6), 6.95 – 6.92 (2H, m, H5/H7/H9), 6.85 – 6.82 (1H, m, H5/H7/H9), 6.08 (1H, ddt, *J* = 17.4, 10.7, 5.2 Hz, H2), 5.44 (1H, dq, *J* = 17.4, 1.5 Hz, H1t), 5.30 (1H, dq, *J* = 10.7, 1.2 Hz, H1c) 4.56 (2H, dt, *J* = 5.5, 1.5 Hz, H3), 3.81 (2H, s, H10/H11), 3.42 (2H, s, H10/H11), 4.22 (2H, q, *J* = 7.3 Hz, H13), 1.30 (3H, t, *J* = 7.3 Hz, H14).

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 172.4 (C12), 158.8 (C4), 141.2 (C8), 133.3 (C2), 129.4 (C6), 120.7 (C5/C7/C9), 117.6 (C1), 114.5 (C5/C7/C9), 113.5 (C5/C7/C9), 68.7 (C3), 60.8 (C13), 53.2 (C10), 50.1 (C11), 14.3 (C14).

HRMS (ESI+): *m/z* found $[M+H]^+$ 250.1434, $C_{14}H_{20}O_3N$ required 250.1443.

Modified from a literature procedure.[61] Novel compound.

4.2.2.3 Ethyl N-(3-(allyloxy)benzyl)-N-(2-(thiophen-2-yl)acetyl)glycinate (24)



Acyl chloride preparation: To a stirred solution of 2-thiopheneacetic acid (260 mg, 1.83 mmol) and oxalyl chloride (201 μL, 2.38 mmol) in CH_2Cl_2 (6 mL), catalytic amounts of DMF were added. After stirring for 5 h until TLC indicated complete turnover, the solvent was removed under reduced pressure and the acyl chloride was used without further purification.

Amide formation: To a stirred solution of the freshly prepared acyl chloride in CH_2Cl_2 (6 mL), **23** (350 mg, 1.40 mmol) and saturated aqueous $NaHCO_3$ (excess) were added. After vigorous stirring for 18 h, the organic solvent was removed under reduced pressure. The residue was diluted with EtOAc (20 mL), washed successively with saturated aqueous $NaHCO_3$ solution (20 mL), aqueous HCl solution (1.0 M, 20 mL), H_2O (20 mL) and brine (20 mL) and dried ($MgSO_4$). The solution was filtered and solvent removed under reduced pressure. The crude product was purified by flash column chromatography on silica, eluting with a gradient from 10% to 40% EtOAc in petroleum ether 40–60 to yield the title compound as a colourless oil (165 mg, 441 μmol, 24%).

R_f = 0.44 (50% EtOAc in petroleum ether 40–60).

IR: λ_{max} = 2982 (w, C–H), 1742 (s, C=O), 1649 (s, C=C), 1601 (m, C=C).

^{1}H NMR (500 MHz, d_6-DMSO, 120 °C): δ_H = 7.41 (1H, dd, *J* = 5.0, 2.9 Hz, ArH), 7.26 – 7.22 (2H, m, ArH), 7.02 (1H, dd, *J* = 5.0, 0.8 Hz, ArH), 6.88 – 6.85 (1H, m, ArH), 6.84 – 6.80 (2H, m, ArH), 6.04 (1H, ddt, *J* = 17.4, 10.5, 5.5 Hz, H2), 5.38 (1H, dq, *J* = 17.2, 1.8 Hz, H1t), 5.26 (1H, dq, *J* = 10.7, 1.3 Hz, H1c), 4.60 (2H, br s, H10/H11), 4.55 (2H, dt, *J* = 5.2, 1.6 Hz, H3), 4.11 (2H, q, *J* = 7.1 Hz, H13), 4.07 (2H, br s, H10/H11), 3.76 (2H, br s, H16), 1.20 (3H, t, *J* = 7.1 Hz, H14).

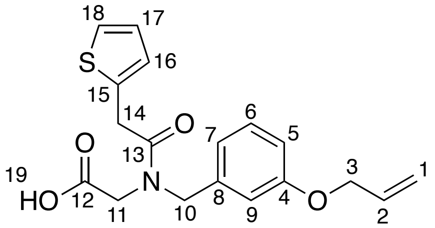
^{13}C NMR (126 MHz, d_6-DMSO, 120 °C): δ_C = 171.1 (*sp*^{2}-C), 135.5 (*sp*^{2}-C), 134.2 (C2), 129.0, 125.7, 122.6 (*sp*^{2}-C), 117.4 (C1), 69.0 (C3), 60.5 (C13), 40.7, 34.8 (*sp*^{3}-C), 14.2 (C14).

Quaternary carbons 4 and 8 were not observed. Due to the rotameric nature of the amide, carbons 15 - 20 were also not observed.

HRMS (ESI+): *m/z* found $[M+H]^+$ 374.1429, $C_{20}H_{24}O_4NS$ required 374.1421.

Modified from a literature procedure.[62]

4.2.2.4 Acid (18)



To a stirred solution of **24** (149 mg, 399 µmol) in THF (1 mL) was added an aqueous LiOH solution (1.0 M, 2 mL). After stirring for 6 h the reaction was acidified to pH 3 with an aqueous HCl solution (37%) and extracted with Et_2O (3 x 30 mL). The organic extracts were combined, washed with H_2O (30 mL), brine (30 mL) and dried ($MgSO_4$) The solvent was removed under reduced pressure to yield the title compound as a pale yellow oil, which was used without further purification (122 mg, 353 µmol, 89%).

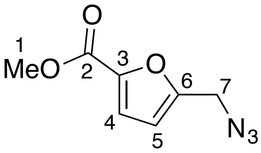
IR: λ_{max} = 2929 (w, C–H), 1733 (s, C=O), 1647 (s, C=C), 1600 (s, C=C).

^{1}H NMR (500 MHz, d_6-DMSO, 120 °C): δ_H = 7.40 (1H, dd, *J* = 5.0, 3.1 Hz, ArH), 7.25 – 7.22 (2H, m, ArH), 7.03 (1H, dd, *J* = 4.7, 1.1 Hz, ArH), 6.88 – 6.85 (1H, m, ArH), 6.83 – 6.80 (2H, m, ArH), 6.05 (1H, ddt, *J* = 17.5, 10.7, 5.3 Hz, H2), 5.39 (1H, dq, *J* = 17.2, 1.7 Hz, H1t), 5.25 (1H, dq, *J* = 10.5, 1.5 Hz, H1c), 4.60 (2H, br s, H10/H11/H13), 4.55 (2H, dt, *J* = 5.2 Hz, 1.6 Hz, H3), 4.00 (2H, br s, H10/H11/H13), 3.75 (2H, br s, H10/H11/H13).

^{13}C NMR (126 MHz, d_6-DMSO, 120 °C): δ_C = 171.1 (C12), 159.4 (C4), 139.4, 135.8 (C8, C17), 134.3 (C2), 130.0, 129.2, 125.7, 122.6, 120.5 (*sp*^{2}-C), 117.5 (C1), 114.7, 114.6 (*sp*^{2}-C) 69.1 (C3), 34.9 (C). Due to the rotameric nature of the amide, two carbons out of 10, 11 and 16 were not observed. C13 was also not observed.

HRMS (ESI+): *m/z* found $[M+H]^+$ 346.1106, $C_{18}H_{20}O_4NS$ required 346.1108.

4.2.2.5 methyl 5-(azidomethyl)furan-2-carboxylate (26)



A solution of methyl 5-(chloromethyl)-2-furoate (800 mg, 4.60 mmol) and NaN_3 (897 mg, 13.8 mmol) in DMF (10 mL) was heated at 65 °C for 1.5 h. The solution was diluted with EtOAc (50 mL), washed successively with H_2O (40 mL), saturated aqueous LiCl solution (2 x 40 mL), brine (40 mL) and dried ($MgSO_4$). The solution was filtered and the solvent removed under reduced pressure to yield the title compound as an orange oil, which was used without further purification (695 mg, 3.84 mmol, 83%).

R_f = 0.14 (10% EtOAc in petroleum ether 40–60).

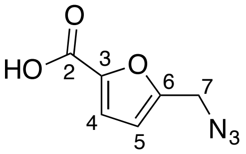
IR: λ_{max} = 2957 (m, C–H), 2096 (s, $-N_3$), 1723 (s, C=O), 1597 (w, C=C), 1534 (m, C=C), 1522 (m, C=C).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.17 (1H, d, *J* = 3.4 Hz, H4), 6.49 (1H, d, *J*= 3.4 Hz, H5), 4.40 (2H, s, H7), 3.92 (3H, s, H1).

^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 158.8 (C2), 153.2 (C3/C6), 144.9 (C3/C6), 118.7 (C4), 111.0 (C5), 52.1 (C7), 46.9 (C1).

HRMS (ESI+): *m/z* found $[M+Na]^+$ 204.0372, $C_7H_7O_3N_3Na$ required 204.0380.
Literature procedure followed.[68]

4.2.2.6 5-(azidomethyl)furan-2-carboxylic acid (27)



To a stirred solution of **26** (650 mg, 3.59 mmol) in THF (17 mL) was added an aqueous LiOH solution (1.0 M, 17 mL). After stirring for 2 h the reaction was acidified to pH 3 with an aqueous HCl solution (3.0 M) and the solvent was removed under reduced pressure. The product was extracted with Et_2O (2 x 50 mL). The organic extracts were combined, washed with H_2O (40 mL), brine (40 mL) and dried ($MgSO_4$). The solution was filtered and the solvent was removed under reduced pressure to yield the title compound as an amorphous pale yellow solid, which was used without further purification (495 mg, 2.96 mmol, 82%).

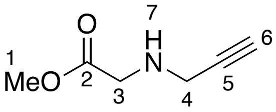
IR: λ_{max} = 2856 (br, O–H), 2084 (m, $-N_3$), 1683 (s, C=O), 1596 (m, C=C), 1536 (s, C=C).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.33 (1H, d, J = 3.4 Hz, H4), 6.54 (1H, d, J = 3.1 Hz, H5), 4.44 (2H, s, H7).

^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 163.1 (C2), 154.5 (C3/C6), 144.0 (C3/C6), 120.9 (C4), 111.3 (C5), 47.0 (C7).

Known compound.[62]

4.2.2.7 Methyl prop-2-yn-1-ylglycinate (30)



A solution of methyl bromoacetate (3.00 mL, 31.7 mmol), propargylamine (1.35 mL, 21.1 mmol) and TEA (4.42 mL, 31.7 mmol) in acetonitrile (60 mL) was stirred at 50 °C for 23 h. The solution was filtered and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography on silica, eluting with a gradient from 10% to 40% EtOAc in petroleum ether 40–60 to yield the title compound as an orange oil (1.87 g, 14.7 mmol, 46%).

R_f = 0.12 (50% EtOAc in petroleum ether 40–60).

IR: λ_{max} = 3284 (w, C–H), 2956 (w, C–H), 1735 (s, C=O).

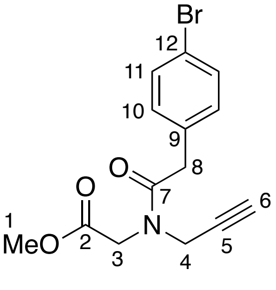
^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 3.76 (3H, s, H1), 3.54 (2H, s, H3), 3.51 (2H, d, J = 2.4 Hz, H4), 2.25 (1H, t, J = 2.4 Hz, H6).

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 172.3 (C2), 81.1 (C5), 72.0 (C6), 51.9 (C1), 49.1 (C3), 37.7 (C4).

HRMS (ESI+): m/z found $[M+H]^+$ 128.0709, $C_6H_{10}O_2N$ required 128.0706.

Literature procedure followed.[69] Data consistent with that reported in the literature.[69]

4.2.2.8 Methyl N-(2-(4-bromophenyl)acetyl)-N-(prop-2-yn-1-yl)glycinate (31)



Acyl chloride preparation: To a stirred solution of 4-bromophenylacetic acid (1.10 g, 5.12 mmol) and oxalyl chloride (565 µL, 6.68 mmol) in CH_2Cl_2 (15 mL), catalytic amounts of DMF were added. After stirring for 8 h until TLC indicated complete turnover, the solvent was removed under reduced pressure and the acyl chloride was used without further purification.

Amide formation: To a stirred solution of the freshly prepared acyl chloride in CH_2Cl_2 (15 mL), **30** (500 mg, 3.93 mmol) and saturated aqueous $NaHCO_3$ solution (excess) were added. After vigorous stirring for 15 h, the layers were separated and the organic phase was washed successively with aqueous HCl solution (1.0 M, 20 mL), saturated aqueous $NaHCO_3$ solution (20 mL), H_2O (20 mL), brine (20 mL) and dried ($MgSO_4$). The solution was filtered and solvent removed under reduced pressure. The crude product was purified by flash column chromatography on silica, eluting with a gradient from 10% to 50% EtOAc in petroleum ether 40–60 to yield the title compound as a colourless oil (901 mg, 2.78 mmol, 71%).

R_f = 0.30 (50% EtOAc in petroleum ether 40–60).

IR: λ_{max} = 3290 (w, C–H), 2953 (w, C–H), 1743 (s, C=O), 1652 (s, C=O).

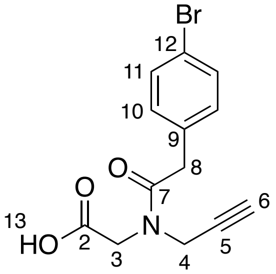
^{1}H NMR (500 MHz, d_6-DMSO, 120 ^{o}C): δ_H = 7.48 (2H, d, *J* = 8.4 Hz, H11), 7.21 (2H, d, *J* = 8.4 Hz, H10), 4.30 – 4.21 (4H, m, H3, H4), 3.76 (2H, br s, H8), 3.68 (3H, s, H1), 3.02 (1H, br s, H6).

^{13}C NMR (126 MHz, d_6-DMSO, 120 ^{o}C): δ_C = 170.6, 169.6 (C2, C7), 135.1 (*sp^2*-C), 131.9, 131.4 (C10, C11), 120.2 (*sp^2*-C), 79.2 (C2/C5), 52.0 (C1), 38.9 (*sp^3-C*). Due to the rotameric effects of the amide, carbons 5/6 and 2 from 3/4/8 were not observed.

HRMS (ESI+): *m/z* found $[M+H]^+$ 324.0225, $C_{14}H_{15}O_3N^{79}Br$ required 324.0230.

Modified from a literature procedure.[62]

4.2.2.9 N-(2-(4-bromophenyl)acetyl)-N-(prop-2-yn-1-yl)glycine (28)



To a stirred solution of **31** (865 mg, 2.67 mmol) in THF (13 mL) was added an aqueous LiOH solution (1.0 M, 13 mL). After stirring for 21 h the reaction was acidified to pH 3 with an aqueous HCl solution (3.0 M) and the solvent was removed under reduced pressure. The product was extracted with Et_2O (2 x 20 mL). The organic extracts were combined, washed with H_2O (30 mL), brine (30 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield the title compound as an amorphous white solid, which was used without further purification (691 mg, 2.23 mmol, 83%).

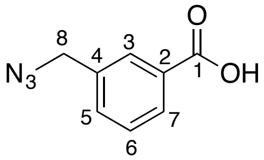
IR: λ_{max} = 3260 (w, C–H), 2929 (br, O–H), 1744 (s, C=O), 1608 (s, C=C).

^{1}H NMR (500 MHz, d_6-DMSO, 120 ^{o}C): δ_H = 7.46 (2H, d, *J* = 8.1 Hz, H11), 7.21 (2H, d, *J* = 7.8 Hz, H10), 4.26 (2H, br s, H3/H4), 4.17 (2H, br s, H3/H4), 3.74 (2H, br s, H8), 3.01 (1H, br s, H6).

^{13}C NMR (126 MHz, d_6-DMSO, 120 ^{o}C): δ_C = 170.7, 170.3 (C2, C7), 135.2 (*sp^2*-C), 131.9, 131.4 (C10, C11), 120.1 (*sp^2*-C), 79.5, 75.1 (C5, C6), 48.3, 38.9 (*sp^3*-C). One *sp^3* carbon missing.

HRMS (ESI+): *m/z* found $[M+Na]^+$ 331.9897, $C_{13}H_{12}O_3N^{79}BrNa$ required 331.9893.

4.2.2.10 3-(azidomethyl)benzoic acid (33)



A stirred solution of 3-(chloromethyl)benzoic acid (1.50 g, 8.79 mmol) and NaN_3 (686 mg, 10.6 mmol) in DMSO was stirred at 30 °C for 1.5 h. The reaction mixture was diluted with EtOAc (50 mL), washed successively with H_2O (2 x 30 mL), brine (30 mL) and dried ($MgSO_4$). The solution was filtered and the solvent removed under reduced pressure to yield the title compound as an off-white crystalline solid, which was used without further purification (1.10 g, 6.21 mmol, 71%).

m.p. =72–74 °C.

IR: λ_{max} = 2740 (br, O–H), 2087 (s, -N_3), 1678 (s, C=O), 1607 (w, C=C), 1587 (w, C=C).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.13 (1H, d, *J* = 7.8 Hz, H5/H7), 8.11 (1H, s, H3), 7.62 (1H, d, *J* = 7.5 Hz, H5/H7), 7.55 (1H, t, *J* = 7.7 Hz, H6), 4.47 (2H, s, H8).

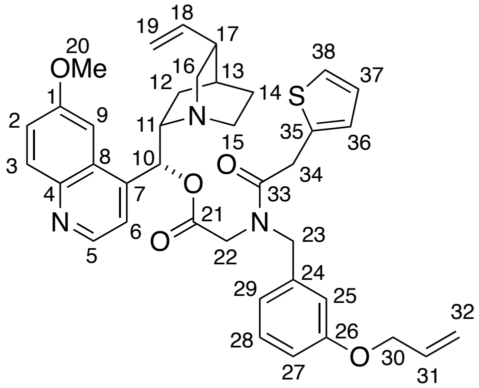
^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 171.6 (C1), 136.1 (C2/C4), 133.4 (C3/C5/C6/C7), 130.1 (C3/C5/C6/C7), 129.9 (C2/C4), 129.8 (C3/C5/C6/C7), 129.2 (C3/C5/C6/C7), 54.3 (C8).

HRMS (ESI+): *m/z* found $[M-H]^-$ 176.0457, $C_8H_6O_2N_3$ required 176.0465.

Literature procedure followed.[62] Data consistent with that reported in the literature.[62]

4.2.3 Macrocycles from structural class Mac1

4.2.3.1 Ester (35)



A solution of quinine (43.8 mg, 135 µmol), **18** (46.6 mg, 135 µmol) and DMAP (1.70 mg, 13.5 µmol) in CH_2Cl_2 (0.5 mL) was cooled to 0 °C, after which a solution of DCC (30.7 mg, 149 µmol) in CH_2Cl_2 (0.5 mL) was added. The solution was stirred at rt for 21 h, after which an additional 0.5 eq. of DCC was added. Stirring was allowed to continue at rt for 27 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed successively with saturated aqueous $NaHCO_3$ solution (2 x 20 mL), H_2O (20 mL), brine (20 mL) and dried ($MgSO_4$). The solution was filtered and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography on silica, eluting with a gradient from 0% to 4% methanol in EtOAc with 1% TEA to yield the title compound as an amorphous pale yellow solid (40.4 mg, 62.0 µmol, 46%).

R_f = 0.37 (10% methanol and 1% TEA in EtOAc).

α_D^{20} = -12.4 (c = 0.17 in $CHCl_3$).

^{1}H NMR (500 MHz, d_6-DMSO, 120 °C): δ_H = 8.69 (1H, d, *J* = 4.4 Hz, H5), 7.97 (1H, d, *J* = 9.1 Hz, H3), 7.50 (1H, d, *J* = 2.6 Hz, H9), 7.43 (1H, dd, *J* = 9.1, 2.6 Hz, H2), 7.40 – 7.36 (2H, m, ArH), 7.21 - 7.15 (2H, m, ArH), 6.99 – 6.94 (1H, m, ArH), 6.86 – 6.82 (1H, m, ArH), 6.78 – 6.73 (2H, m, ArH), 6.37 (1H, d, *J* = 8.1 Hz, H10), 6.02 (1H, ddt, *J* = 17.2, 10.7, 5.2 Hz, H31), 5.92 (1H, ddt, *J* = 17.5, 10.5, 7.1 Hz, H18), 5.37 (1H, dq, *J* = 17.2, 1.6

Hz, H32t), 5.24 (1H, dq, *J* = 10.7, 1.6 Hz, H32c), 5.04 (1H, dt, *J* = 17.2, 1.6 Hz, H19t), 5.01 (1H, dt, *J* = 10.5, 1.6 Hz, H19c), 4.66 - 4.50 (2H, m, H22/H23), 4.52 (2H, dt, *J* = 5.2, 1.6 Hz, H30), 4.17 (2H, br s, H22/H23), 3.94 (3H, s, H20), 3.73 (2H, br s, H34), 3.35 (1H, q, *J* = 8.2 Hz, H11), 3.09 - 3.02 (1H, m, H15a), 2.95 - 2.86 (1H, m, H16a), 2.57 - 2.49 (2H, m, H15b, H16b), 2.27 (1H, br s, H17), 1.88 - 1.86 (1H, m, H12a), 1.83 - 1.79 (1H, m, H13), 1.72 - 1.66 (1H, m, H14a), 1.54 - 1.43 (2H, m, H12b, H14b).

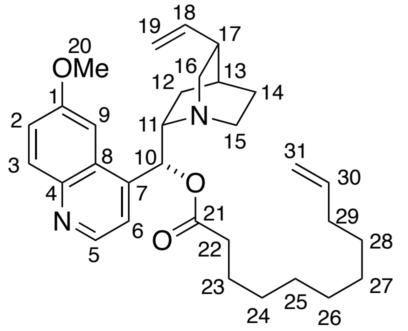
^{13}C NMR (126 MHz, d$_6$-DMSO, 120 °C): δ_C = 147.5 (C5), 142.4 (C18), 135.2 (*sp*^{2}-C), 134.1 (C31), 134.0 (*sp*^{2}-C), 131.5 (C3), 129.6, 128.7, 125.5, 122.3 (*sp*^{2}-C), 121.0 (C2), 120.1, 118.8 (*sp*^{2}-C), 117.2 (C32), 114.3 (2 x *sp*^{2}-C), 103.2 (C9), 74.5 (C10), 68.4 (C30), 59.5 (C11), 56.3 (C16), 55.7 (C20), 42.0 (C15), 39.4 (C17), 27.7 (C13), 27.3 (C14), 24.8 (C12).

Some quaternary peaks were not observed. Due to the rotameric effects of the amide, carbons 22, 23 and 34 were also not observed.

HRMS (ESI+): *m/z* found [M+H]$^+$ 652.2839, $C_{38}H_{42}O_5N_3S$ required 652.2840.

Modified from a literature procedure.[54]

4.2.3.2 Ester (36)



A solution of quinine (1.00 g, 3.08 mmol), undecylenic acid (622 µL, 3.08 mmol) and DMAP (37.6 mg, 308 µmol) in CH_2Cl_2 (6 mL) was cooled to 0 °C, after which a solution of DCC (700 mg, 3.39 mmol) in CH_2Cl_2 (2 mL) was added. The solution was stirred at rt for 24 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed successively with saturated aqueous $NaHCO_3$ solution (2 x 30 mL), H_2O (30 mL), brine (30 mL) and dried ($MgSO_4$). The solution was filtered and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography on TEA-deactivated silica, eluting with CH_2Cl_2 to yield the title compound as a viscous pale yellow oil (950 mg, 1.94 mmol, 63%).

R$_f$ = 0.79 (10% methanol in CH_2Cl_2, TEA-deactivated SiO_2).

$\boldsymbol{\alpha_D^{20}}$ = -22.0 (c = 0.05 in MeOH).

IR: λ$_{max}$ = 2927 (s, C–H), 2857 (m, C–H), 1739 (s, C=O), 1622 (s, C=C), 1593 (w, C=C), 1508 (s, C=C).

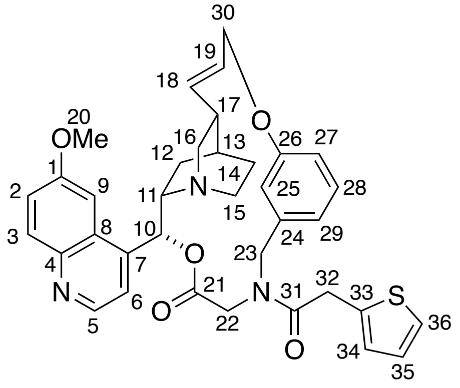
^{1}H NMR (500 MHz, CDCl$_3$): δ_H = 8.76 (1H, d, *J* = 4.4 Hz, H5), 7.84 (1H, d, *J* = 9.2 Hz, H3), 7.47 (1H, d, *J* = 2.7 Hz H9), 7.39 (1H, dd, *J* = 9.2, 2.7 Hz, H2), 7.36 (1H, d, *J* = 4.4 Hz, H6), 6.53 (1H, d, *J* = 7.2 Hz, H10), 5.91 – 5.77 (2H, m, H18, H30) 5.07 – 4.93 (4H, m, H19, H31), 3.98 (3H, s, H20), 3.40 (1H, q, *J* = 8.1 Hz, H11), 3.20 - 3.04 (2H, m, H15a, H16a), 2.72 – 2.61 (2H, m, H15b, H16b), 2.39 (2H, t, *J* = 7.5 Hz, H22), 2.31 (1H, br s, H17), 2.04 (2H, qt, *J* = 6.8, 1.4 Hz, H29), 1.94 – 1.85 (2H, m, H12a, H13), 1.77 – 1.70 (1H, m, H14a), 1.66 – 1.51 (4H, m, H12b, H14b, H23), 1.41 – 1.34 (2H, m, H28), 1.30 – 1.23 (8H, m, H24, H25, H26, H27).

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 72.9 (C21), 157.6 (C1), 147.3 (C5), 144.6 (sp^2-C), 143.2 (sp^2- C), 141.6, 138.9 (C18, C30), 131.6 (C3), 126.9 (sp^2-C), 121.5 (C2), 118.8 (C6), 114.3, 113.9 (C19, C31), 101.3 (C9), 73.5 (C10), 58.9 (C11), 56.4 (C16), 55.4 (C20), 42.2 (C15), 39.6 (C17), 34.3 (C22), 33.6 (C29), 29.1, 29.0, 28.1, 28.9, 28.8 (sp^3-C), 27.7 (C14), 27.5 (C13), 24.8 (C23), 24.4 (C12).

HRMS (ESI+): *m/z* found $[M+H]^+$ 491.3289, $C_{31}H_{43}O_3N_2$ required 491.3268.

Modified from a literature procedure.[54]

4.2.3.3 Macrocycle (12)



35 (33.0 mg, 50.6 μmol) and Grubbs' 2nd generation catalyst (4.30 mg, 5.06 μmol) were dissolved in CH_2Cl_2 (10 mL) and refluxed in a sealed tube at 80 °C for 16 h. The solvent was removed under reduced pressure and the crude product was purified by preparative HPLC (30-65B) to yield the title compound as an amorphous pale yellow solid (3.10 mg, 5.00 μmol, 10%).

R_f = 0.30 (10% methanol and 1% TEA in Et_2O).

$\boldsymbol{\alpha_D^{20}}$ = -1.00 (c = 0.1 in $CHCl_3$).

IR: $\boldsymbol{\lambda_{max}}$ = 2925 (m, C–H), 2853 (w, C–H), 1735 (m, C=O), 1647 (m, C=C), 1623 (m, C=C), 1509 (m, C=C).

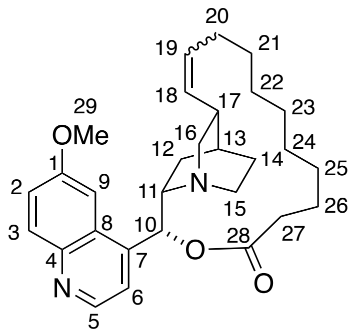
^{1}H NMR (500 MHz, d_6-DMSO, 120 °C): δ_H = 8.67 (1H, d, *J* = 4.4 Hz, H5), 7.93 (1H, d, *J* = 9.1 Hz, H3), 7.45 (1H, d, *J* = 2.6 Hz, H9), 7.41 – 7.37 (2H, m, ArH), 7.35 – 7.32 (1H, m, ArH), 7.10 – 7.03 (4H, m, ArH), 6.91 (1H, d, *J* = 7.6 Hz, ArH), 6.86 (1H, br s, ArH), 6.13 (1H, d, *J* = 8.6 Hz, H10), 5.88 (1H, dd, *J* = 15.9, 3.9 Hz, H18), 5.65 (1H, ddt, *J* = 16.2, 6.0, 2.1 Hz, H19), 4.78 (2H, d, *J* = 5.6 Hz, H30), 4.67 (1H, d, *J* = 15.2 Hz, H22a/H23a), 4.52 (1H, d, *J* = 15.2 Hz, H22b/H23b), 4.14 (2H, br s, H22/H23/H32), 3.93 (3H, s, H20), 3.74 (2H, br s, H22/H23/H32), 2.89 – 2.82 (1H, m, H15a), 2.75 (1H, app q, *J* = 9.4 Hz, H11), 2.65 (1H, dd, *J* = 13.3, 9.4 Hz, H16a), 2.53 – 2.51 (1H, m, H16b), 2.37 (1H, t, *J* = 11.0 Hz, H15b), 2.21 – 2.18 (1H, m, H17), 1.81 (1H, br s, H13), 1.62 – 1.56 (1H, m, H14a), 1.43 - 1.36 (2H, m, H12a, H14b), 0.99 – 0.94 (1H, m, H12b).

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 170.3 (C21), 168.6 (C31), 158.0 (sp^2-C), 157.6 (sp^2-C), 157.5 (sp^2-C), 147.6 (C5), 146.0 (sp^2-C), 140.4 (C18), 138.6 (sp^2-C), 135.5 (sp^2-C), 131.3 (C3), 129.7 (C9), 129.3 (sp^2-C), 126.8 (sp^2-C), 126.0 (sp^2-C), 124.4 (C19), 122.8 (sp^2-C), 121.9 (sp^2-C), 4 x 116.9 (sp^2-C), 102.0 (sp^2-C), 66.7 (C30), 56.0 (C20), 54.2 (C16), 53.1 (C22/C23), 50.4 (C22/C23/C32), 41.7 (C15), 35.5 (C17), 34.2 (C22/C23/C32), 25.2 (C13), 27.1 (C14), 26.1 (C12).

Carbons 10 and 11 were not observed.

HRMS (ESI+): *m/z* found $[M+H]^+$ 624.2523, $C_{36}H_{38}O_5N_3S$ required 624.2527.

4.2.3.4 Macrocycle (13)



To a stirred solution of **36** (50.0 mg, 102 μmol) in CH_2Cl_2 (20 mL) was added Grubbs' 2nd generation catalyst (8.69 mg, 10.2 μmol). The solution was subsequently degassed and refluxed at 40 ^{o}C for 18 h under an Ar atmosphere, after which the solvent was removed under reduced pressure. The crude product was purified by preparative HPLC (40-60B) to yield the title compound as an off-white amorphous solid (8.50 mg, 18.4 μmol, 18%).

$\mathbf{R_f}$ = 0.11 (50% EtOAc in petroleum ether 40-60, TEA-deactivated SiO_2).

α_D^{20} = -52.6 (c = 0.27 in $CHCl_3$).

IR: λ_{max} = 2928 (s, C–H), 2853 (m, C–H), 1731 (s, C=O), 1622 (m, C=C), 1509 (m, C=C).

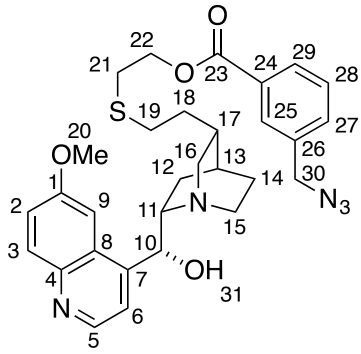
^{1}**H NMR** (400 MHz, d_4-MeOH): δ_H = 8.80 (1H, d, *J* = 4.4 Hz, H5), 8.04 (1H, d, *J* = 9.1 Hz, H3), 7.55 (1H, d, *J* = 2.7 Hz, H9), 7.42 (1H, d, *J* = 4.4 Hz, H6), 7.38 (1H, dd, *J* = 9.3, 2.7 Hz, H2), 6.52 (1H, d, *J* = 10.5 Hz, H10), 5.55 – 5.47 (2H, m, H18, H19), 3.98 (3H, s, H29), 3.50 (1H, q, *J* = 9.0 Hz, H11), 3.01 - 2.93 (1H, m, H15a), 2.88 – 2.80 (2H, m, H16), 2.59 (1H, t, *J* = 11.5 Hz, H15b), 2.39 – 2.24 (4H, m, H12a, H17, H27), 2.22 – 2.13 (2H, m, H20), 2.01 (1H, s, H13), 1.80 – 1.68 (2H, m, H14), 1.63 – 1.25 (13H, m, H12b, H21, H22, H23, H24, H25, H26).

^{13}**C NMR** (101 MHz, d_4-MeOH): δ_C = 172.5 (C28), 158.2 (C1), 146.9 (C5), 144.0 (*sp*^{2}-C), 134.2 (C18), 130.2 (C3), 128.9 (C19), 127.9 (*sp*^{2}-C), 122.4 (*sp*^{2}-C), 121.9 (C2), 120.9 (C6), 102.1 (C9), 73.0 (C10), 58.7 (C11), 54.9 (C29), 53.9 (C16), 41.9 (C15), 36.0 (C17), 34.4 (C27), 32.7 (C20), 28.8, 28.4, 27.8, 2 x 27.7, 27.3, 26.7, 26.6, 24.3 (*sp*^{3}-C).

HRMS (ESI+): *m/z* found $[M+H]^+$ 463.2950, $C_{29}H_{39}O_3N_2$ required 463.2955.

4.2.4 Macrocycles from structural class Mac 2

4.2.4.1 Ester (38)



A solution of **3** (500 mg, 1.24 mmol), **33** (220 mg, 1.24 mmol), EDCI (713 mg, 3.72 mmol) and DMAP (606 mg, 4.96 mmol) in CH_2Cl_2 (10 mL) was stirred at rt for 23 h. The solution was diluted with EtOAc (30 mL), washed successively with H_2O (2 x 20 mL), brine (20 mL) and dried ($MgSO_4$). The solution was filtered and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography on silica, eluting with a gradient from 0% to 8% MeOH in Et_2O with 1% TEA. A small amount of still impure material was then purified by preparative HPLC (30-65B) to yield the title compound as an off-white oil (23.6 mg, 42.0 μmol, 3%).

R$_f$ = 0.11 (10% methanol and 1% TEA in Et_2O).

α_D^{20} = -90.6 (c = 0.31 in MeOH).

IR: **λ_{max}** = 3146 (br, O–H), 2931 (m, C–H), 2096 (s, $-N_3$), 1718 (s, C=O), 1621 (m, C=C), 1591 (m, C=C), 1509 (m, C=C).

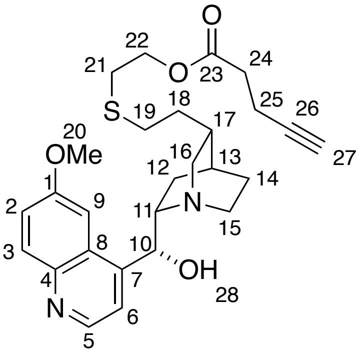
^{1}H NMR (500 MHz, d_4-MeOH): δ_H = 8.68 (1H, d, *J* = 4.6 Hz, H5), 7.96 - 7.94 (2H, m, ArH), 7.91 (1H, dt, *J* = 7.9, 1.5 Hz, H29), 7.71 (1H, d, *J* = 4.6 Hz, H6), 7.58 (1H, d, *J* = 7.6 Hz, H27), 7.48 (1H, t, *J* = 7.6 Hz, H28), 7.43 - 7.41 (2H, m, ArH), 5.73 (1H, s, H10), 4.43 (2H, s, H30), 4.40 (2H, t, *J* = 6.4 Hz, H22), 3.98 (3H, s, H20), 3.89 - 3.83 (1H, m, H15a), 3.35 - 3.26 (2H, m, H11, H16a), 2.91 - 2.85 (1H, m, H15b), 2.82 (2H, t, *J* = 6.7 Hz, H21), 2.67 - 2.62 (1H, m, H16b), 2.55 (2H, t, *J* = 7.3 Hz, H19), 2.03 - 1.85 (4H, m, H12a, H13, H14a, H17), 1.67 - 1.39 (4H, m, H12b, H14b, H18).

^{13}C NMR (126 MHz, d_4-MeOH): δ_C = 167.3 (C23), 159.9 (C1), 148.2 (C5), 149.3, 144.8, 138.0 (*sp*^{2}-C), 134.1 (C27), 131.8, 131.5, 130.3 (*sp*^{2}-C), 130.2 (C29), 130.1 (C28), 127.9, 123.4 (*sp*^{2}-C), 120.3 (C6), 102.5 (C9), 70.8 (C10), 65.4 (C22), 61.6 (C11), 58.4 (C16), 56.7 (C20), 55.0 (C30), 44.6 (C15), 35.1 (C18), 35.0 (C13/17), 31.3 (C21), 30.7 (C19), 27.5 (C14), 26.6 (C13/C17), 20.7 (C12).

HRMS (ESI+): *m/z* found $[M+H]^+$ 562.2478, $C_{30}H_{36}O_4N_5S$ required 562.2483.

Modified from a literature procedure.[55]

4.2.4.2 Ester (39)



A solution of **3** (100 mg, 248 µmol), 4-pentynoic acid (24.3 mg, 248 µmol), EDCI (143 mg, 744 µmol) and DMAP (121 mg mg, 992 µmol) in CH_2Cl_2 (2 mL) was stirred at rt for 16 h. The solution was diluted with EtOAc (30 mL), washed successively with H_2O (2 x 20 mL), brine (20 mL) and dried ($MgSO_4$). The solution was filtered and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography on silica, eluting with 5% MeOH in EtOAc with 1% TEA to yield the title compound as a colourless oil (67.9 mg, 141 µmol, 57%).

R$_f$ = 0.13 (5% methanol and 1% TEA in EtOAc).

α_D^{20} = -82.3 (c = 0.22 in $CHCl_3$).

IR: **λ_{max}** = 2925 (s, C–H), 1736 (s, C=O), 1621 (m, C=C), 1591 (w, C=C), 1509 (m, C=C).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.73 (1H, d, *J* = 4.4 Hz, H5), 8.01 (1H, d, *J* = 9.2 Hz, H3), 7.54 (1H, d, *J* = 4.4 Hz, H6), 7.35 (1H, dd, *J* = 9.2, 2.7 Hz, H2), 7.25 (1H, d, *J* = 2.4 Hz, H9), 5.63 (1H, br s, H10), 4.23 (2H, t, *J* = 7.2 Hz, H22), 3.92 (3H, s, H20), 3.57 – 3.46 (1H, m, H15a), 3.19 – 3.11 (2H, m, H11, H16a), 2.76 – 2.68 (1H, m, H15b), 2.71 (2H, t, *J*

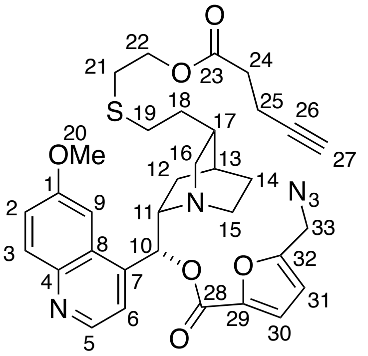
= 7.2 Hz, H21), 2.58 – 2.41 (7H, m, H16b, H19, H24, H25), 1.99 (1H, t, *J* = 2.4 Hz, H27), 1.85 – 1.68 (4H, m, H12a, H13, H14a, H17), 1.64 – 1.47 (4H, m, H12b, H14b, H18).

^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 171.5 (C23), 157.8 (C1), 147.6 (C5), 147.1, 144.3 (*sp*^{2}-C), 131.7 (C3), 126.6 (*sp*^{2}-C), 121.6 (C2), 118.4 (C6), 101.2 (C9), 82.3 (C26), 71.8 (C10), 69.1 (C27), 63.5 (C22), 59.8 (C11), 58.2 (C16), 55.8 (C20), 43.2 (C15), 34.6 (C17), 34.5 (C18), 33.2 (C19/C24/C25), 30.5 (C21), 30.3 (C19/C24/C25), 27.9 (C12), 25.6 (C13), 21.5 (C14), 14.4 (C19/C24/C25).

HRMS (ESI+): *m/z* found $[M+H]^+$ 483.2309, $C_{27}H_{35}O_4N_2S$ required 483.2312.

Modified from a literature procedure.[55]

4.2.4.3 Ester (41)



A solution of **39** (60.0 mg, 124 μmol), **27** (20.78 mg, 124 μmol) and DMAP (1.51 mg, 12.4 μmol) in CH_2Cl_2 (0.5 mL) was cooled to 0 °C, after which a solution of DCC (28.1 mg, 136 μmol) in CH_2Cl_2 (0.5 mL) was added. The solution was stirred at rt for 25 h. The reaction mixture was diluted with EtOAc (10 mL) and washed successively with H_2O (10 mL), saturated aqueous $NaHCO_3$ solution (10 mL), H_2O (10 mL), brine (10 mL) and dried (Na_2SO_4). The solution was filtered and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography on silica, eluting with a gradient from 0% to 2% MeOH in EtOAc with 1% TEA to yield the title compound as an amorphous yellow solid (41.3 mg, 65.4 μmol, 53%).

R_f = 0.24 (1% TEA in EtOAc).

$\boldsymbol{\alpha_D^{20}}$ = +27.0 (c = 0.10 in $CHCl_3$).

IR: $\boldsymbol{\lambda_{max}}$ = 2921 (w, C–H), 2099 (w, $-N_3$), 1729 (m, C=O), 1674 (w, C=O), 1621 (m, C=C), 1593 (w, C=C), 1509 (m, C=C).

^{1}H NMR (500 MHz, d_4-MeOH): δ_H = 8.69 (1H, d, *J* = 4.7 Hz, H5), 8.02 (1H, d, *J* = 9.2 Hz, H3), 7.61 (1H, d, *J* = 4.7 Hz, H6), 7.59 (1H, d, *J* = 2.9 Hz, H9), 7.51 (1H, dd, *J* = 9.2, 2.6 Hz, H2), 7.47 (1H, d, *J* = 3.4 Hz, H30), 6.79 (1H, d, *J* = 4.4 Hz, H10) 6.69 (1H, d, *J* = 3.7 Hz, H31), 4.50 (2H, s, H33), 4.21 (2H, dd, *J* = 7.1, 2.1 Hz, H22), 4.05 (3H, s, H20), 3.60 – 3.56 (1H, m, H11), 3.40 – 3.34 (1H, m, H15a), 3.24 – 3.19 (1H, m, H16a), 2.88 – 2.81 (1H, m, H15b), 2.72 (2H, t, *J* = 7.6 Hz, H21), 2.60 – 2.56 (1H, m, H16b), 2.56 (2H, t, *J* = 7.6 Hz, H19), 2.52 – 2.49 (2H, m, H24), 2.45 – 2.41 (2H, m, H25), 2.26 (1H, t, *J* = 2.6 Hz, H27), 2.09 – 1.84 (5H, m, H12, H13, H14a, H17), 1.73 – 1.61 (3H, m, H14b, H18).

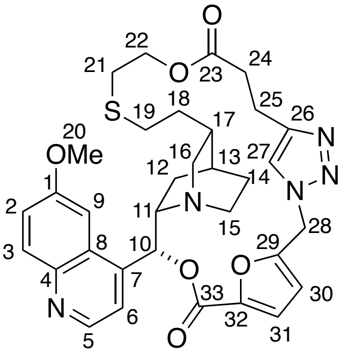
^{13}C NMR (126 MHz, d_4-MeOH): δ_C = 173.3 (C23/C28), 160.1, 158.4, 156.6 (C1, C29, C32), 148.2 (C5), 145.5 (*sp*^{2}-C), 145.1 (*sp*^{2}-C), 131.8 (C3), 128.0 (*sp*^{2}-C), 123.9 (C2), 121.3 (C30), 120.0 (C6), 112.5 (C31), 102.4 (C9), 83.3 (C26), 75.5 (C10), 70.2 (C27), 64.7 (C22), 60.0 (C11), 58.9 (C16), 56.6 (C20), 47.6 (C33), 44.0 (C15), 35.4 (C13/C17), 35.3 (C18), 34.3 (C24), 31.0 (C21), 30.7 (C19), 28.5 (C14), 26.7 (C13/C17), 23.4 (C12), 15.0 (C25).

One carbonyl carbon missing (C23/C28).

HRMS (ESI+): *m/z* found $[M+H]^+$ 632.2520, $C_{33}H_{38}O_6N_5S$ required 632.2537.

Modified from a literature procedure.[54]

4.2.4.4 Macrocycle (14)



41 (20.0 mg, 31.7 μmol) was dissolved in dry THF (30 mL) and DIPEA (16.7 μL, 95.7 μmol) was added. After bubbling argon through the solution for 20 min, CuI (24.2 mg, 127 μmol) was added and the mixture was refluxed for 10 h until HPLC indicated complete conversion of the starting material. Subsequently, the solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2/MeOH/TEA 10:1:0.1 and filtered through a pad of SiO_2. The crude product was purified by preparative HPLC (5-55B) to yield the title compound as an amorphous pale yellow solid (4.2 mg, 6.65 μmol, 21%).

R_f =0.17 (10% methanol and 1% TEA in EtOAc).

$\boldsymbol{\alpha_D^{20}}$ = +137 (c = 0.14 in $CHCl_3$).

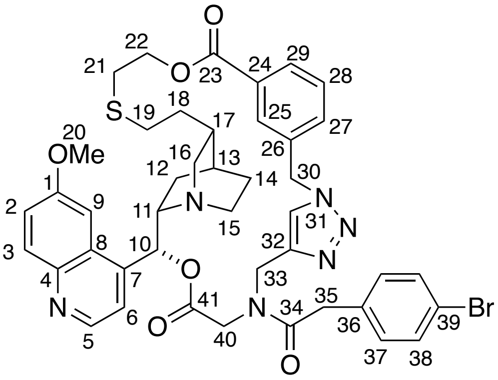
IR: $\boldsymbol{\lambda_{max}}$ = 2924 (m, C–H), 1722 (s, C=O), 1619 (m, C=C), 1598 (w, C=C), 1538 (w, C=C), 1508 (s, C=C).

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 8.68 (1H, d, *J* = 4.6 Hz, H5), 8.01 (1H, s, H27), 7.94 (1H, d, *J* = 9.2 Hz, H3), 7.53 (1H, d, *J* = 2.8 Hz, H9), 7.45 (1H, d, *J* = 4.6 Hz, H6), 7.42 (1H, dd, *J* = 9.2, 2.4 Hz, H2), 7.31 (1H, d, *J* = 3.4 Hz, H31), 6.84 (1H, d, *J* = 3.7 Hz, H30), 6.41 (1H, d, *J* = 7.6 Hz, H10), 5.78 (1H, d, *J* = 15.6 Hz, H28a), 5.74 (1H, d, *J* = 15.8 Hz, H28b), 4.21 (2H, t, *J* = 6.1 Hz, H22), 3.88 (3H, s, H20), 3.47 - 3.40 (1H, m, H11), 3.09 - 3.00 (1H, m, H15a), 2.97 - 2.93 (2H, m, H24/H25), 2.82 - 2.69 (5H, m, H16a, H21, H24/H25), 2.63 - 2.50 (2H, m, H19), 2.47 - 2.41 (1H, m, H15b), 2.12 (1H, d, *J* = 13.1 Hz, H16b), 1.87 - 1.81 (1H, m, H12a), 1.79 - 1.70 (2H, m, H13/H17, H18a), 1.65 - 1.58 (1H, m, H14a), 1.56 - 1.41 (3H, m, H12b, H13/H17, H18b), 1.33 - 1.26 (1H, m, H14b).

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 173.3 (C23/C33), 157.7, 157.3, 153.2 (C1, C29, C32), 148.0 (C5), 146.3 (*sp*^{2}-C), 144.4 (*sp*^{2}-C), 144.3 (*sp*^{2}-C), 131.8 (C3), 127.3 (*sp*^{2}-C), 123.1 (C27), 122.0 (C2), 121.0 (C31), 119.3 (C6), 112.6 (C30), 102.6 (C9), 74.3 (C10), 65.5 (C22), 60.0 (C11), 57.6 (C16), 56.0 (C20), 46.1 (C28), 42.1 (C15), 35.2 (C18), 34.9 (C13/C17), 33.6 (C24/C25), 30.7 (C19), 30.2 (C21), 28.1 (C14), 24.5, 24.5 (C12, C13/C17), 21.2 (C24/C25). Missing C23/C33.

HRMS (ESI+): *m/z* found $[M+H]^+$ 632.2525, $C_{33}H_{38}O_6N_5S$ required 632.2537.

4.2.4.5 Macrocycle (15)



40 (21.3 mg, 24.9 μmol) was dissolved in dry THF (30 mL) and DIPEA (13.0 μL, 74.7 μmol) was added. After bubbling argon through the solution for 20 min, CuI (19.0 mg, 99.8 μmol) was added and the mixture was refluxed for 46 h until HPLC indicated complete conversion of the starting material. Subsequently, the solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2/MeOH/TEA 10:1:0.1 and filtered through a pad of SiO_2. The crude product was purified by preparative HPLC (20-70B) to yield the title compound as an pale brown amorphous solid (2.2 mg, 2.58 μmol, 10%).

HPLC t_r = 8.68 min (20-70B).

α_D^{20} = -8.79 (c = 0.33 in $CHCl_3$).

IR: λ_{max} = 2926 (m, C–H), 2857 (m, C–H), 1720 (s, C=O), 1647 (m, C=C), 1621 (m, C=C), 1510 (s, C=C).

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 8.85 (1H, d, *J* = 4.3 Hz, H5), 8.68 (1H, br s, ArH), 8.22 (1H, br s, ArH), 8.03 (1H, d, *J* = 9.5 Hz, H3), 8.01 (1H, d, *J* = 7.9 Hz, ArH), 7.85* (1H, d, *J* = 7.6 Hz, ArH), 7.53 (2H, d, *J* = 8.5 Hz, ArH), 7.51 (1H, dd, *J* = 9.2, 2.8 Hz, H2), 7.27* (2H, d, *J* = 2.8 Hz, H9), 7.22 - 7.18 (2H, m, ArH), 7.05 (1H, br s, ArH), 6.55 (1H, br s, H10), 5.78 (2H, br s, H30), 5.02 (1H, d, *J* = 15.6 Hz, H33a/H35a/H40a), 4.66 (1H, d, *J* = 16.2 Hz, H33b/H35b/H40b), 4.54 - 4.49 (1H, m, H22a), 4.45 - 4.39 (1H, m, H22b), 4.34 (1H, d, *J* = 16.2 Hz, H33a/H35a/H40a), 4.26 (1H, d, *J* = 15.6 Hz, H33a/H35a/H40a), 4.22 (1H, d, *J* = 16.5 Hz, H33b/H35b/H40b), 3.92 (1H, d, *J* = 16.2 Hz, H33b/H35b/H40b), 3.91 (3H, s, H20) 3.58 - 3.53** (1H, m, H11), 3.31 - 3.00** (1H, m, H15a/H16a), 2.97 - 2.74 (5H, m, H15a/H16a, H15b, H16b, H21), 2.43 - 2.32 (2H, m, H19), 1.67 (1H, br s, H17), 1.29 - 1.01 (5H, m, H12, 13, 14), 0.75 (1H, br s, *sp*^{3}-H), 0.50 (1H, br s, *sp*^{3}-H).

* = HSQC indicates possible presence of rotamers.

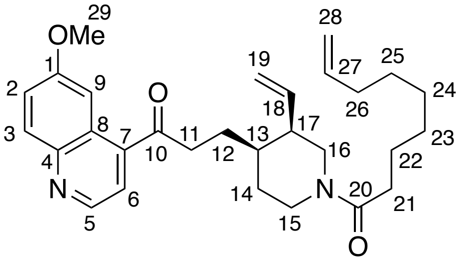
** = obscured by H_2O peak, assigned from HSQC.

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 171.8, 168.3, 165.6 (C23, C34, C41), 158.5, 158.4, 158.3 (*sp*^{2}-C), 147.7 (C5), 144.0, 143.3, 140.6, 136.7, 134.9, 134.8, 132.3 (*sp*^{2}-C), 131.8 (C3), 131.5, 130.4, 129.6, 125.6, 124.5 (*sp*^{2}-C), 122.3 (C2), 120.2, 118.0 (*sp*^{2}-C), 102.3 (C9), 70.1* (C10), 66.0 (C22), 56.8 (C11), 56.4 (C20), 54.4 (C15/C16), 53.1 (C30), 52.1 (C33/C35/C40), 44.4 (C33/C35/C40), 42.2 (C15/C16/C21), 38.9 (C33/C35/C40), 33.7 (*sp*^{3}-C), 32.2 (C17), 31.0 (C15/C16/C21), 30.2 (C19), 29.1* (*sp*^{3}-C), 24.4 (C13), 23.6 (*sp*^{3}-C). * = assigned from HSQC.

HRMS (ESI+): *m/z* found $[M+H]^+$ 853.2353, $C_{43}H_{46}O_6N_6S^{79}Br$ required 853.2383.

4.2.5 Macrocycles from structural class Mac3

4.2.5.1 Amide (42)



A solution of **2** (700 mg, 2.16 mmol) and 8-nonenoic acid (337 mg g, 2.16 mmol) in DMF (10 mL) was cooled to 0 ^{o}C, after which HATU (819 mg, 2.16 mmol), DIPEA (826 μL, 4.75 mmol) and DMAP (26.3 mg, 216 μmol) were added. The solution was allowed to warm to rt and stirred for 15 h. The reaction mixture was quenched with a saturated aqueous LiCl solution (40 mL) and extracted with EtOAc (3 x 40 mL). The organic layers were combined, washed successively with saturated aqueous $NaHCO_3$ (2 x 30 mL), saturated aqueous LiCl (3 x 30 mL) and brine (40 mL) and dried ($MgSO_4$). The solution was filtered and solvent removed under reduced pressure. The crude product was purified by flash column chromatography on TEA-deactivated silica, eluting with a gradient from 0% to 2% MeOH in CH_2Cl_2 to yield the title compound as a yellow oil (628 mg, 1.36 µmol, 63%).

R$_f$ = 0.79 (10% methanol in CH_2Cl_2, TEA-deactivated SiO_2).

$\boldsymbol{\alpha_D^{20}}$ = +22.5 (c = 0.16 in MeOH).

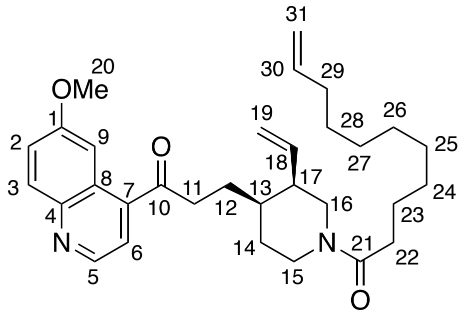
IR: $\boldsymbol{\lambda}_{\mathbf{max}}$ = 2928 (m, C–H), 2855 (m, C–H), 1688 (m, C=O), 1635 (s, C=C), 1618 (s, C=C), 1504 (m, C=C).

^{1}H NMR (500 MHz, d_6-DMSO, 120 ^{o}C): δ_H = 8.88 (1H, d, *J* = 4.4 Hz, H5), 8.03 (1H, d, *J* = 8.4 Hz, H3), 7.78 (1H, d, *J* = 4.4 Hz, H6), 7.70 (1H, d, *J* = 2.9 Hz, H9), 7.49 (1H, dd, *J* = 9.1, 2.9 Hz, H2), 5.88 – 5.76 (2H, m, H18, H27), 5.17 (1H, d, *J* = 17.5 Hz, H19t), 5.11 (1H, d, *J* = 10.5 Hz, H19c), 5.01 (1H, dt, *J* = 17.2, 5.03 Hz, H28t), 4.94 (1H, d, *J* = 10.2 Hz, H28c), 4.12 – 3.88 (2H, m, H15a, H16a), 3.92 (3H, s, H29), 3.16 – 3.04 (1H, m, H16b), 3.12 (2H, t, *J* = 7.6 Hz, H11), 2.99 – 2.88 (1H, m, H15b), 2.46 – 2.42 (1H, m, H17), 2.32 - 2.23 (2H, m, H21), 2.04 (2H, t, *J* = 7.1 Hz, H26), 1.84 – 1.79 (1H, m, H13), 1.73 – 1.62 (2H, m, H12), 1.58 – 1.51 (3H, m, H14a, H25), 1.42 – 1.30 (7H, m, H14b, H22, H23, H24).

^{13}C NMR (126 MHz, d_6-DMSO, 120 ^{o}C): δ_C = 203.3 (C10), 170.2 (C20), 158.1 (C1), 146.8 (C5), 144.4 (*sp*^{2}-C), 140.6 (*sp*^{2}-C), 138.1 (C18/C27), 135.7 (C18/C27), 130.5 (C3), 123.9 (*sp*^{2}-C), 121.0 (C2), 119.4 (C6), 116.9 (C19), 113.6 (C19/C28), 103.6 (C9), 55.0 (C29), 42.6 (C17), 38.7 (C11), 38.6, 38.3 (C15, C16), 37.4 (C13), 32.2 (C26), 31.7 (C21), 27.9, 27.9, 27.5 (C22, C23, C24), 26.8 (C14), 25.9 (C12), 24.2 (C25).

HRMS (ESI+): *m/z* found $[M+H]^+$ 463.2961, $C_{29}H_{39}O_3N_2$ required 463.2955.

4.2.5.2 Amide (43)



A solution of **2** (700 mg, 2.16 mmol) and undecylenic acid (398 mg, 2.16 mmol) in DMF (10 mL) was cooled to 0 ^{o}C, after which HATU (819 mg, 2.16 mmol), DIPEA (826 µL, 4.75 mmol) and DMAP (26.3 mg, 216 µmol) were added. The solution was allowed to warm to rt and stirred for 40 h. The reaction mixture was quenched with a saturated aqueous LiCl solution (30 mL) and extracted with EtOAc (3 x 30 mL). The organic layers were combined, washed successively with saturated aqueous $NaHCO_3$ solution (2 x 30 mL), saturated aqueous LiCl solution (3 x 30 mL), brine (30 mL) and dried ($MgSO_4$). The solution was filtered and solvent removed under reduced pressure. The crude product was purified by flash column chromatography on TEA-deactivated silica, eluting with a gradient from 0% to 2% MeOH in CH_2Cl_2 to yield the title compound as a yellow oil (570 mg, 1.16 µmol, 54%).

R$_f$ = 0.89 (10% methanol in CH_2Cl_2, TEA-deactivated SiO_2).

$\boldsymbol{\alpha_D^{20}}$ = +20.5 (c = 0.19 in MeOH).

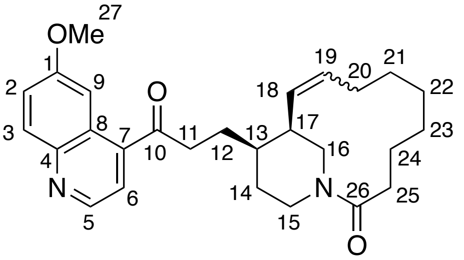
IR: $\boldsymbol{\lambda}_{\mathbf{max}}$ = 2926 (m, C–H), 2854 (m, C–H), 1689 (m, C=O), 1637 (s, C=C), 1617 (s, C=C), 1504 (m, C=C).

^{1}H NMR (500 MHz, d_6-DMSO, 120 ^{o}C): δ_H = 8.87 (1H, d, *J* = 4.2 Hz, H5), 8.03 (1H, d, *J* = 9.1 Hz, H3), 7.78 (1H, d, *J* = 4.4 Hz, H6), 7.70 (1H, d, *J* = 2.6 Hz, H9), 7.49 (1H, dd, *J* = 9.2, 2.9 Hz, H2), 5.87 – 5.76 (2H, m, H18, H30), 5.18 (1H, d, *J* = 18.0 Hz, H19t), 5.11 (1H, d, 10.5 Hz, H19c), 5.00 (1H, d, *J* = 17.2 Hz, H31t), 4.94 (1H, d, *J* = 10.2 Hz, H31c), 4.19 – 3.88 (2H, m, H15a, H16a), 3.93 (3H, s, H20), 3.18 – 3.04 (1H, m, H16b), 3.12 (2H, t, *J* = 7.6 Hz, H11), 2.99 – 2.86 (1H, m, H15b), 2.45 – 2.43 (1H, m, H17), 2.33 – 2.23 (2H, m, H22), 2.04 (2H, t, *J* = 7.1 Hz, H29), 1.84 – 1.77 (1H, m, H13), 1.73 – 1.62 (2H, m, H12), 1.58 – 1.28 (14H, m, H14, H23, H24, H25, H26, H27, H28).

^{13}C NMR (500 MHz, d$_6$-DMSO, 120 °C): δ_C = 204.3 (C10), 171.3 (C21), 159.2 (C1), 147.8 (C5), 145.4 (*sp*^{2}-C), 141.7 (*sp*^{2}-C), 139.1 (C18/C30), 136.7 (C18/C30), 131.5 (C3), 124.9 (*sp*^{2}-C), 122.0 (C2), 120.4 (C6), 116.7 (C19), 114.5 (C31), 104.6 (C9), 56.0 (C20), 42.6 (C17), 39.8 (C11), 39.6 (C15/C16), 39.3 (C15/C16), 38.4 (C13), 35.3 (C29), 32.7 (C22), 29.1, 2 x 29.0, 28.7, 28.6, 27.9*, 26.9, 25.2 (*sp*^{3}-C). * = assigned from HSQC.

HRMS (ESI+): *m*/*z* found [M+H]$^+$ 491.3277, $C_{31}H_{43}O_3N_2$ required 491.3268.

4.2.5.3 Macrocycle (16)



To a stirred solution of **42** (100 mg, 216 µmol) in toluene (30 mL) was added Grubbs' 2nd generation catalyst (18.4 mg, 20.4 µmol). The solution was subsequently degassed and refluxed at 120 °C for 19 h under an Ar atmosphere, after which an additional 0.1 eq. of Grubbs' 2nd generation catalyst was added. The reaction was refluxed for a further 28 h, after which the solvent was removed under reduced pressure. The crude product was purified by preparative HPLC (40-70B) to yield the title compound as an amorphous light brown solid (5.20 mg, 12.0 µmol, 6%).

HPLC t_r = 11.16 min (20-70B).

α_D^{20} = +58.0 (c = 0.05 in $CHCl_3$).

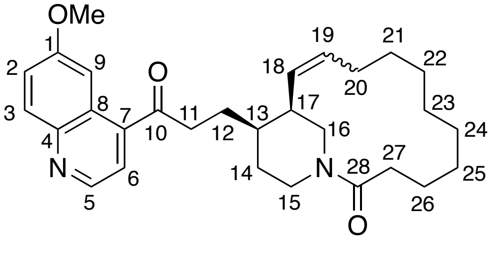
IR: λ_{max} = 2927 (s, C–H), 2857 (m, C–H), 1685 (m, C=O), 1618 (s, C=C), 1506 (m, C=C).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 8.90 (1H, br s, H5), 8.09 (1H, d, *J* = 8.9 Hz, H3), 7.88 (1H, br s, H6), 7.63 (1H, br s, H9), 7.45 (1H, d, *J* = 8.9 Hz, H2), 5.54 - 5.51 (2H, m, H18, H19), 4.89 (1H, d, *J* = 12.3 Hz, H15a), 3.99 - 3.95 (1H, m, H16a), 3.97 (3H, s, H27), 3.31 (1H, d, *J* = 10.7 Hz, H16b), 3.13 - 2.97 (2H, m, H25), 2.76 (1H, t, *J* = 12.0 Hz, H11a), 2.57 - 2.52 (1H, m, H15b), 2.48 - 2.46 (1H, m, H17), 2.27 - 2.17 (2H, m, H11b, H20a), 2.10 - 2.02 (1H, m, H20b), 1.93 - 1.88 (1H, m, H12a), 1.82 - 1.77 (2H, m, H13, H14a), 1.75 - 1.13 (10H, m, H12b, H14b, H21, H22, H23, H24).

^{13}C NMR (126 MHz, d$_6$-DMSO): δ_C = 204.7 (C10), 171.3 (C26), 159.0 (C1), 148.0 (C5), 145.1 (*sp*^{2}-C), 141.0 (*sp*^{2}-C), 131.5 (C18/C19), 131.1 (C3), 130.1 (C18/C19), 124.9 (*sp*^{2}-C), 122.6 (C2), 121.2 (C6), 103.8 (C9), 55.9 (C27), 55.0 (C16), 42.4 (C15), 41.2 (C17), 39.1 (C25), 37.9 (C13), 30.0, 28.5, 27.2, 26.9, 25.0, 24.9, 24.3, 22.8 (*sp*^{3}-C).

HRMS (ESI+): *m*/*z* found [M+H]$^+$ 435.2639, $C_{27}H_{35}O_3N_2$ required 435.2642.

4.2.5.4 Macrocycle (17)



To a stirred solution of **43** (100 mg, 204 µmol) in toluene (40 mL) was added Grubbs' 2nd generation catalyst (17.4 mg, 20.4 µmol). The solution was subsequently degassed and re- fluxed at 80 °C for 20 h under an Ar atmosphere, after which an additional 0.1 eq. of

Grubbs' 2nd generation catalyst was added. The reaction was refluxed for a further 18 h, after which the solvent was removed under reduced pressure. The crude product was purified by preparative HPLC (40-60B) to yield the title compound as an amorphous brown solid (2.80 mg, 6.05 μmol, 3%).

HPLC t_r = 13.47 min (20-70B).

α_D^{20} = +17.1 (c = 0.07 in $CHCl_3$).

IR: λ_{max} = 2924 (s, C–H), 2854 (m, C–H), 1686 (m, C=O), 1620 (s, C=C), 1505 (m, C=C).

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 8.88 (1H, d, *J* = 4.4 Hz, H5), 8.03 (1H, d, *J* = 9.1 Hz, H3), 7.81 (1H, d, *J* = 4.4 Hz, H6), 7.70 (1H, d, *J* = 2.9 Hz, H9), 7.49 (1H, dd, *J* = 9.1, 2.6 Hz, H2), 5.54 - 5.41 (2H, m, H18, H19), 3.91 (3H, s, H29), 3.80 - 3.67 (1H, m, H15a), 3.55 – 3.50 (1H, m, H16a), 3.29 – 3.26 (1H, m, H16b), 3.21 – 3.15 (2H, m, H11a, H15b), 3.08 – 3.02 (1H, m, H11b), 2.78 – 2.73 (1H, m, H17), 2.39 – 2.32 (1H, m, H20a), 2.25 – 2.06 (2H, m, H27), 2.04 – 1.90 (1H, m, H20b), 1.80 – 1.62 (3H, m, H12, H13), 1.59 – 1.14 (14H, m, H14, H21, H22, H23, H24, H25, H26).

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 204.3 (C10), 171.4 (C28), 158.6 (C1), 147.7 (C5), 144.7 (*sp*^{2}-C), 140.7 (*sp*^{2}-C), 132.7 (C18/C19), 131.1 (C3), 127.8 (C18/C19), 124.5 (*sp*^{2}-C), 122.2 (C2), 120.8 (C6), 103.4 (C9), 55.6 (C29), 36.8 (C17), 32.6 (C27), 49.6 (C16), 39.5 (C11), 36.7 (C13), 32.7 (C27), 27.0, 26.9, 26.7, 25.7 (*sp*^{3}-C), 25.4 (C20), 25.3, 25.0, 24.8, 23.5, (*sp*^{3}-C).

HRMS (ESI+): *m/z* found $[M+H]^+$ 463.2957, $C_{29}H_{39}O_3N_2$ required 463.2955.

4.3 Principal Moments of Inertia Computational Procedure

Using the Molecular Operating Environment (MOE) software, a conformational search and energy minimisation was carried out on the library. Specifically, the Merck molecular force field 94X (MMFF94X) with the generalised Born solvation model was used. The lowest-energy conformers were selected and used in the subsequent analyses. Table 1 highlights the conformational search settings used.

Table 1: Conformational search settings

Method	LowModeMD
Rejection Limit	100
RMS Gradient	0.005
Iteration Limit	10000
MM Iteration Limit	500
RMSD Limit	0.15
Energy Window	7
Conformation Limit	100

Acknowledgements

The research leading to these results has received funding from the European Research Council under the European Union's Seventh Framework Programme (FP7/2007-2013)/ERC grant agreement no [279337/DOS]. In addition, the group research was supported by grants from the Engineering and Physical Sciences Research Council, Biotechnology and Biological Sciences Research Council, Medical Research Council, Wellcome Trust and AstraZeneca.

Data accessibility: all data supporting this study are provided as Supplementary data accompanying this paper.

Supplementary data

Supplementary data (Copies of ^{1}H NMR and ^{13}C NMR spectra) associated with this article can be found in the online version.

References

[1] Tan DS, Foley MA, Shair MD, Schreiber SL. Stereoselective Synthesis of over Two Million Compounds Having Structural Features Both Reminiscent of Natural Products and Compatible with Miniaturized Cell-Based Assays
J Am Chem Soc. 1998;120 (33):8565-8566.

[2] Galloway WRJD, Spring DR. Is Synthesis the Main Hurdle for the Generation of Diversity in Compound Libraries for Screening? . *Expert Opinion: Drug Discovery*. 2009;4 (5):467-472.

[3] O'Connell KMG, Galloway WRJD, Ibbeson BM, Isidro-Llobet A, O'Connor CJ, Spring DR. Diversity-Oriented Synthesis. in: P.H. Toy, W. Lam (Eds.) *Solid-Phase Organic Synthesis Concepts, Strategies, and Applications*, Wiley2012: pp. 131-150.

[4] Borman S. Rescueing Combichem. *C&EN: Science & Technology*. 2004;82 (40):32-40.

[5] Barnes EC, Kumar R, Davis RA. The use of isolated natural products as scaffolds for the generation of chemically diverse screening libraries for drug discovery. *Nat Prod Rep*. 2016;33 (3):372-381.

[6] Grabowski K, Baringhaus KH, Schneider G. Scaffold diversity of natural products: inspiration for combinatorial library design. *Nat Prod Rep*. 2008;25 (5):892-904.

[7] Maier ME. Design and synthesis of analogues of natural products. *Org Biomol Chem*. 2015;13 (19):5302-5343.

[8] Wessjohann LA. Synthesis of natural-product-based compound libraries. *Current Opinion in Chemical Biology*. 2000;4 303-309.

[9] Feher M, Schmidt JM. Property Distributions: Differences between Drugs, Natural Products, and Molecules from Combinatorial Chemistry. *J Chem Inf Comput Sci* 2003;43 218-227.

[10] Newman DJ, Cragg GM, Snader KM. Natural Products as Sources of New Drugs over the Period 1981-2002. *J Nat Prod*. 2003;66 1022-1037.

[11] Rouhi AM. Rediscovering Natural Products. *C&EN: Science and Technology*. 2003;81 (41):77-78.

[12] Wessjohann LA, Ruijter E. Strategies for Total and Diversity-Oriented Synthesis of Natural Product (-like) Macrocycles. in: J.H. Mulzer (Ed.) *Natural Product Synthesis I: Targets, Methods, Concepts*, Springer-Verlag Berlin Heidelberg2005: pp. 137.

[13] Henkel T, Brunne RM, Müller H, Reichel F. Statistical Investigation into the Structural Complimentarity of Natural products and Synthetic Compounds. *Angew Chem Int Ed*. 1999;38 (5):643-647.

[14] Link A. Active Substance Development: Custom-Made Needles from Combinatoric Haystacks. *Pharmazeutische Zeitung*. 2001;146 (43):10-16.

[15] Newman DJ, Cragg GM. Natural products as sources of new drugs over the 30 years from 1981 to 2010. *J Nat Prod*. 2012;75 (3):311-335.

[16] Camp D, Garavelas A, Campitelli M. Analysis of Physicochemical Properties for Drugs of Natural Origin. *J Nat Prod*. 2015;78 (6):1370-1382.

[17] Newman DJ, Cragg GM. Natural Products as Sources of New drugs from 1981-2014. *J Nat Prod*. 2016;79 629-661.

[18] Fürstner A. From Total Synthesis to Diverted Total Synthesis: CaseStudies in the Amphidinolide Series. *Isr J Chem* 2011;51 329-345.

[19] Xu L-M, Liang Y-F, Ye Q-D, Yang Z. Diversity-Oriented Syntheses of Natural Products and Natural Product-Like Compounds. in: K. Ding, L.-X. Dai (Eds.) *Organic Chemistry – Breakthroughs and Perspectives*, Wiley-VCH Verlag GmbH & Co2012: pp. 1-31.

[20] Ciardiello JJ, Galloway WRJD, O'Connor CJ, Sore HF, Stokes JE, Wu Y, Spring DR. An expedient strategy for the diversity-oriented synthesis of macrocyclic compounds with natural product-like characteristics. *Tetrahedron*. 2016;72 (25):3567-3578.

[21] Morrison KC, Hergenrother PJ. Natural products as starting points for the synthesis of complex and diverse compounds. *Nat Prod Rep*. 2014;31 (1):6-14.

[22] Rizzo S, Waldmann H. Development of a natural-product-derived chemical toolbox for modulation of protein function. *Chem Rev*. 2014;114 (9):4621-4639.

[23] Ko SK, Jang HJ, Kim E, Park SB. Concise and diversity-oriented synthesis of novel scaffolds embedded with privileged benzopyran motif. *Chem Commun (Camb)*. 2006;(28):2962-2964.

[24] An H, Eum S-J, Koh M, Lee SK, Park SB. Diversity-Oriented Synthesis of Privileged Benzopyranyl Heterocycles from s-cis-Enones. *J Org Chem*. 2008;73 1752-1761.

[25] Oh S, Jang HJ, Ko SK, Ko Y, Park SB. Construction of a Polyheterocyclic Benzopyran Library with Diverse Core Skeletons through Diversity-Oriented Synthesis Pathway. *J Comb Chem* 2010;12 548-558.

[26] Oh S, Park SB. A design strategy for drug-like polyheterocycles with privileged substructures for discovery of specific small-molecule modulators. *Chem Commun (Camb)*. 2011;47 (48):12754-12761.

[27] Park S, Srivastava A, Song H. Diversity-Oriented Synthesis of Functionalized Polyheterocycles from Garner Aldehyde. *Synthesis*. 2011;2011 (14):2215-2222.

[28] Kim H, Tung TT, Park SB. Privileged Substructure-Based Diversity-Oriented Synthesis Pathway for Diverse Pyrimidine-Embedded Polyheterocycles. *Org Lett*. 2013;15 (22):5814-5317.

[29] Galloway WRJD, Stokes JE, Spring DR. New Advances in Diversity-Oriented Synthesis. in: W. Czechtizky, P. Hampley (Eds.) *Small Molecule and Medicinal Chemistry: Strategies and Technologies*, John Wiley & Sons2016.

[30] Huigens RW, 3rd, Morrison KC, Hicklin RW, Flood TA, Jr., Richter MF, Hergenrother PJ. A ring-distortion strategy to construct stereochemically complex and structurally diverse compounds from natural products. *Nat Chem*. 2013;5 (3):195-202.

[31] Balthaser BR, Maloney MC, Beeler AB, Porco JA, Snyder JK. Remodelling of the natural product fumagillol employing a reaction discovery approach. *Nature Chemistry*. 2011;3 (12):969-973.

[32] Rafferty RJ, Hicklin RW, Maloof KA, Hergenrother PJ. Synthesis of complex and diverse compounds through ring distortion of abietic acid. *Angew Chem Int Ed Engl*. 2014;53 (1):220-224.

[33] Paciaroni N, Ratnayake R, Matthews J, Norwood V, Arnold A, Dang L, Luesch H, Huigens Iii RW. A Tryptoline Ring Distortion Strategy Leads to Complex and Diverse Biologically Active Molecules from the Indole Alkaloid Yohimbine. *Chemistry*. 2016.

[34] Krieger JP, Ricci G, Lesuisse D, Meyer C, Cossy J. Efficient and modular synthesis of new structurally diverse functionalized [n]paracyclophanes by a ring-distortion strategy. *Angew Chem Int Ed Engl*. 2014;53 (33):8705-8708.

[35] Rivera DG, Pando O, Bosch R, Wessjohann LA. A Biomimetic Approach for Polyfunctional Secocholanes: Tuning Flexibility and Functionality on Peptidic and Macrocyclic Scaffolds Derived from Bile Acids. *J Org Chem*. 2008;73 6229-6238.

[36] Ricardo MG, Morales FE, Garay H, Reyes O, Vasilev D, Wessjohann LA, Rivera DG. Bidirectional macrocyclization of peptides by double multicomponent reactions. *Org Biomol Chem*. 2015;13 (2):438-446.

[37] Eschenauer G, DePestel DD, Carver PL. Comparison of echinocandin antifungals. *Therapeutics and Clinical Risk Management* 2007;3 (1):71-97.

[38] Scheinfeld N. Telithromycin: a brief review of a new ketolide antibiotic. *J Drugs Dermatol*. 2004;3 (4):409-413.

[39] Wessjohann LA, Ruijter E, Garcia-Rivera D, Brandt W. What can a chemist learn from nature’s macrocycles?–A brief, conceptual view. *Molecular Diversity*. 2005;9 171-186.

[40] Nicolaou KC, Ninkovic S, Sarabia F, Vourloumis D, He Y, Vallberg H, Finlay MR, Yang Z. Total Syntheses of Epothilones A and B via a Macrolactonization-Based Strategy. *J Am Chem Soc*. 1997;119 7974-7991.

[41] O'Connell KM, Beckmann HS, Laraia L, Horsley HT, Bender A, Venkitaraman AR, Spring DR. A two-directional strategy for the diversity-oriented synthesis of macrocyclic scaffolds. *Org Biomol Chem*. 2012;10 (37):7545-7551.

[42] Driggers EM, Hale SP, Lee J, Terrett NK. The exploration of macrocycles for drug discovery--an underexploited structural class. *Nat Rev Drug Discov*. 2008;7 (7):608-624.

[43] Mallinson J, Collins I. Macrocycles in new drug discovery. *Future Med Chem*. 2012;4 (11):1409-1438.

[44] Marsault E, Peterson ML. Macrocycles are great cycles: applications, opportunities, and challenges of synthetic macrocycles in drug discovery. *J Med Chem*. 2011;54 (7):1961-2004.

[45] Xie J, Bogliotti N. Synthesis and Applications of Carbohydrate-Derived Macrocyclic Scaffolds *Chem Rev*. 2014;114 (15):7678-7739.

[46] Terrett NK. Methods for the synthesis of macrocycle libraries for drug discovery. *Drug Discov Today Technol*. 2010;7 (2):e97-e104.

[47] Isidro-Llobet A, Murillo T, Bello P, Cilibrizzi A, Hodgkinson JT, Galloway WR, Bender A, Welch M, Spring DR. Diversity-oriented synthesis of macrocyclic peptidomimetics. *Proc Natl Acad Sci U S A*. 2011;108 (17):6793-6798.

[48] Delorbe JE, Clements JH, Whiddon BB, Martin SF. Thermodynamic and Structural Effects of Macrocyclization as a Constraining Method in Protein-Ligand Interactions. *ACS Med Chem Lett*. 2010;1 (8):448-452.

[49] Aquino C, Sarkar M, Chalmers MJ, Mendes K, Kodadek T, Micalizio GC. A biomimetic polyketide-inspired approach to small-molecule ligand discovery. *Nat Chem*. 2011;4 (2):99-104.

[50] Madsen CM, Clausen MH. Biologically Active Macrocyclic Compounds - from Natural Products to Diversity-Oriented Synthesis. *European Journal of Organic Chemistry*. 2011;2011 (17):3107-3115.

[51] Wells JA, McClendon CL. Reaching for high-hanging fruit in drug discovery at protein-protein interfaces. *Nature*. 2007;450 (7172):1001-1009.

[52] Cummings MD, Lin T, Tahri A, McGowan D, Amssoms K, Last S, Devpgelaere B, Rouan M-C, Vijgen L, Berke JM, Dehertogh P, Fransen E, Cleiren E, Van der Helm L, Fanning G, Van Emelen K, Nyanguile O, Simmen K, Raboisson P, Vendeville S. Structure-Based Macrocyclization Yields Hepatitis C Virus NS5B Inhibitors with Improved Binding Affinities and Pharmacokinetic Properties. *Angew Chem Int Ed*. 2012;51 4637-4640.

[53] Ishii Y, Fujimoto R, Mikami M, Murakami S, Miki Y, Furukawa Y. Practical Syntheses of Chiral α-Amino Acids and Chiral Half-Esters by Kinetic Resolution of Urethane-Protected α-Amino Acid
N-Carboxyanhydrides and Desymmetrization of Cyclic *meso*-Anhydrides with New Modified CinchonavAlkaloid Catalysts. *Organic Process Research & Development*. 2007;11 (3):609-615.

[54] Dogo-Isonagie C, Bekele T, France S, Wolfer J, Weatherwax A, Taggi AE, Lectka T. Scalable Methodology for the Catalytic, Asymmetric r-Bromination of Acid Chlorides *J Org Chem*. 2006;71 8946-8949.

[55] Zhang T, He W, Zhao X, Jin Y. Asymmetric oxaziridination catalyzed by cinchona alkaloid derivatives containing sulfide. *Tetrahedron*. 2013;69 (35):7416-7422.

[56] Sanders NG, Meyers DJ, Sullivan DJ. Antimalarial efficacy of hydroxyethylapoquinine (SN-119) and its derivatives. *Antimicrob Agents Chemother*. 2014;58 (2):820-827.

[57] Zhao M-X, Tang W-H, Chen M-X, Wei D-K, Dai T-L, Shi M. Highly Enantioselective Michael Addition of 3-Aryloxindoles to Phenyl Vinyl Sulfone Catalyzed by Cinchona Alkaloid-Derived Bifunctional Amine-Thiourea Catalysts Bearing Sulfonamide as Multiple Hydrogen-Bonding Donors. *European Journal of Organic Chemistry*. 2011;2011 (30):6078-6084.

[58] Dinio T, Gorka AP, McGinniss A, Roepe PD, Morgan JB. Investigating the activity of quinine analogues versus chloroquine resistant Plasmodium falciparum. *Bioorg Med Chem*. 2012;20 (10):3292-3297.

[59] Rowan SJ, Brady PA, Sanders JKM. Structure-Directed Synthesis under Thermodynamic Control : Macrocyclic Trimers from Cinchona Alkaloids. *Angew Chem Int Ed*. 1996;35 (18):2143-2145.

[60] Debarge S, Thibaudeau S, Violeau B, Martin-Mingot A, Jouannetaud M-P, Jacquesy J-C, Cousson A. Rearrangement or gem-difluorination of quinine and 9-epiquinine and their acetates in superacid. *Tetrahedron*. 2005;61 (8):2065-2073.

[61] Abdel-Magid AF, Carson KG, Harris BD, Maryanoff CA, Shah RD. Reductive Amination of Aldehydes and Ketones with Sodium Triacetoxyborohydride. Studies on Direct and Indirect Reductive Amination Procedures. *J Org Chem*. 1996;61 3849-3862.
[62] Beckmann HS, Nie F, Hagerman CE, Johansson H, Tan YS, Wilcke D, Spring DR. A strategy for the diversity-oriented synthesis of macrocyclic scaffolds using multidimensional coupling. *Nat Chem*. 2013;5 (10):861-867.
[63] Schawrz MK, Sauer WHB. Molecular shape diversity of combinatorial libraries:a prerequisite for broad bioactivity. *J Chem Inf Comput Sci*. 2003;43 987-1003.
[64] Galloway WR, Isidro-Llobet A, Spring DR. Diversity-oriented synthesis as a tool for the discovery of novel biologically active small molecules. *Nat Commun*. 2010;1 80.
[65] Isidro-Llobet A, Hadje Georgiou K, Galloway WRJD, Giacomini E, Hansen MR, Méndez-Abt G, Tan YS, Carro L, Sore H, Spring DROBC, 13, 4570. A Diversity-Oriented Synthesis Strategy Enabling the Combinatorial-Type Variation of Macrocyclic Peptidomimetic Scaffolds. *Org Biomol Chem* 2015;13 4570-4580.
[66] Memeo MG. University of Cambridge, 2012.
[67] Khalil NSAM. Efficient Synthesis of Novel 1,2,4-Trazole fused acyclic and 21-28 Membered Macrocyclic and/or Lariat Macrocyclic Oxaazathia Crown Compounds with Potential Microbial Activity. *Eur J Med Chem*. 2010;45 (11):5265-5277.
[68] Walker DP, Wishka DG, Beagley P, Turner G, Solesbury N. Synthesis of (±)-8-Oxa-3-azabicyclo[3.2.1]octan-2-thione and (±)-2-Oxa-5-azabicyclo[2.2.1]heptan-6-thione: Potential Synthons for the Preparation of Novel Heteroaryl-Annulated Bicyclic Morpholines. *Synthesis*. 2011;7 1113-1119.
[69] Struthers H, Spingler B, Mindt TL, Schibli R. “Click-to-Chelate”: Design and Incorporation of Triazole-Containing Metal-Chelating Systems into Biomolecules of Diagnostic and Therapeutic Interest. *Chem Eur J* 2008;14 6173-6183.