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Synthesis and *in vitro* evaluation of tetrahydroisoquinolines with pendent aromatics as sigma-2 (σ_2) selective ligands†

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5-Bromo-*N*-[4-(6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-butyl)]-2,3-dimethoxybenzamide **1** is a potent and selective σ_2 receptor ligand suitable for further development. A series of new analogues, incorporating a variety of isoquinoline and carboxylic acid moieties, linked together with either a linear or cyclic amine spacer have been synthesised and assessed for their σ_1/σ_2 binding affinity and selectivity. Compounds with a rigid piperidine spacer gave K_i values for the σ_2 receptor between 8.7–845 nM. Changing the configuration of the methoxy groups on the isoquinoline moiety resulted in molecules with σ_2 K_i values of 4.4–133 nM whereas varying the length and flexibility of the carbon spaces gave σ_2 K_i values 0.88–15.0 nM, some of the most active, selective σ_2 ligands to date. Thus, the flexibility and length of the carbon linker and the carboxylic acid moiety are confirmed to be key to the exceptional binding affinity and selectivity for this active series. Additionally, the incorporation of a halogen on selected carboxylic acid moieties provided a convenient strategy for the introduction of a radiohalogen for applications in pharmacological and imaging studies.

Introduction

Sigma (σ) receptors are a distinct non-opioid, class of receptors that are located in the central nervous system as well as in a variety of peripheral tissues and organs.[1] These receptors are unique proteins located in plasma, mitochondrial and endoplasmic reticulum membranes of tissue derived from brain, kidney, liver, immune, endocrine and reproductive organs.[2] Based on drug-binding profiles and specific pharmacological characteristics of σ-receptor ligands, two distinct receptor subtypes denoted sigma-1 (σ_1) and sigma-2 (σ_2) have been identified with molecular weights of ~25 kDa (σ_1), and ~21.5 kDa (σ_2).[3] The σ_1-receptor has recently been identified as a unique ligand-regulated molecular chaperone in the endoplasmic reticulum of cells involved in the regulation and modulation of voltage-regulated and ligand-gated ion channels, including Ca^{2+}, K^+, Na^+, Cl^-, and SK channels, and NMDA and IP3 receptors.[4] The findings that neuroactive steroids bind with moderate affinity to σ_1 sites, suggest that σ_1 receptors may modulate the activity of GABA and NMDA receptors in the CNS.[5] These observations have rekindled interest in assessing their potential role in inhibiting or potentiating ion channels with implications in many neurological diseases, amnesia, pain, depression, schizophrenia, and neuroprotection.[6]

The discovery of the presence of σ_1 and σ_2 receptors in many human and rodent tumours has opened new possibilities in the area of cancer research, particularly the involvement of σ_2 receptors.[7] In an initial screening of human brain tumours, σ receptors were detected in 15 of 16 tumors examined. Strong receptor expression was observed in a brain metastasis from a lung adenocarcinoma and in a human neuroblastoma passaged in nude mice,[8] whereas a 2-to-5-fold overexpressed in renal and colon carcinomas[9] was also found. Observations that a higher number of binding sites was observed for the non-subtype-selective σ agonist [^{3}H]1,3-di-*o*-tolylguanidine ([^{3}H]DTG) than for the σ_1-subtype selective agonist [^{3}H]3-(3-hydroxyphenyl)-*N*-(1-propyl)piperidine ([^{3}H]3-PPP) in renal and colon carcinomas[18] cell lines, suggested that the σ_2 receptor is more abundant than the σ_1 subtype.

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However, immunocytochemical staining did detect σ_1 receptors in the majority of human primary breast carcinomas, particularly in tumours with a positive progesterone receptor status.[10]

Over-expression of σ_2 receptors has been observed in primary colon cancers, renal carcinomas and sarcomas[9] and pancreatic cancers.[11] Recently it was shown that the σ_2 receptor density in proliferative breast cancer cells is about tenfold higher than in quiescent breast cancer cells[12] and that σ_2 receptor expression is up-regulated during the transition from quiescence to proliferation and down-regulated during the transition from proliferation to quiescence.[13] Consequently, σ_2 receptor density has been proposed as a tool to determine the proliferative status of tumours.[23] Most significantly, selective σ_2 receptor ligands *e.g.* SV119 **2** (Fig. 1) were shown to not only bind to these tumour cells, but also induce apoptosis in a dose-dependent fashion *in vitro* and *in vivo*.[13,14] Furthermore, σ_2 expression has been linked to tumour cell proliferation.[15]

Although the exact mechanism for the modulation of the signalling pathways downstream of σ_2 receptors leading to cancer cell death is not known, they are thought to involve changes in cytosolic calcium and sphingolipid signalling.[16] Furthermore, σ_2 receptor ligands may have a potential role in the treatment of tumours[17] while specific radiolabelled σ_2 receptor ligands can be used to image tumour cell proliferation *in vivo* using positron emission tomography (PET) or single-photon emission computed tomography (SPECT).[18]

The σ_2 receptor has not been cloned and its structure has not been determined. However, recently, the σ_2 receptor, was identified as the progesterone receptor membrane component 1 (Pgrmc1) using photo-affinity studies and a σ_2 ligand containing both a photoactive azide moiety and a fluorescein isothiocyanate group for protein visualisation.[19] This protein was also found to be up-regulated in multiple types of cancer and shown that Pgrmc1 is required for tumour cell proliferation, motility and tumour formation *in vivo*. Furthermore, small molecule inhibitors of Pgrmc1, such as AG-205 (**5**, Fig. 1), suppressed the growth of lung, breast and cervical cancer cell lines.[20]

A number of structurally-diverse compounds have been shown to possess high affinity to σ receptors.[21] However, most of these compounds were shown to bind selectively to the σ_1 receptor or have similar affinities to both σ_1 and σ_2 receptors. Some early σ_2 selective ligands reported in the literature include the benzomorphan-7-one analogue CB-64D (**3**),[22] the 3-(ω-aminoalkyl)-1*H*-indole analogue Lu 28-179 (siramesine, **4**),[23] ibogaine,[24] and the tropane analogue WC-59 (**6**).[25] These, and later σ_2 ligands, have been recently comprehensively reviewed.[26]

SAR studies based on a series of conformationally-flexible benzamide analogues, initially developed as D_3-selective ligands,[27d,e,f] produced a class of compounds having a high affinity for σ_2 receptors and excellent $\sigma_2 : \sigma_1$ selectivity ratios.[27] A key development in this series of compounds was the presence of a 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline ring. This not only resulted in compounds having a high affinity and excellent selectivity for σ_2 *versus* σ_1 receptors, but dramatically reduced their affinity for dopamine receptors. Further modifications, including the incorporation of fluorescent and radiolabelled probes produced molecules, *e.g.* WC-59 (**6**) with significant σ_2 affinity and selectivity.[28] These σ_2 selective ligands have subsequently been used to directly identify, locate and quantify this protein using a variety of receptor-binding and molecular imaging techniques.[29]

Molecules based on the conformationally-flexible benzamide **1** have proven to be an important source of σ_2-selective compounds. Preliminary work has shown that having a conformationally flexible spacer unit of four carbon atoms was

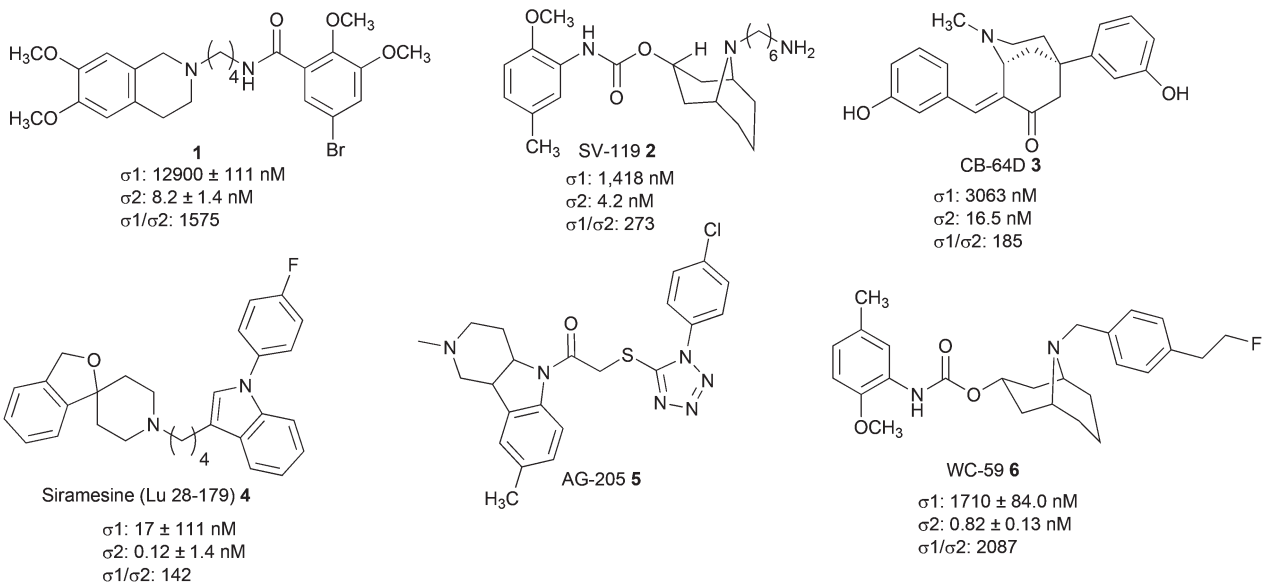


Fig. 1 Selected examples of σ_2 ligands with their corresponding σ_1 activities and the sigma selectivity index between the two targets. The tetrahydroisoquinolylamide **1** was the starting point for this project.

beneficial for σ_2 binding affinity and selectivity.[27a] However, limited work was undertaken on the effects of substitutions on the carboxylic acid and no work had been performed to observe what effect restricting conformational freedom has on σ_2 receptor activity in this class. Further, little work has been conducted on varying the substitution pattern of the methoxy groups on the tetrahydroisoquinoline ring, although, it has been shown that either opening the tetrahydroisoquinyl ring or replacing the methoxy groups with methylene-, ethylene- and propylenedioxy rings decrease the σ_2 activity.[27b,30] Despite these results, there remains considerable scope for further modifications to this structure for the preparation of radiolabeled probes to image this receptor *in vitro* and *in vivo*. In this study, the effect of modulating the conformational freedom of the spacer, varying the carboxylic acid substitution on the amide and modifying the methoxy substitution on the tetrahydroisoquinolyl ring was investigated with the purpose of expanding the scope of analogues synthesised and evaluated to produce a candidate that was suitable for radiolabelling with SPECT and PET isotopes.

Results and discussion

Chemistry

Using the tetrahydroisoquinoline benzamide **1** as our lead compound, we synthesised a series of analogues and tested them as selective σ_2 ligands. Therefore, the substituted piperidines **7–9** were Boc *N*-protected (**10–12**), followed by the incorporation of a leaving group using standard chemistry (Scheme 1). The addition of the 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline unit under S_N2 reaction conditions (**16–18**) followed by N-deprotection yielded the secondary amines **19–21** which underwent coupling with a variety of aromatic carboxylic acids to produce target tetrahydroisoquinolylamides **22–32**. Additionally, the use of variously substituted benzofuran-2-carboxylic acids yielded ligands **33–39**. The synthesis of target ligands with more flexible central linkers (Scheme 2) started with the alkylation of tetrahydroisoquinolines with bromonitriles of varying lengths (**40–46**) followed by $LiAlH_4$ reduction to the corresponding primary amines **47–53**. Coupling of the amines to 5-bromo- or 5-iodobenzofuran-2-carboxylic acids yielded the targets **54–63**.

Discussion

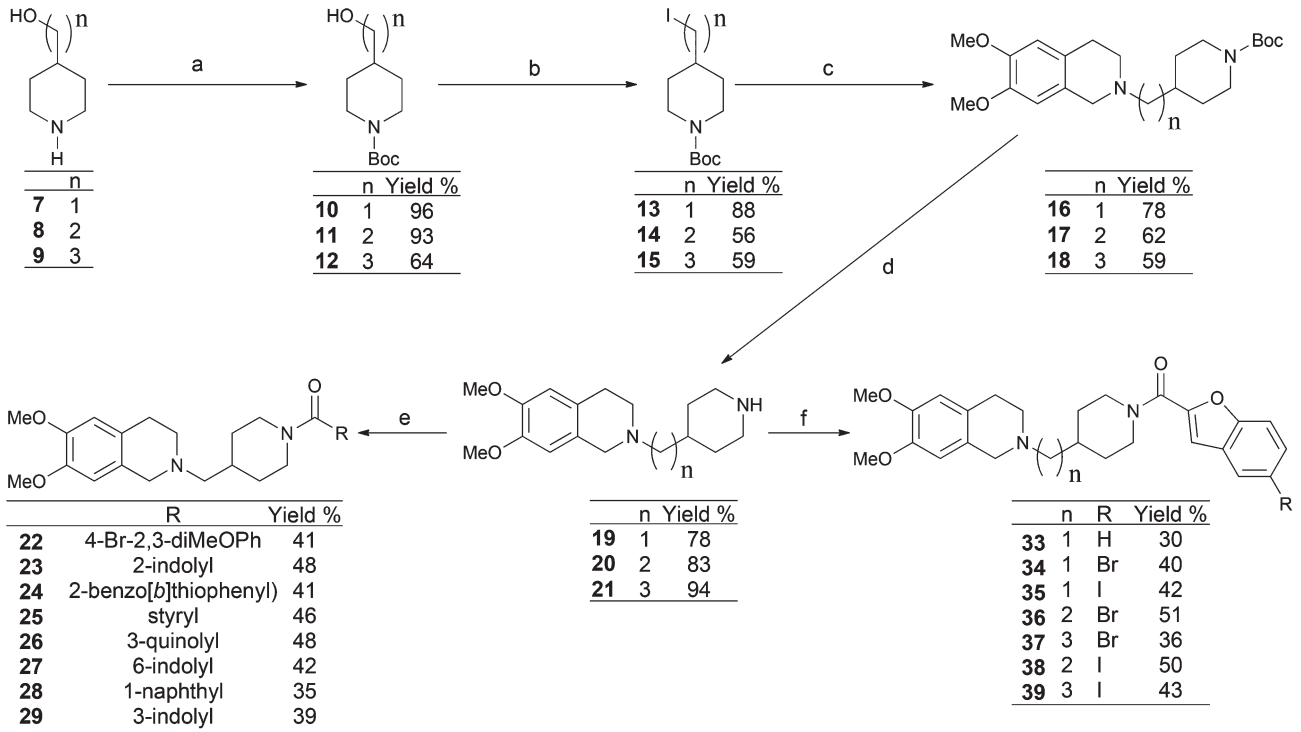
All synthesised ligands were tested for their σ_1 and σ_2 activities, their σ_2 selectivities determined and their *C* log *P* calculated (Tables 1–3). The first series of compounds synthesised investigated the use of a conformationally restricted linker by incorporating a six membered ring into the central chain – it also varied the terminal aromatic moiety, including the use of both aromatic carbocycles and heterocycles. Changing from the aromatic amide as in **22** to the benzofuran amide substitution of **33** gave a more selective and active compound (σ_2 = 44 nM, σ_1/σ_2 = 7.30) when compared to **22**. Compounds **23** and **24** were synthesised to observe the effects of changing the heteroatom from an oxygen, to a nitrogen **23** or sulphur **24**. The compounds were still selective for the σ_2 receptor (σ_1/σ_2 = 4.2 and 0.98 respectively); however, the benzofuran **33** remained the better derivative. Changing to the larger 1-naphthyl (**28**), the 3-quinolyl (**26**) or the styryl (**25**) derivatives substantially weakened the activity. Changing the point of attachment for various heterocycles (*e.g.* indole C6 or C3) resulted in some of the weakest activity observed. However, adding a substituent to indole C5 resulted in increasing activity across the range. Translating this result to the 'best' terminal moiety, the 2-benzofuran with the addition of C5 bromo (**34**) improved the activity by an order of magnitude (σ_2 = 8.7 nM, σ_1/σ_2 = 292). The use of an iodo substituent (**35**) was not as effective (σ_2 = 11.0 nM, σ_1/σ_2 = 62.0). Starting from the bromobenzofuran derivative **34**, and extending the linker by one methylene (**36**) and two methylene units (**37**) resulted in slight improvements in activity but at a significant expense to selectivity.

The lead compound **1** had a flexible four carbon linker and a bromodimethoxyphenyl ring at the terminus. The incorporation of the restricted linker and the methylpiperidine core (**22**) decreased activity and selectivity for the σ_2 receptor (σ_2 = 367 nM, σ_1/σ_2 = 5.9) compared to the lead **1**. Given the best terminal aromatic group was a bromobenzofuran, the corresponding flexible linker versions were synthesised (**54–59**). Surprisingly the C5-iodosubstituted benzofuran **59** produced the best outcome (σ_2 = 0.88 nM, σ_1/σ_2 = 886) with an order of magnitude better σ_2 activity and the best selectivity over σ_1 that we have seen.

Our final series of analogues investigated examined the removal of one of the tetrahydroisoquinoline methoxy substituents and the size of the flexible linker (**60–63**). While significant activity was noted for the monomethoxy derivative **61**, the selectivity was notably reduced.

Therefore, the optimal ligand for σ_2 activity and selectivity was the iodobenzofuran **59** containing a benzofuran carboxamide moiety with a halogen substitution at C5 and a 6,7-dimethoxytetrahydroisoquinoline separated by a six carbon flexible spacer. This possessed a σ_2 activity of 0.88 nM with a selectivity index of 886. On the other hand, the best ligand for σ_1 activity was **61** with a value of 76 nM and a σ_2 value of 4.4 nM. This relatively poor activity for σ_1 was still significantly better than most other derivatives and also still possessed better σ_2 activity. Therefore, the σ_2 activity for this series, along with the consistently good selectivity values can be seen as significant and consistent and validates pursuing this extended SAR study.

Fig. 2 shows a summary of the structure–activity results that have emerged from this study. Of the great variety of terminal aromatic moieties investigated, the benzofuran was the most potent, particularly with the presence of a C5-iodo substituent. The central linker is best if flexible and is optimal at six methylenes. Although the dimethoxy substituted tetrahydroisoquinoline exhibits good *in vitro* activity with just one methoxy substituent, it does at the expense of selectivity



	n
7	1
8	2
9	3

	n	Yield %
10	1	96
11	2	93
12	3	64

	n	Yield %
13	1	88
14	2	56
15	3	59

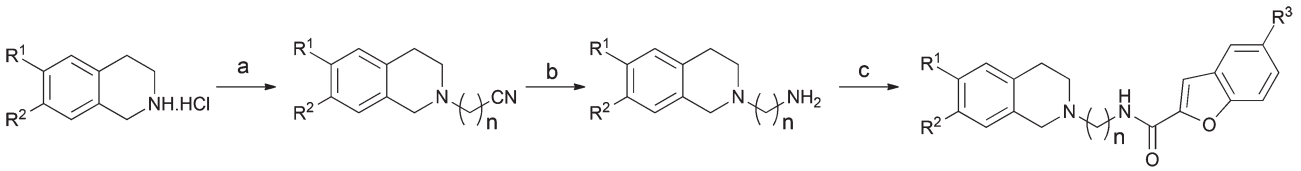
	n	Yield %
16	1	78
17	2	62
18	3	59

	R	Yield %
22	4-Br-2,3-diMeOPh	41
23	2-indolyl	48
24	2-benzo[*b*]thiophenyl)	41
25	styryl	46
26	3-quinolyl	48
27	6-indolyl	42
28	1-naphthyl	35
29	3-indolyl	39
30	2-(5-bromoindolyl)	27
31	4-Br-3-MePh	55
32	3-(5-bromoindolyl)	38

	n	Yield %
19	1	78
20	2	83
21	3	94

	n	R	Yield %
33	1	H	30
34	1	Br	40
35	1	I	42
36	2	Br	51
37	3	Br	36
38	2	I	50
39	3	I	43

Scheme 1 Reagents: (a) di-*tert*-butyldicarbonate, CH_2Cl_2, (b) PPh_3, I_2, imidazole, (c) 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, TBAI, K_2CO_3, DMF, (d) CH_2Cl_2–TFA (2 : 1), (e) EDC, HOBt, DMF, R-COOH, (f) EDC, HOBt, DMF, 5-substituted-benzofuran-2-carboxylic acids.



	R^1	R^2	n	Yield %
40	OMe	OMe	3	85
41	OMe	OMe	4	83
42	OMe	OMe	5	86
43	OMe	H	3	76
44	OMe	H	4	61
45	H	OMe	3	77
46	H	OMe	4	59

	R^1	R^2	n	Yield %
47	OMe	OMe	4	65
48	OMe	OMe	5	62
49	OMe	OMe	6	68
50	OMe	H	4	94
51	OMe	H	5	95
52	H	OMe	4	89
53	H	OMe	5	77

	R^1	R^2	R^3	n	Yield %
54	OMe	OMe	Br	4	23
55	OMe	OMe	Br	5	23
56	OMe	OMe	Br	6	35
57	OMe	OMe	I	4	47
58	OMe	OMe	I	5	30
59	OMe	OMe	I	6	41
60	OMe	H	I	4	51
61	OMe	H	I	5	34
62	H	OMe	I	4	30
63	H	OMe	I	5	36

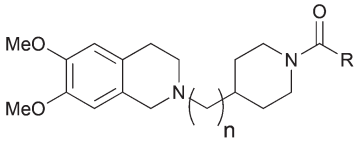
Scheme 2 Reagents: (a) $Br(CH_2)_nCN$, TBAI, K_2CO_3, DMF, (b) $LiAlH_4$, THF, (c) EDC, HOBt, DMF.

and appears to be optimal with 2 methoxy substituents present.

Conclusion

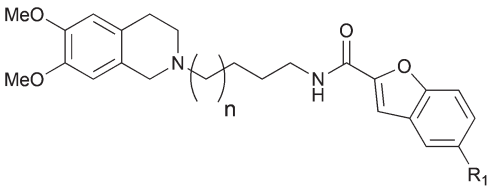
A series of tetrahydroisoquinolyl benzamides were synthesised and tested for their binding affinities to both σ_1 and σ_2. We have shown that this class of derivatives can be highly potent and selective for the σ_2 receptor, with the piperidine based core favoured in most cases. The halogenated benzofuran derivatives **34** (K_i σ_1/σ_2 = 292) and **35** (K_i σ_1/σ_2 = 62.0) displaying good affinity and selectivity and increasing the conformational freedom produced more σ_2 active derivatives. However, this also decreased σ_2 selectivity in all cases except for that of **59** (K_i σ_1/σ_2 = 886). Removal of the methoxy groups from the isoquinoline ring did not produce a more selective or high affinity ligand than that seen for compound **59**, and these

Table 1 σ_1 and σ_2 binding affinities (K_i) for benzamides



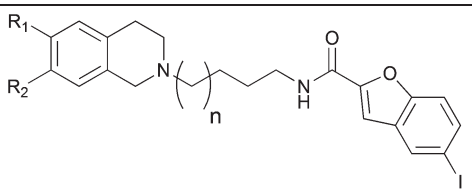
	n	*C* log *P*	σ_2 K_i (nM)	σ_1 K_i (nM)	σ_1/σ_2
22	1	3.16	367 ± 1.0	2180 ± 54	5.90
23	1	3.29	88 ± 5	372 ± 11	4.20
24	1	3.38	97 ± 2	95 ± 1	0.98
25	1	3.05	137 ± 7	818 ± 6	5.97
26	1	2.38	283 ± 2	82 ± 7.5	0.29
27	1	2.77	845 ± 15	164 ± 5	0.19
28	1	3.08	115 ± 9	475 ± 34	4.13
29	1	2.76	752 ± 23	130 ± 12	0.17
30	1	4.20	40 ± 12	3863 ± 153	97
31	1	3.51	44 ± 5	77 ± 11	1.80
32	1	3.63	160 ± 15	395 ± 39	2.20
33	1	3.22	44 ± 7.0	322 ± 56	7.30
34	1	3.96	8.7 ± 0.6	2545 ± 103	292
35	1	4.25	11.0 ± 1.2	682 ± 181	62.0
36	2	3.99	4.9 ± 1.2	360 ± 41	73.0
37	3	4.02	5.3 ± 0.2	209 ± 21	39.0
38	2	3.83	10.6 ± 1.1	184 ± 2	17.0
39	3	4.36	12.4 ± 0.9	97.9 ± 8.0	7.9

Table 2 σ_1 and σ_2 binding affinities (K_i) for benzamides



	R_1	*n*	*C* log *P*	σ_2 K_i (nM)	σ_1 K_i (nM)	σ_1/σ_2
54	Br	1	3.63	15.0 ± 1.4	3718 ± 650	248
55	Br	2	3.81	6.2 ± 0.4	410 ± 18.5	66.1
56	Br	3	3.94	8.0 ± 0.1	157 ± 2	19.6
57	I	1	3.82	6.2 ± 1.2	752 ± 148	121
58	I	2	3.91	8.9 ± 2.1	204 ± 10	22.9
59	I	3	4.47	0.88 ± 0.5	780 ± 127	886

Table 3 σ_1 and σ_2 binding affinities (K_i) for benzamides



	R_1	R_2	*n*	*C* log *P*	σ_2 K_i (nM)	σ_1 K_i (nM)	σ_1/σ_2
60	OMe	H	1	4.08	133 ± 3	1277 ± 52	9.6
61	OMe	H	2	4.31	4.4 ± 1.3	76 ± 16	17.3
62	H	OMe	1	4.33	35 ± 5.3	616 ± 12	17.6
63	H	OMe	2	4.43	31 ± 1.3	241 ± 33	7.8

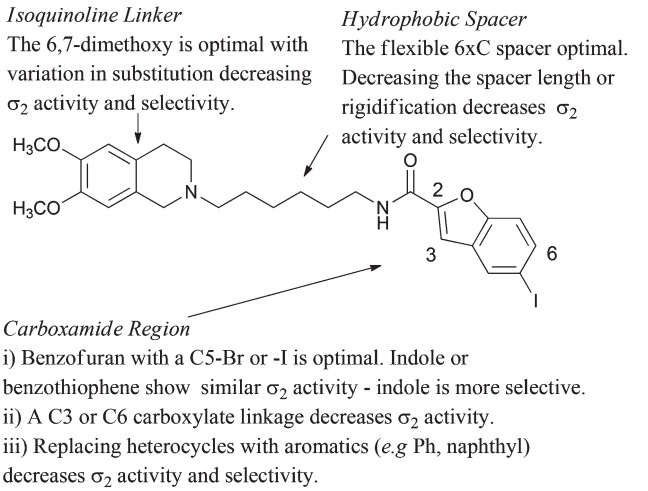


Fig. 2 Structure and activity relationships for the tetrahydroisoquinolines with pendent aromatics as σ_2 selective ligands.

results corroborate the need to have a flexible linker with a 6,7-dimethoxy isoquinyl ring substitution for optimum σ_2 binding affinity. In addition, structural features were identified that result in extremely poor affinity and selectivity for both the σ_1 and σ_2 receptor subtypes. Therefore, the new information from our study offers a useful guide for designing σ_2 specific compounds and promising new lead compounds **34** and **59** were produced, that show highly active σ_2 activity with significant selectivity, and have the potential to be utilised in future SPECT radiochemistry studies.

Experimental

Chemistry – general considerations

All reagents purchased were used without further purification. Air sensitive reactions were performed under a positive pressure of nitrogen gas. THF and Et_2O were distilled from sodium under nitrogen gas. Petroleum ether (PE) of boiling point range 40–60 °C was used. Melting points were recorded on a Gallenkamp (Griffin) melting point apparatus with temperatures reported in degrees Celsius (°C) and are uncorrected. NMR spectra were performed on a Bruker Advance DPX 400 operating at 400 MHz for ^{1}H NMR spectra and 100 MHz for ^{13}C NMR spectra. Electron impact and electrospray mass spectra were obtained using a Shimadzu QP-5000 GC-MS spectrometer by direct insertion technique with a 70 eV electron beam and high resolution on a VG Autospec spectrometer. Ion mass to charge (*m*/*z*) values are stated and their relative abundances as a percentage in parentheses. [^{3}H] Pentazocine and [^{3}H] DTG were purchased from Perkin-Elmer Life Sciences (Boston, MA, USA).

The lipophilicity was assessed using RP-HPLC by determining the log *P* value using literature procedures.[31] Samples, dissolved in methanol, were analyzed using a Waters, Xterra C18 column (5 μm, 4.6 mm × 150 mm) with a mobile phase consisting of methanol/phosphate buffer (0.1 M, pH 7.5) and a

flow rate of 1 mL min^{-1}. The log *P* of a studied compound was estimated by a comparison of its retention time to that of compounds of known log *P* value.

Preparation of compounds 16–18

To a solution of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (1.0 eq.), K_2CO_3 (4 eq.) and TBAI (0.1 eq.) in DMF (20 mL) was added the appropriate piperidine **13**, **14**, or **15** (1.0 eq.). The solution was allowed to stir at rt for 3 days. The solution was diluted with EtOAc (100 mL) and extracted with H_2O (3 × 20 mL), sat. $NaHCO_3$ (25 mL), brine (25 mL) and H_2O (20 mL). The organic layers were combined, dried (Na_2SO_4) and the organic solvent removed. The residue was subjected to column chromatography (EtOAc–MeOH, 9 : 1) to yield compounds **16–18**.

***tert*-Butyl-4-((3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)methyl)piperidine-1-carboxylate [16].** Clear oil, yield 78%; ^{1}H NMR ($CDCl_3$) δ 1.10–1.14 (m, 2H), 1.45 (s, 9H), 1.76–1.80 (m, 3H), 2.33 (m, 2H), 2.67–2.80 (m, 6H), 3.52 (s, 2H), 3.83 (s, 6H), 4.08–4.10 (bs, 2H), 6.52 (s, 1H), 6.59 (s, 1H). ^{13}C NMR δ 28.6, 28.8, 34.1, 35.2, 37.2, 44.2, 51.5, 56.06, 56.08, 56.4, 64.4, 79.4, 109.7, 111.6, 126.4, 126.8, 147.4, 147.7, 155.1. MS-ES$^+$ *m*/*z* 391 (MH^+, 100%); HRMS-ES$^+$ calculated for $C_{22}H_{34}N_2O_4$: 391.2586, found 391.2597.

***tert*-Butyl-4-(2-(3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)ethyl)piperidine-1-carboxylate [17].** Clear oil, yield 62%; ^{1}H NMR ($CDCl_3$) δ 1.12–1.24 (m, 2H), 1.45 (s, 9H), 1.49–1.70 (m, 5H), 2.52 (t, 2H, *J* = 8.0 Hz), 2.66–2.71 (m, 2H), 2.81 (t, 2H, *J* = 5.8 Hz), 3.53 (s, 2H), 3.83 (s, 3H), 3.84 (s, 3H), 4.06–4.15 (m, 2H), 6.51 (s, 1H), 6.59 (s, 1H). ^{13}C NMR δ 28.6, 28.7, 32.4, 34.0, 34.5, 44.2, 51.2, 55.8, 56.0, 56.1, 64.3, 79.4, 109.7, 111.6, 126.3, 126.9, 147.4, 147.5, 156.0. MS-EI *m*/*z* 404 (M^+, 8), 206 (100%); HRMS-EI calculated for $C_{23}H_{36}N_2O_4$: 404.2675, found 404.2672.

***tert*-Butyl-4-(3-(3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)propyl)piperidine-1-carboxylate [18].** Clear oil that solidified upon standing (mp 86–89 °C), yield 59%; ^{1}H NMR ($CDCl_3$) δ 1.06–1.09 (m, 2H), 1.25–1.29 (m, 2H), 1.30–1.44 (m, 1H), 1.42 (s, 9H), 1.58–1.67 (m, 4H), 2.46 (t, 2H, *J* = 7.9 Hz), 2.65–2.69 (m, 4H), 2.80 (t, 2H, *J* = 8.0 Hz), 3.52 (s, 2H), 3.81 (s, 3H), 3.82 (s, 3H), 4.06–4.11 (m, 2H), 6.50 (s, 1H), 6.57 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 24.5, 28.6, 28.7, 32.3, 34.5, 44.1, 51.2, 55.9, 56.01, 56.04, 58.6, 79.3, 109.6, 111.5, 126.3, 126.7, 147.3, 147.7, 155.0. MS-ES$^+$ *m*/*z* 419 (MH^+, 35), 265 (100%); HRMS-ES$^+$ calculated for $C_{24}H_{39}N_2O_4$: 419.2910, found 419.2919.

Preparation of compounds 19–21

A solution of **16**, **17** or **18** in $CHCl_2$–TFA (10 mL, 2 : 1) was stirred for 30 min at rt. The product was basified with aq. K_2CO_3 (1 M, 200 mL) followed by aq. KOH (0.1 M, 50 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were combined, dried (Na_2SO_4) and the solvent removed to yield **19**, **20** or **21** which were used without further purification.

1,2,3,4-Tetrahydro-6,7-dimethoxy-2-((piperidine-4-yl)methyl)-isoquinoline [19]. Yellow oil, yield 78%; ^{1}H NMR ($CDCl_3$) δ 1.11–1.15 (m, 2H), 1.72–1.80 (m, 3H), 2.32 (m, 2H), 2.58–2.68 (m, 4H), 2.75–2.81 (m, 2H), 3.06–3.09 (m, 2H), 3.51 (s, 2H), 3.83 (s, 6H), 6.51 (s, 1H), 6.58 (s, 1H). ^{13}C NMR δ 28.8, 32.4, 34.3, 46.7, 51.5, 56.1, 56.5, 65.2, 109.7, 111.6, 126.5, 127.1, 147.3, 147.6. MS-ES$^+$ *m*/*z* 291 (MH^+, 40), 208 (100%); HRMS-EI calculated for $C_{17}H_{26}N_2O_2$: 290.1994, found 290.1996.

1,2,3,4-Tetrahydro-6,7-dimethoxy-2-(2-(piperidin-4-yl)ethyl)-isoquinoline [20]. Cream solid, mp 102–103 °C, yield 83%; ^{1}H NMR ($CDCl_3$) δ 1.16–1.54 (m, 5H), 1.69–1.78 (m, 2H), 2.50–2.69 (m, 6H), 2.80 (bs, 2H), 3.06 (bd, 2H, *J* = 9.8 Hz), 3.53 (s, 2H), 3.82 (s, 6H), 6.52 (s, 1H), 6.58 (s, 1H). ^{13}C NMR δ 29.0, 33.7, 34.8, 34.9, 46.8, 51.4, 56.0, 56.20, 56.22, 109.8, 111.7, 126.5, 127.0, 147.5, 147.8. MS-ES$^+$ *m*/*z* 305 (MH^+, 100%); HRMS-EI calculated for $C_{18}H_{28}N_2O_2$: 304.2151, found 304.1391.

1,2,3,4-Tetrahydro-6,7-dimethoxy-2-(3-(piperidin-4-yl)propyl)-isoquinoline [21]. Clear oil, yield 94%; ^{1}H NMR ($CDCl_3$) δ 1.12–1.30 (m, 5H), 1.56–1.71 (m, 4H), 2.45 (t, 2H, *J* = 7.7 Hz), 2.58–2.62 (m, 2H), 2.67 (t, 2H, *J* = 6.1 Hz), 2.80 (t, 2H, *J* = 5.8 Hz), 3.08 (bd, 2H, *J* = 12.0 Hz), 3.51 (s, 2H), 3.810 (s, 3H), 3.813 (s, 3H), 6.49 (s, 1H), 6.57 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 24.3, 28.7, 32.8, 34.8, 35.9, 46.2, 51.1, 55.88, 55.92, 58.6, 109.6, 111.4, 126.3, 126.7, 147.2, 147.5. MS-EI *m*/*z* 318 (M^+, 26), 206 (100%); HRMS-EI calculated for $C_{19}H_{30}N_2O_2$: 318.2307, found 318.2305.

Preparation of compounds 22–38

To a stirred solution of the appropriate benzoic acid (1.0 eq.) in anhydrous DMF (10 mL) was added, EDC (1.3 eq.), HOBt (1.1 eq.), and DIPEA (3.0 eq.) and the reaction mixture was stirred at room temperature. After 5 min, a solution of the amine **19**, **20** or **21** (1.0 eq.) was added to this reaction mixture, and then was stirred at room temperature for 2 days under N_2. The reaction mixture was diluted with EtOAc (80 mL), washed with H_2O (3 × 25 mL), sat. Na_2CO_3 (15 mL), H_2O (20 mL) and brine (15 mL). The organic layer was dried (Na_2SO_4) and solvent removed. The residue was subjected to column chromatography (EtOAc–MeOH, 95 : 5) to yield compounds **22–38**.

(5-Bromo-2,3-dimethoxyphenyl)(4-((3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)methyl)piperidin-1-yl)methanone [22]. Prepared as white solid (250 mg, 41%) from 5-bromo-3,4-dimethoxycarboxylic acid,[27] mp 51–52 °C; ^{1}H NMR (DMSO) δ 1.09–1.19 (m, 2H), 1.68–1.71 (bd, 2H, *J* = 12.4 Hz), 1.90–1.96 (m, 1H), 2.35 (d, 2H, *J* = 8.0 Hz), 2.64 (t, 2H, *J* = 5.4 Hz), 2.74 (t, *J* = 5.6 Hz), 3.05 (bs, 2H), 3.49 (s, 2H), 3.737 (s, 3H), 3.742 (s, 3H), 3.75 (s, 3H), 3.89 (s, 3H), 4.51 (bs, 2H), 6.65 (s, 1H), 6.68 (s, 1H), 6.94–6.98 (m, 1H), 7.27 (s, 1H). ^{13}C NMR (DMSO) δ 29.0, 30.8, 34.0, 47.3, 51.8, 56.43, 56.45, 56.47, 57.1, 64.2, 111.2, 113.0, 116.5, 117.2, 121.4, 121.7, 126.9, 127.7, 147.9, 148.1, 154.1, 165.1. MS-ES$^+$ *m*/*z* 534 (MH^+, 100%); HRMS-EI calculated for $C_{26}H_{33}{}^{79}BrN_2O_5$: 533.1651, found 533.1683.

(4-((3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)methyl-piperidin-1-yl)(1*H*-inden-2-yl)methanone [33]. White solid, mp 128–129 °C, yield 30%; ^{1}H NMR (DMSO) δ 1.10–1.20 (m, 2H), 1.80–1.84 (bs, 2H), 1.93 (m, 1H), 2.31 (d, 2H, *J* = 8 Hz), 2.60 (t, 2H, *J* = 6 Hz), 2.69 (t, *J* = 5.5 Hz), 3.03 (bs, 2H), 3.44 (s, 2H), 3.680 (s, 3H), 3.684 (s, 3H), 4.28 (bs, 2H), 6.60 (s, 1H),

6.63 (s, 1H), 7.27–7.32 (m, 2H), 7.40 (m, 1H), 7.61 (d, 1H, J = 8.3 Hz), 7.70 (d, 1H, J = 7.8 Hz). ^{13}C NMR ($CDCl_3$) δ 29.0, 31.4, 34.0, 44.1, 51.7, 55.9, 56.0, 56.4, 64.1, 110.6, 111.2, 112.4, 113.0, 123.0, 124.3, 126.8, 126.9, 127.5, 127.6, 147.9, 148.1, 149.6, 154.6, 159.6. MS: LRMS m/z (ES^+) 435 $[MH]^+$ (100%); HRMS: calculated for $C_{26}H_{30}N_2O_4$: 435.2284, found 435.2291.

4-((3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)methyl)-piperidin-1-yl)(1*H*-indol-2-yl)methanone [23]. White solid, mp 208–210 °C, yield 48%; ^{1}H NMR (DMSO) δ 1.16–1.26 (m, 2H), 1.88 (bd, 2H, J = 12.3 Hz), 1.96–2.03 (m, 1H), 2.38 (d, 2H, J = 7.2 Hz), 2.67 (t, 2H, J = 5.9 Hz), 2.76 (t, 2H, J = 5.3 Hz), 3.09 (bs, 2H), 3.52 (s, 2H), 3.74 (s, 3H), 3.75 (s, 3H), 4.47 (bs, 2H), 6.67 (s, 1H), 6.70 (s, 1H), 6.77 (s, 1H), 7.07 (t, 1H, J = 7.2 Hz), 7.20 (t, 1H, J = 7.2 Hz), 7.45 (d, 1H, J = 8.2 Hz), 7.62 (d, 1H, J = 8.0 Hz). ^{13}C NMR (DMSO) δ 29.0, 31.5, 34.1, 44.1, 51.8, 56.41, 56.44, 64.3, 104.1, 111.2, 112.7, 113.0, 120.3, 121.9, 123.7, 126.9, 127.6, 127.7, 131.2, 136.6, 147.8, 148.1, 162.7. MS-ES^+ m/z 434 (MH^+, 100%); HRMS-EI calculated for $C_{26}H_{31}N_3O_3$: 433.2365, found 433.2356.

(Benzo[*b*]thiophen-2-yl)(4-((3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)methyl)piperidin-1-yl)methanone [24]. Off-white solid, mp 80–82 °C, yield 41%; ^{1}H NMR (DMSO) δ 1.17–1.27 (m, 2H), 1.87 (bd, 2H, J = 12.2 Hz), 1.97–2.02 (m, 1H), 2.37 (d, 2H, J = 7.2 Hz), 2.66 (t, 2H, J = 6.1 Hz), 2.75 (t, J = 5.5 Hz), 3.09 (bs, 2H), 3.51 (s, 2H), 3.74 (s, 3H), 3.75 (s, 3H), 4.32 (bs, 2H), 6.66 (s, 1H), 6.69 (s, 1H), 7.45–7.46 (m, 2H), 7.70 (s, 1H), 7.94–7.97 (m, 1H), 8.02–8.04 (m, 1H). ^{13}C NMR (DMSO) δ 29.0, 31.4, 34.0, 45.6, 51.8, 56.4, 56.5, 64.2, 111.2, 113.0, 123.2, 125.5, 125.52, 125.53, 126.4, 126.9, 127.7, 138.1, 139.4, 140.0, 147.9, 148.1, 163.1. MS-ES^+ m/z 451 (MH^+, 100%); HRMS-EI calculated for $C_{26}H_{30}N_2O_3S$: 450.1977, found 450.1974.

(*E*)-1-(4-((3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)-methyl)piperidin-1-yl)-3-phenylprop-2-en-1-one [25]. White solid, mp 149–150 °C, yield 46%; ^{1}H NMR (DMSO) δ 1.00–1.11 (m, 2H), 1.83 (bd, 2H, J = 12.3 Hz), 1.90–1.95 (m, 1H), 2.35 (d, 2H, J = 7.1 Hz), 2.65 (t, 2H, J = 6.0 Hz), 2.75 (t, J = 5.4 Hz), 3.11 (bs, 2H), 3.50 (s, 2H), 3.74 (s, 3H), 3.75 (s, 3H), 4.38 (bs, 2H), 6.66 (s, 1H), 6.69 (s, 1H), 7.24 (d, 1H, J = 15.5 Hz), 7.37–7.46 (m, 3H), 7.49 (d, 1H, J = 15.5 Hz), 7.70–7.73 (m, 2H). ^{13}C NMR (DMSO) δ 29.0, 31.4, 34.1, 44.1, 51.8, 56.4, 64.3, 111.2, 113.0, 119.6, 126.9, 127.7, 128.6, 129.4, 130.0, 136.1, 141.7, 147.9, 148.1, 165.1. MS-ES^+ m/z 421 (MH^+, 31), 443 $(MHNa)^+$ (100%); HRMS-EI calculated for $C_{26}H_{32}N_2O_3$: 420.2413, found 420.2401.

(4-((3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)methyl)-piperidin-1-yl)(quinolin-3-yl)methanone [26]. Orange solid, mp 70–72 °C, yield 48%; ^{1}H NMR (DMSO) δ 1.19–1.29 (m, 2H), 1.85 (bd, 2H, J = 12.3 Hz), 1.96–2.00 (m, 1H), 2.38 (d, 2H, J = 7.1 Hz), 2.66 (t, 2H, J = 5.9 Hz), 2.75 (t, 2H, J = 5.4 Hz), 3.07 (bs, 2H), 3.50 (s, 2H), 3.739 (s, 3H), 3.742 (s, 3H), 4.51 (bs, 2H), 6.66 (s, 1H), 6.69 (s, 1H), 7.69–7.73 (m, 1H), 7.85–7.89 (m, 1H), 8.10 (m, 2H), 8.44 (d, 1H, J = 2.1 Hz), 8.92 (d, 1H, J = 2.1 Hz). ^{13}C NMR (DMSO) δ 29.0, 31.2, 34.0, 47.5, 51.8, 56.43, 56.46, 64.2, 111.2, 113.0, 126.9, 127.4, 127.6, 128.0, 129.3, 129.5, 130.2, 131.2, 134.8, 147.9, 148.1, 148.3, 149.2, 167.4. MS-ES^+ m/z 446 (MH^+, 100%); HRMS-ES^+ calculated for $C_{27}H_{31}N_3O_3$: 446.2444, found 446.2454.

(4-((3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)methyl)-piperidin-1-yl)(1*H*-indol-6-yl)methanone [27]. Light brown solid, mp 210–213 °C, yield 42%; ^{1}H NMR (DMSO) δ 1.13–1.23 (m, 2H), 1.80–1.83 (m, 2H), 1.92–1.97 (m, 1H), 2.38 (d, 2H, J = 7.2 Hz), 2.66 (t, 2H, J = 6.2 Hz), 2.75 (t, 2H, J = 5.6 Hz), 2.94–3.00 (m, 2H), 3.51 (s, 2H), 3.74 (s, 3H), 3.75 (s, 3H), 4.15–4.24 (m, 2H), 6.51 (d, 1H, J = 2.9 Hz), 6.66 (s, 1H), 6.69 (s, 1H), 7.05 (dd, 1H, J = 8.1 Hz, 1.3 Hz), 7.47 (m, 2H), 7.61 (s, 1H). ^{13}C NMR (DMSO) δ 30.0, 32.4, 35.0, 44.6, 52.7, 57.1, 57.3, 57.6, 65.4, 102.8, 111.7, 112.2, 113.4, 119.6, 121.3, 127.6, 128.4, 128.7, 130.0, 130.6, 136.7, 148.5, 148.8, 171.9. MS-ES^+ m/z 434 (MH^+, 100%); HRMS-ES^+ calculated for $C_{26}H_{31}N_3O_3$: 434.2444, found 434.2450.

(4-((3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)methyl)-piperidin-1-yl)(naphthalen-1-yl)methanone [28]. White solid, mp 58–60 °C, yield 35%; ^{1}H NMR (DMSO) δ 1.10–1.30 (m, 2H), 1.60–1.70 (m, 1H), 1.90–1.97 (m, 2H), 2.36 (m, 2H), 2.64 (t, 2H, J = 5.7 Hz), 2.73 (t, J = 5.6 Hz), 2.93–3.10 (m, 2H), 3.48 (s, 2H), 3.732 (s, 3H), 3.736 (s, 3H), 4.69 (bs, 2H), 6.64 (s, 1H), 6.68 (s, 1H), 7.40–7.50 (m, 1H), 7.56–7.63 (m, 3H), 7.76–7.83 (m, 1H), 7.97–8.03 (m, 2H). ^{13}C NMR (DMSO) δ 29.0, 31.1, 34.1, 47.6, 51.8, 56.46, 56.49, 56.5, 64.2, 111.2, 113.0, 124.1, 125.4, 126.1, 126.9, 127.1, 127.6, 127.7, 129.1, 129.3, 133.8, 135.7, 147.9, 148.2, 168.6. MS-ES^+ m/z 445 (MH^+, 100%); HRMS-ES^+ calculated for $C_{28}H_{32}N_2O_3$: 445.2491, found 445.2488.

(3a,7a-Dihydro-1*H*-indol-3-yl)(4-((3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)methyl)piperidin-1-yl)methanone [29]. Off-white solid, mp 206–207 °C, yield 39%; ^{1}H NMR (DMSO) δ 1.13–1.23 (m, 2H), 1.81–1.84 (m, 2H), 1.95–2.03 (m, 1H), 2.37 (d, 2H, J = 6.2 Hz), 2.66 (t, 2H, J = 5.9 Hz), 2.74 (t, 2H, J = 5.5 Hz), 2.98–3.04 (m, 2H), 3.51 (s, 2H), 3.74 (s, 6H), 4.29–4.33 (m, 2H), 6.66 (s, 1H), 6.69 (s, 1H), 7.13 (t, 1H, J = 7.1 Hz), 7.19 (t, 1H, J = 7.1 Hz), 7.47 (d, 1H, J = 8.1 Hz), 7.64 (d, 1H, J = 2.4 Hz), 7.69 (d, 1H, J = 7.8 Hz). ^{13}C NMR (DMSO) δ 28.1, 30.7, 33.3, 44.4, 50.9, 55.52, 55.54, 56.9, 63.5, 110.3, 110.4, 111.7, 112.1, 119.8, 119.9, 121.5, 125.8, 126.0, 126.8, 127.1, 135.5, 147.0, 147.2, 165.3. MS-ES^+ m/z 434 (MH^+, 100%); HRMS-ES^+ calculated for $C_{26}H_{31}N_3O_3$: 434.2454, found 434.2444.

(5-Bromobenzofuran-2-yl)(4-((3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)methyl)piperidin-1-yl)methanone [34]. Prepared as white solid using 5-bromobenzo[*b*]furan-2-carboxylic acid,[32] mp 75–78 °C, yield 40%; ^{1}H NMR (DMSO) δ 1.15–1.23 (m, 2H), 1.84–1.88 (m, 2H), 1.97–2.01 (m, 1H), 2.35 (d, 2H, J = 7.1 Hz), 2.64 (t, 2H, J = 6.2 Hz), 2.73 (t, J = 5.6 Hz), 3.06 (m, 2H), 3.49 (s, 2H), 3.717 (s, 3H), 3.723 (s, 3H), 4.29 (m, 2H), 6.63 (s, 1H), 6.67 (s, 1H), 7.31 (s, 1H), 7.56–7.59 (m, 1H), 7.65 (d, 1H, J = 1.9 Hz), 7.95 (d, 1H, J = 7.9 Hz). ^{13}C NMR (DMSO) δ 29.0, 31.6, 34.0, 48.2, 51.8, 56.44, 56.46, 56.47, 64.1, 110.0, 111.2, 113.0, 114.5, 116.6, 125.4, 126.9, 127.7, 129.6, 129.8, 147.9, 148.1, 150.8, 153.5, 159.2. MS-EI m/z 512 (M^+, 7), 206 (100%); HRMS-EI calculated for $C_{26}H_{29}{}^{79}BrN_2O_4$: 512.1311, found 512.1309.

(5-Bromo-1*H*-indol-2-yl)(4-((3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)methyl)piperidin-1-yl)methanone [30]. White

solid, mp 212–214 °C, yield 27%; ^{1}H NMR (DMSO) δ 1.15–1.26 (m, 2H), 1.89 (bd, 2H, J = 12.3 Hz), 1.98–2.03 (m, 1H), 2.38 (d, 2H, J = 7.1 Hz), 2.67 (t, 2H, J = 6.3 Hz), 2.76 (t, 2H, J = 5.6 Hz), 3.09 (bs, 2H), 3.51 (s, 2H), 3.74 (s, 3H), 3.75 (s, 3H), 4.42 (bs, 2H), 6.66 (s, 1H), 6.70 (s, 1H), 6.76 (s, 1H), 7.31 (dd, 1H, J = 8.7, 1.9 Hz), 7.42 (d, 1H, J = 8.6 Hz), 7.82 (d, 1H, J = 1.9 Hz). ^{13}C NMR (DMSO) δ 29.0, 31.4, 34.1, 46.0, 51.8, 56.45, 56.46, 64.2, 103.5, 111.2, 112.8, 113.0, 114.7, 124.1, 126.3, 126.9, 127.7, 129.5, 132.7, 135.3, 147.9, 148.1, 162.2. MS-ES$^+$ m/z 511.8 (MH^+, 75), 230 (100%); HRMS-ES$^+$ calculated for $C_{26}H_{30}{}^{79}BrN_3O_3$: 512.1549, found 512.1532.

(4-Bromo-3-methylphenyl)(4-((3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)methyl)piperidin-1-yl)methanone [31]. White solid, mp 50–51 °C, yield 55%; ^{1}H NMR (DMSO) δ 1.09–1.19 (m, 2H), 1.77–1.84 (m, 2H), 1.92–1.98 (m, 1H), 2.35 (d, 2H, J = 7.1 Hz), 2.41 (s, 3H), 2.65 (t, 2H, J = 6.0 Hz), 2.74 (t, J = 5.6 Hz), 2.93–3.04 (m, 2H), 3.50 (s, 2H), 3.73 (s, 3H), 3.74 (s, 3H), 4.05 (bs, 2H), 6.65 (s, 1H), 6.69 (s, 1H), 7.15 (dd, 1H, J = 8.2, 2.1 Hz), 7.38 (s, 1H), 7.66 (d, 1H, J = 8.1 Hz). ^{13}C NMR (DMSO) δ 22.9, 29.0, 31.2, 34.0, 47.5, 51.7, 56.36, 56.38, 64.2, 111.1, 113.0, 125.6, 126.6, 126.9, 127.7, 130.0, 132.8, 136.8, 138.3, 147.8, 148.1, 168.6. MS-ES$^+$ m/z 488 (MH^+, 100%); HRMS-EI calculated for $C_{25}H_{31}{}^{79}BrN_2O_3$: 487.1596, found 487.1581.

(5-Bromo-1*H*-indol-3-yl)(4-((3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)methyl)piperidin-1-yl)methanone [32]. Off-white solid, mp 215–217 °C, yield 38%; ^{1}H NMR (DMSO) δ 1.07–1.18 (m, 2H), 1.78 (bd, 2H, J = 10.9 Hz), 1.89–1.94 (m, 1H), 2.32 (d, 2H, J = 7.1 Hz), 2.61 (t, 2H, J = 6.1 Hz), 2.71 (t, 2H, J = 5.3 Hz), 2.98 (bt, 2H, J = 11.4 Hz), 3.46 (s, 2H), 3.700 (s, 3H), 3.703 (s, 3H), 4.26 (bd, 2H, J = 11.1 Hz), 6.61 (s, 1H), 6.65 (s, 1H), 7.26 (dd, 1H, J = 8.6, 1.9 Hz), 7.40 (d, 1H, J = 8.6 Hz), 7.68 (s, 1H), 7.82 (d, 1H, J = 1.9 Hz). ^{13}C NMR (DMSO) δ 28.1, 30.6, 33.3, 44.4, 50.9, 55.5, 55.6, 56.7, 63.4, 109.7, 110.2, 112.0, 112.6, 113.7, 122.3, 124.2, 126.0, 126.7, 128.0, 128.5, 134.3, 146.9, 147.2, 164.5. MS-EI m/z 512 (M^+, 100%); HRMS-EI calculated for $C_{26}H_{31}N_3O_3{}^{79}Br$: 512.1549, found 512.1542.

(4-((3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)methyl)piperidin-1-yl)(5-iodobenzofuran-2-yl)methanone [35]. Prepared from 5-iodobenzo[*b*]furan-2-carboxylic acid[33] as a clear film, yield 42%; ^{1}H NMR ($CDCl_3$) δ 1.23–1.30 (m, 2H), 1.93–2.03 (m, 3H), 2.39 (d, 2H, J = 6.4 Hz), 2.51 (m, 2H), 2.70 (t, 2H, J = 6.0 Hz), 2.82–2.95 (m, 2H), 3.54 (s, 2H), 3.83 (s, 3H), 3.84 (s, 3H), 4.36–4.66 (m, 2H), 6.52 (s, 1H), 6.60 (s, 1H), 7.14 (s, 1H) 7.27 (d, 1H, J = 8.4 Hz), 7.63 (dd, 1H, J = 8.8, 2.0 Hz), 7.97 (d, 1H, J = 2.0 Hz). ^{13}C NMR ($CDCl_3$) δ 28.8, 30.8, 34.3, 43.5, 47.3, 51.6, 56.07, 56.09, 56.5, 64.2, 87.1, 109.6, 110.1, 111.6, 114.0, 126.4, 126.8, 129.9, 131.1, 135.0, 147.4, 147.7, 150.3, 154.0, 159.5. MS-ES$^+$ m/z 561.2 (MH^+, 100%); HRMS-ES$^+$ calculated for $C_{26}H_{30}N_2O_4I$: 561.4236, found 561.4240.

5-Bromobenzofuran-2-yl)(4-(2-(3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)ethyl)piperidin-1-yl)methanone [36]. White solid, mp 92–95 °C, yield 51%; ^{1}H NMR (DMSO) δ 1.16–1.24 (m, 2H), 1.49 (q, 2H, J = 7.2 Hz), 1.67–1.70 (m, 1H), 1.79 (bd, 2H, J = 12.5 Hz), 2.45–2.51 (m, 2H), 2.60 (t, 2H, J = 6.0 Hz), 2.70 (t, 2H, J = 5.5 Hz), 3.00 (bs, 2H), 3.45 (s, 2H), 3.69 (s, 3H), 3.70 (s, 3H), 4.25 (bs, 2H), 6.62 (s, 1H), 6.64 (s, 1H), 7.28 (s, 1H), 7.48 (d, 1H, J = 8.8 Hz), 7.60 (dd, 2H, J = 8.8, 2.0 Hz), 7.94 (d, 1H, J = 2.0 Hz). ^{13}C NMR (DMSO) δ 28.2, 31.9, 32.8, 33.4, 50.6, 54.6, 54.9, 55.1, 55.51, 55.54, 109.1, 110.2, 112.0, 113.7, 115.7, 124.6, 126.0, 126.8, 128.7, 128.9, 146.9, 147.2, 149.9, 152.6, 158.3. MS-ES$^+$ m/z 528 (MH^+, 100%); HRMS-ES$^+$ calculated for $C_{27}H_{32}N_2O_4{}^{79}Br$: 528.6352, found 528.6360.

(5-Bromobenzofuran-2-yl)(4-(3-(3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)propyl)piperidin-1-yl)methanone [37]. White foam, mp 62–64 °C, yield 36%; ^{1}H NMR ($CDCl_3$) δ 1.23–1.29 (m, 4H), 1.62–1.66 (m, 3H), 1.82 (bd, 2H, J = 11.7 Hz), 2.47–2.51 (m, 2H), 2.70 (t, 2H, J = 6.1 Hz), 2.82 (t, 2H, J = 5.8 Hz), 3.20 (bs, 2H), 3.55 (s, 2H), 3.825 (s, 3H), 3.832 (s, 3H), 4.52 (bd, 2H), 6.51 (s, 1H), 6.58 (s, 1H), 7.15 (s, 1H), 7.31 (d, 1H, J = 8.7 Hz), 7.46 (dd, 2H, J = 8.8, 2.0 Hz), 7.76 (d, 1H, J = 1.9 Hz). ^{13}C NMR ($CDCl_3$) δ 21.6, 24.0, 32.2, 33.4, 35.8, 43.4, 49.1, 52.1, 54.8, 56.1, 56.2, 109.4, 110.6, 111.4, 113.5, 116.7, 118.2, 122.6, 124.8, 129.1, 129.4, 148.8, 149.4, 150.5, 153.3, 159.4. MS-ES$^+$ m/z 542 (MH^+, 100%); HRMS-EI calculated for $C_{26}H_{33}N_2O_4{}^{79}Br$: 541.1689, found 541.1693.

(4-(2-(3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)ethyl)piperidin-1-yl)(5-iodobenzofuran-2-yl)methanone [38]. Brown wax, yield 50%; ^{1}H NMR ($CDCl_3$) δ 1.22–1.29 (m, 2H), 1.57–1.59 (m, 2H), 1.79 (m, 1H), 1.82 (bd, 2H, J = 11.7 Hz), 2.55 (t, 2H, J = 8.0 Hz), 2.69 (t, 2H, J = 6.4 Hz), 2.81 (t, 2H, J = 5.6 Hz), 3.13 (bs, 2H), 3.54 (s, 2H), 3.820 (s, 3H), 3.824 (s, 3H), 4.58 (bd, 2H), 6.51 (s, 1H), 6.58 (s, 1H), 7.13 (s, 1H), 7.27 (d, 1H, J = 8.9 Hz), 7.63 (dd, 1H, J = 8.8, 2.0 Hz), 7.96 (d, 1H, J = 1.2 Hz). ^{13}C NMR ($CDCl_3$) δ 14.8, 28.9, 32.9, 33.7, 34.5, 44.6, 47.3, 51.2, 55.6, 55.9, 56.0, 87.1, 109.6, 110.3, 111.5, 113.9, 126.2, 126.6, 129.8, 131.0, 134.9, 147.3, 147.7, 150.2, 153.9, 159.3. MS-EI m/z 574 (M^+, 39), 206 (100%); HRMS-EI calculated for $C_{27}H_{31}N_2O_4I$: 574.4526, found 574.4530.

(4-(3-(3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)propyl)piperidin-1-yl)(5-iodobenzofuran-2-yl)methanone [39]. White solid, yield 43%, mp 162–163 °C; ^{1}H NMR ($CDCl_3$) δ 1.23–1.29 (m, 4H), 1.62–1.66 (m, 1H), 1.82 (m, 4H), 2.87–3.20 (m, 8H), 3.83 (s, 3H), 3.85 (s, 3H), 4.06 (s, 2H), 4.50 (bd, 2H), 6.52 (s, 1H), 6.61 (s, 1H), 7.14 (s, 1H), 7.28 (d, 1H, J = 1.7 Hz), 7.63 (dd, 1H, J = 8.7, 1.8 Hz), 7.96 (d, 1H, J = 1.7 Hz). ^{13}C NMR ($CDCl_3$) δ 25.5, 29.8, 32.9, 33.6, 35.6, 43.6, 49.6, 53.4, 56.09, 56.14, 60.5, 87.1, 109.5, 110.2, 111.4, 114.0, 124.3, 129.8, 129.9, 131.1, 135.0, 147.9, 148.3, 150.2, 154.0, 159.4. MS-EI m/z 588 (M^+, 42), 341 (100%); HRMS-EI calculated for $C_{28}H_{33}N_2O_4I$: 588.1301, found 588.1289.

Preparation of compounds 40–46

To a solution of the appropriate nitrile derivative (1 eq.) in DMF (20 mL) was added either 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (1 eq.), or 6-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride[34] (1 eq.), or 7-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (1 eq.), followed by K_2CO_3 (4 eq.), TBAI (0.1 eq.) and KI (0.01 eq.) and the solution stirred for 16 h. The reaction mixture was then diluted with EtOAc (100 mL) and extracted with H_2O (3 × 20 mL), sat.

$NaHCO_3$ (25 mL), brine (25 mL) and H_2O (20 mL). The organic layers were combined, dried (Na_2SO_4) and the organic solvent removed. The residue was purified column chromatography (EtOAc–MeOH, 9 : 1).

4-(3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)butanenitrile.[27] **[40].** White solid, mp 106–108 °C, yield 85%; ^{1}H NMR ($CDCl_3$) δ 2.47 (t, 2H, J = 7.1 Hz), 2.62 (t, 2H, J = 6.7 Hz), 2.70 (t, 2H, J = 6.1 Hz), 2.81 (t, 2H, J = 5.8 Hz), 3.54 (s, 2H), 3.83 (s, 3H), 3.84 (s, 3H), 6.51 (s, 1H), 6.59 (s, 1H,). MS-EI m/z 260 (M^+, 42), 164 (100%).

5-(3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)pentanenitrile [41]. Clear oil, yield 83%; ^{1}H NMR ($CDCl_3$) δ 1.73–1.77 (m, 4H), 2.39 (t, 2H, J = 6.6 Hz), 2.53 (t, 2H, J = 6.6 Hz), 2.69 (t, 2H, J = 6.0 Hz), 2.81 (t, 2H, J = 5.8 Hz), 3.54 (s, 2H), 3.83 (s, 3H), 3.84 (s, 3H), 6.52 (s, 1H), 6.59 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 17.2, 23.5, 26.0, 28.6, 51.0, 55.8, 55.99, 56.02 57.0, 109.6, 111.5, 119.8, 126.2, 126.4, 147.4, 147.6. MS-EI m/z 274 (M^+, 33), 206 (100%); HRMS-EI calculated for $C_{16}H_{22}N_2O_2$: 274.3206, found 274.3210.

6-(3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)hexanenitrile [42]. Red oil, yield 86%; ^{1}H NMR ($CDCl_3$) δ 1.73–1.77 (m, 4H), 2.40–2.42 (m, 2H), 2.52–2.55 (m, 2H), 2.69 (t, 2H, J = 6.0 Hz), 2.81 (t, 2H, J = 5.8 Hz), 3.54 (s, 2H), 3.83 (s, 3H), 3.84 (s, 3H), 6.52 (s, 1H), 6.59 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 17.2, 23.5, 25.9, 26.0, 28.6, 51.0, 52.3, 55.7, 56.0, 57.0, 109.6, 111.5, 119.8, 126.2, 126.4, 147.4, 147.7. MS-EI m/z 288 (M^+, 2), 206 (100%); HRMS-EI calculated for $C_{17}H_{24}N_2O_2$: 288.6578, found 288.6583.

4-(3,4-Dihydro-6-methoxyisoquinolin-2(1*H*)-yl)butanenitrile [43]. White solid. yield 76%, from 6-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride;[34] ^{1}H NMR ($CDCl_3$) δ 1.92 (pentet, 2H, J = 6.9 Hz), 2.47 (t, 2H, J = 7.1 Hz), 2.62 (t, 2H, J = 6.7 Hz), 2.71 (t, 2H, J = 6.1 Hz), 2.87 (t, 2H, J = 5.8 Hz), 3.55 (s, 2H), 3.77 (s, 3H), 6.63 (d, 1H, J = 2.6 Hz), 6.70 (dd, 1H, J = 8.4, 2.6 Hz), 6.92 (d, 1H, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$) δ 15.0, 23.3, 29.5, 51.0, 55.4, 55.6, 56.2, 112.3, 113.4, 120.0, 126.8, 127.6, 135.5, 158.2. MS-EI m/z 230 (M^+, 28), 176 (100%); HRMS-EI calculated for $C_{14}H_{18}N_2O$: 230.1340, found 230.1334.

5-(3,4-Dihydro-6-methoxyisoquinolin-2(1*H*)-yl)pentanenitrile [44]. White solid, yield 61%; ^{1}H NMR ($CDCl_3$) δ 1.73–1.76 (m, 4H), 2.39–2.42 (m, 2H), 2.51–2.55 (m, 2H), 2.69 (t, 2H, J = 6.0 Hz), 2.87 (t, 2H, J = 5.8 Hz), 3.54 (s, 2H), 3.77 (s, 3H), 6.63 (d, 1H, J = 2.6 Hz), 6.71 (dd, 1H, J = 8.4, 2.7 Hz), 7.01 (d, 1H, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$) δ 17.2, 23.5, 26.1, 29.5, 51.0, 55.3, 55.8, 57.2, 112.2, 113.3, 119.8, 127.0, 127.6, 135.5, 158.1. MS-EI m/z 244 (M^+, 23), 176 (100%); HRMS-EI calculated for $C_{15}H_{20}N_2O$: 244.1497, found 244.1497.

4-(3,4-Dihydro-7-methoxyisoquinolin-2(1*H*)-yl)butanenitrile [45]. White solid, yield 77%; ^{1}H NMR ($CDCl_3$) δ 1.91 (pentet, 2H, J = 6.9 Hz), 2.45 (t, 2H, J = 7.1 Hz), 2.63 (t, 2H, J = 6.7 Hz), 2.71 (t, 2H, J = 6.1 Hz), 2.82 (t, 2H, J = 5.8 Hz), 3.59 (s, 2H), 3.77 (s, 3H), 6.56 (d, 1H, J = 2.7 Hz), 6.72 (dd, 1H, J = 8.4, 2.7 Hz), 7.01 (d, 1H, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$) δ 15.0, 23.2, 28.3, 51.1, 55.4, 56.0, 56.3, 111.3, 112.7, 119.9, 126.4, 129.7, 135.6, 157.7. MS-EI m/z 230 (M^+, 74), 176 (100%); HRMS-EI calculated for $C_{14}H_{18}N_2O$: 230.1419, found 230.1422.

5-(3,4-Dihydro-7-methoxyisoquinolin-2(1*H*)-yl)pentanenitrile [46]. White solid, yield 59%; ^{1}H NMR ($CDCl_3$) δ 1.74–1.78 (m, 4H), 2.40–2.43 (m, 2H), 2.52–2.56 (m, 2H), 2.60 (t, 2H, J = 6.0 Hz), 2.83 (t, 2H, J = 5.8 Hz), 3.59 (s, 2H), 3.78 (s, 3H), 6.56 (d, 1H, J = 2.6 Hz), 6.71 (dd, 1H, J = 8.4, 2.7 Hz,), 7.01 (d, 1H, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$) δ 17.2, 23.5, 26.1, 28.3, 51.2, 55.4, 56.4, 57.1, 111.4, 112.7, 119.8, 126.5, 129.7, 135.7, 157.7. MS-EI m/z 244 (M^+, 23), 176 (100%); HRMS-EI calculated for $C_{15}H_{20}N_2O$: 244.1576, found 244.1564.

Preparation of compounds 47–53

To a suspension of $LiAlH_4$ (3 eq.) in dry THF (50 mL) was added the appropriate nitrile (1 eq.) in dry THF (25 mL) dropwise under a stream of N_2. The resulting mixture was heated at reflux for 18 h under N_2. To the cooled solution at 0 °C was added iced H_2O (5 mL) and 10% NaOH (15 mL). The solution was warmed to rt and allowed to stir for 15 min. The resulting suspension was filtered through celite and the filter cake washed with EtOAc (50 mL). The organic layer was dried (Na_2SO_4) and solvent removed to give **46–52** which were used without further purification.

4-(3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)butan-1-amine [47]. Yellow oil, yield 65%; ^{1}H NMR ($CDCl_3$) δ 1.49 (m, 2H), 1.62 (m, 2H), 2.49 (t, 2H, J = 8.0 Hz), 2.71 (m, 4H), 2.80 (t, 2H, J = 5.6 Hz), 3.53 (s, 2H), 3.81 (s, 3H), 3.83 (s, 3H), 6.50 (s, 1H), 6.57 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 25.0, 27.2, 30.6, 41.0, 53.1, 54.9, 56.0, 56.1, 58.9, 110.9, 112.5, 126.1, 129.1, 147.2, 148.8. MS-ES$^+$ m/z 265.1 (MH^+, 100%); HRMS calculated for $C_{15}H_{24}N_2O_2$: 264.1838, found 264.1832.

5-(3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)pentan-1-amine [48]. Yellow oil, yield 62%; ^{1}H NMR ($CDCl_3$) δ 1.23–1.62 (m, 6H), 2.45–2.49 (m, 2H), 2.67–2.71 (m, 4H), 2.80 (t, 2H, J = 5.9 Hz), 3.52 (s, 2H), 3.805 (s, 3H), 3.81 (s, 3H), 6.50 (s, 1H), 6.56 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 25.0, 27.2, 28.7, 33.6, 42.0, 51.2, 55.9, 56.0, 56.02, 58.4, 109.6, 111.5, 126.3, 126.8, 147.3, 147.6. MS-ES$^+$ m/z 279 (MH^+, 41), 181 (100%); HRMS-EI calculated for $C_{16}H_{26}N_2O_2$: 278.1994, found 278.1977.

6-(3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)hexan-1-amine [49]. Yellow oil, yield 68%; ^{1}H NMR ($CDCl_3$) δ 1.22–1.46 (m, 8H), 1.58 (bs, 2H), 2.48 (t, 2H, J = 7.8 Hz), 2.60–2.66 (m, 4H), 2.76 (t, 2H, J = 5.6 Hz), 3.48 (s, 2H), 3.77 (s, 3H), 3.78 (s, 3H), 6.51 (s, 1H), 6.57 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 26.9, 27.2, 27.5, 28.7, 33.5, 42.0, 51.1, 55.8, 55.9, 56.0, 58.4, 110.6, 111.9, 126.8, 127.1, 147.6, 147.9. MS-ES$^+$ m/z 293 (MH^+, 50), 188 (100%); HRMS-EI calculated for $C_{17}H_{28}N_2O_2$: 292.2151, found 292.2144.

4-(3,4-Dihydro-6-methoxyisoquinolin-2(1*H*)-yl)butan-1-amine [50]. Yellow oil, yield 94%; ^{1}H NMR ($CDCl_3$) δ 1.54–1.56 (m, 2H), 1.67 (m, 2H), 2.52 (t, 2H, J = 7.6 Hz), 2.64–2.77 (m, 4H), 2.86–2.89 (m, 2H), 3.61 (s, 2H), 3.78 (s, 3H), 6.61 (d, 1H, J = 2.6 Hz), 6.68 (dd, 1H, J = 8.4, 2.6 Hz), 6.90 (dd, 1H, J = 8.3, 2.8 Hz). ^{13}C NMR ($CDCl_3$) δ 24.6, 29.4, 31.7, 42.0, 50.9, 55.2, 55.7, 58.3, 112.1, 113.2, 127.1, 127.5, 135.5, 157.9. MS-EI m/z 234 (M^+, 1), 162 (100%); HRMS-EI calculated for $C_{14}H_{22}N_2O$: 234.1654, found 234.1653.

5-(3,4-Dihydro-6-methoxyisoquinolin-2(1*H*)-yl)pentan-1-amine [51]. Yellow oil, yield 95%; ^{1}H NMR ($CDCl_3$) δ 1.34–1.62 (m, 8H), 2.48 (t, 2H, J = 7.8 Hz), 2.67–2.70 (m, 4H), 2.86 (t, 2H, J = 5.8 Hz), 3.54 (s, 2H), 3.75 (s, 3H), 6.61 (d, 1H, J = 2.4 Hz), 6.66 (dd, 1H, J = 8.4, 2.5 Hz), 6.91 (d, 1H, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$) δ 24.9, 27.1, 29.4, 33.6, 42.0, 51.0, 55.3, 55.7, 58.5, 112.1, 113.2, 127.2, 127.5, 135.5, 158.0. MS-EI m/z 248 (M^+, 18), 42 (100%); HRMS-EI calculated for $C_{15}H_{24}N_2O$: 248.3602, found 248.3612.

4-(3,4-Dihydro-7-methoxyisoquinolin-2(1*H*)-yl)butan-1-amine [52]. Yellow oil, yield 89%; ^{1}H NMR ($CDCl_3$) δ 1.48–1.84 (m, 6H), 2.50 (t, 2H, J = 7.7 Hz), 2.71 (m, 4H), 2.82 (t, 2H, J = 5.8 Hz), 3.59 (s, 2H), 3.76 (s, 3H), 6.55 (d, 1H, J = 2.5 Hz), 6.69 (dd, 1H, J = 8.4, 2.6 Hz), 6.99 (d, 1H, J = 8.4 Hz) ^{13}C NMR ($CDCl_3$) δ 24.7, 28.3, 31.7, 42.1, 51.3, 55.3, 56.4, 62.4, 111.4, 112.6, 126.5, 129.6, 135.9, 157.7. MS-EI m/z 234 (M^+, 15), 162 (100%); HRMS-EI calculated for $C_{14}H_{22}N_2O$: 234.1732, found 234.1737.

5-(3,4-Dihydro-7-methoxyisoquinolin-2(1*H*)-yl)pentan-1-amine [53]. Yellow oil, yield 77%; ^{1}H NMR ($CDCl_3$) δ 1.35–1.63 (m, 6H), 1.79 (bs, 2H), 2.48 (t, 2H, J = 7.6 Hz), 2.67–2.70 (m, 4H), 2.81 (m, 2H, J = 5.6 Hz), 3.57 (s, 2H), 3.75 (s, 3H), 6.54 (dd, 1H, J = 2.4 Hz), 6.68 (dd, 1H, J = 8.4 Hz, 2.4 Hz), 6.98 (d, 1H, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$) δ 24.9, 27.2, 28.3, 33.7, 42.2, 51.3, 55.3, 56.5, 58.4, 111.4, 112.6, 126.6, 129.6, 136.0, 157.7. MS-EI m/z 248 (M^+, 15), 32 (100%); HRMS-EI calculated for $C_{14}H_{22}N_2O$: 248.3604, found 248.3609.

Preparation of compounds 54–63

Compounds **54–63** were prepared using the same method for compounds **22–39**.

5-Bromo-*N*-(4-(3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)butyl)-1-benzofuran-2-carboxamide [54]. Clear film, yield 23%; ^{1}H NMR ($CDCl_3$) δ 1.74 (m, 4H), 2.57 (t, 2H, J = 6.7 Hz), 2.74 (t, 2H, J = 6.2 Hz), 2.83 (t, 2H, J = 5.6 Hz), 3.50 (dt, 2H, J = 5.8 Hz), 3.56 (s, 2H), 3.79 (s, 3H), 3.82 (s, 3H), 7.16 (s, 1H), 7.18 (s, 1H), 7.25 (m, 2H), 7.38 (m, 1H), 7.43 (dd, 1H, J = 8.8, 2.0 Hz), 7.71 (d, 1H, J = 2.0 Hz). ^{13}C NMR δ 24.8, 27.3, 28.5, 39.4, 50.7, 55.9, 55.99, 56.00, 57.4, 109.2, 109.6, 111.5, 113.3, 116.7, 125.2, 126.1, 126.2, 129.5, 129.6, 147.5, 147.8, 150.2, 153.4, 158.6. MS-ES$^+$ m/z 488 (MH^+, 100%); HRMS-ES$^+$ calculated for $C_{24}H_{38}N_2O_4{}^{79}Br$: 488.3659, found 488.3652.

5-Bromo-*N*-(5-(3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)pentyl)-1-benzofuran-2-carboxamide [55]. Clear film, yield 23%; ^{1}H NMR ($CDCl_3$) δ 1.45–1.49 (m, 2H), 1.62–1.69 (m, 4H), 2.48 (t, 2H, J = 7.5 Hz), 2.67 (t, 2H, J = 6.1 Hz), 2.78 (t, 2H, J = 5.6 Hz), 3.44–3.49 (m, 2H), 3.52 (s, 2H), 3.80 (s, 3H), 3.81 (s, 3H), 6.49 (s, 1H), 6.55 (s, 1H), 6.74 (bt, 1H, J = 3.9 Hz), 7.26–7.35 (m, 2H), 7.46 (dd, 1H, J = 8.8, 2.0 Hz), 7.75 (d, 1H, J = 2.0 Hz). ^{13}C NMR ($CDCl_3$) δ 24.8, 26.9, 28.7, 29.6, 39.4, 51.1, 55.87, 55.92, 55.95, 58.1, 109.4, 109.5, 111.4, 113.2, 116.7, 125.3, 126.2, 126.6, 129.6, 129.8, 147.2, 147.5, 150.0, 153.4, 158.4. MS-ES$^+$ m/z 502 (MH^+, 100%); HRMS-ES$^+$ calculated for $C_{25}H_{28}N_2O_4{}^{79}Br$: 502.5639 found 502.5643.

5-Bromo-*N*-(6-(3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)hexyl)-1-benzofuran-2-carboxamide [56]. Clear film, yield 35%; ^{1}H NMR ($CDCl_3$) δ 1.39–1.46 (m, 4H), 1.61–1.68 (m, 4H), 2.48–2.54 (m, 2H), 2.70 (t, 2H, J = 6.1 Hz), 2.81 (t, 2H, J = 5.8 Hz), 3.47 (m, 2H), 3.54 (s, 2H), 3.82 (s, 3H), 3.83 (s, 3H), 6.50 (s, 1H), 6.58 (s, 1H), 6.62 (t, 1H, J = 5.3 Hz), 7.38 (m, 2H), 7.49 (dd, 1H, J = 8.8, 2.0 Hz), 7.80 (d, 1H, J = 1.9 Hz). ^{13}C NMR ($CDCl_3$) δ 26.6, 27.1, 26.8, 27.8, 29.6, 39.5, 50.7, 55.2, 56.01, 56.04, 57.6, 109.5, 109.6, 111.4, 113.4, 116.9, 125.2, 125.4, 129.6, 129.9, 131.2, 147.5, 147.9, 150.1, 153.5, 158.5. MS-ES$^-$ m/z 513 (M − 1, 100%); HRMS-ES$^-$ calculated for $C_{26}H_{30}N_2O_4{}^{79}Br$: 513.1389, found 513.1375.

5-Iodo-*N*-(4-(3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)-butyl)-1-benzofuran-2-carboxamide [57]. White wax, yield 47%; ^{1}H NMR ($CDCl_3$) δ 1.73–1.74 (m, 4H), 2.55 (m, 2H), 2.71 (t, 2H, J = 6.0 Hz), 2.82 (t, 2H, J = 5.6 Hz), 3.50 (m, 2H), 3.55 (s, 2H), 3.79 (s, 3H), 3.82 (s, 3H), 6.47 (s, 1H), 6.56 (s, 1H), 7.05 (d, 1H, J = 8.7 Hz), 7.23 (s, 1H), 7.38 (m, 1H), 7.59 (d, 1H, J = 8.7 Hz,), 7.90 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 24.9, 27.4, 28.6, 39.5, 50.7, 55.99, 56.02, 57.5, 87.2, 108.9, 109.6, 111.5, 113.8, 126.2, 126.5, 130.2, 131.4, 135.2, 147.4, 147.7, 149.8, 154.0, 158.5. MS-ES$^+$ m/z 535 (MH^+, 100%); HRMS-EI calculated for $C_{24}H_{27}N_2O_4I$: 534.1016, found 534.1011.

5-Iodo-*N*-(5-(3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)-pentyl)-1-benzofuran-2-carboxamide [58]. Brown wax, yield 30%; ^{1}H NMR ($CDCl_3$) δ 1.46–1.50 (m, 2H), 1.62–1.70 (m, 4H), 2.51 (m, 2H), 2.69 (t, 2H, J = 6.2 Hz), 2.80 (t, 2H, J = 5.7 Hz), 3.48 (t, 2H, J = 7.0 Hz), 3.53 (s, 2H), 3.82 (s, 3H), 3.82 (s, 3H), 6.50 (s, 1H), 6.56 (s, 1H), 6.71 (m, 1H), 7.22 (d, 1H, J = 8.7 Hz), 7.34 (s, 1H), 7.64 (dd, 1H, J = 8.7, 1.8 Hz), 7.98 (d, 1H, J = 1.7 Hz). ^{13}C NMR ($CDCl_3$) δ 23.7, 24.9, 26.9, 28.7, 39.4, 51.1, 55.9, 56.97, 57.00, 58.1, 87.2, 109.1, 109.6, 111.5, 113.7, 126.3, 126.7, 128.0, 131.5, 135.4, 147.3, 147.6, 149.7, 154.0, 158.4. MS-ES$^+$ m/z 549 (MH^+, 100%); HRMS-ES$^+$ calculated for $C_{25}H_{30}N_2O_4I$: 549.1250, found 549.1262.

5-Iodo-*N*-(6-(3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)-hexyl)-1-benzofuran-2-carboxamide [59]. Brown wax, yield 41%; ^{1}H NMR ($CDCl_3$) δ 1.41 (m, 4H), 1.62 (m, 4H), 2.48 (m, 2H), 2.68 (t, 2H, J = 6.1 Hz), 2.80 (t, 2H, J = 5.7 Hz), 3.45 (t, 2H, J = 7.0 Hz), 3.53 (s, 2H), 3.81 (s, 3H), 3.82 (s, 3H), 6.50 (s, 1H), 6.57 (s, 1H), 6.66 (m, 1H), 7.24 (d, 1H, J = 8.7 Hz), 7.35 (s, 1H), 7.65 (dd, 1H, J = 8.7, 1.8 Hz), 7.98 (d, 1H, J = 1.7 Hz). ^{13}C NMR δ 27.0, 27.2, 27.3, 28.7, 29.7, 39.5, 51.1, 55.9, 56.00, 56.02, 58.4, 87.3, 109.2, 109.6, 111.5, 113.8, 126.3, 126.8, 130.4, 131.6, 135.5, 147.3, 147.6, 149.7, 154.1, 158.4. MS-ES$^+$ m/z 563 (MH^+, 100%); HRMS-ES$^+$ calculated for $C_{26}H_{32}N_2O_4I$: 563.1407, found 563.1413.

5-Iodo-*N*-(4-(3,4-dihydro-6-methoxyisoquinolin-2(1*H*)-yl)butyl)-1-benzofuran-2-carboxamide [60]. White solid, mp 72–74 °C, yield 51%; ^{1}H NMR ($CDCl_3$) δ 1.74 (m, 4H), 2.56 (t, 2H, J = 6.6 Hz), 2.72 (t, 2H, J = 6.0 Hz), 2.88 (t, 2H, J = 5.7 Hz), 3.50 (m, 2H), 3.58 (s, 2H), 3.76 (s, 3H), 6.61 (d, 1H, J = 2.5 Hz), 6.69 (dd, 1H, J = 8.4, 2.6 Hz), 6.91 (d, 1H, J = 8.4 Hz), 7.06 (d, 1H, J = 8.7 Hz), 7.22 (s, 1H), 7.40 (m, 1H), 7.60 (dd, 1H, J = 8.7, 1.7 Hz), 7.90 (d, 1H, J = 1.6 Hz). ^{13}C NMR ($CDCl_3$) δ 24.9, 27.4, 29.4, 39.5, 50.6, 55.4, 55.9, 57.6, 87.2, 108.9, 112.3, 113.4, 113.8, 126.9, 127.6, 130.3, 131.5, 135.3, 135.5, 149.8, 154.1, 158.1, 158.5 (CO). MS-ES$^+$ m/z 505 (MH^+, 100%); HRMS-ES$^+$ calculated for $C_{23}H_{26}N_2O_3I$: 505.0988, found 505.0982.

5-Iodo-*N*-(5-(3,4-dihydro-6-methoxyisoquinolin-2(1*H*)-yl)pentyl)-1-benzofuran-2-carboxamide [61]. Brown wax, yield 34%, ^{1}H NMR ($CDCl_3$) δ 1.47 (m, 2H), 1.66 (m, 4H), 2.50 (t, 2H, J = 6.7 Hz), 2.69 (t, 2H, J = 5.6 Hz), 2.86 (t, 2H, J = 5.3 Hz), 3.47 (dt, 2H, J = 6.3 Hz), 3.54 (s, 2H), 3.76 (s, 3H), 6.61 (s, 1H), 6.67 (m, 3H), 6.91 (d, 1H, J = 8.4 Hz), 7.23 (d, 1H, J = 8.7 Hz), 7.35 (s, 1H), 7.65 (d, 1H, J = 8.7 Hz), 7.99 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 24.9, 26.9, 29.5, 29.6, 39.5, 51.0, 55.3, 55.8, 58.3, 87.2, 109.2, 112.1, 113.3, 113.8, 127.2, 127.6, 130.3, 131.6, 135.4, 135.6, 149.7, 154.1, 158.0, 158.4. MS-ES$^+$ m/z 519 (MH^+, 100%); HRMS-ES$^+$ calculated for $C_{24}H_{28}N_2O_3I$: 519.1145, found 519.1155.

5-Iodo-*N*-(4-(3,4-dihydro-7-methoxyisoquinolin-2(1*H*)-yl)butyl)-1-benzofuran-2-carboxamide [62]. Brown wax, yield 30%; ^{1}H NMR ($CDCl_3$) δ 1.75–1.77 (m, 4H), 2.55–2.58 (m, 2H), 2.74 (t, 2H, J = 6.0 Hz), 2.84 (t, 2H, J = 5.7 Hz), 3.51–3.53 (m, 2H), 3.62 (s, 2H), 3.76 (s, 3H), 6.53 (d, 1H, J = 2.6 Hz), 6.72 (dd, 1H, J = 8.4, 2.7 Hz), 7.00–7.07 (m, 2H), 7.23 (s, 1H), 7.42–7.44 (m, 1H), 7.61 (dd, 1H, J = 8.7, 1.8 Hz), 7.91 (d, 1H, J = 1.7 Hz). ^{13}C NMR ($CDCl_3$) δ 24.9, 27.4, 28.2, 39.4, 50.8, 55.4, 56.6, 57.4, 87.2, 108.9, 111.4, 112.7, 113.8, 126.5, 129.7, 130.3, 131.5, 135.3, 135.7, 149.8, 154.1, 157.8, 158.6. MS-ES$^+$ m/z 505 (MH^+, 100%); HRMS-ES$^+$ calculated for $C_{23}H_{26}N_2O_3I$: 505.0988, found 505.0980.

5-Iodo-*N*-(5-(3,4-dihydro-7-methoxyisoquinolin-2(1*H*)-yl)pentyl)-1-benzofuran-2-carboxamide [63]. Brown wax, yield 36%; ^{1}H NMR ($CDCl_3$) δ 1.43–1.47 (m, 2H), 1.62–1.69 (m, 4H), 2.50 (t, 2H, J = 7.5 Hz), 2.69 (t, 2H, J = 6.0 Hz), 2.80 (t, 2H, J = 5.7 Hz), 3.46 (m, 2H), 3.57 (s, 2H), 3.74 (s, 3H), 6.52 (d, 1H, J = 2.5 Hz), 6.67 (dd, 1H, J = 8.4, 2.6 Hz), 6.75 (m, 1H), 6.96 (d, 1H, J = 8.4 Hz), 7.21 (d, 1H, J = 8.7 Hz), 7.33 (s, 1H), 7.63 (dd, 1H, J = 8.7, 1.7 Hz), 7.96 (d, 1H, J = 1.7 Hz). ^{13}C NMR ($CDCl_3$) δ 24.9, 26.8, 28.2, 29.6, 39.4, 51.2, 55.3, 56.4, 58.0, 87.2, 109.1, 111.4, 112.6, 113.8, 126.5, 129.6, 130.3, 131.5, 135.4, 135.8, 149.7, 154.0, 157.7, 158.4. MS-ES$^+$ m/z 519 (MH^+, 100%); HRMS-ES$^+$ calculated for $C_{24}H_{28}N_2O_3I$: 519.1145, found 519.1133.

Measurement of biological activity

Competition binding assays for ligands at σ_1 and σ_2 receptors were performed using [^{3}H](+)-PTZ (σ_1), [^{3}H]DTG/500 nM (+)-PTZ (σ_2) and membranes from fresh-frozen, male Sprague Dawley rat brains as previously described.[35] The animal experiments were performed according to the *Australian Code of Practice for the Care and Use of Animals for Scientific Purposes* and were approved by the Animal Care and Ethics Committee of Australian Nuclear Science and Technology Organisation. The animals were obtained from the Animal Resource Centre Pty Ltd (Perth, Australia). Receptor binding assays were performed in triplicate and repeated three independent experiments. IC_{50} values were calculated using Prism software and converted to their corresponding K_i values using Cheng-Prusoff equation,[36] based on a K_d of 2.5 nM for [^{3}H](+)-PTZ and a K_d of 77 nM for [^{3}H]DTG.[35]

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