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Synthesis, Antitubulin, and Antiproliferative SAR of C3/C1-Substituted Tetrahydroisoquinolines

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The syntheses and antiproliferative activities of novel substituted tetrahydroisoquinoline derivatives and their sulfamates are discussed. Biasing of conformational populations through substitution on the tetrahydroisoquinoline core at C1 and C3 has a profound effect on the antiproliferative activity against various cancer cell lines. The C3 methyl-substituted sulfamate (±)-7-methoxy-2-(3-methoxybenzyl)-3-methyl-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (**6b**), for example, was found to be ~10-fold more potent than the corresponding non-methylated compound 7-methoxy-2-(3-methoxybenzyl)-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (**4b**) against DU-145 prostate cancer cells (GI_{50} values: 220 nM and 2.1 μM, respectively). Such compounds were also found to be active against a drug-resistant MCF breast cancer cell line. The position and nature of substitution of the *N*-benzyl group in the C3-substituted series was found to have a significant effect on activity. Whereas C1 methylation has little effect on activity, introduction of C1 phenyl and C3-*gem*-dimethyl substituents greatly decreases antiproliferative activity. The ability of these compounds to inhibit microtubule polymerisation and to bind tubulin in a competitive manner versus colchicine confirms the mechanism of action. The therapeutic potential of a representative compound was confirmed in an in vivo multiple myeloma xenograft study.

Introduction

In previous work, we described our discovery of *N*-benzyl tetrahydroisoquinolines (THIQs) as novel microtubule disruptors with potential therapeutic application for the treatment of cancer.[1] The THIQs were designed to mimic the 2-substituted estratriene class of microtubule disruptors (e.g., **1e** and **2a**)[2] in which incorporation of a 3-*O*-sulfamate group is observed to be highly beneficial for both activity and oral bioavailability (Figure 1). The THIQ core was used as a mimic of the steroidal A,B-ring system from which steroidomimetics could be constructed. Substitution of the THIQ at C6 and C7, with those groups requisite for activity in the steroidal series (corresponding to the C3 and C2 positions, respectively, of the latter compounds), was thus required. Attachment at N2 of a group projecting into the area of space occupied by the steroidal D-ring and bearing the H-bond acceptor required for optimal activity completed our prototypical steroidomimetic design. A generic THIQ-based compound set **4** bearing the three key elements of the steroidal pharmacophore was thus elaborated, with encouraging results obtained for compounds bearing a methoxy group at C7, an *O*-sulfamate group at C6, and an *N*2-benzyl group substituted with an H-bond acceptor at the C3′ position. Supporting the hypothesis that such a compound class could mimic its steroidal parents is the finding that removal of any of

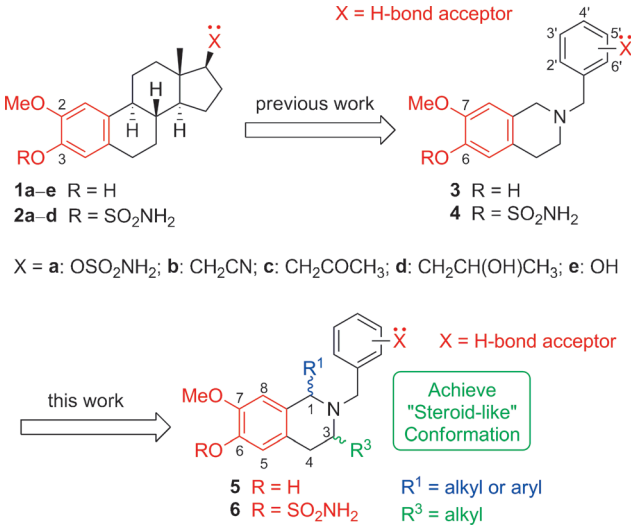

Figure 1. Design of THIQ-based microtubule disruptors **3** and **4** and their modification into conformationally restricted analogues **5** and **6**.

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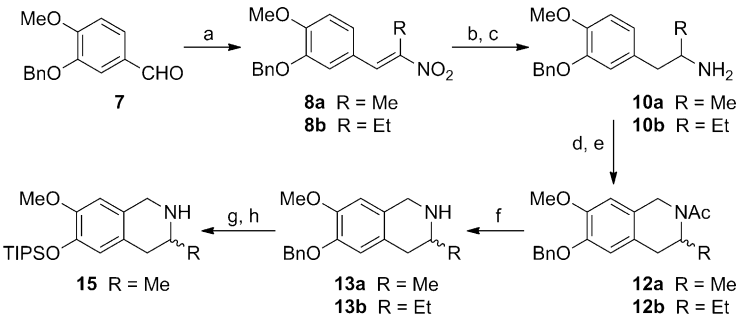
the three key pharmacophore elements (at C6 and C7 of the THIQ moiety and at C3′ of the *N*1-benzyl group) results in biologically inactive compounds. Furthermore, the THIQ derivatives, like the steroids, were found to disrupt the polymerisation of tubulin and inhibit the binding of [^{3}H]colchicine to tubulin. Like the steroid sulfamates, the THIQ compounds inhibit carbonic anhydrase,[3] an interaction believed to contribute to the high oral bioavailability observed for the steroid derivatives.[4] In addition, once more reflecting observations made in the steroidal series, the THIQ compounds proved capable of inhibiting the growth of taxane-resistant cancer cells[5] and HUVEC cell proliferation (a commonly used marker for anti-angiogenic activity),[6] thus supporting the idea that these small-molecule microtubule disruptors work in a similar manner to the 2-substituted estradiol 3-*O*-sulfamates (e.g., **2a**).



Scheme 1. Synthesis of C3-substituted THIQs. *Reagents and conditions*: a) RCH_2NO_2, NH_4OAc, reflux; b) $NaBH_4$, EtOH, 0 °C; c) Raney Ni, $N_2H_4{\cdot}H_2O$, MeOH, 50 °C; d) Ac_2O, Et_3N, CH_2Cl_2, 0→25 °C; e) $(CH_2O)_n$, *p*-TsOH, toluene, 120 °C; f) KOH, EtOH/H_2O, reflux; g) Pd/C (10%, 140 mg cartridge), full H_2, H-cube, THF/MeOH at 1.0 mL min^{-1}, 25 °C; h) TIPSCl, imidazole, CH_2Cl_2, 25 °C.

In the present work our goal was to achieve enhanced anticancer effects through optimisation of the THIQ-based lead compounds. We reasoned that the rotational freedom enjoyed by the *N*-benzyl group would likely lead to a small population of the conformer in which the H-bond acceptor is projected into the region of space occupied by the corresponding group in the steroid series, and that substitution on the THIQ core with groups that could hamper, to some extent, the free rotation of the *N*-benzyl group to favour the postulated active conformations might deliver compounds with improved activity. The likely sites of modification were thus the C1 and C3 positions of the THIQ core (Figure 1), with C3 substitution likely favouring a "steroid-like" conformation and C1 substitution likely forcing the N2 substituent away from the presumed "steroid-like" optimal conformation. Herein we report our full optimisation studies, in vitro biological evaluation, and preliminary in vivo studies to demonstrate the potential of this new compound class.

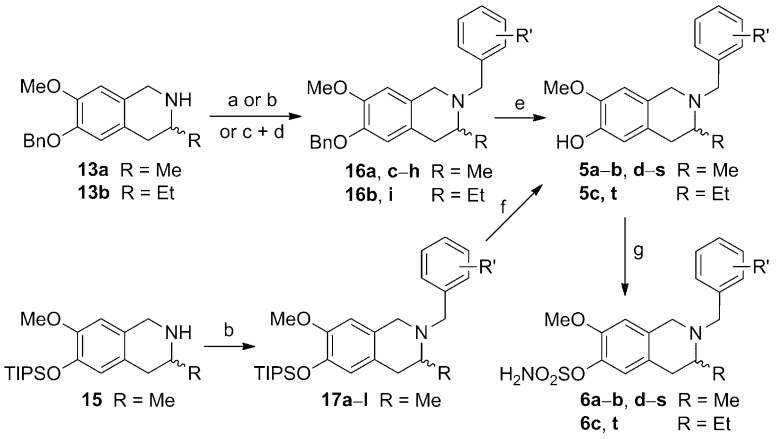
Results and Discussion

Chemistry

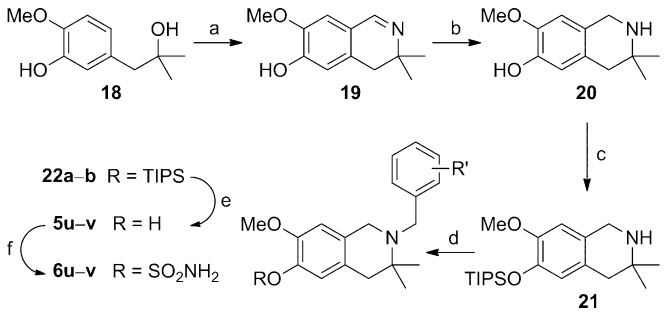
Our previous structure–activity relationship (SAR) studies on *N*-benzyl-7-methoxy-6-*O*-sulfamoyl THIQs indicated that these compounds are good leads for optimisation as anticancer agents.[7] Of the compounds bearing a single H-bond acceptor on the *N*-benzyl group (steroidal D-ring mimic), the 3′-methoxy derivative **4b** and other 3′-substituted compounds proved most active in vitro (micromolar antiproliferative GI_{50} values). We also reported that the 3′,4′,5′-trimethoxybenzyl derivative had greatly improved activity, although the observed SAR is divergent from that exhibited by the monosubstituted *N*-benzyl derivatives **4**.[3] We proposed that this compound is best considered a chimera of the steroid and the class of microtubule disruptors bearing a trimethoxybenzene ring that bind at the colchicine site, including combretastatins, the colchicinoids, and podophyllotoxins.[8]

To investigate conformational effects, we needed to access C1- and C3-substituted THIQs. Installation of the C3 substituent required a simple modification of the synthetic approach we had previously applied to synthesise the THIQ core system (Scheme 1).[3] Thus, commercially available 3-benzyloxy-4-methoxybenzaldehyde **7** was subjected to a Henry aldol reaction[9] with nitroethane and 1-nitropropane to afford requisite nitrostyrenes **8a**,**b** in good yield. Reduction of the styrene double bonds of **8a**,**b** with sodium borohydride furnished the racemic secondary nitroalkanes, the nitro groups of which were then reduced with hydrazine hydrate and Raney nickel to afford the corresponding phenethylamines **10a**,**b**. Although the phenethylamines could be directly transformed into the corresponding THIQ derivatives by Pictet–Spengler annulation,[10] it proved expeditious first to acylate, as this facilitated separation of the THIQ reaction products from impurities and thus afforded an improved yield. The Pictet–Spengler reaction of the *N*-acyl phenethylamines was carried out with paraformaldehyde under acid catalysis in toluene at reflux. Hydrolysis of the amides **12a**,**b** with potassium hydroxide in aqueous ethanol delivered the key intermediate THIQs **13a**,**b**. As there was some degree of incompatibility expected between conditions for the benzyl deprotection procedure and some of the functional groups we wished to evaluate, a quantity of **13a** was debenzylated and then reprotected with TIPSCl to give **15**. The debenzylation step proved much more effective if a flow hydrogenator system (H-cube) was used, as the product of the hydrogenation **14a** proved prone to precipitation on removal of catalyst, with only moderate product recovery (~45%) when conventional hydrogenation was performed.

The C3-substituted THIQs **13a**,**b** and **15** were then converted into the desired *N*-benzyl derivatives, either under various direct *N*-benzylation conditions or by first forming the amide from the appropriate benzoic acid, using an *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide (EDCI) coupling followed by reduction with lithium aluminum hydride, to give **16a**–**h** and **17a**–**l** (Scheme 2). The C6 hydroxy groups were unmasked with hydrogen and palladium on carbon (for **16a**–**h**) or tetra-*n*-butylammonium fluoride (TBAF; for **17a**–**l**) to deliver good yields of **5a**–**t**. Sulfamoylation of **5a**–**t** in *N*,*N*-dimethylaceta-



Scheme 2. Synthesis of *N*-benzyl-substituted THIQs. *Reagents and conditions*: a) BnCl, Et_3N, EtOH, 130 °C, MW; b) BnBr, DIPEA, DMF, 80 °C; c) Benzoic acid, EDCI, CH_2Cl_2/THF, 25 °C; d) $LiAlH_4$, THF, reflux; e) H_2, Pd/C, THF/MeOH, 25 °C; f) TBAF, THF, 25 °C; g) H_2NSO_2Cl, DMA, 25 °C.



Scheme 3. Synthesis of 3,3-*gem*-dimethyl THIQs. *Reagents and conditions*: a) KCN, AcOH, H_2SO_4, 0→25 °C; b) $NaBH_4$, EtOH, 0→25 °C; c) TIPSCl, imidazole, CH_2Cl_2, 25 °C; d) BnCl, Et_3N, EtOH, 130 °C, MW; e) TBAF, THF, 0→25 °C; f) H_2NSO_2Cl, DMA, 25 °C.

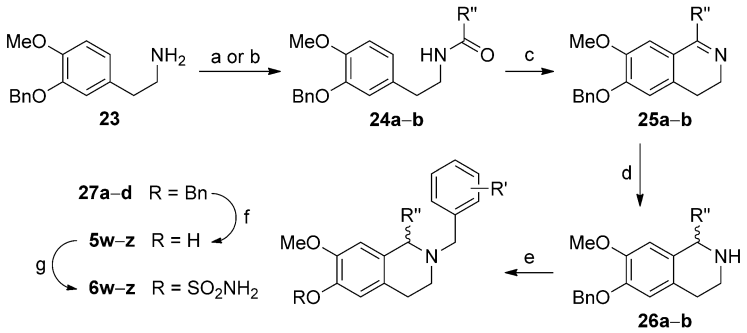
mide (DMA)[11] gave the corresponding sulfamate derivatives **6a–t** (Scheme 2).

To establish whether di-substitution at C3 would be advantageous, we prepared the *gem*-dimethyl THIQ **20** and used it to elaborate the 6-*O*-sulfamate derivatives **6u** and **6v** with 3′-methoxy- or 3′,4′,5′-trimethoxy-substituted benzyl groups, respectively (Scheme 3). Ritter reaction[12] of 5-(2-hydroxy-2-methylpropyl)-2-methoxyphenol **18**[13] with potassium cyanide under strong acidic conditions delivered the 3,4-dihydroisoquinoline **19** in low yield. Borohydride reduction of the imine, followed by triisopropylsilyl (TIPS) protection was then carried out to give the silyl-protected THIQ **21**. N-Benzylation of **21** using the appropriate benzyl chloride with triethylamine in ethanol at 130 °C under microwave irradiation afforded **22a** and **22b**, which were converted into the C3-dimethyl-substituted target sulfamates **6u** and **6v** by TBAF deprotection and sulfamoylation (Scheme 3).

Access to the C1-substituted THIQs was carried out by treating phenethylamine **23** with the appropriate acid chloride or anhydride and then performing the ring closure with phosphorus oxychloride (Scheme 4). The cyclic imines **25a** and **25b** were then reduced with sodium borohydride in ethanol at reflux to give the C1-substituted THIQs **26a** and **26b**, which were elaborated to deliver the desired phenols **5w–z** and sulfamates **6w–z** using conditions analogous to those described for the synthesis of C3-substituted THIQs above.

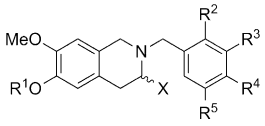
Biology

To assess their potential as anticancer agents, the new THIQ derivatives were assayed for their ability to inhibit the proliferation of DU-145 (androgen-receptor-negative) prostate cancer cells and MDA MB-231 (estrogen-receptor-negative) breast cancer cells in vitro. The assay results obtained for these compounds are listed in Table 1 alongside selected comparator compounds from our earlier studies.[7] Most of the compounds had similar antiproliferative activity against both the DU-145 and MDA MB-231 cells and thus, to simplify the SAR discussion, only the DU-145 data are used for comparison of relative activities. In our earlier study[7] we showed that in the C3-unsubstituted series an H-bond acceptor at the *meta* position of the *N*-benzyl group delivers the greatest antiproliferative activity. In the current series, of the mono-methoxybenzyl C3-methyl derivatives (**6a**, **6b**, and **6d**) the *meta*-methoxy compound **6b** was most active, as was also the case in the C3-unsubstituted series. In contrast to the unsubstituted series, however, **6a**, **6b**, and **6d** all had sub-micromolar GI_{50} values against the DU-145 cells. Activity enhancement was most pronounced in the case of the *para*-methoxy compound **6d**, which was >50-fold more active than **4c**. The high activity obtained by incorporation of the methyl group at C3 with **6b** (GI_{50}: 222 nM) was also observed in a congener with a C3-ethyl group (**6c** has a GI_{50} value of 286 nM). It is thus clear that at least a small C3-alkyl substituent is desirable. This may indicate that the C3-alkyl group contributes a positive lip-



Scheme 4. Synthesis of C1-substituted THIQs. *Reagents and conditions*: a) BzCl, Et_3N, $CHCl_3$, 0 °C; b) Ac_2O, Et_3N, CH_2Cl_2, 0 °C; c) $POCl_3$, toluene, reflux; d) $NaBH_4$, EtOH, reflux; e) BnCl, Et_3N, EtOH, 130 °C, MW; f) H_2, Pd/C, THF/MeOH, 25 °C; g) H_2NSO_2Cl, DMA, 25 °C.

Table 1. Antiproliferative activity of polymethoxylated THIQs against DU-145 human prostate cancer cells and MDA MB-231 human breast cancer cells in vitro.



Compd[a]	R^1	X	R^2	R^3	R^4	R^5	GI_{50} [μM][b] DU-145	MDA MB-231
3a	H	H	OMe	H	H	H	>100	ND
4a	SO_2NH_2	H	OMe	H	H	H	7.8	ND
5a	H	Me	OMe	H	H	H	>100	>100
6a	SO_2NH_2	Me	OMe	H	H	H	3.4	2.9
3b	H	H	H	OMe	H	H	>100	ND
4b	SO_2NH_2	H	H	OMe	H	H	2.1	ND
5b	H	Me	H	OMe	H	H	3.73	1.53
6b	SO_2NH_2	Me	H	OMe	H	H	0.222	0.234
5c	H	Et	H	OMe	H	H	ND	ND
6c	SO_2NH_2	Et	H	OMe	H	H	0.286	0.281
3c	H	H	H	H	OMe	H	>100	ND
4c	SO_2NH_2	H	H	H	OMe	H	57.2	ND
5d	H	Me	H	H	OMe	H	>100	99.8
6d	SO_2NH_2	Me	H	H	OMe	H	1.1	0.7
5e	H	Me	H	H	H	H	>100	>100
6e	SO_2NH_2	Me	H	H	H	H	2.2	1.4
5f	H	Me	Cl	H	H	H	9	9
6f	SO_2NH_2	Me	Cl	H	H	H	0.2	0.2
5g	H	Me	Me	H	H	H	10	7
6g	SO_2NH_2	Me	Me	H	H	H	1	0.5
3d	H	H	H	Et	H	H	>100	>100
4d	SO_2NH_2	H	H	Et	H	H	35	8.0
5h	H	Me	H	Et	H	H	39	9.63
6h	SO_2NH_2	Me	H	Et	H	H	0.324	0.368
5i	H	Me	H	OEt	H	H	20	8.1
6i	SO_2NH_2	Me	H	OEt	H	H	0.3	0.2
5j	H	Me	H	NO_2	H	H	19	9.4
6j	SO_2NH_2	Me	H	NO_2	H	H	0.3	0.2
5k	H	Me	H	Cl	H	H	9.9	9.3
6k	SO_2NH_2	Me	H	Cl	H	H	0.3	0.1
5l	H	Me	H	Ac	H	H	56	94
6l	SO_2NH_2	Me	H	Ac	H	H	0.2	0.2
5m	H	Me	OMe	OMe	H	H	98	84
6m	SO_2NH_2	Me	OMe	OMe	H	H	0.6	0.4
5n	H	Me	H	OMe	OMe	H	30	86
6n	SO_2NH_2	Me	H	OMe	OMe	H	0.9	0.7
5o	H	Me	H	OMe	H	OMe	15.3	3.2
6o	SO_2NH_2	Me	H	OMe	H	OMe	0.73	0.49
5p	H	Me	OMe	H	H	OMe	54.3	>100
6p	SO_2NH_2	Me	OMe	H	H	OMe	0.189	0.16
5q	H	Me	F	H	H	OMe	2	1
6q	SO_2NH_2	Me	F	H	H	OMe	0.299	0.269
5r	H	Me	Cl	H	H	OMe	0.265	0.173
6r	SO_2NH_2	Me	Cl	H	H	OMe	0.4	0.4

[a] All compounds of type **5** and **6** are racemic mixtures; data for **3a–d**, **4a–d**, **5a–b**, **5d**, **6a–b**, and **6d** are taken from the literature.[1,7] [b] Data are the mean of three determinations; ND: not determined.

ophilic interaction, as well as creating a desirable bias in the conformational population with the benzyl group projected into the region of space occupied by the D-ring in the steroidal series. With these preliminary results, we focused on exploration of the SAR at the *meta*-benzyl position. However, we also made several additional control compounds worthy of mention.

Our original plan involved addressing the three key pharmacophore elements required for high activity in the steroidal series, and these three elements had proven essential for activity in the prototypical THIQ series previously prepared.[7] The finding that the unsubstituted benzyl derivative **6e** retains low micromolar antiproliferative activity was consistent with the SAR findings obtained in the steroidal series; 2-methoxyestrone-3-*O*-sulfamate is ~10-fold more active than 2-methoxy-17-deoxyestrone-3-*O*-sulfamate, which lacks an H-bond acceptor in the D-ring.[14] This supports the hypothesis that the C3-methyl THIQs are good mimics of the steroidal series and that the C3-methyl group favours a conformational population in which the *N*-benzyl group occupies the D-ring space in the steroidal series.[1] The positive lipophilic interactions resulting from this conformational biasing thus, in themselves, appear to deliver a reasonable degree of antiproliferative activity. The results obtained with the *ortho*-substituted compounds **6g** and especially **6f** reinforce this hypothesis. In fact, the *ortho*-methyl compound **6g** is more than threefold more active than the *ortho*-methoxy compound **6a**. It thus appears that small *ortho* substituents can contribute a greater positive lipophilic interaction than the methoxy group, and substitution with chlorine at C2′ (**6f** GI_{50}: 0.2 μM) affords a further improvement in activity relative to the methyl substituent (**6g** GI_{50}: 1 μM). Clearly, a further exploration of similarly sized *ortho* substituents is merited.

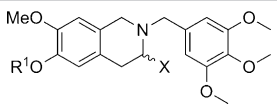
In contrast to the C3-unsubstituted lead series,[7] it was found that, with a C3-methyl group, an H-bond acceptor was not required for optimal activity. Ethyl (**6h**), ethoxy (**6i**), nitro (**6j**), chloro (**6k**), and acetyl (**6l**) derivatives all exhibited GI_{50} values in the 0.2–0.3 μM range and were thus of similar activity to the 3′-methoxy analogue **6b**. The lack of a substantial difference between electron donating and withdrawing substitution suggests that, as observed for the C2′ substituents, the C3′ substituents likely contribute a positive lipophilic interaction that delivers a 10-fold improvement in activity relative to the unsubstituted *N*-benzyl analogue **6e** or the C3-unsubstituted lead **4b**. We also assessed the activity of four dimethoxy benzyl derivatives **6m–p**. Three are moderately less active than **6b**, but the 2′,5′-dimethoxy derivative **6p** is slightly more active. The 2′,5′-substitution pattern of **6p** was explored further with fluorine (**6q**) and chlorine (**6r**) substituents at C2′. Both compounds are slightly less active than **6p**. Evidently, placing an electron-withdrawing group at the *para* position does not significantly modulate the H-bond acceptor capability of the 5′-methoxy group. However, in the absence of the sulfamate substituent, using **5b** with a 2′-methoxy substituent for comparison, the 2′-chloro-5′-methoxy phenol compound **5r** displays a 14-fold increase in activity. In contrast, the 2′-fluoro-5′-methoxy phenol compound **5q**

is only about twice as active as **5b**. In the phenol series, the combination of a 5′-methoxy group with a second substituent at C2′ reveals that Cl ≫ F, H ≫ MeO in terms of antiproliferative activity. Moreover, **5r** is more potent than **6r**, the only example in which the phenol is more potent than the corresponding sulfamate derivative. The origins of this unexpected reversal in potency remain to be determined. When combined with the observations on the activities of the 2′-substituted series, it appears that chloro substitution provides considerable benefit at the site of action and/or enhances the postulated conformational biasing.

We recently reported 3′,4′,5′-trimethoxybenzyl-substituted compounds **3e** and **4e** to show excellent sub-micromolar in vitro antiproliferative activities against the DU-145 and MDA MB-231 cancer cell lines.[3] We consider that these compounds are best described as chimeras composed of the key pharmacophore elements of two series of colchicine site binders, namely 2-methoxyestradiol and the trimethoxyaryl family of colchicine site binders, such as the colchinoids and combretastatins.[3] To establish effects of various C3 monosubstitution patterns, we synthesised compounds **5s,t** and **6s,t**. In the phenol series, incorporation of a C3-methyl group causes a slight decrease in activity (cf. **5s** and **3e**), whereas the ethyl derivative **5t** is <20% as active as **3e** (Table 2). In contrast, in the sulfamate series the C3-methyl derivative **6s** is moderately more active than the unsubstituted **4e**, but it is threefold more active than the ethyl compound **6t**. Thus, any conformational biasing affected by the C3 substituent does not enhance interaction with tubulin significantly in the presence of the 3′,4′,5′-trimethoxy benzyl group.

We also synthesised C3-dimethyl-substituted compounds **5u,v** and **6u,v**, but, as the data listed in Table 3 demonstrate, the additional C3 substituent results in uniformly inactive compounds. The 3,3-*gem*-dimethyl group could simply be too large to be accommodated at the site of action, and thus compounds with this substitution pattern are inactive; alternately, this substitution could interfere with cell uptake, thus rendering the compounds inactive in these assays.

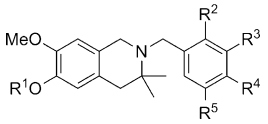
Table 2. Antiproliferative activity of 3′,4′,5′-trimethoxy-substituted THIQs against DU-145 human prostate cancer cells and MDA MB-231 human breast cancer cells in vitro.



Compd[a]	R^1	X	GI_{50} [μM][b] DU-145	MDA MB-231
3e	H	H	0.65	0.62
4e	SO_2NH_2	H	0.297	0.329
5s	H	Me	0.79	0.67
6s	SO_2NH_2	Me	0.196	0.24
5t	H	Et	3.38	2.61
6t	SO_2NH_2	Et	0.735	0.626

[a] All compounds of type **5** and **6** are racemic mixtures; data for compounds **3e** and **4e** are taken from the literature.[3] [b] Results are the mean of three determinations.

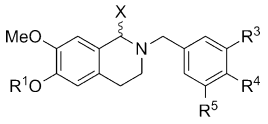
Table 3. Negligible antiproliferative activity of C3-dimethyl-substituted THIQs against DU-145 human prostate cancer cells and MDA MB-231 human breast cancer cells in vitro.



Compd	R^1	R^2	R^3	R^4	R^5	GI_{50} [μM][a] DU-145	MDA MB-231
5u	H	H	OMe	H	H	>100	>100
6u	SO_2NH_2	H	OMe	H	H	>100	>100
5v	H	H	OMe	OMe	OMe	>100	>100
6v	SO_2NH_2	H	OMe	OMe	OMe	>100	>100

[a] Data are the mean of three determinations.

Table 4. Antiproliferative activity of C1-substituted THIQs against DU-145 human prostate cancer cells and MDA MB-231 human breast cancer cells in vitro.



Compd[a]	R^1	X	R^3	R^4	R^5	GI_{50} [μM][b] DU-145	MDA MB-231
5w	H	Me	OMe	H	H	>100	>100
6w	SO_2NH_2	Me	OMe	H	H	1.3	0.97
5x	H	Me	OMe	OMe	OMe	>100	>100
6x	SO_2NH_2	Me	OMe	OMe	OMe	0.36	0.3
5y	H	Ph	OMe	H	H	>100	>100
6y	SO_2NH_2	Ph	OMe	H	H	16	63
5z	H	Ph	OMe	OMe	OMe	>100	>100
6z	SO_2NH_2	Ph	OMe	OMe	OMe	41	58

[a] All compounds of type **5** and **6** are racemic mixtures. [b] Results are the mean of three determinations.

We also investigated incorporating a substituent at the C1 position, which on steric grounds would logically disfavour conformers in which the benzyl group projects into the regions occupied by the steroidal D-ring. The C1-methyl and phenyl THIQ core structure with *N*-3′-methoxybenzyl and *N*-3′,4′,5′-trimethoxybenzyl substituents attached to it were synthesised and evaluated (Table 4). None of phenols **5w–z** exhibits significant activity. However, the sulfamates **6w–z** display micromolar to sub-micromolar activity, with C1-methyl-substituted derivatives proving more active than their C1-phenyl-substituted congeners. Clearly C1 phenyl substitution is poorly tolerated either at the site of action or in terms of cellular uptake. Comparison of compounds **6w** and **6x** with **4b** and **4e** reveals that C1 methylation has little effect on antiproliferative activity, with a slight improvement and a slight decrease

Table 5. Antiproliferative activity of selected compounds against various cancer cell lines from the NCI-60 cell line panel.

Compd[a]	GI_{50} [μM][b]						
	Lung HOP-62	Colon HCT-116	CNS SF-539	Melanoma UACC-62	Ovarian OVCAR-3	Renal SN-12-C	MGM
1e	0.7	0.47	0.32	0.36	0.21	0.95	1.3
2a	0.051	0.045	0.036	< 0.01	< 0.01	0.126	0.087
5b	5.17	2.82	5.31	5.5	4.72	9.11	6.76
6b	0.07	0.051	0.032	0.033	0.039	0.188	0.109
6f	0.217	0.436	0.392	0.324	0.124	0.971	0.447
6l	0.364	0.221	0.12	0.53	0.101	0.612	0.437
6p	0.504	0.446	0.331	0.584	0.298	1.64	0.562
6q	0.122	0.066	0.091	0.074	0.043	0.559	0.145
6r	0.075	0.048	0.042	0.069	0.039	0.372	0.102
6s	0.236	0.267	0.018	0.04	0.028	0.628	0.204

[a] All compounds of type **5** and **6** are racemic mixtures; data for compounds **1** and **2a** are taken from the literature.[2d,15] [b] Results are the mean of three determinations.

in activity obtained in the monomethoxy- and trimethoxy-substituted benzyl derivatives, respectively.

All compounds were submitted to the US National Cancer Institute (NCI) for preliminary screening, and some of them were selected for evaluation in the full 60-cell-line assay (Table 5) across a wide range of cancer types. Data from six cancer cell lines are presented, along with the mean activity across the whole panel (MGM value). Screening is conducted at concentrations ranging from 10 nM to 100 μM. The data obtained in the assay are consistent with those obtained in our antiproliferative screens and demonstrate the potential of these compounds against multiple cancer phenotypes. The sulfamate derivatives **6b**, **6l**, **6q**, **6r**, and **6s** are more active than 2-methoxyestradiol **1e** and, in the best cases, **6b** and **6r** display activities equivalent to that of 2-methoxyestradiol-3,17-*O*,*O*-bis-sulfamate **2a**.

In addition to their antiproliferative activity against wild-type cancer cells, the steroidal sulfamates (e.g., **2a**) inhibit the proliferation of taxane-resistant cancer cells and inhibit angiogenesis.[5,6] The MCF-7_{Dox} cell line is a multidrug-resistant breast cancer cell line that expresses P-glycoprotein (P-gp) and is resistant to taxanes and a range of other anticancer agents.[5c] Compounds **4b**, **6b**, and **6s** were thus evaluated for their ability to inhibit wild-type MCF-7 cells (MCF-7_{WT}) and its resistant subline MCF-7_{Dox}. As a preliminary assessment of potential anti-angiogenic activity, the compounds were also assayed for their ability to inhibit the proliferation of human umbilical vein endothelial cells (HUVECs), a commonly used marker of anti-angiogenic potential (Table 6). The C3-methylated derivatives **6b** and **6s** exhibit good activity against both the wild-type and multidrug-resistant MCF-7 lines, with activity similar to that of **2a**. These compounds thus do not appear to be substrates for the P-gp efflux pump and have potential for the treatment of taxane-resistant tumours. Good activity was also observed for **6b** and **6s** against the proliferation of HUVECs; therefore, these compounds, like the steroids that inspired their design, may have a complementary anti-angiogenic mechanism of action.

Our preliminary studies had shown that the initial lead compound **6b** inhibits tubulin polymerisation.[1] To establish a SAR for these compounds as microtubule disruptors, we selected a number of them with good antiproliferative activity for evaluation as inhibitors of tubulin assembly, as well as inhibitors of the binding of [^{3}H]colchicine to tubulin alongside the established potent microtubule disruptor combretastatin A-4 (CA-4) and the 3′,4′,5′-trimethoxybenzyl THIQ derivatives **3e** and **4e** (Table 7). The majority of our steroidomimetic derivatives bearing a substituent at C3 proved more active than the chimeras **3e** and **4e** as inhibitors of tubulin assembly and colchicine binding to tubulin. 3′-Chlorobenzyl **6k**, 2′-fluoro-5′-methoxybenzyl **6q**, and 2′-chloro-5′-methoxybenzyl **6r** derivatives all display assembly IC_{50} values < 10 μM and > 25% inhibition of [^{3}H]colchicine binding.

Although not quite as active as CA-4, compound **6r** shows very encouraging results, disrupting the

Table 6. Antiproliferative activity of selected compounds against wild-type and resistant MCF-7 breast cancer cells and HUVECs.

Compd[a]	GI_{50} [μM][b]		
	MCF-7_{WT}	MCF-7_{Dox}	HUVEC
2a	0.25	0.38	0.05
4b	2.85	1.4	1.16
6b	0.35	0.09	0.16
6s	0.45	0.3	0.2

[a] All compounds of type **6** are racemic mixtures. [b] Results are the mean of three determinations.

Table 7. Activity of selected THIQs as inhibitors of tubulin polymerisation and [^{3}H]colchicine binding (5 μM inhibitor) to tubulin.[a]

Compd	Tubulin assembly IC_{50} [μM]	Colchicine binding [% inhib]
CA-4	1.2 ± 0.1	98 ± 0.7
3e	> 20 (no act.)	4.1 ± 2
4e	> 20 (partial act.)	10 ± 0.9
5r	14 ± 1	14 ± 1
6b	12 ± 0.6	16 ± 2
6c	> 20 (no act.)	0 ± 3
6e	> 20 (weak act.)	6.7 ± 1
6f	9.7 ± 1	15 ± 4
6g	> 20 (weak act.)	13 ± 2
6h	> 20 (partial act.)	4.1 ± 0.7
6i	19 ± 0.4	12 ± 2
6j	11 ± 1	21 ± 3
6k	9.2 ± 0.2	26 ± 2
6l	13 ± 1	11 ± 2
6p	> 20 (partial act.)	8.2 ± 2
6q	7.0 ± 0.4	26 ± 2
6r	3.2 ± 0.3	47 ± 3
6s	16 ± 2	9.3 ± 0.6

[a] Values are the mean ± SD of at least two determinations. Compounds **4e**, **6e**, **6g**, **6h**, and **6p** inhibited tubulin assembly at 20 μM, whereas **3e** and **6c** are inactive at this concentration. All compounds of type **5** and **6** are racemic mixtures. Data for CA-4, **3e**, and **4e** are taken from the literature.[7]

polymerisation of tubulin with an IC_{50} value of 3.2 ± 0.3 μM and inhibiting colchicine binding to tubulin by 47% at 5 μM. Its phenol **5r** and sulfamates **6b**, **6f**, **6l**, **6p**, and **6s**, which are the most active antiproliferative compounds in vitro (Tables 1 and 2) and are all about twice as active as **6r**, display IC_{50} values of 9.7–14 μM or >20 μM (for the most active compound in vitro **6p**), and inhibition of [^{3}H]colchicine binding to tubulin is not better than 16% at 5 μM (**6b**). Comparison of phenol **5r** and sulfamate **6r** particularly illustrates the relevance of the sulfamate group at C6 for the ability to inhibit tubulin polymerisation and the binding of [^{3}H]colchicine to tubulin effectively. Overall, these data (Table 7) do not exactly correlate with the in vitro data (Tables 1 and 2) and for the 2′-X-5′-methoxy-substituted sulfamates **6b** (X=H), **6p** (X=MeO), **6q** (X=F), and **6r** (X=Cl), the observed trend in terms of activity is opposite (X=Cl>F>H>MeO) to the in vitro data for DU-145 and MDA MB-231 (X=Cl<F<H<MeO) and correlates better with the in vitro data of their phenols **5b** (X=H), **5p** (X=MeO), **5q** (X=F), and **5r** (X=Cl), but the differences are not of the same magnitude (X=Cl≫F>H≫MeO).

Having established in vitro activity and confirmed activity at the postulated site of action, we wished to establish the in vivo activity of this compound series. Compound **6b** was assessed for its ability to inhibit the growth of RPMI-8226 multiple myeloma xenografts in female nude athymic mice. Daily dosing of **6b** at 40 mg kg^{-1}, formulated as a solution in 5% aqueous citric acid, for 28 days was compared with vehicle and **2a** at its optimal dose of 20 mg kg^{-1}. As can be seen in Figure 2a, a substantial 39% inhibition of growth was achieved by **6b** at this non-optimised dose level at cessation of dosing. Furthermore, a prolonged inhibition of tumour growth was observed in the **6b**-treated cohort (48% growth inhibition 18 days after cessation of dosing). In addition, no evidence of toxicity was found in this treatment group, as mouse body weight increased in line with the vehicle group over the course of treatment (Figure 2b). This experiment confirms the potential of THIQ derivatives such as **6b** as antitumour agents in vivo, and suggests that with optimisation of dose, they could well match or even better the activity observed for the steroidal compounds.

Compound **6l** was also selected for in vivo evaluation at the NCI in the hollow fiber assay that involves assessment of activity against the proliferation of various cancer lines in sealed polyvinylidine fluoride fibers implanted i.p. or s.c. in mice.[16] A 50% net cell growth inhibition is awarded a score of 2, and with over 48 fibers (12 cell lines × 2 sites × 2 dose levels) a maximum score of 96 is possible. Dosing of **6l** at 150 mg kg^{-1} results in 50% inhibition of cell growth in ten fibers i.p. and five fibers s.c., and thus delivers a score of 30 (20 for i.p. fibers and 10 for s.c. fibers). Similar scores were obtained for tested steroid derivatives, although at a much lower dose level. Compound **2d**, for example, displaying an excellent MGM value of 28 nM in the NCI 60-cell line assay,[17] was awarded a score of 32 (18 for i.p. and 14 for s.c. fibers) when dosed at 37.5 and 18.75 mg kg^{-1}. Although THIQ derivative **6l** shows far less activity in vitro (MGM=0.437 μM) than most of the steroidal compounds **2a**–**d**, in vivo it is nearly equipotent and also far less toxic. In the hollow fiber assay compound **6l** shows good activity, good tissue distribution, and the activity surpasses normal criteria (score >20) for further investigations at the NCI, but it was not selected for additional study to further develop this class of compounds as in vivo agents. A COMPARE analysis[18] of data obtained for **6l** against the publicly available NCI screening data afforded only two positive correlations, with the highest Pearson correlation coefficient being 0.725 (>0.6 is considered a positive correlation), which was obtained for the well-known microtubule disruptor vincristine. Significantly, there was no correlation found with any of the steroidal derivatives **2a**–**d**. Compound **6b**, on the other hand, did not deliver any positive correlations in the COMPARE analysis.

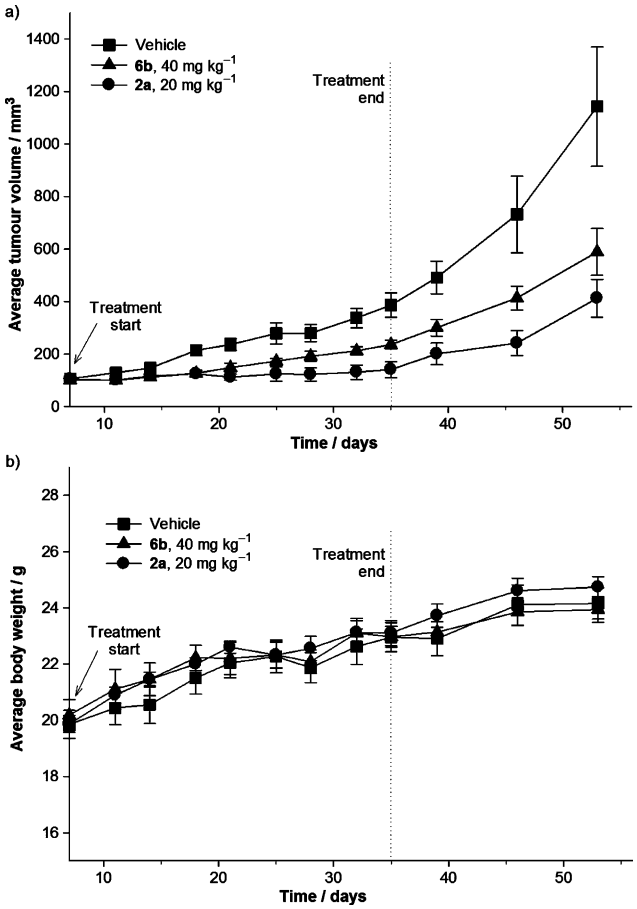


Figure 2. a) The activity of **6b** (40 mg kg^{-1} day^{-1}, 28 d, p.o. in 5% aqueous citric acid) against the growth of RPMI-8226 (multiple myeloma) xenografts in athymic nude mice was assessed alongside the benchmark steroid derivative, 2-methoxyestradiol-3,17-*O*,*O*-bis-sulfamate **2a** (20 mg kg^{-1} day^{-1}, 28 d, p.o.). After 28-day dosing, significant inhibition of tumour growth was observed for both cohorts of treated animals. b) No significant weight loss was observed in either cohort, indicating that **6b** is well tolerated. Data are the mean ± SEM of $n=6$.

Conclusions

This study was aimed at identifying requirements to enhance the level of antiproliferative activity of the tetrahydroisoquinoline derivatives **4b** and **4e** by modification of the C1 and C3

positions. As described above, incorporation of a methyl or ethyl group at C3 has a dramatic effect on antiproliferative activity. It appears reasonable to suggest that the increased activity derives at least in part from the C3 substituent favouring populations of "steroid-like" conformers. In contrast, C1 methylation has little effect on antiproliferative activity, whereas introduction of a larger C1 phenyl group is deleterious to activity. A short summary of the in vitro SAR of these compounds as antiproliferative agents is presented in Figure 3. The potential

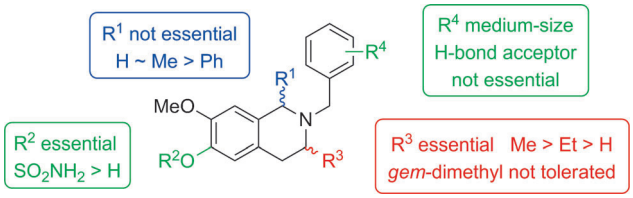


Figure 3. In vitro SAR of C3/C1-substituted THIQs as antiproliferative agents.

of this series of compounds was confirmed by their broad-spectrum activity across the NCI-60 cell line panel and their ability to inhibit proliferation of a taxane-resistant cancer cell line.

In addition, the ability of selected compounds to inhibit HUVEC proliferation and microtubule polymerisation indicates a common mechanism and profile of action as those of the steroidal derivatives (e.g., **2a**) that inspired their design. Finally, the inhibitory activity of **6b** against the growth of an RPMI-8226 multiple myeloma xenograft model at a non-optimised dose confirms the potential of this series of THIQ derivatives as orally active anticancer agents. We have thus established the use of the *N*-benzyl THIQs as steroidomimetics and have elucidated how substitution at C3, through conformational biasing, can be used to enhance activity. All compounds were studied as racemic mixtures, and clearly for exploring potential development compounds for the work, it will be necessary to separate enantiomers. We are currently exploring further optimisation of these compounds as anticancer agents and the application of THIQ-based steroidomimetics to alternate therapeutic targets.

Experimental Section

Biology

In vitro studies, cell lines: DU-145 (brain metastasis carcinoma of the prostate) and MDA-MB-231 (metastatic pleural effusion of breast adenocarcinoma) established human cell lines were obtained from ATCC Global Bioresource Center. Cells were maintained in a 5% CO_2 humidified atmosphere at 37 °C in RPMI-1640 medium, supplemented with 10% fetal bovine serum, penicillin (100 U mL^{-1}), and streptomycin (0.1 mg mL^{-1}). MCF-7 (estrogen-receptor-positive) breast cancer cells were obtained from the ATCC (LGC Promochem) and MCF-7_{Dox} cells were kindly donated by Dr. G. L. Scheffer (Department of Pathology, Free University Hospital, Amsterdam, Netherlands). Cells were maintained in a 5% CO_2 humidified atmosphere at 37 °C in DMEM containing phenol red, supplemented with 10% fetal bovine serum, L-glutamine (2 mM), 1% nonessential amino acids, and 0.075% sodium bicarbonate (Sigma). Human umbilical vein endothelial cells (HUVECs) were obtained from TCS Cellworks (Claydon, UK) and maintained in large-vessel endothelial medium supplemented with basic fibroblast growth factor/heparin, epidermal growth factor and cortisol in the presence of amphotericin/gentamycin (TCS Cellworks). Human adult dermal fibroblasts (TCS Cellworks) were maintained in fibroblast growth medium (TCS Cellworks) with the same supplements as used in the HUVEC media. HUVECs and dermal fibroblasts were used up to passage 10. To ascertain IC_{50} values, 5000–10000 cells in their appropriate growth medium were added to each well of a 96-well microtitre plate (Falcon; BD Biosciences, Cowley, UK). Plates were incubated for 4–5 h at 37 °C in a 5% CO_2 humidified atmosphere before addition of compounds at a final concentration of 10^{-10}–10^{-2} M.

Antiproliferative assays: DU-145 and MDA-MB-231 cells were seeded into 96-well microtitre plates (5000 cells per well) and treated with compound at 10^{-9}–10^{-4} M or with vehicle control. At 96 h post-treatment, live cell counts were determined by WST-1 cell proliferation assay (Roche, Penzberg, Germany), as per the manufacturer's instructions. Viability results were expressed as a percentage of mean control values resulting in the calculation of the 50% growth inhibition (GI_{50}). MCF-7_{WT}, MCF-7_{Dox}, and HUVECs were treated with 10^{-10}–10^{-2} M compound or with vehicle control for 96 h. All compounds were dissolved at 10^{-2} M in tetrahydrofuran (THF) for in vitro experiments (10^{-6}–10^{-1}% final THF concentration). Cells were grown in the absence or presence of the compounds for 5 days. At the end of this period, MTS (20 μL per well; Promega, Southampton, UK) was added and incubated for a further 2 h. Absorbance was recorded at λ 490 nM with a 96-well plate reader (FLUOSTAR; BMG, Aylesbury, UK). All experiments were performed in triplicate.

Tubulin assays: Bovine brain tubulin, prepared as described previously,[19] was used in studies presented herein. Assembly IC_{50} values were determined as described in detail elsewhere.[20] Briefly, 1.0 mg mL^{-1} (10 μM) tubulin was pre-incubated without GTP with varying compound concentrations for 15 min at 30 °C. Reaction mixtures were placed on ice, and GTP (0.4 mM final concentration) was added. The reaction mixtures were transferred to cuvettes, held at 0 °C in a recording spectrophotometer. Baselines were established at 0 °C, and increase in turbidity was followed for 20 min following a rapid (< 30 s) jump to 30 °C. Compound concentrations required to decrease the turbidity increase by 50% were determined. The method for measuring inhibition of the binding of [^{3}H]colchicine to tubulin was described in detail previously.[21] Reaction mixtures contained 0.1 mg mL^{-1} (1.0 μM) tubulin, 5.0 μM [^{3}H]colchicine, and potential inhibitor at 5.0 μM. Compounds were compared with CA-4, a particularly potent inhibitor of the binding of colchicine to tubulin.[22] Reaction mixtures were incubated for 10 min at 37 °C, a time point at which the binding of colchicine in control reaction mixtures is generally 40–60% complete. A minimum of two experiments were performed with each compound.

In vivo studies: Female NCr-nude mice, 4–6 weeks of age (acquired from Harlan Labs), were fed ad libitum water and an autoclaved standard rodent diet consisting of 18% protein, 5% fat, 5% fiber, 8% ash, and 3% minerals. Mice were housed in isolators on a 12 h life cycle at 22 °C and 40–60% humidity. Animal care was in accordance with IPSEN institutional guidelines. Tumour cells (6×10^6 cells per animal) were implanted subcutaneously into the left flank. Multiple myeloma cancer cells were implanted with an equal volume of Matrigel to increase take rate. Tumours were monitored initially twice weekly, and then daily as the neoplasms reached the

desired size, ~100 mm^3 (100 mg). When the tumours attained this predetermined size, the animals were randomised into three groups with six animals per group. Estimated tumour weight (TW) was calculated according to the formula: $TW(mg) = (w^2 \times l)/2$, in which w = width and l = length (mm) of the multiple myeloma tumour.

Chemistry

All chemicals were either purchased from Aldrich Chemical Co. (Gillingham, UK) or Alfa Aesar (Heysham, UK). Organic solvents of A.R. grade were supplied by Fisher Scientific (Loughborough, UK) and used as supplied. CH_3Cl, CH_2Cl_2, DMA and THF were purchased from Aldrich and stored under a positive pressure of N_2 after use. Sulfamoyl chloride was prepared by an adaptation of the method of Appel and Berger[23] and was stored in the refrigerator under positive pressure of N_2 as a solution in toluene as described by Woo et al.[24] An appropriate volume of this solution was freshly concentrated in vacuo immediately before use. Reactions were carried out at room temperature unless stated otherwise. Compounds **23** and **24a** were prepared according to literature procedure.[7] Thin-layer chromatography (TLC) was performed on precoated aluminum plates (Merck, silica gel 60 F_{254}). Product spots were visualised either by UV irradiation at λ 254 nm or by staining with either alkaline $KMnO_4$ solution or 5% dodecamolybdophosphoric acid in EtOH, followed by heating. All final compounds of type **5** and **6** were synthesised as racemic mixtures. Separation of enantiomers was not pursued. Flash column chromatography was performed using gradient elution (solvents indicated in text) on either prepacked columns (Isolute) on a Flashmaster II system (Biotage, Uppsala, Sweden) or on a CombiFlash R_f Automated Flash Chromatography System (Teledyne Isco, Lincoln, NE, USA) with RediSep R_f disposable flash columns. ^1H and ^{13}C NMR spectra were recorded with either a Delta JMN-GX 270 (Jeol, Peabody, MA, USA) at 270 and 67.5 MHz, respectively, or a Mercury VX 400 NMR spectrometer (Varian, Paolo Alto, CA, USA) at 400 and 100 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to tetramethylsilane (TMS) as internal standard. Coupling constants (J) are recorded to the nearest 0.1 Hz. Mass spectra were recorded at the Mass Spectrometry Service Centre, University of Bath (UK). FAB-MS was carried out using *m*-nitrobenzyl alcohol (NBA) as the matrix. Melting points were determined using a Stuart SMP3 or a Stanford research systems Optimelt MPA100 melting point apparatus (Stanford Research Systems, Sunnyvale, CA, USA), and are uncorrected. All compounds were $\geq$98% pure by reversed-phase HPLC carried out with CH_3CN/H_2O or MeOH/H_2O (Sunfire C_{18} reversed-phase column, 4.6×150 mm, 3.5 μm pore size).

2-Benzyloxy-1-methoxy-4-((*E*)-2-nitroprop-1-enyl)benzene (8a): Compound **7** (8.0 g, 33.1 mmol), ammonium acetate (2.55 g, 33.1 mmol) and nitroethane (120 mL, 1.67 mol) were stirred at 120 °C for 22 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was dissolved in EtOAc (200 mL), washed with H_2O (40 mL) and brine (2×40 mL), then dried ($MgSO_4$), filtered and concentrated in vacuo. Crystallisation from hot EtOH afforded compound **8a** as yellow crystals (6.19 g, 63%); mp: 102–104 °C; ^1H NMR (270 MHz, $CDCl_3$): δ = 2.27 (3H, s), 3.94 (3H, s), 5.19 (2H, s), 6.91 (1H, d, J = 2.0 Hz), 6.94 (1H, d, J = 8.4 Hz), 7.05 (1H, dd, J = 8.4, 2.0 Hz), 7.30–7.43 (4H, m), 7.97 ppm (1H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 14.0, 56.2, 71.3, 111.7, 115.8, 124.9, 124.9, 127.2, 128.2, 128.8, 133.8, 136.7, 145.9, 148.0, 151.5 ppm; LC–MS (APCI−): *m/z* 297.93 $[M-H]^-$.

2-Benzyloxy-1-methoxy-4-((*E*)-2-nitrobut-1-enyl)benzene (8b): Method as for **8a** using compound **7** (24.23 g, 100 mmol) and ammonium acetate (7.73 g, 100 mmol) in 1-nitropropane (90 mL, 1.01 mol) at 160 °C for 22 h. Crystallisation from hot EtOH afforded compound **8b** as a yellow powder (14.07 g, 44%); mp: 97–99 °C; ^1H NMR (270 MHz, $CDCl_3$): δ = 1.14 (3H, t, J = 7.3 Hz), 2.71 (2H, q, J = 7.4 Hz), 3.93 (3H, s), 5.19 (2H, s), 6.91 (1H, d, J = 1.9 Hz), 6.94 (1H, d, J = 8.5 Hz), 7.05 (1H, dd, J = 8.4, 1.9 Hz), 7.25–7.48 (5H, m), 7.91 ppm (1H, s); LC–MS (ES+): *m/z* 314.2 $[M+H]^+$.

(±)-2-Benzyloxy-1-methoxy-4-(2-nitropropyl)benzene (9a): Finely powdered $NaBH_4$ (1.52 g, 40.2 mmol) was covered with EtOH (20 mL) and a solution of compound **8a** (6.0 g, 20.1 mmol) in THF (40 mL) was added at 0 °C over 0.5 h. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 0.5 h. HCl (2 M, 20 mL) was added very carefully and the reaction mixture was then extracted with EtOAc (3×100 mL). The combined organics were washed with H_2O (60 mL) and brine (60 mL), then dried ($MgSO_4$) and evaporated. Flash column chromatography (hexane/EtOAc 4:1) afforded compound **9a** as a pale-green solid (3.35 g, 55%); ^1H NMR (270 MHz, $CDCl_3$): δ = 1.44 (3H, d, J = 6.7 Hz), 2.87 (1H, dd, J = 14.1, 6.9 Hz), 3.19 (1H, dd, J = 14.1, 7.4 Hz), 3.85 (3H, s), 4.65 (1H, sept, J = 6.9 Hz), 5.12 (2H, s), 6.65–6.71 (2H, m), 6.81 (1H, d, J = 8.2 Hz), 7.25–7.43 ppm (5H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 18.7, 40.8, 56.1, 71.2, 84.6, 112.0, 115.2, 121.9, 127.5, 127.9, 128.0, 128.7, 137.0, 148.1, 149.1 ppm; LC–MS (APCI−): *m/z* 300.01 $[M-H]^-$.

(±)-2-Benzyloxy-1-methoxy-4-(2-nitrobutyl)benzene (9b): Method as for **9a** using compound **8b** (13.95 g, 44.5 mmol) and finely powdered $NaBH_4$ (3.38 g, 89.3 mmol) in EtOH (40 mL) and THF (160 mL) at 0 °C over 2 h via dropping funnel, at 0 °C for 4 h and at room temperature for 60 h. Flash column chromatography (hexane/EtOAc 9:1) afforded compound **9b** as a yellow solid (8.83 g, 62%); mp: 62–64 °C; ^1H NMR (270 MHz, $CDCl_3$): δ = 0.91 (3H, t, J = 7.4 Hz), 1.62–1.79 (1H, m), 1.81–2.00 (1H, m), 2.88 (1H, dd, J = 14.3, 6.0 Hz), 3.12 (1H, dd, J = 14.3, 8.3 Hz), 3.84 (3H, s), 4.42–4.55 (1H, m), 5.11 (2H, s), 6.65 (1H, d, J = 1.9 Hz), 6.69 (1H, dd, J = 8.2, 1.9 Hz), 6.80 (1H, d, J = 8.0 Hz), 7.25–7.45 ppm (5H, m); LC–MS (ES+): *m/z* 338.3 $[M+Na]^+$.

(±)-1-(3-Benzyloxy-4-methoxyphenyl)propan-2-amine (10a): Raney Ni (50% slurry in H_2O, 3.0 g) was washed in presence of a magnetic stirring bar with MeOH (3×5 mL). Compound **9a** (3.05 g, 10.1 mmol) in MeOH (70 mL) was then introduced, and the reaction mixture was cooled to 0 °C. $N_2H_4 \cdot H_2O$ (2.53 g, 50.5 mmol) was added in a dropwise manner at which stage the reaction was brought to 40 °C for 18 h. After cooling to room temperature the reaction mixture was filtered through Celite, washed with MeOH (4×50 mL) and concentrated in vacuo. Flash column chromatography (EtOAc/MeOH gradient) afforded compound **10a** as a pale-yellow oil (2.074 g, 76%); ^1H NMR (270 MHz, $CDCl_3$): δ = 1.04 (3H, d, J = 6.4 Hz), 2.36 (1H, dd, J = 13.3, 8.2 Hz), 2.58 (1H, dd, J = 13.3, 5.2 Hz), 2.98–3.10 (1H, m), 3.86 (3H, s), 5.13 (2H, s), 6.67–6.83 (3H, m), 7.25–7.43 ppm (5H, m); LC–MS (ES+): *m/z* 272.19 $[M+H]^+$.

(±)-*N*-(1-(3-Benzyloxy-4-methoxyphenyl)propan-2-yl)acetamide (11a): Compound **10a** (2.07 g, 7.6 mmol) was dissolved in CH_2Cl_2 (20 mL) and Et_3N (1.6 mL, 11.4 mmol). Ac_2O was then added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 23 h. H_2O (30 mL) was added carefully and the mixture extracted with CH_2Cl_2 (4×30 mL). The combined organics were washed with brine (30 mL), then dried ($MgSO_4$), filtered and concentrated in vacuo to afford compound **11a** as a white powder (2.268 g, 95%); mp: 139–142 °C; ^1H NMR (270 MHz,

$CDCl_3$): $\delta = 0.99$ (3H, d, $J = 6.7$ Hz), 1.91 (3H, s), 2.57 (1H, dd, $J = 13.6$, 7.2 Hz), 2.70 (1H, dd, $J = 13.6$, 5.7 Hz), 3.85 (3H, s), 4.08–4.22 (1H, m), 5.12 (2H, s), 5.17–5.23 (1H, m), 6.68–6.71 (2H, m), 6.79–6.82 (1H, m), 7.24–7.44 ppm (5H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta = 19.9$, 23.6, 41.8, 46.1, 56.1, 71.1, 111.8, 115.6, 122.2, 127.4, 127.9, 128.6, 130.4, 137.2, 147.9, 148.5, 169.3 ppm; LC–MS (APCI−): *m/z* 312.29 $[M-H]^-$.

(±)-*N*-(1-(3-(Benzyloxy)-4-methoxyphenyl)butan-2-yl)acetamide (11b): Method as for **10a** using compound **9b** (7.88 g, 25.0 mmol), Raney Ni (50% slurry in H_2O, 3.82 g) and $N_2H_4{\cdot}H_2O$ (6.30 g, 126 mmol) in MeOH (100 mL) were reacted at 0 °C for 1 h and at 50 °C for 7 h as described for the synthesis of **10a**. The crude amine **10b**, a brown–green oil (7.72 g), was used without further purification. Acylation was then carried out as described for the synthesis of **11a** with **10b** (7.41 g, max. 24.0 mmol), Et_3N (3.68 g, 36.4 mmol) and Ac_2O (2.96 g, 29.0 mmol) in CH_2Cl_2 (80 mL) at 0 °C for 4 h. The work-up, carried out using HCl (1 M, 50 mL), CH_2Cl_2 (2× 100 mL) and brine (80 mL), afforded compound **11b** as a beige solid (8.73 g, 99%); ^1H NMR (270 MHz, $CDCl_3$): $\delta = 0.83$ (3H, t, $J = 7.4$ Hz), 1.09–1.27 (1H, m), 1.32–1.50 (1H, m), 1.87 (3H, s), 2.64 (2H, d, $J = 6.3$ Hz), 3.85 (3H, s), 3.89–4.07 (1H, m), 5.08 (1H, d, br, $J = 8.8$ Hz), 5.13 (2H, s), 6.63–6.72 (2H, m), 6.77–6.82 (1H, m), 7.24–7.44 ppm (5H, m); LC–MS (ES+): *m/z* 328.2 $[M+H]^+$.

(±)-2-Acetyl-6-benzyloxy-7-methoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (12a): Compound **11a** (2.21 g, 7.04 mmol) was treated with paraformaldehyde (6.32 g, 210 mmol) and *p*-TsOH (120 mg, 0.64 mmol) in toluene (55 mL) at 120 °C for 22 h. The reaction mixture was cooled to room temperature, filtered and evaporated. EtOAc (60 mL) was added, and the organic layer was washed with H_2O (3×50 mL), brine (50 mL) then dried ($MgSO_4$) and evaporated to afford compound **12a** as a colourless oil (2.15 g, 94%); ^1H NMR (270 MHz, $CDCl_3$): $\delta = 1.04$ and 1.12 (3H, 2d, $J = 7.2$ and 6.7 Hz), 2.14 and 2.17 (3H, 2 s), 2.38–2.51 (1H, m), 2.89–3.06 (1H, m), 3.84 and 3.85 (3H, 2 s), 4.06–4.60 (2H, m), 4.96–5.14 (1H, m), 5.08 and 5.10 (2H, 2 s), 6.61 and 6.64 (1H, 2 s), 6.62 and 6.67 (1H, 2 s), 7.28–7.44 ppm (5H, m); LC–MS (ES+): *m/z* 348.19 $[M+Na]^+$.

(±)-2-Acetyl-6-benzyloxy-3-ethyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline (12b): **11b** (8.70 g, 23.0 mmol), paraformaldehyde (4.25 g, 141 mmol) and *p*-TsOH (220 mg, 1.2 mmol) in toluene (140 mL) were reacted at 120 °C for 16 h as described for the synthesis of **12a**. The reaction was worked-up with H_2O (100 mL), EtOAc (3×100 mL), H_2O (50 mL) and brine (2×20 mL) to afford compound **12b** as a viscous orange oil (6.33 g, 81%); ^1H NMR (270 MHz, $CDCl_3$): $\delta = 0.86$ (3H, t, $J = 7.5$ Hz), 1.23–1.64 (2H, m), 2.16 (3H, s), 2.44–2.61 (1H, m), 2.80–3.06 (1H, m), 3.82 (3H, s), 3.92–4.03 (1H, m), 4.33 (1H, d, $J = 16.2$ Hz), 4.55 (1H, d, $J = 16.2$ Hz), 5.08 (2H, s), 6.53–6.64 (2H, m), 7.18–7.44 ppm (5H, m); HRMS (ES+): *m/z* found 340.1903, $C_{21}H_{26}NO_3^+$ $[M+H]^+$ requires 340.1907.

(±)-6-Benzyloxy-7-methoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (13a): Compound **12a** (3.16 g, 9.7 mmol) was treated with KOH (5.44 g, 97.0 mmol) in EtOH (36 mL) and H_2O (12 mL) at 120 °C for 66 h. The reaction mixture was then cooled to room temperature and concentrated. H_2O (30 mL) was then added, and the mixture was then extracted with CH_2Cl_2 (3×50 mL). The combined organics were washed with brine (50 mL), then dried ($MgSO_4$) and evaporated to afford compound **13a** as a beige solid (2.51 g, 91%); mp: 110–112 °C; ^1H NMR (270 MHz, $CDCl_3$): $\delta = 1.20$ (3H, d, $J = 6.4$ Hz), 1.78 (1H, s, br), 2.35 (1H, dd, $J = 15.8$, 10.6 Hz), 2.60 (1H, dd, $J = 15.8$, 3.7 Hz), 2.88–3.01 (1H, m), 3.82 (3H, s), 3.93 (1H, d, $J = 15.6$ Hz), 4.03 (1H, d, $J = 15.6$ Hz), 5.09 (2H, s), 6.53 (1H, s), 6.56 (1H, s), 7.23–7.44 ppm (5H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta = 22.6$, 36.8, 48.4, 49.4, 56.2, 71.2, 109.5, 114.8, 126.8, 127.4, 127.8, 128.1, 128.6, 137.4, 146.6, 148.0 ppm; LC–MS (ES+): *m/z* 284.13 $[M+H]^+$.

(±)-3-Ethyl-6-benzyloxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (13b): Compound **12b** (6.281 g, 18.5 mmol) and KOH (10.14 g, 181 mmol) in EtOH (69 mL) and H_2O (23 mL) were reacted at 120 °C for 88 h following the method described for the synthesis of **13a**. A further aliquot of KOH (10.12 g, 180 mmol) in H_2O (23 mL) was then added and heating was continued at 140 °C for a further 80 h. Flash column chromatography (EtOAc and 0.5% Et_3N to EtOAc/MeOH 4:1 and 0.5% Et_3N) afforded **13b** as a beige solid (4.23 g, 76%); mp: 83–85 °C; ^1H NMR (270 MHz, $CDCl_3$): $\delta = 0.98$ (3H, t, $J = 7.4$ Hz), 1.39–1.63 (2H, m), 1.72 (1H, s, br), 2.34 (1H, dd, $J = 16.0$, 10.2 Hz), 2.63 (1H, dd, $J = 15.8$, 3.8 Hz), 2.65–2.78 (1H, m), 3.82 (3H, s), 3.93 (1H, d, $J = 15.7$ Hz), 4.01 (1H, d, $J = 15.7$ Hz), 5.09 (2H, s), 6.53 (1H, s), 6.58 (1H, s), 7.23–7.45 ppm (5H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta = 10.4$, 29.5, 34.4, 48.3, 55.2, 56.0, 71.0, 109.3, 114.6, 126.6, 127.2, 127.7, 128.1, 128.4, 137.2, 146.5, 147.8 ppm; LC–MS (ES+): *m/z* 298.3 $[M+H]^+$.

(±)-6-Hydroxy-7-methoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (14a): Pd/C (10%, 2.02 g) was covered with MeOH (20 mL) and then treated with **13a** (20.68 g, 73.0 mmol) in MeOH (180 mL). The reaction mixture was degassed then stirred under an atmosphere of H_2 at room temperature for 24 h. The mixture was filtered through Celite which was washed with hot MeOH (10×20 mL). The filtrate was evaporated to afford the desired product **14a** as a white solid (7.90 g, 56%); mp: 206–209 °C; ^1H NMR (270 MHz, CD_3OD): $\delta = 1.24$ (3H, d, $J = 6.3$ Hz), 2.44 (1H, dd, $J = 16.2$, 10.7 Hz), 2.66 (1H, dd, $J = 16.3$, 3.9 Hz), 2.86–3.02 (1H, m), 3.82 and 3.82 (3H, 2 s), 3.89 (1H, d, $J = 15.4$ Hz), 3.97 (1H, d, $J = 15.7$ Hz), 6.53 (1H, s, CH), 6.61 ppm (1H, s, CH); LC–MS (ES+): *m/z* 194.0 $[M+H]^+$.

(±)-7-Methoxy-3-methyl-6-(triisopropylsilyloxy)-1,2,3,4-tetrahydro-isoquinoline (15): **14a** (7.904 g, 40.9 mmol) and imidazole (8.181 g, 121 mmol) in CH_2Cl_2 (200 mL) were treated with chlorotriisopropylsilane (9.496 g, 49.3 mmol) in a dropwise manner. After 22 h stirring at room temperature H_2O (400 mL) was added, and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3×200 mL) and the combined organics were then washed with brine (200 mL), dried (NaCl), and evaporated. Flash column chromatography (hexane/EtOAc 4:1 to 1:1 to 1:1 and 2% Et_3N) afforded **15** as a beige solid (6.81 g, 47%); ^1H NMR (270 MHz, $CDCl_3$): $\delta = 1.06$ (18H, d, $J = 6.9$ Hz), 1.11–1.31 (3H, m), 1.19 (3H, d, $J = 6.0$ Hz), 1.56 (1H, s, br), 2.35 (1H, dd, $J = 16.0$, 10.7 Hz), 2.61 (1H, dd, $J = 16.1$, 3.7 Hz), 2.86–3.02 (1H, m), 3.72 (3H, s), 3.90 (1H, d, $J = 15.7$), 4.02 (1H, d, $J = 16.0$ Hz), 6.45 (1H, s), 6.54 ppm (1H, s); HRMS (ES+): *m/z* found 350.2514, $C_{20}H_{36}NO_2Si^+$ $[M+H]^+$ requires 350.2510.

(±)-6-Benzyloxy-7-methoxy-2-(3-methoxybenzyl)-3-methyl-1,2,3,4-tetrahydroisoquinoline (16a): Compound **13a** (300 mg, 1.1 mmol) was treated with 3-methoxybenzyl chloride (0.18 mL, 1.3 mmol) and Et_3N (0.30 mL, 2.1 mmol) in EtOH (3.0 mL) at 130 °C for 1.5 h under microwave irradiation. The mixture was then evaporated and the residues dissolved in EtOAc (30 mL). The solution was then washed with brine (30 mL), dried, and evaporated. Flash column chromatography (hexane/EtOAc gradient) afforded **16a** as a colourless oil (357 mg, 84%); ^1H NMR (270 MHz, $CDCl_3$): $\delta = 1.12$ (3H, d, $J = 6.4$ Hz), 2.47 (1H, dd, $J = 16.1$, 5.7 Hz), 2.86 (1H, dd, $J = 16.1$, 4.9 Hz), 3.01–3.11 (1H, m), 3.55 (2H, t, $J = 13.4$ Hz), 3.76–3.81 (2H, m), 3.80 (6H, s), 5.10 (2H, s), 6.47 (1H, s), 6.60 (1H,

s), 6.79 (1H, ddd, $J=8.2$, 2.5, 1.0 Hz), 6.94–6.97 (2H, m), 7.15–7.45 ppm (6H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta=15.3$, 35.0, 51.5, 52.3, 55.3, 56.1, 57.2, 71.2, 110.0, 112.5, 114.4, 114.6, 121.3, 125.8, 127.0, 127.4, 127.8, 128.6, 129.3, 137.5, 141.4, 146.7, 147.9, 159.8 ppm; LC–MS (ES+): m/z 404.25 $[M+H]^+$.

(±)-6-Benzyloxy-3-ethyl-7-methoxy-2-(3-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (16b): Compound **13b** (297 mg, 1.0 mmol) was treated with 3-methoxybenzyl bromide (222 mg, 1.1 mmol) and DIPEA (263 mg, 2.0 mmol) in DMF (3.0 mL) at 80 °C for 18 h. After cooling to room temperature the reaction mixture was evaporated then treated with H_2O (100 mL) and NH_4Cl (saturated, 10 mL) before extracting into EtOAc (2×100 mL). The combined organics were dried (NaCl), and evaporated. Flash column chromatography (hexane to hexane/EtOAc 7:3) afforded compound **16b** as a pale-yellow oil (323 mg, 77%); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta=1.02$ (3H, t, $J=7.4$ Hz), 1.46 (1H, sept, $J=7.2$ Hz), 1.73 (1H, sept, $J=6.8$ Hz), 2.55 (1H, dd, $J=16.2$, 6.1 Hz), 2.82 (1H, dd, $J=16.2$, 5.0 Hz), 2.85–2.98 (1H, m), 3.61–3.77 (4H, m), 3.84 (6H, s), 5.16 (2H, s), 6.52 (1H, s), 6.67 (1H, s), 6.81–6.87 (1H, m), 6.95–7.02 (2H, m), 7.23–7.52 (5H, m), 7.27 ppm (1H, t, $J=6.9$); HRMS (ES+): m/z found 418.2381, $C_{27}H_{32}NO_3^+$ $[M+H]^+$ requires 418.2377.

(±)-6-Benzyloxy-2-(3-ethylbenzyl)-7-methoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (16c): Compound **13a** (425 mg, 1.5 mmol) and 3-ethylbenzoic acid (339 mg, 2.25 mmol) were dissolved in CH_2Cl_2 (4.5 mL) and THF (1.5 mL). EDCI (578 mg, 3.0 mmol) was then added, and the reaction mixture was stirred at room temperature for 20 h. The reaction mixture was then diluted with HCl (1 M, 50 mL), extracted with CH_2Cl_2/EtOAc (~9:1, 2×50 mL) and the combined organics were dried and evaporated. Flash column chromatography (hexane to hexane/EtOAc 7:3) afforded the desired amide as a colourless sticky foam (534 mg, 85%); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta=1.14$ (3H, s, br), 1.24 (3H, t, $J=7.6$ Hz), 2.36 and 2.41 (1H, 2 s, br), 2.67 (2H, q, $J=7.5$ Hz), 3.04 and 3.08 (1H, 2 s, br), 3.85 (3H, s, br), 4.25, 4.30 and 4.43 (2H, 3 s, br), 5.06–5.44 (1H, m), 5.11 (2H, s), 6.44 and 6.68 (1H, 2 s, br), 6.63 (1H, s, br), 7.16–7.47 ppm (9H, m); HRMS (ES+): m/z found 416.2223, $C_{27}H_{30}NO_3^+$ $[M+H]^+$ requires 416.2220. A suspension of $LiAlH_4$ (114 mg, 3.0 mmol) in THF (1.0 mL) was then treated with a solution of the amide (250 mg, 0.6 mmol) in THF (3.0 mL) in a dropwise manner. After 0.5 h the reaction mixture was carefully diluted with EtOAc (100 mL), then left to stand for 0.5 h. The reaction mixture was then filtered through Celite, the residues washed with EtOAc (4×10 mL), and the combined filtrates were evaporated to afford compound **16c** as a colourless oil (240 mg, 99%); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta=1.13$ (3H, d, $J=6.6$ Hz), 1.23 (3H, t, $J=7.6$ Hz), 2.48 (1H, dd, $J=16.1$, 5.9 Hz), 2.64 (2H, q, $J=7.6$ Hz), 2.86 (1H, dd, $J=16.0$, 4.7 Hz), 3.06 (1H, sext, $J=6.1$ Hz), 3.44–3.71 (3H, m), 3.73–3.88 (1H, m), 3.79 (3H, s), 5.10 (2H, s), 6.47 (1H, s), 6.60 (1H, s), 7.06–7.51 ppm (9H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta=15.2$, 15.6, 28.8, 34.8, 51.4, 52.1, 56.0, 57.1, 71.1, 109.8, 114.4, 125.7, 126.2, 126.4, 126.8, 127.2, 127.7, 128.4, 128.5, 137.3, 139.3, 144.2, 146.6, 147.8 ppm; HRMS (ES+): m/z found 402.2429, $C_{27}H_{32}NO_2^+$ $[M+H]^+$ requires 402.2428.

(±)-6-Benzyloxy-2-(3-ethoxybenzyl)-7-methoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (16d): Method as for **16c** using compound **13a** (424 mg, 1.5 mmol), 3-ethoxybenzoic acid (374 mg, 2.25 mmol) and EDCI (578 mg, 2.0 mmol) in CH_2Cl_2 (4.5 mL) and THF (1.5 mL) at room temperature for 20 h. Flash column chromatography (hexane to hexane/EtOAc 1:1) afforded the desired amide as a colourless sticky oil (608 mg, 94%); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta=1.06$–1.28 (3H, m), 1.40 (3H, t, $J=7.0$ Hz), 2.30–2.53 (1H, m), 2.96–3.15 (1H, m), 3.85 (3H, s), 4.03 (2H, q, $J=7.0$ Hz), 4.17–4.37 (2H, m), 5.10 (2H, s), 6.36–6.74 (2H, m), 6.88–6.97 (3H, m), 7.23–7.46 ppm (6H, m); HRMS (ES+): m/z found 432.2175, $C_{27}H_{30}NO_4^+$ $[M+H]^+$ requires 432.2169. The amide (432 mg, 1.0 mmol) was then reacted with $LiAlH_4$ (117 mg, 3.0 mmol) in THF (4.0 mL) at 0 °C for 0.5 h, then at room temperature for 18 h. Flash column chromatography (hexane to hexane/EtOAc 3:2) afforded **16d** as a colourless sticky oil (314 mg, 74%); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta=1.12$ (3H, d, $J=6.3$ Hz), 1.40 (3H, t, $J=6.9$ Hz), 2.47 (1H, dd, $J=16.1$, 5.9 Hz), 2.86 (1H, dd, $J=16.0$, 4.7 Hz), 3.06 (1H, sext, $J=6.1$ Hz), 3.47–3.68 (3H, m), 3.74–3.83 (1H, m), 3.79 (3H, s), 4.02 (2H, q, $J=7.0$ Hz), 5.10 (2H, s), 6.47 (1H, s), 6.60 (1H, s), 6.75–6.84 (1H, m), 6.88–6.97 (2H, m), 7.22 (1H, t, $J=8.1$ Hz), 7.24–7.47 ppm (5H, m); HRMS (ES+): m/z found 418.2379, $C_{27}H_{32}NO_3^+$ $[M+H]^+$ requires 418.2377.

(±)-6-Benzyloxy-2-(3,5-dimethoxybenzyl)-7-methoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (16e): Method as for **16a** using compound **13a** (300 mg, 1.1 mmol), 3,5-dimethoxybenzyl bromide (294 mg, 1.3 mmol) and Et_3N (0.30 mL, 2.1 mmol) in EtOH (3.0 mL) in the microwave at 130 °C for 2.5 h. Flash column chromatography (hexane/EtOAc gradient) afforded **16e** as a colourless oil (222 mg, 46%); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta=1.10$ (3H, d, $J=6.4$ Hz), 2.45 (1H, dd, $J=15.9$, 5.8 Hz), 2.86 (1H, dd, $J=15.9$, 4.7 Hz), 3.02–3.11 (1H, m), 3.45–3.71 (4H, m), 3.77 (6H, s), 3.79 (3H, s), 5.09 (2H, s), 6.35 (1H, t, $J=2.2$ Hz), 6.48 (1H, s), 6.54 (2H, d, $J=2.2$ Hz), 6.60 (1H, s), 7.28–7.44 ppm (5H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta=$ 15.2, 34.9, 51.5, 52.2, 55.4, 56.1, 57.4, 71.2, 99.0, 106.7, 110.0, 114.5, 125.8, 126.9, 127.4, 127.8, 128.6, 137.5, 142.2, 146.7, 147.9, 160.8 ppm; LC–MS (ES+): m/z 434.36 $[M+H]^+$; HRMS (ES+): m/z found 434.2330, $C_{27}H_{32}NO_4^+$ $[M+H]^+$ requires 434.2326.

(±)-6-Benzyloxy-2-(2,5-dimethoxybenzyl)-7-methoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (16f): Method as for **16b** using compound **13a** (338 mg, 1.2 mmol), 2,5-dimethoxybenzyl chloride (279 mg, 1.5 mmol) and DIPEA (314 mg, 2.4 mmol) in DMF (3.6 mL) at 80 °C for 20 h. Flash column chromatography (hexane to hexane/EtOAc 1:1) afforded **16f** as an orange oil (395 mg, 76%); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta=1.14$ (3H, d, $J=6.3$ Hz), 2.48 (1H, dd, $J=16.3$, 6.0 Hz), 2.86 (1H, dd, $J=16.1$, 4.8 Hz), 3.11 (1H, sext, $J=$ 6.1 Hz), 3.58–3.77 (4H, m), 3.76 (3H, s), 3.77 (3H, s), 3.81 (3H, s), 5.11 (2H, s), 6.50 (1H, s), 6.61 (1H, s), 6.74 (1H, dd, $J=8.8$, 3.0 Hz), 6.80 (1H, d, $J=8.8$ Hz), 7.07 (1H, d, $J=2.8$ Hz), 7.24–7.47 ppm (5H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta=15.5$, 34.5, 50.0, 51.4, 52.4, 55.7, 56.0, 56.0, 71.0, 109.9, 111.3, 111.9, 114.4, 116.0, 125.8, 127.0, 127.2, 127.7, 128.4, 128.9, 137.3, 146.5, 147.7, 151.9, 153.6 ppm; HRMS (ES+): m/z found 434.2332, $C_{27}H_{32}NO_4^+$ $[M+H]^+$ requires 434.2326.

(±)-6-Benzyloxy-2-(2-fluoro-5-methoxybenzyl)-7-methoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (16g): Method as for **16b** using compound **13a** (339 mg, 1.2 mmol), 2-fluoro-5-methoxybenzyl bromide (401 mg, 74 wt%, 1.35 mmol) and DIPEA (314 mg, 2.4 mmol) in DMF (3.6 mL) at 80 °C for 20 h. Flash column chromatography (hexane to hexane/EtOAc 3:2) afforded **16g** as an orange oil (363 mg, 71%); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta=1.14$ (3H, d, $J=$ 6.3 Hz), 2.47 (1H, dd, $J=16.2$, 6.1 Hz), 2.86 (1H, dd, $J=16.2$, 5.0 Hz), 3.09 (1H, sext, $J=6.1$ Hz), 3.54–3.68 (3H, m), 3.69–3.81 (1H, m), 3.75 (3H, s), 3.80 (3H, s), 5.09 (2H, s), 6.49 (1H, s), 6.59 (1H, s), 6.72 (1H, dt, $J=9.1$, 3.7 Hz), 6.94 (1H, t, $J=9.1$ Hz), 7.01 (1H, dd, $J=5.9$, 3.2 Hz), 7.23–7.45 ppm (5H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta=$ 15.2, 34.8, 49.5 (d, J 1.5), 51.3, 52.4, 55.7, 56.0, 71.0, 109.8, 113.4 (d, J 8.2), 114.4, 115.6 (dd, J 14.2, 9.5), 125.6, 126.5, 126.7, 127.0, 127.2, 127.7, 128.4, 137.3, 146.6, 147.8, 154.0, 155.6 ppm (d, J 2.1); LC–MS (ES^+): m/z 422.3 $[M+H]^+$.

(±)-6-Benzyloxy-7-methoxy-3-methyl-2-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (16h): Method as for **16a** using compound **13a** (227 mg, 0.8 mmol), 3,4,5-trimethoxybenzyl chloride (208 mg, 0.96 mmol) and Et_3N (0.22 mL, 1.6 mmol) in EtOH (3.0 mL) in the microwave at 150 °C for 0.5 h. Flash column chromatography (hexane/EtOAc gradient) afforded compound **16h** as a colourless oil (151 mg, 40%); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.11 (3H, d, J = 6.4 Hz), 2.46 (1H, dd, J = 16.1, 5.7 Hz), 2.87 (1H, dd, J = 16.1, 4.8 Hz), 3.04–3.11 (1H, m), 3.46–3.75 (4H, m), 3.80 (3H, s), 3.84 (3H, s), 3.84 (6H, s), 5.10 (2H, s), 6.50 (1H, s), 6.60 (2H, s), 6.61 (1H, s), 7.26–7.44 ppm (5H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 15.1, 34.8, 51.4, 52.0, 56.1, 56.2, 57.4, 61.0, 71.2, 105.4, 109.9, 114.4, 125.8, 126.8, 127.4, 127.8, 128.6, 135.4, 136.7, 146.7, 146.8, 147.9, 153.2 ppm; LC–MS (ES+): m/z 464.22 $[M+H]^+$; HRMS (ES+): m/z found 464.2436, $C_{28}H_{34}NO_5^+$ $[M+H]^+$ requires 464.2431.

(±)-6-Benzyloxy-3-ethyl-7-methoxy-2-(3,4,5-trimethoxybenzyl)-tetrahydroisoquinoline (16i): Method as for **16b** using compound **13b** (297 mg, 1.0 mmol), 3,4,5-trimethoxybenzyl chloride (238 mg, 1.1 mmol) and DIPEA (264 mg, 2.0 mmol) in DMF (3.0 mL) at 80 °C for 18 h. Flash column chromatography (hexane to hexane/EtOAc 1:1) afforded **16i** as a pale-yellow oil (350 mg, 73%); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.97 (3H, t, J = 7.0 Hz), 1.43 (1H, sept, J = 7.0 Hz), 1.67 (1H, sept, J = 7.0 Hz), 2.42–2.58 (1H, m), 2.72–2.95 (2H, m), 3.51–3.74 (4H, m), 3.80 (3H, s), 3.83 (6H, s), 3.88 (3H, s), 5.10 (2H, s), 6.45–6.56 (1H, m), 6.56–6.70 (3H, m), 7.24–7.52 ppm (5H, m); HRMS (ES+): m/z found 478.2593, $C_{29}H_{36}NO_5^+$ $[M+H]^+$ requires 478.2588.

(±)-7-Methoxy-2-(2-methoxybenzyl)-3-methyl-6-(triisopropylsilyloxy)-1,2,3,4-tetrahydroisoquinoline (17a): Method as for **16b** using compound **15** (524 mg, 1.5 mmol), 2-methoxybenzyl chloride (282 mg, 1.8 mmol) and DIPEA (389 mg, 3.0 mmol) in DMF (4.5 mL) at 80 °C for 18 h. Flash column chromatography (hexane/EtOAc 4:1 to 1:1) afforded **17a** as a yellow wax (572 mg, 81%); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.07 (18H, d, J = 6.9 Hz), 1.15 (3H, d, J = 6.6 Hz), 1.14–1.32 (3H, m), 2.48 (1H, dd, J = 16.0, 6.3 Hz), 2.84 (1H, dd, J = 16.6, 4.3 Hz), 3.10 (1H, sext, J = 6.2 Hz), 3.53–3.88 (4H, m), 3.70 (3H, s), 3.81 (3H, s), 6.41 (1H, s), 6.56 (1H, s), 6.85 (1H, d, J = 8.0 Hz), 6.92 (1H, t, J = 7.4 Hz), 7.20 (1H, dd, J = 7.7, 1.6 Hz), 7.42 ppm (1H, dd, J = 7.4, 1.4 Hz); HRMS (ES+): m/z found 470.3076, $C_{28}H_{44}NO_3Si^+$ $[M+H]^+$ requires 470.3085.

(±)-7-Methoxy-2-(4-methoxybenzyl)-3-methyl-6-(triisopropylsilyloxy)-1,2,3,4-tetrahydroisoquinoline (17b): Method as for **16b** using compound **15** (524 mg, 1.5 mmol), 4-methoxybenzyl bromide (423 mg, 2.1 mmol) and DIPEA (391 mg, 3.0 mmol) in DMF (4.5 mL) at 80 °C for 20 h. Flash column chromatography (hexane/EtOAc 4:1 to 1:1) afforded compound **17b** as a yellow wax (587 mg, 83%); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.07 (18H, d, J = 6.6 Hz), 1.11 (3H, d, J = 6.6 Hz), 1.13–1.31 (3H, m), 2.45 (1H, dd, J = 16.0, 6.1 Hz), 2.84 (1H, dd, J = 16.0, 5.0 Hz), 3.03 (1H, sext, J = 5.9 Hz), 3.41–3.64 (3H, m), 3.69 (3H, s), 3.74 (1H, d, J = 12.7 Hz), 3.79 (3H, s), 6.39 (1H, s), 6.55 (1H, s), 6.85 (2H, d, J = 8.5 Hz), 7.27 ppm (2H, d, J = 8.5 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 12.8, 15.2, 17.9, 34.4, 51.1, 52.1, 55.2, 55.5, 56.2, 110.0, 113.7, 114.8, 120.3, 130.3, 130.8, 149.0, 158.7 ppm; HRMS (ES+): m/z found 470.3084, $C_{28}H_{44}NO_3Si^+$ $[M+H]^+$ requires 470.3085.

(±)-2-Benzyl-7-methoxy-3-methyl-6-(triisopropylsilyloxy)-1,2,3,4-tetrahydroisoquinoline (17c): Method as for **16b** using compound **15** (419 mg, 1.2 mmol), benzyl bromide (249 mg, 1.46 mmol) and DIPEA (391 mg, 3.0 mmol) in DMF (4.5 mL) at 80 °C for 18 h. Flash column chromatography (hexane/EtOAc 9:1) afforded **17c** as an orange oil (361 mg, 68%); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.08 (18H, d, J = 6.6 Hz), 1.13 (3H, d, J = 6.6 Hz), 1.15–1.32 (3H, m), 2.47 (1H, dd, J = 16.0, 6.0 Hz), 2.86 (1H, dd, J = 16.0, 4.9 Hz), 3.05 (1H, sext, J = 6.1 Hz), 3.42–3.86 (4H, m), 3.69 (3H, s), 6.39 (1H, s), 6.57 (1H, s), 7.20–7.41 ppm (5H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 12.9, 15.2, 17.9, 34.8, 51.5, 52.2, 55.5, 57.2, 110.0, 120.4, 125.7, 126.6, 126.8, 128.2, 129.0, 139.4, 143.7, 148.9 ppm; HRMS (ES+): m/z found 440.2970, $C_{27}H_{42}NO_2Si^+$ $[M+H]^+$ requires 440.2980.

(±)-2-(2-Chlorobenzyl)-7-methoxy-3-methyl-6-(triisopropylsilyloxy)-1,2,3,4-tetrahydroisoquinoline (17d): Method as for **16b** using compound **15** (315 mg, 0.9 mmol), 2-chlorobenzyl bromide (278 mg, 1.35 mmol) and DIPEA (234 mg, 1.8 mmol) in DMF (2.5 mL) at 80 °C for 18 h. Flash column chromatography (hexane/EtOAc 9:1 to 9:1 and 2% Et_3N) afforded **17d** as a yellow wax (328 mg, 76%); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.07 (18H, d, J = 6.6 Hz), 1.14 (3H, d, J = 6.6 Hz), 1.16–1.32 (3H, m), 2.47 (1H, dd, J = 16.0, 5.8 Hz), 2.88 (1H, dd, J = 16.1, 4.8 Hz), 3.12 (1H, sext, J = 6.1 Hz), 3.51–3.87 (4H, m), 3.70 (3H, s), 6.41 (1H, s), 6.57 (1H, s), 7.16 (1H, dt, J = 7.4, 1.9 Hz), 7.22 (1H, dt, J = 7.4, 1.8 Hz), 7.33 (1H, dd, J = 7.4, 1.9 Hz), 7.54 ppm (1H, dd, J = 7.4, 1.9 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 12.9, 15.3, 17.9, 34.7, 51.4, 52.8, 53.7, 55.5, 110.0, 120.4, 125.7, 126.6, 126.6, 128.5, 127.8, 129.3, 134.1, 137.1, 143.8, 148.9 ppm; HRMS (ES+): m/z found 474.2575, $C_{27}H_{41}ClNO_2Si^+$ $[M+H]^+$ requires 474.2590.

(±)-7-Methoxy-3-methyl-2-(2-methylbenzyl)-6-(triisopropylsilyloxy)-1,2,3,4-tetrahydroisoquinoline (17e): Method as for **16b** using compound **15** (315 mg, 0.9 mmol), 2-methylbenzyl bromide (251 mg, 1.35 mmol) and DIPEA (236 mg, 2.0 mmol) in DMF (2.5 mL) at 80 °C for 18 h. Flash column chromatography (hexane/EtOAc 9:1 to 9:1 and 2% Et_3N) afforded **17e** as a yellow wax (286 mg, 70%); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.07 (18H, d, J = 6.6 Hz), 1.13 (3H, d, J = 6.3 Hz), 1.16–1.32 (3H, m), 2.35 (3H, s), 2.45 (1H, dd, J = 16.0, 5.8 Hz), 2.86 (1H, dd, J = 16.0, 4.7 Hz), 3.07 (1H, sext, J = 6.0 Hz), 3.42–3.65 (3H, m), 3.69 (3H, s), 3.75 (1H, d, J = 13.2 Hz), 6.39 (1H, s), 6.56 (1H, s), 7.09–7.21 (3H, m), 7.28–7.36 ppm (1H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 12.9, 14.8, 17.9, 19.3, 34.8, 51.1, 52.6, 55.0, 55.5, 110.0, 120.4, 125.5, 125.8, 126.8, 129.7, 130.2, 137.3, 137.5, 143.6, 148.9 ppm; HRMS (ES+): m/z found 454.3128, $C_{28}H_{44}NO_2Si^+$ $[M+H]^+$ requires 454.3136.

(±)-7-Methoxy-3-methyl-2-(3-nitrobenzyl)-6-(triisopropylsilyloxy)-1,2,3,4-tetrahydroisoquinoline (17f): Method as for **16b** using compound **15** (418 mg, 1.2 mmol), 3-nitrobenzyl chloride (248 mg, 1.45 mmol) and DIPEA (310 mg, 2.4 mmol) in DMF (3.6 mL) at 80 °C for 18 h. Flash column chromatography (hexane/EtOAc 9:1) afforded **17f** as a yellow wax (409 mg, 70%); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.07 (18H, d, J = 6.9 Hz), 1.12 (3H, d, J = 6.6 Hz), 1.14–1.32 (3H, m), 2.47 (1H, dd, J = 16.0, 6.1 Hz), 2.87 (1H, dd, J = 16.1, 4.8 Hz), 3.07 (1H, sext, J = 6.1 Hz), 3.41–3.59 (2H, m), 3.65 (1H, d, J = 14.0 Hz), 3.69 (3H, s), 3.84 (1H, d, J = 13.8 Hz), 6.37 (1H, s), 6.57 (1H, s), 7.46 (1H, t, J = 8.0 Hz), 7.72 (1H, d, J = 7.7 Hz), 8.09 (1H, dd, J = 8.2, 1.7 Hz), 8.23 ppm (1H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 12.9, 15.4, 17.9, 34.6, 51.5, 52.6, 55.5, 56.4, 109.9, 120.4, 122.0, 123.6, 125.5, 126.0, 129.1, 134.9, 142.2, 143.9, 148.4, 149.1 ppm; HRMS (ES+): m/z found 485.2813, $C_{27}H_{41}N_2O_4Si^+$ $[M+H]^+$ requires 485.2830.

(±)-2-(3-Chlorobenzyl)-7-methoxy-3-methyl-6-(triisopropylsilyloxy)-1,2,3,4-tetrahydroisoquinoline (17g): Method as for **16b** using compound **15** (418 mg, 1.2 mmol), 3-chlorobenzyl bromide (298 mg, 1.45 mmol) and DIPEA (311 mg, 2.4 mmol) in DMF (3.6 mL) at 80 °C for 18 h. Flash column chromatography (hexane/EtOAc 19:1 to 9:1) afforded **17g** as a yellow wax (338 mg, 59%); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.07 (18H, d, J = 6.6 Hz), 1.11 (3H, d,

J=6.6 Hz), 1.14–1.32 (3H, m), 2.46 (1H, dd, J=16.0, 6.1 Hz), 2.85 (1H, dd, J=16.0, 5.0 Hz), 3.04 (1H, sext, J=6.1 Hz), 3.42–3.64 (3H, m), 3.70 (3H, s), 3.75 (1H, d, J=13.2 Hz), 6.39 (1H, s), 6.56 (1H, s), 7.17–7.26 (3H, m), 7.37 ppm (1H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ=12.9, 15.3, 17.9, 34.7, 51.6, 52.4, 55.5, 56.6, 110.0, 120.4, 125.6, 126.3, 127.0, 127.1, 128.9, 129.5, 134.2, 141.8, 143.9, 149.0 ppm; HRMS (ES+): m/z found 474.2580, $C_{27}H_{41}ClNO_2Si^+$ $[M+H]^+$ requires 474.2590.

(±)-2-(3-Acetylbenzyl)-7-methoxy-3-methyl-6-(triisopropylsilyloxy)-1,2,3,4-tetrahydroisoquinoline (17h): Method as for **16b** using compound **15** (349 mg, 1.0 mmol), 3-acetylbenzyl bromide (445 mg, 72 wt%, 1.5 mmol) and DIPEA (260 mg, 2.0 mmol) in DMF (2.0 mL) at 80 °C for 18 h. Flash column chromatography (hexane/EtOAc 9:1 to 9:1 and 2% Et_3N) afforded **17h** as a yellow glass (272 mg, 56%); ^{1}H NMR (270 MHz, $CDCl_3$): δ=1.06 (18H, d, J=6.9 Hz), 1.12 (3H, d, J=6.6 Hz), 1.15–1.32 (3H, m), 2.46 (1H, dd, J=16.0, 6.1 Hz), 2.59 (3H, s), 2.86 (1H, dd, J=15.8, 4.8 Hz), 3.06 (1H, sext, J=6.1 Hz), 3.41–3.65 (3H, m), 3.69 (3H, s), 3.83 (1H, d, J=13.2 Hz), 6.37 (1H, s), 6.56 (1H, s), 7.40 (1H, t, J=7.6 Hz), 7.60 (1H, d, J=7.5 Hz), 7.83 (1H, d, J=7.7 Hz), 7.92 ppm (1H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ=12.9, 15.2, 17.9, 26.8, 34.7, 51.5, 52.3, 55.5, 56.9, 110.0, 120.4, 125.6, 126.3, 127.0, 128.5, 128.7, 133.8, 137.2, 140.2, 143.8, 149.0, 198.4 ppm; HRMS (ES+): m/z found 482.3089, $C_{29}H_{44}NO_3Si^+$ $[M+H]^+$ requires 482.3085.

(±)-2-(2,3-Dimethoxybenzyl)-7-methoxy-3-methyl-6-(triisopropylsilyloxy)-1,2,3,4-tetrahydroisoquinoline (17i): Method as for **16b** using compound **15** (419 mg, 1.2 mmol), 2,3-dimethoxybenzyl chloride (562 mg, 1.5 mmol) and DIPEA (317 mg, 2.45 mmol) in DMF (3.6 mL) at 80 °C for 18 h. Flash column chromatography (hexane/EtOAc 19:1 to 9:1) afforded **17i** as a yellow wax (445 mg, 74%); ^{1}H NMR (270 MHz, $CDCl_3$): δ=1.06 (18H, d, J=6.9 Hz), 1.12 (3H, d, J=6.6 Hz), 1.12–1.30 (3H, m), 2.45 (1H, dd, J=15.8, 6.2 Hz), 2.85 (1H, dd, J=15.7, 4.1 Hz), 2.98–3.14 (1H, m), 3.47–3.91 (4H, m), 3.67–3.71 (3H, m), 3.77–3.81 (3H, m), 3.84–3.88 (3H, m), 6.39 (1H, d, J=6.0 Hz), 6.54 (1H, d, J=6.3 Hz), 6.81 (1H, dd, J=7.4, 1.9 Hz), 7.00 (1H, dd, J=7.7, 2.5 Hz), 7.03–7.10 ppm (1H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ=12.9, 15.1, 17.9, 34.9, 50.7, 51.5, 52.5, 55.5, 55.7, 60.9, 110.1, 110.8, 120.4, 122.4, 123.7, 125.8, 126.9, 133.5, 143.6, 148.9, 152.7 ppm; HRMS (ES+): m/z found 500.3175, $C_{29}H_{46}NO_4Si^+$ $[M+H]^+$ requires 500.3191.

(±)-2-(3,4-Dimethoxybenzyl)-7-methoxy-3-methyl-6-(triisopropylsilyloxy)-1,2,3,4-tetrahydroisoquinoline (17j): Method as for **16b** using compound **15** (419 mg, 1.2 mmol), 3,4-dimethoxybenzyl bromide (336 mg, 1.45 mmol) and DIPEA (312 mg, 2.4 mmol) in DMF (3.6 mL) at 80 °C for 18 h. Flash column chromatography (hexane/EtOAc 9:1 to 9:1 and 2% Et_3N) afforded **17j** as a yellow wax (411 mg, 68%); ^{1}H NMR (270 MHz, $CDCl_3$): δ=1.07 (18H, d, J=6.0 Hz), 1.10 (3H, d, J=6.3 Hz), 1.14–1.32 (3H, m), 2.45 (1H, dd, J=15.8, 5.6 Hz), 2.85 (1H, dd, J=16.0, 4.4 Hz), 2.95–3.11 (1H, m), 3.39–3.79 (4H, m), 3.67–3.71 (3H, m), 3.81–3.88 (6H, m), 6.39 (1H, d, J=5.2 Hz), 6.56 (1H, d, J=5.5 Hz), 6.74–6.89 (2H, m), 6.92 ppm (1H, dd, J=5.2, 1.6 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ=12.8, 14.8, 17.9, 34.7, 51.4, 51.8, 55.4, 55.8, 55.8, 56.8, 110.0, 110.7, 112.0, 120.3, 121.0, 125.7, 126.6, 131.9, 143.7, 147.9, 148.9, 148.9 ppm; HRMS (ES+): m/z found 500.3149, $C_{29}H_{46}NO_4Si^+$ $[M+H]^+$ requires 500.3191.

(±)-2-(2-Chloro-5-methoxybenzyl)-7-methoxy-3-methyl-6-(triisopropylsilyloxy)-1,2,3,4-tetrahydroisoquinoline (17k): Method as for **16b** using compound **15** (418 mg, 1.2 mmol), 2-chloro-5-methoxybenzyl bromide (471 mg, 76 wt%, 1.5 mmol) and DIPEA (311 mg, 2.4 mmol) in DMF (3.6 mL) at 80 °C for 18 h. Flash column chromatography (hexane/EtOAc 19:1 to 9:1) afforded **17k** as a yellow wax (438 mg, 72%); ^{1}H NMR (270 MHz, $CDCl_3$): δ=1.07 (18H, d, J=6.6 Hz), 1.11 (3H, d, J=6.3 Hz), 1.14–1.32 (3H, m), 2.46 (1H, dd, J=16.0, 5.8 Hz), 2.88 (1H, dd, J=16.0, 4.6 Hz), 3.11 (1H, sext, J=6.1 Hz), 3.43–3.84 (4H, m), 3.71 (3H, s), 3.76 (3H, s), 6.41 (1H, s), 6.57 (1H, s), 6.71 (1H, dd, J=8.8, 3.0 Hz), 7.13 (1H, d, J=3.0 Hz), 7.22 ppm (1H, d, J=8.5 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ=12.9, 15.2, 17.9, 34.6, 51.5, 52.6, 53.8, 55.5, 55.5, 110.1, 113.5, 115.8, 120.5, 125.3, 125.7, 126.6, 129.9, 138.3, 143.8, 149.0, 158.4 ppm; HRMS (ES+): m/z found 504.2683, $C_{28}H_{43}ClNO_3Si^+$ $[M+H]^+$ requires 504.2695.

(±)-6-Hydroxy-7-methoxy-2-(2-methoxybenzyl)-3-methyl-1,2,3,4-tetrahydroisoquinoline (5a): Compound **17a** (564 mg, 1.2 mmol) was treated with TBAF (1 M in THF, 1.44 mL, 1.44 mmol) in THF (3.0 mL) at 0 °C for 0.5 h. MeOH (10 mL) was then added, and the reaction mixture was evaporated. CH_2Cl_2 (30 mL) was added, and the reaction mixture was once more evaporated. Flash column chromatography (hexane/EtOAc 4:1 to 1:1) afforded **5a** as a pale-yellow glass (362 mg, 96%); ^{1}H NMR (270 MHz, $CDCl_3$): δ=1.17 (3H, d, J=6.6 Hz), 2.51 (1H, dd, J=16.2, 6.3 Hz), 2.88 (1H, dd, J=16.0, 5.0 Hz), 3.14 (1H, sext, J=6.2 Hz), 3.51–3.87 (4H, m), 3.80 (3H, s), 3.82 (3H, s), 5.12 (1H, s, br), 6.45 (1H, s), 6.63 (1H, s), 6.86 (1H, d, J=8.3 Hz), 6.93 (1H, dt, J=7.4, 0.8 Hz), 7.23 (1H, dt, J=7.8, 1.6 Hz), 7.44 ppm (1H, d, J=7.4 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ=15.7, 34.2, 49.7, 51.4, 52.6, 55.3, 55.9, 108.7, 110.3, 114.5, 120.3, 125.5, 126.6, 127.3, 127.8, 130.2, 143.9, 144.8, 157.7v; LC–MS (ES+): m/z 314.1 $[M+H]^+$; HRMS (ES+): m/z found 314.1751, $C_{19}H_{24}NO_3^+$ $[M+H]^+$ requires 314.1751.

(±)-6-Hydroxy-7-methoxy-2-(3-methoxybenzyl)-3-methyl-1,2,3,4-tetrahydroisoquinoline (5b): Pd/C (10%, 33 mg) was covered with EtOH (6 mL) and compound **16a** (330 mg, 0.82 mmol) was added as solution in THF (6 mL). The reaction mixture was degassed then placed under H_2 at room temperature for 0.75 h before filtering through Celite. The filtrate was evaporated and purified by flash column chromatography (hexane/EtOAc 2:1) to give an oil which crystallised from hexane to afford **5b** as a pale-yellow solid (118 mg, 46%); mp: 100–105 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ=1.12 (3H, d, J=6.7 Hz), 2.49 (1H, dd, J=16.1, 5.8 Hz), 2.89 (1H, dd, J=16.1, 4.8 Hz), 3.01–3.12 (1H, m), 3.48–3.74 (4H, m), 3.78 (3H, s), 3.79 (3H, s), 5.42 (1H, s), 6.42 (1H, s), 6.63 (1H, s), 6.77–6.81 (1H, m), 6.93–6.96 (2H, m), 7.21 ppm (1H, d, J=8.2 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ=15.4, 34.7, 51.4, 52.3, 55.3, 56.0, 57.1, 108.7, 112.5, 114.4, 114.5, 121.4, 125.5, 126.6, 129.3, 141.2, 144.0, 144.9, 159.8 ppm; LC–MS (ES+): m/z 314.18 $[M+H]^+$; HRMS (ES+): m/z found 314.1748, $C_{19}H_{24}NO_3^+$ $[M+H]^+$ requires 314.1751.

(±)-3-Ethyl-6-hydroxy-7-methoxy-2-(3-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (5c): Method as for **5b** using compound **16b** (292 mg, 0.7 mmol) and Pd/C (10%, 30 mg) in THF (6.0 mL) and EtOH (2.0 mL) at room temperature for 2 h. Flash column chromatography (hexane to hexane/EtOAc 3:2) afforded **5c** as a yellow oil (211 mg, 92%); ^{1}H NMR (270 MHz, $CDCl_3$): δ=0.98 (3H, t, J=7.2 Hz), 1.42 (1H, sept, J=7.1 Hz), 1.69 (1H, sept, J=6.8 Hz), 2.52 (1H, dd, J=16.4, 6.3 Hz), 2.80 (1H, dd, J=16.4, 5.1 Hz), 2.86–2.90 (1H, m), 3.58–3.73 (4H, m), 3.80 (6H, s), 6.42 (1H, s), 6.64 (1H, s), 6.79 (1H, dd, J=8.0, 2.2 Hz), 6.92–6.98 (2H, m), 7.22 ppm (1H, t, J=7.8 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ=11.1, 23.0, 29.5, 50.9, 55.0, 55.1, 55.9, 58.5, 108.8, 112.3, 114.1, 114.6, 121.1, 125.3, 126.7, 129.1, 141.5, 143.9, 144.9, 159.6 ppm; LC–MS (ES+): m/z 328.1 $[M+H]^+$.

(±)-6-Hydroxy-7-methoxy-2-(4-methoxybenzyl)-3-methyl-1,2,3,4-tetrahydroisoquinoline (5d): Method as for **5a** using compound

17b (519 mg, 1.1 mmol) and TBAF (1 M in THF, 1.35 mL, 1.35 mmol) in THF (5.0 mL) at 0 °C for 0.5 h. Flash column chromatography (hexane/EtOAc 4:1 to 1:1) afforded **5d** as a pale-yellow solid (305 mg, 88%); mp: 136–139 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.13 (3H, d, *J* 6.6 Hz), 2.48 (1H, dd, *J* = 16.2, 6.1 Hz), 2.87 (1H, dd, *J* = 16.1, 5.1 Hz), 3.05 (1H, sext, *J* = 6.1 Hz), 3.41–3.80 (4H, m), 3.78 (3H, s), 3.79 (3H, s), 5.37 (1H, s, br), 6.41 (1H, s), 6.61 (1H, s), 6.84 (2H, d, *J* = 8.5 Hz), 7.26 ppm (2H, d, *J* = 8.8 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 15.3, 34.6, 51.2, 52.1, 55.2, 55.9, 56.3, 108.6, 113.6, 114.4, 125.3, 126.5, 130.1, 131.2, 143.9, 144.8, 158.6 ppm; LC–MS (ES+): *m/z* 314.1 $[M+H]^+$; HRMS (ES+): *m/z* found 314.1753, $C_{19}H_{24}NO_3^+$ $[M+H]^+$ requires 314.1751.

(±)-2-Benzyl-6-hydroxy-7-methoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (5e): Method as for **5a** using compound **17c** (310 mg, 0.7 mmol) and TBAF (1 M in THF, 0.84 mL, 0.84 mmol) in THF (3.5 mL) at 0 °C for 0.5 h. Flash column chromatography ($CHCl_3$/acetone 9:1 to 9:1 and 2% MeOH) afforded **5e** as a pale-yellow solid (161 mg, 81%); mp: 131–134 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.15 (3H, d, *J* = 6.3 Hz), 2.50 (1H, dd, *J* = 16.2, 6.0 Hz), 2.89 (1H, dd, *J* = 16.2, 5.0 Hz), 3.08 (1H, sext, *J* = 6.1 Hz), 3.44–3.93 (4H, m), 3.78 (3H, s), 5.27 (1H, s, br), 6.42 (1H, s), 6.63 (1H, s), 7.19–7.41 ppm (5H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 15.4, 34.6, 51.3, 52.3, 55.9, 57.0, 108.6, 114.4, 125.4, 126.5, 126.9, 128.2, 128.9, 139.4, 143.9, 144.8 ppm; LC–MS (ES+): *m/z* 284.1 $[M+H]^+$; HRMS (ES+): *m/z* found 284.1633, $C_{18}H_{22}NO_2^+$ $[M+H]^+$ requires 284.1645.

(±)-2-(2-Chlorobenzyl)-6-hydroxy-7-methoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (5f): Method as for **5a** using compound **17d** (260 mg, 0.55 mmol) and TBAF (1 M in THF, 0.66 mL, 0.66 mmol) in THF (3.0 mL) at 0 °C for 0.5 h. Flash column chromatography ($CHCl_3$/acetone 9:1 to 9:1 and 2% MeOH) afforded **5f** as a yellow glass (149 mg, 85%); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.16 (3H, d, *J* = 6.3 Hz), 2.51 (1H, dd, *J* = 16.3, 5.8 Hz), 2.92 (1H, dd, *J* = 16.2, 5.0 Hz), 3.14 (1H, sext, *J* = 6.1 Hz), 3.48–3.92 (4H, m), 3.79 (3H, s), 6.44 (1H, s), 6.63 (1H, s), 7.16 (1H, dt, *J* = 7.4, 1.9 Hz), 7.22 (1H, dt, *J* = 7.5, 1.6 Hz), 7.34 (1H, dd, *J* = 7.3, 1.8 Hz), 7.55 ppm (1H, dd, *J* = 7.4, 1.9 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 15.3, 34.5, 51.2, 52.7, 53.6, 55.9, 108.6, 114.5, 125.3, 126.4, 126.6, 127.9, 129.3, 130.6, 134.0, 137.0, 143.9, 144.8 ppm; LC–MS (ES+): *m/z* 318.2 $[M+H]^+$; HRMS (ES+): *m/z* found 318.1247, $C_{18}H_{21}ClNO_2^+$ $[M+H]^+$ requires 318.1256.

(±)-6-Hydroxy-7-methoxy-3-methyl-2-(2-methylbenzyl)-1,2,3,4-tetrahydroisoquinoline (5g): Method as for **5a** using compound **17e** (249 mg, 0.55 mmol) and TBAF (1 M in THF, 0.66 mL, 0.66 mmol) in THF (4.0 mL) at 0 °C for 0.5 h. Flash column chromatography ($CHCl_3$/acetone 9:1 to 9:1 and 2% MeOH) afforded **5g** as a yellow glass (138 mg, 84%); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.15 (3H, d, *J* = 6.3 Hz), 2.37 (3H, s), 2.50 (1H, dd, *J* = 16.3, 5.8 Hz), 2.90 (1H, dd, *J* = 16.2, 5.0 Hz), 3.09 (1H, sext, *J* = 6.1 Hz), 3.46–3.65 (3H, m), 3.78 (1H, d, *J* = 12.9 Hz), 3.79 (3H, s), 6.43 (1H, s), 6.64 (1H, s), 7.09–7.22 (3H, m), 7.28–7.35 ppm (1H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 14.8, 19.2, 34.7, 50.9, 52.5, 55.1, 55.9, 108.6, 114.4, 125.4, 125.6, 126.5, 126.8, 129.7, 130.3, 137.2, 137.5, 143.8, 144.7 ppm; LC–MS (ES+): *m/z* 298.2 $[M+H]^+$; HRMS (ES+): *m/z* found 298.1809, $C_{19}H_{24}NO_2^+$ $[M+H]^+$ requires 298.1802.

(±)-2-(3-Ethylbenzyl)-6-hydroxy-7-methoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (5h): Method as for **5b** using compound **16c** (240 mg, 0.6 mmol) and Pd/C (10%, 31 mg) in THF (24 mL) and EtOH (8 mL) at room temperature for 1 h. Flash column chromatography (hexane to hexane/EtOAc 1:1 to 1:1 and 1% MeOH) afforded **5h** as a pale-yellow solid (112 mg, 60%); mp: 105–107 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.16 (3H, d, *J* = 6.6 Hz), 1.24 (3H, t, *J* = 7.6 Hz), 2.51 (1H, dd, *J* = 16.1, 6.2 Hz), 2.64 (2H, q, *J* = 7.5 Hz), 2.90 (1H, dd, *J* = 16.2, 5.0 Hz), 3.09 (1H, sext, *J* = 6.1 Hz), 3.49–3.67 (3H, m), 3.75–3.83 (1H, m), 3.79 (3H, s), 6.43 (1H, s), 6.63 (1H, s, br), 7.07–7.14 (1H, m), 7.15–7.29 ppm (3H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 15.3, 15.6, 28.8, 34.5, 51.3, 52.2, 55.9, 56.9, 108.6, 114.4, 125.3, 126.3, 126.4, 128.2, 128.5, 139.1, 143.9, 144.3, 144.8 ppm; LC–MS (ES+): *m/z* 312.4 $[M+H]^+$.

(±)-2-(3-Ethoxybenzyl)-6-hydroxy-7-methoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (5i): Method as for **5b** using compound **16d** (314 mg, 0.75 mmol) and Pd/C (10%, 28 mg) in THF (24 mL) and EtOH (8 mL) at room temperature for 2 h. Flash column chromatography ($CHCl_3$/acetone 9:1 to 9:1 and 2% MeOH) afforded **5i** as a pale-yellow solid (142 mg, 57%); mp: 98–103 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.15 (3H, d, *J* = 6.6 Hz), 1.40 (3H, t, *J* = 6.9 Hz), 2.49 (1H, dd, *J* = 16.1, 5.9 Hz), 2.89 (1H, dd, *J* = 16.1, 4.8 Hz), 3.08 (1H, sext, *J* = 6.1 Hz), 3.43–3.69 (3H, m), 3.78 (3H, s), 3.79 (1H, d, *J* = 13.2 Hz), 4.02 (2H, q, *J* = 7.0 Hz), 5.33 (1H, s, br), 6.43 (1H, s), 6.62 (1H, s), 6.80 (1H, dd, *J* = 8.3, 2.5 Hz), 6.95 (1H, d, *J* = 7.7 Hz), 6.97 (1H, s), 7.22 ppm (1H, t, *J* = 7.7 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 14.8, 15.3, 34.5, 51.3, 52.2, 55.8, 56.9, 63.3, 108.6, 113.0, 114.5, 114.9, 121.1, 125.1, 126.3, 129.1, 140.8, 144.0, 144.9, 159.0 ppm; LC–MS (ES+): *m/z* 328.2 $[M+H]^+$; HRMS (ES+): *m/z* found 328.1892, $C_{20}H_{26}NO_3^+$ $[M+H]^+$ requires 328.1907.

(±)-6-Hydroxy-7-methoxy-3-methyl-2-(3-nitrobenzyl)-1,2,3,4-tetrahydroisoquinoline (5j): Method as for **5a** using compound **17f** (388 mg, 0.8 mmol) and TBAF (1 M in THF, 0.96 mL, 0.96 mmol) in THF (4.0 mL) at 0 °C for 0.5 h. Flash column chromatography ($CHCl_3$/acetone 49:1 to 49:1 and 2% MeOH) afforded **5j** as a pale-yellow solid (236 mg, 89%); mp: 134–137 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.14 (3H, d, *J* = 6.3 Hz), 2.50 (1H, dd, *J* = 16.0, 6.0 Hz), 2.90 (1H, dd, *J* = 16.2, 5.0 Hz), 3.09 (1H, sext, *J* = 6.1 Hz), 3.47–3.89 (4H, m), 3.78 (3H, s), 6.40 (1H, s), 6.63 (1H, s), 7.46 (1H, t, *J* = 7.8 Hz), 7.72 (1H, d, *J* = 7.4 Hz), 8.09 (1H, dd, *J* = 8.2, 1.1 Hz), 8.22 ppm (1H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 15.5, 34.4, 51.3, 52.6, 55.9, 56.2, 108.6, 114.5, 122.0, 123.5, 124.8, 126.3, 129.1, 134.9, 142.1, 144.1, 144.9, 148.3 ppm; LC–MS (ES+): *m/z* 329.2 $[M+H]^+$; HRMS (ES+): *m/z* found 329.1482, $C_{18}H_{21}N_2O_4^+$ $[M+H]^+$ requires 329.1496.

(±)-2-(3-Chlorobenzyl)-6-hydroxy-7-methoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (5k): Method as for **5a** using compound **17g** (285 mg, 0.6 mmol) and TBAF (1 M in THF, 0.72 mL, 0.72 mmol) in THF (3.0 mL) at 0 °C for 0.5 h. Flash column chromatography ($CHCl_3$/acetone 49:1 to 49:1 and 2% MeOH) afforded **5k** as a yellow glass (156 mg, 81%); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.07 (3H, dd, *J* = 12.1, 6.0 Hz), 2.52 (1H, dd, *J* = 16.0, 5.5 Hz), 2.91 (1H, dd, *J* = 16.1, 4.8 Hz), 3.09 (1H, sext, *J* = 5.8 Hz), 3.44–3.80 (4H, m), 3.79–3.84 (3H, m), 5.45 (1H, s, br), 6.45 (1H, t, *J* = 5.5 Hz), 6.65 (1H, t, *J* = 5.4 Hz), 7.16–7.31 (3H, m), 7.40 ppm (1H, d, *J* = 5.5 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 15.4, 34.5, 51.3, 52.4, 55.9, 56.5, 108.6, 114.5, 125.2, 126.4, 126.9, 127.0, 128.8, 129.5, 134.1, 141.8, 144.0, 144.9 ppm; LC–MS (ES+): *m/z* 318.2 $[M+H]^+$; HRMS (ES+): *m/z* found 318.1249, $C_{18}H_{21}ClNO_2^+$ $[M+H]^+$ requires 318.1256.

(±)-2-(3-Acetylbenzyl)-6-hydroxy-7-methoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (5l): Method as for **5a** using compound **17h** (264 mg, 0.55 mmol) and TBAF (1 M in THF, 0.66 mL, 0.66 mmol) in THF (2.5 mL) at 0 °C for 0.5 h. Flash column chromatography ($CHCl_3$/acetone 9:1 to 9:1 and 2% MeOH) afforded **5l** as a yellow glass (154 mg, 86%); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.14 (3H, d, *J* = 6.6 Hz), 2.48 (1H, dd, *J* = 16.1, 5.9 Hz), 2.58 (3H, s), 2.88 (1H, dd, *J* = 16.2, 5.0 Hz), 3.07 (1H, sext, *J* = 6.1 Hz), 3.45–3.65 (3H, m), 3.76 (3H, s), 3.83 (1H, d, *J* = 13.2 Hz), 6.39 (1H, s), 6.61 (1H, s),

7.40 (1H, t, J=7.7 Hz), 7.60 (1H, d, J=7.4 Hz), 7.83 (1H, dt, J=7.7, 1.4 Hz), 7.93 ppm (1H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ=15.3, 26.7, 34.5, 51.2, 52.4, 55.8, 56.6, 108.6, 114.5, 125.0, 126.3, 127.0, 128.5, 128.7, 133.7, 137.1, 140.0, 144.0, 144.9, 198.4 ppm; LC–MS (ES+): m/z 326.1 $[M+H]^+$; HRMS (ES+): m/z found 326.1742, $C_{20}H_{24}NO_3^+$ $[M+H]^+$ requires 326.1751.

(±)-2-(2,3-Dimethoxybenzyl)-6-hydroxy-7-methoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (5m): Method as for **5a** using compound **17i** (400 mg, 0.8 mmol) and TBAF (1 M in THF, 0.96 mL, 0.96 mmol) in THF (4.0 mL) at 0 °C for 0.5 h. Flash column chromatography ($CHCl_3$/acetone 9:1 to 9:1 and 2% MeOH) afforded **5m** as a yellow glass (204 mg, 74%); ^{1}H NMR (270 MHz, $CDCl_3$): δ=1.14 (3H, d, J=6.6 Hz), 2.48 (1H, dd, J=16.1, 5.9 Hz), 2.89 (1H, dd, J=16.0, 5.0 Hz), 3.09 (1H, sext, J=6.1 Hz), 3.49–3.90 (4H, m), 3.77 (3H, s), 3.81 (3H, s), 3.85 (3H, s), 4.97 (1H, s, br), 6.43 (1H, s), 6.61 (1H, s), 6.82 (1H, dd, J=7.7, 1.9 Hz), 7.01 (1H, t, J=7.7 Hz), 7.07 ppm (1H, dd, J=7.7, 1.9 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ=15.0, 34.9, 50.8, 51.3, 52.4, 55.6, 55.8, 60.4, 108.6, 110.8, 114.4, 122.4, 123.7, 125.7, 126.5, 133.3, 143.8, 144.8, 147.7, 152.7 ppm; LC–MS (ES+): m/z 344.2 $[M+H]^+$; HRMS (ES+): m/z found 344.1851, $C_{20}H_{26}NO_4^+$ $[M+H]^+$ requires 344.1857.

(±)-2-(3,4-Dimethoxybenzyl)-6-hydroxy-7-methoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (5n): Method as for **5a** using compound **17j** (351 mg, 0.7 mmol) and TBAF (1 M in THF, 0.84 mL, 0.84 mmol) in THF (3.5 mL) at 0 °C for 0.5 h. Flash column chromatography ($CHCl_3$/acetone 9:1 to 9:1 and 2% MeOH) afforded **5n** as a pale-yellow solid (218 mg, 90%); mp 98–104 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ=1.12 (3H, d, J=6.4 Hz), 2.46 (1H, dd, J=16.1, 5.9 Hz), 2.86 (1H, dd, J=16.2, 5.0 Hz), 3.06 (1H, sext, J=6.1 Hz), 3.41–3.75 (4H, m), 3.77 (3H, s), 3.84 (3H, s), 3.86 (3H, s), 5.36 (1H, s, br), 6.41 (1H, s), 6.58 (1H, s), 6.79 (1H, d, J=8.3 Hz), 6.86 (1H, dd, J=8.3, 1.6 Hz), 6.95 ppm (1H, d, J=1.7 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ=15.1, 34.5, 51.1, 52.0, 55.8, 55.8, 56.7, 108.6, 110.7, 111.9, 114.5, 121.0, 125.3, 126.4, 131.7, 143.9, 144.9, 147.9, 148.9 ppm; LC–MS (ES+): m/z 344.3 $[M+H]^+$; HRMS (ES+): m/z found 344.1841, $C_{20}H_{26}NO_4^+$ $[M+H]^+$ requires 344.1857.

(±)-2-(3,5-Dimethoxybenzyl)-6-hydroxy-7-methoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (5o): Method as for **5b** using compound **16e** (148 mg, 0.34 mmol) and Pd/C (10%, 30 mg) in THF (3.0 mL) and EtOH (3.0 mL) at room temperature for 18 h. The resulting solid was crystallised from EtOAc/hexane to afford **5o** as a pale-yellow powder (81 mg, 69%); mp 155–158 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ=1.12 (3H, d, J=6.4 Hz), 2.48 (1H, dd, J=16.1, 5.8 Hz), 2.88 (1H, dd, J=16.1, 4.7 Hz), 3.01–3.12 (1H, m), 3.47–3.78 (4H, m), 3.78 (6H, s), 3.79 (3H, s), 5.52 (1H, s, br), 6.35 (1H, t, J=2.3 Hz), 6.43 (1H, s), 6.55 (2H, d, J=2.3 Hz), 6.62 ppm (1H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ=15.2, 34.6, 51.4, 52.1, 55.3, 55.9, 57.2, 98.9, 106.6, 108.6, 114.4, 125.5, 126.5, 142.1, 143.9, 144.8, 160.7 ppm; LC–MS (ES+): m/z 344.16 $[M+H]^+$; HRMS (ES+): m/z found 344.1856, $C_{20}H_{26}NO_4^+$ $[M+H]^+$ requires 344.1857.

(±)-2-(2,5-Dimethoxybenzyl)-6-hydroxy-7-methoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (5p): Method as for **5b** using compound **16f** (346 mg, 0.8 mmol) and Pd/C (10%, 31 mg) in THF (24 mL) and EtOH (8 mL) at room temperature for 2 h. Flash column chromatography (EtOAc/MeOH 99:1) afforded **5p** as a pale-yellow solid (230 mg, 83%). A small sample (24 mg) was further purified by preparative HPLC (RP_{18}, MeCN/H_2O 9:1); ^{1}H NMR (270 MHz, $CDCl_3$): δ=1.14 (3H, d, J=6.3 Hz), 2.49 (1H, dd, J=16.1, 6.2 Hz), 2.87 (1H, dd, J=16.1, 4.8 Hz), 3.11 (1H, sext, J=6.2 Hz), 3.56–3.71 (4H, m), 3.74 (3H, s), 3.76 (3H, s), 3.78 (3H, s), 5.56 (1H, s, br), 6.44 (1H, s), 6.61 (1H, s), 6.73 (1H, dd, J=8.8, 2.7 Hz), 6.79 (1H, d, J=8.8 Hz), 7.07 ppm (1H, d, J=2.8 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ=15.5, 34.3, 50.0, 51.5, 52.5, 55.7, 55.9, 56.0, 108.7, 111.4, 112.0, 114.5, 116.0, 125.6, 126.6, 128.9, 143.8, 144.8, 152.0, 153.6 ppm; LC–MS (ES+): m/z 344.5 $[M+H]^+$.

(±)-2-(2-Fluoro-5-methoxybenzyl)-6-hydroxy-7-methoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (5q): Method as for **5b** using compound **16g** (337 mg, 0.8 mmol) and Pd/C (10%, 30 mg) in THF (24 mL) and EtOH (8 mL) at room temperature for 2 h. Flash column chromatography ($CHCl_3$/acetone 19:1 to 9:1) afforded **5q** as a pale-yellow solid (221 mg, 83%). A small sample (22 mg) was further purified by preparative HPLC (RP_{18}, MeCN/H_2O 9:1); ^{1}H NMR (270 MHz, $CDCl_3$): δ=1.13 (3H, d, J=6.3 Hz), 2.49 (1H, dd, J=16.1, 5.9 Hz), 2.88 (1H, dd, J=16.1, 4.8 Hz), 3.09 (1H, sext, J=6.1 Hz), 3.52–3.66 (3H, m), 3.67–3.81 (1H, m), 3.75 (3H, s), 3.79 (3H, s), 6.44 (1H, s), 6.62 (1H, s), 6.72 (1H, dt, J=8.8, 3.6 Hz), 6.93 (1H, t, J=9.1 Hz), 7.01 ppm (1H, dd, J=5.6, 3.3 Hz); LC–MS (ES+): m/z 332.4 $[M+H]^+$.

(±)-2-(2-Chloro-5-methoxybenzyl)-6-hydroxy-7-methoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (5r): Method as for **5a** using compound **17k** (404 mg, 0.8 mmol) and TBAF (1 M in THF, 0.96 mL, 0.96 mmol) in THF (4.0 mL) at 0 °C for 0.5 h. Flash column chromatography ($CHCl_3$/acetone 49:1 to 49:1 and 2% MeOH) afforded **5r** as a pale-yellow solid (249 mg, 89%); mp: 95–97 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ=1.14 (3H, d, J=6.6 Hz), 2.49 (1H, dd, J=16.3, 5.8 Hz), 2.91 (1H, dd, J=16.2, 5.0 Hz), 3.13 (1H, sext, J=6.1 Hz), 3.48–3.91 (4H, m), 3.76 (3H, s), 3.79 (3H, s), 6.44 (1H, s), 6.63 (1H, s), 6.72 (1H, dd, J=8.8, 3.0 Hz), 7.15 (1H, d, J=3.0 Hz), 7.22 ppm (1H, d, J=8.8 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ=15.2, 34.5, 51.3, 52.6, 53.7, 55.4, 55.9, 108.6, 113.5, 114.5, 115.7, 125.3, 125.4, 126.4, 129.8, 138.2, 144.0, 144.9, 158.3 ppm; LC–MS (ES+): m/z 348.2 $[M+H]^+$; HRMS (ES+): m/z found 348.1347, $C_{19}H_{23}ClNO_3^+$ $[M+H]^+$ requires 348.1361.

(±)-6-Hydroxy-7-methoxy-3-methyl-2-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (5s): Method as for **5a** using compound **16h** (151 mg, 0.33 mmol) and Pd/C (10%, 20 mg) in THF (3 mL) and EtOH (3 mL) at room temperature for 5 h. Flash column chromatography (hexane/CH_2Cl_2 1:1 to CH_2Cl_2 to EtOAc to EtOAc/MeOH 4:1) afforded **5s** as a yellow solid (80 mg, 66%); mp: 127–132 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ=1.13 (3H, d, J=6.2 Hz), 2.49 (1H, dd, J=16.0, 5.8 Hz), 2.90 (1H, dd, J=16.0, 4.9 Hz), 3.08–3.11 (1H, m), 3.47–3.80 (4H, m), 3.80 (3H, s), 3.83 (3H, s), 3.84 (6H, s), 5.52 (1H, s, br), 6.45 (1H, s), 6.61 (2H, s), 6.64 ppm (1H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ=15.2, 34.6, 51.4, 52.1, 56.0, 56.2, 57.3, 60.9, 105.6, 108.8, 114.6, 125.6, 126.6, 135.4, 136.7, 144.1, 145.0, 155.2 ppm; LC–MS (ES−): m/z 372.32 $[M-H]^-$; HRMS (ES+): m/z found 374.1964, $C_{21}H_{28}NO_5^+$ $[M+H]^+$ requires 374.1962.

(±)-3-Ethyl-6-hydroxy-7-methoxy-2-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (5t): Method as for **5b** using compound **16i** (334 mg, 0.7 mmol) and Pd/C (10%, 31 mg) in THF (6 mL) and EtOH (2 mL) at room temperature for 18 h. Crystallisation from Et_2O/CH_2Cl_2 afforded **5t** as yellow solid (253 mg, 93%); mp: 142–145 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ=0.98 (3H, t, J=7.4 Hz), 1.42 (1H, sept, J=7.0 Hz), 1.68 (1H, s, br), 2.51 (1H, dd, J=16.4, 5.9 Hz), 2.75–2.84 (2H, m), 3.51–3.75 (4H, m), 3.80 (3H, s), 3.83 (9H, s), 6.44 (1H, s), 6.60 (2H, s), 6.65 ppm (1H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ=11.1, 23.0, 29.4, 50.8, 55.2, 55.9, 56.0, 58.3, 60.9, 105.3, 108.8, 114.6, 125.4, 126.7, 135.6, 136.5, 143.9, 144.9, 153.1 ppm; LC–MS (ES+): m/z 388.1 $[M+H]^+$.

(±)-7-Methoxy-2-(2-methoxybenzyl)-3-methyl-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (6a): Sulfamoyl chloride (0.5 M in toluene, 4.2 mL, 2.1 mmol) was concentrated in vacuo and cooled

to 0 °C until it solidified. DMA (3.0 mL) was added, and the resulting solution was added directly to **5a** (220 mg, 0.7 mmol) at 0 °C under nitrogen. The reaction mixture was stirred at room temperature for 4 h. $NaHCO_3$ (saturated, 50 mL) was added, and the mixture was extracted with EtOAc (100 mL). The organic layer was washed repeatedly with H_2O (50 mL, up to ten times), then brine, then dried ($MgSO_4$) and evaporated. Crystallisation from Et_2O/CH_2Cl_2 (~9:1) afforded **6a** as a yellow solid (192 mg, 69%); mp: 124–129 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.01–1.17 and 1.34–1.58 (3H, 2m), 1.90–2.07 and 2.34–2.52 (1H, 2m), 2.66–3.30 (3H, m), 3.64, 3.66, 3.68 and 3.71 (6H, 4s), 4.07–4.73 (1H, m), 6.44 and 6.48 (1H, 2s), 6.71–6.91 (2H, m), 6.94 and 6.97 (1H, 2s), 7.03–7.21 (1H, m), 7.22–7.41 ppm (1H, m); LC–MS (ES+): *m/z* 393.2 $[M+H]^+$; HRMS (ES+): *m/z* found 393.1498, $C_{19}H_{25}N_2O_5S^+$ $[M+H]^+$ requires 393.1479.

(±)-7-Methoxy-2-(3-methoxybenzyl)-3-methyl-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (6b): Method as for **6a** using compound **5b** (88 mg, 0.28 mmol) and sulfamoyl chloride (1.4 mmol) in DMA (1.0 mL) at room temperature for 16 h. Flash column chromatography (hexane to EtOAc) afforded **6b** as a pale-yellow solid (56 mg, 51%); mp: 154–156 °C; ^{1}H NMR (270 MHz, [D$_6$]DMSO): δ = 1.06 (3H, d, *J* = 6.5 Hz), 2.44–2.51 (1H, m), 2.89 (1H, dd, *J* = 16.0, 4.6 Hz), 3.01–3.07 (1H, m), 3.46–3.60 (4H, m), 3.70 (3H, s), 3.73 (3H, s), 6.79 (1H, s), 6.82 (1H, dd, *J* = 7.2, 2.0 Hz), 6.89–6.94 (2H, m), 7.02 (1H, s), 7.24 (1H, t, *J* = 8.0 Hz), 7.85 ppm (2H, s, br); ^{13}C NMR (67.5 MHz, [D$_6$]DMSO): δ = 15.0, 39.8, 52.1, 55.5, 56.3, 57.3, 111.5, 112.7, 114.4, 121.2, 123.6, 125.9, 129.8, 133.6, 137.6, 141.7, 150.1, 159.9 ppm; LC–MS (ES+): *m/z* 393.10 $[M+H]^+$.

(±)-3-Ethyl-7-methoxy-2-(3-methoxybenzyl)-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (6c): Method as for **6a** using compound **5c** (164 mg, 0.5 mmol) and sulfamoyl chloride (1.5 mmol) in DMA (2.0 mL) at room temperature for 2 h. Flash column chromatography (hexane to hexane/EtOAc 1:1) gave an oil which was dissolved in CH_2Cl_2 (5 mL) and Et_2O (25 mL) then rapidly evaporated to afford **6c** as a yellow foam (106 mg, 52%); ^{1}H NMR (270 MHz, [D$_6$]DMSO): δ = 0.93 (3H, t, *J* = 7.2 Hz), 1.26–1.39 (1H, sept, *J* = 7.0 Hz), 1.56–1.68 (1H, sept, *J* = 6.8 Hz), 2.47–2.58 (1H, m), 2.74–2.88 (2H, m), 3.51–3.68 (4H, m), 3.62 (3H, s), 3.70 (3H, s), 3.72 (3H, s), 6.78 (1H, s), 6.78–6.83 (1H, m), 6.87–6.93 (2H, m), 7.03 (1H, s), 7.23 (1H, t, *J* = 8.0 Hz), 7.85 ppm (2H, s); ^{13}C NMR (67.5 MHz, [D$_6$]DMSO): δ = 11.1, 22.3, 29.2, 50.6, 55.1, 55.1, 56.0, 57.9, 111.4, 112.4, 114.0, 120.8, 123.5, 125.7, 129.5, 133.1, 137.2, 141.5, 149.9, 159.5 ppm; LC–MS (ES+): *m/z* 405.0 $[M+H]^+$.

(±)-7-Methoxy-2-(4-methoxybenzyl)-3-methyl-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (6d): Method as for **6a** using compound **5d** (220 mg, 0.7 mmol) and sulfamoyl chloride (2.1 mmol) in DMA (3.0 mL) at room temperature for 2 h. Crystallisation from Et_2O/CH_2Cl_2 (~9:1) afforded **6d** as a yellow solid (195 mg, 70%); mp: 115–119 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.01 (3H, d, *J* = 6.3 Hz), 2.40 (1H, dd, *J* = 16.0, 5.2 Hz), 2.80 (1H, dd, *J* = 16.2, 4.4 Hz), 2.83–3.06 (1H, m), 3.24–3.50 (3H, m), 3.50–3.63 (1H, m), 3.65 and 3.67 (3H, 2s), 6.43 (1H, s, br), 6.72 (2H, d, *J* 8.5 Hz), 6.94 (1H, s, br), 7.14 ppm (2H, d, *J* = 8.3 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 14.7, 34.2, 50.8, 51.7, 55.0, 55.8, 56.2, 110.4, 113.4, 123.8, 126.0, 129.7, 130.5, 133.3, 137.2, 149.5, 158.4 ppm; LC–MS (ES+): *m/z* 393.2 $[M+H]^+$; HRMS (ES+): *m/z* found 393.1503, $C_{19}H_{25}N_2O_5S^+$ $[M+H]^+$ requires 393.1479.

(±)-2-Benzyl-7-methoxy-3-methyl-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (6e): Method as for **6a** using compound **5e** (114 mg, 0.4 mmol) and sulfamoyl chloride (1.2 mmol) in DMA (3.0 mL) at room temperature for 2 h. Crystallisation from CH_2Cl_2 afforded **6e** as a pale-yellow solid (81 mg, 56%); mp: 155–157 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.07 (3H, d, *J* = 6.6 Hz), 2.47 (1H, dd, *J* = 16.3, 5.8 Hz), 2.87 (1H, dd, *J* = 16.1, 4.8 Hz), 3.03 (1H, sext, *J* = 6.1 Hz), 3.42–3.87 (4H, m), 3.71 (3H, s), 6.19 (2H, s, br), 6.48 (1H, s), 7.00 (1H, s), 7.13–7.36 ppm (5H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 14.9, 34.2, 51.0, 51.9, 55.9, 56.9, 110.5, 123.9, 126.2, 126.9, 128.1, 128.7, 133.3, 137.3, 149.5 ppm; LC–MS (ES+): *m/z* 363.2 $[M+H]^+$; HRMS (ES+): *m/z* found 363.1362, $C_{18}H_{23}N_2O_4S^+$ $[M+H]^+$ requires 363.1373.

(±)-2-(2-Chlorobenzyl)-7-methoxy-3-methyl-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (6f): Method as for **6a** using compound **5f** (127 mg, 0.4 mmol) and sulfamoyl chloride (1.2 mmol) in DMA (2.0 mL) at room temperature for 6 h. Crystallisation from CH_2Cl_2 afforded **6f** as a pale-yellow solid (58 mg, 36%); mp: 151–153 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.05 (3H, d, *J* = 6.3 Hz), 2.44 (1H, dd, *J* = 16.1, 5.4 Hz), 2.85 (1H, dd, *J* = 16.2, 4.7 Hz), 3.05 (1H, sext, *J* = 5.8 Hz), 3.46–3.83 (4H, m), 3.68 (3H, s), 6.45 (2H, s, br), 6.48 (1H, s), 6.97 (1H, s), 7.04–7.18 (2H, m), 7.23 (1H, dd, *J* = 7.7, 1.6 Hz), 7.40 ppm (1H, dd, *J* = 7.2, 1.9 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 14.8, 34.1, 50.9, 52.2, 53.6, 55.8, 110.4, 123.9, 126.1, 126.4, 127.9, 129.1, 130.3, 133.3, 133.8, 136.4, 137.2, 149.5 ppm; LC–MS (ES+): *m/z* 397.1 $[M+H]^+$; HRMS (ES+): *m/z* found 397.0974, $C_{18}H_{22}ClN_2O_4S^+$ $[M+H]^+$ requires 397.0984.

(±)-7-Methoxy-3-methyl-2-(2-methylbenzyl)-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (6g): Method as for **6a** using compound **5g** (119 mg, 0.4 mmol) and sulfamoyl chloride (1.2 mmol) in DMA (2.0 mL) at room temperature for 6 h. Crystallisation from CH_2Cl_2 afforded **6g** as a pale-yellow solid (34 mg, 22%); mp: 139–144 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.14 (3H, d, *J* = 6.6 Hz), 2.49 (1H, dd, *J* = 16.3, 5.8 Hz), 2.91 (1H, dd, *J* = 16.2, 5.0 Hz), 3.13 (1H, sext, *J* = 6.1 Hz), 3.48–3.91 (4H, m), 3.76 (3H, s), 3.79 (3H, s), 6.40 (1H, s), 6.72 (1H, dd, *J* = 8.8, 3.0 Hz), 6.84 (2H, s, br), 7.04 (1H, s), 7.15 (1H, d, *J* = 3.0 Hz), 7.22 ppm (1H, d, *J* = 8.8 Hz); LC–MS (ES+): *m/z* 377.3 $[M+H]^+$; HRMS (ES+): *m/z* found 377.1517, $C_{19}H_{25}N_2O_4S^+$ $[M+H]^+$ requires 377.1530.

(±)-2-(3-Ethylbenzyl)-7-methoxy-3-methyl-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (6h): Method as for **6a** using compound **5h** (93 mg, 0.3 mmol) and sulfamoyl chloride (0.9 mmol) in DMA (2.0 mL) at room temperature for 18 h. Flash column chromatography (hexane to hexane/EtOAc 1:1) followed by crystallisation from Et_2O afforded **6h** as a pale-yellow solid (66 mg, 56%); mp: 145–147 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.07 (3H, d, *J* = 6.6 Hz), 1.16 (3H, t, *J* = 7.7 Hz), 2.46 (1H, dd, *J* = 16.2, 5.8 Hz), 2.57 (2H, q, *J* = 7.6 Hz), 2.86 (1H, dd, *J* = 16.2, 5.0 Hz), 3.01 (1H, sext, *J* = 5.9 Hz), 3.41–3.62 (3H, m), 3.66–3.77 (1H, m), 3.71 (3H, s), 6.21 (2H, s, br), 6.49 (1H, s), 7.00 (1H, s, br), 7.00–7.25 ppm (4H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 14.9, 15.5, 27.5, 28.6, 51.1, 51.9, 55.9, 57.0, 110.6, 124.0, 126.0, 126.3, 126.4, 128.1, 128.2, 133.5, 137.3, 144.2, 149.5 ppm; LC–MS (ES+): *m/z* 391.4 $[M+H]^+$.

(±)-2-(3-Ethoxybenzyl)-7-methoxy-3-methyl-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (6i): Method as for **6a** using compound **5i** (98 mg, 0.3 mmol) and sulfamoyl chloride (0.9 mmol) in DMA (3.0 mL) at room temperature for 4 h. Crystallisation from CH_2Cl_2 afforded **6i** as a pale-yellow solid (84 mg, 69%); mp: 94–101 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.02 (3H, dd, *J* = 6.6, 2.1 Hz), 1.29 (3H, dt, *J* = 6.9, 2.3 Hz), 2.43 (1H, dd, *J* = 16.0, 5.2 Hz), 2.75–2.89 (1H, m), 2.90–3.05 (1H, m), 3.37–3.60 (3H, m), 3.63–3.72 (1H, m), 3.68 (3H, d, *J* = 2.5 Hz), 3.92 (2H, dq, *J* = 6.9, 2.2 Hz), 6.44 (1H, s), 6.64–6.72 (1H, m), 6.77–6.88 (2H, m), 6.97 (1H, s), 7.11 ppm (1H, dt, *J* = 8.0, 2.3 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 14.6, 14.8, 34.4, 51.1, 51.8, 55.8, 57.0, 63.0, 110.4, 112.6, 114.6, 120.7, 123.9, 126.2,

129.0, 133.5, 137.1, 140.6, 149.4, 158.8 ppm; LC–MS (ES+): *m/z* 407.3 $[M+H]^+$; HRMS (ES+): *m/z* found 407.1627, $C_{20}H_{27}N_2O_5S^+$ $[M+H]^+$ requires 407.1635.

(±)-7-Methoxy-3-methyl-2-(3-nitrobenzyl)-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (6j): Method as for **6a** using compound **5j** (165 mg, 0.5 mmol) and sulfamoyl chloride (1.5 mmol) in DMA (3.0 mL) at room temperature for 2 h. Crystallisation from CH_2Cl_2 afforded **6j** as a pale-yellow solid (80 mg, 49%); mp: 166–169 °C; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta=1.01$ (3H, d, $J=6.3$ Hz), 2.42 (1H, dd, $J=16.3$, 5.5 Hz), 2.84 (1H, dd, $J=16.1$, 4.8 Hz), 2.99 (1H, sext, $J=6.1$ Hz), 3.37–3.70 (3H, m), 3.64 (3H, s), 3.75 (1H, d, $J=14.0$ Hz), 6.42 (1H, s), 6.51 (2H, s, br), 6.96 (1H, s), 7.37 (1H, t, $J=8.0$ Hz), 7.58 (1H, d, $J=7.7$ Hz), 7.97 (1H, dd, $J=8.1$, 1.5 Hz), 8.09 ppm (1H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta=14.7$, 34.2, 50.9, 52.1, 55.7, 56.2, 110.3, 121.8, 122.9, 123.9, 125.8, 129.0, 132.7, 134.5, 137.3, 141.5, 148.1, 149.6 ppm; LC–MS (ES+): *m/z* 408.2 $[M+H]^+$; HRMS (ES+): *m/z* found 408.1219, $C_{18}H_{22}N_3O_6S^+$ $[M+H]^+$ requires 408.1224.

(±)-2-(3-Chlorobenzyl)-7-methoxy-3-methyl-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (6k): Method as for **6a** using compound **5k** (127 mg, 0.4 mmol) and sulfamoyl chloride (1.2 mmol) in DMA (3.0 mL) at room temperature for 2 h. Crystallisation from CH_2Cl_2 afforded **6k** as a pale-yellow solid (92 mg, 58%); mp: 172–175 °C; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta=1.06$ (3H, d, $J=6.3$ Hz), 2.47 (1H, dd, $J=16.2$, 5.8 Hz), 2.87 (1H, dd, $J=16.2$, 4.7 Hz), 3.03 (1H, sext, $J=6.0$ Hz), 3.41–3.62 (3H, m), 3.71 (1H, d, $J=13.2$ Hz), 3.72 (3H, s), 6.22 (2H, s, br), 6.49 (1H, s), 7.01 (1H, s), 7.11–7.22 (3H, m), 7.30 ppm (1H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta=15.0$, 34.3, 51.1, 52.1, 55.9, 56.5, 110.6, 124.1, 126.8, 127.1, 128.5, 129.5, 133.1, 134.0, 137.4, 149.6 ppm; LC–MS (ES+): *m/z* 397.2 $[M+H]^+$; HRMS (ES+): *m/z* found 397.0982, $C_{18}H_{22}ClN_2O_4S^+$ $[M+H]^+$ requires 397.0984.

(±)-2-(3-Acetylbenzyl)-7-methoxy-3-methyl-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (6l): Method as for **6a** using compound **5l** (130 mg, 0.4 mmol) and sulfamoyl chloride (1.2 mmol) in DMA (3.0 mL) at room temperature for 4 h. Crystallisation from CH_2Cl_2 afforded **6l** as a white solid (66 mg, 41%); mp: 172–175 °C; ^{1}H NMR (270 MHz, $CDCl_3$/[D$_6$]DMSO): $\delta=1.07$ and 1.09 (3H, 2d, $J=7.0$ and 7.4 Hz), 2.52 and 2.56 (3H, s and d, $J=1.4$ Hz), 2.42–2.51 and 2.90–2.99 (1H, 2m), 2.83–2.91 (1H, m), 3.07 (1H, sext, $J=5.8$ Hz), 3.41–3.67 (3H, m), 3.70 and 3.73 (3H, 2s), 3.76–3.89 (1H, m), 6.49 and 6.52 (1H, 2s), 6.91 (2H, s, br), 7.01 and 7.04 (1H, 2s), 7.36 and 7.42 (1H, t and dt, $J=8.3$ and 7.6, 1.1 Hz), 7.52 and 7.55 (1H, 2dd, $J=7.4$, 1.1 and 7.7, 1.1 Hz), 7.77 and 7.80 (1H, 2dd, $J=7.5$, 1.1 and 7.7, 1.1 Hz), 7.86 and 7.89 ppm (1H, s and d, $J=1.1$ Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$/[D$_6$]DMSO): $\delta=14.4$, 26.2, 34.1, 50.7, 51.6, 55.4, 56.5, 110.1, 123.5, 125.5, 126.6, 127.7, 128.1, 132.7, 133.0, 136.6, 137.0, 139.5, 149.3, 197.7 ppm; LC–MS (ES+): *m/z* 405.2 $[M+H]^+$; HRMS (ES+): *m/z* found 405.1484, $C_{20}H_{25}N_2O_5S^+$ $[M+H]^+$ requires 405.1479.

(±)-2-(2,3-Dimethoxybenzyl)-7-methoxy-3-methyl-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (6m): Method as for **6a** using compound **5m** (138 mg, 0.4 mmol) and sulfamoyl chloride (1.2 mmol) in DMA (3.0 mL) at room temperature for 2 h. Crystallisation from CH_2Cl_2 afforded **6m** as a pale-yellow solid (41 mg, 24%); mp: 152–155 °C; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta=1.07$ (3H, d, $J=6.3$ Hz), 2.45 (1H, dd, $J=16.1$, 5.6 Hz), 2.85 (1H, dd, $J=16.1$, 4.8 Hz), 3.04 (1H, sext, $J=5.9$ Hz), 3.43–3.84 (4H, m), 3.71 (3H, s), 3.73 (3H, s), 3.79 (3H, s), 6.15 (2H, s, br), 6.50 (1H, s), 6.72–6.80 (1H, m), 6.94 (1H, s), 6.96 (1H, s), 6.98 ppm (1H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta=15.0$, 34.8, 51.0, 51.3, 52.3, 55.7, 56.2, 61.0, 110.8, 111.0, 122.3, 123.9, 124.2, 126.7, 133.0, 134.0, 137.4, 147.7, 149.6, 152.8 ppm; LC–MS (ES+): *m/z* 423.2 $[M+H]^+$; HRMS (ES+): *m/z* found 423.1573, $C_{20}H_{27}N_2O_6S^+$ $[M+H]^+$ requires 423.1584.

(±)-2-(3,4-Dimethoxybenzyl)-7-methoxy-3-methyl-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (6n): Method as for **6a** using compound **5n** (138 mg, 0.4 mmol) and sulfamoyl chloride (1.2 mmol) in DMA (3.0 mL) at room temperature for 2 h. Crystallisation from CH_2Cl_2 afforded **6n** as a pale-yellow solid (63 mg, 37%); mp: 168–170 °C; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta=1.06$ (3H, d, $J=6.3$ Hz), 2.46 (1H, dd, $J=16.2$, 5.5 Hz), 2.86 (1H, dd, $J=16.4$, 4.8 Hz), 3.02 (1H, sext, $J=6.1$ Hz), 3.39–3.73 (4H, m), 3.72 (3H, s), 3.80 (6H, s), 6.14 (2H, s, br), 6.49 (1H, s), 6.74 (1H, d, $J=8.3$ Hz), 6.79 (1H, dd, $J=8.3$, 1.4 Hz), 6.87 (1H, s), 7.00 ppm (1H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta=14.8$, 34.2, 51.0, 51.7, 55.7, 55.7, 55.9, 56.7, 92.3, 110.6, 110.6, 111.8, 120.8, 124.0, 126.3, 133.3, 137.3, 147.9, 148.8, 149.5 ppm; LC–MS (ES+): *m/z* 423.3 $[M+H]^+$; HRMS (ES+): *m/z* found 423.1551, $C_{20}H_{27}N_2O_6S^+$ $[M+H]^+$ requires 423.1584.

(±)-2-(3,5-Dimethoxybenzyl)-7-methoxy-3-methyl-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (6o): Method as for **6a** using compound **5o** (102 mg, 0.3 mmol) and sulfamoyl chloride (1.5 mmol) in DMA (1.0 mL) at room temperature for 23 h. Flash column chromatography (hexane to EtOAc) afforded **6o** as a pale-yellow solid (80 mg, 64%); mp: 146–149 °C; ^{1}H NMR (270 MHz, [D$_6$]DMSO): $\delta=1.05$ (3H, d, $J=6.2$ Hz), 2.43–2.51 (1H, m), 2.88 (1H, dd, $J=16.0$, 4.7 Hz), 2.98–3.07 (1H, m), 3.66–3.99 (4H, m), 3.70 (3H, s), 3.71 (6H, s), 6.37 (1H, t, $J=2.2$ Hz), 6.51 (2H, d, $J=2.2$ Hz), 6.80 (1H, s), 7.02 (1H, s), 7.85 ppm (2H, s, br); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta=$([D$_6$]DMSO) 15.0, 39.4, 51.2, 52.0, 55.6, 56.3, 57.5, 99.1, 106.7, 111.5, 123.6, 125.9, 133.6, 137.6, 142.5, 150.1, 161.0 ppm; LC–MS (ES+): *m/z* 423.09 $[M+H]^+$; HRMS (ES+): *m/z* found 423.1580, $C_{20}H_{27}N_2O_6S^+$ $[M+H]^+$ requires 423.1584.

(±)-2-(2,5-Dimethoxybenzyl)-7-methoxy-3-methyl-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (6p): Method as for **6a** using compound **5p** (206 mg, 0.6 mmol) and sulfamoyl chloride (2.5 mmol) in DMA (3.0 mL) at room temperature for 18 h. Flash column chromatography (hexane to hexane/EtOAc 3:7 and ($CHCl_3$/acetone 4:1 to 3:1) gave a solid that was crystallised from (iPr)$_2$O and washed with Et_2O (~20×1 mL) to afford **6p** as a white foam (33 mg, 12%) still containing (iPr)$_2$O (5.1 wt% by ^{1}H NMR); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta=1.12$ (3H, d, $J=6.3$ Hz), 2.51 (1H, dd, $J=16.0$, 6.1 Hz), 2.90 (1H, dd, $J=16.2$, 4.7 Hz), 3.11 (1H, sext, $J=6.0$ Hz), 3.54–3.71 (4H, m), 3.73 (3H, s), 3.75 (3H, s), 3.77 (3H, s), 5.82 (2H, s, br), 6.56 (1H, s), 6.71 (1H, dd, $J=8.8$, 3.0 Hz), 6.77 (1H, d, $J=8.8$ Hz), 7.01 (1H, d, $J=2.8$ Hz), 7.04 ppm (1H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta=15.0$, 33.9, 49.8, 51.1, 52.0, 55.3, 55.7, 110.4, 111.2, 111.5, 115.7, 123.8, 126.2, 128.4, 133.6, 137.1, 149.4, 151.6, 153.3 ppm; LC–MS (ES+): *m/z* 423.3 $[M+H]^+$.

(±)-2-(2-Fluoro-5-methoxybenzyl)-7-methoxy-3-methyl-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (6q): Method as for **6a** using compound **5q** (199 mg, 0.6 mmol) and sulfamoyl chloride (3.0 mmol) in DMA (5.0 mL) at room temperature for 2 h. Flash column chromatography (hexane to hexane/EtOAc 1:1) and crystallisation from Et_2O afforded **6q** as a white solid (43 mg, 17%); mp: 163–167 °C; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta=1.16$ (3H, d, $J=6.3$ Hz), 2.54 (1H, dd, $J=16.1$, 5.4 Hz), 2.94 (1H, dd, $J=16.2$, 4.4 Hz), 3.12 (1H, sext, $J=5.9$ Hz), 3.56–3.83 (4H, m), 3.77 (3H, s), 3.80 (3H, s), 6.49 (2H, s, br), 6.60 (1H, s), 6.74 (1H, dt, $J=8.8$, 3.7 Hz), 6.95 (1H, t, $J=9.4$ Hz), 6.96–7.04 (1H, m), 7.08 ppm (1H, s); LC–MS (ES+): *m/z* 411.4 $[M+H]^+$.

(±)-2-(2-Chloro-5-methoxybenzyl)-7-methoxy-3-methyl-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (6r): Method as for **6a**

using compound **5r** (173 mg, 0.5 mmol) and sulfamoyl chloride (1.5 mmol) in DMA (3.0 mL) at room temperature for 2 h. Crystallisation from CH_2Cl_2 afforded **6r** as a white solid (81 mg, 38%); mp: 146–148 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.08 (3H, d, J = 6.6 Hz), 2.48 (1H, dd, J = 16.0, 5.5 Hz), 2.90 (1H, dd, J = 16.2, 5.0 Hz), 3.09 (1H, sext, J = 5.9 Hz), 3.52–3.81 (4H, m), 3.72 (3H, s), 3.74 (3H, s), 6.10 (2H, s, br), 6.53 (1H, s), 6.67 (1H, dd, J = 8.7, 3.2 Hz), 7.02 (1H, s), 7.05 (1H, d, J = 3.0 Hz), 7.18 ppm (1H, d, J = 8.8 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 14.9, 34.3, 51.1, 52.3, 53.9, 55.4, 56.0, 110.7, 113.3, 115.7, 124.2, 125.1, 126.4, 129.8, 133.6, 137.3, 149.5, 158.3 ppm; LC–MS (ES+): m/z 427.2 $[M+H]^+$; HRMS (ES+): m/z found 427.1081, $C_{19}H_{24}ClN_2O_5S^+$ $[M+H]^+$ requires 427.1089.

(±)-7-Methoxy-3-methyl-6-sulfamoyloxy-2-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (6s): Method as for **6a** using compound **5s** (65 mg, 0.17 mmol) and sulfamoyl chloride (0.52 mmol) in DMA (1.0 mL) at room temperature for 22 h. The resulting solid was stirred in hexane, filtered and dried to afford **6s** as yellow powder (55 mg, 70%); mp: 137–143 °C; ^{1}H NMR (270 MHz, [D$_6$]DMSO): δ = 1.06 (3H, d, J = 6.4 Hz), 2.44–2.51 (1H, m), 2.90 (1H, dd, J = 16.5, 5.1 Hz), 3.03–3.09 (1H, m), 3.49–3.66 (4H, m), 3.64 (3H, s), 3.71 (3H, s), 3.75 (6H, s), 6.65 (2H, s), 6.82 (1H, s), 7.03 (1H, s), 7.82 ppm (2H, s); ^{13}C NMR (67.5 MHz, [D$_6$]DMSO): δ = 14.8, 39.5, 51.1, 51.9, 56.4, 57.5, 60.5, 105.9, 111.6, 123.6, 125.9, 133.6, 135.6, 136.8, 137.7, 150.2, 153.4 ppm; LC–MS (ES+): m/z 453.38 $[M+H]^+$; HRMS (ES+): m/z found 453.1688, $C_{21}H_{29}N_2O_7S^+$ $[M+H]^+$ requires 453.1690.

(±)-3-Ethyl-7-methoxy-6-sulfamoyloxy-2-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (6t): Method as for **6a** using compound **5t** (194 mg, 0.5 mmol) and sulfamoyl chloride (1.5 mmol) in DMA (3.0 mL) at room temperature for 2 h. Flash column chromatography (hexane to hexane/EtOAc 1:4) gave an oil which was dissolved in CH_2Cl_2 (30 mL) and rapidly concentrated to afford **6t** as a yellow foam (172 mg, 73%); ^{1}H NMR (270 MHz, [D$_6$]DMSO): δ = 0.94 (3H, t, J = 7.4 Hz), 1.33 (1H, sept, J = 7.0 Hz), 1.62 (1H, sept, J = 6.8 Hz), 2.46–2.54 (1H, m), 2.76–2.87 (2H, m), 3.51–3.66 (4H, m), 3.63 (3H, s), 3.70 (3H, s), 3.73 (6H, s), 6.64 (2H, s), 6.81 (1H, s), 7.03 (1H, s), 7.85 ppm (2H, s); ^{13}C NMR (67.5 MHz, [D$_6$]DMSO): δ = 11.2, 22.3, 29.0, 50.5, 55.3, 55.9, 56.0, 57.6, 60.2, 105.3, 111.4, 123.3, 125.7, 133.2, 135.5, 136.3, 137.3, 149.9, 153.0 ppm; LC–MS (ES+): m/z 467.1 $[M+H]^+$.

3,3-Dimethyl-6-hydroxy-7-methoxy-3,4-dihydroisoquinoline (19): KCN (1.29 g, 36.7 mmol) was added in small portions into AcOH (7.2 mL) at 0 °C. A mixture of AcOH (3.6 mL) and H_2SO_4 (7.3 g) was then added slowly with stirring. Finally, a solution of compound **18** (6.0 g, 30.6 mmol) in AcOH (4 mL) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 24 h, then poured into ice-H_2O and neutralised with Na_2CO_3. After saturating with NaCl the mixture was extracted with Et_2O (2×150 mL) and EtOAc (2×150 mL). Flash column chromatography (CH_2Cl_2/EtOAc 1:1 to EtOAc to EtOAc/MeOH 4:1) afforded **19** as a colourless solid (1.72 g, 30%); mp: 152–157 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.21 (6H, s), 2.62 (2H, s), 3.91 (3H, s), 5.69 (1H, s, br), 6.60 (1H, s), 6.85 (1H, s), 8.07 ppm (1H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 28.1, 38.0, 54.7, 56.0, 110.6, 113.8, 120.9, 128.0, 144.9, 149.5, 157.2 ppm; LC–MS (ES+): m/z 205.9 $[M+H]^+$; HRMS (ES+): m/z found 206.1169, $C_{12}H_{16}NO_2^+$ $[M+H]^+$ requires 206.1176.

3,3-Dimethyl-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (20): To a solution of compound **19** (1.67 g, 8.2 mmol) in EtOH (30 mL) at 0 °C was added $NaBH_4$ (618 mg, 16.3 mmol). The reaction mixture was stirred at room temperature for 3 h. H_2O (50 mL) and HCl (2 M) were added, and the mixture was extracted with EtOAc (3×60 mL). The combined organic layers were washed with brine (30 mL), then dried ($MgSO_4$) and evaporated to afford **20** as white solid (1.34 g, 80%); mp: 170–173 °C; ^{1}H NMR (270 MHz, [D$_6$]DMSO): δ = 1.04 (6H, s), 2.42 (2H, s), 3.70 (3H, s), 3.72 (2H, s), 6.43 (1H, s), 6.54 (1H, s), 8.60 ppm (1H, s, br); LC–MS (ES+): m/z 208.23 $[M+H]^+$; HRMS (ES+): m/z found 208.1322, $C_{12}H_{18}NO_2^+$ $[M+H]^+$ requires 208.1332.

3,3-Dimethyl-7-methoxy-6-(triisopropylsilanyloxy)-1,2,3,4-tetrahydroisoquinoline (21): Method as for **15** using compound **20** (1.25 g, 6.0 mmol), chlorotriisopropylsilane (2.71 mL, 12.7 mmol) and imidazole (1.73 g, 25.4 mmol) in CH_2Cl_2 (50 mL) at room temperature for 22 h. Flash column chromatography (EtOAc/MeOH 10:1 and 1% Et_3N) afforded **21** as a colourless oil (1.78 g, 81%); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.06 (18H, d, J = 6.7 Hz), 1.14 (6H, s), 1.14–1.28 (3H, m), 2.51 (2H, s), 3.74 (3H, s), 3.89 (2H, s), 6.46 (1H, s), 6.51 ppm (1H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 13.0, 18.0, 27.8, 41.2, 44.0, 48.8, 55.6, 113.0, 117.4, 126.2, 126.9, 143.6, 149.3 ppm; LC–MS (ES+): m/z 364.36 $[M+H]^+$.

3,3-Dimethyl-7-methoxy-2-(3-methoxybenzyl)-6-(triisopropylsilan-yloxy)-1,2,3,4-tetrahydroisoquinoline (22a): Method as for **16a** using compound **21** (300 mg, 0.83 mmol), 3-methoxybenzyl chloride (0.13 mL, 0.91 mmol) and Et_3N (0.3 mL, 1.65 mmol) in EtOH (3.0 mL) in the microwave at 130 °C for 1.5 h. Flash column chromatography (hexane to hexane/EtOAc 1:1 to EtOAc) afforded **22a** as a colourless oil (246 mg, 62%); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.04 (18H, d, J = 6.7 Hz), 1.12–1.22 (3H, m), 1.17 (6H, s), 2.65 (2H, s), 3.47 (2H, s), 3.64 (2H, s), 3.74 (3H, s), 3.79 (3H, s), 6.41 (1H, s), 6.48 (1H, s), 6.77 (1H, ddd, J = 8.2, 2.2, 1.2 Hz), 6.95–6.98 (2H, m), 7.22 ppm (1H, t, J = 8.2 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 12.4, 17.5, 23.3, 42.3, 49.6, 52.1, 53.2, 54.7, 55.0, 111.4, 111.7, 113.8, 117.2, 120.6, 125.7, 126.3, 128.7, 142.1, 142.9, 148.7, 159.2 ppm; LC–MS (ES+): m/z 484.83 $[M+H]^+$; HRMS (ES+): m/z found 484.3242, $C_{29}H_{46}NO_3Si^+$ $[M+H]^+$ requires 484.3241.

3,3-Dimethyl-7-methoxy-6-(triisopropylsilanyloxy)-2-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (22b): Method as for **16a** using compound **21** (300 mg, 0.83 mmol), 3,4,5-trimethoxybenzyl chloride (214 mg, 0.99 mmol) and Et_3N (0.23 mL, 1.65 mmol) in EtOH (3 mL) in the microwave at 170 °C for 0.5 h. Flash column chromatography (hexane to hexane/CH_2Cl_2 1:1) and (hexane/EtOAc 4:1) afforded **22b** as a colourless oil (127 mg, 28%); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.04 (18H, d, J = 6.7 Hz), 1.12–1.27 (3H, m), 1.17 (6H, s), 2.65 (2H, s), 3.49 (2H, s), 3.60 (2H, s), 3.74 (3H, s), 3.83 (3H, s), 3.84 (6H, s), 6.44 (1H, s), 6.50 (1H, s), 6.61 ppm (2H, s); LC–MS (ES+): m/z 544.46 $[M+H]^+$.

3,3-Dimethyl-6-hydroxy-2-(3-methoxybenzyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (5u): Method as for **5a** using compound **22a** (237 mg, 0.45 mmol) and TBAF (1 M in THF, 0.53 mL, 0.53 mmol) in THF (10 mL) at room temperature for 18 h. Flash column chromatography (hexane to EtOAc) afforded **5u** as a colourless oil (70 mg, 43%); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.18 (6H, s), 2.66 (2H, s), 3.50 (2H, s), 3.65 (2H, s), 3.79 (3H, s), 3.83 (3H, s), 6.47 (1H, s), 6.52 (1H, s), 6.75–6.79 (1H, m), 6.95–6.97 (2H, m), 7.21 ppm (1H, t, J = 8.0 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 23.7, 45.5, 50.0, 52.5, 53.5, 55.1, 55.9, 110.7, 111.7, 111.9, 114.1, 120.9, 125.6, 126.9, 129.1, 142.4, 143.5, 145.0, 159.6 ppm; LC–MS (ES−): m/z 326.27 $[M-H]^-$; HRMS (ES+): m/z found 328.1904, $C_{20}H_{26}NO_3^+$ $[M+H]^+$ requires 328.1907.

3,3-Dimethyl-6-hydroxy-7-methoxy-2-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (5v): Method as for **5a** using compound **22b** (187 mg, 0.34 mmol) and TBAF (1 M in THF, 0.38 mL, 0.38 mmol) in THF (10 mL) at 0 °C for 3 h. Flash column chromatog-

raphy (hexane/EtOAc 2:1 and 1% Et_3N) gave an oil that crystallised on trituration with CH_2Cl_2/hexane/EtOAc to afford **5v** as a yellow powder (72 mg, 54%); mp: 143–147 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.17 (6H, s), 2.66 (2H, s), 3.52 (2H, s), 3.60 (2H, s), 3.82 (3H, s), 3.83 (6H, s), 3.84 (3H, s), 5.44 (1H, s, br), 6.50 (1H, s), 6.53 (1H, s), 6.60 ppm (2H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 23.8, 42.4, 50.0, 52.5, 53.8, 55.9, 56.1, 60.8, 105.0, 110.7, 111.7, 125.6, 126.9, 136.4, 143.5, 145.0, 153.1 ppm; LC–MS (ES−): *m/z* 386.26 $[M-H]^-$; HRMS (ES+): *m/z* found 388.2111, $C_{22}H_{30}NO_5^+$ $[M+H]^+$ requires 388.2118.

3,3-Dimethyl-7-methoxy-2-(3-methoxybenzyl)-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (6u): Method as for **6a** using compound **5u** (78 mg, 0.24 mmol) and sulfamoyl chloride (1.2 mmol) in DMA (1.0 mL) at room temperature for 20 h. Flash column chromatography (hexane to EtOAc) gave an oil that was stirred in Et_2O/hexane, evaporated then suspended in hexane, filtered and dried to afford **6u** as cream coloured foam (31 mg, 32%); ^{1}H NMR (270 MHz, [D$_6$]DMSO): δ = 1.14 (6H, s), 2.69 (2H, s), 3.43 (2H, s), 3.62 (2H, s), 3.73 (3H, s), 3.75 (3H, s), 6.80 (1H, dd, *J* = 8.0, 2.0 Hz), 6.83 (1H, s), 6.89–6.94 (3H, m), 7.23 (1H, t, *J* = 8.0 Hz), 7.79 ppm (2H, s); ^{13}C NMR (67.5 MHz, [D$_6$]DMSO): δ = 42.8, 49.4, 52.1, 53.0, 54.9, 55.8, 111.8, 113.0, 114.1, 120.3, 120.6, 125.8, 129.3, 133.0, 136.8, 142.2, 149.9, 159.3 ppm; LC–MS (ES+): *m/z* 407.28 $[M+H]^+$; HRMS (ES+): *m/z* found 407.1636, $C_{20}H_{27}N_2O_5S^+$ $[M+H]^+$ requires 407.1635.

3,3-Dimethyl-7-methoxy-6-sulfamoyloxy-2-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (6v): Method as for **6a** using compound **5v** (66 mg, 0.17 mmol) and sulfamoyl chloride (0.51 mmol) in DMA (1.0 mL) at room temperature for 23 h. Flash column chromatography (hexane to EtOAc to MeOH) gave a solid that was further purified by preparative HPLC (MeOH/H_2O 4:1) to afford **6v** as a colourless foam (10 mg, 13%); ^{1}H NMR (270 MHz, [D$_6$]DMSO): δ = 1.14 (6H, s), 2.69 (2H, s), 3.46 (2H, s), 3.58 (2H, s), 3.63 (3H, s), 3.74 (6H, s), 3.75 (3H, s), 6.64 (2H, s), 6.83 (1H, s), 6.92 (1H, s), 7.80 ppm (2H, s); LC–MS (ES+): *m/z* 467.18 $[M+H]^+$; HRMS (ES+): *m/z* found 467.1848, $C_{22}H_{31}N_2O_7S^+$ $[M+H]^+$ requires 467.1847.

6-Benzyloxy-7-methoxy-1-methyl-3,4-dihydroisoquinoline (25a): **24a** (2.68 g, 8.9 mmol) was treated with phosphorus oxychloride (8.23 mL, 53.7 mmol) in toluene (50 mL) at 140 °C for 3 h. The reaction mixture was then cooled to room temperature and evaporated. $CHCl_3$ (100 mL) and ice-H_2O (50 mL) were added, the layers were separated and the aqueous layer was basified to pH 9 and extracted with $CHCl_3$ (2×50 mL). The combined organics were washed with H_2O, dried, filtered and evaporated to afford **25a** as a yellow oil (949 mg, 38%); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 2.51 (3H, s), 2.68 (2H, t, *J* = 7.7 Hz), 3.66 (2H, dt, *J* = 7.7, 1.2 Hz), 3.90 (3H, s), 5.19 (2H, s), 6.72 (1H, s), 7.04 (1H, s), 7.28–7.44 ppm (5H, m); LC–MS (ES+): *m/z* 282.06 $[M+H]^+$.

6-Benzyloxy-7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (26a): Compound **25a** (949 mg, 3.4 mmol) was dissolved in EtOH (15 mL) and $NaBH_4$ (256 mg, 6.8 mmol) was added portionwise at 0 °C. The reaction was stirred at room temperature for 1.5 h. H_2O (100 mL) was added, the mixture was neutralised, then saturated (NaCl) and extracted with EtOAc (3×100 mL). The combined organics were washed with $NaHCO_3$ (saturated, 100 mL), dried and evaporated to afford **26a** as a yellow oil (600 mg, 63%); ^{1}H NMR (270 MHz, [D$_6$]DMSO): δ = 1.58 (3H, d, *J* = 6.4 Hz), 2.50 (2H, s), 2.82–2.95 (2H, m), 3.76 (3H, s), 4.42 (1H, q, *J* = 6.4 Hz), 5.06 (2H, s), 6.86 (1H, s), 6.88 (1H, s), 7.31–7.44 (5H, m), 9.40 ppm (1H, s, br); LC–MS (ES+): *m/z* 284.13 $[M+H]^+$.

6-Benzyloxy-7-methoxy-2-(3-methoxybenzyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline (27a): Method as for **16a** using compound **26a** (286 mg, 1.0 mmol), 3-methoxybenzyl bromide (0.17 mL, 1.2 mmol) and Et_3N (0.28 mL, 2.0 mmol) in EtOH (3.0 mL) in the microwave at 170 °C for 0.5 h. Flash column chromatography (hexane/EtOAc gradient) afforded **27a** as a colourless oil (254 mg, 62%); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.18 (3H, d, *J* = 6.8 Hz), 2.49–2.55 (1H, m), 2.66–2.82 (2H, m), 2.99–3.07 (1H, m), 3.72–3.81 (2H, m), 3.80 (3H, s), 3.81–3.86 (1H, m), 3.84 (3H, s), 5.11 (2H, s), 6.56 (1H, s), 6.61 (1H, s), 6.80 (1H, dd, *J* = 8.2, 1.8 Hz), 6.95–6.98 (2H, m), 7.23 (1H, t, *J* = 8.0 Hz), 7.25–7.45 ppm (5H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 19.8, 26.6, 43.8, 55.2, 55.8, 56.1, 58.0, 71.0, 111.0, 112.4, 113.9, 113.9, 121.0, 126.1, 127.3, 127.7, 128.5, 129.1, 132.8, 137.3, 141.4, 146.5, 147.8, 159.6 ppm; LC–MS (ES+): *m/z* 404.06 $[M+H]^+$; HRMS (ES+): *m/z* found 404.2224, $C_{26}H_{30}NO_3^+$ $[M+H]^+$ requires 404.2220.

6-Benzyloxy-7-methoxy-1-methyl-2-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (27b): Method as for **16a** using compound **26a** (170 mg, 0.6 mmol), 3,4,5-trimethoxybenzyl chloride (156 mg, 0.72 mmol) and Et_3N (0.17 mL, 1.2 mmol) in EtOH (3.0 mL) in the microwave at 170 °C for 0.5 h. Flash column chromatography (hexane to hexane/EtOAc 1:1) afforded **27b** as a colourless oil (58 mg, 21%); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.36 (3H, d, *J* = 6.7 Hz), 2.47–2.55 (1H, m), 2.67–2.84 (2H, m), 2.98–3.07 (1H, m), 3.59–3.73 (3H, m), 3.83 (9H, s), 3.88 (3H, s), 5.09 (2H, s), 6.56–6.62 (4H, m), 7.27–7.44 ppm (5H, m); LC–MS (ES+): *m/z* 464.34 $[M+H]^+$.

(±)-6-Hydroxy-7-methoxy-2-(3-methoxybenzyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline (5w): Method as for **5b** using compound **27a** (276 mg, 0.68 mmol) and Pd/C (10%, 30 mg) in THF (5 mL) and EtOH (5 mL) at room temperature for 4 h. Flash column chromatography (hexane/EtOAc gradient) afforded **5w** as a yellow foam (150 mg, 70%); mp: 97–99 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.36 (3H, d, *J* = 6.6 Hz), 2.49–2.61 (1H, m), 2.66–2.88 (2H, m), 3.00–3.12 (1H, m), 3.63–3.83 (3H, m), 3.80 (3H, s), 3.83 (3H, s), 6.51 (1H, s), 6.63 (1H, s), 6.80 (1H, dd, *J* = 8.2, 2.7 Hz), 6.95–6.99 (2H, m), 7.23 ppm (1H, t, *J* = 7.7 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 20.2, 26.4, 43.8, 55.3, 55.9, 56.1, 58.1, 109.7, 112.6, 114.0, 114.4, 126.9, 129.3, 131.6, 141.4, 143.8, 145.0, 159.8 ppm; LC–MS (ES+): *m/z* 314.18 $[M+H]^+$; HRMS (ES+): *m/z* found 314.1752, $C_{19}H_{24}O_3^+$ $[M+H]^+$ requires 314.1751.

(±)-6-Hydroxy-7-methoxy-1-methyl-2-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (5x): Method as for **5b** using compound **27b** (187 mg, 0.4 mmol) and Pd/C (10%, 20 mg) in THF (5 mL) and EtOH (5 mL) at room temperature for 18 h. Flash column chromatography (CH_2Cl_2/EtOAc gradient) afforded compound **5x** as a pale-yellow foam (72 mg, 65%); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.35 (3H, d, *J* = 6.6 Hz), 2.50–2.57 (1H, m), 2.69–2.85 (2H, m), 3.02–3.11 (1H, m), 3.55–3.84 (3H, m), 3.84 (12H, s), 6.51 (1H, s), 6.62 (2H, s), 6.64 ppm (1H, s); LC–MS (ES+): *m/z* 374.21 $[M+H]^+$; HRMS (ES+): *m/z* found 374.1959, $C_{21}H_{28}NO_5^+$ $[M+H]^+$ requires 374.1962.

(±)-2-(3-Methoxybenzyl)-7-methoxy-1-methyl-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (6w): Method as for **6a** using compound **5w** (132 mg, 0.42 mmol) and sulfamoyl chloride (2.1 mmol) in DMA (1.0 mL) at room temperature for 4 days. Flash column chromatography (hexane/EtOAc gradient) gave an oil which was dissolved in Et_2O, then rapidly evaporated to afford **6w** as a pale-yellow foam (127 mg, 77%); ^{1}H NMR (270 MHz, [D$_6$]DMSO): δ = 1.31 (3H, d, *J* = 6.4 Hz), 2.50–2.54 (1H, m), 2.63–2.66 (1H, m), 2.73–2.81 (1H, m), 2.93–2.98 (1H, m), 3.62–3.73 (2H, m), 3.73 (3H, s), 3.74

(3H, s), 3.80 (1H, q, $J=6.5$ Hz), 6.81 (1H, dd, $J=7.8$, 2.2 Hz), 6.86 (1H, s), 6.92–6.93 (2H, m), 7.01 (1H, s), 7.24 (1H, t, $J=8.0$ Hz), 7.86 ppm (2H, s); ^{13}C NMR (67.5 MHz, [D$_6$]DMSO): $\delta=19.2$, 25.9, 43.0, 55.0, 55.2, 55.9, 57.2, 112.1, 112.3, 113.7, 120.6, 122.9, 125.8, 129.3, 136.9, 139.1, 141.1, 146.7, 159.4 ppm; LC–MS (ES+): *m/z* 393.17 $[M+H]^+$; HRMS (ES+): *m/z* found 393.1476, $C_{19}H_{25}N_2O_5S^+$ $[M+H]^+$ requires 393.1479.

(±)-7-Methoxy-1-methyl-6-sulfamoyloxy-2-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (6x): Method as for **6a** using compound **5x** (65 mg, 0.17 mmol) and sulfamoyl chloride (0.87 mmol) in DMA (1.0 mL) at room temperature for 4 days. Flash column chromatography (hexane to hexane/EtOAc 7:3 to EtOAc) gave an oil which was successively dissolved in Et_2O and then evaporated several times to afford **6x** as yellow foam (75 mg, 95%); ^{1}H NMR (270 MHz, [D$_6$]DMSO): $\delta=1.33$ (3H, d, $J=6.8$ Hz), 2.50–2.55 (1H, m), 2.61–2.82 (2H, m), 2.91–3.11 (1H, m), 3.64 (3H, s), 3.65 (2H, s), 3.74 (9H, s), 3.82 (1H, q, $J=6.8$ Hz), 6.67 (2H, s), 6.88 (1H, s), 7.02 (1H, s), 7.87 ppm (2H, s); ^{13}C NMR (67.5 MHz, [D$_6$]DMSO): $\delta=19.4$, 25.7, 42.8, 55.2, 55.8, 55.9, 57.4, 60.0, 105.0, 112.2, 122.9, 125.8, 135.2, 136.1, 136.9, 139.0, 149.7, 152.9 ppm; LC–MS (ES+): *m/z* 453.15 $[M+H]^+$; HRMS (ES+): *m/z* found 453.1695, $C_{21}H_{29}N_2O_7S^+$ $[M+H]^+$ requires 453.1690.

***N*-(3-Benzyloxy-4-methoxyphenethyl)benzamide (24b)**: Method as for **11a** using compound **23** (4.37 g, 17.0 mmol), Et_3N (2.8 mL, 20.0 mmol) and benzoyl chloride (2.1 mL, 18.3 mmol) in CH_2Cl_2 (50 mL) at 0 °C for 1 h. Work-up using H_2O (30 mL), CH_2Cl_2 (50 mL), H_2O and brine gave a solid which was suspended in Et_2O, filtered and dried to afford **24b** as a white powder (5.5 g, 87%); mp: 140–141 °C; ^{1}H NMR (270 MHz, [D$_6$]DMSO): $\delta=2.81$ (2H, t, $J=6.7$ Hz), 3.62 (2H, t, $J=6.7$ Hz), 3.86 (3H, s), 5.09 (2H, s), 6.09 (1H, s, br), 6.75–6.79 (2H, m), 6.82–6.86 (1H, m), 7.25–7.50 (8H, m), 7.63–7.68 ppm (2H, m); ^{13}C NMR (67.5 MHz, CDCl$_3$): $\delta=35.2$, 41.2, 56.2, 71.1, 112.1, 114.8, 121.5, 126.9, 127.4, 128.0, 128.6, 128.7, 131.4, 131.5, 134.7 137.1, 148.3, 148.5, 167.5 ppm; HRMS (ES+): *m/z* found 362.1738, $C_{23}H_{24}NO_3^+$ $[M+H]^+$ requires 362.1751.

6-Benzyloxy-7-methoxy-1-phenyl-3,4-dihydroisoquinoline (25b): Method as for **25a** using compound **24b** (5.0 g, 13.8 mmol) and phosphorous oxychloride (6.6 mL, 69.0 mmol) in toluene (80 mL) at 140 °C for 4 h. The resultant solid that was filtered, washed with H_2O and dried to afford **25b** as light-yellow powder (2.85 g, 61%); mp: 142–143 °C; ^{1}H NMR (270 MHz, CDCl$_3$): $\delta=2.63$–2.69 (2H, m), 3.72 (3H, s), 3.75–3.80 (2H, m), 5.21 (2H, s), 6.79 (1H, s), 6.81 (1H, s), 7.28–7.48 (8H, m), 7.56–7.61 ppm (2H, m); ^{13}C NMR (67.5 MHz, CDCl$_3$): $\delta=26.0$, 47.8, 56.4, 70.9, 112.2, 112.3, 120.0, 127.3, 128.1, 128.3, 128.8, 128.9, 129.4, 132.5, 136.7, 139.3, 147.6, 150.2, 166.8 ppm; HRMS (ES+): *m/z* found 344.1648, $C_{23}H_{22}NO_2^+$ $[M+H]^+$ requires 344.1651.

6-Benzyloxy-7-methoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (26b): Method as for **26a** using compound **25b** (2.5 g, 7.3 mmol) and $NaBH_4$ (0.4 g, 10.6 mmol) in EtOH (50 mL) at 100 °C for 4 h. The reaction mixture was cooled to room temperature and poured into HCl (1 M, 80 mL). The resulting solid was filtered off, washed with H_2O, Et_2O and dried to afford **26b** as a white powder (2.3 g, 92%); mp: 116–117 °C; ^{1}H NMR (270 MHz, CDCl$_3$): $\delta=1.84$ (1H, s, br), 2.62–2.72 (1H, m), 2.81–2.92 (1H, m), 2.96–3.05 (1H, m), 3.14–3.22 (1H, m), 3.63 (3H, s), 5.03 (1H, s), 5.12 (2H, s), 6.26 (1H, s), 6.66 (1H, s), 7.20–7.46 ppm (10H, m); ^{13}C NMR (67.5 MHz, CDCl$_3$): $\delta=$ 29.3, 41.9, 56.1, 61.6, 71.0, 111.6, 114.0, 120.0, 127.4, 127.7, 127.9, 128.5, 128.6, 129.0, 130.5, 137.3, 144.9, 146.9, 147.9 ppm; HRMS (ES+): *m/z* found 346.1811, $C_{23}H_{24}NO_2^+$ $[M+H]^+$ requires 346.1802.

6-Benzyloxy-7-methoxy-2-(3-methoxybenzyl)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (27c): Method as for **16a** using compound **26b** (270 mg, 0.78 mmol), 3-methoxybenzyl bromide (0.11 mL, 0.82 mmol) and Et_3N (0.5 mL, 3.6 mmol) in EtOH (2.5 mL) in the microwave at 130 °C for 1 h. Flash column chromatography (hexane to hexane/EtOAc 1:1) afforded **27c** as a light-yellow powder (410 mg, 59%); mp: 117–118 °C; ^{1}H NMR (270 MHz, CDCl$_3$): $\delta=$ 2.46–2.55 (1H, m), 2.66 (1H, dt, $J=16.0$, 4.1 Hz), 2.88–2.99 (1H, m), 3.07 (1H, dt, $J=11.6$, 4.8 Hz), 3.27 (1H, d, $J=13.5$ Hz), 3.63 (3H, s), 3.77 (1H, d, $J=13.5$ Hz), 3.80 (3H, s), 4.56 (1H, s), 5.12 (2H, s), 6.25 (1H, s), 6.66 (1H, s), 6.76–6.80 (1H, m), 6.90 (1H, d, $J=7.2$ Hz), 6.92 (1H, s), 7.18–7.47 ppm (11H, m); ^{13}C NMR (67.5 MHz, CDCl$_3$): $\delta=$ 28.5, 47.3, 55.3, 56.1, 58.8, 68.3, 71.0, 112.3, 112.5, 113.5, 114.2, 121.1, 127.1, 127.3, 127.4, 127.9, 128.4, 128.6, 129.2, 129.6, 130.9, 137.4, 141.5, 144.4, 146.8, 147.7, 159.7 ppm; HRMS (ES+): *m/z* found 466.2394, $C_{31}H_{32}NO_3^+$ $[M+H]^+$ requires 466.2377.

6-Benzyloxy-7-methoxy-1-phenyl-2-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (27d): Method as for **16a** using compound **26b** (415 mg, 1.2 mmol), 3,4,5-trimethoxybenzyl chloride (277 mg, 1.28 mmol) and Et_3N (0.5 mL, 3.6 mmol) in EtOH (2.5 mL) in the microwave at 130 °C for 1.5 h. Flash column chromatography (hexane to hexane/EtOAc 1:1) afforded **27d** as a yellow solid (220 mg, 35%); mp: 145–146 °C; ^{1}H NMR (270 MHz, CDCl$_3$): $\delta=2.51$–2.58 (1H, m), 2.70 (1H, dt, $J=16.0$, 4.3 Hz), 2.88–2.96 (1H, m), 3.08–3.12 (1H, m), 3.27 (1H, d, $J=13.7$ Hz), 3.63 (3H, s), 3.71 (1H, d, $J=13.7$ Hz), 3.84 (9H, s), 4.58 (1H, s), 5.13 (2H, s), 6.25 (1H, s), 6.58 (2H, s), 6.67 (1H, s), 7.24–7.39 (8H, m), 7.43–7.46 ppm (2H, m); ^{13}C NMR (67.5 MHz, CDCl$_3$): $\delta=28.2$, 46.5, 55.7, 56.1, 58.7, 60.8, 67.7, 69.9, 105.0, 111.1, 113.7, 127.2, 127.5, 127.7, 128.2, 128.4, 129.5, 135.4, 136.7, 137.2, 144.1, 144.3, 144.8, 153.2 ppm; HRMS (ES+): *m/z* found 526.2584, $C_{33}H_{36}NO_5^+$ $[M+H]^+$ requires 526.2588.

(±)-6-Hydroxy-7-methoxy-2-(3-methoxybenzyl)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (5y): Method as for **5b** using compound **27c** (270 mg, 0.58 mmol) and Pd/C (10%, 30 mg) in THF (15 mL) and MeOH (15 mL) at room temperature for 1 h. Flash column chromatography (hexane to hexane/EtOAc 3:1) afforded **5y** as a yellow powder (125 mg, 57%); mp: 116–117 °C; ^{1}H NMR (270 MHz, CDCl$_3$): $\delta=2.45$–2.52 (1H, m), 2.67 (1H, dt, $J=16.0$, 4.3 Hz), 2.88–2.95 (1H, m), 3.04 (1H, dt, $J=11.7$, 4.9 Hz), 3.26 (1H, d, $J=13.7$ Hz), 3.61 (3H, s), 3.74 (1H, d, $J=13.7$ Hz), 3.78 (3H, s), 4.52 (1H, s), 5.44 (1H, br), 6.17 (1H, s), 6.66 (1H, s), 6.76 (1H, dd, $J=8.2$, 2.3 Hz), 6.87–6.91 (2H, m), 7.17–7.23 (2H, m), 7.28–7.36 ppm (4H, m); ^{13}C NMR (67.5 MHz, CDCl$_3$): $\delta=28.2$, 47.0, 55.1, 55.8, 58.6, 68.1, 110.9, 112.1, 113.7, 114.1, 121.0, 127.1, 127.7, 128.2, 129.0, 129.5, 129.6, 141.4, 143.8, 144.4, 144.7, 159.5 ppm; HRMS (ES+): *m/z* found 376.1903, $C_{24}H_{26}NO_3^+$ $[M+H]^+$ requires 376.1907.

(±)-6-Hydroxy-7-methoxy-1-phenyl-2-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (5z): Method as for **5b** using compound **27d** (210 mg, 0.4 mmol) and Pd/C (10%, 30 mg) in THF (10 mL) and MeOH (10 mL) at room temperature for 1 h. Flash column chromatography (hexane to hexane/EtOAc 1:2) afforded **5z** as a yellow powder (150 mg, 82%); mp: 152–154 °C; ^{1}H NMR (270 MHz, CDCl$_3$): $\delta=2.51$–2.58 (1H, m), 2.72 (1H, dt, $J=16.0$, 4.7 Hz), 2.88–2.95 (1H, m), 3.08 (1H, dt, $J=11.7$, 5.1 Hz), 3.28 (1H, d, $J=13.7$ Hz), 3.63 (3H, s), 3.69 (1H, d, $J=13.7$ Hz), 3.82 (3H, s), 3.83 (6H, s), 4.56 (1H, s), 5.47 (1H, s, br), 6.18 (1H, s), 6.57 (2H, s), 6.69 (1H, s), 7.22–7.36 ppm (5H, m); ^{13}C NMR (67.5 MHz, CDCl$_3$): $\delta=28.0$, 46.8, 55.8, 56.0, 58.7, 60.8, 67.7, 105.1, 110.9, 113.7, 127.2, 127.7, 128.2, 129.5, 135.4, 136.5, 143.9, 144.3, 144.8, 153.0 ppm;

HRMS (ES+): *m/z* found 436.2107, $C_{26}H_{30}NO_5^+$ $[M+H]^+$ requires 436.2118.

(±)-7-Methoxy-2-(3-methoxybenzyl)-1-phenyl-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (6y): Method as for **6a** using compound **5y** (80 mg, 0.21 mmol) and sulfamoyl chloride (1.0 mmol) in DMA (1.0 mL) at room temperature for 24 h. Flash column chromatography (hexane/EtOAc 20:1 to 2:1) afforded **6y** as a light-yellow powder (55 mg, 58%); mp: 159–160 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 2.44–2.54 (1H, m), 2.66–2.75 (1H, m), 2.91–3.11 (2H, m), 3.25 (1H, d, *J* = 3.5 Hz), 3.61 (3H, s), 3.73 (1H, d, *J* = 3.5 Hz), 3.78 (3H, s), 4.58 (1H, s), 4.97 (2H, br), 6.33 (1H, s), 6.75–6.78 (1H, m), 6.85–6.88 (2H, m), 7.09 (1H, s), 7.16–7.34 ppm (6H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 28.0, 46.8, 55.0, 55.8, 58.5, 68.1, 112.0, 113.1, 114.0, 120.8, 123.5, 127.4, 127.6, 128.3, 129.0, 129.3, 137.2, 137.6, 140.8, 143.4, 149.3, 159.4 ppm; HRMS (ES+): *m/z* found 455.1647, $C_{24}H_{27}N_2O_5S^+$ $[M+H]^+$ requires 455.1635.

(±)-7-Methoxy-1-phenyl-6-sulfamoyloxy-2-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (6z): Method as for **6a** using compound **5z** (120 mg, 0.28 mmol) and sulfamoyl chloride (1.65 mmol) in DMA (1.0 mL) at room temperature for 24 h. Flash column chromatography (hexane/EtOAc 20:1 to 2:1) afforded **6z** as a white powder (110 mg, 76%); mp: 90–92 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 2.48–2.57 (1H, m), 2.75 (1H, dt, *J* = 11.3, 4.4 Hz), 2.91–3.02 (1H, m), 3.09 (1H, dt, *J* = 11.6, 4.7 Hz), 3.25 (1H, d, *J* = 13.5 Hz), 3.61 (3H, s), 3.67 (1H, d, *J* = 13.5 Hz), 3.81 (3H, s), 3.82 (6H, s), 4.58 (1H, s), 4.95 (2H, s), 6.33 (1H, s), 6.54 (2H, s), 7.11 (1H, s), 7.25–7.33 ppm (5H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 28.0, 46.7, 56.0, 56.2, 58.7, 60.8, 68.0, 105.1, 113.4, 123.9, 127.6, 128.3, 128.4, 129.5, 135.0, 136.7, 137.2, 138.2, 143.4, 149.1, 153.0 ppm; HRMS (ES+): *m/z* found 515.1852, $C_{26}H_{31}N_2O_7S^+$ $[M+H]^+$ requires 515.1846.

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