Simplifying Nature: Towards The Design of Broad Spectrum Kinetoplastid Inhibitors, Inspired by Acetogenins

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Abstract

The need for new treatments for the neglected tropical diseases African sleeping sickness, Chagas disease and Leishmaniasis remains urgent with the diseases widespread in tropical regions, affecting the world's very poorest. We have previously reported bis-tetrahydropyran 1,4-triazole analogues designed as mimics of the annonaceous acetogenin natural product chamuvarinin, which maintained trypanocidal activity. Building upon these studies, we here report related triazole compounds with pendant heterocycles, mimicking the original butenolide of the natural product. Analogues were active against *T. brucei*, with a nitrofuran compound displaying nanomolar trypanocidal activity. Several analogues also showed strong activity against *T. cruzi* and *L. major*. Importantly, select compounds gave excellent selectivity over mammalian cells with a furan-based analogue highly selective while remaining active against all three cell lines, thus representing a potential lead for a new broad spectrum kinetoplastid inhibitor.

1. Introduction

As defined by the World Health Organization, a neglected tropical disease (NTD) is a tropical infection that affects millions of people worldwide[1] but has seen inadequate investigation into treatment.[2,3] This is principally due to the limited financial incentive in treating such conditions, which is linked to their prevalence in developing countries where healthcare spending is low and health infrastructure is poor. Three such diseases are African sleeping sickness,[4] Chagas disease[5] and Leishmaniasis,[6] spread by the related kinetoplastid parasitic causative agents *Trypanosoma brucei*, *Trypanosoma cruzi* and *Leishmania spp*, respectively. These parasites are present in tropical regions across the world; *T. brucei* in sub-Saharan Africa, *T. cruzi* in South America and increasingly in North America[7] and *Leishmania* throughout the tropics and sub-tropics.[8] All three diseases share a genetic similarity and treatments developed for one specific disease have sometimes proved effective in treating another e.g. nifurtimox was originally developed for Chagas disease but has subsequently found application as a combination therapy for African sleeping sickness.[9,10]

The tropical plants of the Annonaceae species have long been known for their therapeutic properties, with the crude extracts of fruits, leaves, roots and bark used in traditional medicinal practices to treat a range of tropical diseases.[11] Interest in this plant species as a source of potential new drugs intensified with the discovery of a family of fatty acid derived natural products, collectively termed the Annonaceous acetogenins, which now number in excess of 400.[12] Structurally, the acetogenins are C32/C34 fatty acids generally characterised by a central array of one to three tetrahydrofuran (THF) rings with flanking hydroxyl groups and appended with a terminal butenolide ring system as found in squamocin **1** and senegalene **2** (Figure 1).[13] In contrast the tetrahydropyran (THP) ring system is less common and only seven acetogenins bear this motif including chamuvarinin **3**. Members of this family
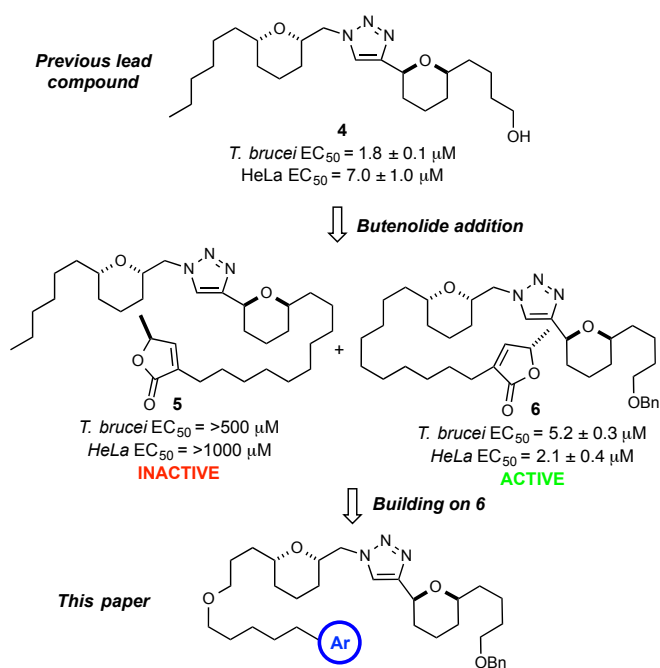
of secondary metabolites are often highly cytotoxic displaying sub-nanomolar activity towards human cancer cell lines.[14]
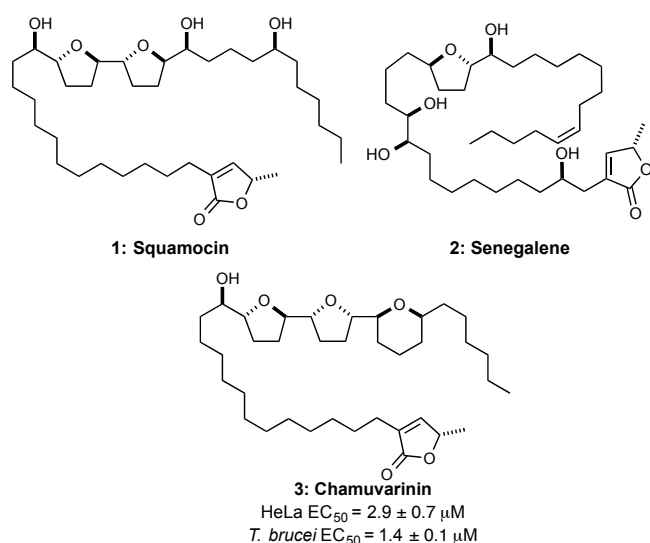
Figure 1 Annonaceous acetogenins with known anti-kinetoplastid activity

By contrast, the biological evaluation of acetogenins for the treatment of NTD has thus far been remarkably limited considering the wide scale use across sub-Saharan Africa of acetogenin-containing crude plant extracts to treat African sleeping sickness.[15] Studies to date have primarily focussed on the phytochemical study of extracts from Annonaceae species for trypanocidal activity, with efforts focused on *T. brucei*,[16] though select compounds such as squamocin **1** have shown encouraging preliminary activity against *T. cruzi* and *Leishmania* strains.[17] In 2003 Laurens *et al.* reported that the root and bark extracts of *Uvaria chamae* are active towards *T. brucei*, which subsequently led to the isolation of chamuvarinin **3**.[18] Chamuvarinin is one of only seven acetogenins to contain a tetrahydropyran ring system and the only acetogenin to contain an all adjacently linked bis-THF-THP core ether ring system. In 2011, we reported the first total synthesis of chamuvarinin thereby establishing its absolute stereochemical structure. In addition our synthetic material displayed single figure micromolar activity towards the bloodstream form of *T. brucei brucei*, albeit with low selectivity over the HeLa human cell line.[19]

We built on these studies by designing a series of analogues inspired by chamuvarinin **3** that maintained *T. brucei* activity commensurate to that of the natural product (Figure 2).[20] These analogues simplified the structure of chamuvarinin principally by replacing the central THF ring of the tricyclic core with a 1,4-triazole. This allowed rapid assembly of enantiomerically enriched THP building blocks via click chemistry, producing initial lead **4**, which displayed low (1.8 μM) trypanocidal activity against bloodstream form *T. brucei*. From this starting point, other features of the natural product were introduced, in particular the pendant butenolide, the orientation of which ('left- or right-hand side' as drawn) was critical to activity with **6** maintaining activity, while **5** was completely inactive. These results encouraged us to explore alternatives to the butenolide, principally on the azide, or 'left-hand side' of the molecule. Inspired by the work of Yamashita and co-workers, we have focused on simple aromatic heterocycles that were found to act as effective butenolide mimics.[21] Our phenotypic screening program has now expanded to the other NTD parasite cell lines, *T. cruzi* and *Leishmania major*, so new potential inhibitors were evaluated against all three protozoa.[22]

Previous lead compound

4
T. brucei EC_{50} = 1.8 ± 0.1 μM
HeLa EC_{50} = 7.0 ± 1.0 μM

Butenolide addition

5
T. brucei EC_{50} = >500 μM
HeLa EC_{50} = >1000 μM
INACTIVE

+

6
T. brucei EC_{50} = 5.2 ± 0.3 μM
HeLa EC_{50} = 2.1 ± 0.4 μM
ACTIVE

*Building on 6*

This paper

Ar

Figure 2 Directionality in our triazole based *T. brucei* inhibitors
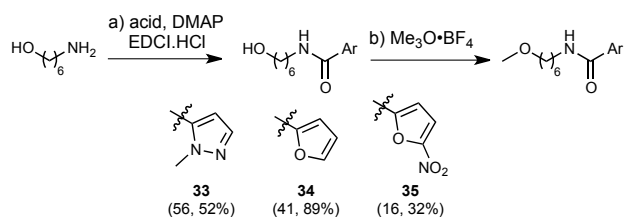
2. Results and Discussion

2.1 Synthesis

In order to rapidly access analogues with varying head groups, we targeted a THP precursor with an extended chain already present. Beginning from alcohol **7**, mesylation followed by S_N2 reaction with 6-((triisopropylsilyl)oxy)hexan-1-ol generated alkene **8** (Scheme 1).[23] After racemic epoxidation, kinetic resolution with Jacobsen salen catalyst produced chiral epoxide **9** with 95% ee.[24] Ring-opening with homoallyl magnesium bromide followed by epoxidation of the resulting double bond and *in situ* cyclisation generated THP alcohol **10** along with its diastereomeric pair (not shown) which were readily separated chromatographically. After conversion of the alcohol to azide **11** with DPPA, a "click" reaction with alkyne **12** generated the key THP-triazole-THP tricyclic core. Straightforward acidic deprotection then gave alcohol **13**.
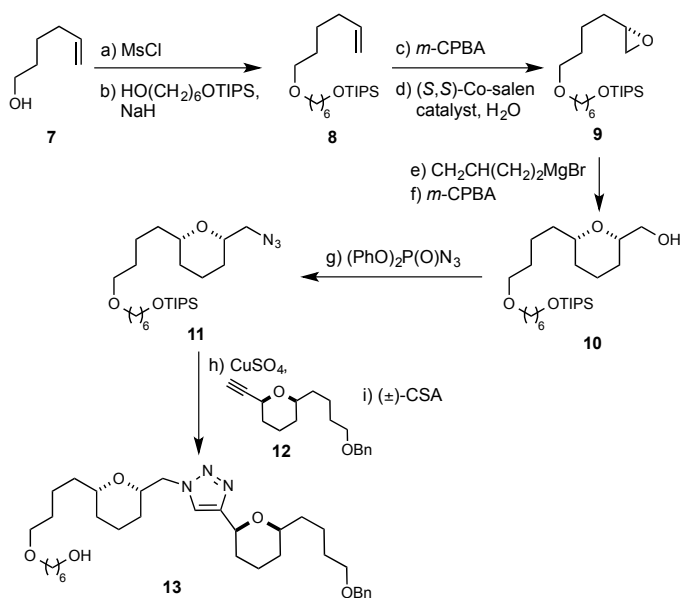
Scheme 1 Synthesis of starting material: a) MsCl, NEt$_3$, CH$_2$Cl$_2$, 0 °C → RT; b) NaH, 6-((triisopropylsilyl)oxy)hexan-1-ol, THF, reflux, 91% (2 steps); c) 3-chloroperbenzoic acid, CH$_2$Cl$_2$, 0 °C → RT, 83%; d) 0.6 mol% (*S,S*)-Co-salen catalyst, 6 mol% AcOH, H$_2$O, THF, 49%; e) CH$_2$CHCH$_2$CH$_2$MgBr, CuI, THF, -40 °C → RT, 84%; f) 3-chloroperbenzoic acid, CH$_2$Cl$_2$, 0 °C → RT; then (±)-camphorsulfonic acid (20 mol%), RT, 43% *syn*, 38% *anti*; g) diphenylphosphoryl azide, K$_2$CO$_3$, MeOH, RT, 83%; h) CuSO$_4$.5H$_2$O, Na ascorbate, H$_2$O, *t*-BuOH, RT, 89%; i) (±)-camphorsulfonic acid (20 mol%), CH$_2$Cl$_2$:MeOH, RT, 88%.

Alcohol **13** served as a key point for derivatisation. Functional group interconversion of the alcohol via the azide provided amine **16** (Scheme 2). This then allowed the complete set of head group analogues **17-32** to be accessed via straightforward coupling with the appropriate acid in generally good yields. Targeted analogues focused on oxygen, nitrogen and sulfur containing five-membered aromatic heterocycles including furan, pyrrole and thiophene derivatives.[21] For comparison with these compounds, benzylation of the free alcohol of **13** gave fully protected **14** while hydrogenation generated diol **15**.

Scheme 2 Synthesis of analogues: a) MsCl, NEt$_3$, CH$_2$Cl$_2$, 0 °C → RT, 87%; b) NaH, benzyl alcohol, THF, reflux, 33%; c) H$_2$, Pd(OH)$_2$, EtOH, RT, 59%; d) NaN$_3$, DMF, 40 °C, 74%; e) PPh$_3$, THF, RT then H$_2$O, 83%; f) carboxylic acid, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride, *N*-dimethylaminopyridine, CH$_2$Cl$_2$, RT.

In an effort to separate the influence of the head group from that of the tricyclic core, a selection of heterocycles with simple alkyl chains were synthesised as controls (Scheme 3). Amide coupling of a pyrazole acid, furoic acid and 5-nitrofuroic acid with a simple amino alcohol gave the corresponding alcohols, which were then capped using trimethyloxonium tetrafluoroborate to give methylated analogues **33**, **34** and **35**.

Scheme 3 Synthesis of control analogues: a) carboxylic acid, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride, *N*-dimethylaminopyridine, CH_2Cl_2, RT; b) $Me_3O \cdot BF_4$, CH_2Cl_2, 0 °C → RT.

2.2 Biological Testing

We began our biological screening by testing relevant synthetic intermediates and compounds without head groups to give a baseline for activity (Table 1). All analogues were screened against our kinetoplastid cell lines: *T. brucei*, *T. cruzi* and *L. major* as well as the human HeLa cell line which we used to assess potential selectivity of our analogues over mammalian cells.[25] All analogues were active at low micromolar concentrations in *T. brucei*, with the exception of diol **15**,[26] consistent with the activity we have observed for the tricyclic core of our molecules (entry 3). In *T. cruzi*, **13** and **16** showed moderate activity, while di-benzyl **14** and diol **15** analogues were essentially inactive. In *L. major*, hydroxyl terminated **13** gave best inhibition at 12.4 μM (entry 1) with all other analogues less active, though amine **16** had moderate 19.8 μM activity (entry 4). Significantly, analogues showed HeLa inhibition comparable to the other lines tested indicating a general lack of selectivity for parasite cells over mammalian cells.

13 R^1 = OH, R^2 = Bn
14 R = OBn, R^2 = Bn
15 R^1 = OH, R^2 = H
16 R = NH$_2$, R^2 = Bn
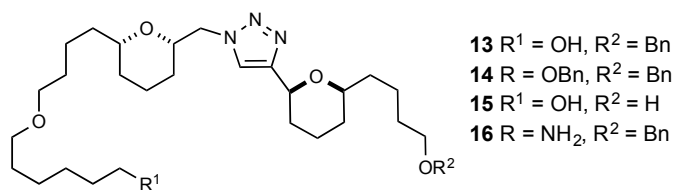
Entry	Analogue	*T. brucei* (BSF) EC$_{50}$ (µM)	*T. cruzi* EC$_{50}$ (µM)	*L. major* EC$_{50}$ (µM)	HeLa EC$_{50}$ (µM)
1	13	3.5 ± 0.3	27.3 ± 1.0	12.4 ± 0.9	21.6 ± 1.3
2	14	4.3 ± 0.3	>500	411 ± 25	>20*
3	15	37.7 ± 3.1	230 ± 19	123 ± 3	69.3 ± 5.6
4	16	5.8 ± 0.5	16.7 ± 0.7	19.2 ± 0.6	8.1 ± 0.6

Table 1 Synthetic intermediates and non-head group analogues (*Toxicity likely due to biophysical effect, rather than on-target interaction)

With selectivity a primary concern, an initial set of our amide analogues was screened against the same cell lines (Table 2). Select compounds were also screened against the Vero cell line as a secondary, non-cancerous mammalian cell line to further assess selectivity over mammalian cells. For *T. brucei*, heterocycle incorporation was well tolerated with all analogues tested falling within a narrow range of 3.8 to 8.4 µM, the best of these being 2-furan **18** (entry 2). The results in *T. cruzi* displayed significantly more variation with furan **18** the most active compound at 8.0 µM inhibition (entry 2). Interestingly, any change of the heteroatom in the simple heterocycles away from oxygen removed activity, as did a change to 3-hetero substitution (entries 3-7). By contrast, 1,3-azoles displayed modest activity, the best being thiazole **24** (entry 8) and methyl oxazole **26** (entry 10). 3-Hetero substitution was tolerated in *L. major* (entries 6 and 7), as were 1,3-azoles (entries 8-10) but again the best compound was furan **18** at 7.8 µM (entry 2).

Most pleasingly, the majority of analogues were essentially inactive against the HeLa cell line, with the exception of oxazoles **25** and **26** (entries 9 and 10). This implies potential added selectivity for parasite over mammalian cells, an essential criterion for any new therapeutic treatment. Furthermore, almost identical results to HeLa were obtained with selected analogues against Vero cells, with lead compound

18 showing no activity against both of these mammalian cell lines. The broad-spectrum anti-parasitic activity and selectivity of **18** was highly encouraging and led us to explore additional furan head groups below.[27]
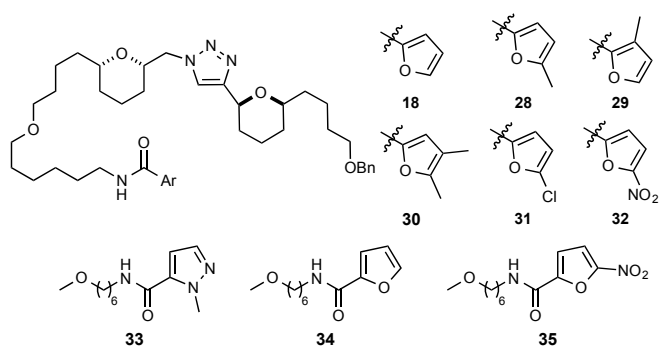

Entry	Analogue	*T. brucei* (BSF) EC$_{50}$ (µM)	*T. cruzi* EC$_{50}$ (µM)	*L. major* EC$_{50}$ (µM)	HeLa EC$_{50}$ (µM)	Vero EC$_{50}$ (µM)
1	**17**	4.4 ± 0.2	>500	>500	>250	-
2	**18**	3.8 ± 0.2	8.0 ± 1.3	7.8 ± 0.3	>500	>500
3	**19**	5.1 ± 0.2	>500	>500	>500	-
4	**20**	5.0 ± 0.4	>500	>500	>100*	-
5	**21**	4.6 ± 0.2	>500	16.3 ± 3.8	177 ± 24	-
6	**22**	3.9 ± 0.4	>500	15.2 ± 0.7	>500	>500
7	**23**	5.8 ± 0.2	>500	15.2 ± 0.8	>500	>500
8	**24**	5.7 ± 0.1	12.6 ± 2.5	21.8 ± 0.7	>100*	-
9	**25**	8.4 ± 0.4	18.3 ± 1.2	21.6 ± 0.5	21.9 ± 1.0	26.6 ± 2.7
10	**26**	8.0 ± 0.2	12.1 ± 0.9	21.5 ± 0.5	19.9 ± 2.3*	13.6 ± 2.6
11	**27**	6.1 ± 0.3	81.8 ± 12	28.7 ± 2.8	>100*	-

Table 2 Initial set of inhibitors **17**-**27** (*Toxicity likely due to biophysical effect, rather than on-target interaction)

We next curated a series of analogues in order to probe both steric and electronic variation of the pendant furan (Table 3). In *T. brucei*, methyl substitution (entries 2-4) was tolerated across the furan ring without loss of activity, as was a moderately electron withdrawing chloride group (entry 5). Introduction of a nitro group in **32** led to a step-change improvement in activity, down to 37.3 nM (entry 6). By contrast, in *T. cruzi* any perturbation of the furan was detrimental to activity with all analogues greater than 100 µM, the only exception being nitro compound **32** with slightly improved activity (entry 6). For *L. major*, 5-methyl and 5-nitro substitution was tolerated (entries 2 and 6) but changing the substitution position or adding electron-withdrawing groups gave reduced activity (entries 3-5). The

compounds showed generally moderate to no activity against HeLa with nitro compound **32** once again the exception at 0.38 μM. **32** was also examined in Vero with an EC_{50} of 4.5 μM.

Although the results for **32** are encouraging, particularly the excellent activity in *T. brucei*, it should be noted that 5-nitroheterocycles are well known to have activity against *T. brucei* and *T. cruzi* and thus we were conscious the increased activity of **32** may result from the nitrofuran head group, with the tricyclic core possibly only helping in cellular localisation.[3,28] We thus accessed pyrazole **33**, furan **34** and nitrofuran **35** that contain a head group and a simple alkyl chain only to aid solubility. We were pleased to see that **33** and **34** were essentially inactive in all lines tested- indicating the primacy of the tricyclic core in these analogues (entries 7 and 8). As expected, nitrofuran **35** showed activity in all cell lines, with the results in *T. cruzi*, *L. major* and HeLa broadly in line with those of **32** (compare entries 6 and 8). However, although activity was sub-micromolar in *T. brucei*, this nonetheless represents an almost a 20-fold reduction in activity from **32** to **35**, suggesting a synergistic effect between the tricyclic core of **32** and the nitrofuran head group. The exact nature of this effect remains under investigation.

Fragment labels: 18, 28, 29, 30, 31, 32, 33, 34, 35

Entry	Analogue	*T. brucei* (BSF) EC$_{50}$ (μM)	*T. cruzi* EC$_{50}$ (μM)	*L. major* EC$_{50}$ (μM)	HeLa EC$_{50}$ (μM)	Vero EC$_{50}$ (μM)
1	**18**	3.8 ± 0.2	8.0 ± 1.3	7.8 ± 0.3	>500	>500
2	**28**	4.9 ± 0.3	187 ± 28	16.1 ± 1.0	42.7 ± 3.9	-
3	**29**	4.7 ± 0.2	>500	67.8 ± 7.3	112 ± 7	-
4	**30**	4.6 ± 0.4	135 ± 17	72.3 ± 3.7	>100*	-
5	**31**	4.5 ± 0.2	>500	>500	>500	-
6	**32**	0.037 ± 0.003	3.1 ± 0.2	11.2 ± 0.3	0.38 ± 0.04	4.5 ± 0.3
7	**33**	107 ± 14	>500	>500	>250	-
8	**34**	113.2 ± 12.8	>500	>500	>500	-
9	**35**	0.73 ± 0.05	8.0 ± 0.3	21.0 ± 1.3	4.1 ± 0.1	15.8 ± 0.9

Table 3 Furan based inhibitors **18**, **28-35** (*Toxicity likely due to biophysical effect, rather than on-target interaction)

3. Conclusion

In summary, we have accessed a new series based upon the previously established THP-triazole-THP motif incorporating a series of heterocycles in a position to mimic the butenolide core of our original natural product inspiration, chamuvarinin. These analogues displayed significant activity in a range of kinetoplastid parasite cell lines; *T. brucei*, *T. cruzi* and *L. major*, with some analogues also showing selectivity over mammalian cell lines Vero and HeLa. Two compounds stand out from the screen: the furan **18** displayed low micromolar activity in all parasite cell lines with excellent selectivity and thus represents a starting point for a potential broad spectrum kinetoplastid inhibitor. Nitrofuran **32** displayed nanomolar *T. brucei* inhibition, with promising selectivity over human cell lines. Our current efforts are

focused on further SAR studies of these key compounds, including expansion into the other heterocyclic linker series currently under investigation within our team.

4. Experimental

4.1 Chemistry

Synthetic details for tested compounds are described below. For details of the synthesis of intermediates, see Supporting Information.

4.1.1 General procedure for amide coupling

The appropriate carboxylic acid (34.2 μmol, 2 eq), EDCI.HCl (5.30 mg, 34.2 μmol, 2 eq) and DMAP (17.1 μmol, 1 eq) were combined in CH$_2$Cl$_2$ (2 mL) and stirred at RT for 10 min. Amine **15** (10.0 mg, 17.1 μmol, 1 eq) was added and the resulting mixture stirred at RT overnight. Reaction was, quenched by the addition of saturated aqueous NH$_4$Cl solution (5 mL), extracted with EtOAc (3 x 5 mL) and the combined organic layers washed with 0.1 M aqueous KOH solution, brine, dried (MgSO$_4$), filtered and concentrated *in vacuo*.

4.2 Compounds

4.2.1 6-(4-((2*S*,6*S*)-6-((4-((2*S*,6*S*)-6-(4-(benzyloxy)butyl)tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-1-yl)methyl)tetrahydro-2*H*-pyran-2-yl)butoxy)hexan-1-ol 13

To a solution of 4-((2*S*,6*S*)-6-(4-(benzyloxy)butyl)tetrahydro-2*H*-pyran-2-yl)-1-(((2*S*,6*S*)-6-(4-((6-((triisopropylsilyl)oxy)hexyl)oxy)butyl)tetrahydro-2*H*-pyran-2-yl)methyl)-1*H*-1,2,3-triazole **S6** (1.62 g, 2.18 mmol) in methanol (15 mL) and CH$_2$Cl$_2$ (15 mL) was added a solution of (±)-CSA (101 mg, 0.440 mmol) in methanol (5 mL) and the mixture stirred at RT for 48 h. Reaction was quenched by the addition of saturated aqueous NaHCO$_3$ (30 mL). The mixture was extracted with CH$_2$Cl$_2$ (3 x 30 mL) and the combined organic extracts washed with brine, dried (MgSO$_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (60% EtOAc/Hexane) provided alcohol **13** (1.12 g, 88%), as a colourless oil.

R$_f$ 0.17 (50% EtOAc/Hexane); $[\alpha]_D^{20}$ −19 (*c* 0.40, CHCl$_3$); **IR** (ATR) 3406, 2932, 2855, 1734 cm^{-1}; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.60 (1H, s, $\underline{H}_{Ar}$), 7.35-7.24 (5H, m, Ar$\underline{H}$), 4.59 (1H, dd, *J* = 10.9, 1.8 Hz, $\underline{H}_{1'}$), 4.48 (2H, s, OC$\underline{H}_2$Ar), 4.42 (1H, dd, *J* = 14.0, 3.3 Hz, $\underline{H}_{1a}$), 4.19 (1H, dd, *J* = 14.0, 8.0 Hz, $\underline{H}_{1b}$), 3.67-3.60 (1H, m, $\underline{H}_2$), 3.61 (2H, t, *J* = 6.6 Hz, $\underline{H}_{16}$), 3.49-3.44 (1H, m, $\underline{H}_{5'}$), 3.46 (2H, t, *J* = 6.6 Hz, $\underline{H}_{9'}$), 3.37 (2H, t, *J* = 6.7 Hz, $\underline{H}_{10}$), 3.36 (2H, t, *J* = 6.8 Hz, $\underline{H}_{11}$), 3.24-3.19 (1H, m, $\underline{H}_6$), 2.02-1.83 (3H, m, $\underline{H}_{3a'}$ + $\underline{H}_4$), 1.66-1.14 (29H, m, $\underline{H}_{2'-4'}$ + $\underline{H}_{3b}$ + $\underline{H}_5$ + $\underline{H}_{6'-8'}$ + $\underline{H}_{7-9}$ + $\underline{H}_{12-15}$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 150.0, 138.8, 128.5, 127.7, 127.6, 122.4, 78.4, 77.8, 76.2, 73.3, 73.0, 71.0, 70.9, 70.5, 62.9, 55.1, 36.4, 36.2, 32.8, 31.9, 31.3, 31.2, 29.9, 29.8, 29.7, 28.7, 26.1, 25.7, 23.7, 23.1, 22.4, 22.3; **HRMS** (ESI$^+$) Calc. for C$_{34}$H$_{56}$O$_5$N$_3$ [M+H]$^+$ 586.4214, found 586.4207.

4.2.2 4-((2*S*,6*S*)-6-(4-(benzyloxy)butyl)tetrahydro-2*H*-pyran-2-yl)-1-(((2*S*,6*S*)-6-(4-((6-(benzyloxy)hexyl)oxy)butyl)tetrahydro-2*H*-pyran-2-yl)methyl)-1*H*-1,2,3-triazole 14

To a solution of sodium hydride (6.00 mg of 60% dispersion in mineral oil, 151 μmol) in dry THF (2ml) at RT was added benzyl alcohol (15.6 μL, 151 μmol). After 15 min, a solution of 6-(4-((2*S*,6*S*)-6-((4-((2*S*,6*S*)-6-(4-(benzyloxy)butyl)tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-1-yl)methyl)tetrahydro-2*H*-pyran-2-yl)butoxy)hexyl methanesulfonate **S7** (20.0 mg, 30.1 μmol) in dry THF (2 mL) was added and the mixture heated at reflux overnight. The mixture was diluted with water (10 mL) and extracted with Et$_2$O (3 x 10 mL). The combined organic extracts were washed with brine, dried (MgSO$_4$) and concentrated *in vacuo*. Purification by flash column chromatography (10% Acetone/Hexane) afforded ether **14** (6.7 mg, 33%), as a colourless oil.

R$_f$ 0.41 (20% Acetone/Hexane); $[\alpha]_D^{20}$ −16 (*c* 0.64, CHCl$_3$); **IR** (ATR) 2932, 2855, 1724 cm^{-1}; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.60 (1H, s, $\underline{H}_{Ar}$), 7.38-7.24 (10H, m, Ar$\underline{H}$), 4.59 (1H, dd, *J* = 10.9, 1.8 Hz, $\underline{H}_{1'}$), 4.49 (2H, s, OC$\underline{H}_2$Ar), 4.48 (2H, s, OC$\underline{H}_2$Ar), 4.43 (1H, dd, *J* = 14.0, 3.4 Hz, $\underline{H}_{1a}$), 4.19 (1H, dd, *J* = 14.0, 8.0 Hz, $\underline{H}_{1b}$), 3.67-3.61 (1H, m, $\underline{H}_2$), 3.50-3.44 (1H, m, $\underline{H}_{5'}$), 3.46 (2H, t, *J* = 6.6 Hz, $\underline{H}_{16}$), 3.46 (2H, t, *J* = 6.6 Hz, $\underline{H}_{9'}$), 3.37 (2H, t, *J* = 6.4 Hz, $\underline{H}_{10}$), 3.36 (2H, t, *J* = 6.9 Hz, $\underline{H}_{11}$), 3.24-3.19 (1H, m, $\underline{H}_6$), 2.03-1.83 (3H, m, $\underline{H}_{3a'}$ + $\underline{H}_4$), 1.66-1.14 (29H, m, $\underline{H}_{2'-4'}$ + $\underline{H}_{3b}$ + $\underline{H}_5$ + $\underline{H}_{6'-8'}$ + $\underline{H}_{7-9}$ + $\underline{H}_{12-15}$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 150.0, 138.8 (2C), 128.5 (2C), 127.7 (2C), 127.6 (2C), 122.4, 78.4, 77.9, 76.3, 73.3, 73.0 (2C), 71.1, 70.9, 70.6, 70.5, 55.1, 36.4, 36.2, 31.9, 31.4, 31.3, 30.0, 29.9 (2C), 29.8, 28.7, 26.2 (2C), 23.8, 23.1, 22.3, 22.2; **HRMS** (ESI$^+$) Calc. for C$_{41}$H$_{61}$O$_5$N$_3$Na [M+Na]$^+$ 698.4503, found 698.4481.

4.2.3 6-(4-((2S,6S)-6-((4-((2S,6S)-6-(4-hydroxybutyl)tetrahydro-2H-pyran-2-yl)-1H-1,2,3-triazol-1-yl)methyl)tetrahydro-2H-pyran-2-yl)butoxy)hexan-1-ol 15

To a solution of alcohol **13** (20.0 mg, 34.1 μmol) in EtOH (2 mL) at RT was added Pd(OH)$_2$ on carbon (6.50 mg of 20% wt on carbon, 6.82 μmol). The reaction system was purged with H$_2$ and left under a positive pressure of H$_2$ overnight. The reaction mixture was filtered through Celite and washed with EtOH. The filtrate was concentrated *in vacuo* and purification by flash column chromatography (EtOAc then 3% MeOH/EtOAc) provided diol **15** (10.0 mg, 59%), as a colourless oil.

R$_f$ 0.24 (EtOAc); $[\alpha]_D^{20}$ −22 (*c* 1.0, CHCl$_3$); **IR** (ATR) 3360, 2932, 2857 cm^{-1}; **^{1}H NMR** (300 MHz, CDCl$_3$) δ 7.62 (1H, s, $\underline{H}_{Ar}$), 4.59 (1H, dd, *J* = 10.9, 1.8 Hz, $\underline{H}_{1'}$), 4.44 (1H, dd, *J* = 14.0, 3.2 Hz, $\underline{H}_{1a}$), 4.20 (1H, dd, *J* = 14.0, 8.0 Hz, $\underline{H}_{1b}$), 3.68-3.60 (1H, m, $\underline{H}_2$), 3.62 (2H, t, *J* = 6.3 Hz, $\underline{H}_{16}$), 3.61 (2H, t, *J* = 6.6 Hz, $\underline{H}_{9'}$), 3.53-3.45 (1H, m, $\underline{H}_{5'}$), 3.33 (2H, t, *J* = 6.6 Hz, $\underline{H}_{10}$), 3.36 (2H, t, *J* = 6.5 Hz, $\underline{H}_{11}$), 3.24-3.18 (1H, m, $\underline{H}_6$), 2.05-1.86 (3H, m, $\underline{H}_{3a'}$ + $\underline{H}_4$), 1.70-1.13 (29H, m, $\underline{H}_{2'-4'}$ + $\underline{H}_{3b}$ + $\underline{H}_5$ + $\underline{H}_{6'-8'}$ + $\underline{H}_{7-9}$ + $\underline{H}_{12-15}$); **^{13}C NMR** (75 MHz, CDCl$_3$) δ 149.9, 122.4, 78.4, 77.8, 76.2, 73.3, 71.0, 70.9, 62.9, 62.8, 55.1, 36.2 (2C), 32.8, 32.8, 31.7, 31.4, 31.3, 29.8 (2C), 28.7, 26.1, 25.7, 23.7, 23.1, 22.2, 21.9; **HRMS** (ESI$^+$) Calc. for C$_{27}$H$_{49}$O$_5$N$_3$Na [M+Na]$^+$ 518.3564, found 518.3549.

4.2.4   4-[(2S',6S')-6'-(4-((6-aminohexyl)oxy)butyl)tetrahydropyran-2-yl]-1-[(2S'',6S'')-6''-(4-hydroxybutyltetrahydropyran-2-yl)methyl]-1H-1,2,3-triazole 16

To a solution of 4-[(2S',6S')-6'-(4-((6-azidohexyl)oxy)butyl)tetrahydropyran-2-yl]-1-[(2S'',6S'')-6''-(4-hydroxybutyltetrahydropyran-2-yl)methyl]-1H-1,2,3-triazole (251 mg, 0.411 mmol) **S7** in THF (4 mL) at 0 °C was added PPh$_3$ (162 mg, 0.617 mmol). The reaction mixture was stirred at RT overnight, then quenched with water (12 drops) and concentrated *in vacuo*. Purification by flash column chromatography (5% MeOH/1% NEt$_3$/CH$_2$Cl$_2$) provided amine **16** (200 mg, 83%), as a colourless oil.

R$_f$ 0.55 (10% MeOH/1% NEt$_3$/CH$_2$Cl$_2$); $[\alpha]_D^{20}$ −21 (*c* 1.1, CHCl$_3$); **IR** (ATR) 2931, 2855, 1560, 1454 cm^{-1}; **^{1}H NMR** (500 MHz, CDCl$_3$) δ 7.60 (1H, s, $\underline{H}_{Ar}$), 7.33-7.27 (5H, m, Ar$\underline{H}$), 4.59 (1H, dd, *J* = 11.0, 1.9 Hz, $\underline{H}_{1'}$), 4.49 (2H, s, OC$\underline{H}_2$Ar), 4.43 (1H, dd, *J* = 14.0, 3.4 Hz, $\underline{H}_{1a}$), 4.19 (1H, dd, *J* = 14.0, 8.0 Hz, $\underline{H}_{1b}$), 3.66-3.61 (1H, m, $\underline{H}_2$), 3.49-3.45 (1H, m, $\underline{H}_{5'}$), 3.46 (2H, t, *J* = 6.6 Hz, $\underline{H}_{9'}$), 3.37 (2H, t, *J* = 6.6 Hz, $\underline{H}_{10}$), 3.35 (2H, t, *J* = 6.8 Hz, $\underline{H}_{11}$), 3.23-3.19 (1H, m, $\underline{H}_6$), 2.70 (2H, br s, $\underline{H}_{16}$), 2.03-1.86 (3H, m, $\underline{H}_{3a'}$ + $\underline{H}_4$), 1.64-1.15 (29H, m, $\underline{H}_{2'-4'}$ + $\underline{H}_{3b}$ + $\underline{H}_5$ + $\underline{H}_{6'-8'}$ + $\underline{H}_{7-9}$ + $\underline{H}_{12-15}$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ 150.0, 138.8, 128.5, 127.8, 127.6, 122.4, 78.4, 77.8, 76.2, 73.3, 73.0, 71.0, 70.9, 70.5, 55.1, 42.1, 36.4, 36.2,

33.5, 31.8, 31.3, 31.2, 30.0, 29.9, 29.8, 28.7, 26.9, 26.2, 23.7, 23.1, 22.3, 22.2; **HRMS** (ESI$^+$) Calc. for C$_{34}$H$_{57}$O$_4$N$_4$ [M+H]$^+$ 585.4374, found 585.4358.

4.2.5   *N*-(6-(4-((2*S*,6*S*)-6-((4-((2*S*,6*S*)-6-(4-(benzyloxy)butyl)tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-1-yl)methyl)tetrahydro-2*H*-pyran-2-yl)butoxy)hexyl)benzamide 17

The general procedure was followed using benzoic acid (4.20 mg, 34.2 μmol). Purification by flash column chromatography (40% EtOAc/Hexane) provided amide **17** (8.7 mg, 74%), as a colourless oil.

R$_f$ 0.51 (60% EtOAc/Hexane); [α]$_D^{20}$ −15 (*c* 0.87, CHCl$_3$); **IR** (ATR) 3323, 2932, 2855, 1717, 1639, 1578, 1537 cm^{-1}; **^{1}H NMR** (500 MHz, CDCl$_3$) δ 7.76-7.75 (2H, m, H$_{19}$), 7.60 (1H, s, H$_{Ar}$), 7.50-7.40 (3H, m, H$_{20}$ + H$_{21}$), 7.33-7.24 (5H, m, ArH), 6.22 (1H, br s, NH), 4.59 (1H, dd, *J* = 11.0, 1.9 Hz, H$_{1'}$), 4.48 (2H, s, OCH$_2$Ar), 4.42 (1H, dd, *J* = 14.0, 3.3 Hz, H$_{1a}$), 4.19 (1H, dd, *J* = 14.0, 8.1 Hz, H$_{1b}$), 3.65-3.61 (1H, m, H$_2$), 3.49-3.42 (5H, m, H$_{5'}$ + H$_{9'}$ + H$_{16}$), 3.39-3.33 (4H, m, H$_{10}$ + H$_{11}$), 3.23-3.19 (1H, m, H$_6$), 2.02-1.83 (3H, m, H$_{3a'}$ + H$_4$), 1.68-1.14 (29H, m, H$_{2'-4'}$ + H$_{3b}$ + H$_5$ + H$_{6'-8'}$ + H$_{7-9}$ + H$_{12-15}$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ 167.6, 149.9, 138.7, 134.9, 131.4, 128.7 (2C), 128.5 (2C), 127.8, 127.6, 127.0, 122.4, 78.4, 77.9, 76.2, 73.3, 73.0, 70.9, 70.5, 55.1, 40.1, 36.4, 36.2, 31.8, 31.3, 29.9, 29.8 (3C), 28.7, 27.0, 26.1, 23.7, 23.1, 22.3, 22.2; **HRMS** (ESI$^+$) Calc. for C$_{41}$H$_{61}$O$_5$N$_4$ [M+H]$^+$ 689.4636, found 689.4637.

4.2.6 *N*-(6-(4-((2*S*,6*S*)-6-((4-((2*S*,6*S*)-6-(4-(benzyloxy)butyl)tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-1-yl)methyl)tetrahydro-2*H*-pyran-2-yl)butoxy)hexyl)furan-2-carboxamide 18

The general procedure was followed at a different scale. Thus, 8.00 mg EDCI.HCl (51.3 μmol) and 3.10 mg DMAP (25.6 μmol) were combined with furan-2-carboxylic acid (5.70 mg, 51.3 μmol) followed by 15.0 mg amine **15** (25.6 μmol). Purification by flash column chromatography (75% EtOAc/Hexane) provided amide **18** (12.0 mg, 69%), as a colourless oil.

R$_f$ 0.39 (75% EtOAc/Hexane); [α]$_D^{20}$ −16 (*c* 0.86, CHCl$_3$); **IR** (ATR) 3314, 2932, 2857, 1651, 1593 cm^{-1}; **^{1}H NMR** (500 MHz, CDCl$_3$) δ 7.60 (1H, s, H$_{Ar}$), 7.41 (1H, dd, *J* = 1.7, 0.8 Hz, H$_{21}$), 7.33-7.25 (5H, m, ArH), 7.09 (1H, dd, *J* = 3.5, 0.8 Hz, H$_{19}$), 6.48 (1H, dd, *J* = 3.5, 1.7 Hz, H$_{20}$), 6.37 (1H, br s, NH), 4.59 (1H, dd, *J* = 11.0, 1.9 Hz, H$_{1'}$), 4.48 (2H, s, OCH$_2$Ar), 4.43 (1H, dd, *J* = 14.0, 3.4 Hz, H$_{1a}$), 4.19 (1H, dd, *J* = 14.0, 8.1 Hz, H$_{1b}$), 3.66-3.61 (1H, m, H$_2$), 3.49-3.44 (1H, m, H$_{5'}$), 3.46 (2H, t, *J* = 6.6 Hz, H$_{9'}$), 3.42-3.33 (6H, m, H$_{10}$ + H$_{11}$ + H$_{16}$), 3.23-3.19 (1H, m, H$_6$), 2.04-1.83 (3H, m, H$_{3a'}$ + H$_4$), 1.66-1.14 (29H, m,

$\underline{H}_{2'-4'} + \underline{H}_{3b} + \underline{H}_5 + \underline{H}_{6'-8'} + \underline{H}_{7-9} + \underline{H}_{12-15}$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ 158.5, 150.0, 148.3, 143.8, 138.8, 128.5, 127.8, 127.6, 122.4, 114.1, 112.2, 78.4, 77.8, 76.2, 73.3, 73.0, 70.9 (2C), 70.5, 55.1, 39.2, 36.4, 36.2, 31.8, 31.3, 31.2, 29.9, 29.8 (2C), 28.7, 26.9, 26.1, 23.7, 23.1, 22.8, 22.3, 22.2; **HRMS** (ESI$^+$) Calc. for C$_{39}$H$_{59}$O$_6$N$_4$ [M+H]$^+$ 679.4429, found 679.4412.

4.2.7 *N*-(6-(4-((2*S*,6*S*)-6-((4-((2*S*,6*S*)-6-(4-(benzyloxy)butyl)tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-1-yl)methyl)tetrahydro-2*H*-pyran-2-yl)butoxy)hexyl)thiophene-2-carboxamide 19

The general procedure was followed using thiophene-2-carboxylic acid (4.40 mg, 34.2 μmol). Purification by flash column chromatography (60% EtOAc/Hexane) provided amide **19** (10.0 mg, 84%), as a colourless oil.

R$_f$ 0.44 (70% EtOAc/Hexane); $[\alpha]_D^{20}$ −20 (*c* 0.84, CHCl$_3$); **IR** (ATR) 3321, 2932, 2855, 1628, 1545, 1512 cm^{-1}; **^{1}H NMR** (500 MHz, CDCl$_3$) δ 7.60 (1H, s, $\underline{H}_{Ar}$), 7.49 (1H, dd, *J* = 3.7, 1.0 Hz, $\underline{H}_{19}$), 7.44 (1H, dd, *J* = 4.8, 1.0 Hz, $\underline{H}_{21}$), 7.33-7.25 (5H, m, Ar$\underline{H}$), 7.06 (1H, dd, *J* = 4.8, 3.7 Hz, $\underline{H}_{20}$), 6.12 (1H, br s, N$\underline{H}$), 4.59 (1H, dd, *J* = 10.9, 1.8 Hz, $\underline{H}_{1'}$), 4.48 (2H, s, OC$\underline{H}_2$Ar), 4.43 (1H, dd, *J* = 14.0, 3.3 Hz, $\underline{H}_{1a}$), 4.19 (1H, dd, *J* = 14.0, 8.1 Hz, $\underline{H}_{1b}$), 3.66-3.62 (1H, m, $\underline{H}_2$), 3.49-3.44 (1H, m, $\underline{H}_{5'}$), 3.46 (2H, t, *J* = 6.6 Hz, $\underline{H}_{9'}$), 3.42-3.32 (6H, m, $\underline{H}_{10} + \underline{H}_{11} + \underline{H}_{16}$), 3.23-3.19 (1H, m, $\underline{H}_6$), 2.02-1.84 (3H, m, $\underline{H}_{3a'} + \underline{H}_4$), 1.66-1.13 (29H, m, $\underline{H}_{2'-4'} + \underline{H}_{3b} + \underline{H}_5 + \underline{H}_{6'-8'} + \underline{H}_{7-9} + \underline{H}_{12-15}$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ 162.0, 149.9, 139.3, 138.8, 129.8, 128.5, 127.9, 127.8, 127.7, 127.6, 122.4, 78.4, 77.9, 76.2, 73.3, 73.0, 70.9 (2C), 70.5, 55.1, 40.1, 36.4, 36.2, 31.8, 31.3 (2C), 29.9, 29.8, 29.7 (2C), 28.8, 26.9, 26.1, 23.8, 23.1, 22.3, 22.2; **HRMS** (ESI$^+$) Calc. for C$_{39}$H$_{59}$O$_5$N$_4$S [M+H]$^+$ 695.4201, found 695.4186.

4.2.8 *N*-(6-(4-((2*S*,6*S*)-6-((4-((2*S*,6*S*)-6-(4-(benzyloxy)butyl)tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-1-yl)methyl)tetrahydro-2*H*-pyran-2-yl)butoxy)hexyl)-1*H*-pyrrole-2-carboxamide 20

The general procedure was followed using pyrrole-2-carboxylic acid (3.80 mg, 34.2 μmol). Purification by flash column chromatography (60% EtOAc/Hexane) provided amide **20** (8.0 mg, 69%), as a colourless oil.

R$_f$ 0.26 (60% EtOAc/Hexane); $[\alpha]_D^{20}$ −18 (*c* 0.80, CHCl$_3$); **IR** (ATR) 3238, 2932, 2855, 1717, 1626, 1562, 1526 cm^{-1}; **^{1}H NMR** (500 MHz, CDCl$_3$) δ 9.43 (1H, br s, N$\underline{H}$), 7.61 (1H, s, $\underline{H}_{Ar}$), 7.33-7.27 (5H, m, Ar$\underline{H}$), 6.90-6.89 (1H, m, $\underline{H}_{21}$), 6.54-6.53 (1H, m, $\underline{H}_{19}$), 5.96 (1H, q, *J* = 2.9 Hz, $\underline{H}_{20}$), 5.96 (1H, br s, N$\underline{H}$), 4.59 (1H, dd, *J* = 10.9, 1.9 Hz, $\underline{H}_{1'}$), 4.49 (2H, s, OC$\underline{H}_2$Ar), 4.43 (1H, dd, *J* = 14.0, 3.3 Hz, $\underline{H}_{1a}$),

4.19 (1H, dd, J = 14.0, 8.1 Hz, $\underline{H}_{1b}$), 3.93 (3H, s, $\underline{H}_{22}$), 3.66-3.62 (1H, m, $\underline{H}_2$), 3.49-3.45 (1H, m, $\underline{H}_{5'}$), 3.46 (2H, t, J = 6.6 Hz, $\underline{H}_{9'}$), 3.41-3.33 (6H, m, $\underline{H}_{10}$ + $\underline{H}_{11}$ + $\underline{H}_{16}$), 3.23-3.19 (1H, m, $\underline{H}_6$), 2.02-1.83 (3H, m, $\underline{H}_{3a'}$ + $\underline{H}_4$), 1.71-1.12 (29H, m, $\underline{H}_{2'-4'}$ + $\underline{H}_{3b}$ + $\underline{H}_5$ + $\underline{H}_{6'-8'}$ + $\underline{H}_{7-9}$ + $\underline{H}_{12-15}$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ 161.1, 150.0, 138.8, 129.7, 128.5, 127.8, 127.6, 122.4, 121.3, 109.9, 108.5, 78.4, 77.9, 76.2, 73.3, 73.0, 70.9, 70.8, 70.5, 55.1, 39.4, 36.4, 36.2, 31.8, 31.3 (2C), 30.0, 29.9, 29.8, 29.7, 28.8, 26.9, 26.1, 23.8, 23.1, 22.3, 22.2; **HRMS** (ESI$^+$) Calc. for C$_{39}$H$_{59}$O$_5$N$_5$Na [M+Na]$^+$ 700.4408, found 700.4395.

4.2.9 N-(6-(4-((2S,6S)-6-((4-((2S,6S)-6-(4-(benzyloxy)butyl)tetrahydro-2H-pyran-2-yl)-1H-1,2,3-triazol-1-yl)methyl)tetrahydro-2H-pyran-2-yl)butoxy)hexyl)-1-methyl-1H-pyrrole-2-carboxamide 21

The general procedure was followed using 1-methyl-2-pyrrolecarboxylic acid (4.30 mg, 34.2 μmol). Purification by flash column chromatography (55% EtOAc/Hexane) provided amide **21** (9.0 mg, 76%), as a colourless oil.

R$_f$ 0.41 (60% EtOAc/Hexane); $[\alpha]_D^{20}$ −17 (c 0.60, CHCl$_3$); **IR** (ATR) 3335, 2932, 2851, 1717, 1636, 1543, 1512 cm^{-1}; **^{1}H NMR** (500 MHz, CDCl$_3$) δ 7.61 (1H, s, $\underline{H}_{Ar}$), 7.35-7.27 (5H, m, Ar$\underline{H}$), 6.69 (1H, app t, J = 2.0 Hz, $\underline{H}_{21}$), 6.50 (1H, dd, J = 3.9, 1.7 Hz, $\underline{H}_{19}$), 6.06 (1H, dd, J = 3.9, 2.4 Hz, $\underline{H}_{20}$), 5.90 (1H, br s, N$\underline{H}$), 4.59 (1H, dd, J = 11.0, 1.9 Hz, $\underline{H}_{1'}$), 4.49 (2H, s, OC$\underline{H}_2$Ar), 4.43 (1H, dd, J = 14.0, 3.3 Hz, $\underline{H}_{1a}$), 4.19 (1H, dd, J = 14.0, 8.0 Hz, $\underline{H}_{1b}$), 3.93 (3H, s, $\underline{H}_{22}$), 3.66-3.61 (1H, m, $\underline{H}_2$), 3.49-3.45 (1H, m, $\underline{H}_{5'}$), 3.46 (2H, t, J = 6.6 Hz, $\underline{H}_{9'}$), 3.38-3.32 (6H, m, $\underline{H}_{10}$ + $\underline{H}_{11}$ + $\underline{H}_{16}$), 3.22-3.19 (1H, m, $\underline{H}_6$), 2.03-1.84 (3H, m, $\underline{H}_{3a'}$ + $\underline{H}_4$), 1.69-1.13 (29H, m, $\underline{H}_{2'-4'}$ + $\underline{H}_{3b}$ + $\underline{H}_5$ + $\underline{H}_{6'-8'}$ + $\underline{H}_{7-9}$ + $\underline{H}_{12-15}$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ 162.1, 149.9, 138.8, 129.7, 128.5, 127.8, 127.7, 127.6, 122.4, 111.2, 107.2, 78.4, 77.9, 76.2, 73.3, 73.0, 71.0, 70.9, 70.5, 55.1, 39.3, 36.8, 36.4, 36.2, 31.9, 31.4, 31.3, 30.0, 29.9, 29.8 (2C), 28.7, 27.0, 26.1, 23.8, 23.1, 22.3, 22.2; **HRMS** (ESI$^+$) Calc. for C$_{40}$H$_{61}$O$_5$N$_5$Na [M+Na]$^+$ 714.4565, found 714.4549.

4.2.10 N-(6-(4-((2S,6S)-6-((4-((2S,6S)-6-(4-(benzyloxy)butyl)tetrahydro-2H-pyran-2-yl)-1H-1,2,3-triazol-1-yl)methyl)tetrahydro-2H-pyran-2-yl)butoxy)hexyl)furan-3-carboxamide 22

The general procedure was followed using furan-3-carboxylic acid (3.80 mg, 34.2 μmol). Purification by flash column chromatography (70% EtOAc/Hexane) provided amide **22** (10.0 mg, 86%), as a colourless oil.

R_f 0.29 (70% EtOAc/Hexane); $[\alpha]_D^{20}$ −15 (*c* 0.97, CHCl$_3$); **IR** (ATR) 3300, 2932, 2855, 1636, 1587, 1572, 1537 cm^{-1}; **^{1}H NMR** (500 MHz, CDCl$_3$) δ 7.92 (1H, dd, *J* = 1.3, 0.8 Hz, H$_{18}$), 7.60 (1H, s, H$_{Ar}$), 7.41 (1H, app t, *J* = 1.6 Hz, H$_{21}$), 7.34-7.25 (5H, m, ArH), 6.61 (1H, dd, *J* = 1.8, 0.8 Hz, H$_{20}$), 6.00 (1H, br s, NH), 4.59 (1H, dd, *J* = 10.9, 1.9 Hz, H$_{1'}$), 4.48 (2H, s, OCH$_2$Ar), 4.42 (1H, dd, *J* = 14.0, 3.3 Hz, H$_{1a}$), 4.18 (1H, dd, *J* = 14.0, 8.1 Hz, H$_{1b}$), 3.66-3.61 (1H, m, H$_2$), 3.49-3.44 (1H, m, H$_{5'}$), 3.45 (2H, t, *J* = 6.6 Hz, H$_{9'}$), 3.40-3.31 (6H, m, H$_{10}$ + H$_{11}$ + H$_{16}$), 3.22-3.19 (1H, m, H$_6$), 2.02-1.84 (3H, m, H$_{3a'}$ + H$_4$), 1.72-1.12 (29H, m, H$_{2'-4'}$ + H$_{3b}$ + H$_5$ + H$_{6'-8'}$ + H$_{7-9}$ + H$_{12-15}$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ 162.7, 149.9, 144.7, 143.8, 138.7, 128.5, 127.8, 127.6, 122.9, 122.4, 108.4, 78.4, 77.9, 76.2, 73.3, 73.0, 70.9, 70.8, 70.5, 55.1, 39.6, 36.4, 36.2, 31.8, 31.3 (2C), 29.9, 29.8 (3C), 28.8, 26.9, 26.1, 23.7, 23.1, 22.4, 22.3; **HRMS** (ESI$^+$) Calc. for C$_{39}$H$_{58}$O$_6$N$_4$Na [M+Na]$^+$ 701.4249, found 701.4229.

4.2.11 *N*-(6-(4-((2*S*,6*S*)-6-((4-((2*S*,6*S*)-6-(4-(benzyloxy)butyl)tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-1-yl)methyl)tetrahydro-2*H*-pyran-2-yl)butoxy)hexyl)thiophene-3-carboxamide 23

The general procedure was followed using thiophene-3-carboxylic acid (4.40 mg, 34.2 μmol). Purification by flash column chromatography (60% EtOAc/Hexane) provided amide **23** (11.0 mg, 92%), as a colourless oil.

R_f 0.38 (70% EtOAc/Hexane); $[\alpha]_D^{20}$ −13 (*c* 1.1, CHCl$_3$); **IR** (ATR) 3318, 2932, 2855, 1715, 1634, 1545, 1508 cm^{-1}; **^{1}H NMR** (500 MHz, CDCl$_3$) δ 7.85 (1H, dd, *J* = 2.9, 1.2 Hz, H$_{18}$), 7.61 (1H, s, H$_{Ar}$), 7.38 (1H, dd, *J* = 5.0, 1.2 Hz, H$_{21}$), 7.33-7.25 (6H, m, H$_{20}$ + ArH), 6.11 (1H, br s, NH), 4.59 (1H, dd, *J* = 10.9, 1.8 Hz, H$_{1'}$), 4.48 (2H, s, OCH$_2$Ar), 4.43 (1H, dd, *J* = 14.0, 3.3 Hz, H$_{1a}$), 4.19 (1H, dd, *J* = 14.0, 8.1 Hz, H$_{1b}$), 3.66-3.62 (1H, m, H$_2$), 3.49-3.44 (1H, m, H$_{5'}$), 3.46 (2H, t, *J* = 6.6 Hz, H$_{9'}$), 3.42-3.32 (6H, m, H$_{10}$ + H$_{11}$ + H$_{16}$), 3.23-3.19 (1H, m, H$_6$), 2.02-1.86 (3H, m, H$_{3a'}$ + H$_4$), 1.69-1.12 (29H, m, H$_{2'-4'}$ + H$_{3b}$ + H$_5$ + H$_{6'-8'}$ + H$_{7-9}$ + H$_{12-15}$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ 163.2, 149.9, 138.8, 137.9, 128.5, 128.1, 127.8, 127.6, 126.5, 126.1, 122.5, 78.4, 77.9, 76.2, 73.3, 73.0, 70.9, 70.8, 70.5, 55.1, 39.9, 36.4, 36.2, 31.8, 31.3 (2C), 29.9, 29.8 (2C), 29.7, 28.8, 26.9, 26.1, 23.8, 23.1, 22.3, 22.2; **HRMS** (ESI$^+$) Calc. for C$_{39}$H$_{58}$O$_5$N$_4$SNa [M+Na]$^+$ 717.4020, found 717.4008.

4.2.12 *N*-(6-(4-((2*S*,6*S*)-6-((4-((2*S*,6*S*)-6-(4-(benzyloxy)butyl)tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-1-yl)methyl)tetrahydro-2*H*-pyran-2-yl)butoxy)hexyl)thiazole-4-carboxamide 24

The general procedure was followed using 1,3-thiazole-4-carboxylic acid (4.40 mg, 34.2 μmol). Purification by flash column chromatography (75% EtOAc/Hexane) provided amide **24** (9.8 mg, 82%), as a colourless oil.

R_f 0.23 (70% EtOAc/Hexane); $[\alpha]_D^{20}$ −19 (*c* 0.72, CHCl$_3$); **IR** (ATR) 3361, 3064, 2932, 2851, 1647, 1541 cm^{-1}; **^{1}H NMR** (500 MHz, CDCl$_3$) δ 8.73 (1H, d, *J* = 2.1 Hz, H$_{20}$), 8.15 (1H, d, *J* = 2.1 Hz, H$_{19}$), 7.60 (1H, s, H$_{Ar}$), 7.39 (1H, br s, NH), 7.35-7.24 (5H, m, ArH), 4.59 (1H, dd, *J* = 10.9, 1.8 Hz, H$_{1'}$), 4.48 (2H, s, OCH$_2$Ar), 4.43 (1H, dd, *J* = 14.0, 3.4 Hz, H$_{1a}$), 4.19 (1H, dd, *J* = 14.0, 8.0 Hz, H$_{1b}$), 3.66-3.61 (1H, m, H$_2$), 3.49-3.42 (5H, m, H$_{16}$ + H$_{5'}$ + H$_{9'}$), 3.38-3.34 (4H, m, H$_{10}$ + H$_{11}$), 3.23-3.19 (1H, m, H$_6$), 2.02-1.83 (3H, m, H$_{3a'}$ + H$_4$), 1.66-1.12 (29H, m, H$_{2'-4'}$ + H$_{3b}$ + H$_5$ + H$_{6'-8'}$ + H$_{7-9}$ + H$_{12-15}$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ 161.0, 152.7, 151.4, 150.0, 138.8, 128.5, 127.8, 127.6, 123.1, 122.4, 78.4, 77.8, 76.2, 73.3, 73.0, 71.0, 70.9, 70.5, 55.1, 39.4, 36.4, 36.2, 31.8, 31.3, 31.2, 29.9, 29.8 (2C), 29.7, 28.7, 27.0, 26.1, 23.7, 23.1, 22.3, 22.2; **HRMS** (ESI$^+$) Calc. for C$_{38}$H$_{58}$O$_5$N$_5$S [M+H]$^+$ 696.4153, found 696.4126.

4.2.13   *N*-(6-(4-((2*S*,6*S*)-6-((4-((2*S*,6*S*)-6-(4-(benzyloxy)butyl)tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-1-yl)methyl)tetrahydro-2*H*-pyran-2-yl)butoxy)hexyl)oxazole-4-carboxamide 25

The general procedure was followed using 1,3-oxazole-4-carboxylic acid (3.90 mg, 34.2 μmol) and DMF (2 mL) as solvent. Purification by flash column chromatography (75% EtOAc/Hexane) provided amide **25** (5.5 mg, 47%), as a colourless oil.

R_f 0.26 (75% EtOAc/Hexane); $[\alpha]_D^{20}$ −21 (*c* 0.50, CHCl$_3$); **IR** (ATR) 3335, 2934, 2857, 1661, 1595, 1514 cm^{-1}; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 8.21 (1H, d, *J* = 1.0 Hz, H$_{19}$), 7.84 (1H, d, *J* =1.0 Hz, H$_{20}$), 7.60 (1H, s, H$_{Ar}$), 7.35-7.24 (5H, m, ArH), 6.92 (1H, br s, NH), 4.59 (1H, dd, *J* = 10.9, 1.9 Hz, H$_{1'}$), 4.49 (2H, s, OCH$_2$Ar), 4.43 (1H, dd, *J* = 14.0, 3.4 Hz, H$_{1a}$), 4.19 (1H, dd, *J* = 14.0, 8.0 Hz, H$_{1b}$), 3.67-3.61 (1H, m, H$_2$), 3.50-3.44 (3H, m, H$_{5'}$ + H$_{9'}$), 3.43-3.33 (6H, m, H$_{10}$ + H$_{11}$+ H$_{16}$), 3.24-3.19 (1H, m, H$_6$), 2.03-1.83 (3H, m, H$_{3a'}$ + H$_4$), 1.63-1.14 (29H, m, H$_{2'-4'}$ + H$_{3b}$ + H$_5$ + H$_{6'-8'}$ + H$_{7-9}$ + H$_{12-15}$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 160.3, 150.6, 150.0, 141.3, 138.8, 136.2, 128.5, 127.8, 127.6, 122.4, 78.4, 77.9, 76.2, 73.3, 73.0, 71.0 (2C), 70.5, 55.1, 39.1, 36.4, 36.2, 31.9, 31.4, 31.3, 29.9, 29.8, 29.7, 28.8 (2C), 26.9, 26.1, 23.8, 23.1, 22.3, 22.3; **HRMS** (ESI$^+$) Calc. for C$_{38}$H$_{57}$O$_6$N$_5$Na [M+Na]$^+$ 702.4201, found 702.4182.

4.2.14 *N*-(6-(4-((2*S*,6*S*)-6-((4-((2*S*,6*S*)-6-(4-(benzyloxy)butyl)tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-1-yl)methyl)tetrahydro-2*H*-pyran-2-yl)butoxy)hexyl)-2-methyloxazole-4-carboxamide 26

The general procedure was followed using 2-methyl-1,3-oxazole-4-carboxylic acid (4.30 mg, 34.2 µmol). Purification by flash column chromatography (75% EtOAc/Hexane) provided amide **26** (9.6 mg, 81%), as a colourless oil.

$\mathbf{R_f}$ 0.23 (75% EtOAc/Hexane); $[\alpha]_D^{20}$ −15 (*c* 0.96, CHCl$_3$); **IR** (ATR) 3362, 2932, 2855, 1668, 1647, 1607, 1518 cm^{-1}; ^{1}**H NMR** (400 MHz, CDCl$_3$) δ 8.05 (1H, s, $\underline{H}_{19}$), 7.60 (1H, s, $\underline{H}_{Ar}$), 7.35-7.24 (5H, m, Ar$\underline{H}$), 6.86 (1H, br s, N$\underline{H}$), 4.59 (1H, dd, *J* = 10.8, 1.8 Hz, $\underline{H}_{1'}$), 4.48 (2H, s, OC$\underline{H}_2$Ar), 4.43 (1H, dd, *J* = 14.0, 3.4 Hz, $\underline{H}_{1a}$), 4.19 (1H, dd, *J* = 14.0, 8.0 Hz, $\underline{H}_{1b}$), 3.66-3.61 (1H, m, $\underline{H}_2$), 3.50-3.44 (1H, m, $\underline{H}_{5'}$), 3.46 (1H, t, *J* = 6.6 Hz, $\underline{H}_{9'}$), 3.41-3.34 (6H, m, $\underline{H}_{10}$ + $\underline{H}_{11}$ + $\underline{H}_{16}$), 3.24-3.19 (1H, m, $\underline{H}_6$), 2.46 (3H, s, $\underline{H}_{21}$), 2.04-1.83 (3H, m, $\underline{H}_{3a'}$ + $\underline{H}_4$), 1.66-1.12 (29H, m, $\underline{H}_{2'-4'}$ + $\underline{H}_{3b}$ + $\underline{H}_5$ + $\underline{H}_{6'-8'}$ + $\underline{H}_{7-9}$ + $\underline{H}_{12-15}$); ^{13}**C NMR** (125 MHz, CDCl$_3$) δ 161.4, 160.8, 150.0, 140.8, 138.8, 136.4, 128.5, 127.8, 127.6, 122.4, 78.4, 77.8, 76.2, 73.3, 73.0, 71.0, 70.9, 70.5, 55.1, 39.1, 36.4, 36.2, 31.8, 31.3, 31.2, 29.9, 29.8 (2C), 29.7, 28.7, 26.9, 26.1, 23.7, 23.1, 22.3, 22.2, 14.0; **HRMS** (ESI$^+$) Calc. for C$_{39}$H$_{60}$O$_6$N$_5$ [M+H]$^+$ 694.4538, found 694.4514.

4.2.15   *N*-(6-(4-((2*S*,6*S*)-6-((4-((2*S*,6*S*)-6-(4-(benzyloxy)butyl)tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-1-yl)methyl)tetrahydro-2*H*-pyran-2-yl)butoxy)hexyl)-1-methyl-1*H*-pyrazole-5-carboxamide 27

The general procedure was followed at a different scale. Thus, 8.00 mg EDCI.HCl (51.3 µmol) and 3.10 mg DMAP (25.6 µmol) were combined with 2-methyl-2*H*-pyrazole-3-carboxylic acid (6.50 mg, 51.3 µmol) followed by 15.0 mg amine **15** (25.6 µmol). Purification by flash column chromatography (75% EtOAc/Hexane) provided amide **27** (12.0 mg, 68%), as a colourless oil.

$\mathbf{R_f}$ 0.29 (75% EtOAc/Hexane); $[\alpha]_D^{20}$ −13 (*c* 0.45, CHCl$_3$); **IR** (ATR) 3323, 2934, 2857, 1724, 1661, 1543 cm^{-1}; ^{1}**H NMR** (500 MHz, CDCl$_3$) δ 7.60 (1H, s, $\underline{H}_{Ar}$), 7.42 (1H, d, *J* = 2.1 Hz, $\underline{H}_{19}$), 7.33-7.27 (5H, m, Ar$\underline{H}$), 6.49 (1H, d, *J* = 2.1 Hz, $\underline{H}_{20}$), 6.18 (1H, br s, N$\underline{H}$), 4.59 (1H, dd, *J* = 11.0, 1.9 Hz, $\underline{H}_{1'}$), 4.48 (2H, s, OC$\underline{H}_2$Ar), 4.42 (1H, dd, *J* = 14.0, 3.3 Hz, $\underline{H}_{1a}$), 4.19 (1H, dd, *J* = 14.0, 8.1 Hz, $\underline{H}_{1b}$), 4.17 (3H, s, $\underline{H}_{21}$), 3.66-3.62 (1H, m, $\underline{H}_2$), 3.49-3.44 (1H, m, $\underline{H}_{5'}$), 3.46 (2H, t, *J* = 6.6 Hz, $\underline{H}_{9'}$), 3.39-3.33 (6H, m, $\underline{H}_{10}$ + $\underline{H}_{11}$ + $\underline{H}_{16}$), 3.22-3.19 (1H, m, $\underline{H}_6$), 2.04-1.91 (3H, m, $\underline{H}_{3a'}$ + $\underline{H}_4$), 1.69-1.15 (29H, m, $\underline{H}_{2'-4'}$ + $\underline{H}_{3b}$ + $\underline{H}_5$ + $\underline{H}_{6'-8'}$ + $\underline{H}_{7-9}$ + $\underline{H}_{12-15}$); ^{13}**C NMR** (125 MHz, CDCl$_3$) δ 160.1, 150.0, 138.7, 137.7, 135.6, 128.5, 127.8, 127.6, 122.4, 106.2, 78.4, 77.9, 76.2, 73.3, 73.0, 70.9, 70.8, 70.5, 55.1, 39.6, 39.4, 36.4, 36.2,

31.8, 31.3 (2C), 29.9, 29.8, 29.7 (2C), 28.8, 26.9, 26.1, 23.7, 23.1, 22.3, 22.2; **HRMS** (ESI$^+$) Calc. for C$_{39}$H$_{61}$O$_5$N$_6$ [M+H]$^+$ 693.4698, found 693.4681.

4.2.16 *N*-(6-(4-((2*S*,6*S*)-6-((4-((2*S*,6*S*)-6-(4-(benzyloxy)butyl)tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-1-yl)methyl)tetrahydro-2*H*-pyran-2-yl)butoxy)hexyl)-5-methylfuran-2-carboxamide 28

The general procedure was followed using 5-methyl-furan-2-carboxylic acid (4.30 mg, 34.2 μmol). Purification by flash column chromatography (75% EtOAc/Hexane) provided amide **28** (8.1 mg, 67%), as a colourless oil.

R$_f$ 0.34 (75% EtOAc/Hexane); $[\alpha]_D^{20}$ –17 (*c* 0.81, CHCl$_3$); **IR** (ATR) 3298, 2932, 2857, 1717, 1647, 1609, 1555 cm^{-1}; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.60 (1H, s, H$_{Ar}$), 7.33-7.24 (5H, m, ArH), 6.98 (1H, d, *J* = 3.3 Hz, H$_{19}$), 6.27 (1H, br s, NH), 6.08 (1H, d, *J* = 3.3 Hz, H$_{20}$), 4.59 (1H, dd, *J* = 10.9, 1.9 Hz, H$_{1'}$), 4.49 (2H, s, OCH$_2$Ar), 4.43 (1H, dd, *J* = 14.0, 3.4 Hz, H$_{1a}$), 4.19 (1H, dd, *J* = 14.0, 8.0 Hz, H$_{1b}$), 3.66-3.61 (1H, m, H$_2$), 3.50-3.44 (1H, m, H$_{5'}$), 3.46 (2H, t, *J* = 6.6 Hz, H$_{9'}$), 3.41-3.34 (6H, m, H$_{10}$ + H$_{11}$ + H$_{16}$), 3.23-3.19 (1H, m, H$_6$), 2.33 (3H, s, H$_{22}$), 2.03-1.83 (3H, m, H$_{3a'}$ + H$_4$), 1.64-1.12 (29H, m, H$_{2'-4'}$ + H$_{3b}$ + H$_5$ + H$_{6'-8'}$ + H$_{7-9}$ + H$_{12-15}$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 158.7, 154.3, 150.0, 146.7, 138.8, 128.5, 127.8, 127.6, 122.4, 115.3, 108.6, 78.4, 77.9, 76.2, 73.3, 73.0, 71.0, 70.9, 70.5, 55.1, 39.1, 36.4, 36.2, 31.9, 31.4, 31.3, 30.0, 29.9, 29.8 (2C), 28.8, 26.9, 26.1, 23.8, 23.1, 22.4, 22.3, 14.0; **HRMS** (ESI$^+$) Calc. for C$_{40}$H$_{60}$O$_6$N$_4$Na [M+Na]$^+$ 715.4405, found 715.4389.

4.2.17 *N*-(6-(4-((2*S*,6*S*)-6-((4-((2*S*,6*S*)-6-(4-(benzyloxy)butyl)tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-1-yl)methyl)tetrahydro-2*H*-pyran-2-yl)butoxy)hexyl)-3-methylfuran-2-carboxamide 29

The general procedure was followed using 3-methyl-furan-2-carboxylic acid (4.30 mg, 34.2 μmol). Purification by flash column chromatography (50% EtOAc/Hexane) provided amide **29** (10.6 mg, 90%), as a colourless oil.

R$_f$ 0.41 (60% EtOAc/Hexane); $[\alpha]_D^{20}$ –15 (*c* 0.96, CHCl$_3$); **IR** (ATR) 2916, 2849, 1734, 1651, 1612, 1526 cm^{-1}; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.60 (1H, s, H$_{Ar}$), 7.33-7.25 (6H, m, H$_{22}$ + ArH), 6.33 (1H, br s, NH), 6.31 (1H, d, *J* = 1.6 Hz, H$_{21}$), 4.59 (1H, dd, *J* = 10.8, 1.9 Hz, H$_{1'}$), 4.48 (2H, s, OCH$_2$Ar), 4.43 (1H, dd, *J* = 14.0, 3.3 Hz, H$_{1a}$), 4.19 (1H, dd, *J* = 14.0, 8.0 Hz, H$_{1b}$), 3.67-3.60 (1H, m, H$_2$), 3.50-3.44 (1H, m, H$_{5'}$), 3.46 (2H, t, *J* = 6.6 Hz, H$_{9'}$), 3.40-3.33 (6H, m, H$_{10}$ + H$_{11}$ + H$_{16}$), 3.23-3.18 (1H, m, H$_6$), 2.39 (3H, s, H$_{20}$), 2.04-1.83 (3H, m, H$_{3a'}$ + H$_4$), 1.67-1.12 (29H, m, H$_{2'-4'}$ + H$_{3b}$ + H$_5$ + H$_{6'-8'}$ + H$_{7-9}$ + H$_{12-}$

$_{15}$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 159.8, 150.0, 142.5, 142.1, 138.8, 128.5, 127.8, 127.6, 127.3, 122.4, 115.5, 78.4, 77.9, 76.2, 73.3, 73.0, 71.0, 70.9, 70.5, 55.1, 38.9, 36.4, 36.2, 31.9, 31.4, 31.3, 29.9 (2C), 29.8 (2C), 28.8, 27.0, 26.1, 23.8, 23.1, 22.4, 22.3, 11.2; **HRMS** (ESI$^+$) Calc. for C$_{40}$H$_{60}$O$_6$N$_4$Na [M+Na]$^+$ 715.4405, found 715.4388.

4.2.18   *N*-(6-(4-((2*S*,6*S*)-6-((4-((2*S*,6*S*)-6-(4-(benzyloxy)butyl)tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-1-yl)methyl)tetrahydro-2*H*-pyran-2-yl)butoxy)hexyl)-4,5-dimethylfuran-2-carboxamide 30

The general procedure was followed using 4,5-dimethylfuran-2-carboxylic acid (4.80 mg, 34.2 μmol). Purification by flash column chromatography (60% EtOAc/Hexane) provided amide **30** (7.6 mg, 63%), as a colourless oil.

R$_f$ 0.29 (60% EtOAc/Petrol); $[\alpha]_D^{20}$ −19 (*c* 0.73, CHCl$_3$); **IR** (ATR) 3310, 2932, 2857, 1717, 1645, 1564 cm^{-1}; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.60 (1H, s, H$_{Ar}$), 7.33-7.28 (5H, m, ArH), 6.86 (1H, d, *J* = 3.3 Hz, H$_{19}$), 6.23 (1H, br s, NH), 4.59 (1H, dd, *J* = 10.8, 1.7 Hz, H$_{1'}$), 4.48 (2H, s, OCH$_2$Ar), 4.43 (1H, dd, *J* = 14.0, 3.4 Hz, H$_{1a}$), 4.19 (1H, dd, *J* = 14.0, 8.0 Hz, H$_{1b}$), 3.66-3.61 (1H, m, H$_2$), 3.50-3.44 (1H, m, H$_{5'}$), 3.46 (2H, t, *J* = 6.6 Hz, H$_{9'}$), 3.40-3.34 (6H, m, H$_{10}$ + H$_{11}$ + H$_{16}$), 3.24-3.18 (1H, m, H$_6$), 2.23 (3H, s, H$_{23}$), 2.04-1.83 (3H, m, H$_{3a'}$ + H$_4$), 1.95 (3H, s, H$_{21}$), 1.65-1.14 (29H, m, H$_{2'-4'}$ + H$_{3b}$ + H$_5$ + H$_{6'-8'}$ + H$_{7-9}$ + H$_{12-15}$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 158.8, 150.0, 149.9, 145.3, 138.8, 128.5, 127.8, 127.6, 122.4, 117.4, 117.1, 78.4, 77.9, 76.2, 73.3, 73.0, 71.0, 70.9, 70.5, 55.1, 39.1, 36.4, 36.2, 31.9, 31.4, 31.3, 29.9 (2C), 29.8 (2C), 28.8, 26.9, 26.1, 23.8, 23.1, 22.3, 22.2, 11.8, 9.9; **HRMS** (ESI$^+$) Calc. for C$_{41}$H$_{62}$O$_6$N$_4$Na [M+Na]$^+$ 729.4562, found 729.4560.

4.2.19   *N*-(6-(4-((2*S*,6*S*)-6-((4-((2*S*,6*S*)-6-(4-(benzyloxy)butyl)tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-1-yl)methyl)tetrahydro-2*H*-pyran-2-yl)butoxy)hexyl)-5-chlorofuran-2-carboxamide 31

The general procedure was followed using 5-chlorofuran-2-carboxylic acid (5.00 mg, 34.2 μmol). Purification by flash column chromatography (45% EtOAc/Hexane) provided amide **31** (6.8 mg, 56%), as a colourless oil.

R$_f$ 0.34 (60% EtOAc/Petrol); $[\alpha]_D^{20}$ −16 (*c* 0.65, CHCl$_3$); **IR** (ATR) 3300, 2934, 2857, 1717, 1647, 1599, 1533 cm^{-1}; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.60 (1H, s, H$_{Ar}$), 7.33-7.24 (5H, m, ArH), 7.07 (1H, d, *J* = 3.5 Hz, H$_{19}$), 6.28 (1H, d, *J* = 3.5 Hz, H$_{20}$), 6.27 (1H, br s, NH), 4.59 (1H, dd, *J* = 10.9, 1.9 Hz, H$_{1'}$), 4.49 (2H, s, OCH$_2$Ar), 4.43 (1H, dd, *J* = 14.0, 3.4 Hz, H$_{1a}$), 4.19 (1H, dd, *J* = 14.0, 8.0 Hz, H$_{1b}$), 3.66-

3.62 (1H, m, $\underline{H}_2$), 3.50-3.44 (1H, m, $\underline{H}_{5'}$), 3.46 (2H, t, J = 6.6 Hz, $\underline{H}_{9'}$), 3.41-3.34 (6H, m, $\underline{H}_{10}$ + $\underline{H}_{11}$ + $\underline{H}_{16}$), 3.24-3.19 (1H, m, $\underline{H}_6$), 2.03-1.80 (3H, m, $\underline{H}_{3a'}$ + $\underline{H}_4$), 1.66-1.14 (29H, m, $\underline{H}_{2'-4'}$ + $\underline{H}_{3b}$ + $\underline{H}_5$ + $\underline{H}_{6'-8'}$ + $\underline{H}_{7-9}$ + $\underline{H}_{12-15}$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 157.4, 150.0, 147.4, 138.8, 138.2, 128.5, 127.8, 127.6, 122.4, 116.2, 109.2, 78.4, 77.9, 76.3, 73.4, 73.0, 70.9 (2C), 70.5, 55.1, 39.3, 36.4, 36.2, 31.9, 31.4, 31.3, 30.0, 29.9, 29.8, 29.7, 28.8, 26.9, 26.1, 23.8, 23.1, 22.4, 22.3; **HRMS** (ESI$^+$) Calc. for C$_{39}$H$_{57}$O$_6$N$_4$ClNa [M+Na]$^+$ 735.3859, found 735.3843.

4.2.20 *N*-(6-(4-(((2*S*,6*S*)-6-((4-((2*S*,6*S*)-6-(4-(benzyloxy)butyl)tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-1-yl)methyl)tetrahydro-2*H*-pyran-2-yl)butoxy)hexyl)-5-nitrofuran-2-carboxamide 32

The general procedure was followed using 5-nitrofuran-2-carboxylic acid (5.40 mg, 34.2 μmol). Purification by flash column chromatography (20% Acetone/Hexane) provided amide **32** (3.5 mg, 28%), as a colourless oil.

R$_f$ 0.35 (60% EtOAc/Hexane); $[\alpha]_D^{20}$ −15 (*c* 0.55, CHCl$_3$); **IR** (ATR) 3296, 2932, 2855, 1717, 1668, 1553 cm^{-1}; **^{1}H NMR** (500 MHz, CDCl$_3$) δ 7.60 (1H, s, $\underline{H}_{Ar}$), 7.35 (1H, d, J = 3.8 Hz, $\underline{H}_{19}$), 7.33-7.27 (5H, m, Ar$\underline{H}$), 7.24 (1H, d, J = 3.8 Hz, $\underline{H}_{20}$), 6.69 (1H, br s, N$\underline{H}$), 4.59 (1H, dd, J = 11.0, 1.9 Hz, $\underline{H}_{1'}$), 4.49 (2H, s, OC$\underline{H}_2$Ar), 4.43 (1H, dd, J = 14.0, 3.4 Hz, $\underline{H}_{1a}$), 4.19 (1H, dd, J = 14.0, 8.1 Hz, $\underline{H}_{1b}$), 3.66-3.63 (1H, m, $\underline{H}_2$), 3.49-3.41 (3H, m, $\underline{H}_{5'}$ + $\underline{H}_{16}$), 3.46 (2H, t, J = 6.6 Hz, $\underline{H}_{9'}$), 3.41-3.34 (4H, m, $\underline{H}_{10}$ + $\underline{H}_{11}$), 3.23-3.19 (1H, m, $\underline{H}_6$), 2.04-1.80 (3H, m, $\underline{H}_{3a'}$ + $\underline{H}_4$), 1.66-1.13 (29H, m, $\underline{H}_{2'-4'}$ + $\underline{H}_{3b}$ + $\underline{H}_5$ + $\underline{H}_{6'-8'}$ + $\underline{H}_{7-9}$ + $\underline{H}_{12-15}$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ 156.4, 151.5, 150.0, 148.4, 138.8, 128.5, 127.8, 127.6, 122.4, 115.9, 112.7, 78.4, 77.9, 76.2, 73.3, 73.0, 70.9, 70.8, 70.5, 55.1, 39.7, 36.4, 36.2, 31.9, 31.3, 29.9, 29.8, 29.7, 29.6, 28.8, 26.9, 26.0, 23.8, 23.1, 22.3, 22.2; **HRMS** (ESI$^+$) Calc. for C$_{39}$H$_{57}$O$_8$N$_5$Na [M+Na]$^+$ 746.4099, found 746.4085.

4.2.21 *N*-(6-methoxyhexyl)furan-2-carboxamide 33

To a solution of *N*-(6-hydroxyhexyl)-1-methyl-1*H*-pyrazole-5-carboxamide **S9** (10.0 mg, 4.44 μmol) and 1,8-bis(dimethylamino)naphthalene (32.9 mg, 221 μmol) in dry CH$_2$Cl$_2$ (2 mL) at 0 °C was added trimethyloxonium tetrafluoroborate (47.4 mg, 221 μmol) and the mixture stirred at RT for 72 h. The mixture was cooled to 0 °C and reaction quenched with saturated NH$_4$OH solution (0.5 mL). Saturated NaHCO$_3$ solution (5 mL) was added and the organics extracted with CH$_2$Cl$_2$ (3 x 5 mL). The combined organic extracts were washed with 0.3N HCl solution, dried (MgSO$_4$), filtered and concentrated *in*

vacuo Purification by flash column chromatography (65% EtOAc/Hexane) provided ether **33** (5.5 mg, 52%), as a colourless oil.

R_f 0.34 (75% EtOAc/Hexane); **IR** (ATR) 3310, 2930, 2858, 1645, 1543 cm^{-1}; **^{1}H NMR** (500 MHz, CDCl$_3$) δ 7.43 (1H, d, J = 1.8 Hz, $\underline{H}_{10}$), 6.46 (1H, d, J = 1.8 Hz, $\underline{H}_{11}$), 6.01 (1H, br s, N$\underline{H}$), 4.17 (3H, s, $\underline{H}_{12}$), 3.41-3.36 (4H, m, $\underline{H}_2$ + $\underline{H}_7$), 3.32 (3H, s, $\underline{H}_1$), 1.63-1.57 (4H, m, $\underline{H}_3$ + $\underline{H}_6$), 1.41-1.38 (4H, m, $\underline{H}_4$ + $\underline{H}_5$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ 160.1, 137.7, 135.5, 106.0, 72.8, 58.7, 39.6, 39.4, 29.7, 29.6, 26.9, 26.0; **HRMS** (ESI$^+$) Calc. for C$_{12}$H$_{21}$O$_3$N$_2$Na [M+Na]$^+$ 262.1526, found 262.1526.

4.2.22 *N*-(6-methoxyhexyl)furan-2-carboxamide 34

To a solution of *N*-(6-hydroxyhexyl)furan-2-carboxamide **S10** (8.00 mg, 37.9 μmol) and 1,8-bis(dimethylamino)naphthalene (81.0 mg, 379 μmol) in dry CH$_2$Cl$_2$ (2 mL) at 0 °C was added trimethyloxonium tetrafluoroborate (56.0 mg, 379 μmol) and the mixture stirred at RT for 72 h. The mixture was cooled to 0 °C and reaction quenched with saturated NH$_4$OH solution (0.5 mL). Saturated NaHCO$_3$ solution (5 mL) was added and the organics extracted with Et$_2$O (3 x 5 mL). The combined organic extracts were washed with 1N HCl solution, dried (MgSO$_4$), filtered and concentrated *in vacuo* Purification by flash column chromatography (40% EtOAc/Petrol) provided ether **34** (7.6 mg, 89%), as a colourless oil.

R_f 0.36 (50% EtOAc/Petrol); **IR** (ATR) 3302, 2930, 2859, 1643, 1593, 1572, 1530 cm^{-1}; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.42 (1H, dd, J = 1.8, 0.8 Hz, $\underline{H}_{12}$), 7.09 (1H, dd, J = 3.5, 0.8 Hz, $\underline{H}_{10}$), 6.48 (1H, dd, J = 3.5, 1.8 Hz, $\underline{H}_{11}$), 6.35 (1H, br s, N$\underline{H}$), 3.41 (2H, app q, J = 6.9 Hz, $\underline{H}_7$), 3.35 (2H, t, J = 6.5 Hz, $\underline{H}_2$), 3.32 (3H, s, $\underline{H}_1$), 1.62-1.54 (4H, m, $\underline{H}_3$ + $\underline{H}_6$), 1.41-1.37 (4H, m, $\underline{H}_4$ + $\underline{H}_5$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 158.5, 148.3, 143.8, 114.1, 112.2, 72.9, 58.7, 39.2, 29.8, 29.7, 26.9, 26.0; **HRMS** (ESI$^+$) Calc. for C$_{12}$H$_{19}$O$_3$NNa [M+Na]$^+$ 248.1257, found 248.1254.

4.2.23 *N*-(6-methoxyhexyl)-5-nitrofuran-2-carboxamide 35

To a solution of *N*-(6-hydroxyhexyl)-5-nitrofuran-2-carboxamide **S11** (9.70 mg, 37.9 μmol) and 1,8-bis(dimethylamino)naphthalene (81.0 mg, 379 μmol) in dry CH$_2$Cl$_2$ (2 mL) at 0 °C was added trimethyloxonium tetrafluoroborate (56.0 mg, 379 μmol) and the mixture stirred at RT for 72 h. The mixture was cooled to 0 °C and reaction quenched with saturated NH$_4$OH solution (0.5 mL). Saturated NaHCO$_3$ solution (5 mL) was added and the organics extracted with Et$_2$O (3 x 5 mL). The combined

organic extracts were washed with 1N HCl solution, dried (MgSO$_4$), filtered and concentrated *in vacuo* Purification by flash column chromatography (30% EtOAc/Petrol) provided ether **35** (3.3 mg, 32%), as a colourless oil.

R$_f$ 0.50 (50% EtOAc/Petrol); **IR** (ATR) 3300, 2932, 2859, 1653, 1584, 1553, 1528 cm^{-1}; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.36 (1H, d, *J* = 3.8 Hz, H$_{10}$), 7.25 (1H, d, *J* = 3.8 Hz, H$_{11}$), 6.61 (1H, br s, NH), 3.45 (2H, app q, *J* = 7.0 Hz, H$_7$), 3.37 (2H, t, *J* = 6.5 Hz, H$_2$), 3.33 (3H, s, H$_1$), 1.66-1.57 (4H, m, H$_3$ + H$_6$), 1.42-1.39 (4H, m, H$_4$ + H$_5$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 156.3, 148.4, 115.9, 112.6, 72.8, 58.7, 39.7, 29.6, 29.6, 26.9, 26.0; **HRMS** (ESI$^+$) Calc. for C$_{12}$H$_{18}$O$_5$N$_2$Na [M+Na]$^+$ 293.1108, found 293.1104.

4.3 Biological Testing

4.3.1 Cell culture

Bloodstream form *T. brucei brucei* strain 427 were grown in HMI-9 media supplemented with 10% foetal bovine serum (Gibco) and 2.5 μg/mL G418 (Calbiochem) at 37°C with 5% v/v CO$_2$ with 10% bovine serum and G418 (2.5 μg/mL) at 37°C with 5% v/v CO$_2$, as described elsewhere.[8] Procyclic form *T. brucei brucei* strain 29-13 were grown in SDM-79 media (Gibco) supplemented with 2g/L sodium bicarbonate (Fisher Scientific), 7.5 μg/mL haemin (Sigma) 10% foetal bovine serum, 12.5 μg/mL G418 and 25 μg/mL hygromycin (Formedium) at 27.5°C with 5% v/v CO$_2$.

HeLa cells (ATCC® CCL-2) and African Green monkey kidney Vero cells (ECACC 84113001) were cultured in Dulbecco's Modified Eagle Medium (DMEM, Sigma) supplemented with 10% foetal bovine serum and grown at 37 °C in 5% CO$_2$ atmosphere.

Epimastigote *Trypanosoma cruzi* CL Brener strain were grown at 28 °C in RPMI 1640 medium (Sigma) supplemented with 20 mM HEPES pH 7.2 (Sigma), 4.9 mg/mL tryptone (Sigma), PGAB (2 mM sodium glutamate, 2 mM sodium pyruvate, 100 μg/mL streptomycin and 100 U/mL penicillin, all Sigma), 20 μg/mL haemin and 10% heat-inactivated foetal bovine serum.

Promastigote *L. major* MHOM/IL/80/Friedlin were grown at 28 °C in M199 media (Sigma) pH 7.4, supplemented with 40 mM HEPES pH 7.4, 100 μM adenosine, 5 μg/mL haemin and 10% heat-inactivated foetal bovine serum.

4.3.2 Cytotoxicity assays

The determination of the EC$_{50}$ of the compounds using Alamar Blue was completed as previously described.[29] Briefly, compounds were made up in DMSO and two-fold serial dilutions of compound in media were carried out in a 96-well plate in quadruplicate. Cells were counted using CASY Cell Counter and seeded as specified below.

Bloodstream form parasites, procyclic form parasites and HeLa cells were plated out at 1x10^3 cells/well, 1x10^4 cells/well and 1x10^3 cells/well, respectively. After 64 hours (3 days) Alamar Blue was added to each well and left for 6-8 hours to develop.

Mid-log *L. major* were diluted in media and seeded at 2 x10^5 per well in 100 μL media. Negative controls of DMSO only were included. Plates were incubated at 28 °C for 72 hours, after which 20 μL Alamar Blue (12.5 mg resazurin salt in 100 mL PBS) was added to all wells and incubated for a further 6 hours.

Mid-log *T. cruzi* were diluted in media and seeded at 5 x10^5 per well in 100 μL media. Negative controls of DMSO only and positive control of nifurtimox were included. Plates were incubated at 28 °C for 72 hours, after which 10 μL Alamar Blue was added to all wells and incubated for a further 6 hours.

For Vero cell assays, the monolayer was trypsinized, diluted in media and cells were seeded at 4 x10^3 cells per well. Cells were incubated at 37 °C with 5% CO$_2$ for 24 hours to allow attachment, after which media was removed and replaced with fresh media containing serial dilutions of compound. Drug diluted in media was added and plates were incubated for 72 hours, after which 10 μL Alamar Blue was added to all wells and incubated for a further 2 hours.

Cell viability was quantified using an FLx 800 plate reader (BioTek) with excitation wavelength 540/35 nm and emission wavelength at 590/10 nm using Gen5 Reader Control 2.0 Software (BioTek). EC$_{50}$ values were determined using a 4-parameter logistic regression equation using GraFit 5.0 (Erithacus Software).

Acknowledgements

Supplementary Information

Supplementary Information (synthesis and characterisation of intermediates, screening against procyclic *T. brucei*) associated with this article can be found in the online version.

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