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Synthesis of 3,7-Disubstituted Imipramines by Palladium-Catalysed Amination/Cyclisation and Evaluation of Their Inhibition of Monoamine Transporters

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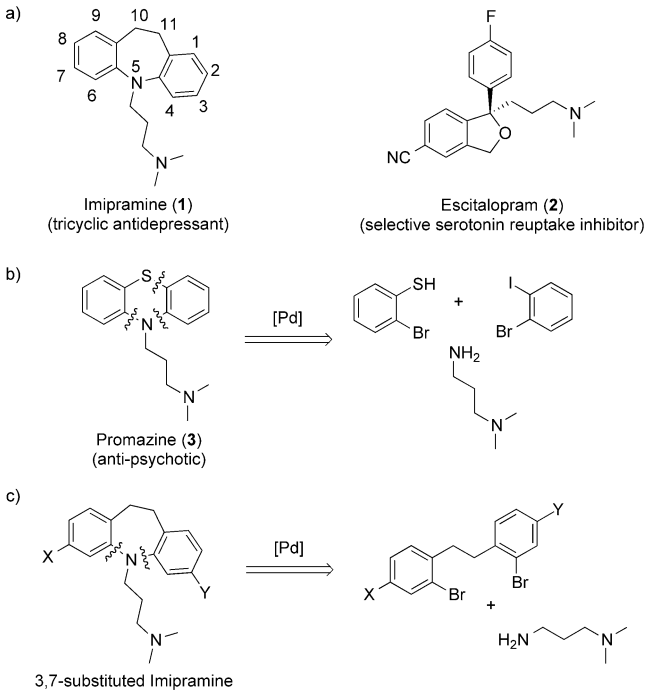
Abstract: We describe a novel approach for the synthesis of a series of 3,7-difunctionalised symmetric and unsymmetrical analogues of the tricyclic antidepressant (TCA) imipramine, which uses a key palladium-catalysed amination/cyclisation of an ester-functionalised dibromide. Of the ester, methyl, hydroxymethyl and methoxymethyl disubstituted compounds prepared, 3,7-dimethyl-imipramine was found to be the most potent against the human serotonin transporter (hSERT). The inhibitory potency of 3,7-dimethyl imipramine was found to be at least as high as the parent imipramine. This novel TCA also exhibits an increased selectivity (relative to imipramine) in binding to hSERT versus the human norepinephrine transporter (hNET). Even higher selectivity could be obtained with 3,7-dihydroxymethyl imipramine, which was found to be 167-fold more selective for hSERT over hNET, representative of a 120-fold gain in selectivity relative to the parent imipramine. These results further validate our previous model for the binding of imipramine and high-affinity analogues of imipramine to the central binding site of hSERT.

Keywords: amination · human serotonin transporter (hSERT) · reuptake inhibitor · palladium · tricyclic antidepressants

Introduction

Depression is a serious disease that results in a significantly reduced quality of life for the patient. It is expected to become the second most costly disease to society by 2020 and is amongst the top five leading causes of disability and disease throughout the world, with treatment options being relatively new.[1] In the 1950s a revolution in psychopharmacology and psychiatry took place with the introduction of the first types of antidepressants.[2] One of the earliest drugs was the tricyclic antidepressant (TCA) imipramine (**1**, Scheme 1 a).[3] To this day, imipramine is considered the "gold-standard" antidepressant because its ability to lift the most severe depressive episodes is still unsurpassed.[4] Its benefits include a high level of inhibition of the human serotonin transporter (hSERT). Imipramine (**1**) and its metabolites can also be toxic,[2] furthermore, **1** has side effects at-



Scheme 1. a) Structure of antidepressants imipramine (**1**) and escitalopram (**2**). b) One-pot palladium-catalysed synthesis of promazine (**3**), see reference [7]. c) Palladium-catalysed cyclisation to 3,7-disubstituted imipramines (this study).

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tributable to inhibition of the human norepinephrine transporter (hNET) or anti-cholinergic effects. Today most antidepressants used to treat mild to moderate depressions are selective serotonin reuptake inhibitors (SSRIs)—for example, escitalopram (**2**, Scheme 1a)—which selectively target hSERT. Due to the transporter specificity, SSRIs generally have fewer side effects than TCAs.

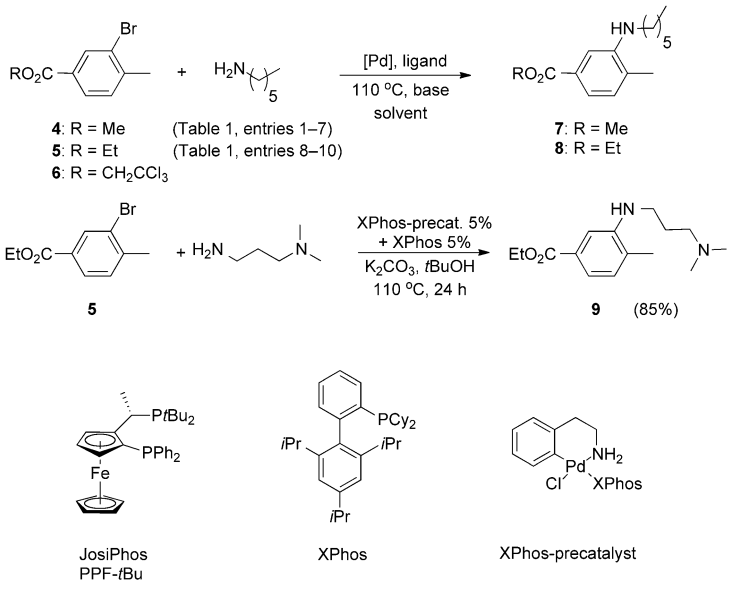
Until recently, knowledge about the molecular architecture of the serotonin transporter upon binding of antidepressants was limited. We have been successful in constructing and experimentally verifying a homology model of hSERT bound to **2**[5] and **1**,[6] which can be used for rational drug design.

In this article, we present the synthesis and inhibition constants of new 3,7-disubstituted imipramine analogues designed to exploit two complementary pockets in hSERT that were established in our previous study.[6] Mutations in these pockets near the 3- and 7-positions of bound imipramine affect the affinity of the 3,7-disubstituted analogues in a manner consistent with our validated model for TCA binding.[6] We further demonstrate that it has been possible to create analogues of **1** that are more selective for hSERT versus hNET by the introduction of substituents in the 3- and 7-positions. This could potentially eliminate some of the side effects associated with hNET inhibition by **1**.

Results and Discussion

Synthesis: For the synthesis of the seven-membered dibenzo-[*b*,*f*]azepine ring of the imipramine analogues we were inspired by the recent elegant approach for the synthesis the anti-psychotic drug promazine (**3**, Scheme 1b), established by Jørgensen and co-workers[7]. The six-membered ring was assembled around the dimethylaminopropyl amine in a three-step one-pot synthesis in the presence of a palladium catalyst and a strong base. In our case, a similar final manoeuvre would require the challenging task of closing a seven-membered ring via an eight-membered intermediate, in the presence of pre-installed ester handles (X and Y) in what would become the 3- and 7-positions of imipramine (Scheme 1c). Although esters are generally incompatible with commonly used strong bases, such as sodium *tert*-butoxide, they facilitate palladium oxidative insertion[8] and can be converted to a variety of other functionalities. Very few examples of Pd-catalysed reactions that result in a seven-membered ring are known.[9] A study by Buchwald and co-workers found that formation of seven-membered rings required long reaction times and, in certain cases, failed to work.[10]

Reaction conditions for the cyclisation process were screened on two monomeric test systems (**4** and **5**, Scheme 2; Table 1). For methyl ester **4** the combination of JosiPhos[11] and $Pd(OAc)_2/K_3PO_4$ in dimethoxyethane (DME) or toluene provided the aniline product **7** in poor yield (Table 1, entries 1 and 2). Changing the palladium source to $[Pd(dba)_2]$, in combination with K_3PO_4 and the XPhos ligand in DME or toluene, gave **7** in improved yields of 29 and 54%, respectively (Table 1, entries 3 and 4). No product, however, was formed when $[Pd(dba)_2]$ (5 mol%) and XPhos (10 mol%) in toluene were used, with either



Scheme 2. Test system for screening the reaction conditions.

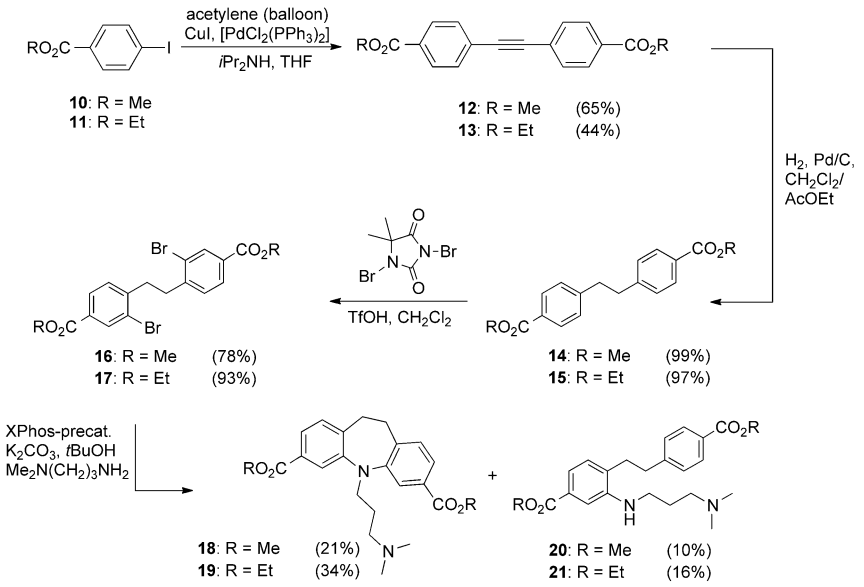
Table 1. Screening of conditions for the reaction shown in Scheme 2 with hexylamine (1.5 equiv).[a]

Entry	Pd cat (mol%)	Ligand (mol%)	Base	Solvent	*t* [h]	Yield [%][b]
1	$Pd(OAc)_2$ (5)	JosiPhos[c] (5)	K_3PO_4	DME	72	5
2	$Pd(OAc)_2$ (5)	JosiPhos[c] (5)	K_3PO_4	$PhCH_3$	72	11
3	$[Pd(dba)_2]$ (5)	XPhos (10)	K_3PO_4	DME	48	29
4	$[Pd(dba)_2]$ (5)	XPhos (10)	K_3PO_4	$PhCH_3$	48	54
5	XPhos precat. (1)	–	K_3PO_4	DME	48	16
6	XPhos precat. (1)	–	K_3PO_4	$PhCH_3$	48	34
7	XPhos precat. (2)	–	K_3PO_4	$PhCH_3$	43	49
8	XPhos precat. (5)	XPhos (5)	K_3PO_4	$PhCH_3$	24	65
9	XPhos precat. (5)	XPhos (5)	K_3PO_4	*t*BuOH	72	48
10	XPhos precat. (5)	XPhos (5)	K_2CO_3	*t*BuOH	18	73

[a] Reactions were carried out in a sealed tube in heating block at 110°C; entries 1–7: R = Me; entries 8–10: R = Et. [b] Isolated product yield after column chromatography. [c] JosiPhos-PPF-*t*Bu.

lithium bis(trimethylsilyl)-amide (LHMDS) or 1,8-diazabicycloundec-7-ene (DBU) as the base.

Buchwald and co-workers have recently developed and commercialised a stable Pd^{II}–XPhos precatalyst, which, upon treatment with base, produces indoline and the active catalyst Pd^0–XPhos (Scheme 2).[12] Reaction with this precatalyst (1 mol%) in the presence of K_3PO_4 in either DME or toluene resulted in incomplete conversion of starting material but did provide the aniline product **7** in moderate yields, again with the latter solvent being superior (Table 1, entries 5 and 6). Increasing the catalyst loading to 2 mol% and performing the reaction in toluene with K_3PO_4 (Table 1, entry 7) resulted in an improved conversion and product yield (49 versus 34%). The yield was further improved to 65% for reaction of the ethyl ester **5** in the presence of additional ligand (Table 1, entry 8) to give aniline **8**.



Scheme 3. Synthetic route to methyl and ethyl ester-substituted imipramines **18** and **19**.

Reaction of ethyl ester **5** in *tert*-butanol was investigated with both K_3PO_4 and K_2CO_3 in combination with the XPhos precatalyst and additional XPhos (Table 1, entries 9 and 10). In a reasonable reaction time (18 h), K_2CO_3 was found to give the best result so far in terms of yield (73%), whereas K_3PO_4 reacted more sluggishly under otherwise identical reaction conditions and produced the same product in 48% yield.

For ease of reaction monitoring by TLC analysis *n*-hexylamine was used as a model amine. Reaction of dimethylaminopropyl amine with **5** under the K_2CO_3/XPhos precatalyst/*tert*-butanol conditions described above gave aniline **9** in 85% isolated yield (Scheme 2).

Having established successful reaction conditions for the monomeric test system (Scheme 2), we progressed to the preparation of the cyclisation precursors (Scheme 1c). Commercially available methyl and ethyl *p*-iodobenzoate (**10** and **11**, respectively) were each reacted in a double Sonogashira coupling with acetylene gas to give alkynes **12** and **13**,[13] respectively, in acceptable yields.[14] Palladium/charcoal-catalysed reduction quantitatively resulted in alkanes **14** and **15**, respectively, which each underwent bromination with 1,3-dibromo-5,5-dimethyl hydantoin (DBMH)[15] and triflic acid (TfOH) in dichloromethane to provide the respective dibromides **16** and **17** in good yields (Scheme 3).

The cyclisation of ethyl ester **17** was first investigated on the basis of the reaction conditions established for the test system (Scheme 2, Table 1, entry 10). The rate of product formation was greatly diminished compared to the test system and reaction completion was not reached when 5 mol% of the precatalyst was used (Table 2, entry 1). Raising the amount of catalyst to 10 mol% (Table 2, entry 2) resulted in full conversion but the reaction yield was a disappointing 21%. We have previously reported shorter reaction times and superior yields for reactions heated under microwave (MW) irradiation[16] and, therefore, decided to explore this in the present case. To our satisfaction this was found to improve both the yield and reaction time (Table 2, entries 3–6).

Table 2. Cyclisation of ethyl ester **17** in *t*BuOH.[a]

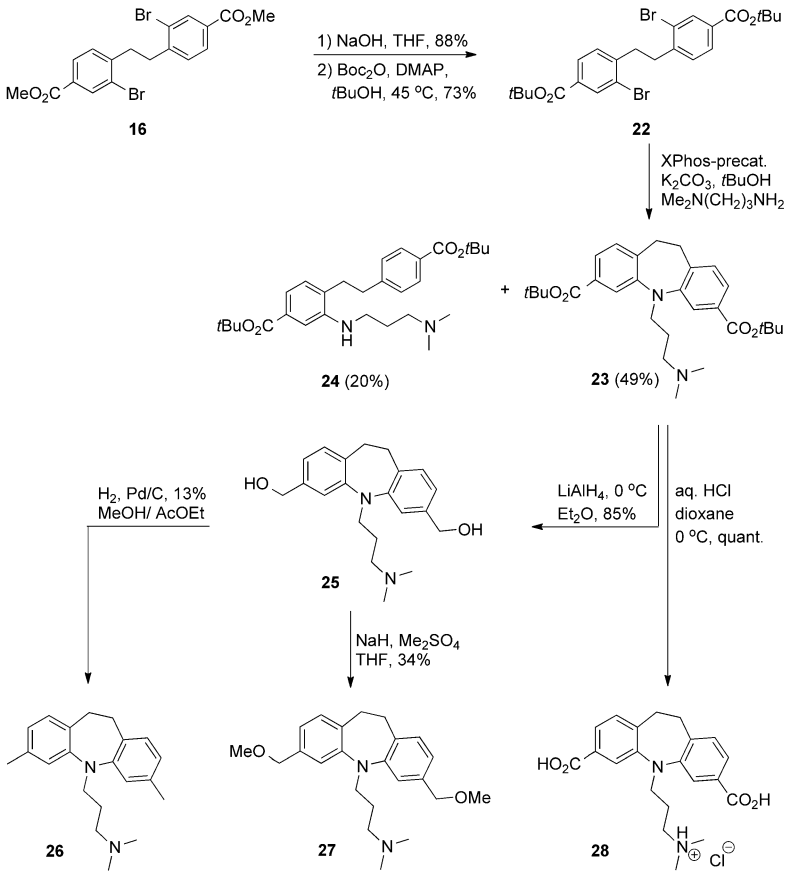
Entry	$Me_2N(CH_2)_3NH_2$ [equiv]	K_2CO_3 [equiv]	XPhos precatalyst [mol%]	*t* [h]	*T* [°C]	Yield [%][d]
1	1.5	3	5	96	110[b]	15[d]
2	1.5	3	10	26	110[b]	21
3	1.5	3	5	6	140[c]	27[e]
4	3.0	3	10	1.5	140[c]	33
5	3.0	6	10	1.5	140[c]	34
6	1.5	3	20	1.5	140[c]	29

[a] Amount of XPhos precatalyst was varied; XPhos (5 mol%) was added to every reaction. [b] Sealed tube in heating block. [c] MW irradiation. [d] Isolated yield after column chromatography. [e] Incomplete conversion of starting material.

With a catalyst loading of only 5 mol%, 27% of the cyclised product **19** (Scheme 3) could be isolated after 6 h of MW irradiation at 140 °C (Table 2, entry 3). This was slightly improved to 34% by raising the catalyst loading to 10 mol% and the amounts of amine and base to three and six equivalents, respectively. Only small changes in the yield of **19** resulted from increasing catalyst loading to 20 mol% or varying the amounts of amine and base (Table 2, entries 4–6).

The methyl ester-substituted cyclisation precursor **16** was cyclised under the conditions described in Table 2, entry 4 to give the expected 3,7-disubstituted imipramine **18** in 21% yield (Scheme 3).

Several side reactions during the cyclisation process could be expected. The only successfully isolated and identified by-products were the products that originated from monoamination and reduction, rather than cyclisation of the second bromide (**20** and **21**). This was generally, regardless of reaction conditions, present in half the amount of the cyclised product. The formation of these side products is consistent with the expectation that formation of a seven-membered ring via an eight-membered intermediate is a slow reaction. No by-products originating from amide formation, ester hydrolysis by minute amounts of water, transesterification with the solvent or palladium-catalysed diamination could be identified.



Scheme 4. Synthesis of imipramine analogues **23** and **25**–**28**.

To further explore the space limitations opposing the imipramine 3- and 7-positions within hSERT it was decided to also prepare the *tert*-butyl ester analogues of **18** and **19**. Because *tert*-butyl esters are acid labile and, therefore, cannot be expected to remain stable during the acid-catalysed bromination reaction, a late ester interchange would be necessary. Dibromo dimethyl ester **16** was hydrolysed in 88% yield and the carboxylic acid reacted with Boc_2O (Boc = *tert*-butoxycarbonyl) and 4-dimethylaminopyridine (DMAP) in *tert*-butanol[17] under gentle heating (Scheme 4). This produced the di-*tert*-butyl ester **22** in 73% yield. Palladium-catalysed cyclisation, as described for the corresponding ethyl ester **17**, gave imipramine analogue **23** in 49% yield, together with 20% of the monoaminated and reduced product **24**. Although this yield seems moderate it has to be kept in mind that two bonds are formed in the cyclisation step.

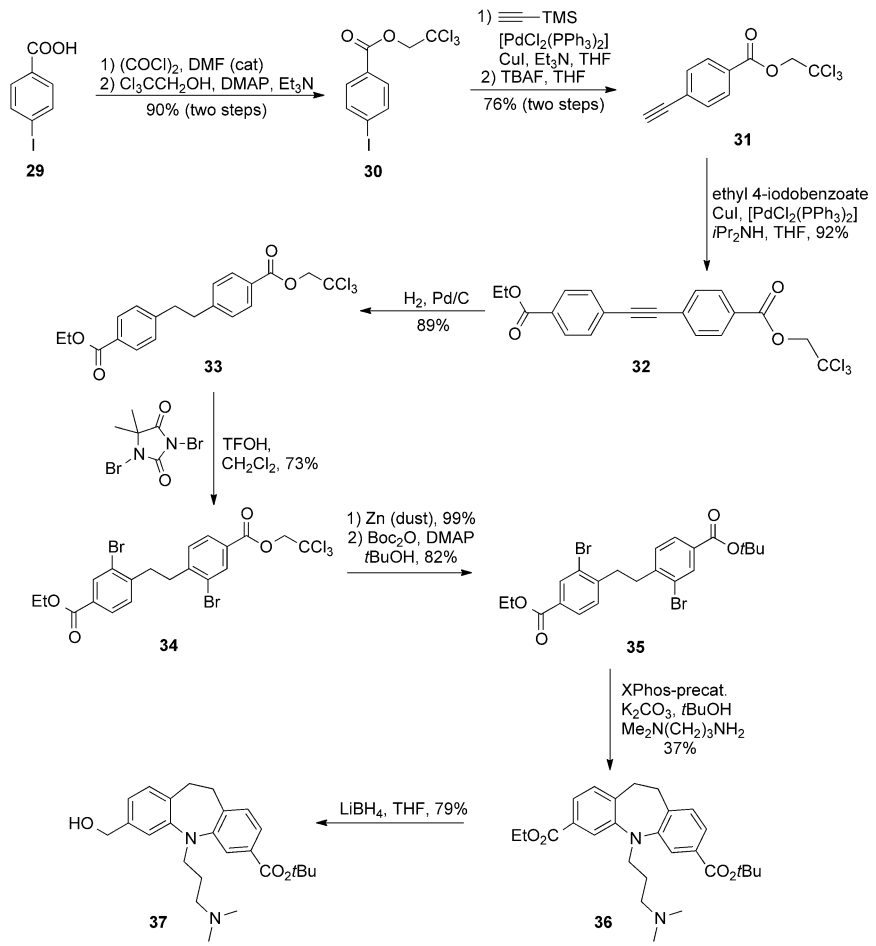
The imipramine analogue **23** next underwent either $LiAlH_4$ reduction to 3,7-dihydroxymethyl imipramine (**25**) or ester deprotection with hydrochloric acid to give dicarboxylic acid **28**. Diol **25** was either methylated by dimethyl sulfate to give 3,7-dimethoxymethyl imipramine (**27**) in 34% yield or removed by hydrogenolysis over Pd/C to give 3,7-dimethyl imipramine (**26**) in 13% yield (Scheme 4).

Until this point, we have prepared six symmetrical 3,7-disubstituted imipramines through our amination/cyclisation approach. We next sought to investigate whether this strategy also could be employed to prepare the more challenging unsymmetrical 3,7-disubstituted imipramines.

First, 2,2,2-trichloroethyl 4-iodobenzoate (**30**) was synthesised from 4-iodobenzoic acid (**29**) (Scheme 5). Compound **30** then underwent a Sonogashira coupling with trimethylsilyl (TMS) acetylene, followed by removal the TMS group with tetrabutylammonium fluoride (TBAF) to yield terminal alkyne **31** in 76% yield. Sonogashira coupling of **31** with ethyl 4-iodobenzoate gave compound **32** in 92% yield. Pd/C-catalysed hydrogenation of alkyne **32** to alkane **33** proceeded in 89% yield and was followed by dibromination with DBMH to give the cyclisation precursor **34** in 73% yield. However, cyclisation of this unsymmetrical dibromide **34** failed. We speculated whether this negative result was due to the trichloroethyl ester moiety. Amination was attempted under the conditions outlined in Table 1, entry 10 on the more simple monomeric test system, trichloroethyl ester bromide **6** (Scheme 2), but no aniline was formed.

As a consequence of the apparent incompatibility of the trichloroethyl ester with our Pd-catalysed amination/cyclisation conditions we decided to introduce a *tert*-butyl ester group.

Trichloroethyl ester deprotection[18] with zinc dust resulted in quantitative yield of the carboxylic acid, which was con-



Scheme 5. Synthesis of unsymmetric imipramine analogues **36** and **37**.

verted into *tert*-butyl ester **35**, in good yield, by treatment with Boc_2O and DMAP in *t*BuOH. Diester **35** was successfully transformed into 3,7-disubstituted imipramine **36** in 37% yield. A second unsymmetric imipramine analogue **37** was attained in 79% yield by $LiBH_4$ reduction of the ethyl ester group in **36** (Scheme 5).

Inhibition of monoamine transporters: We have earlier described how the 3- and 7-positions of substituted imipramine analogues can promote increased affinity for hSERT by interaction with specific residues in the protein.[6] However, neither the full spectrum of favoured substituents, nor the steric limitations of the 3- and 7-substituents, have been described. Furthermore, 3-substituents that increase affinity for hSERT do the complete opposite in hNET.

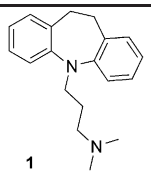
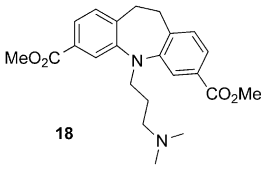
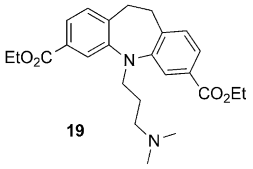
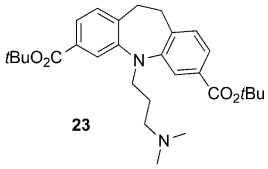
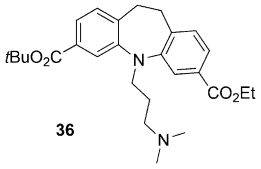
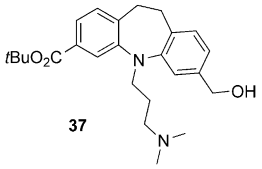
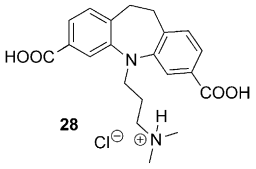
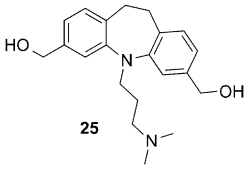
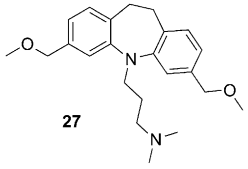
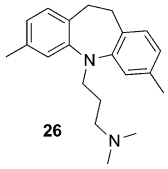
Therefore, the right combination of 3- and 7-substituents might result in an imipramine analogue with increased selectivity. With nine imipramine analogues in hand, inhibition of serotonin, norepinephrine and dopamine uptake by their corresponding transporter proteins was tested (Table 3).

The imipramine analogues with 3,7-diester substitution were found to have a diminished ability to inhibit both hSERT and hNET relative to **1**, with the smaller esters (**18** and **19**) being the most potent compounds of the set (Table 3, entries 2 and 3). This outcome was in agreement with the steric limitations, especially those of the pocket vicinal to the 3-position, predicted by Sinning et al.[6] The fact that the overall affinity for the human dopamine transporter (hDAT) remained low and the inhibitory effect of bulky 3,7-diester functionalities was opposite, with small increases in the level of inhibition compared to the parent imipramine **1** (Table 3, entries 4 and 5), suggests that **1** and its analogues occupy a different site in hDAT, possibly the non-competitive low-affinity S2 site,[6,19,20] Unsymmetric imipramine **37** substituted with *tert*-butylester and hydroxylmethyl substituents showed a significant decrease in hDAT and hNET inhibition, but remained a micromolar inhibitor of hSERT (Table 3, entry 6). As expected, dicarboxylic acid imipramine **28** exhibited poor inhibition of all three monoamine transporters (Table 3, entry 7).

The most potent compound tested against hSERT was found to be 3,7-dimethylimipramine (**26**) with 1.6-fold stronger inhibition than **1** (Table 3, entry 10 versus 1). In addition, **26** has a 1.8-fold lower affinity for hDAT and a 8.1-fold lower affinity for hNET than **1**, which means **26** has both higher affinity and selectivity for hSERT versus **1**. Again, this is very interesting for the development of selective antidepressants with potentially fewer adverse effects.

3,7-Dihydroxymethylimipramine (**25**) (Table 3, entry 8) was found to be a reasonably good inhibitor of hSERT, only 4.3-fold less potent than **1** itself. Whereas hDAT inhibition by **25** essentially remained unchanged relative to **1**, hNET inhibition was reduced 536-fold relative to **1**. As a result, hNET/hSERT selectivity of the TCA **25** for hSERT over hNET increased dramatically by 170-fold; a level superior to the SSRIs fluoxetine (Prozac) and fluvoxamine (Luvox).[21] Also 3,7-dimethoxymethylimipramine (**27**) (Table 3, entry 9) showed a moderate affinity for hSERT but an even higher hNET/hSERT selectivity than **25**. Combined, our findings illustrate that manipulation of the 3- and 7-substituents of imipramines can be successfully utilised to bestow high selectivity onto otherwise unselective TCAs.

Table 3. Inhibition constants[a] (K_i) [μM] of imipramine and analogues for radio-tracer uptake inhibition of hSERT, hNET and hDAT.

Entry	Structure	K_i(hSERT)	K_i(hDAT)	K_i(hNET)	K_i(hDAT)/ K_i(hSERT)	K_i(hNET)/ K_i(hSERT)
1	 **1**	0.051	160	0.069	3100	1.4
2	 **18**	1.3	34	28	26	21
3	 **19**	2.5	33	10	13	4.0
4	 **23**	110	130	180	1.2	1.7
5	 **36**	15	54	40	3.6	2.7
6	 **37**	6.8	>1000	>1000	>148	>148
7	 **28**	150	>1000	440	>6.6	2.9
8	 **25**	0.22	190	37	860	170
9	 **27**	3.8	>1000	>1000	>260	>260
10	 **26**	0.032	280	0.56	8600	17

[a] Data are from at least three independent experiments.

Earlier, we have found that the hSERT mutants A173M and F335L interfere with 3,7-disubstituted imipramine analogues, and that the double mutant A173M_F335L is sensitive to 3-substituted imipramine analogues and even more sensitive to 3,7-disubstituted imipramine analogues.[6]

To confirm that our imipramine analogues adopt the same overall orientation as we have shown for **1**, clomipramine and cyanoimipramine in the central binding site of hSERT, we subjected the mutants A173M, F335L and A173M_F335L to uptake-inhibition studies (Table 4).

Generally, we find a pattern consistent with our existing model[6] for inhibitory potential of imipramines. Whereas no significant negative effect of the mutations is observed for **1**, compounds **25**, **27**, **28** and **37** (Table 4) are sensitive to the A173M_F335L double mutant. These compounds, which all carry at least one small uncharged substituent, adhere to the expected pattern, in which the double mutant interferes considerably with the substituents and produces a 4.4-fold (calculated from **37**, ($p = 0.0219$)) or higher ($p \leq 0.0112$) loss of affinity relative to wild-type (WT) hSERT. Fully consistent with our model, the largest effect is seen with the hydrophilic imipramine **25**, which experiences a 110-fold loss of affinity due to the hydrophobic mutations in A173M_F335L, again confirming the prediction that these residues control the micro-environment vicinal to the 3- and 7-positions of imipramine.[6]

In contrast to the imipramine analogues with small substituents (**25**, **27**, **28** and **37**), imipramines with two bulky ester substituents (**18**, **19**, **23** and **36**) all exhibit micromolar

Table 4. Inhibition constants[a] (K_i) [μM] of imipramine and analogues for radio-tracer uptake inhibition of WT hSERT and mutants.

Structure	K_i(WT hSERT)	K_i(A173M hSERT)	K_i(F335L hSERT)	K_i(A173M_F335L hSERT)	K_i(A173M_F335L hSERT)/K_i(WT hSERT)
1	0.051	0.0073	0.062	0.041	0.8
18	1.3	0.21	5.6	1.5	1.1
19	2.5	0.33	4.9	1.8	2.0
23	110	27	190	76	0.7
36	15	3.0	26	10	0.7
37	6.8	8.7	50	62	9.1
28	150	100	870	660	4.4
25	0.22	2.9	0.96	25	110
27	3.8	2.5	33	44	12
26	0.032	0.038	0.15	0.45	14

[a] Data are from at least three independent experiments.

affinity for WT hSERT and are insensitive to the A173M_F335L mutations, with K_i values not statistically different from WT hSERT. Our experimentally validated model for imipramine binding predicts that substituents of this size cannot be accommodated in the pocket vicinal to the 3-position and the present findings that these analogues have both low affinity and respond atypically to the A173M_F335L double mutation suggests that they bind in a different orientation, if not in a different binding site, than **1**. It is feasible that the bulky substituents prevent them from binding in the central binding site (S1) and only allows them to bind to the promiscuous low-affinity S2 site,[6,20,21] thus retaining the ability to inhibit uptake, albeit with the low affinity associated with this vestibular site.

Conclusion

We have developed a palladium-catalysed amination/intramolecular cyclisation process for the synthesis of symmetric and unsymmetric analogues of the antidepressant imipramine. The challenging seven-membered ring could be formed in up to 49% isolated yield when *tert*-butyl ester groups were present, whereas the cyclisation in the presence of methyl- and ethyl esters proceeded in lower yields. We have shown that the established synthetic route is flexible; the 3,7-di-*tert*-butyl ester-substituted imipramine could easily be converted into a series of 3,7-disubstituted imipramine analogues.

By studying the inhibition of hSERT with the new compounds prepared in this study, our previously published model for the binding of imipramine to the central binding site of hSERT[6] was further validated. Analogues with large substituents, predicted to violate the steric restrictions of the pockets vicinal to the 3- and 7-positions from our experimentally validated model of imipramine binding, were found to exhibit an atypical response to mutations of A173 and F335. This suggested a different orientation within the binding site, if not the utilisation of a different binding site altogether, for these large analogues. Analogues with smaller substitutents at the 3- and 7-positions were found to adhere to the same orientation as imipramine within the central binding site and these positions could be manipulated to achieve higher hSERT selectivity with no, or only slight, loss of affinity. In particular, 3,7-dimethylimipramine (**26**) was found to be a potent inhibitor of hSERT and dihydroxymethyl imipramine (**25**) demonstrated a remarkable 121-fold gain in inhibitory selectivity for hSERT over hNET relative to imipramine (**1**). Thus, with only a few modifications of largely unselective **1** it was possible to obtain imipramine analogues with selectivity superior to existing SSRIs on the market. This suggests an unexploited potential of imipramine analogues that can be accessed through rational drug design by using our experimentally validated model of TCA binding. Furthermore, it could be imagined that compounds such as **25**, which shows good hSERT selectivity, could act as useful starting materials for introduction of radioactive labels (for example, ^{11}C or ^{18}F isotopes) for in vivo positron emission tomography studies.

Experimental Section

General methods: All reagents, unless otherwise stated, were used as purchased without further purification. Reagents for palladium-catalysed amination were mixed in a glovebox but reactions were conducted in sealed tube in an ordinary fumehood or in a microwave vial. Solvents were dried by standard procedures. Columns for flash chromatography were packed with silica gel (60 Å). ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 NMR spectrometer and assigned by using *g*HMQC, and *g*COSY experiments. Mass spectral analyses were carried out as electrospray experiments on a Micromass LC-TOF spectrometer. Melting points were measured on a Büchi B-540 apparatus and are corrected. Microwave experiments were carried out in a Biotage Initiator (Biotage, Sweden). Reaction times listed refer to "hold time" at the specified temperature.

For details on biological assays and the preparation of compounds **7–9**, **12** and **14** see the Supporting Information

Compound 16: TfOH (0.95 mL, 10.7 mmol) and DBMH (1.12 g, 3.94 mmol) were added to a solution of **14** (1.07 g, 3.58 mmol) in dry CH_2Cl_2 (30 mL) in a flask wrapped in aluminium foil. The reaction mixture was stirred for 2 h at RT then CH_2Cl_2 and an aqueous solution of $Na_2S_2O_3$ were added to the reaction mixture. The aqueous phase was extracted with CH_2Cl_2 (×3) and the combined organic phases were washed with an aqueous solution of $KHSO_4$, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (CH_2Cl_2/pentane 2:3) afforded **16** as a white solid (1.27 g, 78%). R_f = 0.20 (CH_2Cl_2/pentane 1:1); m.p. 183.1–185.2 °C (CH_2Cl_2), lit.[6] 180–182 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, J = 1.6 Hz, 2H), 7.85 (dd, J = 1.6, 8.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 3.92 (s, 6H), 3.11 ppm (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0, 145.5, 134.3, 130.9, 130.4, 128.9, 124.7, 52.7, 36.4 ppm; HRMS (ES): m/z calcd for $C_{18}H_{16}O_4{}^{79}Br_2Na$: 476.9313; found: 476.9314. The NMR data were in accordance with those previously reported.[6]

Compound 18: Compound **16** (54 mg, 0.12 mmol), K_2CO_3 (52 mg, 0.38 mmol), Buchwald's XPhos precatalyst (8.7 mg, 0.012 mmol), XPhos (2.8 mg, 0.0059 mmol), 3-dimethylamino-propylamine (45 μL, 0.36 mmol) and *tert*-butanol (1 mL) were added to an oven-dried microwave vial. The reaction mixture was stirred for 2 h at 150 °C under MW irradiation. The solvent was evaporated and the residue purified by column chromatography (pentane/AcOEt/Et_3N 76:19:5) to give a yellow oil (10 mg,

21%). R_f=0.42 (pentane/AcOEt/Et_3N 63:32:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.78 (d, J=1.6 Hz, 2H), 7.60 (dd, J=1.6, 8.0 Hz, 2H), 7.15 (d, J=7.6 Hz, 2H), 3.89 (s, 6H), 3.86 (t, J=6.8 Hz, 2H), 3.21 (s, 4H), 2.31 (t, J=7.2 Hz, 2H), 2.15 (s, 6H), 1.72 ppm (quintet, J=7.2, 14.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.1, 148.1, 139.5, 130.0, 128.7, 124.1, 121.6, 57.6, 52.2, 49.1, 45.6, 32.1, 26.2 ppm; HRMS (ES): m/z calcd for $C_{23}H_{28}O_4N_2H$: 397.2127; found: 397.2137.

Compound 13: [$PdCl_2(PPh_3)_2$] (175 mg, 0.249 mmol) and CuI (91 mg, 0.478 mmol) were added to a solution of **11** (6.69 g, 24.2 mmol) and distilled iPr$_2$NH (45 mL) in dry THF (35 mL). The reaction vessel was evacuated and refilled with acetylene gas (×3). The mixture quickly changed colour from yellow to black. The resulting solution was stirred at RT overnight before it was concentrated under vacuum. The remaining substance was dissolved in CH_2Cl_2 and washed with H_2O, then the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by recrystallisation from hexane and column chromatography (CH_2Cl_2/pentane 1:4) to give **13** as an orange–brown powder (1.73 g, 44%). R_f=0.23 (pentane/CH_2Cl_2 1:2); m.p. 148.2–150.1 °C (CH_2Cl_2), lit.[6] 146–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.04 (d, J=8.4 Hz, 4H), 7.60 (d, J=8.4 Hz, 4H), 4.39 (q, J=7.2 Hz, 4H), 1.41 ppm (t, J=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.3, 131.9, 130.6), 129.9, 127.6, 91.9, 61.6, 14.7 ppm; HRMS (ES): m/z calcd for $C_{20}H_{18}O_4Na$: 345.1103; found: 345.1104. The NMR data are in accordance with those previously reported.[22]

Compound 15: Pd/C (10 mol%, 56 mg) was added to a solution of **13** (493 mg, 1.53 mmol) in 1:1 EtOAc/CH_2Cl_2 (20 mL). The reaction vessel was evacuated and refilled with H_2 gas (×3) and the reaction mixture was stirred at RT overnight under H_2 atmosphere. The mixture was filtered through Celite and the solvent was removed by evaporation under vacuum to afford **15** as white crystals (487 mg, 97%). R_f=0.38 (CH_2Cl_2/pentane 1:2); m.p. 97.3–99.4 °C (CH_2Cl_2), lit[6] 97–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.94 (d, J= 6.4 Hz, 4H), 7.19 (d, J=6.4 Hz, 4H), 4.36 (q, J=6.8 Hz, 4H), 2.99 (s, 4H), 1.38 ppm (t, J=6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.9, 146.7, 130.0, 128.8, 61.2, 37.8, 14.7 ppm; HRMS (ES): m/z calcd for $C_{20}H_{22}O_4Na$: 349.1416; found: 349.1416. The NMR data are in accordance with those previously reported.[23]

Compound 17: TfOH (1.36 mL, 15.4 mmol) and DBMH (1.61 g, 5.63 mmol) were added to a solution of **15** (1.67 g, 5.12 mmol) in dry CH_2Cl_2 (40 mL) in a flask wrapped in aluminium foil. The reaction was stirred at RT and closely followed by TLC analysis. After 2 h, **15** and mono-brominated compound were no longer observed. The reaction mixture was then diluted with CH_2Cl_2 and an aqueous solution of $Na_2S_2O_3$, and was stirred for a few minutes until the organic phase turned light yellow. The aqueous phase was extracted with CH_2Cl_2 (×3) and the combined organic layers were washed with an aqueous solution of $KHSO_4$, dried over $MgSO_4$, filtered and concentrated under vacuum. The product was purified by column chromatography (pentane/CH_2Cl_2 3:2) to afford **17** as white powder (2.30 g, 93%). R_f=0.22 (CH_2Cl_2/pentane 1:1); m.p. 102.3–103.4 °C (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.17 (d, J=1.6 Hz, 2H), 7.81 (dd, J=1.6, 8.0 Hz, 2H), 7.13 (d, J=8.0 Hz, 2H), 4.34 (q, J=7.6 Hz, 4H), 1.36 ppm (t, J=7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=165.5, 145.4, 134.2, 130.8, 130.7, 128.9, 124.7, 61.6, 36.4, 14.6 ppm; HRMS (ES): m/z calcd for $C_{20}H_{20}{}^{81}Br_2O_4Na$: 508.9585; found: 508.9586.

Compounds 19 and 21: Compound **17** (206 mg, 0.43 mmol) and K_2CO_3 (180 mg, 1.30 mmol) were added to an oven-dried microwave vial. The vial was transferred to the glovebox and Buchwald's XPhos precatalyst (31.4 mg, 0.043 mmol), XPhos (10.2 mg, 0.021 mmol), 3-dimethylaminopropylamine (161 μL, 1.28 mmol) and *tert*-butanol (4 mL) were added. The reaction mixture was stirred for 1.5 h at 140 °C under MW irradiation. The solvent was evaporated and the residue was purified by column chromatography (pentane/AcOEt/Et_3N 76:19:5) to give **19** as a yellow oil (62 mg, 34%). R_f=0.55 (EtOAc/pentane 2:5+5% Et_3N); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.78 (d, J=1.6 Hz, 2H), 7.60 (dd, J=1.6, 8.0 Hz, 2H), 7.15 (d, J=8.0 Hz, 2H), 4.36 (q, J=7.2 Hz, 4H), 3.57 (t, J=7.2 Hz, 2H), 3.20 (s, 4H), 2.31 (t, J=7.2 Hz, 2H), 2.15 (s, 6H), 1.72 (quintet, J=7.2 Hz, 2H), 1.38 ppm (t, J=7.2 Hz, 6H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.8, 148.3, 139.6, 130.1, 129.3, 124.2, 121.7, 61.2, 57.8, 49.3, 45.8, 32.3, 26.4, 14.7 ppm; HRMS (ES): m/z calcd for $C_{25}H_{32}N_2O_4Na$: 447.2260; found: 447.2276.

Byproduct **21** (29 mg, 16%) was also isolated, as a thick yellow oil. R_f= 0.30 (EtOAc/pentane 2:5+5% Et_3N); ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.96 (d, J=8.0 Hz, 2H), 7.30 (dd, J=1.6, 7.6 Hz, 1H), 7.25–7.17 (m, 3H), 6.97 (d, J=7.6 Hz, 1H), 4.36 (q, J=7.2 Hz, 4H), 3.27 (t, J=6.0 Hz, 2H), 2.30 (t, J=8.0 Hz, 2H), 2.80 (t, J=8.0 Hz, 2H), 2.46 (t, J=6.0 Hz, 2H), 2.21 (s, 6H), 1.83 (quintet, J=6.0 Hz, 2H), 1.41–1.36 ppm (m, 6H); HRMS (ES): m/z calcd for $C_{25}H_{34}N_2O_4Na$: 449.2416; found: 449.2419.

Compound 22: An aqueous solution of NaOH (2 M, 100 mL) was added to a solution of **16** (1.96 g, 4.29 mmol) in THF (100 mL). The resulting mixture was stirred at RT overnight and then heated at 45 °C for 6 h. THF was removed under reduced pressure and the aqueous phase was acidified by addition an aqueous solution of HCl (1 M) until pH=1, which resulted in a white precipitate. The precipitate was filtered off and washed with diethyl ether, then the white powder was dried under vacuum to afford 4,4′-(ethane-1,2-diyl)bis(3-bromobenzoic acid) as a fluffy powder (1.62 g, 88%), which was pure enough to be used without further purification. R_f=0.25 (CH_3OH/EtOAc 1:10); ^{1}H NMR (400 MHz, [D_6]DMSO): δ=13.24 (br s, OH), 8.10 (s, 2H), 7.89 (d, J=7.8 Hz, 2H), 7.47 (d, J=7.8 Hz, 2H), 3.08 ppm (s, 4H). The ^{1}H NMR data are in accordance with those previously reported.[6]

Boc_2O (254 mg, 1.16 mmol) and DMAP (47 mg, 0.386 mmol) were added to a solution of 4,4′-(ethane-1,2-diyl)bis(3-bromobenzoic acid) (191 mg, 0.446 mmol) in dry *t*BuOH (15 mL). The reaction mixture was stirred overnight at 45 °C under an N_2 atmosphere. The mixture was diluted with brine and CH_2Cl_2, then the aqueous phase was extracted with CH_2Cl_2 (× 3). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by column chromatography (CH_2Cl_2/pentane 1:2) to afford **22** as a white powder (177 mg, 73%). R_f=0.25 (CH_2Cl_2/pentane 1:2); m.p. 139.0–140.4 °C (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.14 (d, J=1.6 Hz, 2H), 7.79 (dd, J=1.6, 8.0 Hz, 2H), 7.13 (d, J=8.0 Hz, 2H), 3.08 (s, 4H), 1.58 ppm (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=164.6, 144.9, 134.1, 132.2, 130.7, 128.7, 124.5, 81.8, 36.4, 28.5 ppm; HRMS (ES): m/z calcd for $C_{24}H_{28}{}^{79}Br_2O_4Na$: 561.0252; found: 561.0254.

Compounds 23 and 24: Compound **22** (217 mg, 0.402 mmol) was added to an oven-dried microwave vial. The vial was transferred to a glovebox and K_2CO_3 (167 mg, 1.21 mmol), Buchwald's XPhos-precatalyst (30 mg, 0.040 mmol) and XPhos (10 mg, 0.020 mmol) were added, followed by dry *t*BuOH (4 mL) and *N,N*-dimethylpropane-1,3-diamine (152 μL, 1.21 mmol). The vial was sealed and heated at 140 °C for 100 min under MW irradiation. The crude mixture was concentrated under vacuum and purified by column chromatography (AcOEt/pentane 1:5+3% Et_3N) to afford **23** as a yellow oil (94 mg, 49%). R_f=0.43 (AcOEt/pentane 1:5+ 5% Et_3N); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.71 (d, J=1.6 Hz, 2H), 7.52 (dd, J=1.6, 8.0 Hz, 2H), 7.11 (d, J=8.0 Hz, 2H), 3.84 (t, J=7.4 Hz, 2H), 3.18 (s, 4H), 2.39 (t, J=7.4 Hz, 2H), 2.20 (s, 6H), 1.73 (quintet, J= 7.4 Hz, 2H), 1.57 ppm (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.1, 148.3, 139.1, 130.8, 130.0, 124.0, 121.6, 81.2, 57.8, 49.2, 45.8, 32.3, 28.6, 26.4 ppm; HRMS (ES): m/z calcd for $C_{29}H_{40}N_2O_4Na$: 503.2886; found: 503.2885.

Byproduct **24** (39 mg, 20%) was also isolated, as a yellow oil. R_f=0.18 (AcOEt/pentane 1:5+3% Et_3N); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.90 (d, J=8.0 Hz, 2H), 7.23–7.17 (m, 4H), 6.96 (d, J=8.0 Hz, 1H), 3.25 (t, J=6.0 Hz, 2H), 2.98 (t, J=10.0 Hz, 2H), 2.79 (t, J=10.0 Hz, 2H), 2.43 (t, J=6.0 Hz, 2H), 2.19 (s, 6H). 1.81 (quintet, J=6.0 Hz, 2H), 1.59 (s, 6H), 1.58 ppm (s, 6H); HRMS (ES): m/z calcd for $C_{29}H_{42}N_2O_4Na$: 505.3042; found: 505.3051.

Compound 25: $LiAlH_4$ (26 mg, 0.688 mmol) was added to a stirred solution of **23** (64 mg, 0.134 mmol) in dry diethyl ether (4 mL) at 0 °C. After stirring for 2 h at 0 °C the mixture was diluted with CH_2Cl_2 and H_2O. An aqueous solution of HCl (1 M) was added until pH=2–3, then the aqueous layer was extracted with CH_2Cl_2 (×3). The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated under vacuum. The product was puri-

fied by column chromatography (AcOEt + 1% CH_3OH + 5% Et_3N) to afford **25** as a colourless oil (39 mg, 85%). R_f = 0.34 (AcOEt/Et_3N/CH_3OH 90:5:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.10–7.06 (m, 4H), 6.89 (d, J = 7.6 Hz, 2H), 4.58 (s, 4H), 3.78 (t, J = 6.4 Hz, 2H), 3.13 (s, 4H), 2.81–2.77 (m, 2H), 2.39 (s, 6H), 2.07 (s, 2H), 1.98–1.91 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.1, 139.9, 133.7, 130.4, 121.8, 118.7, 65.3, 62.9, 51.5, 48.5, 32.0, 22.6 ppm; HRMS (ES): m/z calcd for $C_{21}H_{28}O_2N_2Na$: 363.2048; found: 363.2068.

Compound 26: 10% Pd/C (28 mg) and a concentrated aqueous solution of HCl (2 drops) were added to a solution of **25** (82 mg, 0.24 mmol) in 1:2 CH_3OH/AcOEt (3 mL). The reaction vessel was evacuated and refilled with H_2 gas (×3) then the reaction was stirred for 48 h at RT. The reaction mixture was filtered through Celite with AcOEt. The solvent was removed under reduced pressure and the remaining oil was treated with Pd/C, as above, until the reaction was complete (another 96 h). The mixture was filtered through Celite with AcOEt and purified by chromatography (pentane/AcOEt/Et_3N 76:19:5) to give a colourless oil (10 mg, 13%). R_f = 0.35 (pentane/Et_3N 95:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 6.96 (d, J = 7.6 Hz, 2H), 6.89 (s, 2H), 6.71 (d, J = 7.6 Hz, 2H), 3.75 (t, J = 6.8 Hz, 2H), 3.09 (s, 4H), 2.31 (t, J = 7.2 Hz, 2H), 2.23 (s, 6H), 2.16 (s, 6H), 1.72 ppm (q, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.8, 136.0, 131.3, 129.8, 123.2, 120.7, 57.9, 48.9, 45.7, 32.1, 26.4, 21.3 ppm; HRMS (ES): calcd for $C_{21}H_{28}N_2Na$: 331.2150; found: 331.2150.

Compound 27: NaH (60% in mineral oil, 31 mg, 0.775 mmol) was added to a solution of **25** (37 mg, 0.108 mmol) in dry THF (2 mL) and the mixture was stirred at RT for 1 h. Dimethyl sulfate (31 μL, 0.324 mmol) was added and the reaction mixture was stirred for 1 h at RT. The mixture was diluted with H_2O and extracted with CH_2Cl_2 (×3). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The product was purified by column chromatography (AcOEt/pentane 1:4 + 1% CH_3OH + 1% Et_3N) to afford **27** as a colourless oil (14 mg, 34%). R_f = 0.18 (AcOEt/pentane 1:2 + 2% CH_3OH + 2% Et_3N); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.07 (d, J = 7.6 Hz, 2H), 4.04 (d, J = 1.4 Hz, 2H), 6.89 (dd, J = 1.4, 7.6 Hz, 2H), 4.39 (s, 4H), 3.80 (t, J = 6.4 Hz, 2H), 3.36 (s, 6H), 3.14 (s, 4H), 2.84–2.80 (m, 2H), 2.40 (s, 6H), 2.00–1.93 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.0, 137.0, 133.9, 130.3, 122.6, 119.5, 74.9, 62.9, 58.4, 51.4, 48.5, 32.3, 22.5 ppm; HRMS (ES): m/z calcd for $C_{23}H_{32}N_2O_2Na$: 391.2361; found: 391.2362.

Compound 28: A solution of **23** (49 mg, 0.102 mmol) in dry 1,4-dioxane (2.5 mL) and a concentrated aqueous solution of HCl (12 M, 0.5 mL) were combined and stirred at 0 °C for 1.5 h. The mixture was allowed to warm to RT, stirred for 3 h, then concentrated under reduced pressure to afford **28** as a bright yellow powder (41 mg, 99%). R_f = 0.16 (Et_3N/CH_3OH/CH_2Cl_2 1:3:10); m.p. 199.0–201.7 °C (CH_2Cl_2); ^1H NMR (400 MHz, D_2O): δ = 7.38 (br s, 2H), 7.26 (d, J = 7.0 Hz, 2H), 6.74 (d, J = 7.0 Hz, 2H), 3.58 (br s, 2H), 2.97 (br s, 2H), 2.68 (s, 10H), 1.78 ppm (br s, 2H); ^1H NMR (400 MHz, CD_3OD): δ = 7.91 (d, J = 1.6 Hz, 2H), 7.73 (dd, J = 1.6, 7.8 Hz, 2H), 7.36 (d, J = 7.8 Hz, 2H), 4.06 (t, J = 6.4 Hz, 2H), 3.34 (s, 4H), 3.32–3.28 (m, 2H), 2.90 (s, 6H), 2.13–2.09 ppm (m, 2H); ^{13}C NMR (100 MHz, D_2O): δ = 169.7, 148.9, 141.1, 131.4, 130.7, 125.8, 122.1, 57.2, 43.6, 32.9, 24.2 ppm; HRMS (ES): m/z calcd for $C_{21}H_{24}N_2O_4H$: 369.1814; found: 369.1820.

Compound 30: DMF (one drop) was added to a solution of **29** (400 mg, 1.61 mmol) and oxalyl chloride (211 μL, 2.42 mmol) in dry CH_2Cl_2 (8 mL). The reaction mixture was stirred at RT for 1.5 h and then concentrated under vacuum. The residue was dissolved in dry CH_2Cl_2 (8 mL) then Et_3N (0.34 mL, 2.45 mmol), trichloroethanol (0.31 mL, 3.23 mmol) and a catalytic amount of DMAP (20 mg) were added. The reaction mixture was stirred at RT for 4 h, then diluted with CH_2Cl_2 and H_2O. The organic phase was washed with an aqueous solution of HCl (0.1 M), then a saturated aqueous solution of $NaHCO_3$. The organic phase was dried over $MgSO_4$, filtered and concentrated under vacuum. The product was purified by column chromatography (heptane/CH_2Cl_2 7:1) to afford **30** as an off-white powder (549 mg, 90%). R_f = 0.55 (CH_2Cl_2/heptanes 1:1); m.p. 63.5–65.2 °C (CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.84–7.79 (m, 4H), 4.95 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.6, 138.3, 131.6, 128.4, 102.2, 95.1, 74.7 ppm; GC-MS (EI): m/z calcd for $C_9H_6{}^{35}Cl_3IO_2$: 377.8; found: 378.

Compound 31: [$PdCl_2(PPh_3)_2$] (18 mg, 0.026 mmol), CuI (10 mg, 0.050 mmol) and TMS-acetylene (350 μL, 2.51 mmol) were added sequentially to a solution of **30** (866 mg, 2.28 mmol) in Et_3N (18 mL). A precipitate immediately formed. The reaction mixture was stirred at RT for 4 h, then diluted with H_2O and CH_2Cl_2. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (×3). The combined organic layers were washed with an aqueous solution of HCl (0.1 M) and a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, filtered, concentrated under vacuum and used without further purification in the next step. R_f = 0.39 (CH_2Cl_2/pentane 1:2).

The crude silylated product was dissolved in dry THF (20 mL) and cooled to −78 °C. TBAF (1 M in THF, 2.5 mL, 2.51 mmol) was added and the solution was stirred at −78 °C for 1.5 h. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2 (×3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The product was purified by column chromatography (CH_2Cl_2/pentane 1:10) to afford alkyne **31** as a white powder (484 mg, 76%). R_f = 0.33 (CH_2Cl_2/pentane 1:2); m.p. 196.4–197.6 °C (CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, J = 8.6 Hz, 2H), 7.58 (d, J = 8.6 Hz, 2H), 4.97 (s, 2H), 3.28 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.3, 132.4, 130.0, 128.7, 127.9, 95.1, 82.7, 80.9, 74.7 ppm; GC-MS (EI): m/z calcd for $C_{11}H_7{}^{35}Cl_3O_2$: 275.9; found: 276.

Compound 32: [$PdCl_2(PPh_3)_2$] (42 mg, 0.060 mmol), CuI (52 mg, 0.273 mmol) and distilled iPr$_2$NH (1.55 mL, 11.1 mmol) were added to a solution of ethyl p-iodobenzoic acid (1.15 g, 4.16 mmol) and **31** (770 mg, 2.77 mmol) in dry THF (25 mL). The resulting mixture was stirred at RT overnight. The mixture was diluted with H_2O and CH_2Cl_2 then the aqueous phase was extracted with CH_2Cl_2 (×3). The combined organic layers were washed with an aqueous solution of HCl (0.1 M) and then a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated under vacuum. The product was purified by column chromatography (pentane/CH_2Cl_2 4:1→CH_2Cl_2) to afford **32** as a pale brown powder (1.09 g, 92%). R_f = 0.29 (CH_2Cl_2/pentane 1:1); m.p. 250 °C (decomposed); ^1H (400 MHz, $CDCl_3$): δ = 8.13 (d, J = 8.4 Hz, 2H), 8.05 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 4.99 (s, 2H), 4.40 (quartet, J = 7.3 Hz, 2H), 1.41 ppm (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.1, 164.5, 132.1, 131.9, 130.7, 130.3, 129.8, 128.6, 127.3, 95.2, 92.3, 91.3, 74.8, 61.4, 14.5 ppm; MS (ES): m/z calcd for $C_{40}H_{30}{}^{35}Cl_5{}^{37}ClO_8Na$: 872.99

(dimer); found: 873.0.

Compound 33: 10% Pd/C (149 mg) was added to a solution of **32** (1.09 g, 2.55 mmol) in 1:1 EtOAc/CH_2Cl_2 (30 mL). The reaction vessel was evacuated and refilled with hydrogen gas (×3). The reaction mixture was stirred for 48 h at RT, filtered through a bed of Celite and concentrated under reduced pressure. Alkane **33** was obtained without further purification as an orange–brown solid (971 mg, 89%). R_f = 0.44 (CH_2Cl_2/toluene 1:1); m.p. 136.2–138.8 °C (CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ = 8.04 (d, J = 8.2 Hz, 2H), 7.97 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.2 Hz, 2H), 4.97 (s, 2H), 4.37 (q, J = 7.2 Hz, 2H), 3.02 (s, 4H), 1.40 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6, 164.9, 147.8, 146.3, 130.4, 129.9, 129.0, 128.7, 128.6, 126.8, 95.4, 74.5, 61.0, 37.5, 37.4, 14.5 ppm; HRMS (ES): m/z calcd for $C_{20}H_{19}{}^{35}Cl_3O_4Na$: 451.0247; found: 451.0243.

Compound 34: DBMH (704 mg, 2.46 mmol) and CF_3SO_3H (475 μL, 5.37 mmol) were added to a solution of **33** (962 mg, 2.24 mmol) in dry CH_2Cl_2 (60 mL) in a flask wrapped in aluminium foil. The reaction was stirred at RT and closely monitored by TLC analysis. After 4.25 h, the reaction mixture was diluted with CH_2Cl_2 and an aqueous solution of $Na_2S_2O_3$, then vigorously stirred for 5 min. The aqueous phase was extracted with CH_2Cl_2 (×3) and the combined organic layers were washed with an aqueous solution of $KHSO_4$, dried over $MgSO_4$, filtered and concentrated under vacuum. The product was purified by column chromatography (pentane/CH_2Cl_2 3:1) to afford **34** as a white powder (964 mg, 73%). R_f = 0.36 (pentane/CH_2Cl_2 1:2); m.p. 129.3–131.2 °C (CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, J = 1.6 Hz, 1H), 8.21 (d, J = 1.6 Hz, 1H), 7.93 (dd, J = 1.6, 8.0 Hz, 1H), 7.85 (dd, J = 1.6, 8.0 Hz, 1H), 7.23 (d, J = 7.6 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 4.96 (s, 2H), 4.36 (q, J = 7.2 Hz, 2H), 3.11 (s, 4H), 1.39 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR

(100 MHz, $CDCl_3$): δ = 165.4, 163.8, 146.6, 145.2, 134.7, 134.2, 131.1, 130.8, 130.7, 129.3, 128.9, 128.8, 124.9, 124.6, 95.2, 74.8, 61.6, 36.5, 36.3, 14.6 ppm; HRMS (ES): *m/z* calcd for $C_{20}H_{17}{}^{79}Br_2{}^{35}Cl_3O_4Na$: 606.8457; found: 606.8412.

Compound 35: Freshly activated zinc powder (4.51 g) was added to a solution of **34** (707 mg, 1.20 mmol) in 1:1 dry CH_2Cl_2/99% acetic acid (50 mL). The mixture was stirred at RT overnight under a N_2 atmosphere. The reaction mixture was filtered through a pad of glass wool and concentrated under vacuum. The residue was dissolved in H_2O and EtOAc, then the aqueous phase was extracted with EtOAc (×3). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under vacuum to afford 3-bromo-4-(2-bromo-4-(ethoxycarbonyl)phenethyl)benzoic acid as a white powder (545 mg, 99%). R_f = 0.46 (CH_2Cl_2/CH_3OH 98:2); m.p. 176.4–178.6 °C (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, J = 1.6 Hz, 1H), 8.23 (d, J = 2.0 Hz, 1H), 7.92 (dd, J = 1.6, 8.0 Hz, 1H), 7.87 (dd, J = 2.0, 8.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 4.38 (q, J = 6.8 Hz, 2H), 3.13 (s, 4H), 1.40 ppm (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 165.6, 146.6, 145.3, 134.9, 134.3, 131.0, 130.8, 130.7, 129.5, 128.9, 124.8, 124.7, 61.7, 36.5, 36.3, 14.6 ppm; HRMS (ES): *m/z* calcd for $C_{18}H_{16}{}^{79}Br_2O_4Na$: 476.9313; found: 476.9301.

Boc_2O (124 mg, 0.568 mmol) and DMAP (14 mg, 0.111 mmol) were added to a heterogeneous solution of 3-bromo-4-(2-bromo-4-(ethoxycarbonyl)phenethyl)benzoic acid (145 mg, 0.338 mmol) in 4:1 dry *t*BuOH/1,4-dioxane (12 mL). The mixture was stirred overnight at 45 °C under an N_2 atmosphere. TLC analysis showed unreacted starting material, so additional Boc_2O (52 mg, 0.121 mmol) and dry 1,4-dioxane (3 mL) were added, which resulted in a homogenous mixture. The mixture was stirred for additional 4 h, then diluted with H_2O and extracted with CH_2Cl_2 (× 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. Column chromatography (CH_2Cl_2/pentane 1:7) afforded **35** as a white powder (142 mg, 82%). R_f = 0.37 (CH_2Cl_2/pentane 1:2); m.p. 89.7–91.5 °C (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, J = 1.6 Hz, 1H), 8.23 (d, J = 1.6 Hz, 1H), 7.94 (dd, J = 1.6, 7.7 Hz, 1H), 7.88 (dd, J = 1.6, 8.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.23 (d, J = 7.7 Hz, 1H), 4.46 (q, J = 7.0 Hz, 2H), 3.18 (s, 4H), 1.68 (s, 9H), 1.48 ppm (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 164.7, 145.4, 144.9, 134.2, 134.1, 132.2, 130.9, 130.7, 130.6, 128.9, 128.8, 124.7, 124.5, 81.9, 61.6, 36.5, 36.4, 28.5, 14.6 ppm; HRMS (ES): *m/z* calcd for $C_{22}H_{24}{}^{79}Br_2O_4Na$: 532.9939; found: 532.9922.

Compound 36: Compound **35** (92 mg, 0.179 mmol) and a magnetic stirrer bar were added to an oven-dried microwave vial. The vial was transferred to a glovebox and K_2CO_3 (74 mg, 0.537 mmol), Buchwald's XPhos precatalyst (13 mg, 0.018 mmol), XPhos (4 mg, 0.009 mmol), dry *t*BuOH (2 mL) and *N*,*N*-dimethylpropane-1,3-diamine (68 μL, 0.537 mmol) were added. The vial was sealed and heated under MW irradiation (140 °C, 100 min). The crude mixture was concentrated under vacuum and purified by column chromatography (AcOEt/pentane 1:7 + 3% Et_3N) to afford **36** as a colourless oil (30 mg, 37%). R_f = 0.26 (AcOEt/pentane 1:5 + 5% Et_3N); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, J = 1.6 Hz, 1H), 7.73 (d, J = 1.6 Hz, 1H), 7.59 (dd, J = 1.6, 7.6 Hz, 1H), 7.54 (dd, J = 1.6, 8.0 Hz, 1H), 7.14 (d, J = 7.6 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 4.36 (q, J = 7.2 Hz, 2H), 3.85 (t, J = 7.0 Hz, 2H), 3.20 (s, 4H), 2.31 (t, J = 7.0 Hz, 2H), 2.15 (s, 6H), 1.72 (quintet, J = 7.0 Hz, 2H), 1.58 (s, 9H), 1.38 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.9, 166.0, 148.4, 148.2, 139.5, 139.2, 130.8, 130.2, 129.9, 129.2, 124.1, 124.0, 121.7, 121.6, 81.2, 61.2, 57.9, 49.2, 45.9, 32.4, 32.2, 28.6, 26.4, 14.7 ppm; HRMS (ES): *m/z* calcd for $C_{27}H_{36}N_2O_4Na$: 475.2573; found: 475.2564.

Compound 37: $LiBH_4$ (1 mg, 0.060 mmol) was added to a solution of **36** (20 mg, 0.043 mmol) in dry THF (2 mL). The mixture was stirred at 50 °C under a N_2 atmosphere. After 2.5 h, the mixture was diluted with CH_2Cl_2 and H_2O. An aqueous solution of HCl (1 M) was added until pH = 2–3, then the aqueous layer was extracted with CH_2Cl_2 (×2). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated under vacuum. The product was purified by column chromatography (AcOEt/pentane 2:5 + 5% Et_3N) to afford **37** as a colourless oil (14 mg, 79%). R_f = 0.23 (EtOAc/pentane 1:2 + 5% Et_3N + 5% CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, J = 1.6 Hz, 1H), 7.53 (dd, J = 1.6, 8.0 Hz, 1H), 7.14–7.09 (m, 3H), 6.94 (dd, J = 1.6, 7.6 Hz, 1H), 4.64 (s, 2H), 3.83 (t, J = 6.0 Hz, 2H), 3.20–3.14 (m, 4H), 2.85–2.81 (m, 2H), 2.42 (s, 6H), 1.99–1.95 (m, 2H), 1.58 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0, 148.0, 147.8, 139.9, 139.1, 133.9, 130.7, 130.4, 130.3, 124.1, 122.2, 120.9, 119.0, 81.3, 65.5, 62.9, 51.4, 48.6, 32.7, 31.7, 28.5, 22.4 ppm.

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