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Tetrahydroisoquinolinone-based Steroidomimetic and Chimeric Microtubule Disruptors

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Abstract

A SAR translation strategy was used for the discovery of tetrahydroisoquinoline (THIQ)-based steroidomimetic and chimeric microtubule disruptors based upon a steroidal starting point. A steroid A,B-ring-mimicking THIQ core was connected to methoxy aryl D-ring ring mimics through methylene, carbonyl and sulfonyl linkers to afford a number of steroidomimetic hits (e.g. **20c** GI₅₀ 2.1 μ M). Optimisation and control experiments demonstrate the complementary SAR of this series and the steroid derivatives that inspired its design. Linkage of the THIQ-based A,B-mimic with the trimethoxy aryl motif prevalent in colchicine site binding microtubule disruptors delivered a series of chimeric molecules whose activity (to GI₅₀ 40 nM) surpasses that of the parent steroid derivatives. Validation of this strategy was obtained from the excellent oral activity of **20z** relative to a benchmark steroidal bis-sulfamate in an *in vivo* model of multiple myeloma.

Keywords

tetrahydroisoquinolines; microtubule disruptors; tubulin assembly; colchicine binding

Introduction

Colchicine site binding microtubule disruptors seemingly possess great potential as therapies for cancer yet attempts to translate their preclinical promise into the clinical domain has proven elusive. The vinca alkaloids, taxanes and other taxane site binders, in contrast, have found wide therapeutic application and together they constitute arguably the most successful class of anti-cancer agents.^[1] Problems associated with existing microtubule disruptor drugs remain with, for example, limited therapeutic windows, acquired resistance, lack of oral bioavailability and problematic formulation typifying this class. Considerable potential for new microtubule disruptors with enhanced profiles and tissue-specificity is thus clearly evident. Colchicine site binders such as the combretastatins, 2-methoxyestradiol (2-MeOE2), and molecules inspired by, or derived from, these and related compounds are in clinical development and purportedly address some of the drawbacks associated with the existing clinical agents.^[2] Our own involvement in this field arose from the discovery that a non-estrogenic steroid sulfatase inhibitor 2-methoxyestrone-3-*O*-sulfamate (2-MeOEMATE)

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displays anti-proliferative activity against both estrogen receptor positive and negative cancer cells and, surprisingly, this activity surpasses that of 2-MeOE2.^[3] Further studies demonstrated that 2-MeOEMATE, and a range of related 2-substituted estratriene-3-*O*-sulfamates, possess a dual anti-proliferative and anti-angiogenic mechanism of action that was ascribed to their ability to disrupt normal microtubule assembly.^[4] The estratriene sulfamate derivatives, like 2-MeOE2, bind to tubulin in a competitive manner to colchicine^[5] and their activity is independent of estrogen receptor status.^[3a] Furthermore, these new steroidal sulfamates proved effective in cell lines expressing drug resistance through P-glycoprotein^[6] and BCRP^[7] and class III β -tubulin^[8] expression and are thus able to inhibit the growth of tumors resistant to taxanes and vinca alkaloids. Sulfamate derivatives such as 2-methoxyestradiol-3,17-*O,O*-bis-sulfamate (2-MeOE2bisMATE) **1a** also, in contrast to 2-MeOE2, display high oral bioavailability (> 85% in rodents).^[9] This appears to derive from the ability of the sulfamate groups to block both inactivating metabolism and deactivating conjugation, while also allowing the molecule to interact reversibly with carbonic anhydrase.^[9-10] Through this latter interaction, which has been characterised by protein crystallography,^[12d] first pass liver metabolism may be circumvented through sequestration of the sulfamate drugs in red blood cells.^[9,11] The promising combination of activity, and drug profile, encouraged extensive structure-activity studies to enumerate key elements of the pharmacophore for anti-proliferative activity.^[3b,5,12] These studies revealed that a 2-methoxy, 2-ethyl or 2-methylsulfanyl group, a 3-*O*-sulfamate, and a hydrogen bond acceptor projecting from the steroidal D-ring, as typified in **1**, are the key elements of the pharmacophore.

We investigated whether the SAR acquired in our steroidal series could be employed to design non-steroidal microtubule disruptors anticipating that, by decorating a suitable non-steroidal core structure with motifs key for activity in the steroidal series, new microtubule disruptors might be generated. Tetrahydroisoquinolines (THIQs) are common motifs in natural and synthetic compounds with interesting biological activity.^[13] Reports on the use of THIQs for the generation of SERMs^[14] encouraged our selection of this heterocycle as a prototypical mimic of the estrane A,B-ring system. We envisaged that the C-2 and C-3 pharmacophore elements of the steroidal A-ring could be introduced at C-7 and C-6 respectively of the THIQ core. Groups projecting a hydrogen bond acceptor into the region of space around the D-ring in the steroidal series could then be introduced at *N*-2 to deliver candidate steroidomimetic microtubule disruptors. The *N*-2 site offers an achiral, tractable point for elaboration and could also conceivably allow the products to be salified to promote formulation of any active compounds discovered. We have reported preliminary data from this approach^[15] and now disclose full details of, in particular, our exploration of the optimal linkage between the THIQ core and the aryl group and the nature of the decorating H-bond acceptor. In addition, derivatives with a polymethoxylated aryl group are described and their differential SAR indicate a chimeric nature.

Results and Discussion

Chemistry

The pharmacophore of the steroidal microtubule disruptors **1** is composed of a relatively rigid, lipophilic hydrocarbon core decorated with two substituents in the aromatic A-ring, namely a 2-substituent (optimally MeO, Et or MeS) and an adjacent, unsubstituted, 3-*O*-sulfamate group, in combination with a hydrogen bond acceptor group projecting from C-17 of the steroidal D-ring (Figure 1). In order to translate these features into a non-steroidal system we retained in its entirety the steroidal A-ring and chose to mimic the B-ring with an appropriately fused heterocycle. To expedite the synthesis of compound screening sets it was envisaged that a nitrogen atom in the B-ring mimic would offer a simple extension point into steroidal D-ring space. The tetrahydroisoquinoline (THIQ) ring was thus selected as a

core heterocyclic mimic of the steroidal A,B-ring system for preliminary investigation. For reasons of synthetic ease we chose to extend into the D-ring region of space with benzyl, benzoyl or benzenesulfonyl groups attached at *N*-2, and envisaged that, by making respective 2'-, 3'- and 4'-methoxy derivatives, a meaningful prototypical screening set would be generated for both the 6-hydroxy and 6-*O*-sulfamoylated classes.

A practical approach to protected 6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinolines **8** and **10** via a Pictet-Spengler^[16] based approach was first explored. Benzyl isovanillin **5** was subjected to a Henry aldol reaction with nitromethane and the resultant nitro alkene **6** was reduced in two steps. Sodium borohydride reduction of the alkene,^[17] followed by Raney-Nickel reduction of the nitro-group, proved superior in our hands to other approaches and delivered the desired phenethylamine in reasonable yield. In order to achieve good yields from the key Pictet-Spengler cyclisation it proved expeditious to first acylate the phenethylamine to give **7**, since purification of the cyclised product was greatly simplified and higher isolated yields possible. An alternate Pomeranz-Fritsch based approach to **8** was also explored and proved superior for large scale synthesis. This route involves an initial reductive amination of benzyl vanillin **11** with 2,2-diethoxyethylamine to deliver the acetal precursor **12** to Pomeranz-Fritsch cyclisation. Ring closure was then executed with 6M HCl.^[18] The 4-hydroxytetrahydroisoquinoline **13** was then reduced with NaBH₄/TFA to deliver **8**. In order to access a number of compounds with functions unstable under the hydrogenolytic deprotection conditions required to remove the benzyl protecting group, a batch of **8** was converted to the 6-*O*-TIPS derivative **10**. Hydrogenation of **8** at followed by TIPS protection afforded THIQ **10**.

With the protected THIQ core system in hand we then elaborated the prototypical screening set **17-22a-d** by reacting **8** or **10** with the respective 2-, 3- and 4-methoxy benzyl, benzoyl and benzenesulfonyl halides under the appropriate conditions (Scheme 2). Simple and broadly applicable reactions and commercially available starting materials were used. *N*-Benzyl THIQ derivatives **14** were typically generated by heating the appropriately protected THIQ and benzyl halide with two equivalents of triethylamine in ethanol at reflux, or more conveniently by heating at 130 °C for 0.5 h under microwave irradiation. A few benzyl halides were synthesised by chlorinating the corresponding benzyl alcohol with thionyl chloride, or by brominating the appropriate tolyl derivative at the benzylic position with NBS in tetrachloromethane. In some cases *N*-benzyl derivatives were approached from benzoic acid starting materials, with initial EDCI coupling reactions used to form amides that were then reduced to the *N*-benzyl derivatives **14** with LiAlH₄ in THF. *N*-Benzoyl THIQ derivatives **15** were typically synthesised by reaction of the appropriately protected THIQ with a slight excess of benzoyl halide and two equivalents of triethylamine in chloroform at room temperature. *N*-Benzenesulfonyl THIQ derivatives **16** were synthesised in a similar manner to the benzoyl derivatives, albeit in dichloromethane and with shorter reaction times required. After any requisite functional group inter-conversion, the 6-hydroxy group of the THIQ derivatives could be unmasked by hydrogenation or fluoride mediated desilylation to give the desired phenols **17-19** that in turn were sulfamoylated with sulfamoyl chloride in dimethylacetamide^[19] or, alternatively, with 2,6-di-*t*-butyl-4-methylpyridine and sulfamoyl chloride in dichloromethane^[20] to give the target sulfamates **20-22**. Functional group inter-conversions were carried out by standard literature methods with, for example, ethers being formed from the corresponding phenols by generating the phenolate with sodium hydride and then quenching with the appropriate alkyl halide.

A number of control compounds was also synthesised to test the nascent SAR (Scheme 3). Thus, THIQs in which each of the three key pharmacophore elements were individually deleted were synthesised. The phenols **17-19** that lack the sulfamate group are intermediates in the synthesis of **20-22** (keys enumerating the substituents are provided in the tables

below) and were thus available for biological evaluation. The derivative **20a**, bereft of the H-bond acceptor required in the steroidal D-ring region of space, was also easily accessible through reaction of benzyl bromide with the protected THIQ and conversion of the product to the sulfamate as outlined in Scheme 2. In order to determine whether, as we predicted, a 7-methoxy group would prove necessary for activity 6-benzyloxy-1,2,3,4-tetrahydroisoquinoline **24** was synthesised from commercially available 3-methoxyphenethylamine by a Pictet-Spengler approach analogous to that found in the literature.^[21-22] Compound **24** was then transformed to the target control compounds **25** and **26** by the routes outlined in Scheme 2.

Biology

The THIQ derivatives were initially assayed for their ability to inhibit the proliferation of DU-145 human prostate cancer cells *in vitro*. Where available, activity against the proliferation of MDA MB-231 human breast cancer cells is also presented. The magnitude and trends in activity obtained proved consistent across these two cell lines and thus, to simplify the discussion, only the data for DU-145 are discussed herein. The results obtained for the initial screening set, composed of the 2'-, 3'- and 4'-methoxy benzyl, benzoyl and benzenesulfonyl THIQ derivatives, are presented in Table 1. The corresponding compounds with a 6-*O*-benzyl group were also screened but proved less active ($GI_{50} > 100 \mu M$) and thus these data are omitted in the interests of clarity. As can be seen, phenol derivatives in the benzyl **17**, benzoyl **18** and benzenesulfonyl **19** series show little or no anti-proliferative activity as was expected, since these compounds lack the sulfamate group key to activity in the steroidomimetic series. For the same reason, the finding that the *N*-benzyl derivative **20a** lacking methoxy substitution is inactive was unsurprising. The *N*-benzyl THIQ sulfamate derivatives that possess all pharmacophore elements of the design do however show promising activity, with the 2'- and 3'-methoxy **20b** and **20c** derivatives causing 50% growth inhibition at concentrations in the single figure micromolar range. The activity of the 3'-methoxy derivative **20c** (GI_{50} 2.1 μM) is approximately 4-fold better than the 2'-methoxy compound **20b**. In the case of the sulfamoylated *N*-benzoyl THIQs, the 3'- and 4'-methoxy compounds **21b** and **21c** display promising activity, with the 3'-methoxy derivative **21b** most active. In this case, however, the difference in activity between **21b** and **21c** is not great. The sulfamoylated *N*-benzenesulfonyl compounds **22a-c** show little activity, with very modest growth inhibition only observed for the 3'-methoxy derivative **22b**. It was clear from these results that the nature of the linker between the THIQ core and the aryl group has a significant effect on biological activity and we thus chose to focus our studies on explorations in the *N*-benzyl THIQ series **20**, reasoning that the methylene linker, the smallest of the three groups surveyed in the prototype libraries, should allow for the THIQ derivatives to access all possible conformations and minimize any potential off-target interactions. The fact that the best activity in the simple methoxy substituted series is obtained with the methylene linker also supports this approach.

For clarity, the series of control compounds that lacks one or more element of the pharmacophore from the initial design (compound **20c**) is presented alongside their activity data in Figure 2. As can be seen, all of the control compounds prove inactive. These results provide support for our hypothesis that compounds acting in an analogous manner to the steroids could be generated as the combination of all three pharmacophore elements is required for good activity in the steroidal series prove to be essential for activity in this prototype THIQ-based series. To consolidate these preliminary results we first aimed to establish a preliminary SAR for the 3'-substituent in the *N*-benzyl series and results obtained for a series of ether and ester derivatives are presented in Table 2. As observed in the methoxy series, the phenol derivatives **17e-i** show only modest activity and is not indicative of activity of the corresponding sulfamates. Of the sulfamate derivatives the 3'-hydroxyl

compound **20e** is inactive, while the trifluoromethoxy compound **20f** is essentially equipotent to methoxy compound **20c**. The 3'-ethoxy derivative **20g** (GI₅₀ 1.15 μ M) is the most active, with activity against DU-145 cells approximately 2-fold better than **20c** and against MDA MB-231 cells in the sub-micromolar range. The larger isopropyl **20h** and phenyl **20i** ethers display reduced activity which correlates to their increasing steric size. The 3'-*O*-acetate **20k** and 3'-*O*-sulfamate **20j** derivatives exhibit only modest activity. From these results it is appearing that the pocket available around the 3'-position is relatively small.

We thus explored introduction of alternate motifs at the 3'-position to determine whether an H-bond acceptor group is really requisite for activity. The anti-proliferative activities of the series of 3'-substituted compounds **20l-t** synthesised are presented in Table 3. The series of 3'-substituted phenols **17l-t** presented in Table 3, as with the foregoing phenol derivatives, shows no significant activity. The sulfamate derivatives, in contrast, once more display interesting activity that provides further insights on the SAR at this position. The fluoro-substituted compound **20l**, like the methyl **20n** and ethyl **20o** derivatives, is much less active than those compounds in which substituents offer the potential for H-bonding or alternate electrostatic interactions. It appears, given the activity of ethyl derivative **20o** against MDA MB-231 proliferation, that positive lipophilic interactions make some contribution to activity, an observation in concord with the relative activities of the 3'-hydroxy **20e**, 3'-methoxy **20c** and 3'-ethoxy **20g** compounds discussed above. It is clear, however, that an H-bond acceptor (available lone electron pair) is highly favoured, although its projection from the aromatic ring is not simply limited to a single bond length, since the acetate **20q**, nitro **20r** and cyano **20p** derivatives exhibit reasonable activity.

The 3'-chloro derivative **20m** that is capable of participating in both lipophilic and electrostatic interactions, also displays low micro-molar activity. While we had obtained good preliminary activity from this THIQ design approach it became evident that the degree of rotational freedom of the *N*-benzyl group is likely a limitation to activity and that biasing of the conformational population such that the *N*-benzyl group projects into the area of space occupied by the steroidal D-ring might be desirable. Preliminary results obtained with such conformationally restrained THIQ-based systems have been reported elsewhere.^[15]

In the *N*-benzyl series we also explored whether polysubstituted *N*-benzyl groups could deliver enhanced activity. For reasons of simplicity and availability of starting materials a series of di- **20u-x** and tri- **20y-ab** methoxy derivatives was synthesised and their activities are reported in Table 4. It is useful here to consider what effect on activity can be attributed to the additional substituent by comparing the lead 3'-methoxy compound **20c** and its various dimethoxy analogues. As can be seen for the sulfamoylated 2',3'-dimethoxy derivative **20u**, introduction of an additional substituent at the 2' position can provide a modest enhancement in activity as **20u** is approximately 2-fold more active than **20c**. In contrast, the 3',4'-dimethoxy compound **20v** is 4-fold less active than **20c**. This pattern reflects the structure activity relationship observed in the mono-methoxybenzyl series where 3' > 2' >> 4'. It thus appears reasonable that a 4'-methoxy group might preclude binding of the THIQ derivatives in a manner analogous to the steroidal microtubule disruptors that they are designed to mimic. In contrast, the 2'-substituent appears able to provide extra beneficial interaction(s) at the site of action. Combination of the 3'-methoxy with a methoxy group at either the 5'- or 6'-position has little effect on activity and shows that, while there is space for these groups to be tolerated, they apparently contribute no further positive interaction. Furthermore, it appears that increasing the electron density of the aryl ring provides no apparent enhancement in activity, suggesting that any putative π -facial interactions are not improved.

The activities of the sulfamoylated trimethoxy derivatives **20y-ab** are extremely interesting and in this case it is illustrative to compare them with the corresponding sulfamoylated disubstituted compounds. The 2',3',4'-trimethoxy derivative **20y** displays only modest activity with a GI₅₀ of 17 μ M; this is *ca* 10-fold worse than the 2',3'-dimethoxy compounds **20u** and 2-fold worse than the 3',4'-dimethoxy derivative **20v**. As before, substitution at C-4 appears to be detrimental to activity. The 3',4',5'-trimethoxy compound **20z**, with its GI₅₀ of 297 nM, is extremely active; it is 10-fold more active than the 3',5'-dimethoxy analogue **20w** and *ca* 30-fold better than the 3',4'-dimethoxy compound **20v**. This contrasts strongly with results discussed above, where 4'-methoxy substitution is universally detrimental to activity. The activity of the corresponding phenol **17z** (GI₅₀ 650 nM) is also notable with, for the first time, the activities of phenol **17z** and sulfamate **20z** derivatives proving to be of a similar magnitude. It is thus apparent that the activities of the 3',4',5'-trimethoxy derivatives **17z** and **20z** do not follow the SAR established above for the foregoing mono- and disubstituted *N*-benzyl THIQs, where all three pharmacophore elements from the steroidal series are requisite for activity and 4'-substitution is detrimental to activity. The 3',4',6'-trimethoxy derivatives also show good activity for both the phenol **17aa** (GI₅₀ 7.8 μ M) and sulfamate **20aa** (GI₅₀ 660 nM), with the latter proving 10-fold and 4-fold better than the 3',4'-methoxy **20v** and 3',6'-dimethoxy **20x** derivatives, respectively. Once more, there are two points of divergence from the SAR established for the mono- and di-substituted *N*-benzyl THIQ series. This led us to postulate that trimethoxy-substituted compounds, rather than mimicking steroidal colchicine site binding microtubule disruptors, might better be considered chimeric systems composed of the steroidal A,B-ring mimicking motif and the trimethoxyaryl group prevalent in colchicine site binding natural products. The binding of the trimethoxyaryl group in this case is likely the predominant interaction and the THIQ component can still potentially access the binding site occupied by the steroidal A-ring.

Although not discussed in this paper, it is notable that groups at C-1 and C-3 of the THIQ core that can effect a conformational biasing have no significant effect on activity in the 3',4',5'-trimethoxy series, whereas in mono-substituted *N*-benzyl systems their effects are profound.^[15] The 2',4',6'-trimethoxy compounds **17ab** and **20ab** are inactive, which is unsurprising and they appear to conform to the general steroidomimetic SAR where 4'-substitution is detrimental for activity.

With excellent activity established for the 3',4',5'-trimethoxy compound **20z** we modified the THIQ at C-7 and the linker while retaining this motif and synthesised the C-7-ethyl derivatives **17ac** and **20ac**. Replacing the C-7-methoxy group with an ethyl group leads to a near 10-fold reduction in activity for the phenol **17ac** relative to **17z** and a *ca* 8-fold gain in activity for the sulfamate **20ac** relative to **20z** (see Table 5). Interestingly, this effect on activity reflects the trends in activity change in the steroidal series wherein the 2-ethyl derivatives are, respectively, less and more active than the 2-methoxy-3-hydroxy and 2-methoxy-3-*O*-sulfamoyl derivatives.^{3b,12d} The *N*-3',4',5'-trimethoxybenzoyl THIQ derivatives **18d** and **21d** are less active than the corresponding 3',4',5'-trimethoxybenzyl compounds **17z** and **20z** (see Table 5), albeit **18b** and **21b** display enhanced activity relative to the other *N*-benzoyl derivatives described above. The improvement in activity for phenol **18d** relative to **18b** is more than 30-fold, while the 3',4',5'-trimethoxybenzoyl sulfamate **21d** is more modest and only 2-fold more active than **21b**. It is striking in this case that the phenol is more active than the sulfamate. Although it is not possible to provide a definite explanation, it is plausible to suggest that these compounds are chimeras and that the bulkier carbonyl linker precludes optimal binding of the sulfamate of **21d** and thus the phenol **18d** is the more active. The activities of **18d** and **17z** are comparable, indicating that the carbonyl linker does not significantly inhibit binding in the phenol series.

Several of the more active chimeras were evaluated for their ability to inhibit both tubulin assembly and the binding of tubulin to colchicine alongside combretastatin A-4 (Table 6). IC₅₀ values for both **17z** and **20z** are > 20 μ M, with no observable effect observed at this concentration for **17z**. Compound **20z**, however, shows some activity at 20 μ M and is also better at inhibiting colchicine binding. A better indication of on target activity was however available for **20ac**, the 7-ethyl analogue of **20z** which, with an IC₅₀ of 2.5 μ M against tubulin assembly, is similar in activity to combretastatin A-4 (**CA-4**). Likewise, in terms of inhibition of tubulin binding, the ethyl compound **20ac** proved superior to both **17z** and **20z**. It should be noted that, as with all microtubule disruptors, the concentrations required for catastrophic loss of structure are much higher than those required to trigger cell death, reflecting the fact that simply perturbing normal assembly is sufficient to arrest normal cell division.

The acid test for any promising candidate is whether *in vitro* activity can be translated into the *in vivo* context and preliminary data for **20ac** proved promising.^[23a] Compound **20z**, although clearly less active *in vitro*, was selected for evaluation *in vivo* as, in the steroidal series, we had observed a superior DMPK profile for methoxy derivatives over their ethyl analogues. Assessment of **20z** in the RPMI-8226 xenograft model of multiple myeloma and relative to the steroidal parent **1a** was performed. We determined that this compound could be formulated as a solution in 2% aqueous citric acid and **20z** was dosed orally in this form on a daily basis for 28 days at 40 mg/kg. The results are presented in Figure 3, wherein strong inhibition of tumor growth (64% for both the **20z** and **1a** treated cohorts after 28 days) can be seen.

Furthermore, a prolonged inhibition of tumor growth is observed in both treated cohorts (66% and 64% growth inhibition 18 days after cessation of dosing for the **20z** and **1a** treated cohorts, respectively). This experiment thus both confirms the strong potential and the favourable formulation characteristics of this class of THIQ-based chimeric microtubule disruptors. The apparent equivalence of **20ac** and **20z** in this model (**20ac** showed 48% growth inhibition after 28 days at 40 mg/kg) also confirms that DMPK factors can override apparently superior preliminary *in vitro* activity *in vivo*. In further preclinical evaluations compound **20z** was also shown to be a tubulin disruptor which induces p53 expression, Bcl2 phosphorylation, caspase 3 cleavage, cell cycle arrest and subsequent apoptosis.^[23b] Additionally, it is a potent anti-angiogenic agent both *in vitro* and *in vivo* with additional vascular targeting potential. In a hormone-independent breast cancer xenograft model **20z** suppressed tumor growth by 84% after 35 days of daily dosing, with no signs of toxicity. In contrast to Taxol, the efficacy of **20z** was also unchanged in two clinically relevant models of drug resistance.^[23b]

Conclusion

We have demonstrated that the tetrahydroisoquinoline core is a useful mimic of the steroidal A,B-ring system which, by use of the SAR translation strategy outlined above, may find broader application for the elaboration of steroidomimetic systems. In addition combining pharmacophore elements from different series that address the same target protein, yields molecules with a distinct SAR from steroidomimetic THIQs that are best considered small molecule chimeras. It is notable that chimera construction was achieved remaining within the parameters associated with an orally bioavailable drug and, in confirmation, oral dosing of **20z** in a xenograft model of multiple myeloma reveals excellent inhibition of tumor growth, confirming the promise of this series. We have thus generated a novel series of microtubule disruptors with excellent *in vitro* and *in vivo* activity that may fit the profile of moderate half-life microtubule disruptors explaining the very desirable drug-like profile (good oral efficacy and good tolerability). The compounds are easily synthesised, amenable

to formulation using benign excipients and also inhibit the proliferation of taxane resistant cell lines.^[23] Further optimisation of these series of anti-cancer agents is in progress.

Experimental

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% CO₂ humidified atmosphere at 37 °C in RPMI-1640 medium, supplemented with 10% fetal bovine serum, penicillin, and streptomycin.

Anti-proliferative Assays—DU-145 and MDA-MB-231 cells were seeded into 96-well microtitre plates (5000 cells/well) and treated with 10⁻⁹-10⁻⁴ M of compound 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 (GI₅₀). All experiments were performed in triplicate.

Tubulin Assays—Bovine brain tubulin, prepared as described previously,^[24] was used in studies presented here. Assembly IC₅₀'s were determined as described in detail elsewhere.^[25] Briefly, 1.0 mg/mL (10 μM) tubulin was preincubated without GTP with varying compound concentrations for 15 min at 30 °C. Reaction mixtures were placed on ice, and GTP (final concentration, 0.4 mM) 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 reduce the turbidity increase by 50% were determined. The method for measuring inhibition of the binding of [³H]colchicine to tubulin was described in detail previously.^[26] Reaction mixtures contained 0.1 mg/mL (1.0 μM) tubulin, 5.0 μM [³H]colchicine, and potential inhibitor at 5.0 μM. Compounds were compared to CA-4, a particularly potent inhibitor of the binding of colchicine to tubulin.^[27] Reaction mixtures were incubated 10 min at 37 °C, a time point at which the binding of colchicine in control reaction mixtures is generally 40-60% complete.

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-hour life cycle at 22 °C and 40%-60% humidity. Animal care was in accordance with institutional guidelines. Tumor cells (6 × 10⁶ cells/animal) were implanted subcutaneously into the left flank of mice. Multiple myeloma cancer cells were implanted with an equal volume of Matrigel to increase take rate. Tumors were monitored initially twice weekly, and then daily as the neoplasms reached the desired size, approximately 100 mm³ (100 mg). When the tumors attained this predetermined size, the animals were randomized into 3 groups with 6 animals per group. Estimated tumor weight was calculated using this formula: Tumor Weight (mg) = (w² × l)/2 where w = width and l = length in mm of the multiple myeloma tumor.

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. DMA was purchased from Aldrich and stored

under a positive pressure of N₂ after use. THF was distilled from sodium with benzophenone indicator. Sulfamoyl chloride was prepared by an adaptation of the method of Appel and Berger^[28] and was stored in the refrigerator under positive pressure of N₂ as a solution in toluene as described by Woo *et al.*^[29] An appropriate volume of this solution was freshly concentrated *in vacuo* immediately before use. Reactions were carried out at room temperature unless stated otherwise. Thin layer chromatography (TLC) was performed on pre-coated aluminium plates (Merck, silica gel 60 F₂₅₄). Product spots were visualized either by UV irradiation at 254 nm or by staining with either alkaline potassium permanganate solution or 5% w/v dodecamolybdophosphoric acid in ethanol, followed by heating. Flash column chromatography was performed using gradient elution (solvents indicated in text) on either pre-packed columns (Isolute) on a Flashmaster II system (Biotage) or on a Teledyne ISCO CombiFlash Rf Automated Flash Chromatography System with RediSep Rf disposable flash columns. ¹H NMR and ¹³C NMR spectra were recorded with either a Jeol Delta JMN-GX 270 at 270 and 67.5 MHz, respectively, or a Varian Mercury VX 400 NMR spectrometer at 400 and 100 MHz, respectively. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard. Coupling constants *J*, are recorded to the nearest 0.1 Hz. The precursors of compounds **8**, **14o** and **14ab** and compounds **13**, **15a-b**, **15d**, **18a-b**, **18d** and **21a-c** appear each as a set of two conformers in the ¹H NMR spectra. Mass spectra were recorded at the Mass Spectrometry Service Center, University of Bath, UK. FAB-MS were carried out using *m*-nitrobenzyl alcohol (NBA) as the matrix. Elemental analyses were performed by the Microanalysis Service, University of Bath. Melting points were determined using a Stuart SMP3 or a Stanford research systems Optimelt MPA100 melting point apparatus and are uncorrected. All compounds were 98% pure by reverse phase HPLC run with acetonitrile/water or methanol/water (Sunfire C18 reverse phase column, 4.6 × 150 mm, 3.5 μm pore size).

(E)-2-Benzyloxy-1-methoxy-4-(2-nitrovinyl)benzene (6)—Compound **5** (75.0 g, 0.31 mol) was treated with nitromethane (32.2 mL, 0.6 mol) and ammonium acetate (34.7 g, 0.45 mol) in acetic acid (500 mL) at 140 °C for 2 h. The solution was cooled to rt. Water (800 mL) was added and the resulting solid was filtered, washed with water and dried. The solid was stirred in hot ethanol (800 mL), cooled to rt, filtered and dried to afford compound **6** as a yellow powder (69.0 g, 70%). ¹H NMR (270 MHz, CDCl₃): δ = 3.95 (3H, s), 5.18 (2H, s), 6.94 (1H, d, *J* = 8.4 Hz), 7.04 (1H, d, *J* = 2.4 Hz), 7.18 (1H, dd, *J* = 8.4, 2.0 Hz), 7.31-7.48 (6H, m), 7.92 (1H, s). ¹³C NMR (67.5 MHz, CDCl₃): δ = 56.2 (CH₃), 71.2 (CH₂), 111.7 (CH), 113.1 (CH), 122.7 (C_q), 124.9 (CH), 127.3 (CH), 128.3 (CH), 128.8 (C_q), 135.2 (CH), 136.3 (C_q), 139.3 (CH), 148.7 (C_q), 153.5 (C_q). LC/MS (APCI+): *m/z* 286.46 (M⁺+H).

N-(3-Benzyloxy-4-methoxyphenethyl)acetamide (7)—Sodium borohydride (12.0 g, 317 mmol) was covered with dioxane (250 mL) and DMF (70 mL). Compound **6** (20.0 g, 70.2 mmol) was added dropwise at 0 °C within 5 h as solution in dioxane (200 mL) and DMF (50 mL). The reaction mixture was stirred at rt for 1 h, cooled to 0 °C and carefully quenched with HCl (2M). The reaction mixture was extracted with EtOAc (500 mL), washed with water and brine, then dried (MgSO₄), filtered and concentrated *in vacuo*. Flash column chromatography (hexane/EtOAc 4:1) afforded 2-(3-benzyloxy-4-methoxyphenyl)nitroethane as a light yellow powder (10.0 g, 50%), mp 88-89 °C. ¹H NMR (270 MHz, CDCl₃): δ = 3.21 (2H, t, *J* = 7.4 Hz), 3.87 (3H, s), 4.52 (2H, t, *J* = 7.4 Hz), 5.14 (2H, s), 6.73 (1H, d, *J* = 1.9 Hz), 6.75 (1H, dd, *J* = 8.0, 1.9 Hz), 6.85 (1H, d, *J* = 8.0 Hz), 7.29-7.46 (5H, m). LC/MS (APCI−): *m/z* 286.33 (M[−]-H). Raney nickel (50% slurry in water, 7.5 g) was washed in presence of a magnetic stirring bar with methanol (3 × 5 mL). The nitroalkane (9.0 g, 31.3 mmol) was then added as a solution in methanol (50 mL), the reaction cooled to 0 °C and hydrazine hydrate (6.0 mL, 123 mmol) was added in a dropwise manner. The reaction mixture was stirred at 40 °C for 1 h, cooled to rt, filtered through celite

and washed with methanol (40 mL). The filtrate was concentrated in vacuo and the residue was stirred in EtOAc (80 mL), washed with water (50 mL) and brine, then dried (MgSO₄), filtered and concentrated in vacuo to afford 3-benzyloxy-4-methoxyphenethylamine as a colourless oil (7.2 g, 88%). ¹H NMR (270 MHz, CDCl₃): δ = 1.27 (2H, s, br), 2.62 (2H, t, *J* = 6.7 Hz), 2.86 (2H, t, *J* = 6.7 Hz), 3.85 (3H, s), 5.14 (2H, s), 6.72 (1H, s), 6.75 (1H, d, *J* = 1.7 Hz), 6.82 (1H, dd, *J* = 7.2, 1.5 Hz), 7.26-7.46 (5H, m). The amine (7.2 g, 28.0 mmol) was dissolved in DCM (50 mL) and TEA (5.0 mL, 36.0 mmol) and cooled to 0 °C. Acetic anhydride (3.7 mL, 39.2 mmol) was added dropwise and the solution was stirred at 0 °C for 2 h then at rt for 2 h. The reaction mixture was diluted with DCM (50 mL) and washed with water and brine, then dried (MgSO₄), filtered and concentrated in vacuo. Flash column chromatography (hexane/EtOAc 2:1 to 1:4) afforded compound **7** as a white solid (4.50 g, 54%), mp 126-127 °C. ¹H NMR (270 MHz, CDCl₃): δ = 1.86 (3H, s), 2.68 (2H, t, *J* = 6.9 Hz), 3.40 (2H, q, *J* = 6.9 Hz), 3.86 (3H, s), 5.13 (2H, s), 5.34 (1H, s, br), 6.70 (1H, s), 6.72 (1H, d, *J* = 8.4 Hz), 6.83 (1H, d, *J* = 8.4 Hz), 7.26-7.45 (5H, m).

6-Benzyloxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (8)—Compound **7** (4.20 g, 14.0 mmol) was treated with paraformaldehyde (1.00 g, 33.3 mmol) and *p*-TSA (30 mg, 0.16 mmol) in toluene (80 mL) at 120 °C for 4 h. After cooling to rt the reaction mixture was concentrated in vacuo and EtOAc was added. The mixture was washed with water and brine, then dried (MgSO₄), filtered and concentrated in vacuo to afford the *N*-acetyl-THIQ as a light yellow solid (4.25 g, 98%), mp 121-122 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.14 and 2.16 (3H, 2s), 2.69 and 2.74 (2H, 2t, *J* = 5.9 and 5.7 Hz), 3.62 and 3.77 (2H, 2t, *J* = 5.9 and 5.7 Hz), 3.84 and 3.85 (3H, 2s), 4.53 and 4.61 (2H, 2s), 5.11 (2H, 2s), 6.59 and 6.65 (1H, 2s), 6.64 (1H, s), 7.26-7.45 (5H, m). LC/MS (APCI+): *m/z* 312.34 (M⁺+H). The *N*-acetyl-THIQ (4.25 g, 13.7 mmol) was treated with aqueous sodium hydroxide (10%, 30 mL) in ethanol (120 mL) at 120 °C for 16 h. The reaction mixture was concentrated in vacuo. The residue was stirred in water (50 mL) and extracted with chloroform (2 × 100 mL). The combined organics were washed with brine, dried (MgSO₄), filtered and concentrated in vacuo to give a yellow oil that slowly solidified to afford compound **8** as a yellow solid (3.45 g, 94%), mp 74-75 °C. ¹H NMR (270 MHz, CDCl₃): δ = 1.76 (1H, s, br), 2.63 (2H, t, *J* = 5.7 Hz), 3.07 (2H, t, *J* = 5.7 Hz), 3.81 (3H, s), 3.92 (2H, s), 5.10 (2H, s), 6.52 (1H, s), 6.60 (1H, s), 7.27-7.44 (5H, m). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.3 (CH₂), 43.6 (CH₂), 47.6 (CH₂), 55.5 (CH₃), 70.8 (CH₂), 109.3 (CH), 114.6 (CH), 126.2 (2 × C_q), 126.9 (2 × CH), 127.4 (CH), 128.3 (2 × CH), 137.0 (C_q), 146.2 (C_q), 147.7 (C_q). LC/MS (APCI+): *m/z* 270.40 (M⁺+H).

6-Benzyloxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (8)—Compound **13** (1.95 g, 6.8 mmol) was covered with DCM (14 mL) and TFA (5.1 mL, 68.6 mmol) was added dropwise at 0 °C. Sodium borohydride (515 mg, 13.6 mmol) was added portionwise at 0 °C and the reaction mixture was stirred warming to rt for 18 h then diluted with DCM (100 mL), washed with sodium bicarbonate (2M, 100 mL) and water (100 mL), then dried (NaCl), filtered and concentrated in vacuo. The residue was stirred in diethyl ether, filtered, washed with diethyl ether and dried to afford compound **8** as a white powder (1.762 g, 96%). Data as described above.

6-Hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (9)—Compound **8** (4.30 g, 16.0 mmol) was dissolved in methanol (320 mL) and filtered. The solution was sucked at 1.0 mL/min into the H-cube and treated with full hydrogen over Pd/C (10%, 140 mg cartridge) at rt. The resulting solution was concentrated in vacuo to give a white solid that was stirred in EtOAc, filtered and dried to afford compound **9** as a white solid (2.853 g, 99%), mp 195-197 °C. ¹H NMR (270 MHz, CD₃OD): δ = 3.01 (2H, t, *J* = 6.2 Hz), 3.47 (2H, t, *J* = 6.2 Hz), 3.87 (3H, s), 4.28 (2H, s), 6.68 (1H, s), 6.78 (1H, s). ¹³C NMR (67.5 MHz,

CD₃OD): δ = 25.7 (CH₂), 43.3 (CH₂), 45.9 (CH₂), 56.9 (CH₃), 110.9 (CH), 116.4 (CH), 120.0 (C_q), 125.2 (C_q), 147.9 (C_q), 148.8 (C_q). LC/MS (APCI+): m/z 180.05 (M⁺+H).

7-Methoxy-6-triisopropylsiloxy-1,2,3,4-tetrahydroisoquinoline (10)—Compound **9** (3.136 g, 17.5 mmol) was treated with chlorotriisopropylsilane (4.07 g, 21.1 mmol) and imidazole (3.577 g, 52.5 mmol) in DCM (90 mL) at rt for 48 h. The reaction mixture was washed with water (200 mL) containing ammonium chloride (saturated 20 mL). The aqueous layer was extracted with DCM/EtOAc (4:1, 2 × 100 mL). The combined organics were dried (NaCl), filtered and concentrated in vacuo. Flash column chromatography (SiO₂: 120 g, EtOAc/methanol 4:1 to 1:1 to 1:1 and 2% TEA) afforded compound **10** as a light yellow solid (4.95 g, 84%). ¹H NMR (270 MHz, CDCl₃): δ = 1.05 (18H, d, J = 6.9 Hz), 1.12–1.30 (3H, m), 2.81 (2H, t, J = 6.1 Hz), 3.21 (2H, t, J = 6.0 Hz), 3.72 (3H, s), 4.04 (2H, s), 6.46 (1H, s), 6.58 (1H, s). ¹³C NMR (67.5 MHz, CDCl₃): δ = 12.8 (CH), 17.9 (CH₃), 28.3 (CH₂), 43.9 (CH₂), 48.0 (CH₂), 55.5 (CH₃), 109.7 (CH), 120.7 (CH), 126.4 (C_q), 128.2 (C_q), 143.6 (C_q), 148.9 (C_q).

N-(4-Benzyloxy-3-methoxybenzyl)-N-(2,2-diethoxyethyl)-amine (12)—Compound **11** (25.0 g, 103 mmol) was treated with aminoacetaldehyde diethyl acetal (11.7 mL, 108 mmol) at 60 °C for 8 h. The mixture was dissolved in ethanol (150 mL) and sodium borohydride (4.20 g, 110 mmol) was added portionwise. The mixture was stirred at 120 °C for 4 h, then poured into ice-water, stirred for 0.5 h and extracted with EtOAc. The organic layer was washed with water and brine, then dried, filtered and concentrated in vacuo to afford compound **12** as a light yellow oil (35.90 g, 97%). ¹H NMR (270 MHz, CDCl₃): δ = 1.19 (6H, t, J = 7.2 Hz), 1.51 (1H, s, br), 2.72 (2H, d, J = 5.5 Hz), 3.51 (2H, dq, J = 7.2, 1.9 Hz), 3.67 (2H, dq, J = 7.2, 1.9 Hz), 3.72 (2H, s), 3.88 (3H, s), 4.60 (1H, t, J = 5.5 Hz), 5.13 (2H, s), 6.75 (1H, dd, J = 8.3, 1.4 Hz), 6.81 (1H, d, J = 8.3 Hz), 6.89 (1H, d, J = 1.4 Hz), 7.27–7.44 (5H, m). ¹³C NMR (67.5 MHz, CDCl₃): δ = 15.5 (2 × CH₃), 51.6 (CH₂), 53.8 (CH₂), 56.1 (CH₃), 62.4 (2 × CH₂), 71.2 (CH₂), 102.3 (CH), 111.9 (CH), 114.0 (CH), 120.3 (CH), 127.3 (2 × CH), 127.8 (CH), 128.6 (2 × CH), 133.6 (C_q), 137.4 (C_q), 147.2 (C_q), 149.7 (C_q). HRMS (ES+): m/z found 360.2161; C₂₁H₃₀NO₄⁺ (M⁺+H) requires 360.2169.

6-Benzyloxy-4-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (13)—A suspension of compound **12** (20 g, 55.6 mmol) in dioxane (20 mL) and HCl (6M, 250 mL) was stirred at 45 °C for 1.5 h. After cooling to 0 °C the white solid was filtered, washed successively with cold water and diethyl ether then poured into water (200 mL). The suspension was stirred at 0 °C and made alkaline with sodium hydroxide. After an additional 0.5 h stirring the white solid was filtered off, washed with water then diethyl ether and dried in vacuo to afford compound **13** as a white powder (12.80 g, 81%), mp 148–149 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.33 (2H, s, br), 2.94 (1H, dd, J = 13.0, 2.8 Hz), 3.15 (1H, dd, J = 12.9, 3.0 Hz), 3.69 and 3.79 (2H, 2d, J = 0.5 and 2.2 Hz), 3.84 (3H, s), 4.39 (1H, t, J = 2.8 Hz), 5.12 (2H, s), 6.49 (1H, s), 6.89 (1H, s), 7.27–7.44 (5H, m). ¹³C NMR (67.5 MHz, CDCl₃): δ = 47.8 (CH₂), 51.3 (CH₂), 56.1 (CH₃), 65.4 (CH), 71.1 (CH₂), 109.1 (CH), 114.7 (CH), 127.5 (2 × CH), 127.9 (CH), 128.6 (2 × CH), 128.8 (C_q), 128.9 (C_q), 137.1 (C_q), 147.0 (C_q), 149.5 (C_q). HRMS (ES+): m/z found 286.1425; C₁₇H₂₀NO₃⁺ (M⁺+H) requires 286.1438.

2-Benzyl-6-benzyloxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (14a)—Compound **8** (404 mg, 1.5 mmol) was treated with benzyl bromide (0.19 mL, 1.6 mmol) and TEA (0.42 mL, 3.0 mmol) in ethanol (30 mL) at 120 °C for 18 h. The reaction mixture was concentrated in vacuo. The residue was dissolved in EtOAc (80 mL), washed with water and brine, then dried (MgSO₄), filtered and concentrated in vacuo. Flash column chromatography (hexane/EtOAc 10:1 to 4:1) afforded compound **14a** as a white solid (0.32

g, 59%), mp 97-98 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.66-2.78 (4H, m), 3.53 (2H, s), 3.66 (2H, s), 3.80 (3H, s), 5.10 (2H, s), 6.50 (1H, s), 6.61 (1H, s), 7.25-7.45 (10H, m). LC/MS (APCI+): *m/z* 360.52 (M⁺+H). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.7 (CH₂), 50.9 (CH₂), 55.9 (CH₂), 56.1 (CH₃), 62.9 (CH₂), 71.1 (CH₂), 110.1 (CH), 114.3 (CH), 126.3 (C_q), 127.2 (CH), 127.4 (2 × CH), 127.5 (C_q), 127.8 (CH), 128.4 (2 × CH), 128.6 (2 × CH), 129.2 (2 × CH), 137.4 (C_q), 138.5 (C_q), 146.7 (C_q), 147.9 (C_q). HRMS (ES+): *m/z* found 360.1955; C₂₄H₂₆NO₂⁺ (M⁺+H) requires 360.1958.

6-Benzyloxy-7-methoxy-2-(2-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (14b)—Compound **8** (404 mg, 1.5 mmol) was treated with 2-methoxybenzyl chloride (0.25 mL, 1.8 mmol) and TEA (0.42 mL, 3.0 mmol) in ethanol (4.0 mL) at 120 °C for 1 h in the microwave oven. The mixture was poured into water (20 mL) and extracted with EtOAc (2 × 50 mL). The combined organics were washed with water and brine, then dried (MgSO₄), filtered and concentrated in vacuo. Flash column chromatography (hexane/EtOAc 8:1 to 2:1) afforded compound **14b** as a white solid (0.37 g, 63%), mp 85-86 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.75 (4H, s), 3.59 (2H, s), 3.70 (2H, s), 3.81 (3H, s), 3.83 (3H, s), 5.10 (2H, s), 6.51 (1H, s), 6.63 (1H, s), 6.87 (1H, dd, *J* = 8.4, 1.0 Hz), 6.94 (1H, dt, *J* = 7.4, 1.0 Hz), 7.21-7.45 (7H, m). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.8 (CH₂), 50.9 (CH₂), 55.5 (CH₃), 55.8 (CH₂), 56.1 (CH₃), 60.5 (CH₂), 71.1 (CH₂), 110.2 (CH), 110.4 (CH), 114.3 (CH), 120.4 (CH), 126.4 (C_q), 126.5 (C_q), 127.4 (2 × CH), 127.8 (CH), 127.8 (C_q), 128.1 (CH), 128.5 (2 × CH), 130.5 (CH), 137.4 (C_q), 146.6 (C_q), 147.9 (C_q), 157.9 (C_q). LC/MS (APCI+): *m/z* 390.49 (M⁺+H). HRMS (ES+): *m/z* found 390.2064; C₂₅H₂₈NO₃⁺ (M⁺+H) requires 390.2064.

6-Benzyloxy-7-methoxy-2-(3-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (14c)—Method as for **14a** using compound **8** (404 mg, 1.5 mmol), 3-methoxybenzyl bromide (0.29 mL, 2.1 mmol) and TEA (0.84 mL, 6.0 mmol) in ethanol (20 mL) at 120 °C for 72 h. Flash column chromatography (hexane/EtOAc 10:1 to 3:1) afforded compound **14c** as a white solid (0.39 g, 67%), mp 71-72 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.64-2.76 (4H, m), 3.54 (2H, s), 3.64 (2H, s), 3.80 (3H, s), 3.81 (3H, s), 5.10 (2H, s), 6.51 (1H, s), 6.63 (1H, s), 6.83 (1H, ddd, *J* = 8.2, 2.8, 0.9 Hz), 6.97 (3H, m), 7.25-7.45 (5H, m). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.7 (CH₂), 50.8 (CH₂), 55.3 (CH₃), 55.9 (CH₂), 56.1 (CH₃), 62.8 (CH₂), 71.2 (CH₂), 110.1 (CH), 112.8 (CH), 114.3 (CH), 114.4 (CH), 121.5 (CH), 126.3 (C_q), 127.3 (2 × CH), 127.5 (C_q), 127.8 (CH), 128.5 (2 × CH), 129.3 (CH), 137.3 (C_q), 140.2 (C_q), 146.7 (C_q), 148.0 (C_q), 159.8 (C_q). LC/MS (APCI+): *m/z* 390.55 (M⁺+H). HRMS (ES+): *m/z* found 390.2063; C₂₅H₂₈NO₃⁺ (M⁺+H) requires 390.2064.

6-Benzyloxy-7-methoxy-2-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (14d)—Method as for **14a** using compound **8** (404 mg, 1.5 mmol), 4-methoxybenzyl bromide (0.23 mL, 1.6 mmol) and TEA (0.42 mL, 3.0 mmol) in ethanol (30 mL) at 120 °C for 48 h. Flash column chromatography (hexane/EtOAc 10:1 to 3:1) afforded compound **14d** as a white solid (0.33 g, 57%), mp 96-97 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.65-2.79 (4H, m), 3.53 (2H, s), 3.61 (2H, s), 3.81 (3H, s), 3.81 (3H, s), 5.11 (2H, s), 6.51 (1H, s), 6.63 (1H, s), 6.88 (2H, dd, *J* = 7.4, 2.0 Hz), 7.26-7.45 (7H, m). LC/MS (APCI+): *m/z* 390.49 (M⁺+H). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.7 (CH₂), 50.8 (CH₂), 55.3 (CH₂), 55.7 (CH₃), 56.1 (CH₃), 62.3 (CH₂), 71.2 (CH₂), 110.1 (CH), 113.7 (2 × CH), 114.3 (CH), 126.3 (C_q), 127.3 (2 × CH), 127.5 (C_q), 127.8 (CH), 128.6 (2 × CH), 130.5 (2 × CH), 137.1 (C_q), 146.6 (C_q), 147.8 (C_q), 158.8 (C_q). HRMS (ES+): *m/z* found 390.2065; C₂₅H₂₈NO₃⁺ (M⁺+H) requires 390.2064.

6-Benzyloxy-(2-(3-hydroxybenzyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (14e)—Method as for **14b** using compound **8** (2.15 g, 8.0 mmol), 3-

Triisopropylsilyloxybenzyl chloride³⁰ (3.59 g, 12.0 mmol) and TEA (2.5 mL, 18.0 mmol) in ethanol (10 mL) at 120 °C for 1.5 h in the microwave oven. Flash column chromatography (hexane/EtOAc 6:1) afforded the benzyl-silyl-bisprotected phenol as a white solid (3.50 g, 82%); mp 78-79 °C. ¹H NMR (270 MHz, CDCl₃): δ = 1.08 (18H, d, J = 6.7 Hz), 1.15-1.30 (3H, m), 2.64-2.75 (4H, m), 3.52 (2H, s), 3.60 (2H, s), 3.81 (3H, s), 5.10 (2H, s), 6.49 (1H, s), 6.61 (1H, s), 6.75-6.80 (1H, m), 6.91-6.96 (2H, m), 7.16 (1H, t, J = 7.7 Hz), 7.27-7.44 (5H, m); LC/MS (APCI+): m/z 532.71 (M⁺+H). The silyl-protected phenol (2.70 g, 5.1 mmol) was treated with TBAF (1M in THF, 5.5 mL, 5.5 mmol) in THF (50 mL) at 0 °C for 1.5 h. EtOAc (80 mL) was added and the mixture was washed with water and brine, then dried (MgSO₄), filtered and concentrated in vacuo. The resulting solid was washed with hexane, filtered and dried to afford compound **14e** as a white solid (1.70 g, 90%), mp 141-142 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.63-2.78 (4H, m), 3.52 (2H, s), 3.58 (2H, s), 3.79 (3H, s), 5.08 (2H, s), 6.48 (1H, s), 6.60 (1H, s), 6.68 (1H, dd, J = 8.2, 2.5 Hz), 6.82 (1H, d, J = 2.5 Hz), 6.88 (1H, d, J = 7.7 Hz), 7.15 (1H, dd, J = 8.2, 7.7 Hz), 7.26-7.47 (5H, m). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.3 (CH₂), 50.8 (CH₂), 55.4 (CH₂), 56.0 (CH₃), 62.4 (CH₂), 71.0 (CH₂), 110.0 (CH), 114.1 (CH), 114.4 (CH), 116.3 (CH), 121.4 (CH), 126.0 (C_q), 127.0 (C_q), 127.2 (2 × CH), 127.7 (CH), 128.5 (2 × CH), 129.4 (CH), 137.2 (C_q), 139.7 (C_q), 146.6 (C_q), 147.8 (C_q), 155.9 (C_q). LC/MS (APCI+): m/z 376.59 (M⁺+H).

7-Methoxy-2-(3-trifluoromethoxybenzyl)-6-(triisopropylsiloxy)-1,2,3,4-

tetrahydroisoquinoline (14f)—Method as for **14b** using compound **10** (300 mg, 0.9 mmol), 3-trifluoromethoxybenzyl bromide (0.16 mL, 0.99 mmol) and TEA (0.17 mL, 1.8 mmol) in ethanol (3.0 mL) at 130 °C for 1 h in the microwave oven. Flash column chromatography (hexane/EtOAc gradient) afforded compound **14f** as a pale blue oil (238 mg, 52%). ¹H NMR (270 MHz, CDCl₃): δ = 1.07 (18H, d, J = 6.7 Hz), 1.14-1.28 (3H, m), 2.65-2.74 (4H, m), 3.53 (2H, s), 3.66 (2H, s), 3.71 (3H, s), 6.43 (1H, s), 6.58 (1H, s), 7.09-7.12 (1H, m), 7.20-7.38 (3H, m). LC/MS (ES+): m/z 510.49 (M⁺+H).

6-Benzyloxy-2-(3-ethoxybenzyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline

(14g)—Compound **14e** (450 mg, 1.2 mmol) was treated with iodoethane (0.19 mL, 2.4 mmol) and potassium carbonate (207 mg, 1.5 mmol) in ethanol (10 mL) at rt for 18 h. EtOAc was added and the mixture was washed with water and brine, then dried (MgSO₄), filtered and concentrated in vacuo. Flash column chromatography (hexane/EtOAc 4:1) afforded compound **14g** as a yellow oil (200 mg, 41%). ¹H NMR (270 MHz, CDCl₃): δ = 1.39 (3H, t, J = 6.9 Hz), 2.65-2.79 (4H, m), 3.54 (2H, s), 3.63 (2H, s), 3.80 (3H, s), 4.01 (2H, q, J = 6.9 Hz), 5.09 (2H, s), 6.50 (1H, s), 6.61 (1H, s), 6.79 (1H, ddd, J = 7.9, 2.2, 1.0 Hz), 6.93-6.96 (2H, m), 7.20 (1H, t, J = 7.9 Hz), 7.26-7.44 (5H, m). ¹³C NMR (67.5 MHz, CDCl₃): δ = 15.0 (CH₃), 28.7 (CH₂), 50.8 (CH₂), 55.8 (CH₂), 56.1 (CH₃), 62.8 (CH₂), 63.4 (CH₂), 71.2 (CH₂), 110.1 (CH), 113.3 (CH), 114.3 (CH), 115.1 (CH), 121.4 (CH), 126.3 (C_q), 127.3 (2 × CH), 127.5 (C_q), 127.8 (CH), 128.6 (2 × CH), 129.3 (CH), 137.4 (C_q), 140.1 (C_q), 146.6 (C_q), 147.9 (C_q), 159.1 (C_q). LC/MS (APCI+): m/z 404.59 (M⁺+H).

6-Benzyloxy-2-(3-isopropoxybenzyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline

(14h)—Compound **14e** (300 mg, 0.8 mmol) was treated with sodium hydride (48 mg, 1.2 mmol) in THF (10 mL) at rt for 20 min. 2-Iodopropane (0.12 mL, 1.2 mmol) was then added and the reaction mixture was stirred at 40 °C for 22 h. A further aliquot of 2-iodopropane (0.12 mL, 1.2 mmol) was added and the reaction was heated to 50 °C for 22 h before a final aliquot of 2-iodopropane (0.12 mL, 1.2 mmol) was introduced and the reaction was heated at 60 °C for 3 h. The reaction was then cooled to rt and concentrated in vacuo. Water was added and the mixture was extracted with EtOAc, washed with brine, then dried, filtered and evaporated. Flash column chromatography (hexane/EtOAc gradient) afforded compound **14h** as a colourless oil (259 mg, 77%). ¹H NMR (270 MHz, CDCl₃): δ = 1.31 (6H, d, J = 6.2

Hz), 2.66-2.75 (4H, m), 3.54 (2H, s), 3.62 (2H, s), 3.80 (3H, s), 4.54 (1H, sept, $J = 6.2$ Hz), 5.09 (2H, s), 6.50 (1H, s), 6.61 (1H, s), 6.77-6.81 (1H, m), 6.91-6.94 (2H, m), 7.16-7.47 (6H, m). ^{13}C NMR (67.5 MHz, CDCl_3): $\delta = 22.2$ ($2 \times \text{CH}_3$), 28.8 (CH_2), 50.8 (CH_2), 55.9 (CH_2), 56.2 (CH_3), 62.9 (CH_2), 69.8 (CH), 71.2 (CH_2), 110.1 (CH), 114.3 (CH), 114.6 (CH), 116.5 (CH), 121.3 (CH), 126.3 (C_q), 127.4 ($2 \times \text{CH}$), 127.6 (C_q), 127.8 (CH), 128.6 ($2 \times \text{CH}$), 129.3 (CH), 137.4 (C_q), 140.2 (C_q), 146.7 (C_q), 147.9 (C_q), 158.0 (C_q). LC/MS (APCI-): m/z 416.35 ($\text{M}^- - \text{H}$).

6-Benzyloxy-7-methoxy-2-(3-phenoxybenzyl)-1,2,3,4-tetrahydroisoquinoline

(14i)—Method as for **14b** using compound **8** (404 mg, 1.5 mmol), 3-methylbenzyl bromide (0.24 mL, 1.8 mmol) and TEA (0.42 mL, 3.0 mmol) in ethanol (2.5 mL) at 120 °C for 1 h in the microwave oven. Flash column chromatography (hexane/EtOAc 8:1 to 3:1) afforded compound **14i** as a white solid (0.53 g, 78%), mp 111-112 °C. ^1H NMR (270 MHz, CDCl_3): $\delta = 2.65$ -2.75 (4H, m), 3.54 (2H, s), 3.64 (2H, s), 3.82 (3H, s), 5.10 (2H, s), 6.51 (1H, s), 6.62 (1H, s), 6.91 (1H, ddd, $J = 8.2, 2.5, 1.0$ Hz), 6.98-7.15 (5H, m), 7.25-7.45 (8H, m). ^{13}C NMR (67.5 MHz, CDCl_3): $\delta = 28.7$ (CH_2), 50.8 (CH_2), 55.8 (CH_2), 56.2 (CH_3), 62.5 (CH_2), 71.1 (CH_2), 110.1 (CH), 114.3 (CH), 117.7 (CH), 118.3 ($2 \times \text{CH}$), 119.7 (CH), 123.2 (CH), 124.0 (CH), 126.3 (C_q), 127.3 ($2 \times \text{CH}$), 127.4 (C_q), 127.8 (CH), 128.6 ($2 \times \text{CH}$), 129.6 (CH), 129.8 ($2 \times \text{CH}$), 137.4 (C_q), 140.7 (C_q), 146.7 (C_q), 147.9 (C_q), 157.3 (C_q), 157.4 (C_q). LC/MS (APCI+): m/z 452.56 ($\text{M}^+ + \text{H}$).

2-(3-Acetoxybenzyl)-6-benzyloxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline

(14k)—Compound **14e** (450 mg, 1.2 mmol) was treated with acetic anhydride (0.13 mL, 1.4 mmol) and TEA (0.20 mL, 1.4 mmol) in chloroform (10 mL) at rt for 18 h. The reaction mixture was diluted with chloroform (50 mL), washed with water and brine, then dried (MgSO_4), filtered and concentrated in vacuo. Flash column chromatography (hexane/EtOAc 4:1 to 3:1) afforded compound **14k** as a white powder (450 mg, 90%), mp 94-95 °C. ^1H NMR (270 MHz, CDCl_3): $\delta = 2.28$ (3H, s), 2.65-2.77 (4H, m), 3.52 (2H, s), 3.65 (2H, s), 3.80 (3H, s), 5.10 (2H, s), 6.50 (1H, s), 6.61 (1H, s), 6.98 (1H, ddd, $J = 7.9, 2.2, 1.2$ Hz), 7.13-7.19 (1H, m), 7.21-7.44 (7H, m). ^{13}C NMR (67.5 MHz, CDCl_3): $\delta = 21.3$ (CH_3), 28.7 (CH_2), 50.9 (CH_2), 55.8 (CH_2), 56.1 (CH_3), 62.4 (CH_2), 71.2 (CH_2), 110.1 (CH), 114.3 (CH), 120.4 (CH), 122.0 (CH), 126.2 (C_q), 126.5 (CH), 127.3 ($2 \times \text{CH}$), 127.4 (C_q), 127.8 (CH), 128.6 ($2 \times \text{CH}$), 129.3 (CH), 137.4 (C_q), 140.6 (C_q), 146.7 (C_q), 147.9 (C_q), 150.8 (C_q), 169.7 (C_q). LC/MS (ES+): m/z 418.48 ($\text{M}^+ + \text{H}$).

6-Benzyloxy-2-(3-fluorobenzyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (14l)

—Method as for **14b** using compound **8** (300 mg, 1.1 mmol), 3-fluorobenzyl bromide (0.15 mL, 1.2 mmol) and TEA (0.31 mL, 2.2 mmol) in ethanol (3.0 mL) at 130 °C for 1 h in the microwave oven. Flash column chromatography (hexane to hexane/EtOAc 1:1) afforded compound **14l** as a colourless solid (336 mg, 80%), mp 78-80 °C. ^1H NMR (270 MHz, CDCl_3): $\delta = 2.67$ -2.75 (4H, m), 3.53 (2H, s), 3.64 (2H, s), 3.81 (3H, s), 5.10 (2H, s), 6.50 (1H, s), 6.61 (1H, s), 6.91-6.98 (1H, m), 7.10-7.15 (2H, m), 7.23-7.44 (6H, m). ^{13}C NMR (67.5 MHz, CDCl_3): $\delta = 28.7$ (CH_2), 50.9 (CH_2), 55.8 (CH_2), 56.2 (CH_3), 62.3 (CH_2), 71.2 (CH_2), 110.1 (CH), 114.1 (d, $J = 21.2$ Hz, CH), 114.3 (CH), 115.8 (d, $J = 21.2$ Hz, CH), 124.6 (d, $J = 2.5$ Hz, CH), 126.2 (C_q), 127.3 (C_q), 127.4 ($2 \times \text{CH}$), 127.8 (CH), 128.6 ($2 \times \text{CH}$), 129.8 (d, $J = 8.1$ Hz, CH), 137.4 (C_q), 141.4 (d, $J = 7.5$ Hz, C_q), 146.8 (C_q), 148.0 (C_q), 163.1 (d, $J = 245.6$ Hz, CF). LC/MS (APCI+): m/z 378.52 ($\text{M}^+ + \text{H}$).

2-(3-Chlorobenzyl)-7-methoxy-6-(triisopropylsiloxy)-1,2,3,4-

tetrahydroisoquinoline (14m)—Method as for **14b** using compound **10** (300 mg, 0.9 mmol), 3-chlorobenzyl bromide (221 mg, 1.07 mmol) and TEA (0.25 mL, 1.8 mmol) in ethanol (3.0 mL) at 130 °C for 0.75 h in the microwave oven. Flash column chromatography

(hexane to hexane/EtOAc 1:1) afforded compound **14m** as a yellow oil (322 mg, 78%). ¹H NMR (270 MHz, CDCl₃): δ = 1.08 (18H, d, J = 6.7 Hz), 1.13-1.29 (3H, m), 2.66-2.75 (4H, m), 3.52 (2H, s), 3.62 (2H, s), 3.72 (3H, s), 6.43 (1H, s), 6.59 (1H, s), 7.23-7.28 (3H, m), 7.40 (1H, s). ¹³C NMR (67.5 MHz, CDCl₃): δ = 13.0 (3 $\times$ CH), 18.1 (6 $\times$ CH₃), 28.5 (CH₂), 50.9 (CH₂), 55.7 (CH₃), 55.9 (CH₂), 62.4 (CH₂), 110.3 (CH), 120.2 (CH), 126.2 (C_q), 127.1 (C_q), 127.3 (CH), 127.4 (CH), 129.2 (CH), 129.7 (CH), 134.3 (C_q), 140.8 (C_q), 144.0 (C_q), 149.1 (C_q). LC/MS (APCI+): m/z 460.43 (M⁺+H).

6-Benzyloxy-2-(3-methylbenzyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline

(14n)—Method as for **14b** using compound **8** (404 mg, 1.5 mmol), 3-methylbenzyl bromide (0.24 mL, 1.8 mmol) and TEA (0.42 mL, 3.0 mmol) in ethanol (2.5 mL) at 120 °C for 1 h in the microwave oven. Flash column chromatography (hexane/EtOAc 8:1 to 3:1) afforded compound **14n** as a white solid (0.46 g, 82%), mp 81-82 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.35 (3H, s), 2.69-2.76 (4H, m), 3.52 (2H, s), 3.63 (2H, s), 3.81 (3H, s), 5.10 (2H, s), 6.51 (1H, s), 6.62 (1H, s), 7.07-7.44 (9H, m). ¹³C NMR (67.5 MHz, CDCl₃): δ = 21.5 (CH₃), 28.8 (CH₂), 50.9 (CH₂), 55.8 (CH₂), 56.2 (CH₃), 62.9 (CH₂), 71.1 (CH₂), 110.1 (CH), 114.3 (CH), 126.3 (C_q), 126.4 (CH), 127.3 (2 $\times$ CH), 127.5 (C_q), 127.8 (CH), 128.0 (CH), 128.2 (CH), 128.6 (2 $\times$ CH), 130.0 (CH), 137.4 (C_q), 138.0 (C_q), 138.4 (C_q), 146.7 (C_q), 147.9 (C_q). LC/MS (APCI+): m/z 374.62 (M⁺+H).

6-Benzyloxy-2-(3-ethylbenzyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (14o)

—Compound **8** (592 mg, 2.2 mmol) and 3-ethylbenzoic acid^[30] (495 mg, 3.3 mmol) were dissolved in DCM (4.5 mL) and THF (1.5 mL). EDCI (842 mg, 4.4 mmol) was added and the reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with DCM (200 mL), washed with HCl (1M, 100 mL) and brine (20 mL), dried (MgSO₄), filtered and concentrated in vacuo. Flash column chromatography (hexane to hexane/EtOAc 7:3) afforded the amide as colourless glass (805 mg, 91%). ¹H NMR (270 MHz, CDCl₃): δ = 1.24 (3H, t, J = 7.6 Hz), 2.67 (2H, q, J = 7.6 Hz), 2.71 and 2.83 (2H, 2s, br), 3.59 and 3.95 (2H, 2s, br), 3.77 and 3.87 (3H, 2s, br), 4.50 and 4.82 (2H, 2s, br), 5.11 (2H, s), 6.41 and 6.70 (1H, 2s, br), 6.65 (1H, s, br), 7.18-7.47 (9H, m). HRMS (ES+): m/z found 402.2053; C₂₆H₂₈NO₃⁺ (M⁺+H) requires 402.2064. Lithium aluminium hydride (229 mg, 6.0 mmol) was covered with THF (4.0 mL). The amide (802 mg, 2.0 mmol) was added dropwise via syringe as solution in THF (8.0 mL) and the reaction mixture was stirred at rt for 2 h. The mixture was carefully diluted with EtOAc (100 mL) and left standing without stirring for 0.5 h. After the salts settled the mixture was filtered through celite, washed with EtOAc (4 $\times$ 10 mL) and concentrated in vacuo. Flash column chromatography (hexane/EtOAc 9:1 and 1% TEA) afforded compound **14o** as a pale yellow oil (543 mg, 70%). ¹H NMR (270 MHz, CDCl₃): δ = 1.24 (3H, t, J = 7.7 Hz), 2.63-2.79 (4H, m), 2.65 (2H, q, J = 7.7 Hz), 3.54 (2H, s), 3.64 (2H, s), 3.81 (3H, s), 5.10 (2H, s), 6.51 (1H, s), 6.62 (1H, s), 7.08-7.46 (9H, m). HRMS (ES+): m/z found 388.2258; C₂₆H₃₀NO₂⁺ (M⁺+H) requires 388.2271.

2-(3-Cyanobenzyl)-7-methoxy-6-(triisopropylsiloxy)-1,2,3,4-tetrahydroisoquinoline (14p)

—Method as for **14a** using compound **10** (300 mg, 0.89 mmol), 3-cyanobenzyl bromide (193 mg, 0.98 mmol) and TEA (0.25 mL, 1.8 mmol) in ethanol (20 mL) at 120 °C for 23 h. Flash column chromatography (hexane to hexane/EtOAc 1:1) afforded compound **14p** as a colourless oil (329 mg, 82%). ¹H NMR (270 MHz, CDCl₃): δ = 1.07 (18H, d, J = 6.7 Hz), 1.13-1.28 (3H, m), 2.66-2.75 (4H, m), 3.51 (2H, s), 3.67 (2H, s), 3.71 (3H, s), 6.42 (1H, s), 6.59 (1H, s), 7.42 (1H, t, J = 7.7 Hz), 7.56 (1H, dt, J = 7.7, 1.5 Hz), 7.64 (1H, d, J = 7.7 Hz), 7.70 (1H, s, br). ¹³C NMR (67.5 MHz, CDCl₃): δ = 12.9 (3 $\times$ CH), 18.0 (6 $\times$ CH₃), 28.3 (CH₂), 50.8 (CH₂), 55.6 (CH₃), 55.7 (CH₂), 61.8 (CH₂), 110.1 (CH), 112.4 (C_q), 118.9 (C_q), 120.1 (CH), 125.8 (C_q), 126.5 (C_q), 129.1 (CH), 130.9

(CH), 132.5 (CH), 133.5 (CH), 140.1 (C_q), 144.0 (C_q), 149.1 (C_q). LC/MS (APCI+): *m/z* 451.43 (M⁺+H).

2-(3-Acetylbenzyl)-7-methoxy-6-(triisopropylsilyloxy)-1,2,3,4-

tetrahydroisoquinoline (14q)—Method as for **14a** using compound **10** (320 mg, 0.95 mmol), 3-acetylbenzyl bromide^[31] (59 wt%, 0.82 g, 2.25 mmol) and TEA (2.0 mL, 14.4 mmol) in ethanol (30 mL) at 120 °C for 30 h. Flash column chromatography (hexane/EtOAc 8:1 to 6:1) afforded compound **14q** as a yellow oil (290 mg, 65%). ¹H NMR (270 MHz, CDCl₃): δ = 1.05 (18H, d, *J* = 6.7 Hz), 1.12–1.30 (3H, m), 2.60 (3H, s), 2.65–2.76 (4H, m), 3.54 (2H, s), 3.70 (5H, s), 6.42 (1H, s), 6.58 (1H, s), 7.42 (1H, t, *J* = 7.7 Hz), 7.62 (1H, dt, *J* = 7.7, 1.5 Hz), 7.86 (1H, dt, *J* = 7.7, 1.5 Hz), 7.95 (1H, t, *J* = 1.5 Hz). ¹³C NMR (67.5 MHz, CDCl₃): δ = 13.0 (3 × CH), 18.0 (6 × CH₃), 26.9 (CH₃), 28.4 (CH₂), 50.9 (CH₂), 55.7 (CH₃), 55.9 (CH₂), 62.5 (CH₂), 110.2 (CH), 120.2 (CH), 126.2 (C_q), 126.9 (C_q), 127.3 (CH), 128.7 (CH), 129.0 (CH), 134.1 (CH), 137.3 (C_q), 139.1 (C_q), 144.0 (C_q), 149.1 (C_q), 198.5 (C_q). LC/MS (APCI+): *m/z* 468.57 (M⁺+H).

7-Methoxy-2-(3-nitrobenzyl)-6-(triisopropylsiloxy)-1,2,3,4-

tetrahydroisoquinoline (14r)—Method as for **14b** using compound **10** (387 mg, 1.15 mmol), 3-nitrobenzyl chloride (218 mg, 1.27 mmol) and TEA (0.32 mL, 2.3 mmol) in ethanol (3.0 mL) at 130 °C for 0.75 h in the microwave oven. Flash column chromatography (hexane to hexane/EtOAc 1:1) afforded compound **14r** as a yellow solid (452 mg, 83%). ¹H NMR (270 MHz, CDCl₃): δ = 1.07 (18H, d, *J* = 6.7 Hz), 1.13–1.28 (3H, m), 2.69–2.76 (4H, m), 3.54 (2H, s), 3.71 (3H, s), 3.74 (2H, s), 6.42 (1H, s), 6.59 (1H, s), 7.49 (1H, t, *J* = 7.9 Hz), 7.75 (1H, d, *J* = 7.7 Hz), 8.12 (1H, ddd, *J* = 8.2, 2.5, 1.1 Hz), 8.25 (1H, t, *J* = 1.7 Hz). ¹³C NMR (67.5 MHz, CDCl₃): δ = 13.0 (3 × CH), 18.1 (6 × CH₃), 28.5 (CH₂), 51.0 (CH₂), 55.7 (CH₃), 55.9 (CH₂), 62.0 (CH₂), 110.2 (CH), 120.2 (CH), 122.4 (CH), 123.9 (CH), 126.0 (C_q), 126.7 (C_q), 129.3 (CH), 135.2 (CH), 141.0 (C_q), 144.1 (C_q), 148.4 (C_q), 149.1 (C_q). LC/MS (APCI+): *m/z* 471.58 (M⁺+H).

2-(3-Acetamidobenzyl)-6-benzyloxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline

(14s)—Method as for **14b** using compound **8** (1.62 g, 6.0 mmol), 3-nitrobenzyl chloride (1.24 g, 7.2 mmol) and TEA (2.5 mL, 18.0 mmol) in ethanol (10 mL) at 120 °C for 1.5 h in the microwave oven. Flash column chromatography (hexane/EtOAc 3:1 to 2:1) afforded the nitro compound as a light beige powder (2.00 g, 83%), mp 109–110 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.70–2.74 (2H, m), 2.76–2.78 (2H, m), 3.55 (2H, s), 3.75 (2H, s), 3.81 (3H, s), 5.09 (2H, s), 6.50 (1H, s), 6.63 (1H, s), 7.24–7.44 (5H, m), 7.49 (1H, t, *J* = 7.8 Hz), 7.74 (1H, d, *J* = 7.8 Hz), 8.12 (1H, d, *J* = 7.8 Hz), 8.25 (1H, s). LC/MS (APCI+): *m/z* 405.60 (M⁺+H). The nitro compound (1.61 g, 4.0 mmol) was added to a suspension of Raney nickel (50% slurry in water, 1.5 g, washed with 3 × 5 mL of methanol) in methanol (50 mL). Hydrazine hydrate (1.0 mL, 20.6 mmol) was added dropwise and the mixture was stirred at 80 °C for 0.5 h. After cooling to rt the mixture was filtered through celite and concentrated in vacuo. The resulting yellow solid was stirred in diethyl ether, filtered and dried to afford the aniline as a yellow powder (1.40 g, 93%), mp 114–115 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.68–2.77 (4H, m), 3.53 (2H, s), 3.58 (2H, s), 3.81 (3H, s), 5.11 (2H, s), 6.52 (1H, s), 6.59 (1H, dd, *J* = 8.2, 1.5 Hz), 6.63 (1H, s), 6.75–6.78 (2H, m), 7.12 (1H, t, *J* = 8.0 Hz), 7.29–7.45 (5H, m). LC/MS (APCI+): *m/z* 375.63 (M⁺+H). Method as for **14k** using the aniline (300 mg, 0.8 mmol), acetic anhydride (0.26 mL, 2.7 mmol) and TEA (0.39 mL, 2.7 mmol) in chloroform (30 mL) at rt for 3 h. Flash column chromatography (hexane/EtOAc 1:10) and (DCM/EtOAc 2:1 to 1:5) afforded compound **14s** as a white powder (180 mg, 54%), mp 63–66 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.14 (3H, s), 2.68–2.75 (4H, m), 2.84 (1H, s, br), 3.52 (2H, s), 3.64 (2H, s), 3.79 (3H, s), 5.09 (2H, s), 6.48 (1H, s), 6.60 (1H, s), 7.11 (1H, d, *J* = 7.7 Hz), 7.24–7.43 (7H, m), 7.53 (1H, d, *J* = 8.2 Hz). ¹³C NMR (67.5 MHz,

CDCl₃): δ = 24.7 (CH₃), 28.6 (CH₂), 50.9 (CH₂), 55.6 (CH₂), 56.1 (CH₃), 62.5 (CH₂), 71.2 (CH₂), 110.1 (CH), 114.2 (CH), 118.9 (CH), 120.3 (CH), 125.1 (CH), 126.1 (C_q), 127.1 (C_q), 127.3 (2 $\times$ CH), 127.8 (CH), 128.6 (2 $\times$ CH), 129.1 (CH), 137.3 (C_q), 138.0 (C_q), 139.3 (C_q), 146.7 (C_q), 147.9 (C_q), 168.6 (C_q). LC/MS (APCI+): m/z 417.51 (M⁺+H).

6-Benzyloxy-(2-(3-methanesulfonamido)benzyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (14t)—Methanesulfonyl chloride (0.09 mL, 1.2 mmol) was

added dropwise to a solution of the aniline (374 mg, 1.0 mmol) in pyridine (2.0 mL, 25.9 mmol). The reaction mixture was stirred at rt for 18 h. Water was added slowly and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, then dried (MgSO₄), filtered and concentrated in vacuo. Flash column chromatography (hexane/EtOAc 1:4) afforded compound **14t** as a white powder (260 mg, 58%), mp 132-133 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.64-2.76 (4H, m), 2.97 (3H, s), 3.52 (2H, s), 3.63 (2H, s), 3.80 (3H, s), 5.09 (2H, s), 6.49 (1H, s), 6.61 (1H, s), 7.12-7.44 (10H, m). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.7 (CH₂), 39.5 (CH₃), 50.9 (CH₂), 55.8 (CH₂), 56.2 (CH₃), 62.3 (CH₂), 71.1 (CH₂), 110.1 (CH), 114.3 (CH), 119.5 (CH), 121.3 (CH), 126.1 (CH), 126.2 (C_q), 127.2 (C_q), 127.3 (2 $\times$ CH), 127.8 (CH), 128.6 (2 $\times$ CH), 129.6 (CH), 136.9 (C_q), 137.3 (C_q), 140.6 (C_q), 146.8 (C_q), 148.0 (C_q). LC/MS (ES+): m/z 453.40 (M⁺).

6-Benzyloxy-2-(2,3-dimethoxybenzyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (14u)—Method as for **14b** using compound **8** (404 mg, 1.5

mmol), 2,3-dimethoxybenzyl chloride^[32] (50 wt% in DCM, 0.67 g, 1.8 mmol) and TEA (0.5 mL, 3.6 mmol) in ethanol (2.5 mL) at 120 °C for 1.5 h in the microwave oven. Flash column chromatography (hexane/EtOAc 3:1 to 2:1) gave an oil which was dissolved in acetonitrile (1.0 mL). After evaporation of the solvent, the residue was stirred in diethyl ether, filtered and dried to afford compound **14u** as a yellow powder (430 mg, 68%), mp 106-107 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.73 (4H, s), 3.57 (2H, s), 3.71 (2H, s), 3.80 (3H, s), 3.83 (3H, s), 3.87 (3H, s), 5.09 (2H, s), 6.51 (1H, s), 6.61 (1H, s), 6.84 (1H, dd, J = 7.2, 1.7 Hz), 7.00-7.08 (2H, m), 7.27-7.44 (5H, m). ¹³C NMR (67.5 MHz, CDCl₃): δ = 29.0 (CH₂), 51.0 (CH₂), 55.7 (CH₂), 55.8 (CH₃), 56.1 (CH₃), 56.2 (CH₂), 61.0 (CH₃), 71.2 (CH₂), 110.1 (CH), 111.1 (CH), 114.3 (CH), 122.6 (CH), 123.9 (CH), 126.4 (C_q), 127.4 (2 $\times$ CH), 127.8 (CH), 128.6 (2 $\times$ CH), 132.4 (C_q), 137.4 (C_q), 146.6 (C_q), 147.8 (C_q), 147.9 (C_q), 152.8 (C_q). LC/MS (APCI-): m/z 418.11 (M⁻-H).

6-Benzyloxy-2-(3,4-dimethoxybenzyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (14v)—Method as for **14b** using compound **8** (404 mg, 1.5

mmol), 3,4-dimethoxybenzyl chloride (336 mg, 1.8 mmol) and TEA (0.5 mL, 3.6 mmol) in ethanol (2.5 mL) at 120 °C for 1.5 h in the microwave oven. Flash column chromatography (hexane/EtOAc 3:1 to 1:1) gave a solid that was stirred in diethyl ether, filtered and dried to afford compound **14v** as a white powder (430 mg, 68%), mp 98-99 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.99 (2H, s, br), 3.16 (2H, s, br), 3.81 (3H, s), 3.87 (5H, s), 3.94 (3H, s), 4.01 (2H, s), 5.10 (2H, s), 6.47 (1H, s), 6.64 (1H, s), 6.81 (1H, d, J = 8.2 Hz), 6.91 (1H, dd, J = 8.2, 1.7 Hz), 7.26-7.50 (6H, m). ¹³C NMR (67.5 MHz, CDCl₃): δ = 48.8 (CH₂), 55.9 (CH₃), 56.1 (CH₃), 56.4 (CH₃), 71.0 (CH₂), 109.8 (CH), 110.7 (CH), 113.4 (CH), 113.8 (CH), 122.6 (CH), 127.2 (2 $\times$ CH), 127.9 (CH), 128.6 (2 $\times$ CH), 136.7 (C_q), 147.9 (C_q), 148.8 (C_q), 149.5 (C_q), 149.6 (C_q). LC/MS (ES+): m/z 420.61 (M⁺+H).

6-Benzyloxy-2-(3,5-dimethoxybenzyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (14w)—Method as for **14b** using compound **8** (404 mg, 1.5

mmol), 3,5-dimethoxybenzyl bromide (480 mg, 2.1 mmol) and TEA (0.42 mL, 3.0 mmol) in ethanol (4.0 mL) at 120 °C for 1 h in the microwave oven. Flash column chromatography (hexane/EtOAc 8:1 to 2:1) afforded compound **14w** as a white solid (0.36 g, 62%), mp

95-96 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.65-2.77 (4H, m), 3.54 (2H, s), 3.60 (2H, s), 3.78 (6H, s), 3.81 (3H, s), 5.10 (2H, s), 6.37 (1H, t, *J* = 2.5 Hz), 6.51 (1H, s), 6.56 (2H, d, *J* = 2.5 Hz), 6.62 (1H, s), 7.27-7.44 (5H, m). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.7 (CH₂), 50.7 (CH₂), 55.4 (CH₃), 55.8 (CH₂), 56.1 (CH₃), 63.0 (CH₂), 71.1 (CH₂), 99.2 (CH), 106.8 (2 × CH), 110.1 (CH), 114.2 (CH), 126.2 (C_q), 127.4 (2 × CH), 127.4 (C_q), 127.8 (CH), 128.6 (2 × CH), 137.4 (C_q), 141.0 (C_q), 146.6 (C_q), 147.9 (C_q), 160.8 (2 × C_q). LC/MS (APCI+): *m/z* 420.39 (M⁺+H). HRMS (ES+): *m/z* found 420.2167; C₂₆H₃₀NO₄⁺ (M⁺+H) requires 420.2169.

6-Benzyloxy-2-(2,5-dimethoxybenzyl)-7-methoxy-1,2,3,4-

tetrahydroisoquinoline (14x)—Method as for **14b** using compound **8** (404 mg, 1.5 mmol) and 2,5-dimethoxybenzyl chloride (336 mg, 1.8 mmol) and TEA (0.5 mL, 3.6 mmol) in ethanol (2.5 mL) at 120 °C for 1.5 h in the microwave oven. Flash column chromatography (hexane/EtOAc 3:1 to 2:1) gave an oil that was stirred in diethyl ether, filtered and dried to afford compound **14x** as a yellow powder (440 mg, 70%), mp 103-104 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.73-2.75 (4H, m), 3.61 (2H, s), 3.69 (2H, s), 3.76 (3H, s), 3.79 (3H, s), 3.82 (3H, s), 5.10 (2H, s), 6.53 (1H, s), 6.62 (1H, s), 6.76 (1H, dd, *J* = 8.6, 2.9 Hz), 6.81 (1H, d, *J* 8.6), 7.06 (1H, d, *J* 2.9), 7.28-7.46 (5H, m). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.8 (CH₂), 50.9 (CH₂), 55.9 (2 × CH₂), 56.2 (2 × CH₃), 56.3 (CH₃), 71.2 (CH₂), 110.2 (CH), 111.7 (CH), 112.5 (CH), 114.3 (CH), 116.1 (CH), 126.4 (C_q), 127.4 (2 × CH), 127.8 (CH), 127.9 (C_q), 128.0 (C_q), 128.6 (2 × CH), 137.4 (C_q), 146.7 (C_q), 147.9 (C_q), 152.1 (C_q), 153.7 (C_q). LC/MS (ES-): *m/z* 418.11 (M⁻-H).

6-Benzyloxy-7-methoxy-2-(2,3,4-trimethoxybenzyl)-1,2,3,4-

tetrahydroisoquinoline (14y)—Method as for **14b** using compound **8** (404 mg, 1.5 mmol), 2,3,4-trimethoxybenzyl chloride^[33] (390 mg, 1.8 mmol) and TEA (0.5 mL, 3.6 mmol) in ethanol (2.5 mL) at 120 °C for 1.5 h in the microwave oven. Flash column chromatography (hexane/EtOAc 3:1 to 1:1) afforded compound **14y** as a yellow oil (290 mg, 43%). ¹H NMR (270 MHz, CDCl₃): δ = 2.66-2.75 (4H, m), 3.56 (2H, s), 3.63 (2H, s), 3.81 (3H, s), 3.85 (3H, s), 3.88 (6H, s), 5.09 (2H, s), 6.52 (1H, s), 6.62 (1H, s), 6.65 (1H, d, *J* = 8.6 Hz), 7.08 (1H, d, *J* = 8.6 Hz), 7.27-7.43 (5H, m). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.9 (CH₂), 50.7 (CH₂), 55.7 (CH₂), 56.1 (CH₃), 56.2 (CH₃), 56.4 (CH₂), 60.9 (CH₃), 61.3 (CH₃), 71.2 (CH₂), 107.2 (CH), 110.3 (CH), 114.4 (CH), 124.4 (C_q), 125.0 (CH), 126.5 (C_q), 127.4 (2 × CH), 127.8 (CH), 128.0 (C_q), 128.5 (2 × CH), 137.5 (C_q), 142.4 (C_q), 146.7 (C_q), 148.0 (C_q), 152.7 (C_q), 152.9 (C_q).

6-Benzyloxy-7-methoxy-2-(3,4,5-trimethoxybenzyl)-1,2,3,4-

tetrahydroisoquinoline (14z)—Method as for **14b** using compound **8** (404 mg, 1.5 mmol), 3,4,5-trimethoxybenzyl chloride (390 mg, 1.8 mmol) and TEA (0.5 mL, 3.6 mmol) in ethanol (2.5 mL) at 120 °C for 1.5 h in the microwave oven. Flash column chromatography (hexane/EtOAc 3:1 to 1:1) gave a solid that was stirred in diethyl ether, filtered and dried to afford compound **14z** as a white powder (520 mg, 77%), mp 144-145 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.65-2.78 (4H, m), 3.55 (2H, s), 3.58 (2H, s), 3.82 (3H, s), 3.84 (3H, s), 3.85 (6H, s), 5.10 (2H, s), 6.53 (1H, s), 6.61 (2H, s), 6.63 (1H, s), 7.27-7.44 (5H, m). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.8 (CH₂), 50.7 (CH₂), 56.0 (CH₂), 56.2 (3 × CH₃), 61.0 (CH₃), 63.1 (CH₂), 71.2 (CH₂), 105.7 (2 × CH), 110.2 (CH), 114.3 (CH), 126.3 (C_q), 127.3 (2 × CH), 127.5 (C_q), 127.8 (CH), 128.6 (2 × CH), 134.5 (C_q), 136.9 (C_q), 137.4 (C_q), 146.8 (C_q), 148.0 (C_q), 153.2 (2 × C_q). LC/MS (ES+): *m/z* 450.61 (M⁺+H).

6-Benzyloxy-7-methoxy-2-(2,4,5-trimethoxybenzyl)-1,2,3,4-

tetrahydroisoquinoline (14aa)—Method as for **14b** using compound **8** (404 mg, 1.5

mmol), 2,4,5-trimethoxybenzyl chloride^[34] (390 mg, 1.8 mmol) and TEA (0.5 mL, 3.6 mmol) in ethanol (2.5 mL) at 120 °C for 1.5 h in the microwave oven. Flash column chromatography (hexane/EtOAc 3:1 to 2:3) gave a solid that was stirred in diethyl ether, filtered and dried to afford compound **14aa** as a white powder (240 mg, 35%), mp 110-111 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.65-2.76 (4H, m), 3.58 (2H, s), 3.63 (2H, s), 3.80 (3H, s), 3.81 (3H, s), 3.82 (3H, s), 3.88 (3H, s), 5.09 (2H, s), 6.52 (1H, s), 6.53 (1H, s), 6.61 (1H, s), 7.00 (1H, s), 7.27-7.43 (5H, m). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.8 (CH₂), 50.6 (CH₂), 55.3 (CH₂), 55.9 (CH₂), 56.2 (CH₃), 56.3 (CH₃), 56.7 (CH₃), 56.8 (CH₃), 71.2 (CH₂), 97.9 (CH), 110.3 (CH), 114.3 (CH), 114.5 (CH), 118.3 (C_q), 126.5 (C_q), 127.4 (2 × CH), 127.8 (CH), 127.9 (C_q), 128.5 (2 × CH), 137.5 (C_q), 143.2 (C_q), 146.7 (C_q), 148.0 (C_q), 148.6 (C_q), 152.2 (C_q). LC/MS (ES+): *m/z* 450.61 (M⁺+H).

6-Benzyloxy-7-Methoxy-2-(2,4,6-trimethoxybenzyl)-1,2,3,4-

tetrahydroisoquinoline (14ab)—Method as for **14o** using compound **8** (539 mg, 2.0 mmol), 2,4,6-trimethoxybenzoic acid (446 mg, 2.1 mmol) and EDCI (767 mg, 4.0 mmol) in DCM (25 mL) at rt for 2 h. Flash column chromatography (hexane/EtOAc 5:1 to EtOAc) afforded the amide as white powder (0.74 g, 80%), mp 70-72 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.62 and 2.78 (2H, 2t, *J* = 5.5 and 5.8 Hz), 3.44 and 3.96 (2H, 2t, *J* = 5.5 and 5.8 Hz), 3.66 and 3.75 (6H, 2s), 3.78, 3.82, 3.82 and 3.86 (6H, 4s), 4.32 and 4.85 (2H, 2s), 5.10 and 5.11 (2H, 2s), 6.10 and 6.11 (2H, 2s), 6.41 and 6.60 (1H, 2s), 6.67 and 6.68 (1H, 2s), 7.28-7.44 (5H, m). LC/MS (ES−): *m/z* 404.4 (M⁺+H) and 486.4 (M⁺+Na). HRMS (ES +): *m/z* found 464.2070; C₂₇H₃₀NO₆⁺ (M⁺+H) requires 464.2068. Method as for **14o** using the amide (720 mg, 1.55 mmol) and lithium aluminium hydride (76 mg, 2.0 mmol) in THF (30 mL) at rt for 16 h, then at 80 °C for 2 h. Flash column chromatography (hexane/EtOAc 10:1 to EtOAc) afforded compound **14ab** as a white powder (500 mg, 72%), mp 129-131 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.67-2.78 (4H, m), 3.59 (2H, s), 3.69 (2H, s), 3.80 (6H, s), 3.81 (6H, s), 5.07 (2H, s), 6.14 (2H, s), 6.50 (1H, s), 6.56 (1H, s), 7.24-7.41 (5H, m). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.6 (CH₂), 48.8 (CH₂), 50.5 (CH₂), 55.2 (CH₂), 55.4 (CH₃), 55.9 (2 × CH₃), 56.2 (CH₃), 71.2 (CH₂), 90.6 (2 × CH), 107.2 (C_q), 110.4 (CH), 114.4 (CH), 126.6 (C_q), 127.4 (2 × CH), 127.7 (CH), 128.5 (2 × CH), 137.5 (C_q), 146.5 (C_q), 147.8 (C_q), 160.2 (2 × C_q), 160.6 (C_q). LC/MS (ES−): *m/z* 450.5 (M⁺+H). HRMS (ES +): *m/z* found 450.2263; C₂₇H₃₂NO₅⁺ (M⁺+H) requires 450.2275. Anal. calcd for C₂₇H₃₁NO₅ 0.25H₂O: C 71.42, H 6.99, N 3.08, found: C 71.5, H 6.97, N 3.04.

6-Benzyloxy-2-(2-methoxybenzoyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline

(15a)—Compound **8** (404 mg, 1.5 mmol) was treated with 2-methoxybenzoyl chloride (0.22 mL, 1.65 mmol) and TEA (0.42 mL, 3.0 mmol) in chloroform (10 mL) at rt for 18 h. Water (10 mL) was added and the mixture was extracted with EtOAc (80 mL). The organic layer was washed with water and brine, then dried (MgSO₄), filtered and concentrated in vacuo. Flash column chromatography (hexane/EtOAc 10:1 to 1:1) afforded compound **15a** as a white powder (0.46 g, 79%), mp 92-93 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.59-2.68 and 2.77-2.86 (2H, 2m), 3.39-3.47 and 3.78-3.96 (2H, 2m), 3.72, 3.76, 3.81 and 3.88 (6H, 4s), 4.27, 4.38, 4.80 and 4.88 (2H, 4d, *J* = 16.6, 16.1, 16.6 and 16.1 Hz), 5.11 (2H, s), 6.38 and 6.61 (1H, 2s), 6.67 and 6.69 (1H, 2s), 6.92 (1H, d, *J* = 8.2 Hz), 6.99 (1H, t, *J* = 7.4 Hz), 7.24 (1H, dt, *J* = 7.4, 2.0 Hz), 7.28-7.46 (6H, m). LC/MS (APCI+): *m/z* 402.51 (M⁺-H) and 404.46 (M⁺+H). HRMS (ES+): *m/z* found 404.1856; C₂₅H₂₆NO₄⁺ (M⁺+H) requires 404.1856.

6-Benzyloxy-2-(3-methoxybenzoyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline

(15b)—Method as for **15a** using compound **8** (404 mg, 1.5 mmol), 3-methoxybenzoyl chloride (0.22 mL, 1.65 mmol) and TEA (0.42 mL, 3.0 mmol) in chloroform (10 mL) at rt for 18 h. Flash column chromatography (hexane/EtOAc 10:1 to 1:1) afforded compound **15b**

as a thick colourless oil (0.50 g, 83%). ^1H NMR (270 MHz, CDCl_3): δ = 2.71 and 2.82 (2H, 2s, br), 3.58 and 3.77 (2H, 2s, br), 3.80 (6H, s), 3.86 and 3.93 (1H, 2s, br), 4.49 and 4.79 (1H, 2s, br), 5.11 (2H, s), 6.41 and 6.69 (1H, 2s, br), 6.64 (1H, s, br), 6.92-7.05 (2H, m), 6.97 (1H, s), 7.26-7.46 (6H, m). LC/MS (APCI+): m/z 402.45 ($\text{M}^+\text{-H}$) and 404.46 ($\text{M}^+\text{+H}$). HRMS (ES+): m/z found 404.1858; $\text{C}_{25}\text{H}_{26}\text{NO}_4^+$ ($\text{M}^+\text{+H}$) requires 404.1856. Anal. calcd for $\text{C}_{25}\text{H}_{25}\text{NO}_4$: C 74.42, H 6.25, N 3.47, found: C 74.1, H 6.36, N 3.46.

6-Benzyloxy-2-(4-methoxybenzoyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (15c)—Method as for **15a** using compound **8** (406 mg, 1.5 mmol), 4-methoxybenzoyl chloride (318 mg, 1.8 mmol) and TEA (0.42 mL, 3.0 mmol) in chloroform (30 mL) at rt for 18 h. Flash column chromatography (hexane/EtOAc 10:1 to 1:1) afforded compound **15c** as a white powder (0.52 g, 85%), mp 126-127 °C. ^1H NMR (270 MHz, CDCl_3): δ = 2.77 (2H, s, br), 3.67 (2H, s, br), 3.83 (6H, s), 4.73 (2H, br), 5.11 (2H, s), 6.65 (1H, s), 6.92 (2H, dt, J = 8.6, 2.3 Hz), 7.26-7.45 (8H, m). LC/MS (APCI+): m/z 404.53 ($\text{M}^+\text{+H}$). HRMS (ES+): m/z found 404.1858; $\text{C}_{25}\text{H}_{26}\text{NO}_4^+$ ($\text{M}^+\text{+H}$) requires 404.1856. Anal. calcd for $\text{C}_{25}\text{H}_{25}\text{NO}_4$: C 74.42, H 6.25, N 3.47, found: C 74.1, H 6.45, N 3.53.

6-Benzyloxy-7-methoxy-2-(3,4,5-trimethoxybenzoyl)-1,2,3,4-tetrahydroisoquinoline (15d)—Method as for **15a** using compound **8** (808 mg, 3.0 mmol), 3,4,5-trimethoxybenzoyl chloride (765 mg, 3.3 mmol) and TEA (2.0 mL, 14.4 mmol) in chloroform (20 mL) at rt for 18 h. Flash column chromatography (hexane/EtOAc 3:1 to 1:2) afforded compound **15d** as a white powder (1.10 g, 79%), mp 63-64 °C. ^1H NMR (270 MHz, CDCl_3): δ = 2.78 (2H, s, br), 3.60 and 3.88 (2H, 2s, br), 3.85 (6H, s), 3.86 (6H, s), 4.50 and 4.77 (2H, 2s, br), 5.12 (2H, s), 6.44 and 6.65 (4H, 2s, br), 7.25-7.44 (5H, m). LC/MS (ES+): m/z 464.28 ($\text{M}^+\text{+H}$) and 486.26 ($\text{M}^+\text{+Na}$). HRMS (ES+): m/z found 464.2060; $\text{C}_{27}\text{H}_{30}\text{NO}_6^+$ ($\text{M}^+\text{+H}$) requires 464.2068. Anal. calcd for $\text{C}_{27}\text{H}_{29}\text{NO}_6$: C 69.96, H 6.31, N 3.02, found: C 69.5, H 6.31, N 3.02.

7-Methoxy-2-(2-methoxyphenylsulfonyl)-6-(triisopropylsiloxy)-1,2,3,4-tetrahydroisoquinoline (16a)—Compound **10** (300 mg, 0.9 mmol) was treated with 2-methoxybenzenesulfonyl chloride (204 mg, 0.99 mmol) and TEA (0.14 mL, 0.99 mmol) in DCM (10 mL). The reaction mixture was stirred at rt for 22 h. The reaction mixture was diluted with DCM (30 mL) and washed with sodium bicarbonate (saturated). The aqueous layer was extracted with DCM (2 $\times$ 30 mL). The combined organics were washed with brine (30 mL), dried (MgSO_4), filtered and concentrated in vacuo. Flash column chromatography (hexane to hexane/EtOAc 1:1) afforded compound **16a** as a light beige solid (332 mg, 73%). ^1H NMR (270 MHz, CDCl_3): δ = 1.05 (18H, d, J = 6.7 Hz), 1.13-1.29 (3H, m), 2.57 (2H, t, J = 5.6 Hz), 3.54 (2H, t, J = 5.6 Hz), 3.69 (3H, s), 3.72 (3H, s), 4.41 (2H, s), 6.47 (1H, s), 6.53 (1H, s), 6.88-6.92 (1H, m), 6.99-7.05 (1H, m), 7.44-7.51 (1H, m), 7.94-7.98 (1H, m). LC/MS (ES+): m/z 504.68 ($\text{M}^+\text{-H}$).

6-Benzyloxy-7-methoxy-2-(3-methoxyphenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline (16b)—Method as for **16a** using compound **8** (300 mg, 1.11 mmol), 3-methoxybenzenesulfonyl chloride (0.19 mL, 1.35 mmol) and TEA (0.19 mL, 1.35 mmol) in DCM (10 mL) at rt for 22 h. Flash column chromatography (hexane/EtOAc gradient) afforded compound **16b** as a colourless solid (270 mg, 55%), mp 124-126 °C. ^1H NMR (270 MHz, CDCl_3): δ = 2.76 (2H, t, J = 5.8 Hz), 3.32 (2H, t, J = 5.8 Hz), 3.81 (3H, s), 3.83 (3H, s), 4.18 (2H, s), 5.07 (2H, s), 6.52 (1H, s), 6.56 (1H, s), 7.09 (1H, dt, J = 6.9, 2.7 Hz), 7.28-7.45 (8H, m). ^{13}C NMR (67.5 MHz, CDCl_3): δ = 28.4 (CH_2), 43.9 (CH_2), 47.3 (CH_2), 55.8 (CH_3), 56.2 (CH_3), 71.1 (CH_2), 109.5 (CH), 112.7 (CH), 114.2 (CH), 119.0 (CH), 119.9 (CH), 124.0 (C_q), 125.0 (C_q), 127.3 (2 $\times$ CH), 128.0 (CH), 128.6 (2 $\times$ CH),

130.2 (CH), 137.0 (C_q), 137.6 (C_q), 147.1 (C_q), 148.5 (C_q), 160.0 (C_q). LC/MS (APCI+): *m/z* 440.54 (M⁺+H).

7-Methoxy-2-(4-methoxyphenylsulfonyl)-6-(triisopropylsiloxy)-1,2,3,4-tetrahydroisoquinoline (16c)—Method as for **16a** using compound **10** (300 mg, 0.9 mmol), 4-methoxybenzenesulfonyl chloride (222 mg, 1.07 mmol) and TEA (0.15 mL, 1.07 mmol) in DCM (10 mL) at rt for 18 h. Flash column chromatography (hexane to hexane/EtOAc 1:1) afforded compound **16c** as a colourless solid (292 mg, 65%). ¹H NMR (270 MHz, CDCl₃): δ = 1.04 (18H, d, *J* = 6.8 Hz), 1.12–1.28 (3H, m), 2.76 (2H, t, *J* = 5.8 Hz), 3.28 (2H, t, *J* = 5.8 Hz), 3.71 (3H, s), 3.84 (3H, s), 4.13 (2H, s), 6.44 (1H, s), 6.54 (1H, s), 6.93–6.98 (2H, m), 7.73–7.76 (2H, m). ¹³C NMR (67.5 MHz, CDCl₃): δ = 12.9 (3 × CH), 18.0 (6 × CH₃), 28.1 (CH₂), 44.0 (CH₂), 47.5 (CH₂), 55.6 (CH₃), 55.7 (CH₃), 109.7 (CH), 114.3 (2 × CH), 120.3 (CH), 124.1 (C_q), 125.0 (C_q), 128.0 (C_q), 129.9 (2 × CH), 144.3 (C_q), 149.6 (C_q), 163.1 (C_q). LC/MS (ES+): *m/z* 528.67 (M⁺+Na).

2-Benzyl-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (17a)—A solution of compound **14a** (230 mg, 0.64 mmol) in THF (10 mL) and methanol (10 mL) and Pd/C (10%, 50 mg) was degassed and treated with hydrogen at rt for 2 h. The reaction mixture was filtered through celite and the filtrate was concentrated in vacuo. Flash column chromatography (hexane/EtOAc 3:1 to 1:2) afforded compound **17a** as a light yellow powder (90 mg, 38%), mp 134–135 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.68–2.80 (4H, m), 3.52 (2H, s), 3.66 (2H, s), 3.79 (3H, s), 5.49 (1H, br), 6.44 (1H, s), 6.64 (1H, s), 7.22–7.40 (5H, m). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.5 (CH₂), 50.9 (CH₂), 55.8 (CH₂), 56.0 (CH₃), 62.8 (CH₂), 108.8 (CH), 114.3 (CH), 126.1 (C_q), 127.0 (C_q), 127.2 (CH), 128.4 (2 × CH), 129.3 (2 × CH), 138.4 (C_q), 144.0 (C_q), 144.9 (C_q). LC/MS (APCI+): *m/z* 270.46 (M⁺+H). HRMS (ES+): *m/z* found 270.1488; C₁₇H₂₀NO₂⁺ (M⁺+H) requires 270.1489.

6-Hydroxy-7-methoxy-2-(2-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (17b)—Method as for **17a** using compound **14b** (300 mg, 0.77 mmol) and Pd/C (10%, 30 mg) in THF (15 mL) and methanol (15 mL) at rt for 2 h. Flash column chromatography (hexane/EtOAc 3:1 to 1:2) afforded compound **17b** as a yellow powder (145 mg, 63%), mp 128–129 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.73–2.82 (4H, m), 3.60 (2H, s), 3.71 (2H, s), 3.80 (3H, s), 3.83 (3H, s), 5.47 (1H, s, br), 6.46 (1H, s), 6.63 (1H, s), 6.87 (1H, d, *J* = 7.9 Hz), 6.94 (1H, dt, *J* = 7.4, 1.0 Hz), 7.24 (1H, dt, *J* = 7.4, 1.7 Hz), 7.43 (1H, dd, *J* = 7.4, 1.7 Hz). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.5 (CH₂), 51.0 (CH₂), 55.6 (CH₃), 55.8 (CH₂), 55.9 (CH₂), 56.1 (CH₃), 108.9 (CH), 110.5 (CH), 114.3 (CH), 114.6 (C_q), 120.4 (CH), 120.5 (C_q), 126.4 (C_q), 127.1 (C_q), 128.1 (CH), 130.4 (CH), 144.0 (C_q), 144.8 (C_q), 157.9 (C_q). LC/MS (APCI+): *m/z* 300.44 (M⁺+H).

6-Hydroxy-7-methoxy-2-(3-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (17c)—Method as for **17a** using compound **14c** (300 mg, 0.75 mmol) and Pd/C (10%, 30 mg) in THF (15 mL) and methanol (15 mL) at rt for 0.75 h. Flash column chromatography (hexane/EtOAc 3:1 to 1:2) afforded compound **17c** as a light yellow solid (170 mg, 76%), mp 161–162 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.67–2.80 (4H, m), 3.53 (2H, s), 3.64 (2H, s), 3.79 (6H, s), 5.55 (1H, s, br), 6.45 (1H, s), 6.64 (1H, s), 6.81 (1H, ddd, *J* = 8.1, 2.4, 1.0 Hz), 6.96 (2H, m), 7.23 (1H, t, *J* = 8.1 Hz). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.6 (CH₂), 50.9 (CH₂), 55.3 (CH₃), 55.9 (CH₂), 56.1 (CH₃), 62.9 (CH₂), 108.9 (CH), 112.8 (CH), 114.2 (CH), 114.5 (CH), 121.4 (CH), 126.2 (C_q), 127.0 (C_q), 129.3 (CH), 140.2 (C_q), 144.0 (C_q), 145.0 (C_q), 159.7 (C_q). LC/MS (APCI+): *m/z* 300.44 (M⁺+H). HRMS (ES+): *m/z* found 300.1591; C₁₈H₂₂NO₃⁺ (M⁺+H) requires 300.1594.

6-Hydroxy-7-methoxy-2-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline

(17d)—Method as for **17a** using compound **14d** (220 mg, 0.56 mmol) and Pd/C (10%, 20 mg) in THF (10 mL) and methanol (10 mL) at rt for 1 h. Flash column chromatography (hexane/EtOAc 3:1 to 1:2) afforded compound **17d** as a light yellow solid (100 mg, 60%), mp 162-163 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.69-2.78 (4H, m), 3.49 (2H, s), 3.60 (2H, s), 3.79 (3H, s), 3.80 (3H, s), 5.41 (1H, br), 6.44 (1H, s), 6.62 (1H, s), 6.86 (2H, dt, *J* = 8.6, 2.5 Hz), 7.29 (2H, dt, *J* = 8.8, 2.5 Hz). ¹³C NMR (67.5 MHz, CDCl₃): δ = 27.5 (CH₂), 50.3 (CH₂), 55.1 (CH₂), 55.3 (CH₃), 55.9 (CH₃), 61.6 (CH₂), 109.1 (CH), 113.7 (2 × CH), 114.6 (CH), 124.6 (C_q), 126.2 (C_q), 128.5 (C_q), 130.9 (2 × CH), 144.4 (C_q), 145.5 (C_q), 159.1 (C_q). LC/MS (APCI+): *m/z* 300.50 (M⁺+H).

6-Hydroxy-2-(3-hydroxybenzyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (17e)

—Method as for **17a** using compound **14e** (340 mg, 0.91 mmol) and Pd/C (10%, 40 mg) in THF (20 mL) and methanol (10 mL) at rt for 0.5 h. Flash column chromatography (EtOAc) afforded compound **17e** as a yellow powder (200 mg, 78%), mp 177-178 °C. ¹H NMR (270 MHz, CDCl₃/acetone-*d*₆ 5:1): δ = 2.41-2.51 (4H, m), 3.24 (2H, s), 3.34 (2H, s), 3.53 (3H, s), 6.21 (1H, s), 6.35 (1H, s), 6.49 (1H, ddd, *J* = 7.2, 3.0, 1.2 Hz), 6.61 (1H, d, *J* = 7.2 Hz), 6.64 (1H, d, *J* = 3.0 Hz), 6.88 (1H, t, *J* = 7.2 Hz). ¹³C NMR (67.5 MHz, CDCl₃/acetone-*d*₆ 5:1): δ = 28.3 (CH₂), 50.7 (CH₂), 55.4 (CH₂), 55.7 (CH₃), 62.3 (CH₂), 109.0 (CH), 114.0 (CH), 114.3 (CH), 115.8 (CH), 120.2 (CH), 125.6 (C_q), 126.5 (C_q), 129.1 (CH), 144.1 (C_q), 144.3 (C_q), 145.1 (C_q), 156.9 (C_q). LC/MS (APCI+): *m/z* 286.52 (M⁺+H).

6-Hydroxy-7-methoxy-2-(3-trifluoromethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (17f)

—Method as for **14e** using compound **14f** (238 mg, 0.47 mmol) and TBAF (1M in THF, 0.47 mL, 0.47 mmol) in THF (8 mL) at 0 °C for 1 h. Flash column chromatography (hexane/EtOAc gradient) afforded compound **17f** as a yellow solid (95 mg, 60%), mp 122-124 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.67-2.72 (2H, m), 2.76-2.81 (2H, m), 3.53 (2H, s), 3.67 (2H, s), 3.81 (3H, s), 5.47 (1H, s), 6.45 (1H, s), 6.65 (1H, s), 7.09-7.12 (1H, m), 7.26-7.37 (3H, m). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.5 (CH₂), 50.9 (CH₂), 55.8 (CH₂), 56.1 (CH₃), 62.1 (CH₂), 108.9 (CH), 114.4 (CH), 119.6 (CH), 120.5 (d, *J* = 256.5 Hz, CF₃), 121.4 (CH), 125.9 (C_q), 127.0 (C_q), 127.3 (CH), 129.6 (CH), 141.2 (C_q), 144.2 (C_q), 145.0 (C_q), 149.5 (C_q). LC/MS (ES+): *m/z* 354.57 (M⁺+H).

2-(3-Ethoxybenzyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (17g)

—Method as for **17a** using compound **14g** (180 mg, 0.45 mmol) and Pd/C (10%, 20 mg) in THF (5 mL) and methanol (25 mL) at rt for 0.5 h. Flash column chromatography (hexane/EtOAc 2:1 to 1:1) afforded compound **17g** as a yellow powder (70 mg, 50%), mp 105-106 °C. ¹H NMR (270 MHz, CDCl₃): δ = 1.39 (3H, t, *J* = 7.2 Hz), 2.66-2.80 (4H, m), 3.53 (2H, s), 3.64 (2H, s), 3.79 (3H, s), 4.02 (2H, q, *J* = 7.2 Hz), 6.45 (1H, s), 6.63 (1H, s), 6.80 (1H, ddd, *J* = 8.0, 2.2, 1.0 Hz), 6.93-6.96 (2H, m), 7.22 (1H, t, *J* = 8.0 Hz). ¹³C NMR (67.5 MHz, CDCl₃): δ = 15.0 (CH₃), 28.5 (CH₂), 50.8 (CH₂), 55.8 (CH₂), 56.0 (CH₃), 62.8 (CH₂), 63.4 (CH₂), 108.9 (CH), 113.3 (CH), 114.3 (CH), 115.1 (CH), 121.4 (CH), 126.1 (C_q), 127.0 (C_q), 129.3 (CH), 140.0 (C_q), 144.0 (C_q), 144.9 (C_q), 159.1 (C_q). LC/MS (APCI+): *m/z* 314.55 (M⁺+H).

6-Hydroxy-2-(3-isopropoxybenzyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline

17h—Method as for **17a** using compound **14h** (246 mg, 0.6 mmol) and Pd/C (10%, 50 mg) in THF (7 mL) and methanol (7 mL) at rt for 19 h. Flash column chromatography (hexane/EtOAc gradient) afforded compound **17h** as a pale yellow solid (134 mg, 70%), mp 143-146 °C. ¹H NMR (270 MHz, CDCl₃): δ = 1.31 (6H, d, *J* = 5.9 Hz), 2.68-2.77 (4H, m), 3.52 (2H, s), 3.62 (2H, s), 3.81 (3H, s), 4.55 (1H, sept, *J* = 5.9 Hz), 6.45 (1H, s), 6.63 (1H, s), 6.76-6.80 (1H, m), 6.92-6.94 (2H, m), 7.21 (1H, t, *J* = 7.7 Hz). ¹³C NMR (67.5 MHz,

CDCl₃): δ = 22.2 (2 $\times$ CH₃), 28.6 (CH₂), 50.9 (CH₂), 55.9 (CH₂), 56.1 (CH₃), 62.8 (CH₂), 69.8 (CH), 108.9 (CH), 114.3 (CH), 114.6 (CH), 116.5 (CH), 121.3 (CH), 126.2 (C_q), 127.1 (C_q), 129.3 (CH), 140.2 (C_q), 144.0 (C_q), 144.9 (C_q), 158.0 (C_q). LC/MS (APCI-): m/z 326.09 (M⁻-H). Anal. calcd for C₂₀H₂₅NO₃: C 73.37, H 7.70, N 4.28, found: C 73.5, H 7.90, N 4.13.

6-Hydroxy-7-methoxy-2-(3-phenoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (17i)

—Method as for **17a** using compound **14i** (300 mg, 0.66 mmol) and Pd/C (10%, 50 mg) in THF (15 mL) and methanol (15 mL) rt for 1 h. Flash column chromatography (hexane/EtOAc 3:1 to 1:1) afforded compound **17i** as a yellow powder (170 mg, 71%), mp 139-140 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.67-2.76 (4H, m), 3.53 (2H, s), 3.64 (2H, s), 3.80 (3H, s), 6.45 (1H, s), 6.64 (1H, s), 6.90 (1H, ddd, J = 8.2, 1.6 Hz), 6.99-7.15 (5H, m), 7.28-7.35 (3H, m). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.5 (CH₂), 50.8 (CH₂), 55.7 (CH₂), 56.0 (CH₃), 62.5 (CH₂), 108.8 (CH), 114.2 (CH), 117.6 (CH), 118.8 (2 $\times$ CH), 119.7 (CH), 123.2 (CH), 124.1 (CH), 126.1 (C_q), 127.0 (C_q), 129.6 (CH), 129.8 (2 $\times$ CH), 140.7 (C₃), 144.0 (C_q), 144.9 (C_q), 157.3 (C_q), 157.4 (C_q). LC/MS (APCI+): m/z 362.47 (M⁺+H).

2-(3-Acetoxybenzyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline 17k

—Method as for **17a** using compound **14k** (320 mg, 0.77 mmol) and Pd/C (10%, 40 mg) in THF (5 mL) and methanol (25 mL) at rt for 0.75 h. Flash column chromatography (hexane/EtOAc 2:1 to 1:1) afforded compound **17k** as a light yellow powder (125 mg, 50%), mp 120-122 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.28 (3H, s), 2.67-2.80 (4H, m), 3.51 (2H, s), 3.66 (2H, s), 3.80 (3H, s), 5.46 (1H, s), 6.45 (1H, s), 6.64 (1H, s), 6.98 (1H, ddd, J = 7.9, 2.2, 1.2 Hz), 7.14 (1H, t, J = 1.7 Hz), 7.21-7.26 (1H, m), 7.32 (1H, t, J = 7.7 Hz). ¹³C NMR (67.5 MHz, CDCl₃): δ = 21.3 (CH₃), 28.6 (CH₂), 51.0 (CH₂), 55.8 (CH₂), 56.1 (CH₃), 62.4 (CH₂), 108.9 (CH), 114.3 (CH), 120.4 (CH), 122.0 (CH), 126.1 (C_q), 126.5 (CH), 127.0 (C_q), 129.3 (CH), 140.6 (C_q), 144.0 (C_q), 144.9 (C_q), 150.8 (C_q), 169.7 (C_q). LC/MS (ES+): m/z 328.36 (M⁺+H).

2-(3-Fluorobenzyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (17l)—

Method as for **17a** using compound **14l** (277 mg, 0.93 mmol) and Pd/C (10%, 40 mg) in THF (5 mL) and ethanol (5 mL) at rt for 0.75 h. Flash column chromatography (hexane to hexane/EtOAc 1:1) afforded compound **17l** as a yellow solid (150 mg, 57%), mp 125-127 °C. ¹H NMR (270 MHz, DMSO-*d*₆): δ = 2.60-2.63 (4H, m), 3.40 (2H, s), 3.62 (2H, s), 3.67 (3H, s), 6.49 (1H, s), 6.54 (1H, s), 7.04-7.21 (3H, m), 7.34-7.40 (1H, m), 8.70 (1H, s, br). ¹³C NMR (67.5 MHz, DMSO-*d*₆): δ = 28.1 (CH₂), 50.6 (CH₂), 55.1 (CH₂), 55.6 (CH₃), 61.3 (CH₂), 110.1 (CH), 113.8 (d, J 21.3 Hz, CH), 115.2 (d, J 19.9 Hz, CH), 115.3 (CH), 124.7 (d, J 2.4 Hz, C_q), 124.9 (CH), 125.9 (CH), 130.1 (d, J 8.4 Hz, C_q), 141.8 (d, J 6.9 Hz, C_q), 144.7 (C_q), 145.9 (C_q), 161.3 (d, J 241.9 Hz, CF). LC/MS (APCI+): m/z 288.35 (M⁺+H).

2-(3-Chlorobenzyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (17m)

—Method as for **14e** using compound **14m** (322 mg, 0.7 mmol) and TBAF (1M in THF, 0.7 mL, 0.7 mmol) in THF (15 mL) at 0 °C for 2 h. Flash column chromatography (hexane to EtOAc gradient) afforded compound **17m** as a yellow solid (195 mg, 92%), mp 118-120 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.68-2.72 (2H, m), 2.76-2.80 (2H, m), 3.51 (2H, s), 3.62 (2H, s), 3.80 (3H, s), 6.45 (1H, s), 6.65 (1H, s), 7.22-7.27 (3H, m), 7.40 (1H, d, J = 1.2 Hz). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.5 (CH₂), 51.0 (CH₂), 55.8 (CH₃), 56.1 (CH₂), 62.3 (CH₂), 108.9 (CH), 114.3 (CH), 125.9 (C_q), 126.9 (C_q), 127.3 (CH), 127.4 (CH), 129.1 (CH), 129.7 (CH), 134.3 (C_q), 140.8 (C_q), 144.1 (C_q), 145.0 (C_q). LC/MS (APCI+): m/z 304.53 (M⁺+H).

6-Hydroxy-7-methoxy-2-(3-methylbenzyl)-1,2,3,4-tetrahydroisoquinoline (17n)

—Method as for **17a** using compound **14n** (400 mg, 1.07 mmol) and Pd/C (10%, 50 mg) in THF (20 mL) and methanol (20 mL) at rt for 1 h. Flash column chromatography (hexane/EtOAc 2:1 to 1:2) afforded compound **17n** as a yellow powder (180 mg, 60%), mp 128-129 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.34 (3H, s), 2.68-2.78 (4H, m), 3.52 (2H, s), 3.63 (2H, s), 3.80 (3H, s), 6.45 (1H, s), 6.64 (1H, s), 7.06-7.10 (1H, m), 7.14-7.25 (3H, m). ¹³C NMR (67.5 MHz, CDCl₃): δ = 21.5 (CH₃), 28.5 (CH₂), 51.0 (CH₂), 55.9 (CH₂), 56.0 (CH₃), 62.9 (CH₂), 108.9 (CH), 114.2 (CH), 126.2 (C_q), 126.3 (CH), 127.0 (C_q), 127.9 (CH), 128.2 (CH), 130.0 (CH), 138.0 (C_q), 138.3 (C_q), 144.0 (C_q), 144.9 (C_q). LC/MS (APCI+): *m/z* 284.38 (M⁺+H).

2-(3-Ethylbenzyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (17o)

Method as for **17a** using compound **14o** (502 mg, 1.3 mmol) and Pd/C (10%, 29 mg) in THF (8 mL) and ethanol (8 mL) at rt for 2 h. Flash column chromatography (chloroform/acetone 9:1 to 9:1 and 2% methanol) afforded compound **17o** as a pale yellow solid (260 mg, 67%). ¹H NMR (270 MHz, CDCl₃): δ = 1.24 (3H, t, *J* = 7.6 Hz), 2.65 (2H, q, *J* = 7.6 Hz), 2.72 (2H, d, *J* = 5.2 Hz), 2.77 (2H, d, *J* = 5.2 Hz), 3.53 (2H, s), 3.65 (2H, s), 3.80 (3H, s), 5.51 (1H, s, br), 6.46 (1H, s), 6.64 (1H, s), 7.11 (1H, d, *J* = 7.2 Hz), 7.15-7.29 (2H, m), 7.22 (1H, t, *J* = 6.1 Hz). LC/MS (ES+): *m/z* 298.1 (M⁺+H). HRMS (ES+): *m/z* found 298.1813; C₁₉H₂₄NO₂⁺ (M⁺+H) requires 298.1802.

2-(3-Cyanobenzyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (17p)

—Method as for **14e** using compound **14p** (330 mg, 0.74 mmol) and TBAF (1M in THF, 0.74 mL, 0.74 mmol) in THF (10 mL) at 0 °C for 1 h. Flash column chromatography (hexane/EtOAc gradient) gave a yellow oil that crystallised from diethyl ether/hexane to afford compound **17p** as a light yellow solid (80 mg, 36%), mp 113-115 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.71 (2H, t, *J* = 5.6 Hz), 2.79 (2H, t, *J* = 6.0 Hz), 3.51 (2H, s), 3.68 (2H, s), 3.80 (3H, s), 6.45 (1H, s), 6.65 (1H, s), 7.43 (1H, t, *J* = 8.0 Hz), 7.55 (1H, d, *J* = 8.0 Hz), 7.64 (1H, d, *J* = 8.0 Hz), 7.69 (1H, s). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.3 (CH₂), 50.9 (CH₂), 55.6 (CH₃), 55.9 (CH₂), 61.8 (CH₂), 108.7 (CH), 112.3 (C_q), 114.2 (CH), 118.9 (C_q), 125.5 (C_q), 126.7 (C_q), 129.1 (CH), 130.9 (CH), 132.4 (CH), 133.4 (CH), 140.2 (C_q), 144.1 (C_q), 144.9 (C_q). LC/MS (APCI-): *m/z* 293.45 (M⁻-H).

2-(3-Acetylbenzyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (17q)

—Method as for **14e** using compound **14q** (250 mg, 0.53 mmol) and TBAF (1M in THF, 0.59 mL, 0.59 mmol) in THF (20 mL) at rt for 1 h. Flash column chromatography (hexane/EtOAc 3:1 to 1:2) afforded compound **17q** as a yellow solid (135 mg, 71%), mp 132-134 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.60 (s, 3H), 2.67-2.80 (4H, m), 3.52 (2H, s), 3.71 (2H, s), 3.79 (3H, s), 5.55 (1H, s, br), 6.44 (1H, s), 6.64 (1H, s), 7.42 (1H, t, *J* = 7.7 Hz), 7.62 (1H, dt, *J* = 7.7, 1.6 Hz), 7.85 (1H, dt, *J* = 7.7, 1.2 Hz), 7.95 (1H, m). ¹³C NMR (67.5 MHz, CDCl₃): δ = 26.9 (CH₃), 28.6 (CH₂), 51.0 (CH₂), 55.8 (CH₂), 56.0 (CH₃), 62.5 (CH₂), 108.8 (CH), 114.3 (CH), 126.0 (C_q), 127.0 (C_q), 127.3 (CH), 128.7 (CH), 129.0 (CH), 134.0 (CH), 137.3 (C_q), 139.3 (C_q), 144.1 (C_q), 144.9 (C_q), 198.5 (C_q). LC/MS (APCI+): *m/z* 312.47 (M⁺+H).

6-Hydroxy-7-methoxy-2-(3-nitrobenzyl)-1,2,3,4-tetrahydroisoquinoline (17r)

Method as for **14e** using compound **14r** (410 mg, 0.87 mmol) and TBAF (1M in THF, 0.87 mL, 0.87 mmol) in THF (20 mL) at 0 °C for 1 h. Flash column chromatography (hexane/EtOAc gradient) afforded compound **17r** as a yellow solid (213 mg, 78%), mp 126-129 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.71-2.79 (4H, m), 3.54 (2H, s), 3.74 (2H, s), 3.80 (3H, s), 5.51 (1H, s), 6.44 (1H, s), 6.65 (1H, s), 7.49 (1H, t, *J* = 7.9 Hz), 7.75 (1H, d, *J* = 7.9 Hz), 8.12 (1H, ddd, *J* = 8.2, 2.5, 1.0 Hz), 8.24 (1H, t, *J* = 1.7 Hz). ¹³C NMR (67.5 MHz,

CDCl₃): δ = 28.5 (CH₂), 51.0 (CH₂), 55.8 (CH₂), 56.1 (CH₃), 61.9 (CH₂), 108.8 (CH), 114.4 (CH), 122.4 (CH), 123.8 (CH), 125.6 (C_q), 126.8 (C_q), 126.4 (CH), 135.2 (CH), 141.0 (C_q), 144.2 (C_q), 145.0 (C_q), 148.4 (C_q). LC/MS (APCI+): m/z 315.49 (M⁺+H).

2-(3-Acetamidobenzyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (17s)—Method as for **17a** using compound **14s** (140 mg, 0.34 mmol) and Pd/C (10%, 20 mg) in THF (5 mL) and methanol (30 mL) at rt for 1.5 h. Flash column chromatography (hexane/EtOAc 1:4 to 1:10) afforded compound **17s** as a yellow solid (65 mg, 59%), mp 190–191 °C. ¹H NMR (270 MHz, acetone-*d*₆): δ = 2.06 (3H, s), 2.64–2.73 (4H, m), 3.43 (2H, s), 3.59 (2H, s), 3.75 (3H, s), 6.55 (2H, s), 7.03 (1H, d, *J* = 7.4 Hz), 7.23 (1H, dd, *J* = 8.2, 7.4 Hz), 7.60 (1H, s), 7.63 (1H, d, *J* = 8.2 Hz), 9.13 (1H, s, br). ¹³C NMR (67.5 MHz, acetone-*d*₆): δ = 23.5 (CH₃), 28.7 (CH₂), 51.1 (CH₂), 55.4 (CH₃), 55.6 (CH₂), 62.6 (CH₂), 109.6 (CH), 114.7 (CH), 117.8 (CH), 119.2 (CH), 123.5 (CH), 125.9 (C_q), 126.6 (C_q), 128.5 (CH), 139.8 (2 × C_q), 145.0 (C_q), 145.9 (C_q), 168.1 (C_q). LC/MS (ES–): m/z 325.33 (M[–]-H).

6-Hydroxy-2-(3-(methylsulfonamido)benzyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (17t)—Method as for **17a** using compound **14t** (200 mg, 0.44 mmol) and Pd/C (10%, 40 mg) in THF (15 mL) and methanol (15 mL) at rt for 0.5 h. Flash column chromatography (hexane/EtOAc 1:10) afforded compound **17t** as a yellow powder (150 mg, 94%), mp 99–101 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.66–2.78 (4H, m), 2.98 (3H, s), 3.51 (2H, s), 3.64 (2H, s), 3.79 (3H, s), 6.44 (1H, s), 6.62 (1H, s), 7.14–7.33 (5H, m). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.5 (CH₂), 39.5 (CH₃), 50.9 (CH₂), 55.8 (CH₂), 56.1 (CH₃), 62.3 (CH₂), 108.9 (CH), 114.4 (CH), 119.5 (CH), 121.4 (CH), 125.9 (C_q), 126.1 (CH), 126.9 (C_q), 129.7 (CH), 136.9 (C_q), 140.5 (C_q), 144.1 (C_q), 145.0 (C_q). LC/MS (ES –): m/z 361.54 (M[–]-H).

2-(2,3-Dimethoxybenzyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (17u)—Method as for **17a** using compound **14u** (340 mg, 0.81 mmol) and Pd/C (5%, 60 mg) in THF (20 mL) and methanol (20 mL) at rt for 1.5 h. Flash column chromatography (hexane/EtOAc 1:1 to 1:4) and (DCM/EtOAc 4:1 to 2:1) gave a solid that was stirred in diethyl ether, filtered and dried to afford compound **17u** as a yellow powder (130 mg, 49%), mp 101–102 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.69–2.78 (4H, m), 3.56 (2H, s), 3.72 (2H, s), 3.78 (3H, s), 3.83 (3H, s), 3.86 (3H, s), 5.41 (1H, br), 6.46 (1H, s), 6.61 (1H, s), 6.84 (1H, dd, *J* = 7.4, 2.2 Hz), 6.99–7.08 (2H, m). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.8 (CH₂), 51.0 (CH₂), 55.7 (CH₂), 55.8 (CH₃), 56.0 (CH₃), 56.2 (CH₂), 61.0 (CH₃), 108.9 (CH), 111.1 (CH), 114.2 (CH), 122.6 (CH), 123.9 (CH), 126.5 (C_q), 127.1 (C_q), 132.3 (C_q), 143.9 (C_q), 144.8 (C_q), 147.8 (C_q), 152.8 (C_q). LC/MS (APCI–): m/z 327.98 (M[–]-H).

2-(3,4-Dimethoxybenzyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (17v)—Method as for **17a** using compound **14v** (250 mg, 0.60 mmol) and Pd/C (5%, 50 mg) in THF (15 mL) and methanol (15 mL) at rt for 1 h. Flash column chromatography (hexane/EtOAc 1:1 to 1:4) gave a solid that was stirred in diethyl ether, filtered and dried to afford compound **17v** as a yellow powder (120 mg, 51%), mp 146–147 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.66–2.79 (4H, m), 3.51 (2H, s), 3.59 (2H, s), 3.80 (3H, s), 3.86 (3H, s), 3.87 (3H, s), 5.56 (1H, s, br), 6.45 (1H, s), 6.64 (1H, s), 6.81 (1H, d, *J* = 8.2 Hz), 6.88 (1H, dd, *J* = 8.2, 1.7 Hz), 6.96 (1H, d, *J* = 1.7 Hz). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.5 (CH₂), 50.7 (CH₂), 55.9 (CH₂), 56.0 (2 × CH₃), 56.1 (CH₃), 62.6 (CH₂), 108.9 (CH), 110.7 (CH), 112.1 (CH), 114.3 (CH), 121.3 (CH), 126.2 (C_q), 127.1 (C_q), 131.1 (C_q), 144.1 (C_q), 144.9 (C_q), 148.2 (C_q), 149.0 (C_q). LC/MS (APCI–): m/z 327.98 (M[–]-H).

2-(3,5-Dimethoxybenzyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (17w)—Method as for **17a** using compound **14w** (385 mg, 0.92 mmol) and Pd/C (10%, 30

mg) in THF (15 mL) and methanol (15 mL) at rt for 0.75 h. Flash column chromatography (hexane/EtOAc 3:1 to 1:2) afforded compound **17w** as a yellow powder (260 mg, 86%), mp 127–128 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.68–2.78 (4H, m), 3.53 (2H, s), 3.60 (2H, s), 3.78 (6H, s), 3.80 (3H, s), 6.37 (1H, t, *J* = 2.4 Hz), 6.46 (1H, s), 6.57 (2H, d, *J* = 2.4 Hz), 6.64 (1H, s). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.5 (CH₂), 50.9 (CH₂), 55.5 (CH₃), 55.8 (CH₂), 56.1 (CH₃), 62.9 (CH₂), 99.3 (CH), 106.9 (2 × CH), 109.0 (CH), 114.3 (CH), 126.0 (C_q), 127.0 (C_q), 144.0 (C_q), 144.8 (C_q), 160.8 (2 × C_q). LC/MS (APCI+): *m/z* 330.42 (M⁺+H). HRMS (ES+): *m/z* found 330.1697; C₁₉H₂₄NO₄⁺(M⁺+H) requires 330.1700.

2-(2,5-Dimethoxybenzyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (17x)—Method as for **17a** using compound **14x** (430 mg, 1.03 mmol) and Pd/C (10%, 50 mg) in THF (20 mL) and methanol (20 mL) at rt for 1 h. Flash column chromatography (DCM/EtOAc 3:2 to 1:1) afforded compound **17x** as a yellow powder (260 mg, 77%). ¹H NMR (270 MHz, CDCl₃): δ = 2.71–2.80 (4H, m), 3.60 (2H, s), 3.68 (2H, s), 3.75 (3H, s), 3.79 (3H, s), 3.80 (3H, s), 5.56 (1H, s, br), 6.47 (1H, s), 6.63 (1H, s), 6.75 (1H, dd, *J* = 8.9, 2.7 Hz), 6.79 (1H, s), 6.81 (1H, d, *J* = 8.9 Hz), 7.06 (1H, d, *J* = 2.7 Hz). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.6 (CH₂), 50.9 (CH₂), 55.7 (CH₂), 55.8 (CH₃), 55.9 (CH₂), 56.1 (CH₃), 56.3 (CH₃), 108.9 (CH), 111.7 (CH), 112.5 (CH), 114.3 (CH), 116.1 (CH), 126.5 (C_q), 127.2 (C_q), 127.9 (C_q), 144.0 (C_q), 144.9 (C_q), 152.1 (C_q), 153.7 (C_q). LC/MS (APCI–): *m/z* 328.29 (M⁺-H).

6-Hydroxy-7-methoxy-2-(2,3,4-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (17y)—Method as for **17a** using compound **14y** (280 mg, 0.62 mmol) and Pd/C (10%, 30 mg) in THF (10 mL) and methanol (10 mL) at rt for 2 h. Flash column chromatography (DCM/EtOAc 1:1) afforded compound **17y** as a yellow powder (165 mg, 74%), mp 65–66 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.66–2.75 (4H, m), 3.55 (2H, s), 3.63 (2H, s), 3.80 (3H, s), 3.85 (3H, s), 3.88 (6H, s), 5.49 (1H, s, br), 6.46 (1H, s), 6.63 (1H, s), 6.65 (1H, d, *J* = 8.7 Hz), 7.09 (1H, d, *J* = 8.7 Hz). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.6 (CH₂), 50.7 (CH₂), 55.6 (CH₂), 56.1 (2 × CH₃), 56.2 (CH₂), 60.9 (CH₃), 61.4 (CH₃), 107.1 (CH), 108.9 (CH), 114.2 (CH), 125.2 (CH), 126.1 (C_q), 127.0 (C_q), 142.0 (C_q), 142.8 (C_q), 144.0 (C_q), 144.9 (C_q), 152.7 (C_q), 153.0 (C_q). LC/MS (APCI–): *m/z* 358.21 (M⁺-H).

6-Hydroxy-7-methoxy-2-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (17z)—Method as for **17a** using compound **14z** (335 mg, 0.75 mmol) and Pd/C (10%, 30 mg) in THF (15 mL) and methanol (15 mL) at rt for 1 h. Flash column chromatography (hexane/EtOAc 1:1 to 1:4) gave a solid that was stirred in diethyl ether, filtered and dried to afford compound **17z** as a yellow powder (160 mg, 60%), mp 170–171 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.66–2.81 (4H, m), 3.53 (2H, s), 3.59 (2H, s), 3.81 (3H, s), 3.84 (3H, s), 3.85 (6H, s), 5.49 (1H, s, br), 6.48 (1H, s), 6.62 (2H, s), 6.66 (1H, s). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.6 (CH₂), 50.8 (CH₂), 56.0 (CH₂), 56.1 (CH₃), 56.2 (CH₃), 61.0 (CH₃), 63.0 (CH₂), 105.7 (2 × CH), 108.9 (CH), 114.3 (CH), 126.1 (C_q), 127.1 (C_q), 134.4 (C_q), 136.9 (C_q), 144.1 (C_q), 145.0 (C_q), 153.2 (2 × C_q). LC/MS (APCI–): *m/z* 358.15 (M⁺-H).

6-Hydroxy-7-methoxy-2-(2,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (17aa)—Method as for **17a** using compound **14aa** (210 mg, 0.47 mmol) and Pd/C (10%, 40 mg) in THF (10 mL) and methanol (10 mL) at rt for 2 h. Flash column chromatography (DCM/EtOAc 2:1 to 1:1) afforded compound **17aa** as a yellow powder (80 mg, 48%), mp 152–153 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.67–2.79 (4H, m), 3.57 (2H, s), 3.64 (2H, s), 3.80 (3H, s), 3.81 (3H, s), 3.82 (3H, s), 3.89 (3H, s), 5.61 (1H, s, br), 6.46 (1H, s), 6.53 (1H, s), 6.62 (1H, s), 7.01 (1H, s). ¹³C NMR (67.5 MHz,

CDCl₃): δ = 28.6 (CH₂), 50.6 (CH₂), 55.3 (CH₂), 55.8 (CH₂), 56.0 (CH₃), 56.2 (CH₃), 56.6 (CH₃), 56.8 (CH₃), 97.6 (CH), 108.9 (CH), 114.2 (CH), 114.3 (CH), 118.0 (C_q), 126.4 (C_q), 127.1 (C_q), 143.1 (C_q), 144.0 (C_q), 144.9 (C_q), 148.5 (C_q), 152.1 (C_q). LC/MS (APCI-): m/z 358.21 (M⁻-H).

6-Hydroxy-7-methoxy-2-(2,4,6-trimethoxybenzyl)-1,2,3,4-

tetrahydroisoquinoline (17ab)—Method as for **17a** using compound **14ab** (460 mg, 1.02 mmol) and Pd/C (10%, 50 mg) in THF (20 mL) and methanol (20 mL) at rt for 0.5 h. Flash column chromatography (hexane/EtOAc 10:1 to EtOAc to EtOAc/methanol 19:1) afforded compound **17ab** as a light yellow powder (260 mg, 71%), mp 150-151 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.70-2.77 (4H, m), 3.58 (2H, s), 3.69 (2H, s), 3.80 (9H, s), 3.81 (3H, s), 5.56 (1H, s, br), 6.13 (2H, s), 6.44 (1H, s), 6.56 (1H, s). ¹³C NMR (67.5 MHz, CDCl₃): δ = 27.1 (CH₂), 48.1 (CH₂), 49.7 (CH₂), 55.3 (CH₂), 55.4 (CH₃), 55.8 (2 × CH₃), 56.2 (CH₃), 90.5 (2 × CH), 103.8 (C_q), 108.9 (CH), 114.2 (CH), 125.9 (C_q), 126.1 (C_q), 144.2 (C_q), 145.1 (C_q), 160.2 (2 × C_q), 160.6 (C_q). LC/MS (ES+): m/z 360.5 (M⁺+H). HRMS (ES+): m/z found 360.1790; C₂₀H₂₅NO₅⁺ (M⁺+H) requires 360.1805. Anal. calcd for C₂₀H₂₅NO₅: C 66.83, H 7.01, N 3.90, found: C 66.6, H 7.04, N 3.85.

6-Hydroxy-7-methoxy-2-(2-methoxybenzoyl)-1,2,3,4-tetrahydroisoquinoline

(18a)—Method as for **17a** using compound **15a** (290 mg, 0.72 mmol) and Pd/C (10%, 50 mg) in THF (15 mL) and methanol (15 mL) at rt for 4 h. Flash column chromatography (hexane/EtOAc 2:1 to 3:2) gave a solid that was stirred in diethyl ether, filtered and dried to afford compound **18a** as a white solid (200 mg, 89%), mp 176-177 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.62-2.72 and 2.80-2.87 (2H, 2m), 3.40-3.48 and 4.07-4.21 (2H, m), 3.74, 3.76, 3.81 and 3.87 (6H, 4s), 4.26, 4.37, 4.80 and 4.86 (2H, 4d, J = 16.8, 15.8, 16.0 and 16.1 Hz), 5.55 and 5.57 (1H, 2s), 6.34, 6.64, 6.65 and 6.71 (2H, 4s), 6.92 (1H, d, J = 8.4 Hz), 6.98 (1H, ddt, J = 7.7, 2.2, 0.8 Hz), 7.22-7.27 (1H, m), 7.31-7.40 (1H, m). LC/MS (APCI+): m/z 314.42 (M⁺+H). HRMS (ES+): m/z found 314.1385; C₁₈H₁₉NO₄⁺ (M⁺+H) requires 314.1387. Anal. calcd for C₁₈H₁₉NO₄: C 68.99, H 6.11, N 4.47, found: C 68.8, H 6.13, N 4.42.

6-Hydroxy-7-methoxy-2-(3-methoxybenzoyl)-1,2,3,4-tetrahydroisoquinoline

(18b)—Method as for **17a** using compound **15b** (340 mg, 0.84 mmol) and Pd/C (10%, 50 mg) in THF (15 mL) and methanol (15 mL) at rt for 4 h. Flash column chromatography (hexane/EtOAc 2:1 to 3:2) gave a solid that was stirred in diethyl ether, filtered and dried to afford compound **18b** as a white solid (180 mg, 68%), mp 141-142 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.74 and 2.85 (2H, 2s, br), 3.59 and 3.94 (2H, 2s, br), 3.78 and 3.87 (6H, 2s), 4.48 and 4.79 (2H, 2s, br), 5.57 (1H, s), 6.36 and 6.64 (1H, 2s), 6.69 (1H, s), 6.94-7.01 (2H, m), 6.98 (1H, s), 7.32 (1H, dd, J = 8.8, 7.4 Hz). LC/MS (APCI+): m/z 314.42 (M⁺+H). HRMS (ES+): m/z found 314.1385; C₁₈H₂₀NO₄⁺ (M⁺+H) requires 314.1387.

6-Hydroxy-7-methoxy-2-(4-methoxybenzoyl)-1,2,3,4-tetrahydroisoquinoline

(18c)—Method as for **17a** using compound **15c** (320 mg, 0.79 mmol) and Pd/C (10%, 30 mg) in THF (15 mL) and methanol (15 mL) at rt for 1.5 h. The resulting solid was stirred in hexane/EtOAc (2:5, 14 mL), filtered and dried to afford compound **18c** as a white solid (220 mg, 89%), mp 173-174 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.68 (2H, t, J = 6.9 Hz), 3.56 (2H, s, br), 3.70 (3H, s, br), 3.80 (3H, s), 4.57 (2H, s, br), 6.55 (1H, s), 6.78 (1H, s, br), 7.00 (2H, dt, J = 5.9, 1.7 Hz), 7.41 (2H, dt, J = 5.9, 1.7 Hz), 8.84 (1H, s). LC/MS (APCI+): m/z 314.42 (M⁺+H). HRMS (ES+): m/z found 314.1384; C₁₈H₂₀NO₄⁺ (M⁺+H) requires 314.1387.

6-Hydroxy-7-methoxy-2-(3,4,5-trimethoxybenzoyl)-1,2,3,4-tetrahydroisoquinoline (18d)—Method as for **17a** using compound **15d** (250 mg, 0.54 mmol) and Pd/C (10%, 40 mg) in THF (20 mL) and methanol (20 mL) at rt for 24 h. The resulting solid was stirred in diethyl ether, filtered and dried to afford compound **18d** as a white solid (180 mg, 90%), mp 172-173 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.79 (2H, s, br), 3.62 and 3.83 (2H, 2s, br), 3.85 (12H, s), 4.50 and 4.76 (2H, 2s, br), 5.54 (1H, s), 6.41 and 6.70 (1H, 2s, br), 6.66 (3H, s). LC/MS (ES⁻): *m/z* 372.07 (M⁻-H). HRMS (ES⁺): *m/z* found 374.1581; C₂₀H₂₄NO₆⁺ (M⁺+H) requires 374.1598. Anal. calcd for C₂₀H₂₃NO₆: C 64.33, H 6.21, N 3.75, found: C 63.8, H 6.12, N 3.70.

6-Hydroxy-7-methoxy-2-(2-methoxyphenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline (19a)—Method as for **14e** using compound **16a** (332 mg, 0.66 mmol) and TBAF (1M in THF, 0.66 mL, 0.66 mmol) in THF (10 mL) at 0 °C for 1 h. Flash column chromatography (hexane/EtOAc gradient) afforded compound **19a** as a colourless foam (103 mg, 45%), mp 140-142 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.62 (2H, t, *J* = 5.9 Hz), 3.55 (2H, t, *J* = 5.9 Hz), 3.71 (3H, s), 3.82 (3H, s), 4.41 (2H, s), 5.46 (1H, s), 6.49 (1H, s), 6.61 (1H, s), 6.92 (1H, d, *J* = 8.2 Hz), 7.03 (1H, dt, *J* = 7.7, 1.0 Hz), 7.46-7.51 (1H, m), 7.96 (1H, dd, *J* = 7.7, 1.7 Hz). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.1 (CH₂), 43.8 (CH₂), 46.8 (CH₂), 55.7 (CH₃), 56.0 (CH₃), 108.1 (CH), 111.1 (CH), 114.4 (CH), 120.3 (CH), 124.0 (C_q), 126.4 (C_q), 127.2 (C_q), 131.7 (CH), 134.4 (CH), 144.1 (C_q), 145.3 (C_q), 156.9 (C_q). LC/MS (ES⁻): *m/z* 348.27 (M⁻-H).

6-Hydroxy-7-methoxy-2-(3-methoxyphenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline (19b)—Method as for **17a** using compound **16b** (285 mg, 0.65 mmol) and Pd/C (10%, 30 mg) in THF (5 mL) and ethanol (5 mL) at rt for 3 h. The resulting beige solid was triturated with hexane and collected by filtration to afford compound **19b** as a colourless solid (214 mg, 95%), mp 168-170 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.79 (2H, t, *J* = 5.9 Hz), 3.33 (2H, t, *J* = 5.9 Hz), 3.81 (3H, s), 3.83 (3H, s), 4.18 (2H, s), 5.49 (1H, s), 6.47 (1H, s), 6.61 (1H, s), 7.09 (1H, dt, *J* = 6.9, 2.5 Hz), 7.31-7.42 (3H, m). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.3 (CH₂), 43.9 (CH₂), 47.4 (CH₂), 55.8 (CH₃), 56.1 (CH₃), 108.4 (CH), 112.7 (CH), 114.3 (CH), 119.0 (CH), 119.9 (CH), 122.8 (C_q), 125.8 (C_q), 130.2 (CH), 137.6 (C_q), 144.6 (C_q), 145.4 (C_q), 160.0 (C_q). LC/MS (APCI⁺): *m/z* 350.53 (M⁺+H).

6-Hydroxy-7-methoxy-2-(4-methoxyphenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline (19c)—Method as for **14e** using compound **16c** (272 mg, 0.54 mmol) and TBAF (1M in THF, 0.54 mL, 0.54 mmol) in THF (10 mL) at 0 °C for 2 h. Flash column chromatography (hexane/EtOAc gradient) and crystallisation from hexane/DCM afforded compound **19c** as a colourless solid (177 mg, 94%), mp 147-149 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.79 (2H, t, *J* = 5.9 Hz), 3.29 (2H, t, *J* = 5.9 Hz), 3.82 (3H, s), 3.85 (3H, s), 4.14 (2H, s), 5.46 (1H, s), 6.47 (1H, s), 6.61 (1H, s), 6.95-6.98 (2H, m), 7.73-7.76 (2H, m). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.3 (CH₂), 43.9 (CH₂), 47.4 (CH₂), 55.7 (CH₃), 56.1 (CH₃), 108.4 (CH), 114.3 (3 × CH), 122.9 (C_q), 125.8 (C_q), 128.0 (C_q), 129.9 (2 × CH), 144.4 (C_q), 145.4 (C_q), 163.1 (C_q). LC/MS (ES⁻): *m/z* 348.48 (M⁻-H).

2-Benzyl-7-methoxy-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (20a)—Sulfamoyl chloride (0.6M in toluene, 1.0 mL, 0.6 mmol) was concentrated *in vacuo* and cooled to 0 °C until the sulfamoyl chloride solidified. DMA (1.0 mL) was added and the resulting solution was added directly to compound **17a** (55 mg, 0.20 mmol) at 0 °C under nitrogen. The reaction mixture was stirred at rt for 18 h. Sodium bicarbonate (saturated) was added and the mixture was extracted with EtOAc. The organic layer was washed with water (up to ten times) and brine, then dried (MgSO₄), filtered and concentrated *in vacuo*. Flash column chromatography (hexane/EtOAc 1:1 to 1:3) gave an oil that was stirred in diethyl

ether to afford compound **20a** as a light yellow powder (55 mg, 79%), mp 113-114 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.71-2.84 (4H, m), 3.56 (2H, s), 3.68 (2H, s), 3.80 (3H, s), 4.97 (2H, s, br), 6.60 (1H, s), 7.07 (1H, s), 7.26-7.40 (5H, m). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.2 (CH₂), 50.5 (CH₂), 55.7 (CH₂), 56.4 (CH₃), 62.6 (CH₂), 111.2 (CH), 124.2 (CH), 127.4 (CH), 127.7 (C_q), 128.5 (2 × CH), 129.2 (2 × CH), 134.9 (C_q), 137.3 (C_q), 138.0 (C_q), 149.3 (C_q). LC/MS (APCI+): *m/z* 349.37 (M⁺+H). HRMS (ES+): *m/z* found 349.1213; C₁₇H₂₁N₂O₄S⁺ (M⁺+H) requires 349.1217.

7-Methoxy-2-(2-methoxybenzyl)-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (20b)—Method as for **20a** using compound **17b** (72 mg, 0.24 mmol) and sulfamoyl chloride (0.72 mmol) in DMA (1.0 mL) at rt for 18 h. Flash column chromatography (hexane/EtOAc 1:1 to 1:3) gave an oil that was stirred in diethyl ether to afford compound **20b** as a light yellow powder (50 mg, 55%), mp 126-127 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.78 (4H, m), 3.48 (2H, s, br), 3.62 (2H, s), 3.73 (2H, s), 3.79 (3H, s), 3.83 (3H, s), 6.61 (1H, s), 6.90 (1H, d, *J* = 7.9 Hz), 6.95 (1H, dt, *J* = 7.4, 1.0 Hz), 7.09 (1H, s), 7.25-7.36 (2H, m). ¹³C NMR (67.5 MHz, CDCl₃): δ = 27.6 (CH₂), 50.3 (CH₂), 55.6 (CH₂), 55.6 (2 × CH₃), 60.7 (CH₂), 110.6 (CH), 111.0 (CH), 120.5 (CH), 123.8 (CH), 124.8 (C_q), 126.8 (C_q), 128.9 (CH), 131.2 (CH), 133.8 (C_q), 137.5 (C_q), 149.7 (C_q), 158.1 (C_q). LC/MS (APCI+): *m/z* 379.34 (M⁺+H). HRMS (ES+): *m/z* found 379.1323; C₁₈H₂₃N₂O₅S⁺ (M⁺+H) requires 379.1322.

7-Methoxy-2-(3-methoxybenzyl)-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (20c)—Method as for **20a** using compound **17c** (105 mg, 0.35 mmol) and sulfamoyl chloride (1.05 mmol) in DMA (1.0 mL) at rt for 18 h. Flash column chromatography (hexane/EtOAc 1:1 to 1:3) gave an oil that was stirred in diethyl ether to afford compound **20c** as a light yellow powder (105 mg, 79%), mp 144-145 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.66-2.77 (4H, m), 3.10 (2H, s, br), 3.51 (2H, s), 3.60 (2H, s), 3.74 (3H, s), 3.75 (3H, s), 6.55 (1H, s), 6.79 (1H, d, *J* = 7.9 Hz), 6.82 (2H, s), 7.04 (1H, s), 7.21 (1H, t, *J* = 7.9 Hz). ¹³C NMR (67.5 MHz, CDCl₃): δ = 27.8 (CH₂), 50.4 (CH₂), 55.3 (CH₃), 55.6 (CH₂), 56.2 (CH₃), 62.7 (CH₂), 110.9 (CH), 112.9 (CH), 114.8 (CH), 121.7 (CH), 123.8 (CH), 126.9 (C_q), 129.4 (CH), 133.9 (C_q), 137.7 (C_q), 138.9 (C_q), 149.6 (C_q), 159.7 (C_q). LC/MS (APCI+): *m/z* 379.34 (M⁺+H). HRMS (ES+): *m/z* found 379.1320; C₁₈H₂₃N₂O₅S⁺ (M⁺+H) requires 379.1322.

7-Methoxy-2-(4-methoxybenzyl)-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (20d)—Method as for **20a** using compound **17d** (90 mg, 0.30 mmol) and sulfamoyl chloride (0.90 mmol) in DMA (1.0 mL) at rt for 18 h. Flash column chromatography (hexane/EtOAc 1:1 to 1:3) gave an oil that was stirred in diethyl ether to afford compound **20d** as a light yellow powder (95 mg, 84%), mp 104-105 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.69-2.82 (4H, m), 3.54 (2H, s), 3.61 (4H, s, br), 3.78 (3H, s), 3.79 (3H, s), 6.59 (1H, s), 6.88 (2H, d, *J* = 8.6 Hz), 7.07 (1H, s), 7.26 (2H, d, *J* = 8.6 Hz). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.2 (CH₂), 50.4 (CH₂), 55.4 (CH₃), 55.6 (CH₂), 56.3 (CH₃), 62.1 (CH₂), 111.1 (CH), 113.7 (2 × CH), 124.2 (CH), 127.7 (C_q), 129.9 (C_q), 130.4 (2 × CH), 134.4 (C_q), 138.2 (C_q), 150.4 (C_q), 159.6 (C_q). LC/MS (APCI+): *m/z* 379.34 (M⁺+H). HRMS (ES+): *m/z* found 379.1322; C₁₈H₂₃N₂O₅S⁺ (M⁺+H) requires 379.1322.

2-(3-Hydroxybenzyl)-7-methoxy-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (20e)—Method as for **17a** using the benzyl-silyl-bisprotected phenol (see **14e**: 425 mg, 0.8 mmol) and Pd/C (10%, 40 mg) in THF (10 mL) and methanol (30 mL) at rt for 0.5 h. Flash column chromatography (hexane/EtOAc 5:1 to 4:1) afforded the silyl-protected phenol as a yellow oil (250 mg, 71%). ¹H NMR (270 MHz, CDCl₃): δ = 1.09 (18H, d, *J* = 6.7 Hz), 1.16-1.31 (3H, m), 2.66-2.77 (4H, m), 3.52 (2H, s), 3.61 (2H, s), 3.79 (3H, s), 6.44 (1H, s), 6.62 (1H, s), 6.74-6.81 (1H, m), 6.93-6.96 (2H, m), 7.16 (1H, t, *J* = 7.8 Hz). ¹³C NMR (67.5

MHz, CDCl₃): δ = 12.8 (3 $\times$ CH), 18.0 (6 $\times$ CH₃), 28.5 (CH₂), 50.8 (CH₂), 55.8 (CH₂), 56.0 (CH₃), 62.7 (CH₂), 108.9 (CH), 114.4 (CH), 118.6 (CH), 120.8 (CH), 122.0 (CH), 126.2 (C_q), 127.1 (C_q), 129.2 (CH), 139.9 (C_q), 144.0 (C_q), 145.0 (C_q), 156.1 (C_q). LC/MS (APCI +): m/z 532.71 (M⁺+H). The silyl-protected phenol (200 mg, 0.45 mmol) and 2,6-tert-butyl-4-methylpyridine (205 mg, 1.0 mmol) were dissolved in DCM (5 mL). Sulfamoyl chloride (1.80 mmol) was concentrated in vacuo and dissolved in DCM (~1 mL). The solution was added to the reaction mixture and stirred at rt for 60 h. Sodium bicarbonate (saturated) was added and the mixture was extracted with EtOAc. The organic layer was washed with water, brine, dried (MgSO₄), filtered and concentrated in vacuo. Flash column chromatography (hexane/ethyl acetate 4:1 to 3:2) to afford compound the sulfamate as a yellow powder (100 mg, 63%), mp 110-112 °C. ¹H NMR (270 MHz, CDCl₃): δ = 1.08 (18H, d, J = 6.9 Hz), 1.16-1.30 (3H, m), 2.66-2.81 (4H, m), 3.54 (2H, s), 3.61 (2H, s), 3.79 (3H, s), 5.02 (2H, br), 6.58 (1H, s), 6.78 (1H, ddd, J = 7.9, 2.2, 1.0 Hz), 6.89-6.94 (2H, m), 6.78 (1H, s), 7.05 (1H, s), 7.16 (1H, t, J = 7.9 Hz). ¹³C NMR (67.5 MHz, CDCl₃): δ = 12.7 (3 $\times$ CH), 18.0 (6 $\times$ CH₃), 28.2 (CH₂), 50.3 (CH₂), 55.7 (CH₂), 56.3 (CH₃), 62.5 (CH₂), 111.1 (CH), 118.8 (CH), 120.8 (CH), 121.9 (CH), 124.0 (CH), 127.7 (C_q), 129.3 (CH), 134.9 (C_q), 137.3 (C_q), 139.5 (C_q), 149.3 (C_q), 156.2 (C_q). LC/MS (ES-): m/z 519.56 (M⁻-H). HRMS (ES+): m/z found 521.2504; C₂₆H₄₁N₂O₅SSi⁺ (M⁺+H) requires 521.2500. Method as for **14e** using compound the sulfamate (85 mg, 0.16 mmol) and TBAF (1M in THF, 0.18 mL, 0.18 mmol) in THF (10 mL) at 0 °C for 1 h. Flash column chromatography (hexane/EtOAc 3:2 to 1:5) gave a solid that was stirred in diethyl ether/hexane (1:2), filtered and dried to afford compound **20e** as a yellow powder (38 mg, 66%), mp 134-135 °C. ¹H NMR (270 MHz, acetone-*d*₆): δ = 2.67-2.81 (4H, m), 3.51 (2H, s), 3.59 (2H, s), 3.78 (3H, s), 6.73 (1H, dd, J = 7.9, 2.5 Hz), 6.77 (1H, s), 6.84 (1H, d, J = 7.4 Hz), 6.88-6.93 (2H, m), 7.04 (1H, s), 7.14 (1H, dd, J = 7.9, 7.4 Hz). ¹³C NMR (67.5 MHz, acetone-*d*₆): δ = 28.4 (CH₂), 50.8 (CH₂), 55.4 (CH₃), 55.6 (CH₂), 62.4 (CH₂), 110.9 (CH), 114.0 (CH), 115.6 (CH), 119.9 (CH), 123.7 (CH), 126.5 (C_q), 129.3 (CH), 134.5 (C_q), 137.5 (C_q), 140.5 (C_q), 150.2 (C_q), 157.6 (C_q). LC/MS (ES-): m/z 363.37 (M⁻-H).

7-Methoxy-6-sulfamoyloxy-2-(3-trifluoromethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (20f)—Method as for **20a** using compound **17f** (69 mg, 0.20 mmol) and sulfamoyl chloride (0.60 mmol) in DMA (1.0 mL) at rt for 20 h. Flash column chromatography (hexane/EtOAc gradient) afforded compound **20f** as a yellow powder (60 mg, 69%), mp 109-110 °C. ¹H NMR (270 MHz, DMSO-*d*₆): δ = 2.66-2.69 (2H, m), 2.74-2.76 (2H, m), 3.35 (2H, s), 3.53 (2H, s), 3.71 (3H, s), 6.82 (1H, s), 7.04 (1H, s), 7.26-7.28 (1H, m), 7.34 (1H, s), 7.40 (1H, d, J = 7.6 Hz), 7.49 (1H, t, J = 8.0 Hz), 7.84 (2H, s, br). ¹³C NMR (67.5 MHz, DMSO-*d*₆): δ = 27.8 (CH₂), 50.2 (CH₂), 55.0 (CH₂), 55.8 (CH₃), 60.8 (CH₂), 111.2 (CH), 119.6 (CH), 120.1 (q, J = 254.6 Hz, CF₃), 120.7 (CH), 122.8 (CH), 125.8 (C_q), 127.7 (CH), 130.3 (CH), 133.5 (C_q), 137.1 (C_q), 141.6 (C_q), 148.6 (C_q), 149.7 (C_q). LC/MS (APCI-): m/z 431.02 (M⁻-H).

2-(3-Ethoxybenzyl)-7-methoxy-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (20g)—Method as for **20a** using compound **17g** (50 mg, 0.16 mmol) and sulfamoyl chloride (0.32 mmol) in DMA (1.0 mL) at rt for 60 h. Flash column chromatography (hexane/EtOAc 2:1 to 1:1) afforded compound **20g** as a white solid (45 mg, 71%), mp 64-65 °C. ¹H NMR (270 MHz, CDCl₃): δ = 1.39 (3H, t, J = 6.9 Hz), 2.69-2.84 (4H, m), 3.56 (2H, s), 3.64 (2H, s), 3.80 (3H, s), 4.02 (2H, q, J = 6.9 Hz), 5.00 (2H, s, br), 6.59 (1H, s), 6.80 (1H, dd, J = 7.9, 2.0 Hz), 6.91-6.94 (2H, m), 7.06 (1H, s), 7.22 (1H, t, J = 7.9 Hz). ¹³C NMR (67.5 MHz, CDCl₃): δ = 15.0 (CH₃), 28.2 (CH₂), 50.5 (CH₂), 55.7 (CH₂), 56.4 (CH₃), 62.6 (CH₂), 63.5 (CH₂), 111.2 (CH), 113.4 (CH), 115.1 (CH), 121.4 (CH), 124.1 (CH), 127.7 (C_q), 129.4 (CH), 134.8 (C_q), 137.3 (C_q), 139.6 (C_q), 149.3 (C_q), 159.2 (C_q). LC/MS (APCI+): m/z 393.43 (M⁺+H).

2-(3-Isopropoxybenzyl)-7-methoxy-6-sulfamoyloxy-1,2,3,4-

tetrahydroisoquinoline (20h)—Method as for **20a** using compound **17h** (88 mg, 0.27 mmol) and sulfamoyl chloride (0.8 mmol) in DMA (1.0 mL) at rt for 20 h. Flash column chromatography (hexane to EtOAc gradient) afforded compound **20h** as a yellow solid (78 mg, 72%), mp 80 °C (dec.). ¹H NMR (270 MHz, DMSO-*d*₆): δ = 1.25 (6H, d, *J* = 5.9 Hz), 2.66 (2H, d, *J* = 4.9 Hz), 2.73 (2H, d, *J* = 4.9 Hz), 3.49 (2H, s), 3.60 (2H, s), 3.71 (3H, s), 4.58 (1H, sept, *J* = 5.9 Hz), 6.79-6.81 (2H, m), 6.88-6.89 (2H, m), 7.03 (1H, s), 7.22 (1H, t, *J* = 8.0 Hz), 7.82 (2H, s, br). ¹³C NMR (67.5 MHz, DMSO-*d*₆): δ = 22.4 (2 × CH₃), 28.5 (CH₂), 50.8 (CH₂), 55.7 (CH₂), 56.4 (CH₃), 62.3 (CH₂), 69.4 (CH), 111.6 (CH), 114.6 (CH), 116.2 (CH), 121.2 (CH), 123.3 (CH), 126.5 (C_q), 129.9 (CH), 134.3 (C_q), 137.6 (C_q), 140.6 (C_q), 150.2 (C_q), 158.0 (C_q). LC/MS (APCI–): *m/z* 405.07 (M[–]H).

7-Methoxy-2-(3-phenoxybenzyl)-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (20i)

—Method as for **20a** using compound **17i** (70 mg, 0.25 mmol) and sulfamoyl chloride (0.75 mmol) in DMA (1.0 mL) at rt for 24 h. Flash column chromatography (hexane/EtOAc 3:2 to 1:1) gave a solid that was stirred in diethyl ether, filtered and dried to afford compound **20i** as a yellow powder (105 mg, 82%), mp 68-69 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.68-2.79 (4H, m), 3.56 (2H, s), 3.64 (2H, s), 3.80 (3H, s), 4.80 (2H, s, br), 6.59 (1H, s), 6.90 (1H, dd, *J* = 7.9, 1.7 Hz), 7.00 (2H, dd, *J* = 7.7, 1.0 Hz), 7.05-7.12 (4H, m), 7.25-7.35 (3H, m). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.2 (CH₂), 50.4 (CH₂), 55.7 (CH₂), 56.4 (CH₃), 62.3 (CH₂), 111.2 (CH), 117.7 (CH), 118.9 (2 × CH), 119.6 (CH), 123.3 (CH), 124.0 (CH), 124.1 (CH), 127.6 (C_q), 129.7 (CH), 129.9 (2 × CH), 134.7 (C_q), 137.3 (C_q), 140.2 (C_q), 149.3 (C_q), 157.3 (C_q), 157.4 (C_q). LC/MS (APCI–): *m/z* 439.66 (M[–]H).

7-Methoxy-6-sulfamoyloxy-2-(3-(sulfamoyloxy)benzyl)-1,2,3,4-

tetrahydroisoquinoline (20j)—Method as for **20a** using compound **17e** (114 mg, 0.4 mmol) and sulfamoyl chloride (1.6 mmol) in DMA (1.5 mL) at rt for 24 h. Flash column chromatography (hexane/EtOAc 1:1 to 1:4) gave a pale yellow oil that slowly crystallised upon addition of diethyl ether and evaporation of the solvent to afford compound **20j** as a light yellow solid (135 mg, 76%), mp 187-188 °C. ¹H NMR (270 MHz, CDCl₃/acetone-*d*₆ 5:1): δ = 2.44-2.55 (4H, m), 3.31 (2H, s), 3.43 (2H, s), 3.55 (3H, s), 6.05 (2H, s, br), 6.30 (2H, s, br), 6.36 (1H, s), 6.80 (1H, s), 6.96 (1H, dt, *J* = 7.7, 1.0 Hz), 7.03-7.11 (3H, m). ¹³C NMR (67.5 MHz, CDCl₃/acetone-*d*₆ 5:1): δ = 28.1 (CH₂), 50.4 (CH₂), 55.5 (CH₂), 55.8 (CH₃), 61.7 (CH₂), 110.7 (CH), 120.8 (CH), 122.4 (CH), 123.7 (CH), 126.6 (C_q), 127.0 (CH), 129.3 (CH), 134.0 (C_q), 137.3 (C_q), 140.5 (C_q), 149.7 (C_q), 150.4 (C_q). LC/MS (APCI +): *m/z* 444.32 (M⁺+H).

2-(3-Acetoxy)-7-methoxy-6-sulfamoyloxy-1,2,3,4-tetrahydroiso-quinoline (20k)

—Method as for **20a** using compound **17k** (100 mg, 0.30 mmol) and sulfamoyl chloride (0.6 mmol) in DMA (1.0 mL) at rt for 4 h. Flash column chromatography (hexane/EtOAc 2:1 to 2:3) afforded compound **20k** as a yellow powder (105 mg, 85%), mp 64-65 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.28 (3H, s), 2.70-2.86 (4H, m), 3.55 (2H, s), 3.67 (2H, s), 3.81 (3H, s), 4.98 (2H, s), 6.60 (1H, s), 6.99 (1H, ddd, *J* = 7.9, 2.2, 1.2 Hz), 7.07 (1H, s), 7.12 (1H, dd, *J* = 2.2, 1.2 Hz), 7.20-7.26 (1H, m), 7.34 (1H, t, *J* = 7.9 Hz). ¹³C NMR (67.5 MHz, CDCl₃): δ = 21.3 (CH₃), 28.3 (CH₂), 50.7 (CH₂), 55.7 (CH₂), 56.4 (CH₃), 62.2 (CH₂), 111.1 (CH), 120.5 (CH), 122.0 (CH), 124.2 (CH), 126.4 (CH), 127.7 (C_q), 129.4 (CH), 134.8 (C_q), 137.3 (C_q), 140.2 (C_q), 149.3 (C_q), 150.8 (C_q), 169.8 (C_q). LC/MS (ES–): *m/z* 405.17 (M[–]H).

2-(3-Fluorobenzyl)-7-methoxy-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline

(20l)—Method as for **20a** using compound **17l** (94 mg, 0.33 mmol) and sulfamoyl chloride (0.98 mmol) in DMA (1.0 mL) at rt for 24 h. Flash column chromatography (hexane/EtOAc

gradient) afforded compound **20l** as a yellow powder (103 mg, 78%), mp 120–124 °C. ¹H NMR (270 MHz, DMSO-*d*₆): δ = 2.69 (2H, d, *J* = 5.0 Hz), 2.74 (2H, d, *J* = 4.7 Hz), 3.50 (2H, s), 3.67 (2H, s), 3.71 (3H, s), 6.82 (1H, s), 7.04 (1H, s), 7.04–7.22 (3H, m), 7.35–7.43 (1H, m), 7.85 (2H, s, br). ¹³C NMR (67.5 MHz, DMSO-*d*₆): δ = 27.8 (CH₂), 50.3 (CH₂), 55.0 (CH₂), 55.9 (CH₃), 61.0 (CH₂), 111.2 (CH), 114.0 (d, *J* 20.6 Hz, CH), 115.3 (d, *J* 21.4 Hz, CH), 122.8 (CH), 124.8 (CH), 125.8 (C_q), 130.3 (d, *J* 8.4 Hz, CH), 133.5 (C_q), 137.2 (C_q), 141.4 (d, *J* 6.9 Hz, C_q), 149.7 (C_q), 162.4 (d, *J* 241.6 Hz, CF). LC/MS (APCI+): *m/z* 367.44 (M⁺+H).

2-(3-Chlorobenzyl)-7-methoxy-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (20m)—Method as for **20a** using compound **17m** (153 mg, 0.5 mmol) and sulfamoyl chloride (2.0 mmol) in DMA (1.0 mL) at rt for 24 h. Flash column chromatography (hexane/EtOAc gradient) afforded compound **20m** as a yellow powder (95 mg, 45%), mp 127–129 °C. ¹H NMR (270 MHz, DMSO-*d*₆): δ = 2.69 (2H, d, *J* = 4.6 Hz), 2.74 (2H, d, *J* = 4.6 Hz), 3.49 (2H, s), 3.66 (2H, s), 3.71 (3H, s), 6.82 (1H, s), 7.04 (1H, s), 7.32–7.42 (4H, m), 7.84 (2H, s, br). ¹³C NMR (67.5 MHz, DMSO-*d*₆): δ = 28.4 (CH₂), 50.9 (CH₂), 55.5 (CH₂), 56.4 (CH₃), 61.5 (CH₂), 111.7 (CH), 123.3 (CH), 126.4 (C_q), 127.6 (CH), 127.9 (CH), 128.9 (CH), 130.8 (CH), 133.6 (C_q), 134.1 (C_q), 137.6 (C_q), 141.8 (C_q), 150.2 (C_q). LC/MS (APCI +): *m/z* 382.93 (M⁺+H).

7-Methoxy-2-(3-methylbenzyl)-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (20n)—Method as for **20a** using compound **17n** (70 mg, 0.25 mmol) and sulfamoyl chloride (0.75 mmol) in DMA (1.0 mL) at rt for 24 h. Flash column chromatography (hexane/EtOAc 3:2 to 1:1) gave a solid that was stirred in diethyl ether, filtered and dried to afford compound **20n** as a yellow powder (60 mg, 67%), mp 142–143 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.34 (3H, s), 2.71–2.84 (4H, m), 3.56 (2H, s), 3.64 (2H, s), 3.80 (3H, s), 5.02 (2H, s, br), 6.60 (1H, s), 7.07 (1H, s), 7.10–7.22 (4H, m). ¹³C NMR (67.5 MHz, CDCl₃): δ = 21.5 (CH₃), 28.2 (CH₂), 50.5 (CH₂), 55.7 (CH₂), 56.4 (CH₃), 62.7 (CH₂), 111.2 (CH), 124.2 (CH), 126.3 (CH), 127.6 (C_q), 128.1 (CH), 128.3 (CH), 130.0 (CH), 134.8 (C_q), 137.3 (C_q), 137.8 (C_q), 138.2 (C_q), 149.3 (C_q). LC/MS (APCI–): *m/z* 361.40 (M⁺-H).

2-(3-Ethylbenzyl)-7-methoxy-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (20o)—Method as for **20a** using compound **17o** (149 mg, 0.5 mmol) and sulfamoyl chloride (1.5 mmol) in DMA (3.6 mL) at rt for 4 h. Crystallisation from diethyl ether/DCM (~4:1) afforded compound **20o** as a pale yellow solid (119 mg, 63%). ¹H NMR (270 MHz, CDCl₃): δ = 1.25 (3H, t, *J* = 7.6 Hz), 2.67 (2H, q, *J* = 7.6 Hz), 2.74 (2H, d, *J* = 5.2 Hz), 2.78 (2H, d, *J* = 5.2 Hz), 3.54 (2H, s), 3.64 (2H, s), 3.75 (3H, s), 6.19 (2H, s, br), 6.49 (1H, s), 7.01 (1H, s), 7.11 (1H, d, *J* = 7.2 Hz), 7.15–7.29 (2H, m), 7.22 (1H, t, *J* = 6.1 Hz). LC/MS (ES+): *m/z* 377.3 (M⁺+H). HRMS (ES+): *m/z* found 377.1532; C₁₉H₂₅N₂O₄S⁺ (M⁺+H) requires 377.1530.

2-(3-Cyanobenzyl)-7-methoxy-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (20p)—Method as for **20a** using compound **17p** (127 mg, 0.43 mmol) and sulfamoyl chloride (1.3 mmol) in DMA (1.0 mL) at rt for 22 h. Flash column chromatography (hexane/EtOAc gradient) gave an oil and crystallisation from EtOAc/hexane afforded compound **20p** as a yellow powder (68 mg, 42%), mp 140–141 °C. ¹H NMR (270 MHz, DMSO-*d*₆): δ = 2.69–2.76 (4H, m), 3.50 (2H, s), 3.71 (3H, s), 6.82 (1H, s), 7.04 (1H, s), 7.57 (1H, t, *J* = 7.7 Hz), 7.71–7.84 (5H, m). ¹³C NMR (67.5 MHz, DMSO-*d*₆): δ = 28.4 (CH₂), 50.8 (CH₂), 55.5 (CH₂), 56.3 (CH₃), 61.2 (CH₂), 111.7 (CH), 111.8 (C_q), 119.5 (C_q), 123.3 (CH), 126.3 (C_q), 130.2 (CH), 131.5 (CH), 132.6 (CH), 134.0 (C_q), 134.2 (CH), 137.6 (C_q), 140.9 (C_q), 150.2 (C_q). LC/MS (APCI–): *m/z* 372.54 (M⁺-H).

2-(3-Acetylbenzyl)-7-methoxy-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline

(20q)—Method as for **20a** using compound **17q** (80 mg, 0.26 mmol) and sulfamoyl chloride (0.52 mmol) in DMA (1.0 mL) at rt for 18 h. Flash column chromatography (hexane/EtOAc 2:1 to 1:3) gave a solid that was stirred in diethyl ether, filtered and dried to afford compound **20q** as a yellow powder (65 mg, 65%), mp 144–145 °C. ¹H NMR (270 MHz, CDCl₃/acetone-*d*₆ 4:1): δ = 2.15 (s, 3H), 2.27–2.38 (4H, m), 3.12 (2H, s), 3.29 (2H, s), 3.33 (3H, s), 6.19 (3H, s, br), 6.60 (1H, s), 7.00 (1H, t, *J* = 7.7 Hz), 7.17 (1H, dt, *J* = 7.7, 1.0 Hz), 7.44 (1H, dt, *J* = 7.7, 1.2 Hz), 7.53 (1H, m). ¹³C NMR (67.5 MHz, CDCl₃/acetone-*d*₆ 4:1): δ = 26.1 (CH₃), 27.9 (CH₂), 50.3 (CH₂), 55.3 (CH₂), 55.3 (CH₃), 61.8 (CH₂), 110.4 (CH), 123.5 (CH), 126.1 (C_q), 126.9 (CH), 128.2 (CH), 128.3 (CH), 133.2 (CH), 133.7 (C_q), 136.9 (C_q), 137.1 (C_q), 138.9 (C_q), 149.6 (C_q), 197.3 (C_q). LC/MS (ES[−]): *m/z* 389.56 (M[−]H).

7-Methoxy-2-(3-nitrobenzyl)-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline

(20r)—Method as for **20a** using compound **17r** (131 mg, 0.42 mmol) and sulfamoyl chloride (1.32 mmol) in DMA (1.0 mL) at rt for 24 h. Flash column chromatography (hexane/EtOAc gradient) afforded compound **20r** as a yellow powder (112 mg, 85%), mp 168–170 °C. ¹H NMR (270 MHz, DMSO-*d*₆): δ = 2.72–2.77 (4H, m), 3.54 (2H, s), 3.71 (3H, s), 3.84 (2H, s), 6.81 (1H, s), 7.05 (1H, s), 7.66 (1H, t, *J* = 7.9 Hz), 7.82–7.85 (3H, m), 8.13–8.17 (1H, m), 8.22 (1H, s, br). ¹³C NMR (67.5 MHz, DMSO-*d*₆): δ = 27.8 (CH₂), 50.3 (CH₂), 54.9 (CH₂), 55.8 (CH₃), 60.5 (CH₂), 111.2 (CH), 122.1 (CH), 122.8 (CH), 123.0 (CH), 125.8 (C_q), 129.9 (CH), 133.5 (C_q), 135.4 (CH), 137.1 (C_q), 141.1 (C_q), 147.9 (C_q), 149.7 (C_q). LC/MS (APCI⁺): *m/z* 394.45 (M⁺+H).

2-(3-Acetamidobenzyl)-7-methoxy-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (20s)

—Method as for **20a** using compound **17s** (48 mg, 0.15 mmol) and sulfamoyl chloride (0.6 mmol) in DMA (1.0 mL) at rt for 18 h. The resulting solid was stirred in diethyl ether (5 mL), filtered and dried to afford compound **20s** as a light yellow powder (45 mg, 75%), mp 124–126 °C. ¹H NMR (270 MHz, CDCl₃/acetone-*d*₆ 5:1): δ = 2.06 (3H, s), 2.66–2.77 (4H, m), 3.52 (2H, s), 3.60 (2H, s), 3.73 (3H, s), 5.89 (2H, s, br), 6.53 (1H, s), 6.97 (1H, d, *J* = 7.7 Hz), 7.03 (1H, s), 7.21 (1H, dd, *J* = 8.2, 7.7 Hz), 7.26–7.30 (1H, m), 7.61 (1H, ddd, *J* = 8.2, 2.0, 1.0 Hz). ¹³C NMR (67.5 MHz, CDCl₃/acetone-*d*₆ 5:1): δ = 23.9 (CH₃), 27.3 (CH₂), 50.3 (CH₂), 55.4 (CH₂), 56.1 (CH₃), 62.3 (CH₂), 110.8 (CH), 119.5 (CH), 120.4 (CH), 123.8 (CH), 125.3 (CH), 126.2 (C_q), 129.0 (CH), 133.0 (C_q), 136.9 (C_q), 137.7 (C_q), 138.7 (C_q), 149.8 (C_q), 169.9 (C_q). LC/MS (ES⁺): *m/z* 406.43 (M⁺+H).

7-Methoxy-2-(3-(methylsulfonamido)benzyl)-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (20t)

—Method as for **20a** using compound **17t** (105 mg, 0.29 mmol) and sulfamoyl chloride (0.6 mmol) in DMA (1.0 mL) at rt for 4 h. Flash column chromatography (hexane/EtOAc 1:9) gave a solid that was stirred in diethyl ether, filtered and dried to afford compound **20t** as a light yellow powder (80 mg, 63%), mp 151–152 °C. ¹H NMR (270 MHz, CDCl₃/acetone-*d*₆ 3:1): δ = 2.28–2.39 (4H, m), 2.56 (3H, s), 3.15 (2H, s), 3.26 (2H, s), 3.38 (3H, s), 6.17 (2H, s, br), 6.23 (1H, s), 6.64 (1H, s), 6.74–6.96 (4H, m), 8.00 (1H, s, br). ¹³C NMR (67.5 MHz, CDCl₃/acetone-*d*₆ 3:1): δ = 28.0 (CH₂), 38.5 (CH₃), 50.2 (CH₂), 55.4 (CH₂), 55.4 (CH₃), 61.9 (CH₂), 110.5 (CH), 118.8 (CH), 120.4 (CH), 123.5 (CH), 124.7 (CH), 126.3 (C_q), 129.0 (CH), 133.9 (C_q), 137.1 (C_q), 137.9 (C_q), 139.9 (C_q), 149.6 (C_q). LC/MS (ES[−]): *m/z* 440.43 (M[−]-H).

2-(2,3-Dimethoxybenzyl)-7-methoxy-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (20u)

—Method as for **20a** using compound **17u** (80 mg, 0.24 mmol) and sulfamoyl chloride (0.48 mmol) in DMA (1.0 mL) at rt for 24 h. Flash column chromatography (DCM/EtOAc 1:1 to 1:2) gave a solid that was stirred in diethyl ether, filtered and dried to afford compound **20u** as a yellow powder (65 mg, 66%), mp 145–146

°C. ¹H NMR (270 MHz, CDCl₃): δ = 2.79-2.85 (4H, m), 3.66 (2H, s), 3.79 (2H, s), 3.80 (3H, s), 3.83 (3H, s), 3.87 (3H, s), 4.95 (2H, s, br), 6.61 (1H, s), 6.85-6.89 (1H, m), 7.03-7.07 (3H, m). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.1 (CH₂), 50.4 (CH₂), 55.2 (CH₂), 55.7 (CH₂), 55.8 (CH₃), 56.4 (CH₃), 61.1 (CH₃), 111.1 (CH), 111.6 (CH), 122.8 (CH), 124.1 (CH), 124.1 (CH), 127.4 (C_q), 132.8 (C_q), 137.4 (C_q), 141.3 (C_q), 147.9 (C_q), 149.3 (C_q), 152.8 (C_q). LC/MS (APCI-): *m/z* 407.15 (M⁻-H).

2-(3,4-Dimethoxybenzyl)-7-methoxy-6-sulfamoyloxy-1,2,3,4-

tetrahydroisoquinoline (20v)—Method as for **20a** using compound **17v** (70 mg, 0.21 mmol) and sulfamoyl chloride (0.42 mmol) in DMA (1.0 mL) at rt for 24 h. Flash column chromatography (DCM/EtOAc 1:1 to 1:2) gave a solid that was stirred in diethyl ether, filtered and dried to afford compound **20v** as a yellow powder (60 mg, 70%), mp 155-156 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.65-2.82 (4H, m), 3.52 (2H, s), 3.59 (2H, s), 3.77 (3H, s), 3.78 (3H, s), 3.79 (3H, s), 6.77 (1H, s), 6.89 (2H, s), 6.91-6.93 (2H, m), 7.00 (1H, s), 7.04 (1H, s). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.4 (CH₂), 50.6 (CH₂), 55.2 (CH₃), 55.3 (CH₃), 55.4 (CH₃), 55.6 (CH₂), 62.2 (CH₂), 111.0 (CH), 111.6 (CH), 112.5 (CH), 121.0 (CH), 123.7 (CH), 126.6 (C_q), 131.3 (C_q), 134.5 (C_q), 137.5 (C_q), 148.7 (C_q), 149.5 (C_q), 150.2 (C_q). LC/MS (APCI-): *m/z* 407.21 (M⁻-H).

2-(3,5-Dimethoxybenzyl)-7-methoxy-6-sulfamoyloxy-1,2,3,4-

tetrahydroisoquinoline (20w)—Method as for **20a** using compound **17w** (132 mg, 0.4 mmol) and sulfamoyl chloride (1.2 mmol) in DMA (1.5 mL) at rt for 18 h. Flash column chromatography (hexane/EtOAc 1:1 to 1:3) gave a yellow oil and crystallisation from diethyl ether afforded compound **20w** as a light yellow powder (115 mg, 71%), mp 147-148 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.63-2.77 (4H, m), 3.48 (2H, s), 3.54 (2H, s), 3.61 (2H, s, br), 3.71 (6H, s), 3.72 (3H, s), 6.30 (1H, t, *J* = 2.2 Hz), 6.46 (2H, d, *J* = 2.2 Hz), 6.53 (1H, s), 7.02 (1H, s). ¹³C NMR (67.5 MHz, CDCl₃): δ = 27.7 (CH₂), 50.4 (CH₂), 55.3 (CH₃), 55.6 (CH₂), 56.0 (CH₃), 62.7 (CH₂), 99.3 (CH), 106.1 (2 × CH), 110.8 (CH), 123.6 (CH), 126.6 (C_q), 133.8 (C_q), 137.4 (C_q), 139.6 (C_q), 149.6 (C_q), 160.7 (2 × C_q). LC/MS (APCI+): *m/z* 409.25 (M⁺+H). HRMS (ES+): *m/z* found 409.1428; C₁₉H₂₅N₂O₆S⁺ (M⁺+H) requires 409.1428.

2-(2,5-Dimethoxybenzyl)-7-methoxy-6-sulfamoyloxy-1,2,3,4-

tetrahydroisoquinoline (20x)—Method as for **20a** using compound **17x** (110 mg, 0.33 mmol) and sulfamoyl chloride (0.66 mmol) in DMA (1.0 mL) at rt for 24 h. Flash column chromatography (DCM/EtOAc 1:1 to 2:3) gave a solid that was stirred in diethyl ether, filtered and dried to afford compound **20x** as a yellow powder (100 mg, 74%), mp 138-139 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.73-2.82 (4H, m), 3.63 (2H, s), 3.68 (2H, s), 3.76 (3H, s), 3.79 (3H, s), 3.81 (H, s), 4.90 (2H, s, br), 6.61 (1H, s), 6.76 (1H, dd, *J* = 8.8, 2.9 Hz), 6.82 (1H, d, *J* = 8.8 Hz), 7.02 (1H, d, *J* = 2.9 Hz), 7.06 (1H, s). ¹³C NMR (67.5 MHz, CDCl₃): δ = 28.2 (CH₂), 50.5 (CH₂), 55.7 (CH₂), 55.8 (CH₂), 55.9 (CH₃), 56.3 (CH₃), 56.4 (CH₃), 111.2 (CH), 111.7 (CH), 112.6 (CH), 116.3 (CH), 124.1 (CH), 127.3 (C_q), 127.8 (C_q), 135.1 (C_q), 137.2 (C_q), 149.2 (C_q), 152.1 (C_q), 153.6 (C_q). LC/MS (APCI-): *m/z* 407.02 (M⁻-H).

7-Methoxy-6-sulfamoyloxy-2-(2,3,4-trimethoxybenzyl)-1,2,3,4-

tetrahydroisoquinoline (20y)—Method as for **20a** using compound **17y** (115 mg, 0.32 mmol) and sulfamoyl chloride (0.64 mmol) in DMA (1.0 mL) at rt for 24 h. Flash column chromatography (DCM/EtOAc 1:1 to 2:3) gave a solid that was stirred in diethyl ether, filtered and dried to afford compound **20y** as a yellow powder (110 mg, 79%), mp 79-80 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.71-2.82 (4H, m), 3.61 (2H, s), 3.65 (2H, s), 3.80 (3H, s), 3.85 (3H, s), 3.88 (6H, s), 6.61 (1H, s), 6.65 (1H, d, *J* = 8.6 Hz), 7.05 (1H, s), 7.06

(1H, d, $J = 8.6$ Hz). ^{13}C NMR (67.5 MHz, CDCl_3): $\delta = 28.3$ (CH_2), 50.3 (CH_2), 55.6 (CH_2), 56.0 (CH_3), 56.1 (CH_2), 56.4 (CH_3), 60.9 (CH_3), 61.4 (CH_3), 107.2 (CH), 111.2 (CH), 123.5 (C_q), 124.1 (CH), 125.2 (CH), 127.7 (C_q), 134.8 (C_q), 137.3 (C_q), 142.3 (C_q), 149.3 (C_q), 152.7 (C_q), 153.1 (C_q). LC/MS (APCI-): m/z 437.07 (M^- -H).

7-Methoxy-6-sulfamoyloxy-2-(3,4,5-trimethoxybenzyl)-1,2,3,4-

tetrahydroisoquinoline (20z)—Method as for **20a** using compound **17z** (95 mg, 0.26 mmol) and sulfamoyl chloride (0.52 mmol) in DMA (1.0 mL) at rt for 24 h. Flash column chromatography (DCM/EtOAc 4:1 to 1:2) gave a solid that was stirred in diethyl ether, filtered and dried to afford compound **20z** as a yellow powder (65 mg, 57%), mp 143–144 °C. ^1H NMR (270 MHz, CDCl_3): $\delta = 2.70$ – 2.84 (4H, m), 3.58 (2H, s), 3.61 (2H, s), 3.81 (3H, s), 3.83 (3H, s), 3.84 (6H, s), 5.10 (2H, s, br), 6.61 (3H, s), 7.07 (1H, s). ^{13}C NMR (67.5 MHz, CDCl_3): $\delta = 28.1$ (CH_2), 50.4 (CH_2), 55.7 (CH_2), 56.2 ($2 \times \text{CH}_3$), 56.4 (CH_3), 61.0 (CH_3), 62.8 (CH_2), 105.7 ($2 \times \text{CH}$), 111.2 (CH), 124.2 (CH), 127.6 (C_q), 133.7 (C_q), 134.6 (C_q), 137.0 (C_q), 137.4 (C_q), 149.4 (C_q), 153.3 ($2 \times \text{C}_q$). LC/MS (APCI-): m/z 437.19 (M^- -H).

7-Methoxy-6-sulfamoyloxy-2-(2,4,5-trimethoxybenzyl)-1,2,3,4-

tetrahydroisoquinoline (20aa)—Method as for **20a** using compound **17aa** (45 mg, 0.13 mmol) and sulfamoyl chloride (0.3 mmol) in DMA (0.5 mL) at rt for 24 h. Flash column chromatography (DCM/EtOAc 3:1 to EtOAc) gave a solid that was stirred in diethyl ether, filtered and dried to afford compound **20aa** as a yellow powder (35 mg, 64%), mp 166–167 °C. ^1H NMR (270 MHz, $\text{CDCl}_3/\text{acetone}-d_6$ 5:1): $\delta = 2.63$ – 2.74 (4H, m), 3.54 (2H, s), 3.58 (2H, s), 3.74 (6H, s), 3.75 (3H, s), 3.82 (3H, s), 5.60 (2H, s, br), 6.47 (1H, s), 6.54 (1H, s), 6.91 (1H, s), 6.99 (1H, s). ^{13}C NMR (67.5 MHz, $\text{CDCl}_3/\text{acetone}-d_6$ 5:1): $\delta = 29.8$ (CH_2), 49.7 (CH_2), 55.3 (CH_2), 55.8 (CH_2), 56.0 (CH_3), 56.1 (CH_3), 56.5 (CH_3), 56.6 (CH_3), 97.1 (CH), 110.0 (CH), 110.9 (CH), 114.2 (C_q), 123.8 (CH), 126.4 (C_q), 127.1 (C_q), 143.0 (C_q), 145.4 (C_q), 148.6 (C_q), 149.8 (C_q), 152.2 (C_q). LC/MS (APCI-): m/z 437.20 (M^- -H).

7-Methoxy-6-sulfamoyloxy-2-(2,4,6-trimethoxybenzyl)-1,2,3,4-

tetrahydroisoquinoline (20ab)—Method as for **20a** using compound **17ab** (120 mg, 0.33 mmol) and sulfamoyl chloride (1.7 mmol) in DMA (1.5 mL) at rt for 24 h. Flash column chromatography (hexane/EtOAc 10:1 to EtOAc to EtOAc/methanol 20:1) afforded compound **20ab** as a yellow powder (110 mg, 76%), mp 151–153 °C. ^1H NMR (270 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$ 10:1): $\delta = 2.72$ – 2.76 (4H, m), 3.24 (2H, s, br), 3.58 (2H, s, br), 3.72 (2H, s), 3.75 (9H, s), 3.76 (3H, s), 6.09 (2H, s), 6.53 (1H, s), 7.00 (1H, s). ^{13}C NMR (67.5 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$ 10:1): $\delta = 27.3$ (CH_2), 48.4 (CH_2), 49.7 (CH_2), 54.6 (CH_2), 55.2 (CH_3), 55.5 ($2 \times \text{CH}_3$), 56.0 (CH_3), 90.2 ($2 \times \text{CH}$), 110.8 (CH), 123.4 (CH), 126.5 (C_q), 133.8 (C_q), 137.3 (C_q), 149.4 (C_q), 160.0 ($2 \times \text{C}_q$), 160.9 (C_q). LC/MS (ES+): m/z 439.3 (M^+ +H). HRMS (ES+): m/z found 439.1521; $\text{C}_{20}\text{H}_{27}\text{N}_2\text{O}_7\text{S}^+$ (M^+ +H) requires 439.1533. Anal. calcd for $\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_7\text{S}$: C 54.78, H 5.98, N 6.39, found: C 54.6, H 6.11, N 6.08.

7-Methoxy-2-(2-methoxybenzoyl)-6-sulfamoyloxy-1,2,3,4-

tetrahydroisoquinoline (21a)—Method as for **20a** using compound **18a** (100 mg, 0.32 mmol) and sulfamoyl chloride (0.64 mmol) in DMA (1.0 mL) at rt for 18 h. The resulting solid was stirred in EtOAc/hexane (1:1, 8 mL), filtered and dried to afford compound **21a** as a white solid (90 mg, 72%). ^1H NMR (270 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$ 5:1) $\delta = 2.61$ – 2.73 and 2.80 – 2.87 (2H, 2m), 3.36– 3.45 and 3.99 – 4.09 (2H, 2m), 3.68, 3.71, 3.76 and 3.82 (6H, 4s), 4.27, 4.38, 4.77 and 4.83 (2H, 4d, $J = 16.1$, 16.2, 16.1 and 16.1 Hz), 6.45 and 6.78 (1H, 2s), 6.87– 7.00 (2H, m), 7.06 and 7.11 (1H, 2s), 7.18 (1H, dt, $J = 7.4$, 1.5 Hz), 7.30– 7.39 (1H, m). LC/MS (APCI-): m/z 391.49 (M^- -H). Anal. calcd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_6\text{S}$: C 55.09, H 5.14, N 7.14, found: C 54.7, H 5.15, N 7.05.

7-Methoxy-2-(3-methoxybenzoyl)-6-sulfamoyloxy-1,2,3,4-

tetrahydroisoquinoline (21b)—Method as for **20a** using compound **18b** (115 mg, 0.37 mmol) and sulfamoyl chloride (0.74 mmol) in DMA (1.0 mL) at rt for 18 h. The resulting solid which was stirred in EtOAc, filtered and dried to afford compound **21b** as a white solid (95 mg, 66%), mp 164-166 °C. ¹H NMR (270 MHz, CDCl₃/CD₃OD 5:1): δ = 2.77 and 2.87 (2H, 2s, br), 3.60 and 3.76 (2H, 2s, br), 3.80 and 3.86 (6H, 2s), 4.53 and 4.81 (2H, 2s, br), 6.52 and 6.80 (1H, 2s, br), 6.91-6.99 (3H, m), 7.12 (1H, s, br), 7.32 (1H, t, *J* = 8.2 Hz). LC/MS (APCI−): *m/z* 391.49 (M[−]-H). Anal. calcd for C₁₈H₂₀N₂O₆S: C 55.09, H 5.14, N 7.14, found: C 55.0, H 5.22, N 7.03.

7-Methoxy-2-(4-methoxybenzoyl)-6-sulfamoyloxy-1,2,3,4-

tetrahydroisoquinoline (21c)—Method as for **20a** using compound **18c** (75 mg, 0.24 mmol) and sulfamoyl chloride (0.48 mmol) in DMA (1.0 mL) at rt for 24 h. The residue was stirred in diethyl ether, filtered and dried to afford compound **21c** as a white powder (80 mg, 85%), mp 171-172 °C. ¹H NMR (270 MHz, CDCl₃/CD₃OD 5:1): δ = 2.70 (2H, 2s, br), 3.54 and 3.70 (2H, 2s, br), 3.96 (6H, s), 4.50 and 4.64 (2H, 2s, br), 6.41 and 6.69 (1H, 2s, br), 6.81 (2H, dt, *J* = 8.6, 2.3 Hz), 7.01 (1H, s), 7.27 (2H, dt, *J* = 8.6, 2.3 Hz). LC/MS (APCI+): *m/z* 393.38 (M⁺+H). HRMS (ES+): *m/z* found 393.1112; C₁₈H₂₁N₂O₆S⁺ (M⁺+H) requires 393.1115. Anal. calcd for C₁₈H₂₀N₂O₆S: C 55.09, H 5.14, N 7.14, found: C 54.9, H 5.15, N 6.94.

7-Methoxy-6-sulfamoyloxy-2-(3,4,5-trimethoxybenzoyl)-1,2,3,4-

tetrahydroisoquinoline (21d)—Method as for **20a** using compound **18d** (100 mg, 0.27 mmol) and sulfamoyl chloride (0.6 mmol) in DMA (1.0 mL) at rt for 24 h. The residue was stirred in diethyl ether, filtered and dried to afford compound **21d** as a white solid (90 mg, 74%), mp 174-175 °C. ¹H NMR (270 MHz, CDCl₃/acetone-*d*₆ 1:1) δ = 2.55 (2H, s, br), 3.41 (2H, s, br), 3.54 (6H, s), 3.57 (6H, s), 4.50 (2H, s, br), 6.16 (2H, s, br), 6.40 (2H, s), 6.53 (1H, s, br), 6.84 (1H, s). LC/MS (ES−): *m/z* 451.05 (M[−]-H). HRMS (ES+): *m/z* found 453.1305; C₂₀H₂₄N₂O₈S⁺ (M⁺+H) requires 453.1326. Anal. calcd for C₂₀H₂₄N₂O₈S: C 53.09, H 5.35, N 6.19, found: C 53.0, H 5.39, N 6.03.

7-Methoxy-2-(2-methoxyphenylsulfonyl)-6-sulfamoyloxy-1,2,3,4-

tetrahydroisoquinoline (22a)—Method as for **20a** using compound **19a** (87 mg, 0.25 mmol) and sulfamoyl chloride (0.75 mmol) in DMA (1.0 mL) at rt for 18 h. Flash column chromatography (hexane/EtOAc gradient) gave an oil and crystallisation from diethyl ether/hexane afforded compound **22a** as a colourless powder (74 mg, 69%), mp 160-163 °C. ¹H NMR (270 MHz, DMSO-*d*₆): δ = 2.62 (2H, t, *J* = 5.9 Hz), 3.47 (2H, t, *J* = 5.9 Hz), 3.72 (3H, s), 3.74 (3H, s), 4.37 (2H, s), 7.00 (1H, s), 7.04 (1H, s), 7.11 (1H, dt, *J* = 7.7, 1.0 Hz), 7.18 (1H, d, *J* = 7.9 Hz), 7.59-7.66 (1H, m), 7.82 (1H, dd, *J* = 7.9, 1.7 Hz), 7.85 (2H, s, br). ¹³C NMR (67.5 MHz, DMSO-*d*₆): δ = 27.2 (CH₂), 43.0 (CH₂), 46.6 (CH₂), 55.8 (CH₃), 55.9 (CH₃), 109.0 (CH), 112.9 (CH), 120.2 (CH), 123.0 (CH), 125.3 (C_q), 126.4 (C_q), 130.7 (CH), 131.5 (C_q), 135.0 (CH), 137.3 (C_q), 150.0 (C_q), 156.6 (C_q). LC/MS (ES+): *m/z* 451.38 (M⁺+Na). Anal. calcd for C₁₇H₂₀N₂O₇S₂: C 47.65, H 4.70, N 6.54, found: C 47.7, H 4.73, N 6.54.

7-Methoxy-2-(3-methoxyphenylsulfonyl)-6-sulfamoyloxy-1,2,3,4-

tetrahydroisoquinoline (22b)—Method as for **20a** using compound **19b** (168 mg, 0.48 mmol) and sulfamoyl chloride (0.96 mmol) in DMA (1.0 mL) at rt for 22 h. Flash column chromatography (hexane/EtOAc gradient) afforded compound **22b** as a colourless solid (174 mg, 84%), mp 153-156 °C. ¹H NMR (270 MHz, DMSO-*d*₆): δ = 2.77 (2H, t, *J* = 5.5 Hz), 3.29 (2H, t, *J* = 5.5 Hz), 3.74 (3H, s), 3.83 (3H, s), 4.19 (2H, s), 7.00 (1H, s), 7.05 (1H, s), 7.26-7.30 (2H, m), 7.39 (1H, d, *J* = 7.7 Hz), 7.57 (1H, t, *J* = 7.7 Hz), 7.89 (2H, s). ¹³C NMR

(67.5 MHz, DMSO-*d*₆): δ = 27.8 (CH₂), 44.1 (CH₂), 47.7 (CH₂), 56.2 (CH₃), 56.4 (CH₃), 111.7 (CH), 112.8 (CH), 119.7 (CH), 120.0 (CH), 123.4 (C_q), 123.4 (CH), 131.0 (C_q), 131.3 (CH), 137.6 (C_q), 138.0 (C_q), 150.5 (C_q), 160.1 (C_q). LC/MS (APCI+): *m/z* 429.52 (M⁺+H). Anal. calcd for C₁₇H₂₀N₂O₇S₂: C 47.65, H 4.70, N 6.54, found: C 47.0, H 4.65, N 6.48.

7-Methoxy-2-(4-methoxyphenylsulfonyl)-6-sulfamoyloxy-1,2,3,4-

tetrahydroisoquinoline (22c)—Method as for **20a** using compound **19c** (167 mg, 0.48 mmol) and sulfamoyl chloride (0.96 mmol) in DMA (1.0 mL) at rt for 23 h. Flash column chromatography (hexane/EtOAc gradient) afforded compound **22c** as a colourless solid (147 mg, 72%), mp 83-86 °C. ¹H NMR (270 MHz, DMSO-*d*₆): δ = 2.78 (2H, t, *J* = 5.8 Hz), 3.23 (2H, t, *J* = 5.8 Hz), 3.74 (3H, s), 3.84 (3H, s), 4.12 (2H, s), 6.98 (1H, s), 7.05 (1H, s), 7.13-7.18 (2H, m), 7.72-7.77 (2H, m), 7.88 (2H, s, br). ¹³C NMR (67.5 MHz, DMSO-*d*₆): δ = 28.9 (CH₂), 44.0 (CH₂), 47.7 (CH₂), 56.3 (CH₃), 56.4 (CH₃), 111.7 (CH), 115.2 (2 × CH), 123.4 (CH), 125.4 (C_q), 127.7 (C_q), 130.3 (2 × CH), 131.0 (C_q), 138.0 (C_q), 150.6 (C_q), 163.4 (C_q). LC/MS (ES+): *m/z* 451.38 (M⁺+Na). Anal. calcd for C₁₇H₂₀N₂O₇S₂: C 47.65, H 4.70, N 6.54, found: C 47.7, H 4.78, N 6.31.

6-Hydroxy-1,2,3,4-tetrahydroisoquinoline hydrobromide (24)—Compound **23**^[21] (15.97 g, 80.0 mmol) was treated with HBr (48%, 182 mL, 1.6 mol) at 120 °C for 48 h. The mixture was cooled and concentrated in vacuo. The residue was co-evaporated with ethanol (2 × 30 mL) and toluene (2 × 30 mL) and crystallisation from EtOAc afforded compound **24** as a light beige solid (17.89 g, 97%). ¹H NMR (270 MHz, DMSO-*d*₆): δ = 2.91 (2H, t, *J* = 6.3 Hz), 3.33 (2H, t, *J* = 6.3 Hz), 4.14 (2H, s), 6.60 (1H, d, *J* = 2.5 Hz), 6.69 (1H, dd, *J* = 8.3, 2.5 Hz), 7.01 (1H, d, *J* = 8.3 Hz), 8.97 (2H, s, br), 9.47 (1H, s, br).

6-Hydroxy-2-(3-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (25)—Compound **24**^[22] (345 mg, 1.5 mmol) was treated with 3-methoxybenzyl bromide (332 mg, 1.65 mmol) and DIPEA (1.165 g, 9.0 mmol) in DMF (4.5 mL) at 80 °C for 18 h. After cooling to rt the reaction mixture was concentrated in vacuo, water (100 mL) and ammonium chloride (saturated, 10 mL) were added and extracted with EtOAc (2 × 100 mL). The combined organics were dried (NaCl), filtered and concentrated in vacuo. Flash column chromatography (hexane/EtOAc 3:2) afforded compound **25** as a white powder (328 mg, 81%), mp 223-224 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.67-2.78 (4H, m), 3.55 (2H, s), 3.65 (2H, s), 3.76 (3H, s), 6.40 (1H, d, *J* = 2.5 Hz), 6.51 (1H, dd, *J* = 8.4, 2.5 Hz), 6.79 (1H, d, *J* = 8.4 Hz), 6.81 (1H, dd, *J* = 8.4, 2.0 Hz), 6.93-6.97 (2H, m), 7.22 (1H, t, *J* = 8.4 Hz). ¹³C NMR (67.5 MHz, CDCl₃): δ = 29.0 (CH₂), 50.6 (CH₂), 55.3 (CH₃), 55.6 (CH₂), 62.8 (CH₂), 113.1 (CH), 113.4 (CH), 114.6 (CH), 115.1 (CH), 121.8 (CH), 126.6 (C_q), 127.8 (CH), 129.3 (CH), 135.6 (C_q), 139.5 (C_q), 154.2 (C_q), 159.7 (C_q). LC/MS (APCI+): *m/z* 270.46 (M⁺+H).

2-(3-Methoxybenzyl)-6-sulfamoyloxy-1,2,3,4-tetrahydroisoquinoline (26)—

Method as for **20a** using compound **25** (90 mg, 0.33 mmol) and sulfamoyl chloride (0.67 mmol) in DMA (1.0 mL) at rt for 18 h. Flash column chromatography (hexane/EtOAc 2:1 to 1:1) afforded compound **26** as a white solid (80 mg, 69%), mp 139-140 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.72 (2H, t, *J* = 5.4 Hz), 2.88 (2H, t, *J* = 5.4 Hz), 3.59 (2H, s), 3.65 (2H, s), 3.79 (3H, s), 4.30 (2H, s, br), 6.82 (1H, ddd, *J* = 8.2, 2.5, 1.0 Hz), 6.92-6.96 (2H, m), 6.99-7.03 (3H, m), 7.23 (1H, t, *J* = 8.2 Hz). ¹³C NMR (67.5 MHz, CDCl₃): δ = 29.1 (CH₂), 50.1 (CH₂), 55.3 (CH₃), 55.5 (CH₂), 62.6 (CH₂), 112.9 (CH), 114.7 (CH), 119.4 (CH), 121.6 (CH), 122.0 (CH), 128.1 (CH), 129.4 (CH), 134.1 (C_q), 136.5 (C_q), 139.5 (C_q), 148.3 (C_q), 159.8 (C_q). LC/MS (APCI+): *m/z* 349.56 (M⁺+H).

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Figure 1.
Design of steroidomimetic **2** and chimeric tetrahydroisoquinoline **4** based microtubule disruptors.

Figure 2. Activities of control compounds lacking one or more elements of the target pharmacophore against the proliferation of DU-145 cells *in vitro*.

Figure 3.

a) The activity of **20z** (40 mg/kg, 28d, p.o. in 2% aqueous citric acid) against the growth of RPMI-8226 (multiple myeloma) xenografts in athymic nude mice was assessed alongside the benchmark steroid derivative, 2-MeOE2bisMATE **1a** (20 mg/kg, 28d, p.o.). After 28 day dosing significant inhibition of tumor growth is observed for both cohorts of treated animals.

b) No significant weight loss is observed in either cohort indicating that **20z** is well tolerated.

Scheme 1.

Pictet-Spengler and Pomeranz-Fritsch based approaches to functionalized 1,2,3,4-tetrahydroisoquinolines. *Reagents and conditions:* a) MeNO_2 , NH_4OAc , HOAc , $140\text{ }^\circ\text{C}$; b) NaBH_4 , dioxane/DMF, $0\text{ }^\circ\text{C}$; c) Ra-Ni , hydrazine hydrate, MeOH , $40\text{ }^\circ\text{C}$; d) Ac_2O , TEA, DCM, 0 to $25\text{ }^\circ\text{C}$; e) $(\text{CH}_2\text{O})_n$, $p\text{-TsOH}$, toluene, $120\text{ }^\circ\text{C}$; f) NaOH , EtOH/water , $120\text{ }^\circ\text{C}$; g) Pd/C (10%), full hydrogen, H-cube, MeOH , $25\text{ }^\circ\text{C}$; h) TIPSCl , imidazole, DCM, $25\text{ }^\circ\text{C}$; i) $\text{H}_2\text{NCH}_2\text{CH}(\text{OEt})_2$, $60\text{ }^\circ\text{C}$ then NaBH_4 , EtOH , $120\text{ }^\circ\text{C}$; j) 6M HCl , dioxane, $45\text{ }^\circ\text{C}$; k) NaBH_4 , TFA, DCM, 0 to $25\text{ }^\circ\text{C}$.

Scheme 2.

Synthesis of *N*-2 substituted tetrahydroisoquinoline derivatives. *Reagents and conditions:* a) for $\times = \text{CH}_2$, ArCH_2Cl or ArCH_2Br , EtOH, TEA, MW 130 °C or b) ArCO_2H , EDCI, THF, 25 °C then c) LiAlH_4 , THF, 25 °C; for $\times = \text{CO}$, ArCOCl , CHCl_3 , rt; for $\times = \text{SO}_2$, ArSO_2Cl , DCM, 25 °C; d) for $\text{P} = \text{Bn}$, H_2 , Pd/C, 25 °C, 1 atm; for $\text{P} = \text{TIPS}$, TBAF, THF, 25 °C; e) $\text{H}_2\text{NSO}_2\text{Cl}$, DMA, 25 °C or $\text{H}_2\text{NSO}_2\text{Cl}$, 2,6-di-*t*-butyl-4-methyl pyridine, DCM, 25 °C.

Scheme 3.

Synthesis of control compounds. *Reagents and conditions:* a) HBr (48%), 120 °C; b) ArCH₂Br, DIPEA, DMF, 80 °C; c) H₂NSO₂Cl, DMA, 25 °C.

Table 1

Anti-proliferative activity of mono-methoxy substituted *N*-benzyl, *N*-benzoyl and *N*- benzenesulfonyl THIQs against DU-145 prostate cancer cells *in vitro*.^[a]

Cpd	R ¹	X	R ²	R ³	R ⁴	DU-145
17a	H	CH ₂	H	H	H	>100
17b	H	CH ₂	OMe	H	H	>100
17c	H	CH ₂	H	OMe	H	>100
17d	H	CH ₂	H	H	OMe	>100
18a	H	CO	OMe	H	H	60.2
18b	H	CO	H	OMe	H	31.3
18c	H	CO	H	H	OMe	>100
19a	H	SO ₂	OMe	H	H	>100
19b	H	SO ₂	H	OMe	H	>100
19c	H	SO ₂	H	H	OMe	>100
20a	SO ₂ NH ₂	CH ₂	H	H	H	80.5
20b	SO ₂ NH ₂	CH ₂	OMe	H	H	7.8
20c	SO ₂ NH ₂	CH ₂	H	OMe	H	2.1
20d	SO ₂ NH ₂	CH ₂	H	H	OMe	57.2
21a	SO ₂ NH ₂	CO	OMe	H	H	45.2
21b	SO ₂ NH ₂	CO	H	OMe	H	4.4
22a	SO ₂ NH ₂	SO ₂	OMe	H	H	>100
22b	SO ₂ NH ₂	SO ₂	H	OMe	H	56.7
22c	SO ₂ NH ₂	SO ₂	H	H	OMe	>100

Table 2

Anti-proliferative activity of 3'-hydroxy, 3'-ether and 3'-ester substituted *N*-Benzyl THIQs against DU-145 human prostate cancer cells and MDA MB-231 human breast cancer cells *in vitro*.^[a]

Cpd	R ¹	R ³	DU-145	MDA MB-231
17e	H	OH	>100	>100
17c	H	OMe	>100	ND
17f	H	OCF ₃	55	>100
17g	H	OEt	>100	>100
17h	H	O-iPr	>100	86
17i	H	OPh	37.6	ND
20e	SO ₂ NH ₂	OH	95.8	41
20c	SO ₂ NH ₂	OMe	2.1	ND
20f	SO ₂ NH ₂	OCF ₃	2.39	2.29
20g	SO ₂ NH ₂	OEt	1.15	0.65
20h	SO ₂ NH ₂	O-iPr	6.7	4.65
20i	SO ₂ NH ₂	OPh	35.7	ND
20j	SO ₂ NH ₂	OSO ₂ NH ₂	18.5	34.9
20k	SO ₂ NH ₂	OAc	78.9	37

Table 3

Anti-proliferative activities of 3'-substituted *N*-benzyl THIQs against DU-145 human prostate cancer cells and MDA MB-231 human breast cancer cells *in vitro*.^[a]

Cpd	R ¹	R ³	DU-145	MDA MB-231
17l	H	F	>100	ND
17m	H	Cl	84	ND
17n	H	Me	>100	ND
17o	H	Et	>100	>100
17p	H	CN	>100	ND
17r	H	NO ₂	>100	>100
17s	H	NHAc	>100	>100
17t	H	NHSO ₂ Me	>100	>100
20l	SO ₂ NH ₂	F	51.8	ND
20m	SO ₂ NH ₂	Cl	6.2	ND
20n	SO ₂ NH ₂	Me	41.7	ND
20o	SO ₂ NH ₂	Et	35	8
20p	SO ₂ NH ₂	CN	8.1	4.7
20q	SO ₂ NH ₂	Ac	1.85	0.983
20r	SO ₂ NH ₂	NO ₂	3.03	1.91
20s	SO ₂ NH ₂	NHAc	>100	>100
20t	SO ₂ NH ₂	NHSO ₂ Me	>100	>100

Table 4

Anti-proliferative activity of polymethoxylated THIQs against DU-145 human prostate cancer cells and MDA MB-231 human breast cancer cells *in vitro*.^[a]

Cpd	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	DU-145	MDA MB-231
20b	SO ₂ NH ₂	H	OMe	H	H	H	2.1	ND
17u	H	OMe	OMe	H	H	H	>100	>100
20u	SO ₂ NH ₂	OMe	OMe	H	H	H	1.2	0.888
17v	H	H	OMe	OMe	H	H	>100	ND
20v	SO ₂ NH ₂	H	OMe	OMe	H	H	8.54	3.15
17w	H	H	OMe	H	OMe	H	52.7	ND
20w	SO ₂ NH ₂	H	OMe	H	OMe	H	2.5	ND
17x	H	H	OMe	H	H	OMe	95	37
20x	SO ₂ NH ₂	H	OMe	H	H	OMe	2.61	1.85
17y	H	OMe	OMe	OMe	H	H	>100	>100
20y	SO ₂ NH ₂	OMe	OMe	OMe	H	H	17	11.9
17z	H	H	OMe	OMe	OMe	H	0.65	0.62
20z	SO ₂ NH ₂	H	OMe	OMe	OMe	H	0.297	0.329
17aa	H	OMe	H	OMe	OMe	H	7.8	4.1
20aa	SO ₂ NH ₂	OMe	H	OMe	OMe	H	0.66	0.491
17ab	H	OMe	H	OMe	H	OMe	>100	>100
20ab	SO ₂ NH ₂	OMe	H	OMe	H	OMe	>100	>100

Table 5

Anti-proliferative activity of polymethoxylated THIQs against DU-145 human prostate cancer cells and MDA MB-231 human breast cancer cells *in vitro*.^[a]

Cpd	R ¹	X	Y	DU-145	MDA MB-231
17ac ^[b]	H	CH ₂	CH ₂	3.85	5.41
20ac ^[b]	SO ₂ NH ₂	CH ₂	CH ₂	0.041	0.052
18d	H	O	CO	0.921	0.733
21d	SO ₂ NH ₂	O	CO	1.81	1.72

Table 6

Activities of selected chimeras as inhibitors of tubulin assembly and [³H]colchicine binding to tubulin.

Cpd	Inhibition of tubulin assembly IC ₅₀ (μM) ± SD	Inhibition of colchicine binding (%) 5 μM inhibitor ± SD
CA-4	1.2 ± 0.1	98 ± 0.7
17z	>20 (no activity) ^[a]	4.1 ± 2
20z	>20 (partial activity) ^[a]	10 ± 0.9
20ac	2.5 ± 0.03	49 ± 0.5
	2.5 ± 0.03	