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Inhibition of N-type calcium channels by phenoxyaniline and sulfonamide analogues[†]

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Building on previous investigations, structural modifications to the neuronal calcium ion channel blocker MONIRO-1 and related compounds were conducted that included replacement of the amide linker with an aniline and isosteric sulfonamide moiety, and the previously used strategy of substitution of the quanidinium group with less hydrophilic amine functionalities. A comprehensive SAR study revealed a number of phenoxyaniline and sulfonamide compounds that were more potent or had similar potency for the Ca_V2.2 and Ca_V3.2 channel compared to MONIRO-1 when evaluated in a FLIPR-based intracellular calcium response assay. Cytotoxicity investigations indicated that the sulfonamide analogues were well tolerated by Cos-7 cells at dosages required to inhibit both calcium ion channels. The sulfonamide derivatives were the most promising $Ca_{y}2.2$ inhibitors developed by us to date due, possessing high stability in plasma, low toxicity (estimated therapeutic index > 10), favourable CNS MPO scores (4.0-4.4) and high potency and selectivity, thereby, making this class of compounds suitable candidates for future in vivo studies.

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Introduction

The sensation of pain is an intrinsic self-preservation mechanism that alerts the body to possible dangers. Nociceptive pain, the body's natural response to mechanical, thermal or chemical trauma, can be managed by removal of the noxious stimuli and may also necessitate the usage of analgesics and/or other clinical interventions depending on the severity of the injury.^{1,2} However, chronic pain, especially neuropathic pain, which affects approximately 7-8% of the population, does not respond favourably to traditional therapies even when there is no apparent stimuli acting on the body.^{3,4} Currently, the approved treatment for neuropathic pain includes three potent N-type calcium channel blockers; namely gabapentin 1, pregabalin 2 and ziconotide (Prialt®), a synthetic version of ω-conotoxin MVIIA 3 found naturally in the venom of the marine snail Conus

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Magus (Fig. 1).^{5,7} Unfortunately, the use of ziconotide is severely limited due to the intrathecal mode of administration and narrow therapeutic window. Gabapentin 1 and pregabalin 2, provide only minimal relief and also cause serious unwanted side-effects such as depression, blurred vision and decreased motor coordination.^{6,8} Consequently, several research groups, including our own, have engaged in research programs to develop alternative small molecule Cav2.2 (Ntype) calcium ion channel blockers for the treatment of neuropathic pain.9-27 Likewise, various research studies have shown that the Cav3.2 (T-type) voltage-gated calcium channel is also a promising therapeutic target for alleviating neuropathic pain.^{24–26,28–33}



Fig. 1 Structures of gabapentin 1, pregabalin 2, ω -conotoxin MVIIA 3,⁷ marketed as ziconotide (Prialt®), Z160 4 and ABT-639 5.

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Over the years, a small number of N- and T- type calcium channel blockers were evaluated in clinical trials for the treatment of neuropathic pain arising from various diseases. Unfortunately, the majority of drug candidates failed to meet the primary outcomes and were subsequently terminated. For instance, the drug Z160 4 (Fig. 1), a statedependent Cav2.2 inhibitor originally developed by Zalicus Pharmaceuticals, a subsidiary of Epirus Pharmaceuticals, was well tolerated in Phase I clinical trials, however, Z160 4 failed to demonstrate efficacy in patients with lumbosacral radiculopathy and post-herpetic neuralgia during the relevant phase II clinical evaluations.³⁴ Similarly, the drug ABT-639 5 (Fig. 1), a potent Cav3.2 blocker developed by AbbVie, failed to demonstrate analgesic efficacy in patients with diabetic neuropathy and was eventually terminated during phase II clinical trials.34-37 Due to the limited availability of effective medications for the management of neuropathic pain, our research investigations have focused on the discovery of small molecule Cav2.2 and Cav3.2 inhibitors with a number of phenoxyanilides being evaluated for their activity at the two calcium ion channels (representative structures are shown in Fig. 2).^{15,18,20} Our initial studies using whole-cell clamp patch electrophysiology experiments showed that MONIRO-1 6a demonstrated good selectivity for $Ca_V 2.2$ (IC₅₀ = 34 μ M) and $Ca_V 3.2$ (IC₅₀ = 1.7 μ M) channels over other neuronal calcium channels.²⁰ Moreover, the research outcomes of follow-up SAR studies indicated that the removal of the fluoro substituent in MONIRO-1 6a resulted in the analogous compound 7a exhibiting a 5-fold decrease in potency for the Cav2.2 channel, indicating that the fluoro group was essential for enhanced binding to the channel.²² Encouragingly, the replacement of the guanidinium group with a tertiary amine moiety, which was performed in an effort to improve drug-like characteristics and increase transport across the blood-brain barrier (BBB), resulted in compounds 6b, the tertiary amine variant of MONIRO-1, and 7b displaying comparable potency to that observed for MONIRO-1 6a.²² However, MONIRO-1 6a and related analogues 6b, 7a and 7b tend to be prone to rapid metabolism into toxic phenoxyaniline and as a result they are non-ideal drug leads. Therefore, we explored constrained tertiary amine functionalised analogues, with the aim of enhancing activity and decreasing metabolic degradation.²² While, the activity of the constrained analogues 8-10 for the Cav2.2 channel was similar to MONIRO-1 6a and analogues, the restriction of rotation in most cases led to a decrease in activity for the Cav3.2 channel.²² The acylated phenoxazine 8 was observed to rapidly hydrolyse in rat plasma ($t_{\pm} = 13.9$ min) to the corresponding carboxylic acid and phenoxazine, the dihydrodibenzoazepine 9 and dibenzoazepine 10 analogues were more stable, with both having a half-life greater than 60 h.22 Noting the structural similarity of these latter compounds to tricyclic antidepressants (TCAs), we recently reported Cav2.2 inhibition results that support the off-label use of TCAs with neuropathic pain.²³

The research findings highlighted above provided valuable insights for further optimisation of compounds to give improved activity at the Cav2.2 and Cav3.2 channels, superior pharmacokinetic profiles when compared to MONIRO-1 6a, and more favourable drug-like properties. To overcome the stability challenges observed in several of the phenoxyanilides analogues, two libraries of compounds, replacing the labile amide bond with either a secondary aniline or an isosteric sulfonamide functional group, were prepared. Additionally, the previously used strategy of replacing the guanidinium group of MONIRO-1 6a with less hydrophilic amine functionalities could lead to the development of more drug-like compounds with greater potential to cross the BBB. In this paper we report the synthesis and activity at the Cav2.2 and Cav3.2 channels of 54 compounds (Fig. 3), and for a representative subset, their plasma stability and an evaluation of their cytotoxicity.



Fig. 2 Chemical structures and their activity, determined by calcium influx fluorescence-imaging assays, of MONIRO-1 6a, and related analogues 6b, 7a and 7b, and the constrained analogues 8–10.



Fig. 3 Schematic depiction of the library of compounds synthesised and tested; replacement of the labile amide bond of MONIRO-1 **6a** with either a secondary aniline or an isosteric sulfonamide functional group, and replacement of the guanidinium group with less hydrophilic amines.



Results and discussion

Chemistry - compound design and synthesis

For all compounds, substituents on the aromatic phenoxy ring (\mathbb{R}^1) were positioned *para* to the phenoxy linkage, consistent with the location of this group in the MONIRO-1 analogues. The substituents, -F, $-CF_3$ and -CN, selected for their pharmacological relevance, were used to investigate the influence of electronic factors on the activity for the Ca_v2.2 and Ca_v3.2 channels with the unsubstituted analogue ($\mathbb{R}^1 =$ H) included for comparison purposes. For the phenoxyaniline analogues the position of the secondary aniline functionality was varied to evaluate how structural differences would affect binding to the calcium ion channels. The choice of amines was based on our previous findings and the various amine groups present in CNS drugs or drug candidates. The terminal amine groups investigated were dimethylamine, pyrrolidine, piperidine, imidazole and methylamine (Fig. 3). This allowed us to assess the effect of pK_a , the number of hydrogen bond donors (HBD) and ring size on potency. For the sulfonamide analogues a smaller library was synthesised, which was guided by the biological findings with the phenoxyanilines. All compounds were assessed for their inhibition of the Ca_V2.2 and Ca_V3.2 channels, with representative compounds analysed for plasma stability and cytotoxicity.

A library of 44 phenoxyaniline analogues that vary in substitution of the terminal aromatic ring, regiochemistry of the central ring and the terminal amine moiety were synthesised according to Scheme 1. A reductive amination





Fig. 4 Dose response curves, determined by calcium influx fluorescence-imaging assays of the sulfonamide compounds **42–51** in a) $hCa_V 2.2$ and b) $hCa_V 3.2$ channels. Data are presented as mean \pm SEM from n = 3-5 independent experiments. The calculated IC₅₀ values are shown in the relevant tables.

reaction between the corresponding anilines **11–20** (see ESI†) and the aromatic aldehyde **21** (ref. 27) provided the required chloro species **22–31**, from which the desired phenoxyaniline analogues **32**(**a–e**)–**41**(**a–c**) could be derived. The dimethylamine sulfonamide–based analogues **42–51** were synthesised from the sulfonyl acid **52** (see ESI†) and the corresponding aniline **11–20** (Scheme 2). Prior to biological testing, all final compounds were purified by preparative RP–HPLC using a mobile phase containing TFA. The TFA: amine stoichiometry in the purified products was determined by ¹⁹F NMR spectroscopic analysis as described in detail in the ESI.†

Biology - Cav2.2 and Cav3.2 activity, cytotoxicity studies

The activity of all analogues for the Ca_v2.2 and Ca_v3.2 channels was evaluated using the previously reported FLIPR calcium imaging assay.^{22,23} Ca_v2.2 inhibition was evaluated with the neuroblastoma SH-SY5Y cell line, in the presence of the Ca_v1 blocker nifedipine, and HEK 293T cells expressing recombinant human Ca_v3.2 α_1 subunit were used to evaluate Ca_v3.2 inhibition. The positive control for the Ca_v2.2 channel and Ca_v3.2 channel assay was NNC 55-0396. Representative dose response curves are shown in Fig. 4, and IC₅₀ values are summarised in Tables 1–3.

As the ortho-phenoxyanilines generally exhibited superior Ca_v2.2 activity, representative ortho-phenoxyanilines (32e $R^{1} = H, R^{2} = NHMe; 33a R^{1} = F, R^{2} = NMe_{2}; 33c R^{1} = F, R^{2} =$ piperidine; 34b $R^1 = CF_3$, $R^2 = pyrrolidine and 35d R^1 = CN$, R^2 = imidazole), were evaluated for their stability in rat plasma,^{21,38} in addition to the sulfonamides 45, 47 and 48. For these experiments the internal standard, diazepam, was added directly to the plasma along with the test compound. Diazepam was selected as the reference compound due to the stability of the compound in rat plasma over the period assessed and also because it had a different retention time on RP-HPLC analysis than the test compounds. Additionally, the activity of plasma enzymes in each batch of plasma utilized in this study was assessed using the positive control, diltiazem, and this experiment was performed in parallel with the test compounds. The phenoxyanilines 32e, 33a, 33c, 34b and 35d, and sulfonamides 45, 47 and 48 tested were all highly stable in rat plasma, each with a half-life greater than 60 hours. Comparing these findings to that obtained for MONIRO-1 6a and 6b,²² a vast increase in stability is apparent. Both MONIRO-1 6a and the corresponding dimethylamine 6b were determined to have a half-life in rat plasma of only ~90 min, whereas all the analogues tested in this study showed considerably greater stability with half-lives of >60 hours. These research findings indicate that replacement of the amide functional

	Ca _v 2.2			Ca _v 3.2				Ca _v 2.2			Ca _v 3.2		
Compd.	$\frac{IC_{50}}{(\mu M)}$	SEM	95% CI (μM)	IC_{50} (μ M)	SEM	95% CI (μM)	Compd.	$\frac{\mathrm{IC}_{50}}{(\mu\mathrm{M})}$	SEM	95% CI (μM)	IC_{50} (μM)	SEM	95% CI (μM)
32a	49	10.9	45-55	379	13.8	346-416	35e	65	6.2	61-70	157	8.2	146-168
33a	55	8.4	50-61	267	19.0	240-294	42	5.5	0.8	4.9-6.1	75	9.6	68-83
34a	30	5.7	27-32	238	25.5	216-261	43	2.8	1.0	2.4 - 3.4	63	19.0	54-73
35a	47	3.7	43-51	319	57.6	290-348	44	8.8	2.3	7.7-9.9	88	22.6	76-101
36a	54	10.6	49-60	258	37.2	228-288	45	4.8	1.4	4.0 - 5.4	90	14.2	81-100
37a	40	6.2	36-45	228	15.7	205-252	46	10	1.8	9.0-11	142	14.1	126-160
38a	81	27.4	69-95	308	32.3	272-344	47	9.9	2.0	9.0-11	68	8.9	60-77
39a	39	12.4	33-46	227	22.0	207-248	48	18	0.6	16-19	137	7.2	121-154
40a	60	10.7	54-67	271	47.5	244-300	49	21	0.7	19-24	61	15.9	54-69
41a	59	4.5	55-63	216	67.3	192-244	50	53	1.0	39-76	85	18.1	75-96
32e	84	13.1	77-92	178	24.8	163-194	51	14	0.5	12-15	99	3.2	88-112
33e	63	10.5	57-68	167	5.2	151-184	NNC55-0396	24.3	2.8	21-28	30.9	3.0	28-34
34e	58	12.5	53-64	204	17.2	189-219							

Table 1 Functional inhibition of the calcium channels $hCa_V 2.2$ and $hCa_V 3.2$ by the dimethylated anilines **32a–41a**, mono methylated anilines **32e–35e**, sulfonamides **42–51** and the control NNC 55–0396. Data are presented as mean \pm SEM and 95% CI from n = 3-5 independent experiments

Table 2 Functional inhibition of the calcium channels $hCa_V 2.2$ and $hCa_V 3.2$ by the pyrrolidine- and piperidine-based phenoxyaniline analogues 32b/ c-41b/c. Data are presented as mean \pm SEM and 95% CI from n = 3-5 independent experiments

	Ca _v 2.2			Ca _v 3.2				Ca _v 2.2			Ca _v 3.2		
Compd.	IC_{50} (μM)	SEM	95% CI (μM)	$\frac{IC_{50}}{(\mu M)}$	SEM	95% CI (μM)	Compd.	$\frac{IC_{50}}{(\mu M)}$	SEM	95% CI (μM)	IC_{50} (μM)	SEM	95% CI (µM)
32b	34	8.8	30-38	111	11.2	102-121	32c	62	17.5	55-69	188	15.0	171-206
33b	33	8.4	30-36	154	10.7	142-166	33c	18	2.2	16-20	126	3.5	114-141
34b	51	11.6	46-58	110	15.5	101-120	34c	27	3.4	23-30	146	18	118-175
35b	23	2.0	21-25	123	3.1	110-138	35c	8.0	0.6	7-9	67	8.0	36-127
36b	29	3.4	27-31	158	34.2	142 - 176	36c	63		59-67	200	14.0	182-219
37b	43	4.0	40-45	196	54.3	176-218	37c	20	0.8	18-23	292	20	245-327
38b	36	4.0	34-39	201	30.6	184-219	38c	54		49-60	237	13.7	218-258
39b	48	3.1	44-51	208	39.8	191-226	39c	30	1.7	27-36	67	5.9	36-128 (~50% inhibition at 500 µM)
40b	50	2.6	46-55	182	9.2	165-202	40c	37	3.9	33-40	26.0	4.5	18-41 (~50% inhibition at 500 μM)
41b	28	1.6	26-31	146	24.3	134-160	41c	19	1.3	17-22	22	5.6	14–38 (~60% inhibition at 500 µM)

Table 3 Functional inhibition of the calcium channels $hCa_V 2.2$ and $hCa_V 3.2$ by the imidazole-based phenoxyanilines 32d–41d. Data are presented as mean \pm SEM and 95% CI from n = 3-5 independent experiments

Compd.	Ca _v 2.2			Ca _v 3.2				Ca _v 2.2			Ca _v 3.2		
	$\frac{IC_{50}}{(\mu M)}$	SEM	95% CI (μM)	IC_{50} (μ M)	SEM	95% CI (μM)	Compd.	IC ₅₀ (μM)	SEM	95% CI (μM)	IC_{50} (μ M)	SEM	95% CI (μM)
32d	78	27.3	55-111	316	52.1	283-349	37d	70	15.5	51-96	385	27.3	353-426
33 d	33	8.8	28-38	196	28.0	174-220	38d	70	24.4	58-86	234	26.1	206-265
34d	125	8.9	116-136	287	29.4	262-312	39d	68	20.2	59-79	337	51.1	308-366
35 d	39	16.1	32-48	238	50.2	215-262	40d	283	31.1	257-309	170	40.6	150-192
36d	68	32.6	55-84	258	26.1	236-281	41d	75	35.2	55-100	371	38.0	344-407

group with either a secondary amine or sulfonamide had the expected effect of significantly reducing the compound's susceptibility to plasma hydrolysis.

The probability of the phenoxyaniline and sulfonamide analogues permeating the BBB and the CNS was assessed using the central nervous system multiparameter optimisation (CNS MPO) desirability tool.^{39,40} This algorithm, developed by Pfizer, assesses six physicochemical parameters; MW, clogP, clogD at a pH of 7.4, topological polar surface area (TPSA); number of hydrogen-bond donors (HBDs), and the pK_a of the most basic centre, to identify lead compounds with an increased chance of penetrating the CNS. A CNS MPO score of ≥ 4 , on a scale of 0–6, is indicative that the molecule has a high likelihood of entering the CNS. The phenoxyanilines prepared in this study typically had scores in the order of <3.5 and the sulfonamides were approximately 4 (see ESI[†] for the calculated CNS MPO scores).

For the first time we have also evaluated representative compounds, consisting of phenoxyanilide 7b,²² the phenoxyanilines **32e**, **33a**, **33c**, **34b** and **35d**, and the sulfonamides **42**, **44**, **45**, **47** and **48**, for their cytotoxicity to Cos-7 cells. The Cos-7 cell line was chosen as it is an immortalised cell line with fibroblast-like morphology and originates from the African green monkey (*Cercopithecus aethiops*) kidney cells,⁴¹ that has previously been used for toxicity studies.^{42,43} A resazurin reduction assay, Promega CellTitre-Blue® viability assay, was utilized for this study.^{44,45} Metabolically viable cells were detected by measuring the

reduction of resazurin to resorufin, a fluorescent molecule, by oxidoreductases in the mitochondrial electron transport chain. The number of viable cells were determined by fluorimetry and the 50% cytotoxic concentration (CC_{50}) values were determined from the fitted dose–response curve (Table 4). Additionally, the molecules' therapeutic index (TI), which is the ratio between the dosage of a drug that elicits an adverse effect (CC_{50}) and the dosage required to produce a therapeutic response (IC_{50}), was estimated.⁴⁶ Generally, a TI value >10 is indicative of a drug with a good safety profile as in clinical settings drugs with a narrow TI usually require constant monitoring of the levels in plasma to prevent toxic

Table 4 CC_{50} values obtained for representative compounds, their functional inhibition of the calcium channels $hCa_V2.2$ and $hCa_V3.2$, and their estimated therapeutic index (TI) at the Ca_V2.2 and Ca_V3.2 channel

	CC=0	Ca _v 2.2		Ca _v 3.2			
Compound	(μM)	IC_{50} (μM)	TI	IC_{50} (μM)	TI		
7b	>100	49	>2.0	19	>5.3		
32e	33	84	0.4	178	0.2		
33a	93	55	1.7	267	0.3		
33c	37	18	2.1	126	0.3		
34b	30	51	0.6	110	0.3		
35d	211	39	5.4	238	0.9		
42	>100	5.5	> 18	75	>1.3		
44	109	8.8	12	88	1.2		
45	100	4.8	21	90	1.1		
47	92	9.9	9.3	68	1.4		
48	54	21	2.6	137	0.4		

effects in the patient.⁴⁷ The amide **7b** was found to be well tolerated by Cos-7 cells up to concentrations as high as 100 μ M as were the sulfonamides **42**, **44** and **45**. Overall, the sulfonamide analogues had lower cytotoxicity than the phenoxyanilines.

Discussion

The large number of phenoxyaniline compounds 32-35a-e and 36-41a-d (44 compounds) synthesised and tested allowed us to further explore the structure-activity relationship by evaluating the influence of the substitution pattern of the aniline functional group, the substituent at the R^1 position, and the effect of varying the guanidinium group with less hydrophilic amine functionalities. For a given series of the phenoxyaniline analogues, those containing the same substituent at both R^1 and R^2 , the position of the aniline substituent on the central aromatic ring (ortho, meta or para) generally did not have a significant effect on the potency of the compounds for the Cav2.2 channel. However, in some cases, for instance with the -CN analogues, the ortho-substituted compounds 35a,c,d were found to be 2-fold more active than the analogous para-substituted compounds 41a,c,d for the Cav2.2 channel. Similarly, for the -F imidazole-based analogues, the ortho-derivative 33d was 2-fold more active at the Cav2.2 channel compared to the corresponding para- (39d) and meta-substituted (37d) compounds. Similarly, the substituent at R^1 for a particular series of compounds did not have a substantial effect on potency for the Cav2.2 channel, except for the piperidine and imidazole-based analogues. There was a more than 3-fold increase in affinity for the Ca_v2.2 for both the -F (33c, 37c, 39c) and -CF₃ (34c and 40c) piperidine-based analogues regardless of the substitution of the aniline group when compared to the corresponding unsubstituted compound (R¹ = H) 32c, 36c, 38c. For the -CN derivatives, there was about a 3-fold in potency for 41c and more importantly an 8-fold increase in potency for 35c versus 38c and 32c respectively. Based on the biological results obtained for the piperidinebased phenoxyanilines, the affinity for the Cav2.2 channel generally increased as the electron-withdrawing nature of R¹ increased suggesting that an electron-deficient aromatic ring and was critical for binding whilst an increase in the hydrogen bond acceptor (HBA) properties of the substituent led to reduction in affinity for the channel. For the ortho substituted imidazole-based anilines, a similar trend was observed where there was a 2-fold increase in potency for the Cav2.2 channel for both the -F 33d and -CN 35d compounds versus the unsubstituted derivative 32c. However, the additional HBA properties of the -CF3 imidazole-based analogues, 34d and 40d, potentially resulted in this compound having decreased affinity for the receptor when assessed against the analogous unsubstituted derivatives, 32d and 38d respectively. By modifying the tail amine functionality, it was observed that the tertiary amines are preferred with the order of activity following the trend of piperidine > pyrrolidine > N,N-dimethylated > imidazole when evaluated against the Cav2.2 channel. The monomethylated analogues 32e-35e were generally less active than the respective dimethylated derivatives (32a-35a) suggesting that the incorporation of the HBD at the tail group was not essential for binding to the receptor. The incorporation of the piperidine and pyrrolidine rings at R² resulted in compounds (32b/c-41b/c) with improved binding affinity for the Cav2.2 channel compared to MONIRO-1 6a with the 6-membered heterocycle generally being preferred. The imidazole moiety has a pK_a value of approximately 6.5, therefore, at physiological pH this group would only be partially ionised whereas the pyrrolidine and piperidine groups, which both have a pK_a of about 9.9, would be completely protonated. As the imidazole derivatives 32d-41d were less active than the corresponding pyrrolidine 32b-41b and piperidine 32c-41c analogues, it can be concluded that a fully ionised tertiary amine group, R² was critical for binding to the Cav2.2 channel. With regards to the Cav3.2 channel, the phenoxyanilines were overall inactive at this channel, however, the results obtained for the -CF₃ 40c and -CN 41c piperidine-based derivatives were promising.

Unlike the analogous phenoxyaniline 32a-41a, the position of the sulfonamide group on the central aromatic ring did affect the affinity of the sulfonamide analogues 42-51 for the Cav2.2 channel where the activity followed the trend such that ortho- 42-45 > meta- 46 and 47 > para-substituted 48-51 sulfonamide derivatives. Overall, the ortho- 42-45 and meta-substituted 46 and 47 compounds were highly active for the Cav2.2 channel, with IC₅₀ values less than 10 µM. Among them the ortho-substituted fluorinated compound 43 exhibited the highest potency of 2.8 µM. This is the highest activity that we have observed in our research program focused on the rationally designed small-molecule inhibitors targeting the Cav2.2 channel. Within the para-substituted series the -CN analogue was the most active, which mirrors that observed in the aniline series. In contrast, the substitution of the sulfonamide on the aromatic ring did not influence the binding to the Cav3.2 channel. Whilst the sulfonamide analogues showed higher potency against the $Ca_v 3.2$ channel compared to the corresponding phenoxyaniline derivatives; they were still deemed to be essentially inactive against this channel.

The current research study also allowed us to do a preliminary evaluation of how the substitution of the amide linker with the aniline and sulfonamide functionalities affected binding to the two calcium ion channels of interest. For the unsubstituted compounds, $R^1 = H$, the replacement of the amide group 7b with the aniline moiety did not affect the binding affinity for the Ca_v2.2 channel whereas there was a 2-fold increase in potency for the fluorinated phenoxyaniline analogue **33a** *versus* the analogous amide compound **6b**. On the other hand, a 9-fold and 36-fold increase in activity at the Ca_v2.2 channel was observed for the -H **42** and -F **43** substituted sulfonamide derivatives respectively *versus* the analogous amide compounds, **7b** and

6b. Conversely, the replacement of the amide moiety (7**b** and **6b**), with the aniline (**32a** and **33a**), and sulfonamide (**42** and **43**), groups led to decreased binding affinity for the $Ca_v3.2$ channel.

The preliminary results obtained from the cytotoxicity studies were encouraging. The previously synthesised compound 7b (ref. 22) was well tolerated by Cos-7 cells up to concentrations as high as 100 µM, however, cleavage of the amide bond ($t_{1/2}$ = 89 min) is still a major bioavailability and toxicity concern. Cytotoxicity studies with the evaluated phenoxyaniline compounds revealed unacceptable levels of toxicity, and the majority of compounds had low estimated TI values, which were less than 2. The phenoxyanilines typically had CNS MPO scores in the order of <3.5, and, combined with their high toxicity, means that replacement of the amide functionality of MONIRO-1 6a with an amine will not result in an acceptable drug-lead. However, the comprehensive SAR of this functionality has provided useful information that can be utilised in the rational design of future molecules. In contrast, the sulfonamide compounds tested were well tolerated by Cos-7 cells, and compounds 42 and 45 had estimated TI values greater than 18. From this study it can be concluded that the sulfonamide analogues 42-47 were the most promising drug leads, particularly 42, 43 and 45, due to their safe toxicological profile (estimated TI > 10), high CNS MPO scores (4.0-4.4) and, most importantly, high potency and selectivity for the Cav2.2 channel.

Conclusions

Although it was recognised that the phenoxyaniline series were likely to be toxic and this was confirmed by the results of the cytotoxicity studies, which showed that the majority of the phenoxyaniline compounds evaluated had low estimated TI values < 2 at both receptors, removing anilines completely from the drug design space can severely limit the discovery process. Therefore, it was of interest to study the SAR of these compounds as they can be synthesised with relative ease. Overall, it was found that a tertiary amine functionality that can fully ionise at physiological pH was critical for binding to both calcium ion channels. Additionally, an electronwithdrawing substituent particularly the -CN group can potentially improve the potency for the Cav2.2 channel, whilst, an increase in the HBA properties may result in a decrease in activity for the receptor as seen in the imidazolebased -CF₃ derivatives. The affinity of the piperidine-based phenoxyaniline compounds particularly the -CN derivatives 35c and 41c for both the Cav2.2 and Cav3.2 channel respectively was promising as they provide valuable insights into the factors that affect binding to channel. Additionally, there are opportunities to make modifications to 35c and 41c to produce compounds that are more potent for both receptors and have more favourable drug-like properties.

The activity for the sulfonamide compounds for the $Ca_V 3.2$ channel was somewhat encouraging, however, optimisation studies and further modifications is still

required to obtain improved activity at this receptor. Fortunately, the replacement of the amide linker of MONIRO-1 **6a** with an isosteric sulfonamide group combined with substituting the guanidinium group with a dimethylated amine moiety led to the discovery of the most potent $Ca_V 2.2$ blockers developed in our research group to date. Considering the $Ca_V 2.2$ activity of the sulfonamide derivatives, their plasma stability and cytotoxicity, as well as their ability to cross the BBB, it can be concluded that **42** and **45** are the most promising compounds to take forward in future *in vivo* studies.

Experimental

Chemistry

General experimental. Column chromatography was conducted using Merck silica gel 60 (0.040-0.063 mm) unless otherwise state. Thin-layer chromatography (TLC) was performed using Merck Millipore TLC silica gel 60 F254 coated on aluminium sheets. Compounds were visualised under UV lamp at 254 UV irradiation or through the use of an appropriate stain such as potassium permanganate and ninhydrin. The mobile phase reported for the R_f value was also utilised for the purification of the compound by column chromatography unless otherwise stated. Proton nuclear magnetic resonance (¹H NMR), carbon-13 nuclear magnetic resonance (13C NMR) and fluorine-19 (19F NMR) were recorded on a Bruker DRX400 spectrometer operating at 400 MHz (¹H), 100 MHz (¹³C) and 376 MHz (¹⁹F), Bruker DRX600 operating at 600 MHz (¹H) and 151 MHz (¹³C) or Bruker AV500P spectrophotometer operating at 500 MHz (¹H) and 126 MHz (¹³C), as solutions in specified deuterated solvents at 298 K unless otherwise stated. The resonance shifts were assigned based on the chemical shift (δ – measured in ppm), multiplicity (s - singlet, d - doublet, t - triplet, q - quartet, etc.), number of protons, observed coupling constant (J measured in Hz). Chemical shifts (δ), measured in parts per million (ppm), are referenced to residual solvent signal or TMS unless otherwise stated. High-resolution mass spectrometry (APCI, ESI) was conducted on a Thermo® Scientific Q Exactive Fourier transform mass spectrometry (FT-MS). Positive ion EI mass spectra were performed using a Thermo® Scientific DFS mass spectrometer using an ionisation energy of 70 eV. Accurate mass measurements were obtained with a resolution of 5000-10000 using perfluorokerosene (PFK) as the reference compound. Infrared spectra (IR) were recorded on an Agilent Technologies Cary 630 FTIR as thin films. Infrared band frequencies are reported in wavenumbers (cm⁻¹). Analytical grade reagents and solvents were used as purchased without further purification unless otherwise stated. Aldehyde 21 was synthesised according to the procedure noted in ref. 27. Airsensitive reactions were performed under an atmosphere of N₂ using a standard Schlenk line and glassware for moisturesensitive reactions were dried overnight in the oven at 110 °C. Microwave reactions were conducted on a CEM Discover

SP microwave synthesiser at 150 W. Compounds were purified by preparative RP-HPLC using a 1260 infinity quaternary LC system with a Phenomenex Luna C8 column $(150 \times 21.5 \text{ mm}, 5 \mu\text{m})$, buffer A – 100% MilliQ H₂O/0.1% TFA and buffer B - 80% ACN/20% MilliQ H₂O /0.1% TFA, flow rate: 10 mL min⁻¹, elution method: 90% buffer A and 10% buffer B for 2 min, gradient run 90% buffer A and 10% buffer B to 10% buffer A and 90% buffer B from 2 to 30 min, 10% buffer A and 90% buffer B from 30 to 40 min, 90% buffer A and 10% buffer B from 40 to 42 min.

General procedure 1: synthesis of reductive amination products 22-31. The respective aniline 11-20 (1 equiv., see ESI[†]), aldehyde 21 (1.5-3 equiv.) and p-TSA (0.05 mol equiv.) was dissolved in toluene. The resulting solution was deoxygenated by bubbling with N2 for 30 min and then refluxed using a Dean-Stark apparatus for 5-10 days. The reaction was monitored continuously by ¹H NMR spectroscopy. After removal of the solvent in vacuo, NaBH₄ (4-8 equiv.) and dry MeOH were added to the resulting imine and the mixture refluxed overnight. The solvent was removed and water (80 mL) was added to the flask. The crude product 13-22 was extracted with DCM (3 \times 60 mL). The organic layers were combined, washed with brine (80 mL), dried over Na₂SO₄ and the solvent removed in vacuo. The reductive amination product 22-31 was purified by column chromatography.

General procedure 2a: synthesis of dimethylated and monomethylated phenoxyaniline compounds. The reductive amination product 22-31, KI, ACN (1 mL) and the respective amine; 2 M dimethylamine in THF or 2 M methylamine in THF (3 mL, 6.0 mmol); and was heated in a microwave reactor at 100 °C for 3 h. The mixture was filtered and the solvent was removed under a stream of N2. The product was purified by column chromatography using neutral alumina (3% MeOH: 40% CHCl₃: 57% petroleum benzine). A portion was purified by preparative RP-HPLC to obtain an analytically pure sample for biological studies and the ¹H,¹³C and 19F NMR spectra of the respective compound was recorded.

General procedure 2b: Synthesis of pyrrolidine- and piperidine-based phenoxyaniline compounds. A mixture of the reductive amination product 22-31, KI, K₂CO₃, dry ACN and the respective amine; pyrrolidine or piperidine; was heated in a microwave reactor at 120 °C for 3-5 h. The mixture was filtered and the solvent was removed under a stream of N₂. The reaction progress was monitored by ¹H NMR spectroscopy from which the reaction yield was calculated. A portion was purified by preparative RP-HPLC to obtain an analytically pure sample for biological studies and the ¹H,¹³C and ¹⁹F NMR spectra of the respective TFA salt was recorded.

General procedure 2c: synthesis of imidazole-based phenoxyaniline compounds. A mixture of the reductive amination product 22–31, KI, imidazole and dry ACN (3 mL) was heated in a microwave reactor at 120 °C for 3 h. The mixture was filtered, the solvent was removed under a stream

of N₂ and the compound was purified by column chromatography using neutral alumina (3% MeOH: 30% CHCl₃:67% petroleum benzine). A portion was purified by preparative RP-HPLC to obtain an analytically pure sample for biological studies. The ¹H and ¹³C NMR spectra of the compound was recorded while the ¹⁹F NMR spectrum of the TFA salt was recorded.

General procedure 3: synthesis of sulfonamide compounds. A mixture of the sulfonic acid 52 and SOCl₂ was stirred and heated at reflux overnight. The reaction progress was monitored by LC-MS analysis whereby a small aliquot was removed and quenched in MeOH. SOCl₂ was removed under a stream of N₂ to yield the corresponding sulfonyl chloride in a quant. conversion. A mixture of the sulfonyl chloride, aniline 3-12, Cs₂CO₃ and dry ACN (10 mL) was heated at 70 °C under N2 for 1-2 days. The solvent was removed in vacuo and water (10 mL) was added to the flask. The crude product 42-51 was extracted with DCM (3 \times 50 mL). The organic layers were combined, dried over Na₂SO₄ and the solvent removed in vacuo. The compound was purified by column chromatography on neutral alumina (3% MeOH: 50% CHCl₃: 47% petroleum benzine). A portion was purified by preparative RP-HPLC to obtain an analytically pure sample biological studies and the ¹H,¹³C and ¹⁹F NMR spectra of the respective TFA salt was recorded.

N-(4-(3-Chloropropoxy)benzyl)-2-phenoxyaniline (22). The title compound was synthesised according to general procedure 1. The aniline 11 (1.30 g, 7.02 mmol), aldehyde 21 (2.32 g, 11.7 mmol), p-TSA (66 mg, 0.38 mmol) and toluene (80 mL) was refluxed for 7 days. The resulting imine was reduced using NaBH₄ (1.49 g, 39.6 mmol) and dry MeOH (80 mL).The title compound 22 was obtained as a colourless oil (2.24 g, 93%); Rf: 0.26 (7% EtOAc: 93% petroleum benzine); IR (neat, cm⁻¹): 3445, 2969, 2927, 1607, 1511, 1490, 1243, 1215, 1174, 1051, 745; ¹H NMR (400 MHz, CDCl₃-d) δ 7.35-7.27 (m, 2H), 7.25-7.18 (m, 2H), 7.10-6.94 (m, 4H), 6.88-6.81 (m, 3H), 6.72 (dd, J = 8.0, 1.5 Hz, 1H), 6.64 (td, J = 7.7, 1.5 Hz, 1H), 4.54 (t, J = 5.6 Hz, 1H), 4.30 (d, J = 5.7 Hz, 2H), 4.10 (t, J = 6.1 Hz, 2H), 3.74 (t, J = 6.1 Hz, 2H), 2.23 (p, J = 6.1 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 158.05, 157.67, 143.16, 140.49, 131.72, 129.80, 128.67, 125.02, 122.85, 119.34, 117.57, 116.99, 114.75, 111.87, 64.47, 47.37, 41.65, 32.44; HRMS (APCI): m/z calcd $C_{22}H_{23}CINO_2 [M + H]^+$ 368.1417, found, 368.1413.

N-(4-(3-Chloropropoxy)benzyl)-2-(4-fluorophenoxy)aniline (23). The title compound was synthesised according to general procedure 1. Compound 12 (0.91 g, 4.5 mmol), aldehyde 21 (2.67 g, 13.5 mmol) and p-TSA (43 mg, 0.25 mmol) in toluene (80 mL) was refluxed for 5 days. The resulting imine was reduced using NaBH₄ (1.28 g, 33.7 mmol) and dry MeOH (100 mL). The title compound 23 was obtained as a colourless oil (1.03 g, 60%); Rf: 0.34 (10% EtOAc: 90% petroleum benzine); IR (neat, cm^{-1}): 3403, 2872, 1602, 1498, 1435, 1243, 1201, 1115, 1044, 849, 809, 735; ¹H NMR (600 MHz, CDCl₃-d) δ 7.26–7.22 (m, 2H), 7.03–6.96 (m, 3H), 6.96-6.90 (m, 2H), 6.88-6.84 (m, 2H), 6.79 (dd, J = 7.7, 1.5 Hz, 1H), 6.72 (dd, J = 8.1, 1.5 Hz, 1H), 6.63 (td, J = 7.7, 1.5

Hz, 1H), 4.54 (d, J = 5.4 Hz, 1H), 4.30 (d, J = 5.1 Hz, 2H), 4.10 (t, J = 6.1 Hz, 2H), 3.74 (t, J = 6.1 Hz, 2H), 2.23 (p, J = 6.1 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃-d) δ 158.56 (d, J = 240.8 Hz), 158.06, 153.37 (d, J = 2.4 Hz), 143.67, 140.18, 128.68, 124.91, 119.05 (d, J = 8.1 Hz), 118.57, 116.98, 116.24 (d, J = 23.1 Hz), 114.73, 111.85, 64.42, 47.34, 41.61, 32.38; ¹⁹F NMR (376 MHz, CDCl₃-d) δ -121.56; HRMS (APCI): m/z calcd C₂₂H₂₂O₂NClF [M + H]⁺ 386.1318, found, 386.1319.

N-(4-(3-Chloropropoxy)benzyl)-2-(4-(trifluoromethyl)

phenoxy)aniline (24). The title compound was synthesised according to general procedure 1. The aniline 13 (986 mg, 3.90 mmol), aldehyde 21 (1.75 g, 8.84 mmol), p-TSA (41.5 mg, 0.24 mmol) and toluene (80 mL) was refluxed for 8 days. The resulting imine was reduced using NaBH₄ (870 mg, 23.0 mmol) and dry MeOH (50 mL). The title compound 24 was obtained as a colourless oil (1.43 g, 84%); $R_{\rm f}$: 0.26 (7% EtOAc : 93% petroleum benzine); IR (neat, cm⁻¹): 3444, 3419, 2927, 1608, 1511, 1330, 1238, 1165, 1101, 1068, 836, 740; ¹H NMR (400 MHz, CDCl_3 -*d*) δ 7.57 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.2 Hz, 2H), 7.09 (t, J = 7.9 Hz, 1H), 7.03 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 7.9 Hz, 1H), 6.86 (d, J = 8.1 Hz, 2H), 6.77 (d, J = 7.9 Hz, 1H), 6.70-6.64 (t, J = 7.9 Hz, 1H), 4.43 (s, 1H), 4.30 (s, 2H), 4.10 (t, J = 6.1 Hz, 2H), 3.75 (t, J = 6.1 Hz, 2H), 2.24 (p, J = 6.1 Hz, 2H); 13 C NMR (101 MHz, CDCl₃-d) δ 160.55, 158.04, 141.63, 140.58, 131.31, 128.48, 127.11 (q, J = 4.5 Hz), 126.10, 124.48 (q, J = 32.7 Hz), 124.40 (q, J = 271.5 Hz), 120.32 (d, J = 1.9 Hz), 117.12, 116.73, 114.60, 112.29, 64.24, 47.04, 41.48, 32.21; ¹⁹F NMR (377 MHz, CDCl₃) δ -62.17; HRMS (APCI): m/*z* calcd C₂₃H₂₁O₂NClF₃ [M]⁺ 435.1207, found, 435.1208.

4-(2-((4-(3-Chloropropoxy)benzyl)amino)phenoxy)

benzonitrile (25). The title compound was synthesised according to general procedure 1. The aniline 14 (1.28 g, 6.09 mmol), aldehyde 21 (3.62 g, 18.2 mmol), p-TSA (70.1 mg, 0.41 mmol) and toluene (80 mL) was refluxed for 10 days. The resulting imine was reduced using NaBH₄ (1.77 g, 46.9 mmol) and dry MeOH (50 mL). The title compound 25 was obtained as a yellow oil (1.29 g, 54%); R_f: 0.31 (15% EtOAc:85% petroleum benzine); IR (CDCl₃, cm⁻¹): 3411, 2931, 2225, 1602, 1501, 1230, 1163, 1036, 907, 834, 797; ¹H NMR (600 MHz, $CDCl_3$ -*d*) δ 7.58 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.5 Hz, 2H), 7.10 (ddd, J = 8.1, 7.6, 1.5 Hz, 1H), 6.99 (d, J = 8.8 Hz, 2H), 6.91 (dd, J = 7.6, 1.5 Hz, 1H), 6.84 (d, J = 8.5 Hz, 2H), 6.77 (d, J = 8.1 Hz, 1H), 6.70 (t, J = 7.6 Hz, 1H), 4.33 (s, 1H), 4.28 (s, 2H), 4.09 (t, J = 6.1 Hz, 2H), 3.74 (t, J = 6.1 Hz, 2H), 2.23 (p, J = 6.1 Hz, 2H); 13 C NMR (101 MHz, CDCl₃) δ 161.08, 157.73, 140.71, 140.00, 133.84, 130.77, 128.27, 126.26, 120.37, 118.60, 117.13, 116.82, 114.35, 112.46, 105.35, 64.04, 46.82, 41.36, 31.94; HRMS (APCI): *m*/*z* calcd C₂₃H₂₂O₂N₂Cl [M]⁺ 392.1286, found, 392.1285.

N-(4-(3-Chloropropoxy)benzyl)-3-phenoxyaniline (26). The title compound was synthesised according to general procedure 1. The aniline 15 (1.23 g, 6.65 mmol), aldehyde 21 (1.52 g, 7.68 mmol), *p*-TSA (63 mg, 0.37 mmol) and toluene (80 mL) was refluxed for 7 days. The resulting imine was reduced using NaBH₄ (1.51 g, 40.0 mmol) and dry MeOH (80 mL).The title compound 26 was obtained as a yellow oil (2.24

g, 91%); $R_{\rm f}$: 0.33 (15% EtOAc : 85% petroleum benzine); IR (neat, cm⁻¹): 3400, 3061, 2881, 1615, 1578, 1505, 1487, 1240, 1215, 1145, 818, 752; ¹H NMR (400 MHz, CDCl₃-*d*) δ 7.39– 7.28 (m, 2H), 7.30–7.19 (m, 2H), 7.16–7.06 (m, 2H), 7.06–6.97 (m, 2H), 6.94–6.84 (m, 2H), 6.42–6.32 (m, 2H), 6.31 (t, *J* = 2.3 Hz, 1H), 4.21 (d, *J* = 5.3 Hz, 2H), 4.11 (t, *J* = 6.1 Hz, 2H), 3.99 (s, 1H), 3.75 (t, *J* = 6.1 Hz, 2H), 2.24 (p, *J* = 6.1 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 158.52, 158.14, 157.33, 149.83, 131.45, 130.30, 129.69, 128.95, 123.11, 119.07, 114.79, 108.17, 107.88, 103.42, 64.47, 47.82, 41.63, 32.39; HRMS (APCI): *m/z* calcd C₂₂H₂₂ClNO₂ [M]⁺ 367.1339, found, 367.1332.

N-(4-(3-Chloropropoxy)benzyl)-3-(4-fluorophenoxy)aniline (27). The title compound was synthesised according to general procedure 1. The aniline 16 (0.90 g, 4.42 mmol), aldehyde 21 (2.19 g, 11.1 mmol), p-TSA (42 mg, 0.24 mmol) and toluene (80 mL) was refluxed for 5 days. The resulting imine was reduced using NaBH₄ (1.05 g, 27.8 mmol) and dry MeOH (100 mL). The title compound 27 was obtained as pale yellow wax (1.24 g, 73%); Rf: 0.28 (15% EtOAc: 85% petroleum benzine); IR (neat, cm⁻¹): 3398, 2884, 1603, 1579, 1495, 1446, 1232, 1197, 1047, 828; ¹H NMR (400 MHz, CDCl₃-d) δ 7.25 (d, J = 8.7 Hz, 2H), 7.09 (t, J = 8.1 Hz, 1H), 7.04–6.93 (m, 4H), 6.87 (d, J = 8.7 Hz, 2H), 6.36 (ddd, J = 8.1, 2.3, 0.9 Hz, 1H), 6.29 (ddd, J = 8.1, 2.3, 0.9 Hz, 1H), 6.23 (t, J = 2.3 Hz, 1H), 4.21 (d, J = 5.3 Hz, 2H), 4.11 (t, J = 5.8 Hz, 2H), 4.01 (t, J = 6.1 Hz, 1H), 3.75 (t, J = 6.1 Hz, 2H), 2.24 (p, J = 6.1 Hz, 2H); ¹³C NMR (101 MHz, $CDCl_3$ -*d*) δ 159.02, 158.82 (d, J = 241.3 Hz), 158.17, 152.96, 149.85, 130.36, 128.94, 120.73 (d, J = 8.2 Hz), 116.22 (d, J = 23.3 Hz), 114.80, 108.10, 107.20, 102.79, 64.46, 47.83, 41.65, 32.40; ¹⁹F NMR (376 MHz, CDCl₃-d) δ -120.99; HRMS (APCI): m/z calcd $C_{22}H_{22}O_2NClF [M + H]^+$ 386.1318, found, 386.1313.

N-(4-(3-Chloropropoxy)benzyl)-4-phenoxyaniline (28). The title compound was synthesised according to general procedure 1. The aniline 17 (1.25 g, 6.75 mmol), aldehyde 21 (1.82 g, 9.20 mmol), p-TSA (63 mg, 0.3 mmol) and toluene (80 mL) was refluxed for 7 days. The resulting imine was reduced using NaBH₄ (1.51 g, 40.0 mmol) and dry MeOH (80 mL). The title compound 28 was obtained as a cream solid (2.28 g, 92%); Rf: 0.30 (15% EtOAc: 85% petroleum benzine); mp: 54.3-56.1 °C; IR (neat, cm⁻¹): 3390, 2970, 2902, 1610, 1587. 1508,1490, 1230, 1047, 818, 750; ¹H NMR (400 MHz, CDCl₃-d) δ 7.36–7.30 (m, 2H), 7.30–7.24 (m, 2H), 7.03 (ddt, J = 7.4, 5.9, 1.1 Hz, 1H), 6.98-6.87 (m, 6H), 6.70-6.60 (m, 2H), 4.27 (s, 2H), 4.15 (t, J = 6.1 Hz, 2H), 3.90 (s, 1H), 3.78 (t, J = 6.1 Hz, 2H), 2.27 (p, J = 6.1 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 159.17, 158.15, 147.87, 144.96, 131.74, 129.60, 128.97, 122.05, 121.31, 117.25, 114.80, 113.94, 64.48, 48.45, 41.64, 32.40; HRMS (APCI): m/z calcd $C_{22}H_{22}ClNO_2$ [M]⁺ 367.1339, found, 367.1331.

N-(4-(3Chloropropoxy)benzyl)-4-(4-fluorophenoxy)aniline (29). The title compound was synthesised according to general procedure 1. The aniline 18 (1.02 g, 5.02 mmol), aldehyde 21 (2.49 g, 12.6 mmol), *p*-TSA (48 mg, 0.28 mmol) and toluene (80 mL) was refluxed for 5 days. The resulting imine was reduced using NaBH₄ (0.83 g, 21.9 mmol) and dry MeOH (100 mL). The title compound **29** was obtained as a pale brown solid (1.66 g, 86%); $R_{\rm f}$: 0.26 (15% EtOAc:85% petroleum benzine); mp: 72.4–74.8 °C; IR (neat, cm⁻¹): 3386, 2936, 1609, 1496, 1243, 1208, 1171, 1048, 827, 807; ¹H NMR (400 MHz, CDCl₃-*d*) δ 7.34–7.27 (m, 2H), 7.02–6.92 (m, 2H), 6.92–6.82 (m, 6H), 6.66–6.57 (m, 2H), 4.24 (s, 2H), 4.12 (t, J = 6.1 Hz, 2H), 3.88 (s, 1H), 3.75 (t, J = 6.1 Hz, 2H), 2.24 (p, J = 6.1 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃-*d*) δ 158.12, 158.09 (d, J = 240.0 Hz), 154.93 (d, J = 2.3 Hz), 148.33, 144.89, 128.90, 120.77, 118.62 (d, J = 8.1 Hz), 115.99 (d, J = 23.2 Hz), 114.76, 113.91, 64.56, 48.35, 41.61, 32.35; ¹⁹F NMR (376 MHz, CDCl₃-*d*) δ -122.70; HRMS (APCI): m/z calcd C₂₂H₂₂O₂NClF [M + H]⁺ 386.1318, found, 386.1315.

N-(4-(3-Chloropropoxy)benzyl)-4-(4-(trifluoromethyl)

phenoxy)aniline (30). The title compound was synthesised according to general procedure 1. The aniline 19 (974 mg, 3.84 mmol), aldehyde 21 (1.56 g, 7.88 mmol), p-TSA (37.6 mg, 0.22 mmol) and toluene (80 mL) was refluxed for 9 days. The resulting imine was reduced using NaBH₄ (841 mg, 22.2 mmol) and dry MeOH (50 mL). The title compound 30 was obtained as a pale yellow solid (1.41 g, 84%); $R_{\rm f}$: 0.26 (7%) EtOAc: 93% petroleum benzine); mp: 69.5-72.1 °C; IR (neat, cm⁻¹): 3409, 2946, 1611, 1504, 1323, 1239, 1154, 1104, 1063, 840, 823; ¹H NMR (400 MHz, CDCl₃-d) δ 7.55-7.48 (m, 2H), 7.34-7.27 (m, 2H), 7.00-6.93 (m, 2H), 6.93-6.88 (m, 4H), 6.68-6.62 (m, 2H), 4.26 (s, 2H), 4.12 (t, J = 6.1 Hz, 2H), 4.10-3.84 (m, 1H), 3.76 (t, J = 6.1 Hz, 2H), 2.24 (p, J = 6.1 Hz, 2H); $^{13}{\rm C}$ NMR (101 MHz, CDCl₃-d) δ 162.03, 158.10, 146.23, 145.62, 131.44, 128.83, 126.92 (q, J = 3.7 Hz), 124.45 (q, J = 272.9 Hz), 123.65 (q, J = 32.6 Hz), 121.70, 116.50, 114.68, 113.85, 64.32, 48.08, 41.54, 32.23; ¹⁹F NMR (377 MHz, CDCl₃) δ -62.12; HRMS (APCI): m/z calcd $C_{23}H_{21}O_2NClF_3$ [M]⁺ 435.1207, found, 435.1208.

4-(4-((4-(3-Chloropropoxy)benzyl)amino)phenoxy)

benzonitrile (31). The title compound was synthesised according to general procedure 1. The aniline 20 (738 mg, 3.51 mmol), aldehyde 21 (1.50 g, 7.57 mmol), p-TSA (34.1 mg, 0.20 mmol) and toluene (80 mL) was refluxed for 10 days. The resulting imine was reduced using NaBH₄ (1.12 g, 29.6 mmol) and dry MeOH (50 mL). The title compound 31 was obtained as a yellow solid (1.00 g, 72%); *R*_f: 0.21 (15% EtOAc: 85% petroleum benzine); mp: 74.3–76.7 °C; IR (neat, cm^{-1}): 3368, 2873, 2226, 1600, 1497, 1238, 1165, 1108, 829; ¹H NMR (600 MHz, $CDCl_3$ -d) δ 7.55(d, J = 8.9 Hz, 2H), 7.30 (d, J = 8.6 Hz, 2H), 6.94 (d, J = 8.9 Hz, 2H), 6.92–6.87 (m, 4H), 6.66 (d, J = 8.6 Hz, 2H), 4.26 (s, 2H), 4.12 (t, J = 6.1 Hz, 2H), 3.75 (t, J = 6.1 Hz, 2H), 2.24 (p, J = 6.1 Hz, 2H); ¹³C NMR (101 MHz, ${\rm CDCl}_3$) δ 162.83, 157.99, 145.71, 145.42, 133.90, 131.17, 128.74, 121.70, 119.01, 116.84, 114.61, 113.89, 104.65, 64.28, 48.01, 41.50, 32.16; HRMS (APCI): m/z calcd C23H22O2N2Cl [M]⁺ 392.1286, found, 392.1285.

N-(4-(3-(Dimethylamino)propoxy)benzyl)-2-phenoxyaniline (32a). The title compound was synthesised from the reductive amination product 22 (40.4 mg, 0.11 mmol) and KI (38.3 mg, 0.23 mmol) following general procedure 2a to afford the product 32a as a pale yellow oil (33.4 mg, 81%); $R_{\rm f}$: 0.37 (10%)

MeOH: 90% DCM); IR (neat, cm⁻¹): 3425, 2942, 2765, 1608, 1509, 1215, 1173, 1035, 822, 739, 691; ¹H NMR (400 MHz, MeOD- d_4) δ 7.31–7.21 (m, 2H), 7.19–7.10 (m, 2H), 7.04–6.97 (m, 1H), 6.96–6.85 (m, 3H), 6.81–6.73 (m, 3H), 6.67 (dd, J = 8.1, 1.4 Hz, 1H), 6.57 (td, J = 7.7, 1.5 Hz, 1H), 4.22 (s, 2H), 3.92 (t, J = 6.2 Hz, 2H), 2.54–2.42 (m, 2H), 2.24 (s, 6H), 1.95–1.85 (m, 2H); ¹³C NMR (101 MHz, MeOD- d_4) δ 159.34, 159.25, 144.21, 141.87, 133.10, 130.67, 129.36, 126.04, 123.54, 120.67, 118.06, 117.76, 115.47, 113.43, 67.00, 57.37, 47.75, 45.39, 28.18; ¹⁹F NMR (376 MHz, MeOD- d_4) δ –76.55; HRMS (APCI): m/z calcd C₂₄H₂₉N₂O₂ [M + H]⁺ 377.2224, found, 377.2214.

N-(4-(3-(Dimethylamino)propoxy)benzyl)-2-(4fluorophenoxy)aniline (33a). The title compound was synthesised from the reductive amination product 23 (22.9 mg, 0.06 mmol) and KI (24.7 mg, 0.15 mmol) following general procedure 2a to afford the product 33a as a yellow oil (19.6 mg, 84%); Rf: 0.34 (10% MeOH: 90% DCM); IR (neat, cm⁻¹): 3424, 1672, 1499, 1195, 1173, 1123, 829, 720; ¹H NMR (400 MHz, MeOD-d₄) δ 7.21-7.12 (m, 2H), 7.04-6.95 (m, 2H), 6.94-6.84 (m, 3H), 6.84-6.77 (m, 2H), 6.73 (dd, J = 7.9, 1.4 Hz, 1H), 6.67 (dd, J = 8.1, 1.4 Hz, 1H), 6.56 (td, J = 7.7, 1.5 Hz, 1H), 4.24 (s, 2H), 3.94 (t, J = 6.1 Hz, 2H), 2.55–2.43 (m, 2H), 2.25 (s, 6H), 1.97-1.85 (m, 2H); ¹³C NMR (101 MHz, MeOD d_4) δ 159.65 (d, J = 239.2 Hz), 159.37, 155.21 (d, J = 2.4 Hz), 144.67, 141.70, 133.13, 129.38, 126.02, 120.18, 119.62 (d, J = 8.2 Hz), 117.77, 116.96 (d, J = 23.5 Hz), 115.48, 113.47, 67.00, 57.37, 47.74, 45.38, 28.17; ¹⁹F NMR (377 MHz, MeOD- d_4) δ -123.70, -76.55; HRMS (APCI): m/z calcd C₂₄H₂₈N₂O₂F [M + H]⁺ 395.2129, found, 395.2118.

N-(4-(3-(Dimethylamino)propoxy)benzyl)-2-(4-

(trifluoromethyl)phenoxy)aniline (34a). The title compound was synthesised from the reductive amination product 24 (37.4 mg, 0.09 mmol) and KI (36.1 mg, 0.21 mmol) following general procedure 2a to afford the product 34a as a colourless oil (32.8 mg, 86%). The 1H, 13C and 19F NMR spectra of the TFA salt was recorded; R_f: 0.34 (10% MeOH: 90% DCM); IR (neat, cm⁻¹): 3434. 2966, 1673, 1609, 1510, 1324, 1166, 1105, 1064 829, 799, 720; ¹H NMR (400 MHz, MeOD- d_4) δ 7.59 (d, J = 8.6 Hz, 2H), 7.19 (d, J = 8.6 Hz, 2H), 7.02 (d, J = 8.6 Hz, 2H), 7.00 (dd, J = 7.8, 1.5 Hz, 1H), 6.88 (dd, J = 7.8, 1.5 Hz, 1H), 6.85 (d, J = 8.6 Hz, 2H), 6.71 (dd, J = 7.8, 1.5 Hz, 1H), 6.64 (td, J = 7.8, 1.5 Hz, 1H), 4.29 (s, 2H), 4.07 (t, J = 5.7 Hz, 2H), 3.37-3.32 (m, 2H), 2.93 (s, 6H), 2.26-2.11 (m, 2H); ¹³C NMR (151 MHz, MeOD-d₄) δ 162.52, 158.87, 142.79, 142.12, 133.87, 129.42, 128.06 (q, J = 3.8 Hz), 127.15, 125.85 (q, J = 270.2 Hz), 125.22 (q, J = 32.5 Hz), 121.87, 117.92, 117.59, 115.51, 113.87, 65.92, 56.93, 47.46, 43.65, 25.77; ¹⁹F NMR (376 MHz, MeOD- d_4) δ -62.87; HRMS (APCI): m/z calcd C₂₅H₂₈N₂O₂F₃ [M + H]⁺ 445.2097, found, 405.2085.

4-(2-((4-(3-(Dimethylamino)propoxy)benzyl)amino) phenoxy)benzonitrile (35a). The title compound was synthesised from the reductive amination product 25 (42.8 mg, 0.11 mmol) and KI (43.9 mg, 0.26 mmol) following general procedure 2a to afford the product 35a as a white solid (39.8 mg, 91%). The ¹H, ¹³C and ¹⁹F NMR spectra of the TFA salt was recorded; $R_{\rm f}$: 0.32 (10% MeOH:90% DCM); IR (neat, cm⁻¹): 3420, 2968, 2226, 1678, 1610, 1512, 1236, 1171, 1130, 1056, 832, 721; ¹H NMR (400 MHz, MeOD- d_4) δ 7.63 (d, J = 9.0 Hz, 2H), 7.17 (d, J = 8.7 Hz, 2H), 7.06–7.01 (m, 1H), 6.98 (d, J = 9.0 Hz, 2H), 6.88 (dd, J = 7.9, 1.5 Hz, 1H), 6.84 (d, J = 8.7 Hz, 2H), 6.73 (dd, J = 7.9, 1.5 Hz, 1H), 6.65 (td, J = 7.9, 1.5 Hz, 1H), 4.26 (s, 2H), 4.06 (t, J = 5.7 Hz, 2H), 3.37–3.31 (m, 2H), 2.92 (s, 6H), 2.26–2.13 (m, 2H); ¹³C NMR (101 MHz, MeOD- d_4) δ 163.33, 158.90, 142.23, 142.03, 135.24, 133.70, 129.40, 127.53, 122.08, 119.85, 118.05, 118.02, 115.51, 114.12, 106.23, 65.92, 56.84, 47.48, 43.60, 25.74; ¹⁹F NMR (376 MHz, MeOD- d_4) δ –76.55; HRMS (APCI): m/z calcd C₂₅H₂₈N₃O₂ [M + H]⁺ 402.2176, found, 402.2166.

N-(4-(3-(Dimethylamino)propoxy)benzyl)-3-phenoxyaniline (36a). The title compound was synthesised from the reductive amination product 26 (36.8 mg, 0.10 mmol) and KI (38.6 mg, 0.23 mmol) following general procedure 2a to afford the product 36a as a colourless oil (30.3 mg, 80%); Rf: 0.30 (10% MeOH: 90% DCM); IR (neat, cm⁻¹): 3409, 2941, 2765, 1581, 1486, 1216, 1148, 1005, 823, 754, 688; ¹H NMR (400 MHz, MeOD-d₄) δ 7.31-7.22 (m, 2H), 7.22-7.15 (m, 2H), 7.06-6.96 (m, 2H), 6.93–6.85 (m, 2H), 6.85–6.79 (m, 2H), 6.37 (ddd, J = 8.2, 2.2, 0.9 Hz, 1H), 6.22 (t, J = 2.2 Hz, 1H), 6.18 (ddd, J = 8.2, 2.2, 0.9 Hz, 1H), 4.14 (s, 2H), 3.95 (t, J = 6.1 Hz, 2H), 2.50 $(t, J = 6.1 \text{ Hz}, 2\text{H}), 2.26 (s, 6\text{H}), 1.99-1.86 (m, 2\text{H}); {}^{13}\text{C} \text{ NMR}$ (101 MHz, MeOD- d_4) δ 159.46, 159.30, 158.85, 151.73, 133.12, 130.92, 130.59, 129.54, 123.81, 119.64, 115.45, 109.52, 107.99, 104.46, 67.01, 57.39, 45.39, 28.18; ¹⁹F NMR (376 MHz, MeOD d_4) δ -76.55; HRMS (APCI): m/z calcd $C_{24}H_{29}N_2O_2$ [M + H]⁺ 377.2224, found, 377.2215.

N-(4-(3-(Dimethylamino)propoxy)benzyl)-3-(4-

fluorophenoxy)aniline (37a). The title compound was synthesised from the reductive amination product 27 (33.3 mg, 0.09 mmol) and KI (35.8 mg, 0.22 mmol) following general procedure 2a to afford the product 37a as a colourless oil (27.2 mg, 80%); Rf: 0.29 (10% MeOH:90% DCM); IR (MeOH, cm⁻¹): 3405, 2969, 1672, 1608, 1498, 1195, 1128, 1027, 830, 799, 721; ¹H NMR (400 MHz, MeOD- d_4) δ 7.23-7.13 (m, 2H), 7.03-6.93 (m, 3H), 6.93-6.85 (m, 2H), 6.84-6.79 (m, 2H), 6.40-6.33 (m, 1H), 6.21-6.12 (m, 2H), 4.15 (s, 2H), 3.97 (t, J = 6.2 Hz, 2H), 2.55-2.47 (m, 2H), 2.27 (s, 6H), 1.98–1.88 (m, 2H); 13 C NMR (101 MHz, MeOD- d_4) δ 159.88, 159.87 (d, J = 239.6 Hz), 159.32, 154.74 (d, J = 2.5 Hz), 151.77, 133.12, 130.95, 129.47, 121.36 (d, J = 1.6 Hz), 121.28, 116.93 (d, J = 23.5 Hz), 115.44, 109.53, 107.45, 103.95, 67.02, 57.42, 48.00, 45.40, 28.23; 19 F NMR (377 MHz, MeOD- d_4) δ -76.55, -122.36; HRMS (APCI): m/z calcd C₂₄H₂₈N₂O₂F [M + H[†] 395.2129, found, 395.2118.

N-(4-(3-(Dimethylamino)propoxy)benzyl)-4-phenoxyaniline (38a). The title compound was synthesised from the reductive amination product 28 (42.3 mg, 0.11 mmol) and KI (41.9 mg, 0.25 mmol) following general procedure 2a to afford the product 38a as a white solid (37.4 mg, 86%); $R_{\rm f}$: 0.29 (10% MeOH:90% DCM); IR (neat, cm⁻¹): 3250, 2957, 2825, 1612, 1510, 1498, 1227, 1041, 1005, 831, 746, 689; ¹H NMR (400 MHz, CDCl₃-*d*) δ 7.27 (ddd, J = 8.4, 6.8, 2.6 Hz, 4H), 7.03–6.97 (m, 1H), 6.97–6.85 (m, 6H), 6.67–6.59 (m, 2H), 4.23 (s, 2H),

4.02 (t, J = 7.2 Hz, 2H), 3.87 (s, 1H), 2.47 (t, J = 7.2 Hz, 2H), 2.27 (s, 6H), 1.98 (p, J = 7.2 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 159.20, 158.47, 147.81, 145.02, 131.34, 129.61, 128.96, 122.04, 121.36, 117.22, 114.78, 113.92, 66.39, 56.55, 48.51, 45.64, 27.68; ¹⁹F NMR (376 MHz, MeOD- d_4) δ -76.55; HRMS (APCI): m/z calcd $C_{24}H_{29}N_2O_2$ [M + H]⁺ 377.2224, found, 377.2213.

N-(4-(3-(Dimethylamino)propoxy)benzyl)-4-(4-

fluorophenoxy)aniline (39a). The title compound was synthesised from the reductive amination product 29 (24.6 mg, 0.06 mmol) and KI (25.4 mg, 0.15 mmol) following general procedure 2a to afford the product 39a as a white solid (21.6 mg, 86%); Rf: 0.28 (10% MeOH: 90% DCM); IR (neat, cm⁻¹): 3247, 2959, 2777, 1609, 1495, 1239, 1205, 1177, 1007, 822, 722, 670; ¹H NMR (400 MHz, CDCl₃-d) δ 7.32-7.26 (m, 2H), 7.00-6.93 (m, 2H), 6.93-6.80 (m, 6H), 6.66-6.56 (m, 2H), 4.23 (d, J = 4.2 Hz, 2H), 4.02 (t, J = 6.6 Hz, 2H), 3.87 (s, 1H), 2.47 (t, J = 6.6 Hz, 2H), 2.27 (s, 6H), 1.97 (p, J = 6.6 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃-d) δ 158.48, 158.16 (d, J = 240.0 Hz), 154.99 (d, J = 2.4 Hz), 148.37, 144.97, 131.31, 128.95, 120.86, 118.65 (d, J = 8.0 Hz), 116.05 (d, J = 23.1 Hz), 114.79, 113.96, 66.38, 56.55, 48.50, 45.62, 27.65; ¹⁹F NMR (376 MHz, CDCl₃) δ -122.20; HRMS (APCI): m/z calcd C₂₄H₂₈- $N_2O_2F[M + H]^+$ 395.2129, found, 395.2116.

N-(4-(3-(Dimethylamino)propoxy)benzyl)-4-(4-

(trifluoromethyl)phenoxy)aniline (40a). The title compound was synthesised from the reductive amination product 30 (25.6 mg, 0.06 mmol) and KI (25.1 mg, 0.15 mmol) following general procedure 2a to afford the product 40a as a white solid (23.2 mg, 89%); Rf: 0.28 (10% MeOH: 90% DCM); IR (neat, cm⁻¹): 3251, 2958, 2826, 1677, 1504, 1326, 1237, 1156, 1104, 1065, 1008, 831, 721; ¹H NMR (400 MHz, $CDCl_3-d$) δ 7.51 (d, J = 8.6 Hz, 2H), 7.29 (d, J = 6.5 Hz, 3H), 6.96 (d, J = 8.6 Hz, 2H), 6.93-6.86 (m, 4H), 6.65 (d, J = 8.9 Hz, 2H), 4.25 (d, J = 5.0 Hz, 2H), 4.02 (t, J = 6.4 Hz, 2H), 3.96 (t, J = 5.0 Hz, 1H), 2.46 (t, J = 6.4 Hz, 2H), 2.26 (s, 6H), 1.97 (p, J = 6.4 Hz, 2H); ¹³C NMR (151 MHz, CDCl₃-d) δ 162.14, 158.55, 146.42, 145.73, 131.13, 128.94, 127.03 (q, J = 3.7 Hz), 124.47 (q, J = 270.9 Hz), 123.90 (q, J = 32.8 Hz), 121.84, 116.60, 114.83, 113.97, 66.43, 56.55, 48.39, 45.67, 27.72; ¹⁹F NMR (377 MHz, MeOD- d_4) δ -76.55, -62.99; HRMS (APCI): m/z calcd C₂₅H₂₈- $N_2O_2F_3$ [M + H]⁺ 445.2097, found, 405.2085.

4-(4-((4-(3-(Dimethylamino)propoxy)benzyl)amino)

phenoxy)benzonitrile (41a). The title compound was synthesised from the reductive amination product 31 (34.8 mg, 0.09 mmol) and KI (35.4 mg, 0.21 mmol) following general procedure 2a to afford the product 41a as a pale yellow solid (32.5 mg, 91%). The ¹H, ¹³C and ¹⁹F NMR spectra of the TFA salt was recorded; $R_{\rm f}$: 0.29 (10% MeOH:90% DCM); IR (neat, cm⁻¹): 3348, 2963, 2225, 1666, 1610, 1494, 1240, 1167, 1124, 1056, 828, 708, 720; ¹H NMR (400 MHz, MeOD- d_4) δ 7.68 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.6 Hz, 2H), 7.12–6.99 (m, 6H), 6.95 (d, J = 8.6 Hz, 2H), 4.40 (s, 2H), 4.10 (t, J = 5.7 Hz, 2H), 3.40–3.32 (m, 2H), 2.91 (s, 6H), 2.29–2.16 (m, 2H); ¹³C NMR (101 MHz, MeOD- d_4) δ 163.30, 159.99, 152.07, 140.09, 135.45, 131.43, 128.93, 122.46, 120.92, 119.66,

118.99, 115.77, 106.87, 65.99, 56.75, 52.61, 43.58, 25.71;¹⁹F NMR (376 MHz, MeOD- d_4) δ –76.55; HRMS (APCI): m/z calcd C₂₅H₂₈N₃O₂ [M + H]⁺ 402.2176, found, 402.2161.

2-Phenoxy-N-(4-(3-(pyrrolidin-1-yl)propoxy)benzyl)aniline (32b). The title compound was synthesised from the reductive amination product 22 (270 mg, 0.73 mmol) and KI (122 mg, 0.74 mmol), K₂CO₃ (153 mg, 1.10 mmol), pyrrolidine (188 mg, 2.65 mmol) and dry ACN (12 mL) for 4 h following general procedure 2b to afford the product 32b in a quant. conversion; Rf: 0.15 (5% MeOH:95% DCM); IR (MeOH, cm⁻¹): 3423, 2926, 1672, 1608, 1510, 1198, 1125, 829, 746, 721; ¹H NMR (400 MHz, MeOD-*d*₄) δ 7.38–7.29 (m, 2H), 7.27– 7.19 (m, 2H), 7.16-7.07 (m, 1H), 7.06-6.98 (m, 1H), 6.98-6.90 (m, 3H), 6.90–6.82 (m, 3H), 6.80 (dd, *J* = 8.1, 1.5 Hz, 1H), 4.38 (s, 2H), 4.06 (t, J = 5.8 Hz, 2H), 3.77-3.59 (m, 2H), 3.42-3.34 (m, 2H), 3.18-2.98 (m, 2H), 2.29-2.09 (m, 4H), 2.09-1.88 (m, 2H); ¹³C NMR (101 MHz, MeOD- d_4) δ 159.64, 158.08, 147.12, 136.15, 130.91, 130.40, 125.50, 124.59, 122.77, 119.87, 119.13, 117.82, 115.64, 65.88, 55.27, 53.77, 50.40, 27.03, 23.95; ¹⁹F NMR (376 MHz, MeOD- d_4) δ -76.55; HRMS (APCI): m/z calcd $C_{26}H_{31}N_2O_2 [M + H]^+ 403.238$, found, 403.2372.

2-(4-Fluorophenoxy)-*N*-(4-(3-(pyrrolidin-1-yl)propoxy)

benzyl)aniline (33b). The title compound was synthesised from the reductive amination product 23 (103 mg, 0.27 mmol) and KI (48.2 mg, 0.29 mmol), K₂CO₃ (90.1 mg, 0.65 mmol), pyrrolidine (65.1 mg, 0.91 mmol) and dry ACN (5 mL for 3.5 h following general procedure 2b to afford the product 33b in a quant. conversion; R_f : 0.28 (5% MeOH: 95% DCM); IR (neat, cm⁻¹): 3422, 2881, 1673, 1609, 1500, 1243, 1195, 1124, 829, 742, 720; ¹H NMR (400 MHz, MeOD- d_4) δ 7.29– 7.19 (m, 2H), 7.13-7.04 (m, 2H), 7.00 (ddd, J = 8.1, 7.2, 1.5 Hz, 1H), 6.98-6.93 (m, 2H), 6.93-6.87 (m, 3H), 6.84 (ddd, J = 8.1, 7.2, 1.5 Hz, 1H), 6.78 (dd, J = 8.1, 1.5 Hz, 1H), 4.39 (s, 2H), 4.08 (t, J = 5.7 Hz, 2H), 3.78-3.62 (m, 2H), 3.50-3.35 (m, 2H), 3.18-3.03 (m, 2H), 2.26-2.10 (m, 4H), 2.10-1.93 (m, 2H); ¹³C NMR (101 MHz, MeOD- d_4) δ 59.71 (d, J = 238.8 Hz), 158.87, 155.33 (d, J = 2.5 Hz), 144.71, 141.71, 133.93, 129.50, 126.01, 120.31, 119.57 (d, J = 8.3 Hz), 117.83, 116.96 (d, J = 23.7 Hz), 115.50, 113.52, 65.85, 55.42, 53.95, 47.66, 27.13, 23.96; ¹⁹F NMR (376 MHz, MeOD- d_4) δ -121.99; -76.55; HRMS (APCI): m/z calcd $C_{26}H_{30}N_2O_2F [M + H]^+$ 421.2286, found, 421.2279.

N-(4-(3-(Pyrrolidin-1-yl)propoxy)benzyl)-2-(4-

(trifluoromethyl)phenoxy)aniline (34b). The title compound was synthesised from the reductive amination product 24 (102 mg, 0.23 mmol) and KI (38.1 mg, 0.23 mmol), K₂CO₃ (57.7 mg, 0.42 mmol), pyrrolidine (86.1 mg, 1.21 mmol) and dry ACN (5 mL) for 3 h following general procedure 2b to afford the product 34c in a quant. conversion; $R_{\rm f}$: 0.30 (5% MeOH:95% DCM); IR (neat, cm⁻¹): 3421, 1673, 1609, 1510, 1324, 1230, 1167, 1105, 1064, 829, 743, 720; ¹H NMR (600 MHz, MeOD- d_4) δ 7.59 (d, J = 8.7 Hz, 2H), 7.23–7.13 (m, 2H), 7.06–6.97 (m, 3H), 6.88 (dd, J = 7.9, 1.5 Hz, 1H), 6.86–6.82 (m, 2H), 6.71 (dd, J = 7.9, 1.5 Hz, 1H), 6.64 (td, J = 7.9, 1.5 Hz, 1H), 4.28 (s, 2H), 4.07 (t, J = 5.7 Hz, 2H), 3.69 (s, 2H), 3.42–3.35 (m, 2H), 3.10 (s, 2H), 2.26–2.09 (m, 4H), 2.03 (s, 2H); ¹³C

NMR (151 MHz, MeOD- d_4) δ 162.50, 158.89, 142.80, 142.09, 133.79, 129.42, 127.26, 125.84 (q, J = 270.4 Hz), 125.22 (q, J = 32.5 Hz), 121.85, 117.93, 117.59, 115.48, 113.88, 65.85, 55.37, 53.92, 47.47, 27.11, 23.96; ¹⁹F NMR (376 MHz, MeOD- d_4) δ -62.54, -76.55; HRMS (APCI): m/z calcd C₂₇H₃₀N₂O₂F₃ [M + H]⁺ 471.2254, found, 471.2250.

4-(2-((4-(3-(Pyrrolidin-1-yl)propoxy)benzyl)amino)phenoxy) benzonitrile (35b). The title compound was synthesised from the reductive amination product 25 (88.2 mg, 0.22 mmol) and KI (54.3 mg, 0.33 mmol), pyrrolidine (120 mg, 1.69 mmol) and dry ACN (5 mL) for 3 h following general procedure 2b to afford the product 35b in a quant. conversion; $R_{\rm f}$: 0.16 (5% MeOH: 95% DCM); IR (neat, cm⁻¹): 3387, 2933, 2222, 1672, 1603, 1499, 1231, 1163, 1125, 833, 759, 718; ¹H NMR (400 MHz, MeOD- d_4) δ 7.68–7.59 (m, 2H), 7.22-7.14 (m, 2H), 7.07-6.95 (m, 3H), 6.89 (dd, J = 7.9, 1.5 Hz, 1H), 6.86–6.80 (m, 2H), 6.73 (dd, J = 7.9, 1.5 Hz, 1H), 6.65 (td, J = 7.9, 1.5 Hz, 1H), 4.27 (s, 2H), 4.07 (t, J = 5.7 Hz, 2H), 3.57-3.32 (m, 6H), 2.28–2.14 (m, 2H), 2.14–2.00 (m, 4H); ¹³C NMR (101 MHz, MeOD- d_4) δ 163.38, 158.90, 142.18, 142.15, 135.25, 133.76, 129.39, 127.54, 122.13, 119.85, 118.03, 117.93, 115.47, 114.05, 106.22, 65.86, 55.36, 53.91, 47.42, 27.14, 23.96; ¹⁹F NMR (376 MHz, MeOD- d_4) δ -76.55; HRMS (APCI): m/z calcd $C_{27}H_{30}N_3O_2 [M + H]^+$ 428.2333, found 428.2327.

3-Phenoxy-N-(4-(3-(pyrrolidin-1-yl)propoxy)benzyl)aniline (36b). The title compound was synthesised from the reductive amination product 26 (271 mg, 0.73 mmol) and KI (127 mg, 0.76 mmol), K₂CO₃ (126 mg, 0.91 mmol), pyrrolidine (159 mg, 2.24 mmol) and dry ACN (12 mL) for 5 h following general procedure 2b to afford the product 36b in a quant. conversion; R_f : 0.15 (5% MeOH: 95% DCM); IR (neat, cm⁻¹): 3429, 2964, 1664, 1611, 1486, 1228, 1125, 828, 720, 688; ¹H NMR (400 MHz, MeOD-d₄) δ 7.39-7.17 (m, 4H), 7.009-6.96 (m, 2H), 6.95-6.81 (m, 4H), 6.39 (ddd, J = 8.2, 2.2, 0.9 Hz, 1H), 6.23 (t, J = 2.3 Hz, 1H), 6.20 (ddd, J = 8.2, 2.2, 0.9 Hz, 1H), 4.20 (s, 2H), 4.08 (t, J = 5.7 Hz, 2H), 3.69 (s, 2H), 3.45-3.34 (m, 2H), 3.17-3.01 (m, 2H), 2.28-2.09 (m, 4H), 2.03 (s, 2H); ¹³C NMR (101 MHz, MeOD- d_4) δ 159.52, 158.85, 151.41, 133.64, 130.94, 130.62, 129.66, 123.88, 119.65, 115.47, 109.76, 108.26, 104.69, 65.85, 55.36, 53.91, 48.13, 27.13, 23.96; ¹⁹F NMR (376 MHz, MeOD- d_4) δ -76.55; HRMS (APCI): m/z calcd $C_{26}H_{31}N_2O_2 [M + H]^+ 403.238$, found, 403.2375.

3-(4-Fluorophenoxy)-N-(4-(3-(pyrrolidin-1-yl)propoxy)

benzyl)aniline (37b). The title compound was synthesised from the reductive amination product **27** (135 mg, 0.35 mmol) and KI (57.4 mg, 0.35 mmol), K_2CO_3 (98.4 mg, 0.72 mmol), pyrrolidine (85.4 mg, 1.20 mmol) and dry ACN (5 mL) for 5 h following general procedure 2b to afford the product **37b** in a quant. conversion; R_f : 0.27 (5% MeOH:95% DCM); IR (MeOH, cm⁻¹):3353, 1672, 1605, 1497, 1240, 1195, 1126, 830, 721; ¹H NMR (400 MHz, MeOD- d_4) δ 7.30–7.20 (m, 2H), 7.20–7.11 (m, 1H), 7.10–6.99 (m, 2H), 6.98–6.84 (m, 4H), 6.58 (ddd, J = 8.1, 2.2, 0.9 Hz, 1H), 6.41 (ddd, J = 8.1, 2.2, 0.9 Hz, 1H), 6.42 (s, 2H), 4.10 (t, J = 5.7 Hz, 2H), 3.76–3.64 (m, 2H), 3.46–3.37 (m, 2H), 3.19–3.04 (m, 2H), 2.29–2.11 (m, 4H), 2.11–1.94 (m, 2H); ¹³C NMR (101 MHz,

MeOD- d_4) δ 159.94 (d, J = 239.6 Hz), 159.91, 158.88, 154.71 (d, J = 2.5 Hz), 151.25, 133.51, 131.00, 129.64, 121.36 (d, J = 8.3 Hz), 116.96 (d, J = 23.6 Hz), 115.48, 109.88, 107.89, 104.30, 65.86, 55.36, 53.91, 48.19, 27.13, 23.96; ¹⁹F NMR (376 MHz, MeOD- d_4) δ -76.55, -121.78; HRMS (APCI): m/z calcd C₂₆H₃₀N₂O₂F [M + H]⁺ 421.2286, found, 421.2278.

4-Phenoxy-N-(4-(3-(pyrrolidin-1-yl)propoxy)benzyl)aniline

(38b). The title compound was synthesised from the reductive amination product 28 (280.1 mg, 0.76 mmol) and KI (135.8 mg, 0.82 mmol), K₂CO₃ (141 mg, 1.02 mmol), pyrrolidine (197 mg, 2.77 mmol) and dry ACN (12 mL) for 3.5 h following general procedure 2b to afford the product 38b in a quant. conversion; $R_{\rm f}$: 0.15 (5% MeOH: 95% DCM); IR (neat, cm⁻¹): 3389, 2952, 1656, 1610, 1510, 1227, 1178, 1129, 830, 755, 720, 688; ¹H NMR (400 MHz, MeOD- d_4) δ 7.36–7.28 (m, 2H), 7.28– 7.20 (m, 2H), 6.97 (tt, J = 7.4, 1.1 Hz, 1H), 6.94–6.88 (m, 2H), 6.88-6.81 (m, 2H), 6.81-6.75 (m, 2H), 6.69-6.62 (m, 2H), 4.24 (s, 2H), 4.09 (t, J = 5.7 Hz, 2H), 3.69 (s, 2H), 3.44-3.37 (m, 2H), 3.27–2.85 (m, 2H), 2.32–1.89 (m, 6H); ¹³C NMR (101 MHz, MeOD-d₄) δ 160.56, 158.92, 148.97, 146.40, 133.78, 130.52, 129.82, 122.96, 121.85, 117.98, 115.49, 65.86, 55.39, 53.94, 48.98, 27.14, 23.96; $^{19}{\rm F}$ NMR (376 MHz, MeOD- $d_4)$ δ -76.55; HRMS (APCI): m/z calcd $C_{26}H_{31}N_2O_2$ [M + H]⁺ 403.238, found, 403.2373.

4-(4-Fluorophenoxy)-*N*-(4-(3-(pyrrolidin-1-yl)propoxy)

benzyl)aniline (39b). The title compound was synthesised from the reductive amination product 29 (100 mg, 0.26 mmol) and KI (43.2 mg, 0.26 mmol), K₂CO₃ (74.3 mg, 0.54 mmol), pyrrolidine (137 mg, 1.92 mmol) and dry ACN (5 mL) for 3 h following general procedure 2b to afford the product **39b** in a quant. conversion; *R*_f: 0.24 (5% MeOH: 95% DCM); IR (MeOH, cm⁻¹): 3375, 1674, 1606, 1496, 1244, 1201, 1132, 832, 721; ¹H NMR (400 MHz, MeOD- d_4 , 50 °C) δ 7.36–7.26 (m, 2H), 7.17-7.11 (m, 2H), 7.11-7.03 (m, 2H), 7.02-6.89 (m, 6H), 4.42 (s, 2H), 4.11 (t, J = 5.8 Hz, 2H), 3.71 (s, 2H), 3.44-3.36 (m, 2H), 3.11 (s, 2H), 2.38-2.19 (m, 2H), 2.19-1.84 (m, 4H); ¹³C NMR (101 MHz, MeOD- d_4 , 50 °C) δ 160.42 (d, J = 240.9 Hz), 160.39, 156.86, 154.30, 135.61, 132.09, 127.20, 122.83, 121.56 (d, J = 8.4 Hz), 120.38, 117.35 (d, J = 23.7 Hz), 115.93, 66.13, 55.38, 54.24, 53.84, 27.01, 23.98; ¹⁹F NMR (377 MHz, MeOD- d_4) δ –121.01, –76.55; HRMS (APCI): m/z calcd $C_{26}H_{30}N_2O_2F[M + H]^+$ 421.2286, found, 421.2278.

N-(4-(3-(Pyrrolidin-1-yl)propoxy)benzyl)-4-(4-

(trifluoromethyl)phenoxy)aniline (40b). The title compound was synthesised from the reductive amination product 30 (129 mg, 0.30 mmol) and KI (68.4 mg, 0.41 mmol), K₂CO₃ (58.4 mg, 0.42 mmol), pyrrolidine (72.1 mg, 1.01 mmol) and dry ACN (12 mL) for 3 h following general procedure 2b to afford the product 40b in a quant. conversion; $R_{\rm f}$: 0.26 (5% MeOH: 95% DCM); IR (neat, cm⁻¹): 3357, 1665, 1613, 1506, 1324, 1235, 1160, 1106, 1064, 830, 799, 720; ¹H NMR (400 MHz, MeOD- d_4) δ δ 7.61 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.7 Hz, 2H), 7.04 (d, J = 8.4 Hz, 2H), 6.99–6.89 (m, 6H), 4.36 (s, 2H), 4.10 (t, J = 5.7 Hz, 2H), 3.79–3.62 (m, 2H), 3.46–3.36 (m, 2H), 3.17–3.04 (m, 2H), 2.26–2.10 (m, 4H), 2.10–1.95 (m, 2H); ¹³C NMR (151 MHz, MeOD- d_4) δ 163.87, 158.91, 147.70,

147.05, 133.98, 129.68, 127.98 (q, J = 3.8 Hz), 125.88 (q, J = 270.2 Hz), 124.61 (q, J = 32.5 Hz), 122.48, 117.46, 115.50, 115.11, 65.93, 55.40, 53.98, 48.45, 27.26, 23.98; ¹⁹F NMR (376 MHz, MeOD- d_4) δ –62.72; HRMS (APCI): m/z calcd $C_{27}H_{30}N_2$ - O_2F_3 [M + H]⁺ 471.2254, found, 471.2250.

4-(4-((4-(3-(Pvrrolidin-1-vl)propoxy)benzyl)amino)phenoxy) benzonitrile (41b). The title compound was synthesised from the reductive amination product 31 (130 mg, 0.33 mmol) and KI (60.9 mg, 0.37 mmol), K₂CO₃ (138.2 mg, 1.00 mmol), pyrrolidine (200 mg, 2.81 mmol) and dry ACN (5 mL) for 3 h following general procedure 2b to afford the product 41b in a quant. conversion; Rf: 0.14 (5% MeOH:95% DCM); IR (MeOH, cm⁻¹): 3358, 2954, 2223, 1656, 1601, 1493, 1242, 1171, 1130, 811, 799, 720; ¹H NMR (400 MHz, MeOD- d_4) δ 7.62 (d, J = 8.9 Hz, 2H), 7.31 (d, J = 8.6 Hz, 2H), 6.95 (d, J =8.9 Hz, 3H), 6.91 (d, J = 8.6 Hz, 3H), 6.84 (d, J = 8.9 Hz, 2H), 6.69 (d, J = 8.9 Hz, 2H), 4.26 (s, 2H), 4.09 (t, J = 5.7 Hz, 2H), 3.70 (s, 2H), 3.44-3.37 (m, 2H), 3.11 (s, 2H), 2.26-2.10 (m, 4H), 2.04 (s, 2H); ¹³C NMR (101 MHz, MeOD- d_4) δ 164.66, 158.96, 147.54, 146.69, 135.24, 133.63, 129.76, 122.56, 119.87, 118.01, 115.51, 115.38, 105.68, 65.87, 55.39, 53.93, 48.67, 27.14, 23.97; ¹⁹F NMR (376 MHz, MeOD- d_4) δ -76.55; HRMS (APCI): m/z calcd $C_{27}H_{30}N_3O_2$ $[M + H]^+$ 428.2333, found 428.2327.

2-Phenoxy-N-(4-(3-(piperidin-1-yl)propoxy)benzyl)aniline

(32c). The title compound was synthesised from the reductive amination product 22 (270 mg, 0.73 mmol) and KI (134 mg, 0.81 mmol), K₂CO₃ (167 mg, 1.21 mmol), piperidine (217 mg, 2.55 mmol) and dry ACN (12 mL) for 3.5 h following general procedure 2b to afford the product 32c in a quant. conversion; $R_{\rm f}$: 0.16 (5% MeOH: 95% DCM); IR (neat, cm⁻¹): 3425, 2959, 1671, 1608, 1510, 1242, 1196, 1173, 1121, 798, 719, 692; ¹H NMR (400 MHz, MeOD- d_4) δ 7.37–7.25 (m, 2H), 7.25-7.17 (m, 2H), 7.05 (ddt, J = 8.5, 7.9, 1.5 Hz, 1H), 7.00-6.88 (m, 3H), 6.88–6.82 (m, 2H), 6.78 (dd, J = 7.9, 1.5 Hz, 1H), 6.72 (dd, J = 7.9, 1.5 Hz, 1H), 6.63 (td, J = 7.9, 1.5 Hz, 1H), 4.30 (s, 2H), 4.06 (t, J = 5.7 Hz, 2H), 3.58 (d, J = 12.5 Hz, 2H), 3.30-3.22 (m, 2H), 2.94 (td, J = 12.5, 3.0 Hz, 2H), 2.26-2.13 (m, 2H), 1.96 (d, J = 12.5 Hz, 2H), 1.90-1.80 (m, 1H), 1.81-1.67 (m, 2H), 1.60–1.44 (m, 1H); ¹³C NMR (101 MHz, MeOD d_4) δ 159.12, 158.98, 144.71, 140.98, 133.30, 130.71, 129.69, 125.94, 123.72, 120.59, 118.57, 118.21, 115.50, 114.13, 65.94, 55.96, 54.44, 48.09, 25.22, 24.31, 22.67; ¹⁹F NMR (376 MHz, MeOD- d_4) δ -76.55; HRMS (APCI): m/z calcd C₂₇H₃₃N₂O₂ [M + H⁺ 417.2537, found, 417.2533.

2-(4-Fluorophenoxy)-*N*-(4-(3-(piperidin-1-yl)propoxy)benzyl) aniline (33c). The title compound was synthesised from the reductive amination product 23 (114 mg, 0.30 mmol) and KI (51.4 mg, 0.31 mmol), K_2CO_3 (87.3 mg, 0.63 mmol), piperidine (137 mg, 1.61 mmol) and dry ACN (5 mL) for 3.5 h following general procedure 2b to afford the product 33c in a quant. conversion; R_f : 0.29 (5% MeOH:95% DCM); IR (neat, cm⁻¹): 3422, 1671, 1608, 1499, 1241, 1195, 1121, 827, 742, 719; ¹H NMR (501 MHz, MeOD- d_4) δ 7.23 (d, J = 8.6, 2H), 7.07–6.98 (m, 2H), 6.97–6.89 (m, 3H), 6.86 (d, J = 8.6, 2H), 6.76 (dd, J = 7.9, 1.5 Hz, 1H), 6.68 (dd, J = 8.1, 1.5 Hz, 1H), 6.59 (td, J = 7.7, 1.5 Hz, 1H), 4.30 (s, 2H), 4.08 (t, J = 5.7 Hz, 2H), 3.58 (d, J = 12.7 Hz, 2H), 3.30–3.24 (m, 2H), 2.95 (t, J = 12.7 Hz, 2H), 2.27–2.14 (m, 2H), 2.04–1.66 (m, 5H), 1.62–1.45 (m, 1H); ¹³C NMR (126 MHz, MeOD- d_4) δ 159.72 (d, J = 239.0 Hz), 158.88, 155.33 (d, J = 2.3 Hz), 144.72, 141.71, 133.91, 129.51, 126.01, 120.30, 119.58 (d, J = 8.1 Hz), 117.83, 116.96 (d, J = 23.6 Hz), 115.48, 113.52, 65.95, 56.02, 54.49, 47.67, 25.27, 24.37, 22.69; ¹⁹F NMR (376 MHz, MeOD- d_4) δ –76.55, –123.54; HRMS (APCI): m/z calcd $C_{27}H_{32}N_2O_2F$ [M + H]⁺ 435.2442, found, 435.2429.

N-(4-(3-(Piperidin-1-yl)propoxy)benzyl)-2-(4-

(trifluoromethyl)phenoxy)aniline (34c). The title compound was synthesised from the reductive amination product 24 (156 mg, 0.36 mmol) and KI (62.0 mg, 0.37 mmol), K₂CO₃ (89.0 mg, 0.64 mmol), piperidine (153 mg, 1.79 mmol) and dry ACN (5 mL) for 3 h following general procedure 2b to afford the product 34c in a quant. conversion; $R_{\rm f}$: 0.29 (5%) MeOH: 95% DCM); IR (neat, cm⁻¹): 3425, 2951, 1671, 1609, 1510, 1325, 1230, 1165, 1105, 1064, 828, 742, 719; ¹H NMR (501 MHz, MeOD- d_4 , -15 °C) δ 7.62 (d, J = 8.6 Hz, 2H), 7.21 (d, J = 8.6 Hz, 2H), 7.03 (d, J = 8.6 Hz, 2H), 6.99 (td, J = 7.8)1.5 Hz, 1H), 6.89 (dd, J = 7.8, 1.5 Hz, 1H), 6.85 (d, J = 8.6 Hz, 2H), 6.69-6.59 (m, 2H), 4.29 (s, 2H), 4.05 (t, J = 5.6 Hz, 2H), 3.87-3.37 (m, 2H), 3.29-3.21 (m, 2H), 2.92 (s, 2H), 2.29-2.11 (m, 2H), 2.11–1.36 (m, 6H); ¹³C NMR (126 MHz, MeOD- d_4) δ 162.52, 158.89, 142.78, 142.14, 133.82, 129.43, 128.07 (q, J = 3.8 Hz), 127.16, 125.86 (q, J = 269.7 Hz), 125.21 (q, J = 32.5 Hz), 121.88, 117.90, 117.59, 115.46, 113.86, 65.99, 56.06, 54.52, 47.45, 25.34, 24.43, 22.77; ¹⁹F NMR (376 MHz, MeOD d_4) δ -62.73, -76.55; HRMS (APCI): m/z calcd C₂₈H₃₂N₂O₂F₃ $[M + H]^+$ 485.2410, found, 485.2406.

4-(2-((4-(3-(Piperidin-1-yl)propoxy)benzyl)amino)phenoxy)

benzonitrile (35c). The title compound was synthesised from the reductive amination product 25 (130 mg, 0.33 mmol) and KI (62.2 mg, 0.37 mmol), K₂CO₃ (140 mg, 1.02 mmol), piperidine (188 mg, 2.21 mmol) and dry ACN (3 mL) for 3.5 h following general procedure 2b to afford the product 35c in a quant. conversion; Rf: 0.37 (5% MeOH: 95% DCM); IR (neat, cm⁻¹): 3388, 2951, 2225, 1672, 1610, 1501, 1231, 1165, 1123, 828, 744, 719; ¹H NMR (400 MHz, MeOD- d_4) δ 7.64 (d, J = 9.0 Hz, 2H), 7.17 (d, J = 8.8 Hz, 2H), 7.07–7.01 (m, 1H), 6.99 (d, J = 9.0 Hz, 2H), 6.89 (dd, J = 7.9, 1.5 Hz, 1H), 6.83 (d, J = 8.8 Hz, 2H), 6.73 (dd, J = 7.9, 1.5 Hz, 1H), 6.65 (td, J = 7.9, 1.5 Hz, 1H), 4.27 (s, 2H), 4.06 (t, J = 5.7 Hz, 2H), 3.72–3.45 (m, 2H), 3.30-3.24 (m, 2H), 3.11-2.78 (m, 2H), 2.29-2.13 (m, 2H), 2.07-1.63 (m, 5H), 1.63-1.40 (m, 1H); ¹³C NMR (101 MHz, MeOD-d₄) δ 163.38, 158.88, 142.19, 142.13, 135.25, 133.77, 129.40, 127.54, 122.12, 119.85, 118.03, 117.94, 115.45, 114.06, 106.22, 65.95, 55.98, 54.46, 47.43, 25.25, 24.33, 22.68; ¹⁹F NMR (376 MHz, MeOD- d_4) δ -76.55; HRMS (APCI): m/z calcd $C_{28}H_{32}N_3O_2 [M + H]^+ 442.2489$, found 442.2486.

3-Phenoxy-N-(4-(3-(piperidin-1-yl)propoxy)benzyl)aniline (**36c**). The title compound was synthesised from the reductive amination product **26** (131 mg, 0.36 mmol) and KI (64.0 mg, 0.38 mmol), K₂CO₃ (84.3 mg, 0.61 mmol), piperidine (120 mg, 1.41 mmol) and dry ACN (3 mL) for 3.5 h following general procedure 2b to afford the product **36c** in a quant. conversion; $R_{\rm f}$: 0.16 (5% MeOH: 95% DCM); IR (neat, cm⁻¹): 3353, 2949, 1671, 1609, 1488, 1219, 1198, 1126, 830, 721, 691; ¹H NMR (400 MHz, MeOD- d_4) δ 77.36–7.17 (m, 4H), 7.16–7.02 (m, 2H), 6.96–6.81 (m, 4H), 6.53 (ddd, J = 8.1, 2.2, 0.9 Hz, 1H), 6.41–6.32 (m, 2H), 4.26 (s, 2H), 4.09 (t, J = 5.7 Hz, 2H), 3.59 (d, J = 12.5 Hz, 2H), 3.30–3.26 (m, 2H), 2.95 (td, J = 12.5, 3.0 Hz, 2H), 2.28–2.16 (m, 2H), 1.97 (d, J = 12.5 Hz, 2H), 1.90–1.68 (m, 3H), 1.62–1.44 (m, 1H); ¹³C NMR (101 MHz, MeOD- d_4) δ 159.52, 158.87, 158.83, 151.25, 133.56, 130.95, 130.62, 129.71, 123.90, 119.66, 115.46, 109.86, 108.39, 104.80, 65.95, 56.00, 54.47, 48.20, 25.26, 24.34, 22.68; ¹⁹F NMR (376 MHz, MeOD- d_4) δ –76.55; HRMS (APCI): m/z calcd $C_{27}H_{33}N_2O_2$ [M + H]⁺ 417.2537, found, 417.2536.

3-(4-Fluorophenoxy)-N-(4-(3-(piperidin-1-yl)propoxy)benzyl) aniline (37c). The title compound was synthesised from the reductive amination product 27 (130 mg, 0.34 mmol) and KI (56.1 mg, 0.34 mmol), K₂CO₃ (91.2 mg, 0.66 mmol), piperidine (96.1 mg, 1.13 mmol) and dry ACN (5 mL) for 4 h following general procedure 2b to afford the product 37c in a quant. conversion; Rf: 0.29 (5% MeOH: 95% DCM); IR (neat, cm⁻¹): 3343, 2950, 1671, 1605, 1494, 1240, 1195, 1125, 828, 720, 689; ¹H NMR (501 MHz, MeOD- d_4) δ 7.24 (d, J = 8.6 Hz, 2H), 7.05-6.95 (m, 3H), 6.93-6.81 (m, 4H), 6.37 (ddd, J = 8.1, 2.1, 1.0 Hz, 1H), 6.20-6.10 (m, 2H), 4.19 (s, 2H), 4.08 (t, J = 5.7 Hz, 2H), 3.86-3.36 (m, 2H), 3.30-3.27 (m, 2H), 3.21-2.71 (m, 2H), 2.28–2.16 (m, 2H), 1.85 (s, 6H); ¹³C NMR (126 MHz, MeOD- d_4) δ 159.92 (d, J = 239.4 Hz), 159.91, 158.80, 154.79 (d, J = 2.5 Hz), 151.77, 133.88, 130.94, 129.53, 121.32 (d, J = 8.4 Hz), 116.94 (d, J = 23.6 Hz), 115.44, 109.58, 107.47, 103.96, 65.96, 56.04, 54.50, 47.91, 25.31, 24.38, 22.71; ¹⁹F NMR (376 MHz, MeOD-d₄) δ -76.55, -122.77; HRMS (APCI): m/z calcd C₂₇H₃₂N₂O₂F [M + H]⁺ 435.2442, found, 435.2436.

4-Phenoxy-N-(4-(3-(piperidin-1-yl)propoxy)benzyl)aniline (38c). The title compound was synthesised from the reductive amination product 28 (250 mg, 0.68 mmol) and KI (112 mg, 0.68 mmol), K₂CO₃ (141 mg, 1.02 mmol), piperidine (200 mg, 2.35 mmol) and dry ACN (12 mL) for 3 h following general procedure 2b to afford the product 38c in a quant. conversion; $R_{\rm f}$: 0.26 (5% MeOH: 95% DCM); IR (neat, cm⁻¹): 3378, 2958, 1664, 1610, 1511, 1228, 1179, 1130, 830, 720, 689; ¹H NMR (400 MHz, MeOD- d_4) δ 7.35–7.28 (m, 2H), 7.28–7.18 (m, 2H), 6.97 (tt, J = 7.4, 1.1 Hz, 1H), 6.93-6.86 (m, 2H), 6.86-6.81 (m, 2H), 6.81-6.73 (m, 2H), 6.70-6.59 (m, 2H), 4.23 (s, 2H), 4.08 (t, J = 5.7 Hz, 2H), 3.57 (s, 2H), 3.30-3.23 (m, 2H), 2.95 (s, 2H), 2.31-2.13 (m, 2H), 2.10-1.36 (m, 6H); ¹³C NMR (101 MHz, MeOD-*d*₄) δ 160.57, 158.89, 148.83, 146.56, 133.83, 130.52, 129.79, 122.93, 121.87, 117.95, 115.46, 115.37, 65.95, 55.99, 54.45, 48.75, 25.25, 24.33, 22.68; ¹⁹F NMR (376 MHz, MeOD- d_4) δ -76.55; HRMS (APCI): m/z calcd C₂₇H₃₃N₂O₂ [M + H⁺ 417.2537, found, 417.2532.

4-(4-Fluorophenoxy)-*N*-(4-(3-(piperidin-1-yl)propoxy)benzyl) aniline (39c). The title compound was synthesised from the reductive amination product 29 (210 mg, 0.54 mmol) and KI (88.7 mg, 0.53 mmol), K_2CO_3 (153 mg, 1.11 mmol), piperidine (175 mg, 2.05 mmol) and dry ACN (12 mL) for 3 h following

general procedure 2b to afford the product **39c** in a quant. conversion; $R_{\rm f}$: 0.25 (5% MeOH:95% DCM); IR (MeOH, cm⁻¹): 3347, 2951, 1672, 1608, 1495, 1242, 1198, 1130, 830, 800, 721; ¹H NMR (400 MHz, MeOD- d_4) δ 7.35–7.26 (m, 2H), 7.04–6.93 (m, 2H), 6.88–6.82 (m, 2H), 6.82–6.74 (m, 2H), 6.73–6.64 (m, 2H), 4.25 (s, 2H), 4.09 (t, J = 5.7 Hz, 2H), 3.59 (d, J = 12.2 Hz, 2H), 3.30–3.26 (m, 2H), 2.95 (td, J = 12.2, 3.0 Hz, 2H), 2.30–2.13 (m, 2H), 1.97 (d, J = 12.2 Hz, 2H), 1.91–1.67 (m, 3H), 1.63–1.44 (m, 1H); ¹³C NMR (101 MHz, MeOD- d_4) δ 159.45 (d, J = 238.6 Hz), 159.01, 156.40 (d, J = 2.4 Hz), 149.90, 145.65, 133.31, 129.97, 121.43, 119.61 (d, J = 8.2 Hz), 116.86 (d, J = 23.6 Hz), 115.99, 115.48, 65.96, 56.00, 54.48, 49.24, 25.27, 24.36, 22.69; ¹⁹F NMR (376 MHz, MeOD- d_4) δ –123.98; HRMS (APCI): m/z calcd C₂₇H₃₂N₂O₂F [M + H]⁺ 435.2442, found, 435.2440.

N-(4-(3-(Piperidin-1-yl)propoxy)benzyl)-4-(4-

(trifluoromethyl)phenoxy)aniline (40c). The title compound was synthesised from the reductive amination product 30 (130 mg, 0.30 mmol) and KI (58.1 mg, 0.35 mmol), K₂CO₃ (69.1 mg, 0.50 mmol), piperidine (192 mg, 2.25 mmol) and dry ACN (5 mL) for 3 h following general procedure 2b to afford the product 40c in a quant. conversion; $R_{\rm f}$: 0.29 (5%) MeOH: 95% DCM); IR (neat, cm⁻¹): 3356, 2953, 1665, 1606, 1505, 1324, 1236, 1160, 1105, 830, 800, 719; ¹H NMR (600 MHz, MeOD- d_4) δ 7.55 (d, J = 8.6 Hz, 2H), 7.32 (d, J = 8.7 Hz, 2H), 6.96 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.9 Hz, 2H), 6.67 (d, J = 8.9 Hz, 2H), 4.25 (s, 2H), 4.09 (t, J = 5.7 Hz, 2H), 3.59 (d, J = 11.9 Hz, 2H), 3.31-3.27 (m, 2H), 2.96 (s, 2H), 1.96 (s, 2H), 1.90–1.69 (m, 3H), 1.53 (s, 1H); ¹³C NMR (151 MHz, MeOD-d₄) δ 162.45, 157.48, 146.23, 145.68, 132.56, 128.29, 126.57 (q, J = 3.8 Hz), 124.47 (q), 123.20 (q, J = 32.6 Hz), 121.06, 116.06, 114.08, 113.74, 64.57, 54.62, 53.09, 47.06, 23.88, 22.96, 21.28; $^{19}{\rm F}$ NMR (376 MHz, MeOD- d_4) δ –62.76, -76.55; HRMS (APCI): m/z calcd $C_{28}H_{32}N_2O_2F_3$ [M + H]⁺ 485.2410, found, 485.2401.

4-(4-((4-(3-(Piperidin-1-yl)propoxy)benzyl)amino)phenoxy) benzonitrile (41c). The title compound was synthesised from

the reductive amination product 31 (107 mg, 0.27 mmol) and KI (60.4 mg, 0.36 mmol), K₂CO₃ (140 mg, 1.01 mmol), piperidine (170 mg, 2.00 mmol) and dry ACN (3 mL) for 3 h following general procedure 2b to afford the product 41c in a quant. conversion; Rf: 0.25 (5% MeOH: 95% DCM); IR (neat, cm⁻¹): 3371, 2950, 2223, 1656, 1602, 1493, 1242, 1170, 1132, 822, 770, 721; ¹H NMR (400 MHz, MeOD- d_4 , -15 °C) δ 7.64 (d, J = 8.9 Hz, 2H), 7.32 (d, J = 8.6 Hz, 2H), 6.94 (d, J = 8.9 Hz, 3H), 6.90 (d, J = 8.6 Hz, 3H), 6.83 (d, J = 8.9 Hz, 2H), 6.66 (d, J = 8.9 Hz, 2H), 4.25 (s, 2H), 4.07 (t, J = 5.6 Hz, 2H), 3.52 (s, 2H), 3.28 (dd, J = 6.8, 3.9 Hz, 2H), 2.94 (s, 2H), 2.30-2.12 (m, 2H), 2.10–1.36 (m, 6H); ¹³C NMR (126 MHz, MeOD- d_4) δ 164.75, 158.90, 147.99, 146.38, 135.23, 133.93, 129.67, 122.57, 119.88, 117.96, 115.48, 115.06, 105.62, 66.00, 56.05, 54.52, 48.36, 25.34, 24.41, 22.73; ¹⁹F NMR (376 MHz, MeOD- d_4) δ -76.55; HRMS (APCI): m/z calcd $C_{28}H_{32}N_3O_2$ [M + H]⁺ 442.2489, found 442.2484.

N-(4-(3-(1*H*-Imidazol-1-yl)propoxy)benzyl)-2-phenoxyaniline (32d). The title compound was synthesised from the reductive

amination product 22 (40.6 mg, 0.11 mmol) and KI (40.8 mg, 0.25 mmol) and imidazole (94.3 mg, 1.38 mmol) following general procedure 2c to afford the product 32d as a colourless oil (35.2 mg, 80%). The 1H, 13C and 19F NMR spectra of the respective TFA salt of 32d was recorded; Rf: 0.40 (5% MeOH: 95% DCM); IR (MeOH, cm⁻¹): 3418, 3148, 2509, 1671, 1607, 1509, 1201, 1130, 801, 743, 692; ¹H NMR (501 MHz, MeOD- d_4 , – 15 °C) δ 9.01 (s, 1H), 7.70 (s, 1H), 7.58 (s, 1H), 7.38–7.26 (m, 2H), 7.21 (d, J = 8.4 Hz, 2H), 7.05 (td, J = 7.7, 1.5 Hz, 1H), 6.98–6.87 (m, 3H), 6.79 (td, J = 7.7, 1.5 Hz, 3H), 6.65 (dd, J = 7.7, 1.5 Hz, 1H), 6.61 (td, J = 7.7, 1.5 Hz, 1H), 4.47 (t, J = 6.8 Hz, 2H), 4.29 (s, 2H), 3.99 (t, J = 5.5 Hz, 2H), 2.35 (p, J = 6.3 Hz, 2H); ¹³C NMR (126 MHz, MeOD- d_4 , – 15 °C) δ 159.27, 158.79, 144.22, 141.31, 136.73, 133.34, 130.72, 129.47, 126.01, 123.56, 123.43, 121.14, 120.72, 118.02, 115.11, 113.68, 65.33, 48.01, 47.51, 30.69; ¹⁹F NMR (376 MHz, MeOD- d_4) δ -76.55; HRMS (APCI): m/z calcd C₂₅H₂₆N₃O₂ [M + H]⁺ 400.202, found, 400.2017.

N-(4-(3-(1H-Imidazol-1-yl)propoxy)benzyl)-2-(4-

fluorophenoxy)aniline (33d). The title compound was synthesised from the reductive amination product 23 (32.5 mg, 0.08 mmol) and KI (30.1 mg, 0.18 mmol) and imidazole (73.8 mg, 1.08 mmol) following general procedure 2c to afford the product 33d as a colourless oil (27.5 mg, 78%); Rf: 0.30 (5% MeOH: 95% DCM); IR (neat, cm⁻¹): 3420, 2933, 2877, 1607, 1498, 1231, 1195, 1108, 818, 738, 663; ¹H NMR (600 MHz, acetone- d_6) δ 7.58 (s, 1H), 7.27 (d, J = 8.8 Hz, 2H), 7.18 (s, 1H), 7.13-7.06 (m, 2H), 7.04-6.90 (m, 4H), 6.87 (d, J = 8.8 Hz, 2H), 6.79 (dd, J = 7.9, 1.5 Hz, 1H), 6.72 (dd, J = 7.9, 1.5 Hz, 1H), 6.59 (td, J = 7.9, 1.5 Hz, 1H), 4.35 (d, J = 5.7 Hz, 2H), 4.25 (t, J = 6.9 Hz, 2H), 3.94 (t, J = 6.9 Hz, 2H), 2.24 (p, J = 6.9 Hz, 2H); ¹³C NMR (101 MHz, acetone- d_6) δ 159.07 (d, J = 238.5 Hz), 158.76, 154.91 (d, J = 2.3 Hz), 143.93, 141.49, 138.35, 133.08, 129.71, 129.18, 125.90, 120.21, 120.09, 119.37 (d, J = 8.3 Hz), 117.12, 116.82 (d, J = 23.5 Hz), 115.27, 112.78, 65.16, 47.05, 44.11, 31.58; ¹⁹F NMR (376 MHz, MeOD- d_4) δ -76.55, -122.20; HRMS (APCI): m/z calcd C₂₅H₂₅N₃O₂F [M + H]⁺ 418.1925, found, 418.1921.

N-(4-(3-(1H-Imidazol-1-yl)propoxy)benzyl)-2-(4-

(trifluoromethyl)phenoxy)aniline (34d). The title compound was synthesised from the reductive amination product 24 (30.1 mg, 0.07 mmol) and KI (25.7 mg, 0.15 mmol) and imidazole (62.7 mg, 0.92 mmol) following general procedure 2c to afford the product 34d as a colourless oil (25.7 mg, 81%); $R_{\rm f}$: 0.30 (5% MeOH: 95% DCM); IR (neat, cm⁻¹): 3419, 2933, 1608, 1509, 1322, 1226, 1158, 1105, 1063, 819, 739, 663; ¹H NMR (400 MHz, acetone- d_6) δ 77.68 (d, J = 8.6 Hz, 2H), 7.55 (s, 1H), 7.24 (d, J = 8.6 Hz, 2H), 7.13 (s, 1H), 7.09-6.99 (m, 3H), 6.98-6.89 (m, 2H), 6.85 (d, J = 8.6 Hz, 2H), 6.76 (dd, J = 8.2, 1.5 Hz, 1H), 6.65 (td, J = 8.2, 1.5 Hz, 1H), 4.34 (d, J = 4.5 Hz, 2H), 4.23 (t, J = 6.9 Hz, 2H), 3.93 (t, J = 6.9 Hz, 2H), 2.23 (p, J = 6.9 Hz, 2H); ¹³C NMR (101 MHz, acetone- d_6) δ 162.10, 158.75, 142.00, 141.85, 138.32, 132.95, 129.69, 129.11, 127.92 (q, J = 3.8 Hz), 127.04, 125.49 (q, J = 270.6 Hz), 124.41 (q, J = 32.5 Hz), 121.67, 120.04, 117.40, 117.30, 115.25, 113.22, 65.14, 46.90, 44.04, 31.58; ¹⁹F NMR (376 MHz, MeOD-

 $d_4)~\delta$ –62.46, –76.55; HRMS (APCI): m/z calcd $\rm C_{26}H_{24}N_3O_2F_3$ $\rm [M+H]^+$ 468.1890, found, 468.1890.

4-(2-((4-(3-(1H-Imidazol-1-yl)propoxy)benzyl)amino)

phenoxy)benzonitrile (35d). The title compound was synthesised from the reductive amination product 25 (28.7 mg, 0.07 mmol) and KI (30.2 mg, 0.18 mmol) and imidazole (63.4 mg, 0.93 mmol) following general procedure 2c to afford the product 35d as a white solid (26.6 mg, 86%). The ¹H, ¹³C and ¹⁹F NMR spectra of the respective TFA salt of 35d was recorded; Rf: 0.37 (5% MeOH:95% DCM); IR (neat, cm⁻¹): 3400, 2928, 2522, 2221, 1673, 1602, 1499, 1232, 1175, 1115, 872, 831, 741, 720; ¹H NMR (501 MHz, MeOD-d₄, - 15 °C) δ 9.00 (s, 1H), 7.82–7.63 (m, 3H), 7.58 (s, 1H), 7.17 (d, J = 8.2 Hz, 2H), 7.07-6.96 (m, 3H), 6.90 (dd, J = 7.9, 1.4 Hz, 1H), 6.79 (d, J = 8.2 Hz, 2H), 6.70–6.59 (m, 2H), 4.47 (t, J = 6.7 Hz, 2H), 4.27 (s, 2H), 3.99 (t, J = 6.7 Hz, 2H), 2.48-2.20 (m, 2H); ¹³C NMR (126 MHz, MeOD- d_4 , - 15 °C) δ 163.43, 158.73, 142.11, 141.76, 136.76, 135.27, 133.56, 129.22, 127.60, 123.40, 122.27, 121.25, 119.86, 117.87, 117.65, 115.09, 113.78, 106.06, 65.32, 47.96, 46.94, 30.71; ¹⁹F NMR (376 MHz, MeOD- d_4) δ -76.55; HRMS (APCI): m/z calcd $C_{26}H_{25}N_4O_2$ [M + H]⁺ 425.1969, found 425.1968.

N-(4-(3-(1H-Imidazol-1-yl)propoxy)benzyl)-3-phenoxyaniline (36d). The title compound was synthesised from the reductive amination product 26 (43.8 mg, 0.12 mmol), KI (44.1 mg, 0.27 mmol) and imidazole (100 mg, 1.47 mmol)following general procedure 2c to afford the product 36d as a colourless oil (39.6 mg, 83%), which solidified on standing; $R_{\rm f}$: 0.30 (5% MeOH: 95% DCM); IR (neat, cm⁻¹): 3242, 2948, 2873, 1614, 1512, 1488, 1244, 1212, 1145, 817, 754, 692; ¹H NMR (400 MHz, acetone-*d*₆) δ 7.55 (s, 1H), 7.38–7.30 (m, 2H), 7.30-7.23 (m, 2H), 7.13 (s, 1H), 7.10-7.02 (m, 2H), 7.01-6.90 (m, 3H), 6.90-6.84 (m, 2H), 6.45 (ddd, J = 8.1, 2.2, 0.8 Hz, 1H), 6.31 (t, J = 2.2 Hz, 1H), 6.20 (ddd, J = 8.1, 2.3, 0.8 Hz, 1H), 4.30-4.16 (m, 4H), 3.94 (t, J = 6.5 Hz, 2H), 2.24 (p, J = 6.5 Hz, 2H); 13 C NMR (101 MHz, acetone) δ 159.02, 158.73, 158.39, 151.46, 138.37, 132.94, 130.79, 130.48, 129.77, 129.38, 123.64, 120.05, 119.37, 115.24, 108.97, 107.41, 103.91, 65.14, 47.47, 44.01, 31.57; ¹⁹F NMR (376 MHz, MeOD- d_4) δ -76.55; HRMS (APCI): m/z calcd $C_{25}H_{26}N_3O_2 [M + H]^+$ 400.202, found, 400.2011.

N-(4-(3-(1H-Imidazol-1-yl)propoxy)benzyl)-3-(4-

fluorophenoxy)aniline (37d). The title compound was synthesised from the reductive amination product 27 (37.8 mg, 0.10 mmol) and KI (39.4 mg, 0.24 mmol) and imidazole (80.1 mg, 1.18 mmol) following general procedure 2c to afford the product 37d as a colourless oil (33.8 mg, 83%), which solidified on standing; R_f : 0.29 (5% MeOH:95% DCM); IR (neat, cm⁻¹): 3225, 2944, 2835, 1609, 1497, 1234, 1195, 1109, 1034, 824, 728, 661; ¹H NMR (600 MHz, acetone- d_6) δ 7.52 (s, 1H), 7.27 (d, J = 8.6 Hz, 2H), 7.15–7.06 (m, 3H), 7.04 (t, J = 8.2 Hz, 1H), 7.01–6.95 (m, 2H), 6.91 (s, 1H), 6.90–6.85 (m, 2H), 6.44 (ddd, J = 8.2, 2.3, 0.8 Hz, 1H), 6.27 (t, J = 2.3 Hz, 1H), 6.17 (ddd, J = 8.2, 2.3, 0.8 Hz, 1H), 4.27–4.21 (m, 4H), 3.94 (t, J = 6.0 Hz, 2H), 2.24 (p, J = 6.4 Hz, 2H); ¹³C NMR (101 MHz, acetone- d_6) δ 159.47, 159.35 (d, J = 239.0 Hz),

158.74, 154.26 (d, J = 2.4 Hz), 151.47, 138.40, 132.92, 130.83, 129.82, 129.37, 121.24 (d, J = 8.3 Hz), 120.04, 116.87 (d, J = 23.4 Hz), 115.24, 108.90, 106.85, 103.38, 65.14, 47.49, 43.99, 31.58; ¹⁹F NMR (376 MHz, MeOD- d_4) δ –121.54; HRMS (APCI): m/z calcd $C_{25}H_{25}N_3O_2F$ [M + H]⁺ 418.1925, found, 418.1931.

N-(4-(3-(1H-Imidazol-1-yl)propoxy)benzyl)-4-phenoxyaniline (38d). The title compound was synthesised from the reductive amination product 28 (47.3 mg, 0.13 mmol) and KI (50.5 mg, 0.30 mmol) and imidazole (112 mg, 1.65 mmol) following general procedure 2c to afford the product 38d as a white solid (40.9 mg, 80%); Rf: 0.29 (5% MeOH:95% DCM); IR (neat, cm⁻¹): 3247, 2939, 2821, 1608, 1509, 1489, 1228, 1064, 824, 741, 662; ¹H NMR (600 MHz, acetone- d_6) δ 7.55 (s, 1H), 7.33 (d, J = 8.8 Hz, 2H), 7.31-7.26 (m, 2H), 7.13 (s, 1H), 6.99 (tt, J = 7.3, 1.1 Hz, 1H), 6.93 (s, 1H), 6.92-6.89 (m, 2H), 6.88-6.85 (m, 2H), 6.85-6.80 (m, 2H), 6.73-6.67 (m, 2H), 4.27 (s, 2H), 4.25 (t, J = 6.9 Hz, 2H), 3.95 (t, J = 6.9 Hz, 2H), 2.25 (p, J = 6.9 Hz, 2H); ¹³C NMR (151 MHz, acetone) δ 160.33, 158.78, 147.63, 146.72, 138.43, 133.24, 130.37, 129.77, 129.46, 122.57, 121.84, 120.13, 117.56, 115.28, 114.37, 65.18, 48.06, 44.06, 31.59; ¹⁹F NMR (376 MHz, MeOD- d_4) δ -76.55; HRMS (APCI): m/z calcd C₂₅H₂₆N₃O₂ [M + H]⁺ 400.202, found, 400.2015.

N-(4-(3-(1H-Imidazol-1-yl)propoxy)benzyl)-4-(4-

fluorophenoxy)aniline (39d). The title compound was synthesised from the reductive amination product 29 (39.8 mg, 0.10 mmol), KI (41.0 mg, 0.25 mmol) and imidazole (87.9 mg, 1.29 mmol) following general procedure 2c to afford the product 39d as a cream solid (36.7 mg, 85%); Rf: 0.28 (5% MeOH: 95% DCM); IR (neat, cm⁻¹): 3236, 2943, 2835, 1606, 1494, 1241, 1207, 1035, 821, 729, 659; ¹H NMR (400 MHz, acetone- d_6) δ 7.56 (s, 1H), 7.32(d, J = 8.6 Hz, 2H), 7.13 (s, 1H), 7.09-6.99 (m, 2H), 6.94 (s, 1H), 6.92-6.84 (m, 4H), 6.85-6.76 (m, 2H), 6.73-6.64 (m, 2H), 4.33-4.17 (m, 4H), 3.94 (t, J = 6.5 Hz, 2H), 2.23 (p, J = 6.5 Hz, 2H); ¹³C NMR (101 MHz, acetone- d_6) δ 158.74, 158.66 (d, J = 237.7 Hz), 156.33 (d, J = 2.2 Hz), 148.04, 146.68, 138.36, 133.19, 129.73, 129.44, 121.47, 119.99, 119.10 (d, J = 8.4 Hz), 116.68 (d, J = 23.4 Hz), 115.25, 114.36, 65.13, 48.01, 44.01, 31.55; ¹⁹F NMR (376 MHz, acetone) δ -124.75, -76.55; HRMS (APCI): m/z calcd C₂₅H₂₅N₃- $O_2F [M + H]^+$ 418.1925, found, 418.1922.

N-(4-(3-(1H-Imidazol-1-yl)propoxy)benzyl)-4-(4-

(trifluoromethyl)phenoxy)aniline (40d). The title compound was synthesised from the reductive amination product 30 (32.2 mg, 0.07 mmol), KI (29.3 mg, 0.18 mmol) and imidazole (70.1 mg, 1.03 mmol) following general procedure 2c to afford the product 40d as a pale yellow oil (28.7 mg, 83%); $R_{\rm f}$: 0.28 (5% MeOH:95% DCM); IR (neat, cm⁻¹): 3243, 2939, 1614, 1508, 1324, 1236, 1104, 1065, 830, 742, 662; ¹H NMR (400 MHz, acetone- d_6) δ 7.63 (d, J = 8.8 Hz, 2H), 7.57 (s, 1H), 7.34 (d, J = 8.6 Hz, 2H), 7.28–7.06 (m, 1H), 7.02 (d, J = 8.8 Hz, 2H), 6.96 (s, 1H), 6.93–6.85 (m, 4H), 6.74 (d, J = 8.9 Hz, 2H), 4.29 (s, 2H), 4.25 (t, J = 6.9 Hz, 2H), 3.95 (t, J = 6.9 Hz, 2H), 2.25 (p, J = 6.9 Hz, 2H); ¹³C NMR (101 MHz, acetone- d_6) δ 163.50, 158.80, 147.47, 146.13, 138.49, 133.08, 129.80, 129.47, 127.87 (q, J = 3.8 Hz), 125.52 (q, J = 270.0 Hz), 123.81 (q, J = 32.4 Hz), 122.35, 120.21, 117.25, 115.28, 114.42, 65.15, 47.93,

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44.04, 31.57; ¹⁹F NMR (376 MHz, MeOD- d_4) δ -62.72, -76.55; HRMS (APCI): m/z calcd $C_{26}H_{24}N_3O_2F_3$ [M + H]⁺ 468.1890, found, 468.1890.

4-(4-((4-(3-(1H-Imidazol-1-yl)propoxy)benzyl)amino)

phenoxy)benzonitrile (41d). The title compound was synthesised from the reductive amination product 31 ((34.9 mg, 0.09 mmol), KI (37.3 mg, 0.22 mmol) and imidazole (74.5 mg, 1.09 mmol) following general procedure 2c to afford the product **41d** as a pale yellow solid (30.9 mg, 82%); $R_{\rm f}$: 0.28 (5% MeOH:95% DCM); IR (MeOH, cm⁻¹): 3389, 2926, 2225, 1610, 1496, 1239, 1168, 1110, 830, 743; ¹H NMR (501 MHz, acetone- d_6) δ 7.70 (d, J = 9.0 Hz, 2H), 7.55 (s, 1H), 7.33 (d, J = 8.6 Hz, 2H), 7.15 (s, 1H), 7.00 (d, J = 9.0 Hz, 2H), 6.94 (s, 1H), 6.93-6.87 (m, 4H), 6.74 (d, J = 8.9 Hz, 2H), 4.29 (s, 2H), 4.25 (t, J = 6.9 Hz, 2H), 3.95 (t, J = 6.9 Hz, 2H), 2.25 (p, J = 6.9 Hz, 2H); ¹³C NMR (101 MHz, acetone) δ 164.08, 158.81, 147.68, 145.62, 138.18134.98, 133.04, 129.74, 129.46, 122.41, 120.86, 119.41, 117.68, 115.29, 114.42, 105.54, 65.16, 47.90, 44.09, 31.55; ¹⁹F NMR (376 MHz, MeOD- d_4) δ -76.55; HRMS (APCI): m/z calcd $C_{26}H_{25}N_4O_2$ $[M + H]^+$ 425.1969, found 425.1966.

N-(4-(3-(Methylamino)propoxy)benzyl)-2-phenoxyaniline

(32e). The title compound was synthesised from the reductive amination product 22 (106 mg, 0.29 mmol) and KI (109 mg, 0.65 mmol) following general procedure 2a to afford the product 32e as a colourless oil (77.3 mg, 74%), which solidified on standing; Rf: 0.27 (10% MeOH: 90% DCM); IR (neat, cm⁻¹): 3401, 2951, 1667, 1607, 1490, 1242, 1174, 1047, 838, 746, 724, 691; ¹H NMR (501 MHz, MeOD-*d*₄) δ 7.34–7.25 (m, 2H), 7.22 (d, J = 8.6 Hz, 2H), 7.08–7.00 (m, 1H), 6.97–6.89 (m, 3H), 6.87 (d, J = 8.6 Hz, 2H), 6.78 (dd, J = 7.9, 1.5 Hz, 1H), 6.68 (dd, J = 7.9, 1.5 Hz, 1H), 6.59 (td, J = 7.9, 1.5 Hz, 1H), 4.29 (s, 2H), 4.08 (t, J = 6.1 Hz, 2H), 3.20 (t, J = 6.1 Hz, 2H), 2.72 (s, 3H), 2.14 (p, J = 6.1 Hz, 2H); ¹³C NMR (126 MHz, MeOD- d_4) δ 159.34, 158.88, 144.29, 141.88, 133.88, 130.67, 129.47, 126.01, 123.55, 120.73, 118.04, 117.81, 115.53, 113.47, 66.20, 47.69, 33.88, 27.18; ¹⁹F NMR (376 MHz, MeOD- d_4) δ -76.55; HRMS (APCI): m/z calcd $C_{23}H_{27}N_2O_2$ [M + H]⁺ 363.2067, found, 363.2066.

2-(4-Fluorophenoxy)-N-(4-(3-(methylamino)propoxy)benzyl) aniline (33e). The title compound was synthesised from the reductive amination product 23 (125 mg, 0.32 mmol) and KI (103 mg, 0.62 mmol) following general procedure 2a to afford the product 33e as a colourless oil (89.4 mg, 72%); $R_{\rm f}$: 0.32 (10% MeOH:90% DCM); IR (neat, cm⁻¹): 3421, 2933, 1607, 1498, 1240, 1196, 1110, 1035, 824, 738; ¹H NMR (400 MHz, MeOD-d₄) 7.28-7.20 (m, 2H), 7.13-7.04 (m, 2H), 7.04-6.93 (m, 3H), 6.93-6.73 (m, 5H), 4.39 (d, J = 5.7 Hz, 2H), 4.09 (t, J = 6.3 Hz, 2H), 3.21 (t, J = 6.3 Hz, 2H), 2.73 (s, 3H), 2.16 (p, J = 6.3 Hz, 2H); ¹³C NMR (101 MHz, MeOD- d_4) δ 160.12 (d, J = 239.9 Hz), 159.43, 154.45, 146.63, 137.79, 131.55, 130.38, 125.67, 121.28, 120.42 (d, J = 8.3Hz), 119.72, 117.18 (d, J = 23.7 Hz), 116.52, 115.63, 66.21, 49.57, 48.36, 33.85, 27.16; ¹⁹F NMR (377 MHz, MeOD- d_4) δ -76.55, -122.35; HRMS (APCI): m/z calcd C₂₃H₂₆N₂O₂F [M + H⁺ 381.1973, found, 381.1963.

N-(4-(3-(Methylamino)propoxy)benzyl)-2-(4-

(trifluoromethyl)phenoxy)aniline (34e). The title compound was synthesised from the reductive amination product 24 (115 mg, 0.26 mmol) and KI (96.6 mg, 0.59 mmol) following general procedure 2a to afford the product 34e as a colourless oil (86.3 mg, 76%); Rf: 0.31 (10% MeOH: 90% DCM); IR (neat, cm⁻¹): 3420, 2761, 1666, 1609, 1510, 1230, 1165, 1105, 1064, 836, 799, 721; ¹H NMR (600 MHz, MeOD- d_4) δ 7.59 (d, J = 8.7 Hz, 2H), 7.19 (d, J = 8.6 Hz, 2H), 7.02 (d, J = 8.7 Hz, 2H), 6.99 (dd, J = 8.0, 1.5 Hz, 1H), 6.88 (dd, J = 8.0, 1.5 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.71 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.64 (td, *J* = 8.0, 1.5 Hz, 1H), 4.28 (s, 2H), 4.08 (t, J = 5.7 Hz, 2H), 3.20 (t, J = 5.7 Hz, 2H), 2.72 (s, 3H), 2.18–2.10 (m, 2H); ¹³C NMR (151 MHz, MeOD- d_4) δ 162.52, 158.88, 142.78, 142.14, 133.83, 129.40, 128.07 (q, J = 3.8 Hz), 127.15, 125.85 (q, J = 271.3 Hz), 125.22 (q, J = 32.6 Hz), 121.87, 117.91, 117.59, 115.51, 113.86, 66.19, 48.47, 47.46, 33.87, 27.18; ¹⁹F NMR (376 MHz, MeOD d_4) δ -62.83, -76.55; HRMS (APCI): m/z calcd $C_{24}H_{26}N_2O_2F_3$ $[M + H]^+$ 431.1941, found, 431.1929.

4-(2-((4-(3-(Methylamino)propoxy)benzyl)amino)phenoxy) benzonitrile (35e). The title compound was synthesised from the reductive amination product 25 (120 mg, 0.31 mmol) and KI (107 mg, 0.64 mmol) following general procedure 2a to afford the product 35e as a white solid (94.1 mg, 79%); Rf: 0.30 (10% MeOH: 90% DCM); IR (neat, cm⁻¹): 3411, 2940, 2222, 1677, 1603, 1499, 1235, 1176, 1133, 1051, 837, 762, 720; ¹H NMR (501 MHz, MeOD- d_4) δ 7.64 (d, J = 8.9 Hz, 2H), 7.18 (d, J = 8.6 Hz, 2H), 7.03 (dd, J = 7.6, 1.5 Hz, 1H), 6.99 (d, J = 8.9 Hz, 2H), 6.89 (dd, J = 7.9, 1.5 Hz, 1H), 6.85 (d, J = 8.6 Hz, 2H), 6.72 (dd, J = 7.6, 1.5 Hz, 1H), 6.65 (td, J = 7.6, 1.5 Hz, 1H), 4.27 (s, 2H), 4.08 (t, J = 6.1 Hz, 2H), 3.20 (t, J = 6.1 Hz, 2H), 2.73 (s, 3H), 2.14 (p, J = 6.1 Hz, 2H); ¹³C NMR (126 MHz, MeOD- d_4) δ 163.38, 158.90, 142.20, 142.12, 135.25, 133.76, 129.37, 127.53, 122.11, 119.83, 118.04, 117.94, 115.51, 114.04, 106.24, 66.18, 48.43, 47.43, 33.85, 27.17; ¹⁹F NMR (376 MHz, MeOD- d_4) δ -76.55; HRMS (APCI): m/z calcd C₂₄H₂₆N₃O₂ [M + H]⁺ 388.2020, found, 388.2009.

4-(3-(Dimethylamino)propoxy)-N-(2-phenoxyphenyl)

benzenesulfonamide (42). The title compound was prepared using the general procedure 3. The sulfonyl chloride was synthesised from the sulfonic acid 52 (142 mg, 0.47 mmol) and SOCl₂ (2.5 mL, 27.2 mmol). The sulfonyl chloride (0.47 mmol), aniline 11 (102, 0.55 mmol) and Cs_2CO_3 (784 mg, 2.41 mmol) after heating for 1.5 days afforded the product 42 as a cream solid (164 mg, 80%); Rf: 0.33 (10% MeOH:90% DCM); IR (neat, cm⁻¹): 3044, 1672, 1490, 1333, 1252, 1152, 751; ¹H NMR (600 MHz, MeOD-*d*₄) δ 7.65–7.60 (m, 2H), 7.60– 7.55 (m, 1H), 7.27-7.19 (m, 2H), 7.11-7.06 (m, 1H), 7.04 (dd, J = 6.1, 3.6 Hz, 2H), 6.90-6.84 (m, 2H), 6.68-6.63 (m, 1H), 6.63-6.58 (m, 2H), 4.10 (t, J = 5.8 Hz, 2H), 3.37-3.33 (m, 2H), 2.94 (s, 6H), 2.28–2.20 (m, 2H); ¹³C NMR (151 MHz, MeOD- d_4) δ 163.24, 157.69, 150.93, 133.43, 130.70, 130.46, 129.21, 127.45, 126.68, 124.65, 124.49, 119.75, 119.10, 115.52, 66.30, 56.51, 43.60, 25.56; ¹⁹F NMR (376 MHz, MeOD- d_4) δ -76.55; HRMS (APCI): m/z calcd $C_{23}H_{26}O_4N_2S$ 426.1608 [M]⁺, found, 426.1609; $C_{23}H_{27}O_4N_2S$ 427.1686 $[M + H]^+$, found, 427.1684.

4-(3-(Dimethylamino)propoxy)-N-(2-(4-fluorophenoxy)

phenyl)benzenesulfonamide (43). The title compound was prepared using the general procedure 3. The sulfonyl chloride was synthesised from the sulfonic acid 52 (219 mg, 0.74 mmol) and SOCl₂ (5.0 mL, 69 mmol). The sulfonyl chloride (0.74 mmol), aniline 12 (168, 0.83 mmol) and Cs₂-CO₃ (1.59 g, 4.87 mmol) after heating for 1.5 days afforded the product **43** as a cream solid (265 mg, 81%); *R*_f: 0.33 (10%) MeOH: 90% DCM); IR (neat, cm⁻¹): 3072, 1672, 1493, 1333, 1153, 830; ¹H NMR (600 MHz, MeOD- d_4) δ 7.64–7.60 (m, 2H), 7.60-7.56 (m, 1H), 7.09-7.04 (m, 2H), 6.99-6.93 (m, 2H), 6.89-6.85 (m, 2H), 6.69-6.64 (m, 1H), 6.62-6.56 (m, 2H), 4.10 (t, J = 5.8 Hz, 2H), 3.37-3.33 (m, 2H), 2.95 (s, 6H), 2.28-2.20 (m, 2H); 13 C NMR (151 MHz, MeOD- d_4) δ 163.22, 160.11 (d, J = 240.4 Hz), 153.82 (d, J = 2.6 Hz), 151.07, 133.59, 130.42, 129.21, 127.63, 127.14, 124.71, 121.02 (d, J = 8.4 Hz), 119.08, 117.04 (d, J = 23.7 Hz), 115.50, 66.29, 56.55, 43.61, 25.59; ¹⁹F NMR (376 MHz, MeOD- d_4) δ -76.55, -121.81; HRMS (APCI): m/z calcd $[M + H]^+$, found, HRMS (APCI): m/z calcd $C_{2,3}H_{2,5}O_4$ -N₂FS 444.1514 [M]⁺, found, 444.1516; C₂₃H₂₇O₄N₂FS 445.1592 $[M + H]^+$, found, 445.159.

4-(3-(Dimethylamino)propoxy)-N-(2-(4-(trifluoromethyl)

phenoxy)phenyl)benzenesulfonamide (44). The title compound was prepared using the general procedure 3. The sulfonyl chloride was synthesised from the sulfonic acid 52 (244 mg, 0.83 mmol) and SOCl₂ (5.0 mL, 69 mmol). The sulfonyl chloride (0.83 mmol), aniline 13 (251, 0.99 mmol) and Cs₂CO₃ (1.46 g, 4.49 mmol) after heating at reflux for 2 days afforded the product 44 as an orange oil (139 mg, 34%); $R_{\rm f}$: 0.37 (10% MeOH: 90% DCM); IR (neat, cm⁻¹): 3079, 1671, 1595, 1494, 1324, 1255, 1106, 831; ¹H NMR (600 MHz, MeOD d_4) δ 7.67–7.63 (m, 1H), 7.59–7.54 (m, 2H), 7.50–7.45 (m, 2H), 7.16 (pd, J = 7.5, 1.8 Hz, 2H), 6.88–6.84 (m, 1H), 6.83–6.78 (m, 2H), 6.75-6.69 (m, 2H), 4.08 (t, J = 5.8 Hz, 2H), 3.35-3.32 (m, 2H), 2.94 (s, 6H), 2.30-2.16 (m, 2H); ¹³C NMR (151 MHz, MeOD- d_4) δ 163.21, 161.33, 149.09, 133.54, 130.32, 130.29, 127.97 (q, J = 3.8 Hz), 127.75, 127.17, 126.15, 125.74 (q, J = 270.6 Hz), 125.66 (q, J = 32.5 Hz), 121.24, 118.54, 115.51, 66.25, 56.49, 43.59, 25.52; ¹⁹F NMR (376 MHz, MeOD- d_4) δ -62.63, -76.55; HRMS (APCI): m/z calcd $C_{24}H_{25}O_4N_2F_3S$ 494.1482 $\left[M \right]^{\!+}\!,$ found, 494.1482; $C_{24}H_{26}O_4N_2F_3S$ 495.156 $\left[M \right. +$ H]⁺, found, 495.1555.

N-(2-(4-Cyanophenoxy)phenyl)-4-(3-(dimethylamino)

propoxy)benzenesulfonamide (45). The title compound was prepared using the general procedure 3. The sulfonyl chloride was synthesised from the sulfonic acid 52 (198.9 mg, 0.67 mmol) and SOCl₂ (2.5 mL, 34 mmol). The sulfonyl chloride sulfonyl chloride (0.67 mmol), aniline 14 (153, 0.73 mmol) and Cs₂CO₃ (1.20 g, 3.69 mmol) after heating at reflux for 2 days afforded the product 45 as a white oil (90.6 mg, 30%); $R_{\rm f}$: 0.31 (10% MeOH : 90% DCM); IR (neat, cm⁻¹): 3385, 3069, 2214, 1672, 1595, 1496, 1367, 1331, 1161, 829; ¹H NMR (600 MHz, MeOD- d_4) δ 7.58–7.53 (m, 2H), 7.47 (dd, J = 8.2, 1.4 Hz, 1H), 7.38–7.32 (m, 2H), 7.31–7.24 (m, 2H), 7.15 (ddd, J = 8.6, 6.9, 2.1 Hz, 1H), 6.71–6.67 (m, 2H), 6.67–6.62 (m, 2H), 3.93 (t, J = 5.9 Hz, 2H), 3.38–3.33 (m, 2H), 2.96 (s, 6H), 2.28–

2.20 (m, 2H); ¹³C NMR (151 MHz, MeOD- d_4) δ 164.16, 149.43, 143.17, 134.48, 134.25, 131.66, 128.82, 128.33, 126.10, 125.31, 124.32, 121.48, 115.66, 115.52, 101.02, 66.26, 56.46, 43.69, 25.62; ¹⁹F NMR (376 MHz, MeOD- d_4) δ –76.55; HRMS (APCI): m/z calcd C₂₄H₂₅O₄N₃S 451.156 [M]⁺, found, 451.1562; C₂₄-H₂₅O₄N₃S 452.1639 [M + H]⁺, found, 452.1628.

4-(3-(Dimethylamino)propoxy)-N-(3-phenoxyphenyl)

benzenesulfonamide (46). The title compound was prepared using the general procedure 3. The sulfonyl chloride was synthesised from the sulfonic acid 52 (186 mg, 0.63 mmol) and SOCl₂ (5.0 mL, 69 mmol). The sulfonyl chloride (0.63 mmol), aniline 15 (140 mg, 0.76 mmol) and Cs₂CO₃ (986 mg, 3.02 mmol) after heating for 1 day afforded the product 46 as a yellow oil (239 mg, 89%); Rf: 0.19 (10% MeOH: 90% DCM); IR (neat, cm⁻¹): 3078, 1676, 1592, 1489, 1339, 1202, 1162, 1120, 771; ¹H NMR (600 MHz, MeOD- d_4) δ 7.67 (d, J = 8.9 Hz, 2H), 7.37-7.31 (m, 2H), 7.16 (t, J = 8.1 Hz, 1H), 7.13 (tt, J = 8.1, 1.1 Hz, 1H), 7.01 (d, J = 8.9 Hz, 2H), 6.90-6.86 (m, 2H), 6.81 (ddd, J = 8.1, 2.1, 0.9 Hz, 1H), 6.70 (t, J = 2.2 Hz, 1H), 6.64 (ddd, J = 8.1, 2.1, 0.9 Hz, 1H), 4.15 (t, J = 5.7 Hz, 2H), 3.36-3.32 (m, 2H), 2.93 (s, 6H), 2.28-2.19 (m, 2H); ¹³C NMR $(151 \text{ MHz}, \text{MeOD-}d_4) \delta 163.29, 159.43, 158.07, 140.63, 132.91,$ 131.28, 130.91, 130.48, 124.74, 120.13, 116.35, 115.70, 115.39, 111.66, 66.37, 56.54, 43.61, 25.54; ¹⁹F NMR (376 MHz, MeOD d_4) δ -76.55; HRMS (APCI): m/z calcd $C_{23}H_{26}O_4N_2S$ 426.1608 $[M]^+$, found, 426.161; $C_{23}H_{27}O_4N_2S$ 427.1683 $[M + H]^+$, found, 427.1684.

4-(3-(Dimethylamino)propoxy)-N-(3-(4-fluorophenoxy) phenyl)benzenesulfonamide (47). The title compound was prepared using the general procedure 3. The sulfonyl chloride was synthesised from the sulfonic acid 52 (380 mg, 1.29 mmol) and SOCl₂ (6.0 mL, 82 mmol). The sulfonyl chloride (1.29 mmol), aniline 16 (284 mg, 1.40 mmol) and Cs₂CO₃ (2.10 g, 6.44 mmol) after heating for 1 day afforded the product 47 as a brown oil (515.8 mg, 90%); Rf: 0.20 (10% MeOH: 90% DCM); IR (neat, cm⁻¹): 3077, 2888, 1672, 1594, 1496, 1339, 1200, 1120, 1086, 773; ¹H NMR (501 MHz, MeOD d_4) δ 7.67 (d, J = 8.9 Hz, 2H), 7.16 (t, J = 8.1 Hz, 1H), 7.11-7.03 (m, 2H), 7.01 (d, J = 8.9 Hz, 2H), 6.92-6.85 (m, 2H), 6.81 (ddd, J = 8.1, 2.1, 0.9 Hz, 1H), 6.67 (t, J = 2.1 Hz, 1H), 6.64 (ddd, J = 8.1, 2.1, 0.9 Hz, 1H), 4.15 (t, J = 5.8 Hz, 2H), 3.37-3.32 (m, 2H), 2.93 (s, 6H), 2.29–2.17 (m, 2H); ¹³C NMR (126 MHz, MeOD- d_4) δ 163.31, 160.39 (d, J = 240.7 Hz), 159.75, 154.00 (d, J = 2.5 Hz), 140.65, 133.01, 131.33, 130.45, 121.89 (d, J = 8.3 Hz), 117.29 (d, J = 23.6 Hz), 116.48, 115.74, 115.06, 111.37, 66.41, 56.57, 43.65, 25.54; ¹⁹F NMR (377 MHz, MeOD d_4) δ -76.55, -121.33; HRMS (APCI): m/z calcd C₂₃H₂₅O₄N₂FS 444.1514 [M]⁺, found, 444.1516; C₂₃H₂₇O₄N₂FS 445.1592 [M + H]⁺, found, 445.159.

4-(3-(Dimethylamino)propoxy)-*N*-(4-phenoxyphenyl) benzenesulfonamide (48). The title compound was prepared using the general procedure 3. The sulfonyl chloride was synthesised from the sulfonic acid 52 (148 mg, 0.50 mmol) and SOCl₂ (3.0 mL, 41 mmol). The sulfonyl (0.50 mmol), aniline 17 (105 mg, 0.57 mmol) and Cs_2CO_3 (826 mg, 2.54 mmol) after heating for 1 day afforded the product 48 as a cream solid (176 mg, 82%); $R_{\rm f}$: 0.19 (10% MeOH: 90% DCM); IR (neat, cm⁻¹): 3047, 1670, 1488, 1331, 1245, 1150, 831; ¹H NMR (501 MHz, MeOD- d_4) δ 7.77–7.71 (m, 2H), 7.41–7.35 (m, 2H), 7.18–7.10 (m, 3H), 7.10–7.05 (m, 2H), 7.00–6.94 (m, 2H), 6.91–6.86 (m, 2H), 4.21 (t, J = 5.8 Hz, 2H), 3.45–3.36 (m, 2H), 3.00 (s, 6H), 2.39–2.27 (m, 2H); ¹³C NMR (126 MHz, MeOD d_4) δ 161.88, 157.19, 154.58, 132.78, 131.53, 129.47, 129.04, 123.56, 123.03, 118.89, 118.25, 114.30, 65.06, 55.09, 42.25, 24.09; ¹⁹F NMR (376 MHz, MeOD- d_4) δ –76.55; HRMS (APCI): m/z calcd C₂₃H₂₆O₄N₂S 426.1608 [M]⁺, found, 426.1609; C₂₃-H₂₇O₄N₂S 427.1686 [M + H]⁺, found, 427.1683.

4-(3-(Dimethylamino)propoxy)-N-(4-(4-fluorophenoxy) phenyl)benzenesulfonamide (49). The title compound was prepared using the general procedure 3. The sulfonyl chloride was synthesised from the sulfonic acid 52 (379 mg, 1.28 mmol) and SOCl₂ (6.0 mL, 82 mmol). The sulfonyl chloride (1.28 mmol), aniline 18 (280, 1.38 mmol) and Cs₂-CO₃ (2.623 g, 8.05 mmol) after heating for 1 day afforded the product 49 as a white solid (495 mg, 87%); Rf: 0.19 (10% MeOH: 90% DCM); IR (neat, cm⁻¹): 3072, 1671, 1494, 1331, 1255, 1190, 1151, 831; ¹H NMR (501 MHz, MeOD- d_4) δ 7.70 (d, J = 8.8 Hz, 2H), 7.15-7.04 (m, 4H), 7.02 (d, J = 8.8 Hz, 2H),6.82 (d, J = 8.9 Hz, 2H), 6.86-6.77 (m, 2H), 4.16 (t, J = 5.8 Hz, 2H), 3.43–3.30 (m, 2H), 2.97 (s, 6H), 2.25–2.22 (m, 2H); ¹³C NMR (126 MHz, MeOD- d_4) δ 163.22, 160.15 (d, J = 240.7 Hz), 156.27, 154.35 (d, J = 2.8 Hz), 134.08, 132.81, 130.38, 124.93, 121.42 (d, J = 8.4 Hz), 119.80, 117.22 (d, J = 23.6 Hz), 115.68, 66.38, 56.48, 43.63, 25.46; 19 F NMR (376 MHz, MeOD- d_4) δ -76.55, -121.84; HRMS (APCI): m/z calcd C₂₃H₂₅O₄N₂FS 444.1514 [M]⁺, found, 444.1515; C₂₃H₂₇O₄N₂FS 445.1592 [M + H]⁺, found, 445.159.

4-(3-(Dimethylamino)propoxy)-N-(4-(4-(trifluoromethyl)

phenoxy)phenyl)benzenesulfonamide (50). The title compound was prepared using the general procedure 3. The sulfonyl chloride was synthesised from the sulfonic acid 52 (240 mg, 0.81 mmol) and SOCl₂ (3.0 mL, 41 mmol). The sulfonyl chloride (0.81 mmol), aniline 19 (275, 1.09 mmol) and Cs₂CO₃ (1.36 g, 4.19 mmol) after heating for 1 day afforded the product 50 as a light brown oil (381 mg, 94%); $R_{\rm f}$: 0.19 (10% MeOH: 90% DCM); IR (neat, cm⁻¹): 3054, 1671, 1595, 1499, 1324, 1249 1151, 1105, 832; ¹H NMR (600 MHz, MeOD- d_4) δ 7.70 (d, J = 8.9 Hz, 2H), 7.61 (d, J = 9.0 Hz, 2H), 7.12 (d, J = 8.9 Hz, 2H), 7.05–6.99 (m, 4H), 6.93 (d, J = 8.9 Hz, 2H), 4.15 (t, J = 5.8 Hz, 2H), 3.36-3.32 (m, 2H), 2.93 (s, 6H), 2.27–2.19 (m, 2H); ¹³C NMR (151 MHz, MeOD- d_4) δ 163.28, 162.22, 153.96, 135.69, 133.04, 130.47, 128.27 (q, J = 3.8 Hz), 125.82 (q, J = 32.6 Hz), 125.70 (q, J = 270.5 Hz), 124.62, 121.72, 118.72, 115.68, 66.37, 56.55, 43.61, 25.54; ¹⁹F NMR (376 MHz, MeOD- d_4) δ -63.14, -76.55; HRMS (APCI): m/zcalcd C₂₄H₂₅O₄N₂F₃S 494.1482 [M]⁺, found, 494.1482; C₂₄H₂₆- $O_4N_2F_3S$ 495.156 [M + H]⁺, found, 495.155.

N-(4-(4-Cyanophenoxy)phenyl)-4-(3-(dimethylamino)

propoxy)benzenesulfonamide (51). The title compound was prepared using the general procedure 3. The sulfonyl chloride was synthesised from the sulfonic acid 52 (272 mg, 0.92 mmol) and SOCl₂ (5.0 mL, 69 mmol). The sulfonyl

chloride (0.92 mmol), aniline **20** (201, 0.96 mmol) and Cs₂-CO₃ (1.71 g, 5.24 mmol) after heating for 1 day afforded the product 51 as a yellow solid (381 mg, 92%); R_f : 0.19 (10% MeOH:90% DCM); IR (neat, cm⁻¹): 3047, 2227, 1670 1596, 1494, 1334, 1245, 1155, 1094, 832; ¹H NMR (600 MHz, MeOD- d_4) δ 7.73 (d, J = 8.7 Hz, 2H), 7.69 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 8.9 Hz, 2H), 7.05 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.9 Hz, 2H), 4.17 (t, J = 5.8 Hz, 2H), 3.39–3.34 (m, 2H), 2.96 (s, 6H), 2.31–2.21 (m, 2H); ¹³C NMR (151 MHz, MeOD- d_4) δ 163.30, 163.16, 153.15, 136.16, 135.43, 132.96, 130.46, 124.52, 122.12, 119.63, 118.90, 115.70, 106.84, 66.38, 56.53, 43.61, 25.53; ¹⁹F NMR (376 MHz, MeOD- d_4) δ -76.55; HRMS (APCI): m/z calcd C₂₄H₂₅O₄N₃S 452.1639 [M + H]⁺, found, 452.1629.

Biology

Calcium influx bioassays. The bioactivity of the test drugs and inhibition control NNC 55-0396 (Alomone, Jerusalem, Israel) were evaluated by calcium influx assays using the Fluorescence-Imaging Plate Reader Tetra (FLIPR^{TETRA}, Molecular Devices, CA, USA). Calcium influx measures were used for the evaluation of Cav2.2 channels and Cav3.2 channel assay. Endogenously expressed in the neuroblastoma SH-SY5Y and HEK 293 T cells expressing recombinant human $Ca_v 3.2 \alpha_1$ subunit were used for $Ca_v 2.2$ and $Ca_v 3.2$ channel assay, respectively. The HEK 293T were obtained from American type culture collection (ATCC) and the SH-SY5Y human neuroblastoma cells were a kind gift from Victor Diaz (Max Planck Institute for Experimental Medicine, Goettingen, Germany). Briefly, neuroblastoma SH-SY5Y and HEK 293 T cells were seeded at 40 000 and 10 000 cells per well, respectively, in 384-well flat clear-bottom black plates (Corning, NY, USA) and cultured at 37 °C in a humidified 5% CO2 incubator 48 h before assay. Cells were loaded with 20 µL per well of calcium 6 dye (Molecular Devices) reconstituted in assay buffer containing (in mM) 140 NaCl, 11.5 glucose, 5.9 KCl, 1.4 MgCl₂, 1.2 NaH₂PO₄, 5 NaHCO₃, 1.8 CaCl₂,10 HEPES pH 7.4 and 0.1% bovine serum albumin (BSA, Sigma), and incubated for 30 min at 37 °C in a humidified 5% CO₂ incubator. For Ca_v2.2 assays, nifedipine 10 µM (Cav1 blocker) was added to the dye solution. The Ca²⁺ fluorescence responses were recorded at excitation 470– 495 nm and emission 515-575 nm for 10 s to set the baseline, 300 s after addition of compound and for further 300 s after channel activation induced by the addition of 90 mM KCl and 5 mM CaCl2 for Cav2.2, or 40 mM KCl and 5 mM CaCl₂ for Ca_v3.2. Compound stock solutions were prepared at 100 mM in 100% DMSO and diluted further in the assay buffer to 1% DMSO, for the highest tested concentration of 100 µM of compound, and serial-diluted 3-fold in assay buffer.

The maximum or maximum-minimum fluorescence signals were used to calculate the half-maximum inhibition effect (IC_{50}). Curve fitting was achieved using GraphPad Prism Version 10 (GraphPad Software Inc, San Diego, CA,

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USA) with non-linear regression with log[inhibitor] *versus* normalized response and variable Hill slope for doseresponses. Data were represented as mean \pm 95% CI and SEM from n = 3-5 independent experiments.

Rat plasma stability assessments. Rat plasma sourced from Sprague Dawley was purchased from Monash Animal Research Platform (MARP) and stored at -80 °C. Samples were defrosted at room temperature prior to usage.

Rat plasma (4 mL) was transferred into an Eppendorf tube and incubated at 37 °C for 15 min. An aliquot of the incubated rat plasma (995 µL) was transferred to an Eppendorf tube containing a solution of the test compound and internal standard (5 µL of solution: 30 mM test compound and 25 mM diazepam in DMSO). The final concentration of the test compound and diazepam in plasma was 150 and 125 μ M respectively (n = 3). The compoundplasma mixtures were incubated at 37 °C. At timed intervals of 0, 5, 15, 30, 45, 60, 75, 90, 105, 120, 180 and 3600 min, aliquots (50 µL) of each incubate were removed and acetonitrile (50 µL) was added immediately. For the sulfonamide compounds, the samples were vortexed, diluted with H₂O (150 µL), vortexed again and cooled on ice for 30 min whilst the phenoxyaniline compounds were vortex and placed immediately on ice for 30 min. The samples were centrifuged for 15 min at 14000 rpm and the supernatant collected and analysed by RP-HPLC. The ratio of the test compound to diazepam was calculated and the data normalised. The stability curves were plotted using GraphPad Prism 8.0.2. Curve fitting was done using "one-phase decay non-linear regression" to calculate the half-life $(t_{1/2})$.

Cytotoxicity studies. Cell culture: Cos-7 cells were cultured and maintained in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% heat inactivated foetal bovine serum, 1% penicillin–streptomycin and 1% glutamax (purchased from GibcoTM) at 37 °C in a 5% CO₂ incubator.

In vitro testing towards Cos-7 cells. The compounds were solubilised in DMSO to make up a 10 mM stock solution and sequentially diluted out in the DMEM culture media to give the final working concentrations ranging from 0.5–100 μ M. Assays were set up in triplicate in Falcon 96 well plates, where volumes of 10⁵ Cos-7 per mL were seeded and adhered to the 96 well plates 24 hours prior to compound addition. The Promega ™ CellTiter-Blue Cell Viability Assay was used for the determination of the percentage viability of Cos-7. The compound and Cos-7 cells were incubated for 20 h after which 20 μ L of CellTiter-Blue was added to each well in the 96 well plates, then incubated for a further 4 h for a total of 24 h incubation with compound. All cell assays were measured spectroscopically using fluorescence excitation at 544 nm and emission at 590 nm. The compounds were compared to a positive control of no compound and the percent inhibition calculated. Fluorescence measurements were conducted on a BMG-Labtech ClarioStar microplate reader. Experiments were conducted independently at least two times, with values averaged between the experiments. The dose-response curve was fitted using "log[compound] *versus* normalised response-variable slope" and the CC_{50} values calculated using GraphPad Prism (version 8.0.2).

Author contributions

Synthesis: AB, RW. Calcium influx bioassays: AB, FCC, MH, YD. Rat plasma stability and cytotoxicity: AB. Data analysis: AB, FCC, MH, YD, RJL. Manuscript preparation: AB, PJD, KLT. Project conception and supervision: PJD, KLT.

Conflicts of interest

There are no conflicts to declare.

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