**Optimisation of the Synthesis of Second Generation 1,2,4,5 Tetraoxane Antimalarials**

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Abstract; An efficient route to the synthesis of potent antimalarial aryloxy 1,2,4,5-tetraoxanes is described that permits parallel synthesis for Structure Activity Relationship (SAR) investigations. Brief details of the *in vitro* and *in vivo* antimalarial evaluation are included which enables identification of antimalarial leads for further development. Also described is an improved approach to the synthesis of a selected late-lead compound in just four or five synthetic steps from commercially available starting materials.

1.0 Introduction

Artemisinin (**1a**) and its semi-synthetic derivatives **1b** and **1c** remain at the forefront of antimalarial chemotherapy due to their high potencies, safety and their ability to clear malaria parasites more rapidly than any other clinically used class (Figure 1).1-3 In spite of these properties, first generation compounds have short plasma half lives that result in malaria parasite recrudescence.1 This has led to extensive medicinal chemistry efforts to find fully synthetic endoperoxide alternatives with improved potency and pharmacokinetic characteristics. In addition to very short plasma half-lives, there are now reports of resistance to the artemisinins in South East Asia and it is hoped that novel fully synthetic, structurally distinct, longer half-life endoperoxides can circumvent parasite resistance.4



**Figure 1** Structure of Artemisinin (**1a**), Semi-synthetic Analogues Artesunate (**1b**), Artemether (**1c**) and Synthetic Peroxides Under Development

Currently, the most advanced synthetic peroxide drug developed is OZ277 (**2c**), an endoperoxide with outstanding antimalarial activity and improved pharmacokinetic characteristics when compared with the artemisinins. OZ277 was approved in 2012 and is used a drug-combination with piperaquine (trade name; Synriam).5 The structure of this drug contains a 1,2,4-trioxolane core and a spiroadamantane unit. The 1,2,4 trioxolane group mimics the endoperoxide bridge found in artemisinin and mechanistic studies have shown that if the peroxide bond is too exposed, as in structure **2a**, the peroxide bond becomes susceptible to cleavage, and therefore expresses no antimalarial activity. Functionalisation of the endoperoxide group with a spiroadamantane group on one side, results in a compound **2b**, that expresses high antimalarial potency. This SAR observation is thought to be as a result of accessibility of the peroxide bridge to Fe(II) via an energetically favourable approach, whilst the O-O linkage still has steric protection from the bulky adamantane caged ring system (Figure 1).6

Over time, further medicinal chemistry optimisation of the 1,2,4-trioxolane core was performed to provide a second generation compound, OZ439 (**3a**). Aryloxy substituted 1,2,4-trioxolane OZ439 demonstrates increased drug exposure and half-life when compared to the alkyl substituted OZ277 with an improvement in antimalarial properties.7 A full review of the OZ439 trials can be found in the report by Charman *et. al.* andPhase II clinical trials are currently underway.8

Reliance on semi-synthetic artemisinin derivatives with a single synthetic peroxide back-up class limits the ability to respond to the malaria elimination challenge in terms of ensuring we have options in the face of potential resistance and the need to generate new drug combinations with a range of pharmacological and chemical characteristics going forward. Following the early seminal work of Vennerstrom on tetraoxane antimalarials,10 we initiated studies on the development of orally active tetraoxane molecules and produced an optimized lead compound RKA182 (**3b**) with *in vitro* antimalarial activity in the single digit nanomolar range versus multi-drug resistant isolates, improved rodent pharmacokinetic (PK) profiles and oral activity versus the artemisinins in the mouse model of malaria.10 However, the PK of this molecule is not compatible for its potential use within a single dose cure regimen, the new benchmark for developmental antimalarial drugs. As a result, additional optimisation was deemed necessary to extend the stability, PK and *in vivo* performance of this molecule.11

2.0 Results and Discussion

Based upon the beneficial effects seen by incorporation of an aryl ring into the side-chain of the OZ series, we decided to investigate the synthesis and SAR of a head to head series of 1,2,4,5-tetraoxanes. For this programme we decided to pursue a route that would enable divergent parallel synthesis at the penultimate step of the synthetic sequence (Scheme 1). Following identification of a lead compound this paper also will describe approaches to a shortened sequence to reduce the overall cost for our advanced antimalarial compound (**5f**).

Our initial route commenced with acetate protection of the commercially available 4-(4-hydroxyphenyl)cyclohexanone **4a** followed by formation of the gem dihydroperoxide **4b**, under acid-catalysed conditions.12 After work-up and without any further purification, this intermediate was subjected to a cyclisation reaction with adamantanone in the presence of Re2O7 according to a procedure previously published by O’Neill *et al.* to give the acetate tetraoxane **4c** in 46% yield.9 In this key reaction 2 mol % of the rhenium oxide catalyst was used and the reaction was complete within 2 hours. It is thought that this catalyst stabilises the reactive bishydroperoxide intermediate in addition to activating the adamantanone.13 Phenol acetate protected tetraoxane **4c** was hydrolysed with LiOH and alkylation of the resultant **4d** with allyl bromide 14 and ozonolysis provided aldehyde **4e**. Reductive amination of **4e** with a range of cyclic amines delivered target molecules **5a-f** in excellent overall yields. The analogous 3 carbon-linked analogues were available, by a similar route, by alkylation of phenol **4d** with 4-bromo butene and elaboration as shown in Scheme 1, B.



**Scheme 1** Synthesis of Aryloxy amino Tetraoxanes

Table 1 records the antimalarial activity of selected analogues. All tetraoxanes were active in the nanomolar region and they all outperformed artesunate following a single oral dose of 30 mg/kg. E209 (**5f**) displayed the best activity in this model with a 66% cure rate and an average mean survival time of 26 days (control animals MST = 4 days in this study). Based on the *in vitro* and *in vivo* activity (and additional PK analysis, data not shown) analogue **5f** was selected as our lead compound. Three approaches were then investigated to optimise and scale up the synthesis of this compound.

**Table 1.** Antimalarial activity of selected analogues

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Analogue | R= | *In vitro* activity versus *P. falciparum* (3D7) Strain (nM)\* | % Activity in *Plasmodium bergehi* following single 30 mg/kg dose (%)\*\* | Mean Survival Time in days (MST) (Single oral dose 30 mg/kg) |
| **5a** |  | 10.1± 1.0 | 99.21 | 16 (14, 21, 14) |
| **5b** |  | 8.2 ± 2.1 | 99.20 | 14 (14, 14, 14) |
| **5c** |  | 3.5 ± 0.2 | 99.53 | 19 (14, **30**, 14) |
| **5d** |  | 7.5 ± 0.2 | 99.42 | 14 (14, 14, 14) |
| **5e** |  | 0.5 ± 0.1 | 99.07 | 11 (11, 11, 11) |
| **5f** (**E209**) |  | 5.1 ± 0.81 | 99.65 | 26 (**30, 30**, 15) 66% cure |
| **5g** |  | 7.5 ± 0.2 | 99.48 | 15 (14, 14, 16) |
| **5h** |  | 3.7 ±0.12 | 99.65 | 14 (14, 14, 14) |
| **5i** |  | 7.2 ± 0.4 | 99.53 | 13.3 (13, 14, 13) |
| **5j** |  | 4.5 ± 0.2 | 99.53 | 10 (10, 10, 10) |
| Artesunate |  | 2.2 ± 0.4 | 92.00 | 9 (9, 8, 10) |
| Control |  |  |  | 4 (4, 4, 4) |

* \* *In vitro* activity was measured according to the method reported by Smilkstein et al 15
* \*\*Groups of three *P. berghei*-infected mice were treated orally one day post-infection with tetraoxanes dissolved or suspended in SSV. Antimalarial activity was measured by percent reduction in parasitemia on day three post-infection. Individual measurements differed by less than 10%. MST- mean survival time in days post infection.

The original synthesis (Scheme 1) was a seven-step process involving the use of an ozonolysis step. To produce a more cost effective synthetic route to E209, we proposed a much simpler route (Scheme 2A) that utilises inexpensive reagents, allowing for the production of **5f** (E209) in a shorter, 4-step sequence. This approach is based on the elegant synthetic process reported by Ley for the synthesis of OZ439 which utilises flow chemistry.16 In their approach, a direct alkylation of chloroacetyl morpholine and subsequent conversion of the amide to the amine led to OZ439 in an 86% yield when Zn(OAc)2 and triethoxysilane were used for the key amide reduction step (Scheme 2A).17,18 These conditions provide a promising precedent for the use of similar conditions in the production of E209.

Starting with acetate **4c** we were able to prepare the alkylated product **4f** in a one-pot reaction as shown in Scheme 2B. This sequence involves acetate hydrolysis and alkylation in the presence of tetrabutyl ammonium hydrogen sulfate as a phase transfer catalyst.



**Scheme 2** Chemoselective Amide Reduction Route to Lead Tetraoxane **5f**

For the reduction step we explored a range of silanes with 10 mol % of Zn(OAc)2 and 3 equivalents of hydrosilane, but in each case only starting material was recovered. Increasing the concentration of the catalyst to 30 mol% and leaving for 3 days had no effect. The more powerful reducing reagent LiAlH4 was also tested however, this reagent led to a variety of side products due to cleavage of the peroxide bond.

Alternative reagents compatible with selective reduction of tertiary amides such as Tf2O/NaBH4, Zn(OAc)2/HSi(OEt)3, BF3 .Et2O/ NaBH4, and Zn(Et)2/PMHS/LiCl were based on our previous experience with semi-synthetic artemisinin and tetraoxane chemistry

 We initially examined Tf2O/NaBH4 for the reduction as described by Xiang *et. Al.* 19The proposed mechanism (Scheme 3) involves activation of the amide with trifluoromethanesulfonic anhydride (Tf2O) to form a highly electrophilic iminium triflate which is susceptible by sodium borohydride to produce an N, O-acetal. The acetal then eliminates –OTf, assisted by the nitrogen lone pair to form a new iminium ion which is trapped by a second hydride, yielding the target amine. Studies have shown these conditions are highly chemoselective for tertiary amides over other functional groups, which is what is required to avoid cleavage of the tetraoxane unit.20 Initially we examined the reaction of amide **4f** with 1.1 eq of Tf2O and 1.3 eq of NaBH4 which delivered E209 in a yield of 28%. The amide carbonyl was effectively reduced with no tetraoxane cleavage products appearing in either the mass spectrum or NMR spectra. The reaction was not particularly efficient and required purification via column chromatography due to the presence of a starting material in the final product. Following purification, the mass spectrum of the final compound contains only one significant peak at m/z = 502.3 and the 1H NMR spectrum of **5f** shows the expected two sets of triplets at 4.09 and 2.83 ppm from the ethylene linker between the oxygen and nitrogen atoms, confirming that reduction had occurred with additional spectroscopic data consistent with a sample prepared earlier using the reductive amination chemistry depicted in Scheme 1.

 Following the success of this initial reaction, it was hypothesised that altering the number of equivalents of Tf2O and NaBH4 could lead to an increased yield. As a result, a series of repeat experiments were conducted to try and identify the optimal ratios of Tf2O and NaBH4.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Entry** | **Number of Equivalents of Tf2O** | **Number of Equivalents of NaBH4** | **Reaction time (h)** | **Yield of E209 (7) (%)** |
| 1 | 1.1 | 1.3 | 24 | 28 |
| 2 | 1.1 | 1.5 | 24 | 48 |
| 3 | 1.2 | 1.5 | 24 | 55 |
| 4 | 1.4 | 1.5 | 24 | 0 |
| 5 | 1.1 | 1.5 | 48 | 46 |

It was found that increasing the amount of sodium borohydride to 1.5 equivalents whilst keeping Tf2O at 1.1 produced an increased yield of 48%. The mass spectrum and NMR results matched those of the first trial, and so showed no signs of any side products produced from the tetraoxane cleavage. It was thought that, based on the proposed mechanism in Scheme 3 that the availability of Tf2O could limit the efficiency. As Tf2O acts to activate the amide towards reduction, having insufficient amounts would result in a large amount of inactivated intermediate that will not be reduced by the borohydride, or cleavage could occur at the tetraoxane unit instead. However, when trials were conducted with increased equivalents of the triflate, the reactions were unsuccessful. The final experiement (entry 5) examined the same conditions with a longer reaction time, but no increase in yield was observed. Additional approaches were briefly examined including the methods of Su-Dong21 (NaBH4/ BF3.Et2O) and Kovalenko22 (ZnEt2/ poly(methylhydrosiloxane PMHS) but neither of these methods provided yields greater than 20%.

Seeking to improve upon the overall synthesis of E209, we attempted two additional approaches; first to optimise the key tetraoxane forming step and second to access the solubilising side-chain by alkylation of the phenol in the final step. Rhenium oxide is an expensive catalyst so we investigated the alternative catalyst Bi(OTf)3 which has been reported to be an efficient catalyst for simple cyclic ketones.23



**Scheme 3** Convergent Synthesis of **5f** Through Improved Synthesis of **4d**

On a 30g scale over two steps, the target acetate **4c** was obtained in 31-37% yield with 50% recovery of the starting ketone (Scheme 3). Since the reaction showed complete conversion to the peroxyketal **4b**, the starting material recovery was due to hydrolysis of the cyclohexane peroxyketal intermediate to the starting ketone due to the presence of water in the reaction mixture. Addition of pellet-sized molecular sieves to control water led to an increase in yield to approximately 50%. Replacing the pellets with powdered molecular sieves led to a further increase in yield to 60%. The reduction in costs for the catalysts and increase in yield makes this a significant improvement over previous approaches.

With the phenol acetate to hand we then set out to preare the requisite 1-(2-chloroethyl)-4-fluoropiperidine hydrochloride **4h**. This was prepared in a two -step procedure as shown in Scheme 3 in quantitative yield. Hydrolysis of the acetate of **4c** and reaction of **4d** and **4h** provided the target molecule in 62% yield.

3.0 Conclusion

 In conclusion, we have investigated three approaches to the synthesis of potent next generation antimalarial 1,2,4,5-tetraoxanes. Route 1 provides a parallel approach for analogue design by incorporating a divergent step in the last step of the sequence. The shortest potential route to our lead compound E209 involved synthesis of amide **4f** with chemoselective reduction of the amide bond without cleavage of the labile endoperoxide bridges of the tetraoxane heterocycle. Other methods were tested that utilised other activating and reducing agents, however, all were unsuccessful in selectively reducing the amide. The third approach that employs a convergent strategy looks most suited for further development and includes an improved Bi(OTf)3 catalysed 1,2,4,5-tetraoxane forming reaction with subsequent direct alkylation of the phenol 1,2,4,5-tetraoxane under phase transfer catalysis conditions. The chemistry reported herein will be suitable for additional SAR investigations with this template and it is hoped further optimisation to an industrially viable, safe and cost-effective synthesis will be achieved.

**4. Experimental 24**

**4.1 General**

Air and moisture-sensitive reactions were performed in oven dried glassware sealed with rubber septa under an atmosphere of nitrogen from manifold or balloon. Anhydrous solutions and sensitive liquids were transferred via syringe or stainless steel cannula. Reactions were stirred using Teflon-coated magnetic stir bards. Organic Air and moinsture-sensitive reactions were performed in oven dried glassware sealed with rubber septa under an atmosphere of nitrogen from manifold or balloon. Organic solutions were concentrated using a Bϋchi rotary evaporator with a diaphragm vacuum pump. Anhydrous solvents were either purchased from Sigma Aldrich or dried and distilled immediately prior to use under a constant flow of dry nitrogen. Tetrahydrofuran was distilled from Na, dichloromethane and Et3N were distilled from CaH2. All reagents were purchased from Sigma Aldrich, Alfa Aesar, Frontier Scientific, Apollo Scientific and were used without any purification unless otherwise indicated. Thin layer chromatography (TLC) was performed on 0.25 mm Merck silica gel 60 F254 plates and visualised by ultraviolet light (u.v). U.V. inactive compounds were visualised using Iodine, *p*-anisaldehyde solution, ninhydrin or potassium permanganate followed by gentle heating. Flash column chromatography was performed on ICN ecochrom 60 (32-63 mesh) silica gel eluting with various solvent mixtures and using an airline to apply pressure. 1H NMRspectra were recorded on Bruker AMX 400 (400 MHz) spectrometer and reported as chemical shift in parts per million (ppm, δ) relative to tetramethylsilane as the internal reference, integration, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q =quartet, sex = sextet, m = multiplet), coupling constant (*J*, Hz), assignment. 13C NMR spectra were recorded on Bruker AMX400 (100 MHz) spectrometer and reported in terms of chemical shift (ppm, δ) relative to residual solvent peak. Mass spectra (MS) and high resolution mass spectra (HRMS) were recorded on a VG analytical 7070E machine, Fisons TRIO spectrometers using electron ionisation (EI) and chemical ionisation (CI), and Micromass LCT mass spectrometer using electron spray ionisation (ESI). All mass values are within error limits of ±5 ppm. Elemental analyses (%C, %H, %N) were either determined by the University of Liverpool Microanalysis Laboratory or the London Metropolitan University Elemental Analysis Service. Reported percentages are within error limits of ±0.5 %.

**4.2 Acetylation of 4-(4-hydroxyphenyl)cyclohexan-1-one (4a)**

To a stirred solution of 4-(4-hydroxyphenyl)cyclohexanone (100.0 g, 526.3 mmol) and triethylamine (220 mL, 1.05 mol) in DCM (1.0 L) was added acetic anhydride (107.0 g, 1.58 mol) dropwise at 0 °C. The reaction mixture was then allowed to warm up to rt and stirred for 2 h at rt. The reaction mixture was then washed with water (3 x 300 mL), saturated NaHCO3 (2 x 300 mL) and brine (300 mL). The organic layer was dried with MgSO4, filtered and concentrated under reduced pressure to give 4-(4-oxocyclohexyl)phenyl acetate (120.0 g, 98.3%) as a white solid. **1H NMR**(400 MHz, CDCl3) δH 7.25 (d, 2H, *J* = 8.6 Hz), 7.04 (d, 2H, *J* = 8.6 Hz), 3.04 (tt, 1H, *J* = 3.3, 12.12 Hz), 2.45-2.59 (m, 4H), 2.30 (s, 3H), 2.27-2.15 (m, 2H), 2.00-1.80 (m, 2H);**13C NMR** (100 MHz, CDCl3) δc 210.9, 169.6, 149.1, 142.3, 127.6, 121.6, 42.2, 41.3, 34.0, 21.1; **LC-MS**: *m/z* [M+H]+ = 233, **HRMS** (ES, m/z) calcd for [C14H16NaO3] ([M +Na]+) 255.0997, found 255.0995. purity 98.63% (UV214 nm).

**4.3 Synthesis of 1,2,4,5-Tetraoxane Aldehyde (4e)**

4.3.1 Rhenium (VII) Oxide Method;

**4-(dispiro[cyclohexane-1,3'-[1,2,4,5]tetroxane-6',2''-tricyclo[3.3.1.13,7]decan]-4-yl) phenyl acetate (4c)**

4-(4-oxocyclohexyl)phenyl acetate (2.00 g, 8.59 mmol) was dissolved in acetonitrile (10 mL) and formic acid (10 mL). 50% Hydrogen Peroxide (10 mL) was slowly pipetted in over ice and left to stir for 1 h at rt. The mixture was then diluted with distilled water (30 mL) and extracted with DCM (3 x 30 mL). The organic layer was washed with distilled water (3 x 30 mL) and brine (30 mL), dried with MgSO4 and reduced under vacuum to about 10 mL of solvent. The product was then dissolved in anhydrous DCM (10 mL), followed by the addition of 2-adamantanone (1.68 g, 11.2 mmol) and Rhenium (VII) Oxide (83.0 g, 0.17 mmol). The flask was flushed and sealed with nitrogen and left to stir for 2 h. The resulting solution was then filtered through silica using DCM and concentrated under vacuo leaving a yellow oil. The oil was then purified using column chromatography starting with an eluent of 5% EtOAc in hexane, gradually increasing the amount of EtOAc to 40%. The product containing fractions were collected and reduced under vacuo leaving a 1.64 g, 46%white solid. m.p. = 195-197°C **1H NMR**(400 MHz, CDCl3) δH 7.22 (d, 2H, *J* = 8.50 Hz,), 7.00 (d, 2H, *J* = 8.50 Hz,), 3.48-2.92 (m, 2H), 2.61 (tt, 1H, 11.8, 3.6 Hz), 2.29 (s, 3H, CH3), 1.48 - 2.13 (m, 20H,)**13C NMR** (100 MHz, CDCl3) δc 169.6, 148.9, 143.4, 127.8, 121.4, 110.5, 107.4, 46.9, 43.1, 39.2, 36.9, 33.1, 27.0, 21.1; MS (ES+), [M + H ]+ (100) 437.2 **HRMS** calculated for 437.1940 C24H30O6Na, found 437.1954. **LC-MS:** *m/z* [M + Na] + = 437, purity 98.04% (UV214 nm).

4.3.2Bi(OTf)3 Oxide Method;

To a stirred solution of 4-(4-oxocyclohexyl)phenyl acetate (25.0 g, 108.0 mmol) in acetonitrile (50 mL) and HCO2H (50 mL) was slowly added 30% H2O2 (50 mL) at 0 °C. The reaction mixture was stirred at rt for 1 h. The mixture was added to water (100 mL), extracted with DCM (2 x 100 mL). The combined organic layers were washed with aqueous NaHCO3 solution (150 mL) and brine (150 mL). The mixture was dried over MgSO4, filtered and the filtrate **4b** (~200 mL) was used for next step without further purification. To a solution of **4b** (200 mL) was added 2-adamantanone (22.6 g, 151.0 mmol), and activated powdered 4Å molecular sieves (20 g). The mixture was cooled to below 5 °C and then Bi(OTf)3 (10.6 g, 21.5 mmol) was added. The mixture was then warmed and stirred for 1 h at rt. The reaction mixture was filtered through a plug of Celite® which was rinsed with dichloromethane. The filtrates were then concentrated. Purification by column chromatography on silica gel eluting with 20% hexane:EtOAc to give-(dispiro[cyclohexane-1,3'-[1,2,4,5]tetroxane-6',2''-tricycle-[3.3.1.13,7]decan] -4-yl)phenyl acetate (27.2 g, 61.1% two-step) as a white solid. **1H NMR**(400 MHz, CDCl3) δH 7.22 (d, 2H, *J* = 8.5 Hz), 7.00 (d, 2H, *J* = 8.5 Hz), 3.48-2.92 (m, 2H), 2.61 (tt, 1H, 11.8, 3.6 Hz), 2.29 (s, 3H, CH3), 1.48-2.13 (m, 20H);**13C NMR** (100 MHz, CDCl3) δc 169.6, 148.9, 143.4, 127.8, 121.4, 110.5, 107.4, 46.9, 43.1, 39.2, 36.9, 33.1, 27.0, 21.1; MS (ES+), [M+H]+ (100) 437.2 **HRMS** calculated for 437.1940 C24H30O6Na, found 437.1954. **LC-MS:** *m/z* [M + Na] + = 437, purity 98.04% (UV214 nm).

**4.4 Preparation of 4-(Dispiro[cyclohexane-1,3'-[1,2,4,5]tetroxane-6',2''-tricyclo[3.3.1.13,7] decan]-4-yl)phenol (4d**)

To a solution of 4-(dispiro[cyclohexane-1,3'-[1,2,4,5]tetroxane-6',2''-tricyclo[3.3.1.13,7] decan]-4-yl)phenyl acetate (60.0 g, 145 mmol) in THF (500 mL) and water (200 mL) was added LiOH.H2O (18.2 g, 435 mmol). The reaction mixture was then stirred at rt for 2 h and then neutralised with dilute HCl. After evaporation of the majority of THF under reduced pressure, the mixture was extracted with DCM (2 x 300 mL). The combined organic layers were dried over MgSO4, filtered and concentrated under reduced pressure. Purified by column chromatography on silica gel eluting with 10% EtOAc: hexane to give 4-(Dispiro[cyclohexane-1,3'-[1,2,4,5]-tetroxane-6',2''-tricyclo[3.3.1.13,7] decan]-4-yl)phenol(45.0 g, 83.5%) as white solid. **1H NMR** (400 MHz, CDCl3) δH 7.09 (d, 2H, *J* = 8.5 Hz), 6.76 (d, 2H, *J* = 8.5 Hz), 4.73 (bs, 1H), 3.47-2.99 (m, 2H), 2.55 (tt, 1H, *J* = 3.5, 11.5 Hz), 2.10-1.56 (m, 20H); **13C NMR** (100 MHz, CDCl3) δc 153.8, 138.2, 127.9, 115.2, 110.5, 107.6, 47.1, 42.7, 39.5, 36.9, 33.1, 27.0. **HRMS** (ES, m/z) calcd for [C22H28NaO5]+ [M + Na]+ 395.1834, found 395.1835. **LC-MS**: *m/z* [M + Na] + = 395, purity 98.72% (UV214 nm).

**4.5 Preparation of** **(1''*R*,3''*R*,5''*R*,7''*R*)-4-[4-(prop-2-en-1-yloxy)phenyl]dispiro [cyclohexane-1,3'-[1,2,4,5]tetroxane-6',2''-tricyclo[3.3.1.13,7]decane]**

4.5.1 General procedure.

To a solution of 4-(Dispiro[cyclohexane-1,3'-[1,2,4,5]tetroxane-6',2''-tricyclo [3.3.1.13,7] decan]-4-yl)-phenol(20.0 g, 53.8 mmol) in acetone (500 mL) was added potassium carbonate (37.0 g, 106 mmol) and allyl bromide (13.0 g, 106 mmol). The reaction mixture was heated to reflux for 24 h. The resulting suspension was cooled to rt, filtered to remove the solid and concentrated. Purification by column chromatography on silica gel eluting with 10% EtOAc:hexane to give (1''*R*,3''*R*5''*R*,7''*R*)-4-[4-(prop-2-en-1-yloxy)phenyl]dispiro[cyclohexane-1,3'-[1,2,4,5]-tetroxane-6',2''-tricyclo-[3.3.1.13,7]deca-ne](21.5 g, 97%) as a white solid. **1H NMR**(400 MHz, CDCl3) δH 7.13 (d, 2H, *J* = 8.7 Hz), 6.85 (d, 2H, *J* = 8.7 Hz,), 6.05 (ddt, 1H, *J* = 17.2, 10.6, 5.3 Hz), 5.34 (ddd, 2H, *J* = 13.9, 11.9, 1.5 Hz), 4.51 (dt, 2H, *J* = 5.3 Hz, 1.5 Hz), 2.66 (ddd, 1H, *J* = 15.4, 7.8, 3.8 Hz), 2.09-1.53 (m, 22H) **13C NMR** (100 MHz, CDCl3) δc 157.0, 138.3, 133.5, 127, 117.6, 114.6, 110.5, 107.6, 68.9, 42.8, 37.0, 34.3, 33.2, 29.7, 27.1.**MS** (ES+), [M + Na]+ (100) 435.2 **LC-MS**: *m/z* [M + Na]+= 435, purity 98.37% (UV214nm).

4.5.2 Preparation of (1''*R*,3''*R*,5''*R*,7''*R*)-4-[4-(but-3-en-1-yloxy)phenyl]dispiro[cyclo-hexane-1,3'-[1,2,4,5]tetroxane-6',2''-tricyclo[3.3.1.13,7]decane]. Prepared according to the procedure above with 4-bromobut-1-ene (120 mg, 74%) as white foam **1H NMR**(400 MHz, CDCl3) δH 7.13 (d, 2H, *J* = 8.7 Hz), 6.83 (d, 2H, *J* = 8.7 Hz), 5.97-5.83 (m, 1H), 5.23-5.05 (m, 2H), 3.99 (d, 2H, *J* = 6.7 Hz), 2.60-2.48 (m, 3H), 2.10-1.55 (m, 22H,) **13C NMR** (100 MHz, CDCl3) δc 157.7, 138.5, 135.0, 128.2, 117.4, 114.9, 110.9, 108.0, 67.6, 43.2, 37.4, 34.7, 34.1, 33.6, 32.4, 30.4, 27.5 **MS** (ES+), [M + Na]+ (100) 449.2. HRMS (ES+ *m*/*z*) calcd for 449.2304 C26H34O5 Na found: 449.2324.

**4.6 Formation of {4-[(1''*R*,3''*R*,5''*R*,7''*R*)-dispiro[cyclohexane-1,3'-[1,2,4,5]tetro-xane-6',2''tricyclo[3.3.1.13,7]decan]-4-yl]phenoxy}acetaldehyde by ozonolysis (4e)**

4.6.1 General procedure.

Ozone was bubbled through a solution of (1''*R*,3''*R*,5''*R*,7''*R*)-4-[4-(but-3-en-1-yloxy)phenyl]dispiro[cyclohexane-1,3'-[1,2,4,5]tetroxane-6',2''-tricyclo[3.3.1.13,7]decane] (10.0 g, 24.3 mmol) in methanol (20 mL) and DCM (160 mL) at -78 oC until the solution became saturated with ozone and appeared blue. Nitrogen was then bubbled through the solution for 20 min to purge excess ozone. DMS(7.52 g, 121 mmol) was added dropwise to the stirring solution at -78 oC. The mixture was stirred at -78 oC for 1 hr, then allowed to warm up to rt and stirred for 1 h. The reaction mixture was concentrated under vacuum to give crude product. Purification by column chromatography on silica gel eluting with 20% EtOAc:DCM to give {4-[(1''*R*,3''*R*,5''*R*,7''*R*)-dispiro[cyclohexane-1,3'-[1,2,4,5]tetroxane-6',2''-tricyclo[3.3.1.13,7]-decan]-4-yl]phenoxyacetaldehyde (12.0 g, 86%) as white foam. **1H NMR**(400 MHz, CDCl3) δH 9.86 (s, 1H), 7.17 (d, 2H, *J* = 8.7 Hz), 6.83 (d, 2H, *J* = 8.7 Hz), 3.57 (s, 2H), 2.66-2.52 (m, 1H), 2.04-1.57 (m, 22H) **13C NMR** (100 MHz, CDCl3) δc 200.7, 157.32, 139.1, 128.3, 115.6, 114.9, 110.9, 108.0, 62.1, 43.7, 43.2, 37.4, 33.6, 30.2, 27.5 **MS** (ES+), [M + Na + CH3OH ] + (100) 469.2 HRMS calculated for 469.2202 C25H34O7Na, found 469.2216. **LC-MS**: *m/z* [M + Na + Methanol] + = 469, purity 92.87% (UV214nm).

**4.6.2 3-{4-[(1''*R*,3''*R*,5''*R*,7''*R*)-dispiro[cyclohexane-1,3'-[1,2,4,5]tetroxane-6',2''-tricyclo[3.3.1.13,7]decan]-4-yl]phenoxy}propanal (4g)**

Prepared according to the ozonolysis procedure above for **4e** with (1''*R*,3'*'R*,5''*R*,7''*R*)-4-[4-(but-3-en-1-yloxy)phenyl]dispiro[cyclohexane-1,3'-[1,2,4,5]tetroxane-6',2''-tricyclo[3.3.1.13,7]decane] (1.5 g, 68%) as white foam **1H NMR**(400 MHz, CDCl3) δH 9.86 (s, 1H), 7.15 (d, 2H, *J* = 8.7 Hz), 6.84 (d, 2H, *J* = 8.7 Hz), 4.29 (t, 2H, *J* = 6.1 Hz), 2.89 (dt, 2H, *J* = 6.1 Hz, 1.6 Hz,), 2.61-2.52 (m, 1H), 2.10-1.53 (m, 22H) **13C NMR** (100 MHz, CDCl3) δc 200.7, 157.3, 139.1, 128.3, 115.6, 114.9, 110.9, 108.0, 62.1, 43.7, 43.2, 37.4, 33.6, 30.2, 27.5 **MS** (ES+), [M + Na + CH3OH] + (100) 483.2. HRMS calcd for 483.2359 C26H36O7Na found 483.2362.

**4.7 Preparation of the tetraoxanes 5a-5f**

4.7.1 General procedure

To a solution of aldehyde (1 eq) in DCM (15 mL) was added the respective amine (1.5 eq) and the resulting mixture stirred at rt for 30 min. Sodium triacetoxyborohydride (1.5 eq) was then added, stirred at rt for 16 h. The reaction mixture was quenched by adding saturated NaHCO3 (5 mL) and extrated with DCM (3 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO4, filtered and concentrated. Purification by column chromatography eluting with 5% MeOH/DCM afforded the amines **5a-5f.**

**4.7.2 4-(2-(4-((1*R*,3*R*,5*R*,7*R*)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-4''-yl)phenoxy)ethyl)morpholine (5a)**

Prepared according to the procedure with **4e** and morpholine to give **5a** (0.6 g, 75%) as a white powder. A small sample was converted into the mesylate according to the method described by Wang et al. mp = 180 °C, lit mp = 182-183 °C; **1H NMR**(400 MHz, CDCl3) δH 7.13 (d, 2H, *J* = 8.7 Hz), 6.83 (d, 2H, *J* = 8.7 Hz), 4.09 (t, 2H, *J* = 5.7 Hz), 3.77-3.68 (m, 4H), 2.79 (t, 2H, *J* = 5.7 Hz), 2.61-2.48 (m, 5H), 2.09-1.52 (m, 22H) **13C NMR** (100 MHz, CDCl3) δc 157.6, 138.8, 127.4, 114.9, 110.9, 107.6, 67.3, 66.1, 58.1, 54.5, 43.4, 37.5, 33.6, 27.6 **MS** (ES+), [M + H]+ (100) 486.3 **HRMS** calculated for 486.2862 C28H40NO6, found 486.2854.

**4.7.3 *Tert*-butyl 4-(2-(4-((1*R*,3*R*,5*R*,7*R*)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-4''-yl)phenoxy)ethyl)piperazine-1-carboxylate**

Prepared according to the procedure with **4e** and tert-butyl piperazine-1-carboxylate The crude product was purified by column chromatography eluting with DCM:EtOAc, 1:4 to give pure Boc-protected **5b** (320 mg, 76%) as white foam. **1H NMR**(400 MHz, CDCl3) δH 7.14 (d, 2H, *J* = 8.6 Hz), 6.83 (d, 2H, *J* = 8.6 Hz), 4.07-4.14 (m, 2H), 3.47 (t, 4H*, J* = 4.5 Hz), 3.06-3.40 (m, 2H), 2.83 (t, 2H*, J* = 5.0 Hz), 2.44-2.66 (m, 5H), 1.52-2.14 (m, 20H), 1.46 (s, 9H); **13C NMR** (101 MHz, CDCl3) δc 157.0, 154.6, 138.3, 127.7, 114.4, 110.4, 107.5, 79.6, 65.7, 57.2, 53.3, 42.7, 36.9, 33.1, 28.4, 27.0; **HRMS** (ES+): *m*/*z* ([M + H]+):calcd for 585.3540 C33H49N2O7 found 585.3519.

A solution of *N*-Boc-protected **5b** (305 mg, 0.522 mmol) in dioxane (5.0 mL) and MeOH (15.0 mL) was cooled to 0 °C and acetyl chloride (0.40 mL, 0.52 mmol) was added drop-wise and the reaction mixture stirred at this temperature for 20 min. The reaction mixture was then warmed to rt and stirred for 16 h. The mixture was concentrated in vacuuo and the residue washed with Et2O (20 mL) to give the hydrochloride salt (270 mg, 93%) as a white solid. The hydrochloride salt was dissolved in water (15 mL) and 1M HCl was added until pH 7. The resulting mixture was extracted with DCM (3 X 15 mL). The combined organic extracts were dried in MgSO4 and concentrated to give the free amine 5c in quantitative yield as white foam **1H NMR**(400 MHz, CDCl3) δH 7.13 (d, 2H*, J* = 8.7 Hz), 6.83 (d, 2H*, J* = 8.7 Hz), 4.08 (t, 2H, *J* = 5.8 Hz,), 3.09 - 3.41 (m, 2H), 2.95 (t, 4H*, J* = 4.8 Hz), 2.79 (t, 2H*,J* = 5.8 Hz), 2.70 (br.s.,1H), 2.45-2.64 (m, 5H), 1.48-2.14 (m, 20H); **13C NMR** (101 MHz, CDCl3) δc 157.5, 138.7, 128.1, 114.9, 110.9, 108.0, 66.2, 58.1, 54.7, 46.1, 43.2, 37.4, 33.6, 27.5; **HRMS** (ES+): *m*/*z* calcd for C28H41N2O5 ([M+ H]+): 485.3015, found: 485.3028.

**4.7.4 4-(2-(4-((1*R*,3*R*,5R,7R)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-4''-yl)phenoxy)ethyl)-1,4-oxazepane (5d)**

Prepared according to the procedure with **4e** and 1,4-oxazepan to give **5d** (150 mg, 62%) as a white foam. **1H NMR** (400 MHz, CDCl3) δH 7.14 (d, 2H, *J* = 8.0 Hz), 6.83 (d, 2H, *J* = 8.0Hz), 4.10 (t, 2H, *J* = 6.0 Hz), 3.82-3.75 (m, 4H), 3.29-3.20 (m, 2H), 3.01 (t, 3H, *J* = 6 Hz), 2.89-2.88 (m, 2H), 2.59-2.52 (m, 4H), 2.05-1.25 (m, 20H). **13C NMR** (100 MHz, CDCl3) δC 157.5, 138.7, 128.13, 114.9, 110.9, 108.0, 69.0, 66.6, 58.3, 56.8, 54.6, 43.2, 37.4, 33.6, 27.5 26.1 **MS** (ES+), [M + H]+ 100) 500.3 HRMS calc for 500.3012 C29H42NO6 found 500.3012.

**4.7.5 *N*-(2-{4-[(1''*R*,3''*R*,5''*R*,7''*R*)-dispiro[cyclohexane-1,3'-[1,2,4,5]tetroxane-6',2''-tricyclo[3.3.1.13,7]decan]-4-yl]phenoxy}ethyl)tetrahydro-2*H*-pyran-4-amine (5e)**

Prepared according to the procedure with **4e** and and tetrahydro-2*H*-pyran-4-amine. The crude was then purified via column chromatography (5% MeOH/DCM) to give the target product **5e** (208 mg, 84%) as a white foam 1H NMR (400 MHz, CDCl3) δH 7.13 (d, 2H, *J* = 8.7 Hz), 6.83 (d, 2H, *J* = 8.7 Hz), 5.70 (bs, 1H), 4.15 (t, 2H, *J* = 5.0 Hz), 3.96 (dd, 2H, *J* = 11.7 Hz, 2.7 Hz), 3.34 (dt, 2H, *J* = 19.8 Hz, 9.9 Hz), 3.16 (t, 2H, *J* = 5.0 Hz), 3.07-2.97 (m, 1H), 2.63-2.51 (m, 1H), 2.09-1.56 (m, 26 H) 13C NMR (100 MHz, CDCl3) δc 157.0, 139.2, 128.2, 114.8, 110.9, 107.9, 66.8, 66.2, 54.5, 44.6, 43.2, 37.4, 33.6, 31.9, 30.0, 27.5, 22.5 MS (ES+), [M + H ]+ (100) 500.3 HRMS calculated for 500.3012 C29H42NO6, found 500.30011.

**4.7.6 4-(3-(4-((1*R*,3*R*,5R,7R)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-4''-yl)phenoxy)propyl)morpholine (5g)**

Prepared according to 4.7.1 with **4g** and morpholine to give **5g** (200 mg**,** 54 %) as a white powder. m.p.=111-113°C **1H NMR** (400 MHz, CDCl3) δH 7.13 (d, 2H, *J* = 8.7 Hz), 6.83 (d, 2H, *J* = 8.7 Hz), 4.00 (t, 2H, *J* = 6.3 Hz), 3.74 (t, 4H, *J* = 4.5 Hz), 3.05-3.38 (m, 2H), 2.38-2.63 (m, 7H), 1.42-2.14 (m, 22H), **13C NMR** (100 MHz, CDCl3) δc 157.3, 138.1, 127.7, 114.4, 110.5, 107.5, 66.8, 66.0, 55.6, 53.7, 42.8, 36.9, 33.1, 27.0, 26.4 **MS** (ES+), [M + H]+ (100) 500.3 HRMS calculated for 500.3012 C29H42NO6, found 500.3008.

**4.7.7 1-(3-(4-((1*R*,3*R*,5*R*,7*R*)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclo-hexan]-4''-yl)phenoxy)propyl)-4-(methylsulfonyl)piperazine (5h)**

Prepared according to the procedure 4.7.1 with **4g** and *N*-methane sulfonyl piperazine to give **5h** (156 mg**,** 80%) as a white powder **1H NMR** (400 MHz, CDCl3) δH 7.13 (d, 2H, *J* = 8.7Hz), 6.82 (d, 2H, *J* = 8.7 Hz,), 3.99 (t, 2H, *J* = 6.2 Hz), 2.78 (s, 3H), 2.64-2.52 (m, 5H), 2.11-1.53 (m, 24H) **13C NMR** (100 MHz, CDCl3) δc 157.7, 138.6, 128.1, 114.8, 110.9, 107.9, 66.2, 55.1, 52.8, 46.2, 43.2, 37.4, 34.5, 33.6, 30.1, 27.5 **MS** (ES+), [M + H]+ (100) 577.3 HRMS calculated for 577.2947 C30H45N2O7S, found 577.2944.

**4.7.8 1-(3-(4-((1*R*,3*R*,5*R*,7*R*)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-4''-yl)phenoxy)propyl)-4-fluoropiperidine (5i)**

Prepared according to the procedure 4.7.1 with **4g** and 4-fluoropiperidine.The crude was then purified via column chromatography (5% MeOH/DCM) to give the target product **5i** (80 mg, 63%). **1H NMR** (400 MHz, CDCl3) δH 7.13 (d, 2H, *J* = 8.1 Hz), 6.82 (d, 2H, *J* = 8.1 Hz), 4.77-4.64 (m, 1 H,) 4.00-3.97 (t, 2H, *J* = 6.0 Hz), 3.27-3.20 (m, 1H), 2.64-2.29 (m, 3H), 2.01-1.25 (m, 31H). **13C NMR** (100 MHz, CDCl3) δC 157.7, 138.5, 128.1, 114.8, 110.9, 108.0, 66.5, 55.6, 49.8, 4.2, 37.4, 33.6, 27.5. **MS** (ES+), [M + H]+ (100) 516.1 HRMS calculated for 516.3266 C30H43NO5 found 516.3268.

**4.7.7 Preparation of 4-(3-{4-[(1''*R*,3''R,5''*R*,7''*R*)-dispiro[cyclohexane-1,3'-[1,2,4,5]tetro-xane-6',2''-tricyclo[3.3.1.13,7]decan]-4-yl]phenoxy}propyl)-1,4-oxazepane (5j)**

Prepared according to the procedure 4.7.1 with **4g** and 1,4-oxazepane to give the product **5j** as a white foam (200 mg, 56 %) 1H NMR (400 MHz, CDCl3) δH 7.14 (d, 2H, *J* = 8.7 Hz), 6.82 (d, 2H, *J* = 8.7 Hz), 4.03 (t, 2H, *J* = 5.9 Hz), 3.88-3.94 (m, 2H), 3.84 (t, 2H, *J* = 6.1 Hz), 3.17-3.36 (m, 2H), 3.09-3.17 (m, 2H), 2.98 - 3.09 (m, 4H), 2.57 (ddd, 1H, *J* = 3.64, 7.94, 11.46 Hz), 2.11-2.32 (m, 4H), 1.52 - 2.10 (m, 20H); 13C NMR (100 MHz, CDCl3) δc 156.8, 138.4, 127.6, 114.2, 110.4, 107.4, 68.0, 65.9, 65.3, 57.2, 55.0, 53.5, 42.6, 36.8, 33.0, 26.9, 25.7; MS (ES+), [M + H] + (100) 514.3 HRMS calculated for 514.3169 C30H44NO6 found 514.3170.

**4.8 2-(4-((1*R*,3*R*,5*R*,7*R*)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-4''-yl)phenoxy)-1-(4-fluoropiperidin-1-yl)ethan-1-one (4f)**

**4c** (0.54 g, 1.45 mmol) was dissolved in MeCN (15 mL). Powdered NaOH (0.3 g, 7.5 mmol) and tetrabutylammonium hydrogen sulfate (0.09 g, 0.27 mmol) were added and then left to stir at 25 oC for 30 min. 2-chloro-1-(4-fluoropiperidin-1-yl)ethan-1-one (0.46 g, 2.56 mmol) was added and the reaction mixture was stirred at 60 oC for 16 h. The yellow solution was filtered and washed with DCM and reduced under vacuum. The resulting yellow oil was redissolved in EtOAc (20 mL) and washed with (2 x 30 mL) and brine (30 mL). The organic layer was dried with MgSO4 and concentrated under vacuum leaving yellow oil. (120 mg, 97%) **1H NMR** (400 MHz, CDCl3) δH 7.14 (d, 2H, *J* = 7.1 Hz), 6.87 (d, 2H, *J* = 7.0 Hz), 4.96 (d, 1H, *J* = 31.8 Hz), 4.75 (d, 1H, *J* = 40.9 Hz), 4.65 (d, 2H, *J* = 14.5 Hz), 3.91 (d, 1H, *J* = 12.9 Hz), 3.63 (s, 2H), 3.24 (d, 2H, *J* = 24.7 Hz), 2.55 (s, 2H), 2.01–1.65 (m, 23H); **13C NMR** (100MHz, CDCl3) δC 166.6, 156.3, 139.2, 127.9, 114.5, 110.5, 107.5, 88.3, 68.0, 60.4, 42.8, 39.3, 37.0, 33.2, 27.5, 27.1, 14.2; **HRMS** [M + Na]+ calculated for C29H38NO6FNa 538.61, found 538.30.

**4.9** **Amide Reduction Method for Synthesis of (5f)**

**4f** (0.17 g, 0.33 mmol) was dissolved in anhydrous DCM (15 mL). Trifluoro-methanesulfonic anhydride (0.14 mL, 1.59 mmol) was added and the mixture was stirred on at 0oC for 30 min. Sodium borohydride (0.04 g, 1.06 mmol) was added along with THF (6.5 mL) and the mixture was left to stir at room temperature for 1 h. The flask was then stored at 10 oC for 4 days before quenching with distilled water (10 mL). The solution was basified to pH 11 with Na2CO3. The organic product was extracted with diethyl ether (5 x 20 mL), dried with MgSO4 and concentrated under vacuo. The brown oil was then purified using column chromatography eluting with 10% EtOAc:Hex to 80% EtOAc:Hex which afforded the desired product **5f** as a white foam. (56 mg, 48% yield) 1H NMR (400 MHz, CDCl3) δH 7.14 (d, 2H, *J* = 8.6 Hz), 6.83 (d, 2H, *J* = 8.6 Hz),4.86-4.64 (m, 1H), 4.17 (t, 2H, *J* = 5.4 Hz), 2.96 (t, 2H, *J* = 5.4 Hz), 2.89-2.70 (m, 4H), 2.16-1.51 (m, 26H) 13C NMR (100 MHz, CDCl3) δc 157.2, 139.0, 128.2, 114.9, 110.9, 107.9, 66.3, 65.5, 57.3, 49.7, 43.2, 37.4, 34.8, 33.6, 30.9, 27.5, 22.2 MS (ES+), [M + H ]+ (100) 502.3 HRMS calculated for 502.2969 C29H41NO5F, found 502.2970.

**4.10 4-(2-(4-((1R,3R,5R,7R)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-4''-yl)phenoxy)ethyl)morpholine (5c)**

To a solution of **5b** (150 mg, 0.27 mmol) and Et3N (0.35 mL, 256 mg, 2.53 mmol) in anhydrous. DCM (10 mL) at 0 °C, CH3SO2Cl (0.1 mL, 148 mg, 1.29 mmol) was added. After stirring at 0 °C for 20 min, the ice bath was removed and the reaction mixture was stirred for 16 h at rt. The volatiles were evaporated and the crude product was purified by gradient LC (EtOAc/Hexane 1:4) to give pure **5c** (160 mg, 77%). **1H NMR**(400 MHz, CDCl3) δH 7.14 (d, 2H, *J* = 8.7 Hz), 6.83 (d, 2H, *J* = 8.7 Hz), 4.09 (t, 2H, *J* = 5.4 Hz), 3.28 (t, 4H, *J* = 4.6 Hz), 3.12-3.4 (m, 2H), 2.86 (t, 2H, *J* = 5.4 Hz), 2.78 (s, 3H), 2.67-2.76 (m, 4H), 2.49-2.63 (m, 1H), 1.51-2.10 (m, 20H); **13C NMR** (101 MHz, CDCl3) δC 156.9, 138.5, 127.7, 114.4, 110.5, 107.5, 65.8, 56.9, 52.7, 45.7, 42.8, 36.9, 34.1, 33.1, 27.0, 15.3; **HRMS** (ES+): *m*/*z* calcd for C29H43N2O7S ([M+ H]+): 563.2791, found: 563.2799.

**4.11 4-(2-(4-((1R,3R,5R,7R)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-4''-yl)phenoxy)ethyl)-1,4-oxazepane (5f)**

To a solution of **4e** (2.03 g, 4.90 mmol) in anhydrous DCM (100 mL), HCl salt of monofluropiperidine (1.03 g, 7.35 mmol) and NaBH(OAc)3 (1.56 g, 7.35 mmol) were added and the reaction was stirred for 16 h at rt. The reaction was quenched with aqueous sat. NaHCO3 (2 mL) and the aqueous layer was extracted with DCM (2 x 75 mL) and EtOAc (1 x 50 mL). The combined organic layers were dried with MgSO4, filtered and evaporated under reduced pressure to give crude product. The crude product was then purified by gradient LC (EtOAc/n-Hex, 1:1) to give pure **5f** as white foam (2.22 g, 90 %). **1H NMR** (400 MHz, CDCl3) δH 7.14 (d, 2H, *J* = 8.7 Hz), 6.84 (d, 2H, *J* = 8.7 Hz), 4.70 (d, 1H, *J* = 48.7 Hz), 4.10 (t, 2H, *J* = 5.8 Hz), 3.09-3.38 (m, 2H), 2.83 (t, 2H, *J* = 5.2 Hz), 2.73 (br. s., 2H), 2.47-2.64 (m, 3H), 1.55-2.10 (m, 24H); **13C NMR** (101 MHz, CDCl3) δC 157.0, 138.3, 127.7, 114.4, 110.5, 107.5, 65.8, 57.1, 49.8, 42.8, 36.9, 33.1, 31.2, 29.6, 27.0; **HRMS** (ES+): *m*/*z* calcd for C29H41NO5F ([M+ H]+): 502.2969, found: 502.2975.

**4.12 Preparation of 2-(4-fluoropiperidin-1-yl)ethan-1-ol**

To 4-fluoro piperidine (1.00 g, 7.10 mmol) and K2CO3 (3.98 g, 35.5 mmol) in MeCN (50 mL) was added 2 bromo-ethanol (1.77 g, 14.2 mmol) and the reaction was allowed to stir at rt for 12 h. The reaction was evaporated to dryness, diluted with water (10 mL) and extracted with DCM (3 x 20 mL) before washing the combined organics with brine (10 mL) and dried using Na2SO4,concentrated under reduced pressure to give 2-(4-fluoropiperidin-1-yl)ethan-1-ol (1.05 g, 100%) as a white powder. **1H NMR** (400 MHz, CDCl3) δH 5.02 (d, 1H, *J* = 47.6 Hz), 3.58 (t, 2H, *J* = 6.5 Hz), 2.73 (t, 2H, *J* = 6.5 Hz), 2.62-2.65 (m, 2H), 2.45-2.49 (m, 2H), 1.86-2.00 (m, 4H) **HRMS** (CI, CH4+ m/z) calcd for 148.1132 [C7H15FNO]+ ([M +H])+, found 148.1132.

**4.13 Preparation of 1-(2-chloroethyl)-4-fluoropiperidine hydrochloride (4h)**

To 2-(4-fluoropiperidin-1-yl)ethan-1-ol (0.50 g, 3.40 mmol) in DCE (10 mL) was added thionyl chloride (0.74 mL, 10.20 mmol) and the reaction mixture was heated at reflux for 3 h. The resultant precipitate was filtered and washed with diethyl ether to give 1-(2-chloroethyl)-4-fluoropiperidine hydrochloride (0.68 g, 99%) as a white powder which was used in the next step without further purification. **1H NMR** (500 MHz, CDCl3) δH 4.05-4.08 (m, 1H), 3.66 (t, 2H, *J* = 6.6 Hz), 2.86 (t, 2H, *J* = 6.6 Hz), 2.69-2.73 (m, 4H), 1.89-2.02 (m, 4H). **MS** (CI, CH4+ m/z) calcd for [C7H13FNCl]+ ([M + H]+) 166, found 166.1 (100), 168.1 (32)

**4.14 1-(2-(4-((1R,3R,5R,7R)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-4''-yl)phenoxy)ethyl)-4-fluoropiperidine (5f)**

To a solution of 4-(dispiro[cyclohexane-1,3’-[1,2,4,5]tetroxane-6’,2”-tricyclo[3.3.1.13,7]decan]4-yl)phenol (0.15 g, 0.40 mmol) in dry MeCN (15 mL) was added powered NaOH (80.0 mg, 1.20 mmol) and tetrabutylammonium hydrogen sulfate (0.47 g, 0.14 mmol). The mixture was stirred at rt for 1 h before **4h** (2.41 g, 1.20 mmol) was added. The reaction mixture was stirred at 60 °C for 12 h, cooled to rt, filtered, and washed with DCM (30 mL). After the filtrate was concentrated, the residue was dissolved in DCM (10 mL), washed with water (10 mL) and brine (10 mL), dried over MgSO4, filtered, and concentrated. The residue was dissolved in a small amount of EtOAc (2 mL) to which was added a solution of 1M HCl in ether (2 mL). The precipitate was collected and purified by column chromatography eluting with 80% EtOAc:Hexane to EtOAc to give the desired product. (1.25 g, 62%): mp 182-183 as a white solid. **1H NMR** (400 MHz, CDCl3) δH 7.14 (d, 2H, *J* = 8.7 Hz), 6.84 (d, 2H, *J* = 8.7 Hz), 4.70 (d, 1H, *J* = 48.7 Hz), 4.10 (t, 2H, *J* = 5.8 Hz), 3.09-3.38 (m, 2H), 2.83 (t, 2H, *J* = 5.2 Hz), 2.73 (br. s, 2H), 2.47-2.64 (m, 3H), 1.55-2.10 (m, 24H); **13C NMR** (101 MHz, CDCl3) δC 157.0, 138.3, 127.7, 114.4, 110.5, 107.5, 65.8, 57.1, 49.8, 42.8, 36.9, 33.1, 31.2, 29.6, 27.0; **HRMS** (ES+): *m*/*z* calcd for 502.2969, C29H41NO5F found 502.2975.

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24 As noted in reference 13 caution should be applied when handling organic peroxides: We experienced no hazards in the course of this work; however, any preparative work with peroxides, particularly molecules in which the additional or “active” oxygen forms a substantial fraction of the molecular mass, should be conducted with an awareness of the potential for spontaneous and exothermic decomposition reactions. (a) Medard, L. A. *Accidental Explosions: Types of Explosi*v*e Substances*; Ellis Horwood Limited: Chichester, 1989; Vol. 2. (b) Patnaik, P . A. *Comprehensi*V*e Guide to the* Sons: New York, 1999. (c) Shanley, E. S. In *Organic Peroxides*; Swern, D., Ed.; Wiley-Interscience: New York, 1970; Vol. 3, p 341. (d) Zabicky, J. In *The Chemistry of the Peroxide Group*, v. *2*; Rappoport, Z., Ed.; John Wiley & Sons: Chichester, 2006; pt 2, pp 597-773. (e) Sanchez, J.; Myers, T. N. Organic Peroxides. In *Kirk-Othmer Encyclo- pedia of Chemical Technology*, 5th ed.; John Wiley & Sons: Hoboken, NJ, 2006; vol. 18, pp 489-496.

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Graphical Abstract

