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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 guanidinium 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 $Ca_V2.2$ 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.

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 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 $Ca_V2.2$ (N-type) calcium ion channel blockers for the treatment of neuropathic pain.[9–27] Likewise, various research studies have shown that the $Ca_V3.2$ (T-type) voltage-gated calcium channel is also a promising therapeutic target for alleviating neuropathic pain.[24–26,28–33]

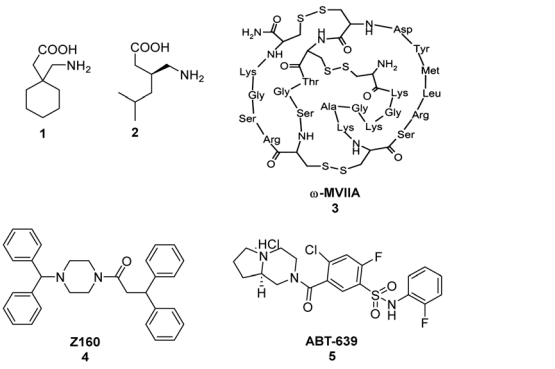

Fig. 1 Structures of gabapentin **1**, pregabalin **2**, ω-conotoxin MVIIA **3**,[7] marketed as ziconotide (Prialt®), Z160 **4** and ABT-639 **5**.

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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 state-dependent $Ca_V2.2$ 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 $Ca_V3.2$ 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 $Ca_V2.2$ and $Ca_V3.2$ 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 patch clamp electrophysiology experiments showed that MONIRO-1 **6a** demonstrated good selectivity for $Ca_V2.2$ (IC_{50} = 34 μM) and $Ca_V3.2$ (IC_{50} = 1.7 μM) 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 $Ca_V2.2$ 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 $Ca_V2.2$ channel was similar to MONIRO-1 **6a** and analogues, the restriction of rotation in most cases led to a decrease in activity for the $Ca_V3.2$ channel.[22] The acylated phenoxazine **8** was observed to rapidly hydrolyse in rat plasma ($t_{\frac{1}{2}}$ = 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 $Ca_V2.2$ 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 $Ca_V2.2$ and $Ca_V3.2$ 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 $Ca_V2.2$ and $Ca_V3.2$ channels of 54 compounds (Fig. 3), and for a representative subset, their plasma stability and an evaluation of their cytotoxicity.

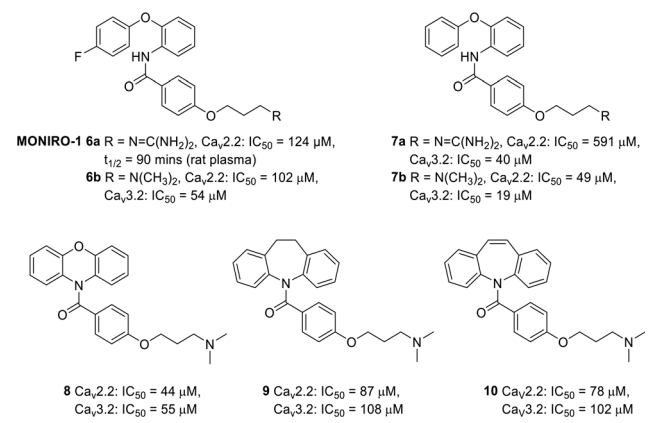


Fig. 2 Chemical structures and their activity, determined by calcium influx fluorescence-imaging assays, of MONIRO-1 **6a**, and related analogues **6b**, **7a** and **7b**, and the constrained analogues **8–10**.

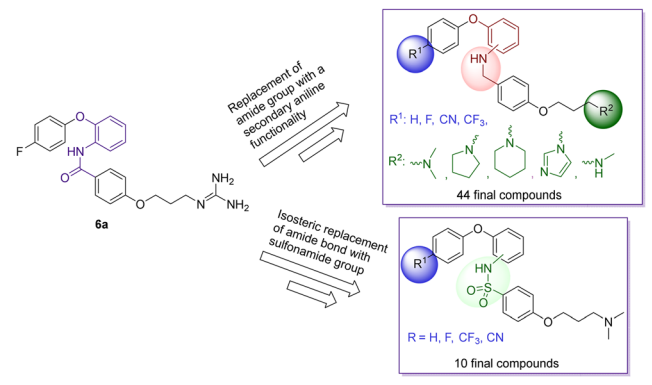
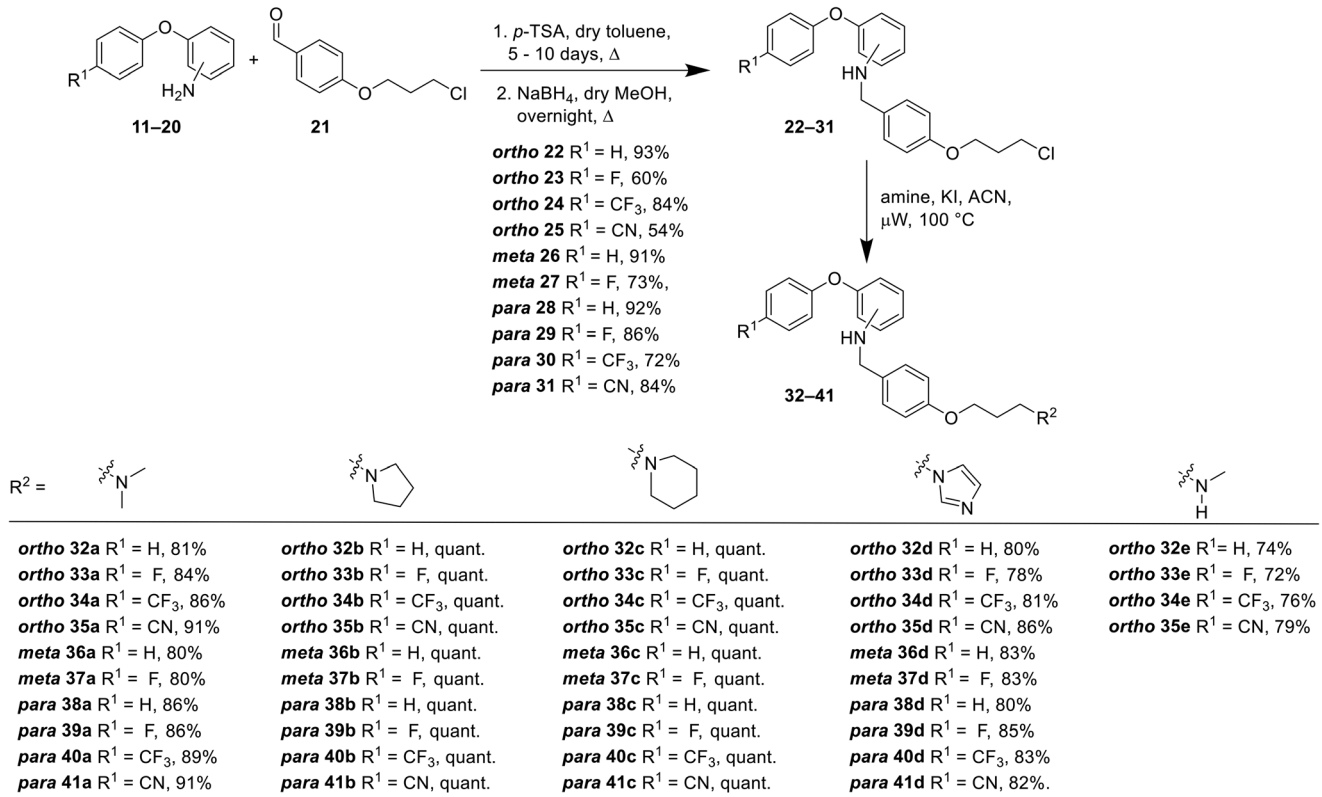


Fig. 3 Schematic depiction of the library of compounds synthesised and tested; replacement of the labile amide bond of MONIRO-1 **6a** with either a secondary aniline or an isosteric sulfonamide functional group, and replacement of the guanidinium group with less hydrophilic amines.



***ortho* 22** R^1 = H, 93%
***ortho* 23** R^1 = F, 60%
***ortho* 24** R^1 = CF_3, 84%
***ortho* 25** R^1 = CN, 54%
***meta* 26** R^1 = H, 91%
***meta* 27** R^1 = F, 73%,
***para* 28** R^1 = H, 92%
***para* 29** R^1 = F, 86%
***para* 30** R^1 = CF_3, 72%
***para* 31** R^1 = CN, 84%

***ortho* 32a** R^1 = H, 81%	***ortho* 32b** R^1 = H, quant.	***ortho* 32c** R^1 = H, quant.	***ortho* 32d** R^1 = H, 80%	***ortho* 32e** R^1= H, 74%
***ortho* 33a** R^1 = F, 84%	***ortho* 33b** R^1 = F, quant.	***ortho* 33c** R^1 = F, quant.	***ortho* 33d** R^1 = F, 78%	***ortho* 33e** R^1 = F, 72%
***ortho* 34a** R^1 = CF_3, 86%	***ortho* 34b** R^1 = CF_3, quant.	***ortho* 34c** R^1 = CF_3, quant.	***ortho* 34d** R^1 = CF_3, 81%	***ortho* 34e** R^1 = CF_3, 76%
***ortho* 35a** R^1 = CN, 91%	***ortho* 35b** R^1 = CN, quant.	***ortho* 35c** R^1 = CN, quant.	***ortho* 35d** R^1 = CN, 86%	***ortho* 35e** R^1 = CN, 79%
***meta* 36a** R^1 = H, 80%	***meta* 36b** R^1 = H, quant.	***meta* 36c** R^1 = H, quant.	***meta* 36d** R^1 = H, 83%	
***meta* 37a** R^1 = F, 80%	***meta* 37b** R^1 = F, quant.	***meta* 37c** R^1 = F, quant.	***meta* 37d** R^1 = F, 83%	
***para* 38a** R^1 = H, 86%	***para* 38b** R^1 = H, quant.	***para* 38c** R^1 = H, quant.	***para* 38d** R^1 = H, 80%	
***para* 39a** R^1 = F, 86%	***para* 39b** R^1 = F, quant.	***para* 39c** R^1 = F, quant.	***para* 39d** R^1 = F, 85%	
***para* 40a** R^1 = CF_3, 89%	***para* 40b** R^1 = CF_3, quant.	***para* 40c** R^1 = CF_3, quant.	***para* 40d** R^1 = CF_3, 83%	
***para* 41a** R^1 = CN, 91%	***para* 41b** R^1 = CN, quant.	***para* 41c** R^1 = CN, quant.	***para* 41d** R^1 = CN, 82%.	

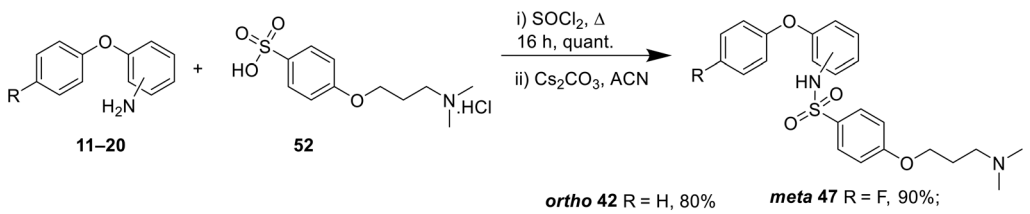
Scheme 1 Synthesis of the phenoxyaniline analogues **32**–**41**.

Results and discussion

Chemistry – compound design and synthesis

For all compounds, substituents on the aromatic phenoxy ring (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 (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



***ortho* 42** R = H, 80%
***ortho* 43** R = F, 81%
***ortho* 44** R = CF_3, 34%
***ortho* 45** R = CN, 30%
***meta* 46** R = H, 89%;
***meta* 47** R = F, 90%;
***para* 48** R = H, 82%
***para* 49** R = F, 87%
***para* 50** R = CF_3, 95%
***para* 51** R = CN, 92%

Scheme 2 Synthesis of the sulfonamide analogues **42**–**51**.

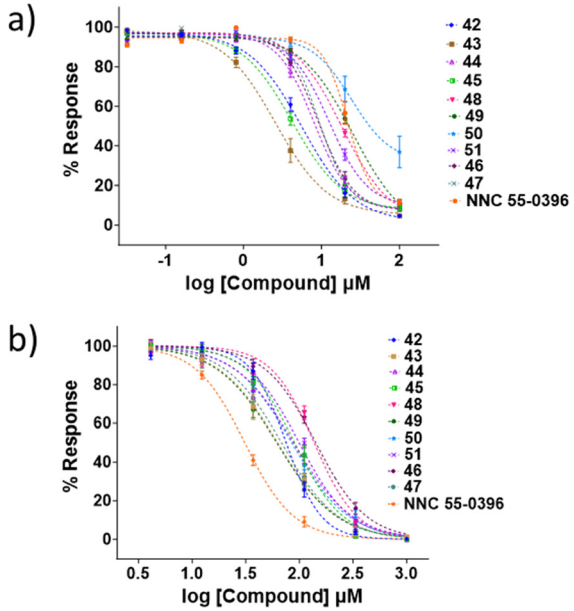


Fig. 4 Dose response curves, determined by calcium influx fluorescence-imaging assays of the sulfonamide compounds **42**–**51** in a) *h*$Ca_V2.2$ and b) *h*$Ca_V3.2$ channels. Data are presented as mean ± SEM from *n* = 3–5 independent experiments. The calculated IC_{50} values are shown in the relevant 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 ^{19}F NMR spectroscopic analysis as described in detail in the ESI.†

Biology – $Ca_V2.2$ and $Ca_V3.2$ 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 IC_{50} 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

Table 1 Functional inhibition of the calcium channels *h*$Ca_V2.2$ and *h*$Ca_V3.2$ 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 ± SEM and 95% CI from *n* = 3–5 independent experiments

	$Ca_V2.2$			$Ca_V3.2$				$Ca_V2.2$			$Ca_V3.2$		
Compd.	IC_{50} (μM)	SEM	95% CI (μM)	IC_{50} (μM)	SEM	95% CI (μM)	Compd.	IC_{50} (μM)	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 2 Functional inhibition of the calcium channels *h*$Ca_V2.2$ and *h*$Ca_V3.2$ by the pyrrolidine- and piperidine-based phenoxyaniline analogues **32b/c–41b/c**. Data are presented as mean ± SEM and 95% CI from *n* = 3–5 independent experiments

	$Ca_V2.2$			$Ca_V3.2$				$Ca_V2.2$			$Ca_V3.2$		
Compd.	IC_{50} (μM)	SEM	95% CI (μM)	IC_{50} (μM)	SEM	95% CI (μM)	Compd.	IC_{50} (μM)	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 *h*$Ca_V2.2$ and *h*$Ca_V3.2$ by the imidazole-based phenoxyanilines **32d–41d**. Data are presented as mean ± SEM and 95% CI from *n* = 3–5 independent experiments

	$Ca_V2.2$			$Ca_V3.2$				$Ca_V2.2$			$Ca_V3.2$		
Compd.	IC_{50} (μM)	SEM	95% CI (μM)	IC_{50} (μM)	SEM	95% CI (μM)	Compd.	IC_{50} (μM)	SEM	95% CI (μM)	IC_{50} (μM)	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
33d	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
35d	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 *h*$Ca_V2.2$ and *h*$Ca_V3.2$, and their estimated therapeutic index (TI) at the $Ca_V2.2$ and $Ca_V3.2$ channel

	CC_{50}	$Ca_V2.2$		$Ca_V3.2$	
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 μM 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 $Ca_V2.2$ 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 $Ca_V2.2$ channel. Similarly, for the –F imidazole-based analogues, the *ortho*-derivative **33d** was 2-fold more active at the $Ca_V2.2$ 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 $Ca_V2.2$ 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 $-CF_3$ (**34c** and **40c**) piperidine-based analogues regardless of the substitution of the aniline group when compared to the corresponding unsubstituted compound (R^1 = 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 piperidine-based phenoxyanilines, the affinity for the $Ca_V2.2$ channel generally increased as the electron-withdrawing nature of R^1 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 $Ca_V2.2$ channel for both the –F **33d** and –CN **35d** compounds *versus* the unsubstituted derivative **32c**. However, the additional HBA properties of the $-CF_3$ 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 $Ca_V2.2$ channel. The mono-methylated 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 R^2 resulted in compounds (**32b**/**c–41b**/**c**) with improved binding affinity for the $Ca_V2.2$ 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, R^2 was critical for binding to the $Ca_V2.2$ channel. With regards to the $Ca_V3.2$ channel, the phenoxyanilines were overall inactive at this channel, however, the results obtained for the $-CF_3$ **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 $Ca_V2.2$ 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 $Ca_V2.2$ channel, with IC_{50} 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 $Ca_V2.2$ 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 $Ca_V3.2$ channel. Whilst the sulfonamide analogues showed higher potency against the $Ca_V3.2$ 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 (**7b** 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 $Ca_V2.2$ 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 electron-withdrawing substituent particularly the –CN group can potentially improve the potency for the $Ca_V2.2$ channel, whilst, an increase in the HBA properties may result in a decrease in activity for the receptor as seen in the imidazole-based $–CF_3$ derivatives. The affinity of the piperidine-based phenoxyaniline compounds particularly the –CN derivatives **35c** and **41c** for both the $Ca_V2.2$ and $Ca_V3.2$ 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 $Ca_V3.2$ 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 $Ca_V2.2$ blockers developed in our research group to date. Considering the $Ca_V2.2$ 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 (^{1}H NMR), carbon-13 nuclear magnetic resonance (^{13}C NMR) and fluorine-19 (^{19}F NMR) were recorded on a Bruker DRX400 spectrometer operating at 400 MHz (^{1}H), 100 MHz (^{13}C) and 376 MHz (^{19}F), Bruker DRX600 operating at 600 MHz (^{1}H) and 151 MHz (^{13}C) or Bruker AV500P spectrophotometer operating at 500 MHz (^{1}H) and 126 MHz (^{13}C), 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 5000–10 000 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. Air-sensitive reactions were performed under an atmosphere of N_2 using a standard Schlenk line and glassware for moisture-sensitive 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 × 21.5 mm, 5 μm), buffer A – 100% MilliQ H_2O/0.1% TFA and buffer B – 80% ACN/20% MilliQ H_2O /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 N_2 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*, $NaBH_4$ (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 × 60 mL). The organic layers were combined, washed with brine (80 mL), dried over Na_2SO_4 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 N_2. The product was purified by column chromatography using neutral alumina (3% MeOH : 40% $CHCl_3$: 57% petroleum benzine). A portion was purified by preparative RP–HPLC to obtain an analytically pure sample for biological studies and the ^1H,^{13}C and ^{19}F 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, K_2CO_3, 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 N_2. 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,^{13}C and ^{19}F 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 N_2 and the compound was purified by column chromatography using neutral alumina (3% MeOH : 30% $CHCl_3$: 67% petroleum benzine). A portion was purified by preparative RP–HPLC to obtain an analytically pure sample for biological studies. The ^1H and ^{13}C NMR spectra of the compound was recorded while the ^{19}F NMR spectrum of the TFA salt was recorded.

General procedure 3: synthesis of sulfonamide compounds. A mixture of the sulfonic acid **52** and $SOCl_2$ 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. $SOCl_2$ was removed under a stream of N_2 to yield the corresponding sulfonyl chloride in a quant. conversion. A mixture of the sulfonyl chloride, aniline **3–12**, Cs_2CO_3 and dry ACN (10 mL) was heated at 70 °C under N_2 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 × 50 mL). The organic layers were combined, dried over Na_2SO_4 and the solvent removed *in vacuo*. The compound was purified by column chromatography on neutral alumina (3% MeOH : 50% $CHCl_3$: 47% petroleum benzine). A portion was purified by preparative RP–HPLC to obtain an analytically pure sample biological studies and the ^1H,^{13}C and ^{19}F 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 $NaBH_4$ (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%); R_f: 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, $CDCl_3$-*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); ^{13}C NMR (101 MHz, $CDCl_3$) 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 $C_{22}H_{23}ClNO_2$ $[M + H]^+$ 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 $NaBH_4$ (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%); R_f: 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, $CDCl_3$-*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); ^{13}C NMR (101 MHz, $CDCl_3$-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; ^{19}F NMR (376 MHz, $CDCl_3$-d) δ −121.56; HRMS (APCI): m/z calcd $C_{22}H_{22}O_2NClF$ $[M + H]^+$ 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 $NaBH_4$ (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_f: 0.26 (7% EtOAc : 93% petroleum benzine); IR (neat, cm^{-1}): 3444, 3419, 2927, 1608, 1511, 1330, 1238, 1165, 1101, 1068, 836, 740; ^{1}H 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, $CDCl_3$-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; ^{19}F NMR (377 MHz, $CDCl_3$) δ −62.17; HRMS (APCI): m/z calcd $C_{23}H_{21}O_2NClF_3$ $[M]^+$ 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 $NaBH_4$ (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 ($CDCl_3$, cm^{-1}): 3411, 2931, 2225, 1602, 1501, 1230, 1163, 1036, 907, 834, 797; ^{1}H 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, $CDCl_3$) 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 $C_{23}H_{22}O_2N_2Cl$ $[M]^+$ 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 $NaBH_4$ (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_f: 0.33 (15% EtOAc : 85% petroleum benzine); IR (neat, cm^{-1}): 3400, 3061, 2881, 1615, 1578, 1505, 1487, 1240, 1215, 1145, 818, 752; ^{1}H NMR (400 MHz, $CDCl_3$-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); ^{13}C NMR (101 MHz, $CDCl_3$) 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 $C_{22}H_{22}ClNO_2$ $[M]^+$ 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 $NaBH_4$ (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%); R_f: 0.28 (15% EtOAc : 85% petroleum benzine); IR (neat, cm^{-1}): 3398, 2884, 1603, 1579, 1495, 1446, 1232, 1197, 1047, 828; ^{1}H NMR (400 MHz, $CDCl_3$-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); ^{13}C 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; ^{19}F NMR (376 MHz, $CDCl_3$-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 $NaBH_4$ (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%); R_f: 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; ^{1}H NMR (400 MHz, $CDCl_3$-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); ^{13}C NMR (101 MHz, $CDCl_3$) 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 $NaBH_4$ (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_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; ^{1}H NMR (400 MHz, $CDCl_3$-*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); ^{13}C NMR (101 MHz, $CDCl_3$-*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; ^{19}F NMR (376 MHz, $CDCl_3$-*d*) δ −122.70; HRMS (APCI): *m*/*z* calcd $C_{22}H_{22}O_2NClF$ $[M + H]^+$ 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 $NaBH_4$ (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_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; ^{1}H NMR (400 MHz, $CDCl_3$-*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}C NMR (101 MHz, $CDCl_3$-*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; ^{19}F NMR (377 MHz, $CDCl_3$) 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 $NaBH_4$ (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; ^{1}H 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); ^{13}C NMR (101 MHz, $CDCl_3$) 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 $C_{23}H_{22}O_2N_2Cl$ $[M]^+$ 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_f: 0.37 (10% MeOH : 90% DCM); IR (neat, cm^{-1}): 3425, 2942, 2765, 1608, 1509, 1215, 1173, 1035, 822, 739, 691; ^{1}H 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); ^{13}C 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; ^{19}F 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, 377.2214.

***N*-(4-(3-(Dimethylamino)propoxy)benzyl)-2-(4-fluorophenoxy)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%); R_f: 0.34 (10% MeOH : 90% DCM); IR (neat, cm^{-1}): 3424, 1672, 1499, 1195, 1173, 1123, 829, 720; ^{1}H NMR (400 MHz, MeOD-d_4) 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); ^{13}C 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; ^{19}F NMR (377 MHz, MeOD-d_4) δ −123.70, −76.55; HRMS (APCI): *m*/*z* calcd $C_{24}H_{28}N_2O_2F$ $[M + H]^+$ 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 ^{1}H, ^{13}C and ^{19}F 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, 1 064 829, 799, 720; ^{1}H 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); ^{13}C NMR (151 MHz, MeOD-d_4) 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; ^{19}F NMR (376 MHz, MeOD-d_4) δ −62.87; HRMS (APCI): *m*/*z* calcd $C_{25}H_{28}N_2O_2F_3$ $[M + H]^+$ 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 ^{1}H, ^{13}C and ^{19}F NMR spectra of the TFA salt was recorded; R_f: 0.32 (10% MeOH : 90% DCM); IR

(neat, cm^{-1}): 3420, 2968, 2226, 1678, 1610, 1512, 1236, 1171, 1130, 1056, 832, 721; ^{1}H 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); ^{13}C 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; ^{19}F NMR (376 MHz, MeOD-d_4) δ −76.55; HRMS (APCI): m/z calcd $C_{25}H_{28}N_3O_2$ $[M + H]^+$ 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%); R_f: 0.30 (10% MeOH : 90% DCM); IR (neat, cm^{-1}): 3409, 2941, 2765, 1581, 1486, 1216, 1148, 1005, 823, 754, 688; ^{1}H NMR (400 MHz, MeOD-d_4) 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 Hz, 2H), 2.26 (s, 6H), 1.99–1.86 (m, 2H); ^{13}C 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; ^{19}F 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%); R_f: 0.29 (10% MeOH : 90% DCM); IR (MeOH, cm^{-1}): 3405, 2969, 1672, 1608, 1498, 1195, 1128, 1027, 830, 799, 721; ^{1}H 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 $C_{24}H_{28}N_2O_2F$ $[M + H]^+$ 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_f: 0.29 (10% MeOH : 90% DCM); IR (neat, cm^{-1}): 3250, 2957, 2825, 1612, 1510, 1498, 1227, 1041, 1005, 831, 746, 689; ^{1}H NMR (400 MHz, $CDCl_3$-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); ^{13}C NMR (101 MHz, $CDCl_3$) 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; ^{19}F 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%); R_f: 0.28 (10% MeOH : 90% DCM); IR (neat, cm^{-1}): 3247, 2959, 2777, 1609, 1495, 1239, 1205, 1177, 1007, 822, 722, 670; ^{1}H NMR (400 MHz, $CDCl_3$-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); ^{13}C NMR (101 MHz, $CDCl_3$-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; ^{19}F NMR (376 MHz, $CDCl_3$) δ −122.20; HRMS (APCI): m/z calcd $C_{24}H_{28}N_2O_2F$ $[M + H]^+$ 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%); R_f: 0.28 (10% MeOH : 90% DCM); IR (neat, cm^{-1}): 3251, 2958, 2826, 1677, 1504, 1326, 1237, 1156, 1104, 1065, 1008, 831, 721; ^{1}H 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); ^{13}C NMR (151 MHz, $CDCl_3$-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; ^{19}F NMR (377 MHz, MeOD-d_4) δ −76.55, −62.99; HRMS (APCI): m/z calcd $C_{25}H_{28}N_2O_2F_3$ $[M + H]^+$ 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 ^{1}H, ^{13}C and ^{19}F NMR spectra of the TFA salt was recorded; R_f: 0.29 (10% MeOH : 90% DCM); IR (neat, cm^{-1}): 3348, 2963, 2225, 1666, 1610, 1494, 1240, 1167, 1124, 1056, 828, 708, 720; ^{1}H 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); ^{13}C 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; ^{19}F NMR (376 MHz, MeOD-d_4) δ −76.55; HRMS (APCI): m/z calcd $C_{25}H_{28}N_3O_2$ $[M + H]^+$ 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), K_2CO_3 (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; R_f: 0.15 (5% MeOH : 95% DCM); IR (MeOH, cm^{-1}): 3423, 2926, 1672, 1608, 1510, 1198, 1125, 829, 746, 721; ^{1}H 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); ^{13}C 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; ^{19}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, 403.2372.

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), K_2CO_3 (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; ^{1}H 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); ^{13}C 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; ^{19}F 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), K_2CO_3 (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_f: 0.30 (5% MeOH : 95% DCM); IR (neat, cm^{-1}): 3421, 1673, 1609, 1510, 1324, 1230, 1167, 1105, 1064, 829, 743, 720; ^{1}H 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); ^{13}C 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; ^{19}F NMR (376 MHz, MeOD-d_4) δ −62.54, −76.55; HRMS (APCI): m/z calcd $C_{27}H_{30}N_2O_2F_3$ $[M + H]^+$ 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_f: 0.16 (5% MeOH : 95% DCM); IR (neat, cm^{-1}): 3387, 2933, 2222, 1672, 1603, 1499, 1231, 1163, 1125, 833, 759, 718; ^{1}H 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); ^{13}C 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; ^{19}F 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), K_2CO_3 (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; ^{1}H NMR (400 MHz, MeOD-d_4) 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); ^{13}C 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; ^{19}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, 403.2375.

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; ^{1}H 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), 6.33 (t, J = 2.3 Hz, 1H), 4.28 (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); ^{13}C 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; ^{19}F NMR (376 MHz, MeOD-d_4) δ −76.55, −121.78; HRMS (APCI): m/z calcd $C_{26}H_{30}N_2O_2F$ $[M + H]^+$ 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), K_2CO_3 (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_f: 0.15 (5% MeOH : 95% DCM); IR (neat, cm^{-1}): 3389, 2952, 1656, 1610, 1510, 1227, 1178, 1129, 830, 755, 720, 688; ^{1}H 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); ^{13}C NMR (101 MHz, MeOD-d_4) 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}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), K_2CO_3 (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; ^{1}H 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); ^{13}C 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; ^{19}F 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), K_2CO_3 (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_f: 0.26 (5% MeOH : 95% DCM); IR (neat, cm^{-1}): 3357, 1665, 1613, 1506, 1324, 1235, 1160, 1106, 1064, 830, 799, 720; ^{1}H 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); ^{13}C 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; ^{19}F NMR (376 MHz, MeOD-d_4) δ −62.72; HRMS (APCI): m/z calcd $C_{27}H_{30}N_2O_2F_3$ $[M + H]^+$ 471.2254, found, 471.2250.

4-(4-((4-(3-(Pyrrolidin-1-yl)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), K_2CO_3 (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; R_f: 0.14 (5% MeOH : 95% DCM); IR (MeOH, cm^{-1}): 3358, 2954, 2223, 1656, 1601, 1493, 1242, 1171, 1130, 811, 799, 720; ^{1}H 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); ^{13}C 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; ^{19}F 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), K_2CO_3 (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_f: 0.16 (5% MeOH : 95% DCM); IR (neat, cm^{-1}): 3425, 2959, 1671, 1608, 1510, 1242, 1196, 1173, 1121, 798, 719, 692; ^{1}H 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); ^{13}C 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; ^{19}F 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, 417.2533.

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; ^{1}H 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); ^{13}C 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; ^{19}F 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), K_2CO_3 (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_f: 0.29 (5% MeOH : 95% DCM); IR (neat, cm^{-1}): 3425, 2951, 1671, 1609, 1510, 1325, 1230, 1165, 1105, 1064, 828, 742, 719; ^{1}H 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); ^{13}C 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; ^{19}F NMR (376 MHz, MeOD-d_4) δ −62.73, −76.55; HRMS (APCI): m/z calcd $C_{28}H_{32}N_2O_2F_3$ $[M + H]^+$ 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), K_2CO_3 (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; R_f: 0.37 (5% MeOH : 95% DCM); IR (neat, cm^{-1}): 3388, 2951, 2225, 1672, 1610, 1501, 1231, 1165, 1123, 828, 744, 719; ^{1}H 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); ^{13}C NMR (101 MHz, MeOD-d_4) 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; ^{19}F 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), K_2CO_3 (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_f: 0.16 (5% MeOH : 95% DCM); IR (neat, cm^{-1}): 3353, 2949, 1671, 1609, 1488, 1219, 1198, 1126, 830, 721, 691; ^{1}H 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); ^{13}C 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; ^{19}F 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), K_2CO_3 (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; R_f: 0.29 (5% MeOH : 95% DCM); IR (neat, cm^{-1}): 3343, 2950, 1671, 1605, 1494, 1240, 1195, 1125, 828, 720, 689; ^{1}H 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); ^{13}C 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; ^{19}F NMR (376 MHz, MeOD-d_4) δ −76.55, −122.77; HRMS (APCI): m/z calcd $C_{27}H_{32}N_2O_2F$ $[M + H]^+$ 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), K_2CO_3 (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_f: 0.26 (5% MeOH : 95% DCM); IR (neat, cm^{-1}): 3378, 2958, 1664, 1610, 1511, 1228, 1179, 1130, 830, 720, 689; ^{1}H 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); ^{13}C 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; ^{19}F 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, 417.2532.

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_f: 0.25 (5% MeOH : 95% DCM); IR (MeOH, cm^{-1}): 3347, 2951, 1672, 1608, 1495, 1242, 1198, 1130, 830, 800, 721; ^{1}H 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); ^{13}C 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; ^{19}F NMR (376 MHz, MeOD-d_4) δ −123.98; HRMS (APCI): m/z calcd $C_{27}H_{32}N_2O_2F$ $[M + H]^+$ 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), K_2CO_3 (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_f: 0.29 (5% MeOH : 95% DCM); IR (neat, cm^{-1}): 3356, 2953, 1665, 1606, 1505, 1324, 1236, 1160, 1105, 830, 800, 719; ^{1}H 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); ^{13}C NMR (151 MHz, MeOD-d_4) 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}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), K_2CO_3 (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; R_f: 0.25 (5% MeOH : 95% DCM); IR (neat, cm^{-1}): 3371, 2950, 2223, 1656, 1602, 1493, 1242, 1170, 1132, 822, 770, 721; ^{1}H 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); ^{13}C 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; ^{19}F 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 ^{1}H, ^{13}C and ^{19}F NMR spectra of the respective TFA salt of **32d** was recorded; R_f: 0.40 (5% MeOH : 95% DCM); IR (MeOH, cm^{-1}): 3418, 3148, 2509, 1671, 1607, 1509, 1201, 1130, 801, 743, 692; ^{1}H 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); ^{13}C 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; ^{19}F 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, 400.2017.

***N*-(4-(3-(1*H*-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%); R_f: 0.30 (5% MeOH : 95% DCM); IR (neat, cm^{-1}): 3420, 2933, 2877, 1607, 1498, 1231, 1195, 1108, 818, 738, 663; ^{1}H 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); ^{13}C 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; ^{19}F NMR (376 MHz, MeOD-d_4) δ −76.55, −122.20; HRMS (APCI): m/z calcd $C_{25}H_{25}N_3O_2F$ $[M + H]^+$ 418.1925, found, 418.1921.

***N*-(4-(3-(1*H*-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_f: 0.30 (5% MeOH : 95% DCM); IR (neat, cm^{-1}): 3419, 2933, 1608, 1509, 1322, 1226, 1158, 1105, 1063, 819, 739, 663; ^{1}H 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); ^{13}C 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; ^{19}F NMR (376 MHz, MeOD-

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

4-(2-((4-(3-(1*H*-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 ^{1}H, ^{13}C and ^{19}F NMR spectra of the respective TFA salt of **35d** was recorded; R_f: 0.37 (5% MeOH : 95% DCM); IR (neat, cm^{-1}): 3400, 2928, 2522, 2221, 1673, 1602, 1499, 1232, 1175, 1115, 872, 831, 741, 720; ^{1}H NMR (501 MHz, MeOD-d_4, − 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); ^{13}C 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; ^{19}F 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-(1*H*-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_f: 0.30 (5% MeOH : 95% DCM); IR (neat, cm^{-1}): 3242, 2948, 2873, 1614, 1512, 1488, 1244, 1212, 1145, 817, 754, 692; ^{1}H 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; ^{19}F 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-(1*H*-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; ^{1}H 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); ^{13}C 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; ^{19}F 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-(1*H*-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%); R_f: 0.29 (5% MeOH : 95% DCM); IR (neat, cm^{-1}): 3247, 2939, 2821, 1608, 1509, 1489, 1228, 1064, 824, 741, 662; ^{1}H 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); ^{13}C 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; ^{19}F 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, 400.2015.

***N*-(4-(3-(1*H*-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%); R_f: 0.28 (5% MeOH : 95% DCM); IR (neat, cm^{-1}): 3236, 2943, 2835, 1606, 1494, 1241, 1207, 1035, 821, 729, 659; ^{1}H 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); ^{13}C 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; ^{19}F NMR (376 MHz, acetone) δ −124.75, −76.55; HRMS (APCI): m/z calcd $C_{25}H_{25}N_3O_2F$ $[M + H]^+$ 418.1925, found, 418.1922.

***N*-(4-(3-(1*H*-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_f: 0.28 (5% MeOH : 95% DCM); IR (neat, cm^{-1}): 3243, 2939, 1614, 1508, 1324, 1236, 1104, 1065, 830, 742, 662; ^{1}H 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); ^{13}C 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,

44.04, 31.57; ^{19}F 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-(1*H*-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_f: 0.28 (5% MeOH : 95% DCM); IR (MeOH, cm^{-1}): 3389, 2926, 2225, 1610, 1496, 1239, 1168, 1110, 830, 743; ^{1}H 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); ^{13}C 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; ^{19}F 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; R_f: 0.27 (10% MeOH : 90% DCM); IR (neat, cm^{-1}): 3401, 2951, 1667, 1607, 1490, 1242, 1174, 1047, 838, 746, 724, 691; ^{1}H 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); ^{13}C 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; ^{19}F 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_f: 0.32 (10% MeOH : 90% DCM); IR (neat, cm^{-1}): 3421, 2933, 1607, 1498, 1240, 1196, 1110, 1035, 824, 738; ^{1}H NMR (400 MHz, MeOD-d_4) 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); ^{13}C 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 = 8.3 Hz), 119.72, 117.18 (d, J = 23.7 Hz), 116.52, 115.63, 66.21, 49.57, 48.36, 33.85, 27.16; ^{19}F NMR (377 MHz, MeOD-d_4) δ −76.55, −122.35; HRMS (APCI): m/z calcd $C_{23}H_{26}N_2O_2F$ $[M + H]^+$ 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%); R_f: 0.31 (10% MeOH : 90% DCM); IR (neat, cm^{-1}): 3420, 2761, 1666, 1609, 1510, 1230, 1165, 1105, 1064, 836, 799, 721; ^{1}H 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); ^{13}C 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; ^{19}F 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%); R_f: 0.30 (10% MeOH : 90% DCM); IR (neat, cm^{-1}): 3411, 2940, 2222, 1677, 1603, 1499, 1235, 1176, 1133, 1051, 837, 762, 720; ^{1}H 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); ^{13}C 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; ^{19}F NMR (376 MHz, MeOD-d_4) δ −76.55; HRMS (APCI): m/z calcd $C_{24}H_{26}N_3O_2$ $[M + H]^+$ 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 $SOCl_2$ (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%); R_f: 0.33 (10% MeOH : 90% DCM); IR (neat, cm^{-1}): 3044, 1672, 1490, 1333, 1252, 1152, 751; ^{1}H 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); ^{13}C 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; ^{19}F 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 $SOCl_2$ (5.0 mL, 69 mmol). The sulfonyl chloride (0.74 mmol), aniline **12** (168, 0.83 mmol) and Cs_2CO_3 (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; ^{19}F NMR (376 MHz, MeOD-d_4) δ −76.55, −121.81; HRMS (APCI): m/z calcd $[M + H]^+$, found, HRMS (APCI): m/z calcd $C_{23}H_{25}O_4N_2FS$ 444.1514 $[M]^+$, found, 444.1516; $C_{23}H_{27}O_4N_2FS$ 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 $SOCl_2$ (5.0 mL, 69 mmol). The sulfonyl chloride (0.83 mmol), aniline **13** (251, 0.99 mmol) and Cs_2CO_3 (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_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); ^{13}C 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; ^{19}F 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 $[M]^+$, found, 494.1482; $C_{24}H_{26}O_4N_2F_3S$ 495.156 $[M + H]^+$, 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 $SOCl_2$ (2.5 mL, 34 mmol). The sulfonyl chloride sulfonyl chloride (0.67 mmol), aniline **14** (153, 0.73 mmol) and Cs_2CO_3 (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_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); ^{13}C 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; ^{19}F NMR (376 MHz, MeOD-d_4) δ −76.55; HRMS (APCI): m/z calcd $C_{24}H_{25}O_4N_3S$ 451.156 $[M]^+$, found, 451.1562; $C_{24}H_{25}O_4N_3S$ 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 $SOCl_2$ (5.0 mL, 69 mmol). The sulfonyl chloride (0.63 mmol), aniline **15** (140 mg, 0.76 mmol) and Cs_2CO_3 (986 mg, 3.02 mmol) after heating for 1 day afforded the product **46** as a yellow oil (239 mg, 89%); R_f: 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); ^{13}C NMR (151 MHz, MeOD-d_4) δ 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; ^{19}F 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 $SOCl_2$ (6.0 mL, 82 mmol). The sulfonyl chloride (1.29 mmol), aniline **16** (284 mg, 1.40 mmol) and Cs_2CO_3 (2.10 g, 6.44 mmol) after heating for 1 day afforded the product **47** as a brown oil (515.8 mg, 90%); R_f: 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); ^{13}C 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; ^{19}F NMR (377 MHz, MeOD-d_4) δ −76.55, −121.33; HRMS (APCI): m/z calcd $C_{23}H_{25}O_4N_2FS$ 444.1514 $[M]^+$, found, 444.1516; $C_{23}H_{27}O_4N_2FS$ 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 $SOCl_2$ (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_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); ^{13}C 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; ^{19}F 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, 427.1683.

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 $SOCl_2$ (6.0 mL, 82 mmol). The sulfonyl chloride (1.28 mmol), aniline **18** (280, 1.38 mmol) and Cs_2CO_3 (2.623 g, 8.05 mmol) after heating for 1 day afforded the product **49** as a white solid (495 mg, 87%); R_f: 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); ^{13}C 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 $C_{23}H_{25}O_4N_2FS$ 444.1514 $[M]^+$, found, 444.1515; $C_{23}H_{27}O_4N_2FS$ 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 $SOCl_2$ (3.0 mL, 41 mmol). The sulfonyl chloride (0.81 mmol), aniline **19** (275, 1.09 mmol) and Cs_2CO_3 (1.36 g, 4.19 mmol) after heating for 1 day afforded the product **50** as a light brown oil (381 mg, 94%); R_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); ^{13}C 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; ^{19}F NMR (376 MHz, MeOD-d_4) δ −63.14, −76.55; HRMS (APCI): m/z calcd $C_{24}H_{25}O_4N_2F_3S$ 494.1482 $[M]^+$, found, 494.1482; $C_{24}H_{26}O_4N_2F_3S$ 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 $SOCl_2$ (5.0 mL, 69 mmol). The sulfonyl chloride (0.92 mmol), aniline **20** (201, 0.96 mmol) and Cs_2CO_3 (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); ^{13}C 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; ^{19}F NMR (376 MHz, MeOD-d_4) δ −76.55; HRMS (APCI): m/z calcd $C_{24}H_{25}O_4N_3S$ 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 $Ca_V2.2$ channels and $Ca_V3.2$ channel assay. Endogenously expressed in the neuroblastoma SH-SY5Y and HEK 293 T cells expressing recombinant human $Ca_V3.2$ α_1 subunit were used for $Ca_V2.2$ and $Ca_V3.2$ 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% CO_2 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 $MgCl_2$, 1.2 NaH_2PO_4, 5 $NaHCO_3$, 1.8 $CaCl_2$,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% CO_2 incubator. For $Ca_V2.2$ assays, nifedipine 10 μM (Ca_V1 blocker) was added to the dye solution. The Ca^{2+} 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 $CaCl_2$ for $Ca_V2.2$, or 40 mM KCl and 5 mM $CaCl_2$ 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,

USA) with non-linear regression with log[inhibitor] *versus* normalized response and variable Hill slope for dose–responses. Data were represented as mean ± 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 μM respectively (n = 3). The compound–plasma 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 H_2O (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 Gibco™) at 37 °C in a 5% CO_2 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 μM. Assays were set up in triplicate in Falcon 96 well plates, where volumes of 10^5 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 μL 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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