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Synthesis of 2′-aminoalkyl-1-benzylisoquinoline derivatives and medium sized ring analogues with mu opiod receptor binding activities

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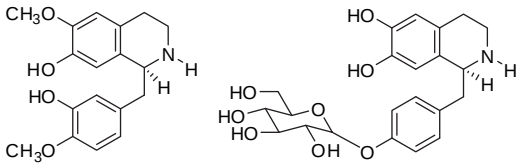
ABSTRACT

Novel 2′-aminoalkyl-1-benzylisoquinoline compounds and medium size ring analogues have been prepared using reductive alkylation methods. Four of these analogues were tested for biological activity across 48 different CNS receptors and were showed to have binding activities at the mu opiod receptor.

1. Introduction

The 1-benzylisoquinolines alkaloids constitute a group of natural products of diverse structure that are widely present in many plants and mammalian species.[1,2] About 2500 1-benzylisoquinoline alkaloids have been identified and shown to have a wide range of biological activities including anticancer,[2] antimalarial,[3] anti-HIV,[4] antiplatelet and vasorelaxant.[5,6] Several natural and synthetic benzylisoquinoline derivatives have also displayed affinities for dopamine and seretonin receptors, which are important neurotransmitters in the central nervous system (CNS).[7] Examples of some of these 1-benzylisoquinoline derivatives are shown in Figure 1. Compounds with these biological activities have potential application in the treatment of numerous physiological and behavioural disorders such as schizophrenia, anxiety, Parkinson's and Huntington's disease.[7]

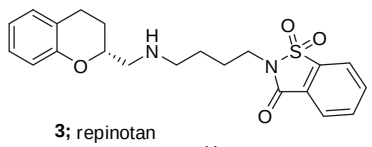


1; *(S)-N*-Norreticuline **2**; SCH71450

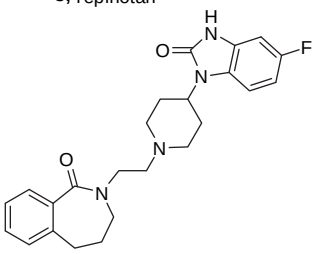
Figure 1. 1-Benzylisoquinoline derivatives that were found to be dopaminergic ligands in the micromolar range.[7]

There are also an emerging class of CNS active compounds that contain an amino group appended to a heterocyclic base structure (Fig. 2), for example, the high affinity $5HT_{1A}$ receptor agonist repinotan **3**[8] and the $5HT_7$ active molecule SB-691673 **4**.[9] Medium sized ring CNS active compounds are known, including the D1-antagonist LE 300 **5**[10] and the partial D1/D5 agonist SCH 39166 **6**.[10–12]

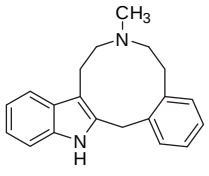
In our continuing project concerned with the discovery of new bioactive benzylisoquinoline derivatives,[13–15] the 2′-aminoalkyl-1-benzylisoquinoline compound **7** and the medium side ring analogues **8** were of interest. We report here our attempts to synthesise these compounds and the biological activities of four of these analogues on 48 different CNS receptors (Fig. 3).



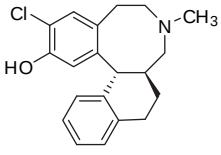
3; repinotan



4; SB-691673



5; LE 300



6; SCH 39166

Figure 2. The structures of known CNS active compounds.[8–12]

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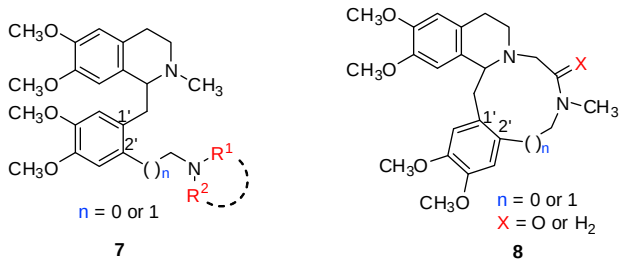
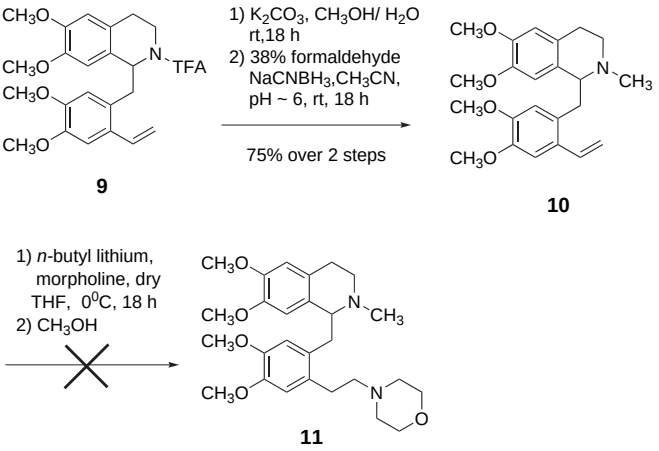


Figure 3. The targeted 1-benzylisoquinoline derivatives containing 2′-aminoalkyl substituents (**7**) and the medium sized ring targets (**8**).

2. Results and discussion

With the aim of preparing 2′-aminoethyl-1-benzylisoquinoline derivatives, we first examined the method reported by Seijas et al. towards the preparation of β-phenylethylamines derivatives by addition of primary and secondary lithium amides to styrene.[16] The racemic 2′-vinyllaudanosine derivative **10** was prepared from the known *N*-TFA derivative **9**[14,15] in 75% overall yield. Morpholine was treated with *n*-butyl lithium and the resulting solution of lithium morpholinamide in THF was added to compound **10** at 0 °C. The mixture was left at 0 °C for 18 h. ^{1}H NMR analysis only showed unreacted starting material **10** and no morpholine ethylene signals were observed. This suggests that the vinyl group of **10** was too electron rich to react with the lithium morpholinamide nucleophile. Therefore an alternative synthesis of the 2′-aminoethyl-1-benzylisoquinoline and 2′-aminomethyl-1-benzylisoquinoline derivatives was examined using a reductive amination method (Schemes 1 and 2). Here the racemic aldehydes **15** and **16** were prepared in good yields from the known alkenes **9** and **12**,[14,15] respectively, using the two-step sequence of dihydroxylation, followed by oxidative cleavage.[17,18]

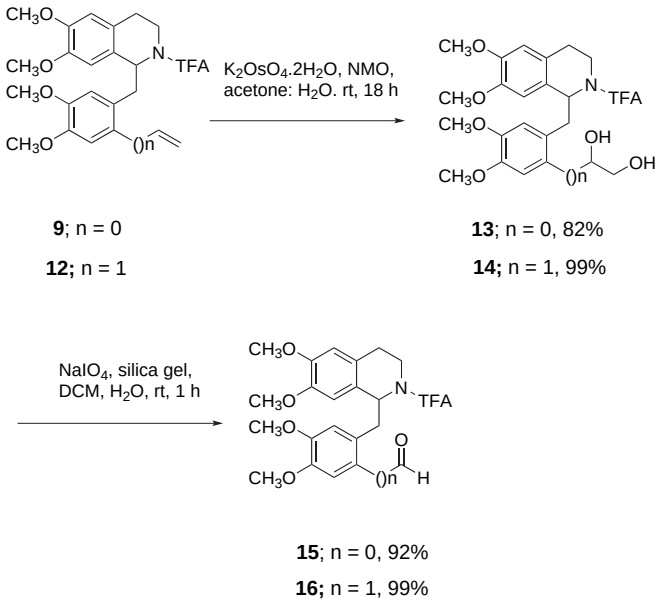


Scheme 1. Attempted synthesis of **11** using lithium morpholinamide and the 2′-vinyllaudanosine derivative **10**.

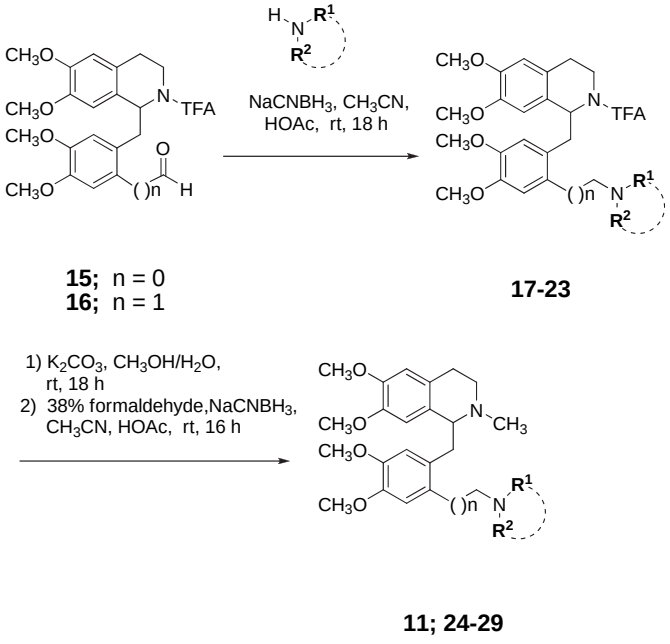
The aldehydes **15** and **16** were subjected to reductive amination reactions with several amines to give the corresponding aminated products in moderate to good yields (Scheme 3, Table 1).

The final 2′-aminoalkyl-1-benzylisoquinoline derivatives required for biological testing were obtained by basic hydrolysis of the TFA group of **17**–**23**, followed by reductive N-methylation using a literature procedure.[19] The final products **11** and **24**–**29** were obtained in moderate to high yields (Table 1).

Overall, the above reductive amination procedure was an effective method used to synthesise a small library of seven 2′-aminoalkyl-1-benzylisoquinoline derivatives, which represent a new class of 1-benzylisoquinolines.



Scheme 2. Preparation of the aldehydes **15** and **16** via oxidative cleavage of the diols **13** and **14**, respectively.

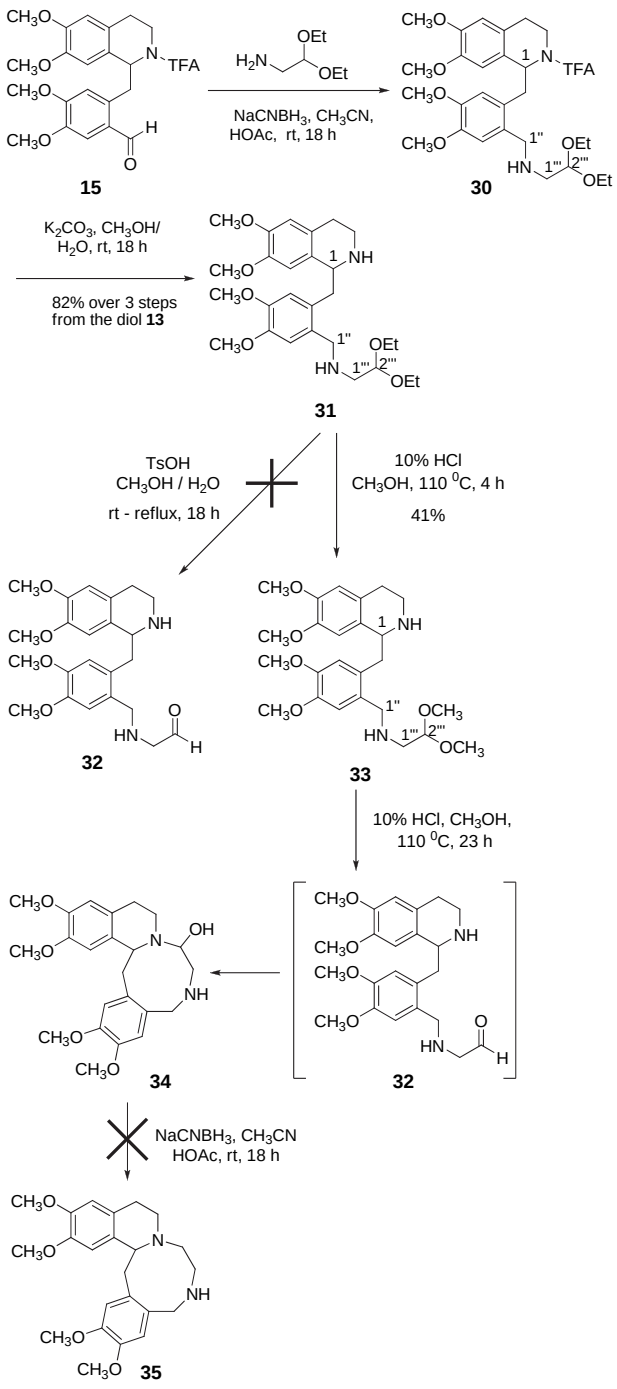


Scheme 3.

The synthesis of the medium sized ring 1-benzylisoquinoline derivative **35** was attempted utilising an intramolecular reductive amination reaction between the aldehyde and the amine group of **32** to provide the medium ring compound **35** (Scheme 4). The synthesis started with the reductive amination reaction between the aldehyde **15** and commercially available aminoacetaldehyde diethylacetal, followed by basic hydrolysis of the *N*-TFA group to afford the desired product **31** in 82% overall yield. Conversion of the diethoxyl acetal group of the bis-amine **31** into the corresponding aldehyde **32** was attempted using TsOH/CH_3OH/H_2O at rt to reflux temperature, however no product was obtained. Alternatively, the amine **31** was heated in a solution of 10% aqueous HCl/MeOH at 110 °C to afford only the corresponding dimethoxyl acetal

Table 1
Synthesis of 2′-aminomethyl-1-benzylisoquinoline analogues by reductive amination, followed by *N*-TFA cleavage and N-methylation

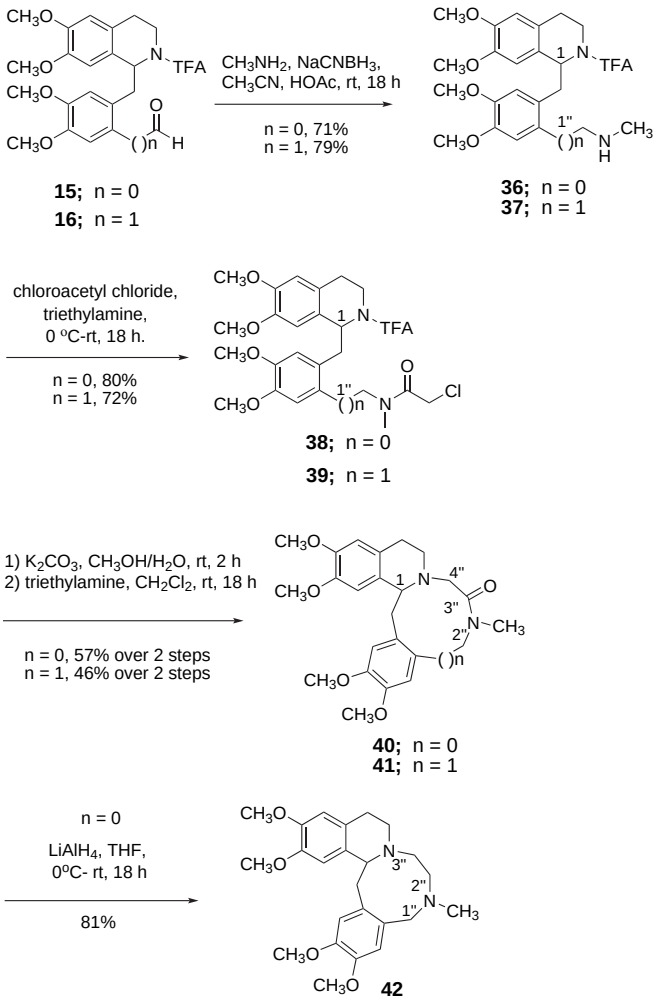
Entry	Aldehyde	Amine			Reductive amination		*N*-TFA cleavage and N-methylation	
		R^1		R^2	Product	Yield (%)	Product	Yield (%)
1	**15**		$-CH_2CH_2-O-CH_2CH_2-$		**17**	60	**24**	73
2	**15**		$-CH_2CH_2CH_2CH_2-$		**18**	74	**25**	71
3	**15**	CH_2CH_3		CH_2CH_3	**19**	75	**26**	58
4	**15**	H		$CH(CH_3)_2$	**20**	64	**27** (R^1=CH_3)	59
5	**16**		$-CH_2CH_2-O-CH_2CH_2-$		**21**	64	**11**	85
6	**16**		$-CH_2CH_2CH_2CH_2-$		**22**	74	**28**	69
7	**16**	CH_2CH_3		CH_2CH_3	**23**	68	**29**	69



Scheme 4.

compound **33**, which arose from exchange of the diethoxyl acetal group with the solvent methanol. Further heating of compound **33** in 10% aqueous HCl/MeOH afforded a crude product, which when ^{1}H NMR analysis was performed, showed that the dimethoxy signal at δ 3.36 (s, 6H, $CH(OCH_3)_2$) had disappeared, however, the expected aldehyde signal in the δ 9–10 region was not observed. ESIMS analysis showed an MH^+ signal at m/z 415.0, which would correspond to the hemiacetal **34**. The crude compound was subjected to the reductive amination conditions with $NaCNBH_3$, however no identifiable products were obtained.

Alternatively (Scheme 5), the aldehydes **15** and **16** were reductively coupled with methylamine to afford the corresponding benzylisoquinolines **36** and **37** in 71% and 79% yield, respectively. The amines **36** and **37** subsequently underwent N-acylation with chloroacetyl chloride to give the corresponding α-chloroacetamides **38** and **39** in good yields (72–80%). Hydrolysis of the *N*-TFA group of



Scheme 5.

38 and **39** exposed the free amino groups for an intramolecular S_N2 displacement of the chloride under basic conditions with triethylamine to provide the desired medium ring compounds **40** and **41** in moderate yields (46–57% over two steps). The 9-membered ring compound **40** was subjected to carbonyl reduction using lithium aluminium hydride to afford the corresponding cyclic amino compound **42** in 81% yield. Analysis of the ^{1}H NMR spectrum of **42** revealed the newly formed methylene proton resonances for H2″ at δ 2.79 (m, 1H), 2.57 (m, 1H) and for H3″ at δ 3.10 (m, 1H), 2.79 (m, 1H). These newly observed methylene proton signals confirmed the successful amide reduction to the amine **42**. The benzylic protons of **42** were observed more prominently at δ 4.49 (d, 1H, *J* 12.5 Hz, H1″) and 3.42 (d, 1H, *J* 12.5 Hz, H1″).

3. In vitro CNS receptor binding studies

The in vitro testing was conducted at Cerep Corporation in France. Four 2′-aminoalkyl-1-benzylisoquinoline derivatives **11**, **25**, **26** and **27** were tested for biological activities on 48 different CNS receptors.[20] The activities were expressed as % inhibition of control specific binding (Table 2), which is the measure of the direct inhibition activity of the tested drug exerted on the controlled ligand. Therefore the drug is considered active when the % inhibition of control specific binding is high at the CNS receptor type tested.

In conclusion, seven novel 2′-aminoalkyl-1-benzylisoquinoline analogues and three medium sized ring 1-benzylisoquinoline analogues were successfully synthesised. Four analogues **11**, **25**, **26** and **27** showed moderate to good inhibition of control specific binding activities at 1–10 μM concentrations against the mu receptor. Unfortunately, compounds **24**, **28**, **29** and **40**–**42** were unable to be tested.

4. Experimental

4.1. General

Petrol refers to the fraction of petroleum spirit with a boiling point of 40–60 °C. All ^{1}H NMR spectra were performed at 300 MHz and all ^{13}C NMR and DEPT spectra at 75 MHz in $CDCl_3$ solution, unless otherwise noted. All spectra were referenced to $CDCl_3$ (^{1}H δ 7.26 ppm and ^{13}C NMR δ 77.00 ppm). ^{1}H NMR assignments were achieved with the aid of gCOSY, and in some cases NOESY and TOCSY experiments. ^{13}C NMR assignments were based on DEPT, gHSQC and gHMBC experiments. All compounds were homogeneous by TLC analysis and judged to be of >95% purity based upon ^{1}H NMR analysis. Compound numbering of 1-benzylisoquinoline derivatives is based on that of compounds **11** and **24**. Compound numbering of the medium ring benzylisoquinoline derivatives is based on that of compounds **40** and **41**.

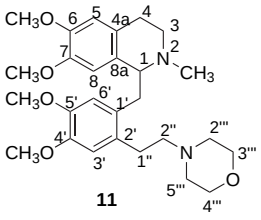
Table 2
In vitro CNS receptor binding activities of compounds **11** and **25**–**27**. Across the 48 CNS receptors, only the receptors with 25% or more of inhibition activities are illustrated below

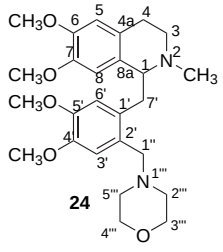
Assay	Reference compounds		% Inhibition of control specific binding at 1 μM			
	Reference compound	IC_{50} (nM)	Compound **11**	Compound **25**	Compound **26**[a]	Compound **27**
μ (h) (MOP)	DAMGO	1.2	46	25	52	35
κ (KOP)	U 50488	1.2	—	—	40	—
V_{1a} (h)	[d(CH_2)51,Tyr(Me)$_2$]-AVP	1.8	—	—	37	—
α_1 (non-selective)	Prazosin	0.30	—	—	25	—
Na^+ channel	Veratridine	4650	—	—	25	—

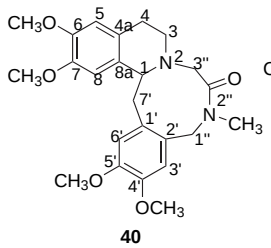
The symbol '—' indicates binding inhibition of less than 25%.
[a] Testing was conducted at 10 μM concentration.

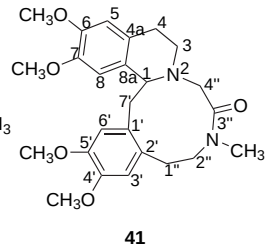
The CNS binding activities of the four derivatives **11**, **25**–**27** are shown in Table 2. All four compounds showed binding activities at the mu (μ) opiod receptor (MOP), with compound **11** having the highest mu receptor activity with 46% inhibition of the control (DAMGO) specific binding at 1 μM concentration. Compound **26** was tested at 10 μM concentration and was shown to have binding activities against several receptors, most prominently at the mu and kappa opiod (KOP) receptors, with inhibition activities of 52% and 40%, respectively. The IC_{50} of these compounds are yet to be determined, but that of compound **11** and **27** would be estimated to be in the low micromolar range activities against the mu receptor.

The mu opiod receptor is one major class of opiod receptors, which has been targeted for its analgesic properties.[21] Opiod agonists such as morphine exert their activities mainly at the mu opiod receptor and have been widely used in pain therapy.[21] Chronic morphine therapy, however, can produce unwanted side effects such as tolerance, respiratory suppression and constipation.[21] Mu opiod antagonists are commonly used as a rescue medication to reverse these side effects as well as combating alcohol and narcotic addiction.[22,23] Mu opiod antagonists also have potential applications in the treatment of obesity, psychosis and Parkinson's disease.[22] Therefore, depending on their agonist or antagonist properties, compounds **11** and **25**–**27** and their analogues could be used in pain treatment therapy, or for the treatment of narcotic addictions as well as obesity, psychosis and Parkinson's disease.









4.2. (*RS*) 1-(2′-Ethenyl-4′,5′-dimethoxyphenyl)methyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (10)

To a solution of the 2′-vinyllaudanosine derivative **9** (227 mg, 0.487 mmol) in a mixture of CH_3OH (20 mL) and H_2O (3 mL) at rt

was added K_2CO_3 (339 mg, 2.44 mmol). The reaction mixture was stirred for 18 h at rt. The CH_3OH was evaporated and the residue was dissolved in CH_3CN (10 mL). Formaldehyde of 38% (8 mL) was added to the solution, followed by $NaCNBH_3$ (41 mg, 0.633 mmol). The reaction mixture was stirred for 20 min at rt and the pH was adjusted to ~6 using glacial acetic acid. The reaction mixture was stirred for 18 h at rt. The solvent was evaporated and the residue was dissolved in CH_2Cl_2 and washed with 1 M aqueous NaOH, H_2O (2×) and dried (K_2CO_3) to give an oil. The oil was purified by column chromatography (CH_3OH/EtOAc/NH_3 (3:7:0.1)) to give **10** (140 mg, 75% overall) as a yellow oil. R_f 0.25 (CH_3OH/EtOAc (1:1)). ^{1}H NMR: δ 6.97 (s, 1H, H3′), 6.73 (dd, 1H, *J* 17.4, 10.8 Hz, H1″), 6.54 (s, 1H, H5), 6.39 (s, 1H, H6′), 5.72 (s, 1H, H8), 5.45 (dd, 1H, *J* 17.4, 1.2 Hz, H2″(*E*)), 5.11 (dd, 1H, *J* 10.8, 1.2 Hz, H2″(*Z*)), 3.86 (s, 3H, OC*H*$_3$-4′), 3.80 (s, 3H, OC*H*$_3$-6), 3.72 (s, 3H, OC*H*$_3$-7), 3.68–3.62 (m, 1H, H1), 3.43 (s, 3H, OC*H*$_3$-5′), 3.28–3.25 (m, 1H, H3), 3.24 (dd, 1H, *J* 13.5, 4.8 Hz, H7′), 2.94–2.78 (m, 2H, H3, H4), 2.76 (dd, 1H, *J* 13.5, 9.0 Hz, H7′), 2.64–2.57 (m, 1H, H4), 2.54 (s, 3H, NC*H*$_3$). MS (ESI$^+$): *m*/*z* 384 (MH$^+$, 20%). HRMS (ESI$^+$): calcd for $C_{23}H_{30}NO_4$, 384.2175 (MH$^+$), found 384.2180.

4.3. Attempted synthesis of (*RS*) 1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4′,5′-dimethoxy-2′-(2″-morpholinoethyl)-phenyl)methyl-2-methylisoquinoline (11)

To a solution of **10** (139.5 mg, 0.364 mmol) in dry THF (4 mL) was added a solution of lithium morpholinamide, prepared by the addition of 2.5 M *n*BuLi in hexane (0.2 mL, 0.5 mmol) to a solution of morpholine (79.3 mg, 0.91 mmol, 0.1 mL) in dry THF (1 mL) at 0 °C. The reaction mixture was kept at 0 °C for 18 h. The reaction mixture was quenched with CH_3OH and the solvent was evaporated. The residue was purified by column chromatography to retrieve only a quantitative amount of starting material **10**.

4.4. General method for dihydroxylation[17,18]

To a solution of the olefin in acetone was added potassium osmate dihydrate ($K_2OsO_4 \cdot 2H_2O$), followed by *N*-methylmorpholine *N*-oxide (NMO). H_2O was subsequently added and the mixture was stirred at rt for 18 h. Sodium sulfite (Na_2SO_3) (ca. 10 equiv) was added and stirred for 30 min before the acetone was evaporated. Water was added and the mixture was extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with brine, dried ($MgSO_4$) and evaporated to give an oil. The oil was purified by column chromatography (EtOAc) to afford the desired product.

*4.4.1. (1RS,1″RS) and (1RS,1″SR) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-1-[2′-(1″,2″-dihydroxyethyl)-4′,5′-dimethoxypheny]methyl-6,7-dimethoxyisoquinoline (**13**).* A solution of the olefin **9** (135 mg, 0.290 mmol) in acetone (3 mL) was treated as described above in the general dihydroxylation reaction procedure using $K_2OsO_4 \cdot 2H_2O$ (6 mg, 0.015 mmol), NMO (72 mg, 0.609 mmol) and H_2O (1 mL). Purification by column chromatography gave the diol **13** (119 mg, 82%) as a light yellow oil. The diol **13** was obtained as a 4:1 mixture of diastereomers. R_f 0.39 (EtOAc). ^{1}H NMR of the major diastereomer: δ 6.99 (s, 1H, H3′), 6.61 (s, 1H, H5), 6.31 (s, 1H, H6′), 6.08 (s, 1H, H8), 5.48 (dd, 1H, *J* 8.2, 5.8 Hz, H1), 5.08 (dd, 1H, *J* 8.1, 4.2 Hz, H1″), 3.94 (dt, 1H, *J* 13.5, 3.6 Hz, H3), 3.85 (s, 3H, OC*H*$_3$-7), 3.84 (s, 3H, OC*H*$_3$-5′), 3.78 (dt, 1H, *J* 12.6, 4.8 Hz, H3), 3.69 (s, 3H, OC*H*$_3$-4′), 3.68–3.60 (m, 2H, 2×H2″), 3.57 (s, 3H, OC*H*$_3$-6), 3.17 (dd, 1H, *J* 13.5, 5.8 Hz, H7′), 3.03 (dd, 1H, *J* 13.5, 8.2 Hz, H7′), 2.98–2.93 (m, 1H, H4), 2.84–2.76 (m, 1H, H4). ^{1}H NMR of the minor diastereomer (in part): δ 6.95 (s, 1H, H3′), 6.49 (s, 1H, H5), 6.23 (s, 1H, H6′), 5.59 (t, 1H, *J* 7.5 Hz, H1), 4.94 (dd, 1H, *J* 8.1, 4.2 Hz, H1″), 3.77 (s, 3H, OC*H*$_3$-7), 3.73–3.71 (m, 2H, 2H2″), 3.68 (s, 3H, OCH$_3$-4′), 3.28–3.23 (m, 1H, H7′). ^{13}C NMR of the major diastereomer: δ 156.3 (q, *J* 36.1 Hz, *C*OCF$_3$), 148.1 (C5′, C7), 147.6 (C4′), 147.0 (C6), 131.8 (C1′), 126.2 (C2′), 125.9 (C4a), 124.6 (C8a), 118.2 (q, *J* 285.1, CO*C*F$_3$), 114.2 (CH-6′), 111.4 (CH-8), 110.8 (CH-5), 109.6 (CH-3′), 70.7 (CH-1″), 67.3 (CH$_2$-2″), 55.7 (4×OCH$_3$), 55.5 (CH-1), 40.6 (CH$_2$-3), 38.0 (CH$_2$-7′), 28.2 (CH$_2$-4). ^{13}C NMR of the minor diastereomer (in part): δ 132.1 (C1′), 126.1 (C2′), 124.4 (C8a), 114.4 (CH-6′), 110.2 (CH-5′), 109.5 (CH-3′), 67.5 (CH$_2$-2″), 28.3 (CH$_2$-4). MS (EI$^+$): *m*/*z* 499 (M$^+$, 20%). HRMS (ESI$^+$): calcd for $C_{24}H_{28}F_3NNaO_7$, 522.1716 (M+Na$^+$), found 522.1724.

*4.4.2. (1RS,2″RS) and (R,S) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-1-[2′-(2″,3‴-dihydroxypropyl)-4′,5′-dimethoxyphenyl]methyl-6,7-dimethoxyisoquinoline (**14**).* A solution of the olefin **12** (120 mg, 0.255 mmol) in acetone (7 mL) was treated as described above in the general dihydroxylation reaction procedure using $K_2OsO_4 \cdot 2H_2O$ (6 mg, 0.015 mmol), followed by NMO (63 mg, 0.537 mmol) and H_2O (1 mL) except the reaction mixture stirred for 5 h at rt. The crude oil was purified by column chromatography (EtOAc) to give the diol **14** (130 mg, 99%) as clear oil. The diol **14** was obtained as a 60:40 mixture of diastereomers. R_f 0.38 (EtOAc). ^{1}H NMR of the major diastereomer: δ 6.71 (s, 1H, H3′), 6.61 (s, 1H, H5), 6.39 (s, 1H, H6′), 6.27 (s, 1H, H8), 5.47 (dd, 1H, *J* 5.4, 3.3 Hz, H1), 4.02 (dt, 1H, *J* 8.1, 3.0 Hz, H3), 3.97–3.91 (m, 1H, H2″), 3.84 (s, 3H, OC*H*$_3$-7), 3.83 (s, 3H, OC*H*$_3$-5′), 3.81–3.78 (m, 1H, H3″), 3.75–3.70 (m, 1H, H3), 3.69 (s, 3H, OC*H*$_3$-4′), 3.58–3.54 (m, 1H, H3″), 3.52 (s, 3H, OC*H*$_3$-6), 3.13 (dd, 1H, *J* 8.1, 3.3 Hz, H7′), 3.02 (dd, 1H, *J* 8.1, 5.4 Hz, H7′), 2.94–2.89 (m, 1H, H1″), 2.88–2.85 (m, 1H, H4), 2.83–2.79 (m, 1H, H4), 2.68–2.62 (m, 1H, H1″). ^{1}H NMR of the minor diastereomer (in part): δ 6.70 (s, 1H, H3′), 6.44 (s, 1H, H6′), 6.01 (s, 1H, H8), 5.59 (dd, 1H, *J* 5.4, 3.3 Hz, H1), 3.88–3.84 (m, 1H, H2″), 3.74 (s, 3H, OC*H*$_3$-4′), 3.66 (s, 3H, OC*H*$_3$-6), 3.15 (dd, 1H, *J* 8.1, 3.3 Hz, H7′), 3.03 (dd, 1H, *J* 8.1, 5.4 Hz, H7′), 2.97–2.94 (m, 1H, H1″), 2.75–2.71 (m, 1H, H1″). ^{13}C NMR of the major diastereomer: (signals for *C*OCF$_3$ and CO*C*F$_3$ were not observed) δ 148.3 (C7), 148.2 (C5′), 147.5 (C6), 147.3 (C4′), 129.3 (C1′), 127.7 (C2′), 126.2 (C4a), 124.6 (C8a), 114.5 (CH-6′), 113.3 (CH-3′), 111.0 (CH-8, CH-5), 73.1 (CH-2″), 66.2 (CH$_2$-3″), 55.0 (4×OCH$_3$), 55.7 (CH-1), 40.8 (CH$_2$-3), 38.6 (CH$_2$-7′), 35.7 (CH$_2$-1″), 28.5 (CH$_2$-4). ^{13}C NMR of the minor diastereomer (in part): δ 148.3 (C7), 147.3 (C6), 148.0 (C5′), 147.1 (C4′), 129.0 (C1′), 127.9 (C2′), 126.6 (C4a), 124.8 (C8a), 114.0 (CH-6′), 113.1 (CH-3′), 110.9 (CH-5), 110.4 (CH-8), 72.9 (CH-2″), 66.0 (CH$_2$-3″), 55.6 (CH-1), 40.4 (CH$_2$-3), 38.5 (CH$_2$-7′), 36.0 (CH$_2$-1″), 28.6 (CH$_2$-4). MS (EI$^+$): *m*/*z* 513 (M$^+$, 20%). HRMS (ESI$^+$): calcd for $C_{25}H_{31}F_3NO_7$, 514.2053 (MH$^+$), found 514.2064.

4.5. General method for oxidative cleavage of diols

To a warm solution (ca. 40 °C) of $NaIO_4$ in H_2O was added silica gel with vigorous stirring. The powder was cooled and a solution of the diol in CH_2Cl_2 was added. The mixture was stirred vigorously for 1 h at rt. The CH_2Cl_2 layer was collected by pipetting and the silica was washed several times with CH_2Cl_2. The combined CH_2Cl_2 washings were evaporated to give pure aldehydes without the need for further purification.

*4.5.1. (RS) 1-(2′-Formyl-4′,5′-dimethoxyphenyl)methyl-2-trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**15**).* Silica gel coated with $NaIO_4$ was prepared as above using $NaIO_4$ (827 mg, 3.89 mmol), H_2O (2 mL) and silica gel (1.7 g). To this powder was added a solution of the vicinal diol **14** (167 mg, 0.335 mmol) in CH_2Cl_2 (3 mL), which was treated as described above in the general oxidative cleavage reaction procedure to afford the pure aldehyde **15** (144 mg, 92%) as a white solid. R_f 0.80 (EtOAc). Mp 154–158 °C. ^{1}H NMR: δ 9.90 (br s, 1H, C*H*O), 7.28 (s, 1H, H3′), 6.74 (s, 1H, H5), 6.59 (s, 2H, H6′, H8), 5.64 (dd, 1H, *J* 8.7, 5.7 Hz, H1), 3.92 (s, 3H, OC*H*$_3$-7), 3.88 (s, 3H, OC*H*$_3$-5′), 3.84 (s, 3H, OC*H*$_3$-4′), 3.79 (s, 3H, OC*H*$_3$-6), 3.71–3.54 (m, 3H, 2×H3, H7′), 3.15 (dd, 1H, *J* 13.5, 8.1 Hz, H7′), 2.94–2.88 (m, 1H, H4), 2.86–2.70 (m, 1H,

H4). ^{13}C NMR: (signals for $COCF_3$ and $COCF_3$ were not observed) δ 190.8 (*C*HO), 153.0 (C4′), 148.3 (C6), 148.0 (C5′), 147.8 (C7), 134.1 (C2′), 127.6 (C4a), 126.5 (C1′), 124.7 (C8a), 114.6 (CH-6′), 113.9 (CH-3′), 110.9 (CH-8), 110.3 (CH-5), 56.0 (OCH_3-7, OCH_3-5′), 55.9 (OCH_3-4′, OCH_3-6), 55.1 (CH-1), 40.3 (CH_2-3), 37.7 (CH_2-7′), 28.6 (CH_2-4). MS (EI$^+$): *m*/*z* 467 (M^+, 10%). HRMS (ESI$^+$): calcd for $C_{23}H_{25}F_3NO_6$, 468.1634 (MH^+), found 468.1642.

*4.5.2. (RS) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-[4′,5′-dimethoxy-2′-(2″-oxoethyl)phenyl]methylisoquinoline (**16**).* Silica gel coated with $NaIO_4$ was prepared as above using $NaIO_4$ (676 mg, 3.18 mmol), H_2O (2 mL) and silica gel (1.7 g). To this solution was added a solution of diol **14** (134 mg, 0.265 mmol) in CH_2Cl_2 (3 ml), which was reacted as described above in the general oxidative cleavage reaction procedure to give the pure aldehyde **16** (127 mg, 99%) as a clear oil. Compound **16** was a 95:5 mixture of rotamers. R_f 0.88 (EtOAc). ^{1}H NMR of the major rotamer: δ 9.61 (t, 1H, *J* 2.1 Hz, *CH*O), 6.60 (s, 2H, H3′, H5), 6.50 (s, 1H, H6′), 6.02 (s, 1H, H8), 5.33 (dd, 1H, *J* 8.7, 5.4 Hz, H1), 3.90 (dt, 1H, *J* 12.6, 4.5 Hz, H3), 3.86 (s, 6H, O*CH*$_3$-7, O*CH*$_3$-5′), 3.74 (s, 3H, O*CH*$_3$-4′), 3.67 (dd, 1H, *J* 8.4, 3.6 Hz, H3), 3.55 (s, 3H, O*CH*$_3$-6), 3.55–3.47 (m, 2H, 2×H1″), 3.07 (dd, 1H, *J* 13.5, 5.4 Hz, H7′), 2.91 (dd, 1H, *J* 13.5, 8.9 Hz, H7′), 2.89–2.85 (m, 1H, H4), 2.83–2.78 (m, 1H, H4). ^{1}H NMR of the minor rotamer (in part): δ 9.43 (br s, *CH*O), 5.87 (s, 1H, H8). ^{13}C NMR of the major rotamer: δ 199.6 (*C*HO), 156.1 (q, *J* 35.8 Hz, *COCF*$_3$), 148.3 (C4′), 148.2 (C6), 148.2 (C5′), 147.2 (C7), 128.4 (C2′), 125.9 (C4a), 124.9 (C1′), 123.4 (C8a), 116.5 (q, *J* 286.4 Hz, *COCF*$_3$), 114.5 (CH-6′), 113.9 (CH-3′), 110.9 (CH-8), 110.8 (CH-5), 56.0 (O*CH*$_3$-7), 55.9 (O*CH*$_3$-5′, O*CH*$_3$-4′), 55.7 (O*CH*$_3$-6), 55.6 (CH-1), 47.8 (CH_2-1″), 40.8 (CH_2-3), 38.5 (CH_2-7′), 28.6 (CH_2-4). ^{13}C NMR of the minor rotamer (in part): δ 199.0 (*C*HO), 40.9 (CH_2-3), 55.4 (CH-1), 47.9 (CH_2-1″). MS (EI$^+$): *m*/*z* 481 (M^+, 10%). HRMS (ESI$^+$): calcd for $C_{24}H_{27}F_3NO_6$, 482.1790 (MH^+), found 482.1812.

4.6. General method of reductive amination

To a solution of the aldehyde and the amine in CH_3CN was added $NaCNBH_3$. The reaction was stirred at rt for 20 min before glacial acetic acid was added to adjust the pH to ~6. The resulting solution was stirred for 18 h at rt. The CH_3CN was evaporated and the residue was dissolved in CH_2Cl_2. The solution was washed subsequently with H_2O (3×), satd Na_2CO_3, brine and dried ($MgSO_4$) to give an oil. The oil was purified by column chromatography to afford the pure product.

*4.6.1. (RS) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-[4′,5′-dimethoxy-2′-(morpholino)methylphenyl]methylisoquinoline (**17**).* A mixture of the aldehyde **22** (58 mg, 0.125 mmol), morpholine (0.10 mL, 1.16 mmol), CH_3CN (15 mL) and $NaCNBH_3$ (10 mg, 0.162 mmol) was treated as described above in the general reductive amination reaction procedure to give an oil. The oil was purified by column chromatography (EtOAc) to afford **28** (40 mg, 60%) as a clear oil. Compound **28** was a 95:5 mixture of rotamers. R_f 0.38 (EtOAc). ^{1}H NMR of the major rotamer: δ 6.73 (s, 1H, H3′), 6.59 (s, 1H, H5), 6.47 (s, 1H, H6′), 6.24 (s, 1H, H8), 5.78 (t, 1H, *J* 7.2 Hz, H1), 4.04–3.95 (m, 1H, H3), 3.83 (s, 6H, O*CH*$_3$-7, O*CH*$_3$-5′), 3.75 (dt, 1H, *J* 7.8, 6.7 Hz, H3), 3.74 (s, 3H, O*CH*$_3$-4′), 3.65 (t, 4H, *J* 4.8 Hz, 2×H3‴, 2×H4‴), 3.61 (s, 3H, O*CH*$_3$-6), 3.41 (d, 1H, *J* 12.9 Hz, H1″), 3.22 (dd, 1H, *J* 13.5, 7.2 Hz, H7′), 3.19 (d, 1H, *J* 12.9 Hz, H1″), 3.08 (dd, 1H, *J* 13.5, 7.2 Hz, H7′), 3.00–2.90 (m, 1H, H4), 2.81–2.73 (m, 1H, H4), 2.44–2.39 (m, 4H, 2×H2″, 2×H5‴). ^{1}H NMR of the minor rotamer (in part): δ 6.71 (s, 1H, H3′), 6.50 (s, 1H, H6′), 5.96 (s, 1H, H8). ^{13}C NMR of the major rotamer: (signals for $COCF_3$ and $COCF_3$ were not observed) δ 148.2 (C4′), 147.9 (C6), 147.4 (C5′, C7), 128.9 (C2′), 128.7 (C8a), 127.2 (C1′), 124.8 (C4a), 114.2 (CH-3′), 114.1 (CH-6′), 111.0 (CH-5), 110.4 (CH-8), 67.0 (CH_2-3‴, CH_2-4″), 61.4 (CH_2-2‴, CH_2-5‴), 55.9 (OCH_3-7, OCH_3-5′), 55.8 (OCH_3-4′), 55.7 (OCH_3-6), 55.0 (CH-1), 53.7 (CH_2-1″), 40.1 (CH_2-3), 37.9 (CH_2-7′), 28.7 (CH_2-4). MS (EI$^+$): *m*/*z* 538 (M^+, 30%). HRMS (ESI$^+$): calcd for $C_{27}H_{34}F_3N_2O_6$, 539.2369 (MH^+), found 539.2363.

*4.6.2. (RS) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-[4′,5′-dimethoxy-2′-(pyrrolidinyl)methylphenyl]methylisoquinoline (**18**).* A mixture of the aldehyde **15** (91 mg, 0.194 mmol), pyrrolidine (0.10 mL, 1.13 mmol), CH_3CN (3 mL) and $NaCNBH_3$ (16 mg, 0.252 mmol) was treated as described above in the general reductive amination reaction procedure to give an oil. The oil was purified by column chromatography (CH_3OH/EtOAc (4:6)) to afford **18** (77 mg, 74%) as a light yellow oil. Compound **18** was a 95:5 mixture of rotamers. R_f 0.20 (CH_3OH/EtOAc (4:6)). ^{1}H NMR of the major rotamer: δ 6.97 (s, 1H, H3′), 6.59 (s, 1H, H5), 6.34 (s, 1H, H6′), 6.04 (s, 1H, H8), 5.44 (dd, 1H, *J* 8.1, 6.1 Hz, H1), 3.93–3.87 (m, 1H, H3), 3.87 (s, 3H, O*CH*$_3$-7), 3.83 (s, 3H, O*CH*$_3$-5′), 3.80–3.75 (m, 1H, H3), 3.69 (s, 3H, O*CH*$_3$-4′), 3.56 (s, 3H, O*CH*$_3$-6), 3.42 (d, 1H, *J* 6.6 Hz, H1″), 3.38 (d, 1H, *J* 6.6 Hz, H1″), 3.16 (dd, 1H, 13.5, *J* 6.1 Hz, H7′), 3.08 (dd, 1H, *J* 13.5, 8.1 Hz, H7′), 2.97–2.87 (m, 1H, H4), 2.83–2.74 (m, 5H, H4, H2‴, 2×H5‴), 1.92–1.84 (m, 4H, 2×H3‴, 2×H4‴). ^{1}H NMR minor rotamer (in part): δ 6.79 (s, 1H, H3′), 6.56 (s, 1H, H5), 6.44 (s, 1H, H6′), 6.04 (s, 1H, H8). ^{13}C NMR of the major rotamer: (signals for $COCF_3$ and $COCF_3$ were not observed) δ 148.3 (C4′, C6), 148.1 (C5′), 147.2 (C7), 128.3 (C2′), 126.9 (C1′), 126.2 (C4a), 125.1 (C8a), 114.4 (CH-6′), 113.5 (CH-3′), 111.0 (CH-5), 110.7 (CH-8), 56.5 (CH_2-1″), 56.2 (OCH_3-7), 56.0 (OCH_3-5′), 55.8 (OCH_3-4′, OCH_3-6), 55.7 (CH-1), 53.6 (CH_2-2‴, CH_2-5‴), 40.8 (CH_2-3), 38.4 (CH_2-7′), 28.5 (CH_2-4), 23.3 (CH_2-3‴, CH_2-4‴). MS (EI$^+$): *m*/*z* 522 (M^+, 20%). HRMS (ESI$^+$): calcd for $C_{27}H_{34}F_3N_2O_5$, 523.2420 (MH^+), found 523.2435.

*4.6.3. (R,S) 1-[2′-(Diethylamino)methyl-4′,5′-dimethoxyphenyl]methyl-2-trifluoroacetyl-1,2,3,4-dihydro.-6,7-dimethoxyisoquinoline (**19**).* A mixture of aldehyde **15** (112 mg, 0.239 mmol), diethylamine (0.2 mL, 1.93 mmol), CH_3CN (3 mL) and $NaCNBH_3$ (16 mg, 0.252 mmol) was treated as described above in the general reductive amination reaction procedure to give an oil. The oil was purified by column chromatography (CH_3OH/EtOAc (4:6)) to afford **19** (83 mg, 75%) as a light yellow oil. Compound **19** was a 95:5 mixture of rotamers. R_f 0.33 (CH_3OH:EtOAc (4:6)). ^{1}H NMR of the major rotamer: δ 6.85 (s, 1H, H3′), 6.57 (s, 1H, H5), 6.56 (s, 1H, H6′), 6.12 (s, 1H, H8), 5.55 (t, 1H, *J* 7.8, 6.0 Hz, H1), 3.92 (dt, 1H, *J* 7.8, 3.3 Hz, H3), 3.82 (s, 6H, O*CH*$_3$-7, O*CH*$_3$-5′), 3.76 (s, 3H, O*CH*$_3$-4′), 3.73–3.66 (m, 1H, H3), 3.57 (s, 3H, O*CH*$_3$-6), 3.32 (dd, 1H, *J* 13.5, 7.8 Hz, H7′), 3.28 (d, 1H, *J* 13.5 Hz, H1″), 3.16 (d, 1H, *J* 13.5 Hz, H1″), 3.04 (dd, 1H, *J* 13.5, 6.0 Hz, H7′), 2.98–2.85 (m, 1H, H4), 2.77–2.69 (m, 1H, H4), 2.43 (q, 4H, *J* 6.9 Hz, 2×N*CH*$_2$CH$_3$), 0.93 (t, 6H, *J* 6.9 Hz, 2×NCH$_2$*CH*$_3$). ^{1}H NMR of the minor rotamer (in part): δ 6.79 (s, 1H, H3′), 5.85 (s, 1H, H8), 3.79 (s, 6H, O*CH*$_3$-7, O*CH*$_3$-5′), 3.48 (s, 3H, O*CH*$_3$-6). ^{13}C NMR of the major rotamer: (signals for $COCF_3$ and $COCF_3$ were not observed) δ 148.4 (C4′), 147.7 (C6), 147.7 (C5′), 147.5 (C7), 128.5 (C2′, C8a), 127.2 (C1′), 125.0 (C4a), 114.0 (CH-3′), 113.6 (CH-6′), 111.2 (CH-5), 110.7 (CH-8), 55.2 (OCH_3-7), 56.1 (OCH_3-5′), 55.1 (OCH_3-4′), 55.9 (OCH_3-6), 55.7 (CH-1), 55.5 (CH_2-1″), 46.5 (2×NCH_2CH_3), 40.6 (CH_2-3), 37.7 (CH_2-7′), 28.8 (CH_2-4), 11.5 (2×NCH_2CH_3). MS (EI$^+$): *m*/*z* 524 (M^+, 10%). HRMS (ESI$^+$): calcd for $C_{27}H_{35}F_3N_2O_5$, 525.2576 (MH^+), found 525.2563.

*4.6.4. (R,S) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-[4′,5′-dimethoxy-2′-(isopropylamino)methylphenyl]methylisoquinoline (**20**).* A mixture of aldehyde **15** (112 mg, 0.239 mmol), isopropylamine (0.2 mL, 2.33 mmol), CH_3CN (3 mL) and $NaCNBH_3$ (16 mg, 0.252 mmol) was reacted as described above in the general reductive amination reaction procedure to give an oil. The oil was purified by column chromatography (CH_3OH/EtOAc (4:6)) to afford **20** (67 mg, 64%) as a light yellow oil. Compound **20** was a 95:5 mixture of rotamers. R_f 0.17 (CH_3OH/EtOAc (4:6)). ^{1}H NMR of the major rotamer: δ 6.80 (s, 1H, H3′), 6.57 (s, 1H, H5), 6.54 (s, 1H, H6′),

6.12 (s, 1H, H8), 5.58 (t, 1H, *J* 8.1, 6.6 Hz, H1), 3.95–3.85 (m, 1H, H3), 3.83 (s, 3H, OC*H*$_3$-7), 3.81 (s, 3H, OC*H*$_3$-5′), 3.76 (s, 3H, OC*H*$_3$-4′), 3.71–3.65 (m, 1H, H3), 3.56 (s, 3H, OC*H*$_3$-6), 3.48 (d, 1H, *J* 12.6 Hz, H1″), 3.43 (d, 1H, *J* 12.6 Hz, H1″), 3.20 (dd, 1H, *J* 13.8, 8.1 Hz, H7′), 3.05 (dd, 1H, *J* 13.8, 6.6 Hz, H7′), 2.96–2.85 (m, 1H, H4), 2.82–2.70 (m, 2H, H2″, H4), 1.04 (d, 3H, *J* 2.4 Hz, CH(C*H*$_3$)CH$_3$), 1.02 (d, 3H, *J* 2.4 Hz, CH(CH$_3$)C*H*$_3$). ^{1}H NMR of the minor rotamer (in part): δ 6.76 (s, 1H, H3′), 5.92 (s, 1H, H8), 3.77 (s, 3H, OC*H*$_3$-5′), 3.49 (s, 3H, OC*H*$_3$-6). ^{13}C NMR of the major rotamer: (signals for *C*OCF$_3$ and CO*C*F$_3$ were not observed) δ 148.4 (C4′), 148.0 (C6), 147.9 (C5′), 147.5 (C7), 131.9 (C2′), 127.9 (C8a), 126.9 (C1′), 125.1 (C4a), 114.1 (CH-3′), 113.1 (CH-6′), 111.2 (CH-5), 110.7 (CH-8), 56.0 (O*C*H$_3$-7), 56.1 (O*C*H$_3$-5′), 55.1 (O*C*H$_3$-4′), 55.9 (O*C*H$_3$-6), 55.8 (CH-1), 49.3 (CH$_2$-1″), 49.2 (CH-2″), 40.7 (CH$_2$-3), 38.0 (CH$_2$-7′), 28.8 (CH$_2$-4), 23.1 (CH(*C*H$_3$)CH$_3$), 22.1 (CH(CH$_3$)*C*H$_3$). MS (EI$^+$): *m*/*z* 510 (M$^+$, 10%). HRMS (ESI$^+$): calcd for $C_{26}H_{34}F_3N_2O_5$, 511.2421 (MH$^+$), found 511.2395.

*4.6.5. (RS) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-[4′,5′-dimethoxy-2′-(2″-(morpholino)ethyl)phenyl]methylisoquinoline (**21**).* A mixture of aldehyde **16** (80 mg, 0.166 mmol), morpholine (0.1 mL, 1.16 mmol), CH$_3$CN (6 mL) and NaCNBH$_3$ (16 mg, 0.252 mmol) was treated as described above in the general reductive amination reaction procedure to give an oil. The oil was purified by column chromatography (CH$_3$OH/EtOAc (4:6)) to afford **21** (59 mg, 64%) as a clear oil. Compound **21** was a 95:5 mixture of rotamers. R_f 0.25 (CH$_3$OH/EtOAc (4:6)). ^{1}H NMR of the major rotamer: δ 6.66 (s, 1H, H3′), 6.57 (s, 1H, H5), 6.52 (s, 1H, H6′), 6.01 (s, 1H, H8), 5.48 (t, 1H, *J* 6.9 Hz, H1), 3.92 (dt, 1H, *J* 13.5, 5.1 Hz, H3), 3.81 (s, 6H, OC*H*$_3$-7, OC*H*$_3$-5′), 3.72 (s, 3H, OC*H*$_3$-4′), 3.67 (t, 4H, *J* 4.7 Hz, 2×H3‴, 2×H4‴), 3.67–3.62 (m, 1H, H3), 3.53 (s, 3H, OC*H*$_3$-6), 3.05 (d, 2H, *J* 6.9 Hz, 2×H7′), 2.96–2.86 (m, 1H, H4), 2.78–2.70 (m, 1H, H4), 2.63–2.57 (m, 1H, H2″), 2.56–2.49 (m, 1H, H2″), 2.40 (t, 4H, *J* 4.7 Hz, 2×H2‴, 2×H5‴), 2.37–2.25 (m, 2H, 2×H1″). ^{1}H NMR of the minor rotamer (in part): δ 6.64 (s, 1H, H3′), 6.56 (s, 1H, H5), 5.75 (s, 1H, H8), 3.81 (s, 6H, OC*H*$_3$-7, OC*H*$_3$-5′), 3.77 (s, 3H, OC*H*$_3$-4′), 3.45 (s, 3H, OC*H*$_3$-6). ^{13}C NMR of the major rotamer: δ 156.1 (q, *J* 35.3 Hz, *C*OCF$_3$), 148.5 (C4′), 148.1 (C6), 147.5 (C5′), 147.4 (C7), 131.5 (C1′), 127.2 (C2′), 126.6 (C4a), 125.2 (C8a), 116.7 (q, *J* 286.5 Hz, CO*C*F$_3$), 114.2 (CH-6′), 113.1 (CH-3′), 111.2 (CH-5), 110.9 (CH-8), 67.2 (CH$_2$-3‴, CH$_2$-4‴), 60.5 (CH$_2$-2″), 55.8 (4×O*C*H$_3$), 55.7 (CH-1), 53.9 (CH$_2$-2‴, CH$_2$-5‴), 40.9 (CH$_2$-3), 38.2 (CH$_2$-7′), 29.7 (CH$_2$-1″), 28.7 (CH$_2$-4). ^{13}C NMR of the minor rotamer (in part): δ 147.9 (C5′), 147.1 (C7), 131.8 (C1′), 127.0 (C2′), 126.0 (C4a), 111.2 (CH-5), 110.4 (CH-8), 65.9 (CH$_2$-3‴, CH$_2$-4‴), 60.1 (CH$_2$-2″), 53.8 (CH$_2$-2‴, CH$_2$-5‴), 40.9 (CH$_2$-3), 39.2 (CH$_2$-7′), 31.8 (CH$_2$-1″), 27.4 (CH$_2$-4). MS (ESI$^+$): *m*/*z* 552.81 (MH$^+$, 100%). HRMS (ESI$^+$): calcd for $C_{28}H_{36}F_3N_2O_6$, 553.2525 (MH$^+$), found 553.2486.

*4.6.6. (RS) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-[4′,5′-dimethoxy-2′-(2″-(N-pyrrolidinyl)ethyl)phenyl]methylisoquinoline (**22**).* A mixture of aldehyde **16** (71 mg, 0.149 mmol), pyrrolidine (0.2 mL, 2.26 mmol), CH$_3$CN (3 mL) and NaCNBH$_3$ (12 mg, 0.194 mmol) was treated as described above in the general reductive amination reaction procedure to give an oil. The oil was purified by column chromatography (CH$_3$OH/EtOAc (4:6)) to afford **22** (61 mg, 74%) as a light yellow oil. Compound **22** was a 95:5 mixture of rotamers. R_f 0.20 (CH$_3$OH/EtOAc (4:6)). ^{1}H NMR of the major rotamer: δ 6.64 (s, 1H, H3′), 6.60 (s, 1H, H5), 6.56 (s, 1H, H6′), 6.02 (s, 1H, H8), 5.50 (dd, 1H, *J* 8.4, 5.7 Hz, H1), 3.93 (dt, 1H, *J* 13.8, 5.4 Hz, H3), 3.89 (s, 6H, OC*H*$_3$-7, OC*H*$_3$-5′), 3.76 (s, 3H, OC*H*$_3$-4′), 3.71–3.62 (m, 1H, H3), 3.53 (s, 3H, OC*H*$_3$-6), 3.05 (dd, 1H, *J* 13.5, 8.4 Hz, H7′), 3.02 (dd, 1H, *J* 13.5, 5.7 Hz, H7′), 2.96–2.81 (m, 1H, H4), 2.78–2.69 (m, 1H, H4), 2.58–2.35 (m, 8H, 2×H2‴, 2×H5‴, 2×H1″, 2×H2″), 1.80–1.76 (m, 4H, 2×H3‴, 2×H4‴). ^{1}H NMR of the minor rotamer (in part): 6.61 (s, 1H, H3′), 5.75 (s, 1H, H8), 3.39 (s, 3H, OC*H*$_3$-6). ^{13}C NMR of the major rotamer: (signals for *C*OCF$_3$ and CO*C*F$_3$ were not observed) δ 148.2 (C4′), 148.8 (C6), 147.2 (C5′, C7), 131.44 (C2′), 127.0 (C4a), 126.3 (C1′), 124.8 (C8a), 113.6 (CH-5), 111.7 (CH-3′), 110.9 (CH-6′), 110.4 (CH-8), 57.7 (CH$_2$-2″), 55.9 (OCH$_3$-7, OCH$_3$-5′), 55.6 (OCH$_3$-4′, OCH$_3$-6, CH-1), 54.0 (CH$_2$-2‴, CH$_2$-5‴), 40.5 (CH$_2$-3), 37.8 (CH$_2$-7′), 31.9 (CH$_2$-1″), 28.5 (CH$_2$-4), 23.4 (CH$_2$-3‴, CH$_2$-4‴). MS (EI$^+$): *m*/*z* 536 (M$^+$, 10%). HRMS (ESI$^+$): calcd for $C_{28}H_{36}F_3N_2O_5$, 537.2576 (MH$^+$), found 537.2581.

*4.6.7. (RS) 1-[2′-(2″-(Diethylamino)ethyl)-4′,5′-dimethoxyphenyl]methyl-2-trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**23**).* A mixture of aldehyde **16** (132 mg, 0.274 mmol), diethylamine (0.2 mL, 1.93 mmol), CH$_3$CN (3 mL) and NaCNBH$_3$ (22 mg, 0.356 mmol) was treated as described above in the general reductive amination reaction procedure to give an oil. The oil was purified by column chromatography (CH$_3$OH/EtOAc (4:6)) to afford **23** (100 mg, 68%) as a light yellow oil. Compound **23** was a 95:5 mixture of rotamers. R_f 0.21 (CH$_3$OH/EtOAc (4:6)). ^{1}H NMR of the major rotamer: δ 6.63 (s, 1H, H3′), 6.57 (s, 2H, H5, H6′), 6.03 (s, 1H, H8), 5.49 (dd, 1H, *J* 8.4, 6.0 Hz, H1), 3.93 (dt, 1H, *J* 13.5, 5.7 Hz, H3), 3.82 (s, 3H, OC*H*$_3$-7), 3.82 (s, 3H, OC*H*$_3$-5′), 3.75 (s, 3H, OC*H*$_3$-4′), 3.71–3.64 (m, 1H, H3), 3.54 (s, 3H, OC*H*$_3$-6), 3.10 (dd, 1H, *J* 13.5, 8.4 Hz, H7′), 3.03 (dd, 1H, *J* 13.5, 6.0 Hz, H7′), 2.94–2.86 (m, 1H, H4), 2.79–2.71 (m, 1H, H4), 2.55 (q, 4H, *J* 6.9 Hz, 2×NC*H*$_2$CH$_3$), 2.59–2.42 (m, 4H, 2×H1″, 2×H2″), 1.01 (t, 6H, *J* 6.9 Hz, 2×NCH$_2$C*H*$_3$). ^{1}H NMR of the minor rotamer (in part): δ 6.60 (s, 1H, H3′), 3.52 (s, 3H, OC*H*$_3$-6). ^{13}C NMR of the major rotamer: δ 155.6 (q, *J* 36.2 Hz, *C*OCF$_3$), 148.2 (C4′), 147.89 (C6), 147.2 (C5′, C7), 131.5 (C2′), 127.0 (C4a), 126.3 (C1′), 124.9 (C8a), 116.0 (q, *J* 286.3 Hz, COCF$_3$), 113.8 (CH-5), 112.8 (CH-3′), 110.9 (CH-6′), 110.5 (CH-8), 55.9 (OCH$_3$-7, OCH$_3$-5′, CH-1), 54.6 (OCH$_3$-4′, OCH$_3$-6), 54.2 (CH$_2$-2″), 46.6 (2×NCH$_2$CH$_3$), 40.7 (CH$_2$-3), 38.0 (CH$_2$-7′), 29.6 (CH$_2$-1″), 28.5 (CH$_2$-4), 11.5 (2×NCH$_2$CH$_3$). MS (EI$^+$): *m*/*z* 538 (M$^+$, 10%). HRMS (ESI$^+$): calcd for $C_{28}H_{38}N_2O_5F_3$, 539.2733 (MH$^+$), found 539.2734.

4.7. General method for *N*-trifluoroacetyl deprotection and reductive N-methylation

The *N*-TFA protected amine was dissolved in a mixture of CH$_3$OH and H$_2$O. To this was added K$_2$CO$_3$ and the resulting solution was stirred at rt for 18 h. CH$_3$OH was removed and the residue was dissolved in CH$_3$CN. Formaldehyde of 38% was added followed by NaCNBH$_3$. Glacial acetic acid was added after 20 min of stirring to adjusted the pH to ~6. The reaction mixture was stirred at rt for 18 h. CH$_3$CN was evaporated and the residue was redissolved in CH$_2$Cl$_2$. The CH$_2$Cl$_2$ layer was washed with satd K$_2$CO$_3$ and dried (MgSO$_4$). Evaporation of the CH$_2$Cl$_2$ extracts gave the crude product, which was purified by column chromatography to afford the pure *N*-methylated analogues.

*4.7.1. (RS) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[4′,5′-dimethoxy-2′-(morpholino)methyl phenyl]methyl-2-methylisoquinoline (**24**).* The *N*-TFA protected amine **17** (40 mg, 0.074 mmol) was treated as described above in the general *N*-TFA deprotection and reductive N-methylation reaction procedure by initially using K$_2$CO$_3$ (50 mg, 0.370 mmol), CH$_3$OH (5 mL) and H$_2$O (1 mL), except it was stirred at 80 °C for 3 h, then using 38% formaldehyde (3 mL), CH$_3$CN (3 mL) and NaCNBH$_3$ (6 mg, 0.096 mmol) to give an oil. The oil was purified by column chromatography (CH$_3$OH/EtOAc/NH$_3$ (4:6:0.1)) to afford **24** (25 mg, 73%) as a clear oil. R_f 0.34 (CH$_3$OH/EtOAc/NH$_3$ (4:6:0.1)). ^{1}H NMR: δ 6.80 (s, 1H, H3′), 6.58 (s, 1H, H5), 5.41 (s, 1H, H6′), 5.71 (s, 1H, H8), 3.85 (s, 3H, OC*H*$_3$-7), 3.84 (s, 3H, OC*H*$_3$-5′), 3.81 (dd, 1H, *J* 9.0, 5.2 Hz, H1), 3.76 (s, 3H, OC*H*$_3$-4′), 3.66 (t, 4H, *J* 2.7 Hz, 2×H3‴, 2×H4‴), 3.44 (s, 3H, OC*H*$_3$-6), 3.29–3.25 (m, 1H, H3), 3.19 (d, 1H, *J* 12.9 Hz, H1″), 3.17 (dd, 1H, *J* 13.5, 5.2 Hz, H7′), 2.96 (dd, 1H, *J* 13.4, 9.0 Hz, H7′), 3.07 (d, 1H, *J* 12.9 Hz, H1″), 2.88–2.85 (m, 1H, H4), 2.81 (dt, 1H, *J* 9.3, 3.0 Hz, H3), 2.63 (dd, 1H, *J* 5.7, 3.0 Hz, H4), 2.56 (s, 3H, NC*H*$_3$), 2.36 (t, 4H, *J* 2.7 Hz, H2‴, H5‴). MS (ESI$^+$):

m/*z* 457.1 (MH^+, 40%). HRMS (ESI^+): calcd for $C_{27}H_{39}N_2O_5$, 471.2859 (MH^+), found 471.2865.

*4.7.2. (RS) 1,2,3,4-Tetrahydro-6,7-dimethoxy 1-[4′,5′-dimethoxy-2′-(pyrrolidinyl)methyl phenyl]methyl-2-methylisoquinoline (**25**).* The *N*-TFA protected amine **18** (79 mg, 0.148 mmol) was treated as described above in the general *N*-TFA deprotection and reductive N-methylation reactions procedure by initially using K_2CO_3 (101 mg, 0.740 mmol), CH_3OH (5 mL) and H_2O (1 mL) and then 38% formaldehyde (3 mL), CH_3CN (3 mL) and $NaCNBH_3$ (20 mg, 0.328 mmol) to give an oil. The oil was purified by column chromatography (CH_3OH/EtOAc/NH_3 (4:6:0.1)) to afford **25** (48 mg, 71% yield) as a light yellow oil. R_f 0.34 (CH_3OH/EtOAc/NH_3 (4:6:0.1)). ^1H NMR: δ 6.91(s, 1H, H3′), 6.55 (s, 1H, H5), 5.44 (s, 1H, H6′), 5.76 (s, 1H, H8), 3.85 (s, 3H, OC*H*$_3$-7), 3.81 (s, 3H, OC*H*$_3$-5′), 3.86–3.80 (m, 1H, H1), 3.72 (s, 3H, OC*H*$_3$-6), 3.49 (d, 1H, *J* 12.9 Hz, H1″), 3.44 (s, 3H, OC*H*$_3$-4′), 3.29 (d, 1H, *J* 12.9 Hz, H1″), 3.23–3.11 (m, 2H, H3, H7′), 2.94–2.78 (m, 3H, H7′, H3, H4), 2.63–2.54 (m, 1H, H4), 2.52 (s, 3H, NC*H*$_3$), 2.41 (br s, 4H, 2×H2‴, 2×H5‴), 1.70 (br s, 4H, 2×H3‴, 2×H4‴). ^{13}C NMR: δ 147.5 (C4′, C6), 147.2 (C5′), 147.2 (C7), 130.8 (C2′, C4a), 129.4 (C1′), 125.9 (C8a), 114.9 (CH-5), 113.4 (CH-3′), 111.8 (CH-6′), 111.5 (CH-8), 64.1 (CH-1), 57.8 (CH_2-1″), 56.3 (OCH_3-7), 56.1 (OCH_3-5′, OCH_3-4′), 55.5 (OCH_3-6), 54.3 (CH_2-2‴, CH_2-5‴), 46.3 (CH_2-3), 42.7 (NCH_3), 37.1 (CH_2-7′), 25.1 (CH_2-4), 23.8 (CH_2-3‴, CH_2-4‴). MS (ESI^+): *m*/*z* 441.1 (MH^+, 100%). HRMS (ESI^+): calcd for $C_{26}H_{36}N_2O_4$, 441.2753 (MH^+), found 441.2777.

*4.7.3. (RS) 1-[2′-(Diethylamino)methyl-4′,5′-dimethoxyphenyl]methyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (**26**).* The *N*-TFA protected amine **19** (75 mg, 0.161 mmol) was treated as described above in the general *N*-TFA deprotection and reductive N-methylation reaction procedure by initially using K_2CO_3 (109 mg, 0.810 mmol), CH_3OH (2 mL) and H_2O (1 mL), except it was stirred for 4 h and then using 38% formaldehyde (3 mL), CH_3CN (3 mL) and $NaCNBH_3$ (20 mg, 0.328 mmol) to give an oil. The oil was purified by column chromatography (CH_3OH/EtOAc/NH_3 (4:6:0.1)) to afford **26** (41 mg, 58%) as a light yellow oil. R_f 0.32 (CH_3OH/EtOAc/NH_3 (4:6:0.1)). ^1H NMR: δ 6.88 (s, 1H, H3′), 6.54 (s, 1H, H5), 5.51 (s, 1H, H6′), 5.69 (s, 1H, H8), 3.83 (s, 3H, OC*H*$_3$-7), 3.80 (s, 3H, OC*H*$_3$-5′), 3.74 (s, 3H, OC*H*$_3$-6), 3.70 (dd, 1H, *J* 9.0, 4.8 Hz, H1), 3.40 (s, 3H, OC*H*$_3$-4′), 3.31–3.24 (m, 1H, H3), 3.18 (d, 1H, *J* 13.5 Hz, H1″), 3.08 (dd, 2H, *J* 13.5, 4.8 Hz, H7′), 2.98 (d, 1H, *J* 13.5 Hz, H1″), 2.89 (dd, 1H, *J* 9.6, 3.0 Hz, H3), 2.84 (dd, 1H, *J* 13.5, 9.0 Hz, H7′), 2.80–2.76 (m, 1H, H4), 2.60–2.56 (m, 1H, H4), 2.54 (s, 3H, NC*H*$_3$), 2.49–2.29 (m, 4H, 2×NC*H*$_2$CH$_3$), 0.90 (t, 6H, *J* 6.9 Hz, 2×NCH$_2$C*H*$_3$). ^{13}C NMR: δ 147.3 (C4′), 147.2 (C6), 146.9 (C5′), 145.9 (C7), 131.1 (C2′), 130.7 (C4a), 128.9 (C1′), 125.6 (C8a), 114.8 (CH-5), 113.1 (CH-3′), 111.3 (CH-6′), 111.2 (CH-8), 64.1 (CH-1), 56.0 (CH_2-1″), 55.9 (OCH_3-7), 55.8 (OCH_3-5′), 55.3 (OCH_3-4′), 55.0 (OCH_3-6), 46.6 (2×NCH_2CH$_3$), 46.0 (CH_2-3), 42.5 (NCH_3), 36.5 (CH_2-7′), 25.1 (CH_2-4), 11.6 (2×NCH$_2$CH_3). MS (ESI^+): *m*/*z* 443.2 (MH^+, 100%). HRMS (ESI^+) calcd for $C_{26}H_{39}N_2O_4$, 443.2910 (MH^+), found 443.2928.

*4.7.4. (RS) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[4′,5′-dimethoxy-2′-(2″-(isopropylamino)methyl)phenyl]methyl-2-methylisoquinoline (**27**).* The *N*-TFA protected amine **20** (60 mg, 0.136 mmol) was treated as described above in the general *N*-TFA deprotection and reductive N-methylation reaction procedure by initially using K_2CO_3 (91 mg, 0.680 mmol), CH_3OH (3 mL) and H_2O (1 mL), except it was stirred for 4 h, and then using 38% formaldehyde (3 mL), CH_3CN (3 mL) and $NaCNBH_3$ (20 mg, 0.328 mmol) to give an oil. The oil was purified by column chromatography (CH_3OH/EtOAc/NH_3 (4:6:0.1)) to afford **27** (36 mg, 59%) as a light yellow oil. R_f 0.34 (CH_3OH/EtOAc/NH_3 (4:6:0.1)). ^1H NMR: δ 6.82 (s, 1H, H3′), 6.54 (s, 1H, H5), 5.52 (s, 1H, H6′), 5.67 (s, 1H, H8), 3.82 (s, 3H, OC*H*$_3$-7), 3.80 (s, 3H, OC*H*$_3$-5′), 3.75 (s, 3H, OC*H*$_3$-6), 3.76–3.70 (m, 1H, H1), 3.39 (s, 3H, OC*H*$_3$-4′), 3.32–3.20 (m, 1H, H3), 3.12 (d, 1H, *J* 12.9 Hz, H1″), 2.95 (d, 1H, *J* 12.9 Hz, H1″), 2.96–2.77 (m, 5H, H4, 2×H7′, H3, H2″), 2.61–2.52 (m, 1H, H4), 2.54 (s, 3H, NC*H*$_3$), 0.94 (t, 6H, *J* 2.1 Hz, CH(C*H*$_3$)C*H*$_3$). ^{13}C NMR: δ 147.6 (C4′), 147.5 (C6), 147.2 (C5′), 146.0 (C7), 130.5 (C2′, C4a), 128.0 (C1′), 125.1 (C8a), 114.3 (CH-5), 113.4 (CH-3′), 111.3 (CH-6′), 111.1 (CH-8), 64.2 (CH-1), 56.1 (OCH_3-7), 55.9 (OCH_3-5′), 55.8 (OCH_3-4′), 55.3 (OCH_3-6), 54.4 (CH_2-1″), 53.2 (CH-2‴), 45.9 (CH_2-3), 36.7 (CH_2-7′), 35.8 (NCH_3), 24.9 (CH_2-4), 17.7 (CH(CH_3)CH$_3$), 17.2 (CH(CH$_3$)CH_3). MS (ESI^+): *m*/*z* 443.1 (MH^+, 100%). HRMS (ESI^+): calcd for $C_{26}H_{39}N_2O_4$, 443.2910 (MH^+), found 443.2910.

*4.7.5. (RS) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[4′,5′-dimethoxy-2′-(2‴-(morpholino)ethyl)phenyl]methyl-2-methylisoquinoline (**1**).* The *N*-TFA protected amine **21** (50 mg, 0.092 mmol) was treated as described above in the general *N*-TFA deprotection and reductive N-methylation reaction procedure by initially using K_2CO_3 (91 mg, 0.68 mmol), CH_3OH (3 mL) and H_2O (1 mL), then 38% formaldehyde (3 mL), CH_3CN (3 mL) and $NaCNBH_3$ (10 mg, 0.164 mmol) to give an oil. The oil was purified by column chromatography (CH_3OH/EtOAc/NH_3 (4:6:0.1)) to afford **11** (37 mg, 85%) as a light yellow oil. R_f 0.30 (CH_3OH/EtOAc/NH_3 (4:6:0.1)). ^1H NMR: δ 6.61 (s, 1H, H3′), 6.55 (s, 1H, H5), 6.53 (s, 1H, H6′), 5.68 (s, 1H, H8), 3.80 (s, 3H, OC*H*$_3$-7), 3.78 (s, 3H, OC*H*$_3$-5′), 3.75 (s, 3H, OC*H*$_3$-4′), 3.67 (t, 4H, *J* 4.5 Hz, 2H2‴, 2H5‴), 3.65–3.62 (m, 1H, H1), 3.38 (s, 3H, OC*H*$_3$-6), 3.28–3.20 (m, 1H, H3), 3.15 (dd, 1H, *J* 13.2, 4.2 Hz, H7′), 2.94–2.87 (m, 1H, H4), 2.85–2.81 (m, 1H, H3), 2.74 (dd, 1H, *J* 13.2, 9.6 Hz, H7′), 2.61–2.54 (m, 1H, H4), 2.53 (s, 3H, NC*H*$_3$), 2.38 (t, 4H, *J* 5.1 Hz, 2×H3‴, 2×H4‴), 2.34–2.27 (m, 2H, H2″), 2.24–2.17 (m, 2H, H1″). ^{13}C NMR: δ 147.4 (C4′), 147.3 (C6), 147.1 (C5′), 146.0 (C7), 131.0 (C2′), 129.4 (C4a), 128.1 (C1′), 125.2 (C8a), 114.0 (CH-5), 112.8 (CH-3′), 111.2 (CH-6′, CH-8), 66.8 (CH_2-3‴, CH_2-4‴), 64.3 (CH-1), 59.9 (CH_2-2″), 55.9 (OCH_3-7), 55.9 (OCH_3-5′), 55.7 (OCH_3-4′), 55.3 (OCH_3-6), 53.5 (CH_2-2‴, CH_2-5‴), 45.9 (CH_2-3), 42.2 (NCH_3), 37.1 (CH_2-7′), 29.5 (CH_2-1″), 24.7 (CH_2-4). MS (ESI^+): *m*/*z* 471.1 (MH^+, 40%). HRMS (ESI^+): calcd for $C_{27}H_{39}N_2O_5$, 471.2859 (MH^+), found 471.2865.

*4.7.6. (RS) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[4′,5′-dimethoxy-2′-(2‴-(pyrrolidino)ethyl) phenyl]methyl-2-methylisoquinoline (**28**).* The *N*-TFA protected amine **22** (38 mg, 0.076 mmol) was treated as described above in the general *N*-TFA deprotection and reductive N-methylation reaction procedure by using initially K_2CO_3 (52 mg, 0.381 mmol), CH_3OH (5 mL) and H_2O (1 mL), then 38% formaldehyde (3 mL), CH_3CN (3 mL) and $NaCNBH_3$ (10 mg, 0.164 mmol) to give an oil. The oil purified by column chromatography (CH_3OH/EtOAc/NH_3 (4:6:0.1)) to afford **28** (25 mg, 69%) as a light yellow oil. R_f 0.30 (CH_3OH/EtOAc/NH_3 (4:6:0.1)). ^1H NMR: δ 6.63 (s, 1H, H3′), 6.56 (s, 1H, H5), 6.54 (s, 1H, H6′), 5.74 (s, 1H, H8), 3.81 (s, 3H, OC*H*$_3$-7), 3.80 (s, 3H, OC*H*$_3$-5′), 3.76 (s, 3H, OC*H*$_3$-4′), 3.66 (dd, 1H, *J* 9.0, 4.5 Hz, H1), 3.42 (s, 3H, OC*H*$_3$-6), 3.24 (m, 1H, H3), 3.09 (dd, 1H, *J* 13.5, 4.5 Hz, H7′), 2.94–2.87 (m, 1H, H4), 2.82–2.74 (m, 1H, H3), 2.78 (dd, 1H, *J* 13.5, 9.0 Hz, H7′), 2.61–2.58 (m, 1H, H4), 2.54 (s, 3H, NC*H*$_3$), 2.52–2.30 (m, 8H, 2×H1″, 2×H2″, 2×H2‴, 2×H5‴), 1.75 (t, 4H, *J* 3.9 Hz, 2×H3‴, 2×H4‴). ^{13}C NMR: δ 149.4 (C4′), 148.9 (C6), 148.4 (C5′), 147.0 (C7), 128.4 (C2′), 126.3 (C4a), 121.5 (C1′), 120.2 (C8a), 115.0 (CH-5), 113.0 (CH-3′), 111.7 (CH-6′), 111.5 (CH-8), 65.2 (CH_2-2″), 56.4 (OCH_3-7, OCH_3-5′), 56.2 (OCH_3-4′), 55.6 (OCH_3-6), 53.3 (CH_2-1), 47.1 (CH_2-2‴, CH_2-5‴), 45.3 (CH_2-3), 44.3 (NCH_3), 40.0 (CH_2-7′), 37.8 (CH_2-1″), 27.4 (CH_2-4), 21.4 (CH_2-3‴, CH_2-4‴). MS (ESI^+): *m*/*z* 454.92 (MH^+, 20%). HRMS (ESI^+): calcd for $C_{27}H_{39}N_2O_4$, 455.2910 (MH^+), found 455.2907.

*4.7.7. (RS) 1-[2′-(2‴-(Diethylamino)ethyl)-4′,5′-dimethoxyphenyl]-methyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (**29**).* The *N*-TFA protected amine **23** (80 mg, 0.149 mmol) was treated as described above in the general *N*-TFA deprotection and reductive N-methylation reaction procedure by initially using

K_2CO_3 (100 mg, 0.735 mmol), CH_3OH (5 mL) and H_2O (1 mL), then 38% formaldehyde (3 mL), CH_3CN (3 mL) and $NaCNBH_3$ (20 mg, 0.328 mmol) to give an oil. The oil was purified by column chromatography (CH_3OH/EtOAc/NH_3 (4:6:0.1)) to afford **29** (65 mg, 69%) as a light yellow oil. R_f 0.31 (CH_3OH/EtOAc/NH_3 (4:6:0.1)). ^1H NMR: δ 6.61 (s, 1H, H3′), 6.57 (s, 1H, H5), 6.54 (s, 1H, H6′), 5.71 (s, 1H, H8), 3.81 (s, 3H, OC*H*$_3$-7), 3.79 (s, 3H, OC*H*$_3$-5′), 3.76 (s, 3H, OC*H*$_3$-4′), 3.66 (dd, 1H, *J* 9.0, 4.2 Hz, H1), 3.40 (s, 3H, OC*H*$_3$-6), 3.27–3.21 (m, 1H, H3), 3.09 (dd, 1H, *J* 13.0, 4.2 Hz, H7′), 2.92–2.86 (m, 1H, H4), 2.83–2.78 (m, 1H, H3), 2.78 (dd, 1H, *J* 13.0, 9.0 Hz, H7′), 2.59–2.54 (m, 1H, H4), 2.55 (s, 3H, NC*H*$_3$), 2.52 (q, 4H, *J* 4.2 Hz, 2×NC*H*$_2$CH$_3$), 2.52–2.44 (m, 2H, 2×H2″), 2.35 (dt, 2H, *J* 12.3, 4.1 Hz, 2×H1″), 1.00 (t, 6H, *J* 4.2 Hz, 2×NCH$_2$C*H*$_3$). ^{13}C NMR: δ 148.2 (C4′, C6), 148.0 (C5′), 146.5 (C7), 129.0 (C2′, C4a), 125.9 (C1′), 124.8 (C8a), 114.0 (CH-5), 112.7 (CH-3′), 111.2 (CH-6′), 111.0 (CH-8), 64.5 (CH-1), 56.0 (OCH$_3$-7, OCH$_3$-5′), 55.7 (OCH$_3$-4′, OCH$_3$-6), 55.2 (CH$_2$-2″), 45.9 (2×NCH$_2$CH$_3$), 45.3 (CH$_2$-3), 41.2 (NCH$_3$), 36.8 (CH$_2$-7′), 27.3 (CH$_2$-1″), 23.4 (CH$_2$-4), 8.8 (2×NCH$_2$CH$_3$). MS (ESI$^+$): *m*/*z* 456.94 (MH$^+$, 30%). HRMS (ESI$^+$): calcd for $C_{27}H_{41}N_2O_4$, 457.3066 (MH$^+$), found 457.3060.

4.8. (*RS*) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1[2′-((2‴,2‴-diethoxyethylamino)methy)-4′,5′-dimethoxyphenyl]methylisoquinoline (31)

The aldehyde **15** was freshly generated from the diol **13** (139 mg, 0.278 mmol) as described in the general oxidative cleavage reaction procedure using a suspension of silica gel coated with $NaIO_4$, using $NaIO_4$ (827 mg, 3.89 mmol), H_2O (2 mL), silica gel (1.7 g) and CH_2Cl_2 (5 mL). To the solution of the aldehyde **15** in CH_3CN (4 mL) was added aminoacetaldehyde diethylacetal (487 mg, 3.67 mmol, 0.5 mL) and $NaCNBH_3$ (12 mg, 0.475 mmol). The reaction mixture was stirred at rt for 20 min and the pH was adjusted to ~6 using glacial acetic acid. The reaction mixture was stirred for 18 h at rt. The CH_3CN was evaporated and the residue was dissolved in a mixture of CH_3OH (10 mL) and H_2O (3 mL). K_2CO_3 (100 mg, 0.737 mmol) was added and the mixture was stirred at rt for 18 h. CH_3OH was evaporated and the residue was dissolved in CH_2Cl_2. The solution was washed with H_2O (3×), brine and dried (K_2CO_3) to give an oil, which was purified by column chromatography (EtOAc increase to CH_3OH/EtOAc/NH_3 (3:7:0.1)) to give **31** (118 mg, 82% over three steps) as a yellow oil. R_f 0.07 (CH_3OH/EtOAc (5:5)). ^1H NMR: (500 MHz) δ 6.84 (s, 1H, H3′), 6.61 (s, 1H, H5), 6.60 (s, 1H, H6′), 6.54 (s, 1H, H8), 4.61 (t, 1H, *J* 5.0 Hz, H2‴), 4.19 (dd, 1H, *J* 8.0, 4.5 Hz, H1), 3.83 (s, 3H, OC*H*$_3$-7), 3.81 (s, 3H, OC*H*$_3$-5′), 3.83–3.70 (m, 2H, 2H3), 3.78 (s, 3H, OC*H*$_3$-4′), 3.75 (s, 3H, OC*H*$_3$-6), 3.65 (dq, 2H, *J* 14.5, 6.5, OC*H*HCH$_3$), 3.50 (dq, 2H, *J* 14.5, 6.5, OCH*H*CH$_3$), 3.22 (dd, 1H, *J* 13.5, 4.5 Hz, H7′), 3.07 (dd, 1H, *J* 12.5, 6.5 Hz, H1″), 2.89–2.84 (m, 2H, H7′, H1″), 2.76 (d, 2H, *J* 5.0 Hz, 2×H1‴), 2.64–2.62 (m, 2H, 2×H4), 1.14 (t, 6H, *J* 6.5 Hz, 2×OCH$_2$C*H*$_3$). ^{13}C NMR: δ 147.7 (C4′), 147.3 (C6), 147.1 (C5′), 146.9 (C7), 130.1 (C2′), 129.5 (C8a), 129.1 (C1′), 127.1 (C4a), 113.1 (CH-5), 112.8 (CH-3′), 111.4 (CH-6′), 109.3 (CH-8), 101.6 (CH-2‴), 62.1 (2×OCH$_2$CH$_3$), 55.8 (CH-1), 55.9 (OCH$_3$-7), 55.6 (OCH$_3$-5′, OCH$_3$-4′), 55.5 (OCH$_3$-6), 51.4 (CH$_2$-1‴), 50.7 (CH$_2$-3), 40.4 (CH$_2$-1″), 38.6 (CH$_2$-7′), 28.8 (CH$_2$-4), 15.0 (2×OCH$_2$CH$_3$). MS (ESI$^+$): *m*/*z* 488.6 (MH$^+$, 100%).

4.9. Attempted synthesis of (*RS*) 1,2,3,4-tetrahydro-1[4′,5′-dimethoxy-2′-(2-oxoethylamino)methyphenyl]methyl-6,7-dimethoxyisoquinoline (32)

To a solution of **31** (71.3 mg, 0.146 mmol) in a mixture of CH_3OH (2 mL) and H_2O (1 mL) was added TsOH (75.3 mg, 0.438 mmol) to bring the pH to ~3. The reaction mixture was stirred at rt for 18 h. ESMS indicated only the unreacted **31**. The reaction mixture was heated at 80 °C for 18 h, however only the precursor **31** was recovered and none of the desired aldehyde **32** was obtained.

4.10. (*RS*) 1,2,3,4-Tetrahydro-1[4′,5′-dimethoxy-2′-(2,2-dimethoxyethylamino)methyl phenyl]methyl-6,7-dimethoxyisoquinoline (33)

To a solution of the amine **31** (116 mg, 0.225 mmol) in CH_3OH (3 mL) was added 10% aqueous HCl (1 mL). The mixture was heated at reflux for 4 h. The solution was basified with K_2CO_3 (excess) to about pH ~6. The CH_3OH was evaporated and the residue was dissolved in CH_2Cl_2. The solution was washed with H_2O (3×), brine and dried (K_2CO_3) to give **33** (37 mg, 41%) as a yellow oil. R_f 0.1 (CH_3OH/EtOAc/NH_3 (5:5:0.1)). ^1H NMR: δ 6.86 (s, 1H, H3′), 6.75 (s, 1H, H5), 6.65 (s, 1H, H6′), 6.60 (s, 1H, H8), 4.51 (t, 1H, *J* 5.3 Hz, H2‴), 4.26 (dd, 1H, *J* 8.7, 3.9 Hz, H1), 3.86 (s, 3H, OC*H*$_3$-7), 3.83 (s, 3H, OC*H*$_3$-5′), 3.81 (s, 3H, OC*H*$_3$-4′), 3.84–3.78 (m, 2H, 2×H3), 3.79 (s, 3H, OC*H*$_3$-6), 3.37 (s, 6H, 2×OC*H*$_3$), 3.32–3.27 (m, 1H, H7′), 3.11 (dd, 1H, *J* 12.6, 4.2 Hz, H1″), 2.94–2.89 (m, 2H, H7′, H1″), 2.80 (dd, 2H, *J* 5.3, 2.1 Hz, 2×H1‴), 2.72–2.66 (m, 2H, 2×H4). ^{13}C NMR: δ 148.4 (C4′), 148.3 (C6), 147.9 (C5′), 147.7 (C7), 133.4 (C2′), 129.4 (C8a), 128.6 (C1′), 127.6 (C4a), 114.7 (CH-5), 113.6 (CH-3′), 111.9 (CH-6′), 109.8 (CH-8), 103.8 (CH-2‴), 56.2 (OCH$_3$-7, OCH$_3$-5′), 56.1 (OCH$_3$-4′, OCH$_3$-6), 54.6 (CH-1), 54.5 (2×OCH$_3$), 51.3 (CH$_2$-1‴), 53.9 (CH$_2$-3), 40.9 (CH$_2$-1″), 39.1 (CH$_2$-7′), 29.0 (CH$_2$-4). MS (ESI$^+$): *m*/*z* 461.1 (MH$^+$, 50%).

4.11. (*RS*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-1[4′,5′-dimethoxy-2′-(methylamino)methylphenyl]methyl-6,7-dimethoxyisoquinoline (36)

To a solution of the aldehyde **15** (136 mg, 0.290 mmol) and 33% aqueous methylamine (0.05 mL) in CH_3CN (3 mL) was added $NaCNBH_3$ (24 mg, 0.377 mmol). The reaction mixture was stirred at rt for 20 min before the pH was adjusted to ~6 using glacial acetic acid. The resulting solution was stirred for 18 h at rt. The CH_3CN was evaporated and the residue was dissolved in CH_2Cl_2. The solution was washed with H_2O (3×), satd Na_2CO_3, brine and dried ($MgSO_4$) to give an oil. The oil was purified by column chromatography (CH_3OH/EtOAc/NH_3 (5:5:0.1)) to afford **36** as a clear oil (100 mg, 71%). Compound **36** was a 95:5 mixture of rotamers. R_f 0.35 (CH_3OH/EtOAc/NH_3 (5:5:0.1)). ^1H NMR of the major rotamer (500 MHz): δ 6.83 (s, 1H, H3′), 6.57 (s, 1H, H5), 6.48 (s, 1H, H6′), 6.08 (s, 1H, H8), 5.53 (t, 1H, *J* 7.0 Hz, H1), 3.89 (dt, 1H, *J* 13.5, 4.5 Hz, H3), 3.82 (s, 3H, OC*H*$_3$-7), 3.80 (s, 3H, OC*H*$_3$-5′), 3.72 (s, 3H, OC*H*$_3$-4′), 3.69 (dt, 1H, *J* 13.5, 3.5 Hz, H3), 3.54 (s, 3H, OC*H*$_3$-6), 3.50 (br s, 2H, 2×H1″), 3.11 (d, 2H, *J* 7.0 Hz, 2×H7′), 2.96–2.85 (m, 1H, H4), 2.80–2.72 (m, 1H, H4), 2.37 (s, 3H, NC*H*$_3$). ^1H NMR of the minor rotamer (in part): δ 6.77 (s, 1H, H3′), 6.53 (s, 1H, H5), 6.52 (s, 1H, H6′), 5.95 (s, 1H, H8), 5.09 (t, 1H, *J* 6.0 Hz, H1), 4.56 (dd, 1H, *J* 6.5 Hz, H3), 3.75 (s, 3H, OC*H*$_3$-5′). ^{13}C NMR of the major rotamer: δ 156.0 (q, *J* 36.5 Hz, *C*OCF$_3$), 148.1 (C4′), 147.7 (C6), 147.7 (C5′), 147.2 (C7), 130.4 (C2′), 127.7 (C8a), 126.5 (C1′), 124.8 (C4a), 116.4 (q, *J* 287.5 Hz, CO*C*F$_3$), 114.0 (CH-5), 112.7 (CH-3′), 110.9 (CH-6′), 110.6 (CH-8), 58.9 (OCH$_3$-7), 55.8 (OCH$_3$-5′), 55.8 (OCH$_3$-4′), 55.6 (CH-1), 55.5 (OCH$_3$-6), 52.8 (CH$_2$-1″), 40.6 (CH$_2$-3), 37.8 (CH$_2$-7′), 36.0 (NCH$_3$), 28.4 (CH$_2$-4). MS (ESI$^+$): *m*/*z* 483 (MH$^+$, 30%). HRMS (ESI$^+$): calcd for $C_{24}H_{30}N_2O_5F_3$, 483.2107 (MH$^+$), found 483.2135.

4.12. (*RS*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-1[4′,5′-dimethoxy-2′-(methylamino)ethyl phenyl]methyl-6,7-dimethoxyisoquinoline (37)

A mixture of aldehyde **16** (131 mg, 0.272 mmol) and 33% aqueous methylamine (0.05 mL) in CH_3CN (3 mL) was added $NaCNBH_3$ (22 mg, 0.354 mmol). The mixture was treated as described above

for the synthesis of **36** to give an oil. The oil was purified by column chromatography (CH_3OH/EtOAc/NH_3 (5:5:0.1)) to afford **37** as a yellow oil (82 mg, 62% yield). Compound **37** was a 95:5 mixture of rotamers. R_f 0.25 (CH_3OH/EtOAc/NH_3 (5:5:0.1)). ^{1}H NMR of the major rotamer: δ 6.65 (s, 1H, H3′), 6.58 (s, 1H, H5), 6.53 (s, 1H, H6′), 5.98 (s, 1H, H8), 5.48 (t, 1H, *J* 6.0 Hz, H1), 3.93 (dt, 1H, *J* 13.5, 5.0 Hz, H3), 3.82 (s, 6H, OC*H*$_3$-7, OC*H*$_3$-5′), 3.73 (s, 3H, OC*H*$_3$-4′), 3.69 (td, 1H, *J* 12.5, 3.0 Hz, H3), 3.52 (s, 3H, OC*H*$_3$-6), 3.08 (d, 2H, *J* 6.0 Hz, 2×H7′), 2.95–2.88 (m, 1H, H4), 2.81–2.76 (m, 1H, H4), 2.64 (t, 2H, *J* 6.5 Hz, 2×H2″), 2.63–2.58 (m, 1H, H1″), 2.55 (dd, 1H, *J* 13.5, 6.5 Hz, H1″), 2.37 (s, 3H, NC*H*$_3$). ^{1}H NMR of the minor rotamer (in part): δ 6.62 (s, 1H, H3′), 3.78 (s, 3H, OC*H*$_3$-4′), 3.45 (s, 3H, OC*H*$_3$-6). ^{13}C NMR of the major rotamer: δ 156.0 (q, *J* 36.9 Hz, *C*OCF$_3$), 148.5 (C4′), 147.2 (C6), 147.5 (C5′), 147.4 (C7), 131.2 (C2′), 127.5 (C4a), 126.0 (C1′), 125.1 (C8a), 114.3 (CH-5), 116.9 (q, *J* 287.5 Hz, CO*C*F$_3$), 112.9 (CH-3′), 111.2 (CH-6′), 110.9 (CH-8), 56.2 (O*C*H$_3$-7), 556.1 (O*C*H$_3$-5′), 56.1 (O*C*H$_3$-4′), 55.9 (CH-1), 55.8 (O*C*H$_3$-6), 53.1 (CH$_2$-2″), 40.9 (CH$_2$-3), 38.2 (CH$_2$-7′), 36.3 (N*C*H$_3$), 32.4 (CH$_2$-1″), 28.7 (CH$_2$-4). MS (ESI$^+$): *m*/*z* 497.1 (MH$^+$, 100%). HRMS (ESI$^+$): calcd for $C_{25}H_{32}F_3N_2O_5$, 497.2263 (MH$^+$), found 497.2237.

4.13. (*RS*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-1[4′5′-dimethoxy-2′-(*N*-(2-chloromethylcarbonyl)-*N*-methyl-aminomethyl)phenyl]methyl-6,7-dimethoxyisoquinoline (38)

To a solution of **36** (99 mg, 0.206 mmol) in dry CH_2Cl_2 (5 mL) was added triethylamine (42 mg, 0.412 mmol, 0.06 mL) at 0 °C followed by chloroacetyl chloride (30 mg, 0.268 mmol, 0.02 mL). The reaction mixture was brought to rt and was stirred for 18 h. The CH_2Cl_2 layer was diluted and extracted with 10% aqueous NaOH, washed with H_2O (2×) and brine. The CH_2Cl_2 layer was dried (K_2CO_3) and evaporated to give an oil. The oil was purified by column chromatography (EtOAc) to give **38** (92 mg, 80% yield) as a clear oil. Compound **38** was a 95:5 mixture of rotamers. R_f 0.67 (EtOAc). ^{1}H NMR of the major rotamer: δ 6.63 (s, 2H, H3′, H6′), 6.58 (s, 1H, H5), 6.25 (s, 1H, H8), 5.45 (t, *J* 7.3 Hz, H1), 4.48 (d, 1H, *J* 14.7 Hz, H1″), 4.26 (d, 1H, *J* 14.7 Hz, H1″), 4.01 (ABq, 2H, 6.6 Hz, 2×H2‴), 3.66 (dd, 1H, *J* 4.5, 1.8 Hz, H3), 3.81 (s, 6H, OC*H*$_3$-7, OC*H*$_3$-5′), 3.79 (s, 3H, OC*H*$_3$-4′), 3.78–3.74 (m, 1H, H3), 3.62 (s, 3H, OC*H*$_3$-6), 3.18 (dd, 1H, *J* 13.5, 8.1 Hz, H7′), 2.95 (dd, 1H, *J* 13.5, 6.9 Hz, H7′), 2.87–2.83 (m, 2H, 2×H4), 2.83 (s, 3H, NC*H*$_3$). ^{1}H NMR of the minor rotamer (in part): δ 6.50 (s, 1H, H5), 6.20 (s, 1H, H8). ^{13}C NMR of the major rotamer: (signals for *C*OCF$_3$ and CO*C*F$_3$ were not observed) δ 166.5 (*C*OCH$_2$Cl), 148.7 (C4′), 147.4 (C7), 148.1 (C5′), 147.5 (C6), 128.8 (C2′), 127.4 (C1′), 126.5 (C4a), 125.1 (C8a), 114.4 (CH-3′), 113.4 (CH-6′), 111.1 (CH-5), 110.9 (CH-8), 56.3 (O*C*H$_3$-7), 56.1 (O*C*H$_3$-5′, O*C*H$_3$-4′), 56.0 (O*C*H$_3$-6), 55.4 (CH-1), 48.3 (CH$_2$-1″), 41.9 (CH$_2$-2‴), 40.8 (CH$_2$-3), 37.7 (CH$_2$-7′), 34.6 (N*C*H$_3$), 28.8 (CH$_2$-4). ^{13}C NMR of the minor rotamer (in part): δ 114.9 (CH-3), 113.6 (CH-6′), 111.3 (CH-5), 50.6 (CH$_2$-1″), 42.7 (CH$_2$-2‴), 41.1 (CH$_2$-3), 38.0 (CH$_2$-7′), 28.5 (CH$_2$-4). MS (ESI$^+$): *m*/*z* 581.0 (M (^{35}Cl)+Na$^+$, 10%), 583.0 (M (^{37}Cl)+Na$^+$, 4%). HRMS (ESI$^+$): calcd for $C_{26}H_{30}F_3N_2NaO_6{}^{35}Cl$, 581.1642 (M (^{35}Cl)+Na$^+$), found 581.1641.

4.14. (*RS*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-1[4′,5′-dimethoxy-2′-(*N*-(2-chloromethyl carbonyl)-*N*-ethyl-aminomethyl)phenyl]methyl-6,7-dimethoxyisoquinoline (39)

To a solution of **38** (73 mg, 0.152 mmol) in dry CH_2Cl_2 (5 mL) was added triethylamine (31 mg, 0.304 mmol, 0.041 mL) at 0 °C, followed by chloroacetyl chloride (22 mg, 0.198 mmol, 0.013 mL). The reaction mixture was brought to rt and stirred for 18 h. The mixture was worked up as described above in the synthesis of **38** to give an oil. The oil was purified by column chromatography (EtOAc) to give **39** (63 mg, 72%) as a clear oil. Compound **39** was a 95:5 mixture of rotamers. R_f 0.60 (EtOAc). ^{1}H NMR of the major rotamer: δ 6.61 (s, 1H, H3′), 6.58 (s, 1H, H6′), 6.55 (s, 1H, H5), 6.13 (s, 1H, H8), 5.46 (dd, 1H, *J* 8.4, 6.3 Hz, H1), 4.01 (s, 2H, 2×H2‴), 3.90 (dt, 1H, *J* 5.4, 2.1 Hz, H3), 3.81 (s, 6H, OC*H*$_3$-7, OC*H*$_3$-5′), 3.82–3.78 (m, 1H, H3), 3.75 (s, 3H, OC*H*$_3$-4′), 3.57 (s, 3H, OC*H*$_3$-6), 3.45 (dt, 1H, *J* 9.6, 3.6 Hz, H2″), 3.29–3.19 (m, 2H, H2″, H7′), 3.06–2.99 (m, 1H, H7′), 2.97 (s, 3H, NC*H*$_3$), 2.89–2.84 (m, 2H, 2×H4), 2.61–2.53 (m, 2H, 2×H1″). ^{1}H NMR of the minor rotamer (in part): δ 6.59 (s, 1H, H3′), 6.40 (s, 1H, H5), 5.90 (s, 1H, H8), 5.36 (dd, 1H, *J* 9.3, 4.8 Hz, H1), 3.67 (s, 6H, OC*H*$_3$-7, OC*H*$_3$-5′), 3.63 (s, 3H, OC*H*$_3$-4′), 3.50 (s, 3H, OC*H*$_3$-6). ^{13}C NMR of the major rotamer: (signals for *C*OCF$_3$ and CO*C*F$_3$ were not observed) δ 116.1 (*C*OCH$_2$Cl), 148.1 (C4′), 147.9 (C7), 147.4 (C5′), 147.1 (C6), 129.8 (C2′), 127.6 (C1′), 126.3 (C4a), 124.8 (C8a), 114.0 (CH-3′), 112.8 (CH-6), 110.8 (CH-5), 110.6 (CH-8), 56.9 (O*C*H$_3$-7), 56.8 (O*C*H$_3$-5′), 55.8 (O*C*H$_3$-4′), 55.7 (O*C*H$_3$-6), 55.6 (CH-1), 50.4 (CH$_2$-2‴), 41.3 (CH$_2$-2″), 40.5 (CH$_2$-3), 37.8 (CH$_2$-7′), 36.3 (N*C*H$_3$), 29.7 (CH$_2$-1″), 28.4 (CH$_2$-4). ^{13}C NMR of the minor rotamer (in part): δ 129.2 (C2′), 127.2 (C1′), 125.1 (C8a), 114.4 (CH-3), 112.6 (CH-6′), 110.9 (CH-5). MS (ESI$^+$): *m*/*z* 573.0 (M (^{35}Cl)H$^+$, 100%), 575.0 (M (^{37}Cl)H$^+$, 40%). HRMS (ESI$^+$): calcd for $C_{27}H_{33}N_2O_6F_3{}^{35}Cl$, 573.1979 (M (^{35}Cl)H$^+$), found 573.1985.

4.15. (*RS*) 3-(1,2)-Benzena-5-(1,2)-isoquinolinacyclo-1-aza-7-oxo-heptaphane (40)

To a solution of **38** (92 mg, 0.165 mmol) in CH_3OH (4 mL) and H_2O (1 mL) was added K_2CO_3 (112 mg, 0.825 mmol), and the mixture was stirred at rt for 3 h. The CH_3OH was gently removed under pressure (without warming the water bath) to give an aqueous residue. To the mixture was added CH_2Cl_2 (10 mL), followed by the addition of triethylamine (0.3 mL). The reaction mixture was stirred for 18 h at rt. The CH_2Cl_2 layer was washed with H_2O (3×), brine and then dried (K_2CO_3). The solvent was removed to give an oil, which was purified by column chromatography (EtOAc) to give **40** (41 mg, 57% yield) as a yellow oil. R_f 0.35 (EtOAc). ^{1}H NMR δ 6.69 (s, 1H, H3′), 6.61 (s, 1H, H5), 6.41 (s, 1H, H6′), 5.96 (s, 1H, H8), 4.22 (br s, 1H, H1″), 3.99 (t, 1H, *J* 7.0 Hz, H1), 3.88 (s, 3H, OC*H*$_3$-7), 3.82 (s, 3H, OC*H*$_3$-5′), 3.79 (s, 3H, OC*H*$_3$-4′), 3.52 (s, 3H, OC*H*$_3$-6), 3.52 (br s, 6H, OC*H*$_3$-6, 2×H3″, H1″), 3.38–3.32 (m, 1H, H7′), 3.09 (s, 3H, NC*H*$_3$), 2.86 (dt, 1H, *J* 10.5, 3.6 Hz, H3), 2.77 (dd, 1H, *J* 14.0, 3.0 Hz, H7′), 2.56 (ddd, 1H, *J* 14.0, 10.5, 2.5 Hz, H3), 2.27 (br s, 2H, 2×H4). ^{13}C NMR δ 172.1 (*C*O), 147.6 (C4′), 147.5 (C7), 147.4 (C5′, C6), 130.0 (C2′), 129.8 (C1′), 129.2 (C4a), 129.0 (C8a), 115.0 (CH-8), 112.0 (CH-5), 111.0 (CH-6′), 110.4 (CH-3′), 64.0 (CH-1), 62.1 (CH$_2$-3″), 56.6 (O*C*H$_3$-7), 56.1 (O*C*H$_3$-5′, O*C*H$_3$-4′), 55.8 (O*C*H$_3$-6), 54.5 (CH$_2$-1″), 49.7 (CH$_2$-3), 40.7 (CH$_2$-7′), 36.2 (N*C*H$_3$), 30.0 (CH$_2$-4). MS (ESI$^+$): *m*/*z* 427.1 (MH$^+$, 100%). HRMS (ESI$^+$): calcd for $C_{24}H_{31}N_2O_5$, 427.2233 (MH$^+$), found 427.2227.

4.16. (*RS*) 4-(1,2)-Benzena-6-(1,2)-isoquinolinacyclo-1-aza-8-oxo-octaphane (41)

The synthesis of the title compound **41** was carried out using the conditions described above for the synthesis of **40** starting with compound **39** (63 mg, 0.108 mmol), CH_3OH (3 mL), H_2O (1 mL) and K_2CO_3 (112 mg, 0.825 mmol). This was followed by intramolecular cyclisation using CH_2Cl_2 (10 mL) and triethylamine (0.3 mL) to give an oil, which was purified by column chromatography (EtOAc) to give **41** (31 mg, 46% yield) as a yellow oil. R_f 0.48 (EtOAc). ^{1}H NMR: δ 6.71 (s, 1H, H3′), 6.60 (s, 1H, H6′), 6.53 (s, 1H, H5), 6.36 (s, 1H, H8), 4.06–4.01 (m, 1H, H1), 3.90 (s, 3H, OC*H*$_3$-7), 3.86 (s, 3H, OC*H*$_3$-5′), 3.85 (s, 3H, OC*H*$_3$-4′), 3.70 (s, 3H, OC*H*$_3$-6), 3.47 (br s, 2H, 2×H4″), 3.29–3.27 (m, 1H, H7′), 3.12–3.08 (m, 2H, 2×H2″), 3.05 (s, 3H, NC*H*$_3$), 3.00–2.93 (m, 1H, H3), 2.89–2.81 (m, 1H, H7′), 2.77–2.64 (m, 3H, 2×H1″, H3), 2.22–2.16 (m, 2H, 2×H4). ^{13}C NMR: δ 171.4 (*C*O), 148.5 (C4′), 147.9 (C7), 147.5 (C5′), 147.1 (C6), 131.7 (C2′), 131.6 (C1′), 128.6 (C4a), 127.9 (C8a), 114.7 (CH-8), 113.4 (CH-6′), 111.4 (CH-5),

110.6 (CH-3′), 65.1 (CH-1), 60.8 (CH_2-4″), 56.4 (OCH_3-7), 56.3 (OCH_3-5′), 56.2 (OCH_3-4′), 56.1 (OCH_3-6), 53.0 (CH_2-2″), 52.7 (CH_2-3, CH_2-7′), 35.3 (NCH_3), 33.8 (CH_2-1″, CH_2-4). MS (ESI^+): *m*/*z* 441.1 (MH^+, 100%). HRMS (ESI^+): calcd for $C_{25}H_{33}N_2O_5$, 441.2389 (MH^+), found 441.2380.

4.17. (*RS*)-3-(1,2)-Benzena-5-(1,2)-isoquinolinacyclo-1-aza-heptaphane (42)

To a slurry of $LiAlH_4$ (38 mg, 1.02 mmol) in dry THF (1 mL) was added a solution of the amide **41** (21 mg, 0.048 mmol) in dry THF (1 mL) under a N_2 atmosphere at 0 °C. The resulting mixture as brought to rt and stirred for 18 h. H_2O (0.2 mL), 1 M aqueous NaOH (0.2 mL) and H_2O (0.5 mL) were added subsequently and the reaction mixture was stirred for 1 h. The solid was filtered and washed with EtOAc. The solution was dried (K_2CO_3) and evaporated to give **42** (16 mg, 81%) as a clear oil without the need for further purification. R_f 0.15 (CH_3OH/EtOAc/NH_3 (5:5:0.1)). ^1H NMR δ 6.84 (s, 1H, H3′), 6.64 (s, 1H, H6′), 6.58 (s, 2H, H5, H8), 4.50 (d, 1H, *J* 12.5 Hz, H1″), 4.22 (br s, 1H, H1), 3.89 (s, 3H, OC*H*$_3$-7), 3.86 (s, 6H, OC*H*$_3$-5′, OC*H*$_3$-4′), 3.83 (s, 3H, OC*H*$_3$-6), 3.42 (d, 1H, *J* 12.5 Hz, H1″), 3.40 (dd, 1H, *J* 14.0, 7.0 Hz, H7′), 3.15–3.09 (m, 2H, 2×H3″), 2.81–2.72 (m, 3H, H3, 2×H2″), 2.68 (dd, 1H, *J* 14.0, 2.0 Hz, H7′), 2.59–2.51 (m, 3H, H3, 2×H4), 2.52 (s, 3H, NC*H*$_3$). ^{13}C NMR δ 147.6 (C4′), 147.4 (C7), 147.3 (C5′), 147.1 (C6), 134.0 (C2′), 132.2 (C1′), 131.5 (C4a), 127.5 (C8a), 114.4 (CH-3′), 113.8 (CH-6), 111.2 (CH-5), 110.7 (CH-8), 61.5 (CH-1), 58.1 (CH_2-1″), 56.2 (OCH_3-7), 56.0 (OCH_3-5′), 56.0 (OCH_3-4′), 55.8 (OCH_3-6), 52.0 (CH_2-2″), 51.9 (CH_2-3), 48.0 (CH_2-7′), 42.6 (NCH_3), 29.7 (CH_2-3″), 27.1 (CH_2-4). MS (ESI^+): *m*/*z* 413.2 (MH^+, 100%).

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20. *CNS receptors tested*: μ (h) (MOP); A_1 (h); A_{2A} (h); A_3; α_1; α_2; β_1; AT_1 (h); BZD (central); B_2 (h); CCKA (h); D_1 (h); D2S (h); ET_A (h); GABA (non-selective); GAL2 (h); CXCR2 (h); CCR1; H_1 (h); H_2 (h); MC_4 (h); ML_1; M_1 (h); M_2 (h); M_3 (h); NK_2 (h); NK_3 (h); NT_1 (h); δ_2 (h); κ(KOP); ORL1 (h) (NOP); 5-HT_{1A} (h); 5-HT_{1B}; 5-HT_{2A} (h); 5-HT_3 (h); 5-HT_{5A} (h); 5-HT_6 (h); 5-HT_7 (h); sst (non-selective); VIP_1 (h); V_{1a} (h); Ca^{2+} channel; K^+ channel; Na^+ channel; SK^+ Ca channel; Cl^- channel; NE transporter; DA transporter.
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