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Synthesis of C4-substituted 1,2,3,4-tetrahydroisoquinolin-6-ols as potential estrogen receptor modulators

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Dedicated to the accomplishments of Professors Charles Rees and Alan Katritzky, and to the memory of PhD candidate, Chan Vinh Lam[†]

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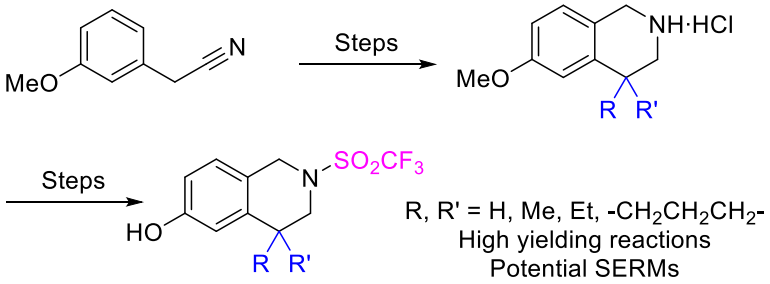
Abstract

Substituted tetrahydroisoquinolines (THIQs) have recently served as scaffolds for therapeutics with function as selective estrogen receptor modulators (SERMs) or downregulators/degraders (SERDs). A small library of 4,4-disubstituted 6-hydroxy-tetrahydroisoquinolines was synthesized by the following step-wise procedure: bis-alkylation of 2-(3-methoxyphenyl)acetonitrile, followed by reduction of the nitrile group and application of a Pictet-Spengler cyclization. Acid-mediated hydrolysis of the aminals provided the tetrahydroammonium chlorides which were converted into their trifluoromethylsulfonamido derivatives. Final conversion of the 6-aryl methyl ethers into their respective phenols provided the desired series of 4,4-bisalkylated 2-[(trifluoromethyl)sulfonyl]-1,2,3,4-tetrahydroisoquinolin-6-ols. These compounds were evaluated in a SUMO-tagged ERα cofactor recruitment assay, but unfortunately were found to be devoid of activity.



Keywords: Tetrahydroisoquinolines, 6-hydroxytetrahydroisoquinolines, selective estrogen receptor modulators, α-nitrile alkylations

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Introduction

The basic 1,2,3,4-tetrahydroisoquinoline (THIQ) motif has in the past played a central role in the synthesis of small molecule libraries possessing bioactivities.[1,2] One of our research interests involves the important mammalian estrogen receptor (ER).[3-5] It has long been known that nuclear receptors are involved in estrogen response and that these occur in two isoforms, namely *alpha* and *beta* (ERα and ERβ), and that the most important endogenous small molecule associated with these receptors is estradiol **1** (Figure 1). ERα is mainly expressed in the uterus and mammary glands, while ERβ is distributed in tissue throughout the body.[6] The complex nature of the relationship between hormonal steroids like estradiol, their receptors and their resultant physiological effects in healthy and diseased states, has resulted in considerable scientific research and debate.[7-9] In terms of medicinal chemistry efforts, intensive research has resulted in the development of important pharmaceutical classes which include the selective estrogen receptor modulators (SERMs)[10,11] and downregulators/degraders (SERDs),[8,12-14] of which Lasofoxifene **3** (Figure 1) is a well-known SERM example in clinical use.[15]

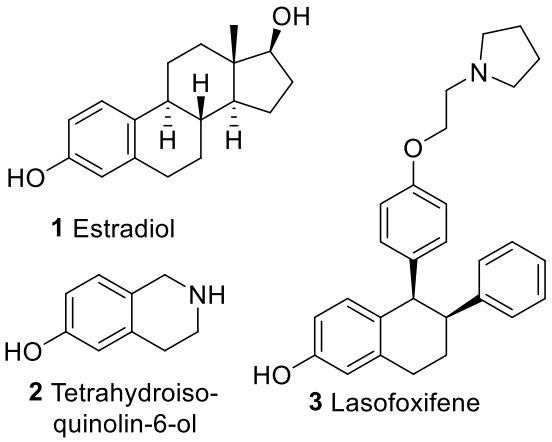


Figure 1. Structures of estradiol **1**, THIQ-6-ol **2** and Lasofoxifene **3.**

An important theme described in this manuscript is based on the fact that the 6-hydroxy-tetrahydroisoquinoline (THIQ) motif **2** (Figure 1) has been extensively utilized by academia and the pharmaceutical industry as a basic scaffold for compounds to interact with the ER system. It was therefore envisioned that this scaffold holds good potential for further investigation. As prior examples, Novartis[16,17] and Pfizer[18] developed compounds that possess good SERM characteristics (**4** and **5**, Figure 2a) and the quest for orally-bioavailable SERDs (to supplement the well-known intramuscularly injected Fulvestrant) has resulted in THIQ-based compounds **6-8** from AstraZeneca[19-25] and Novartis,[26] as shown in Figure 2b.

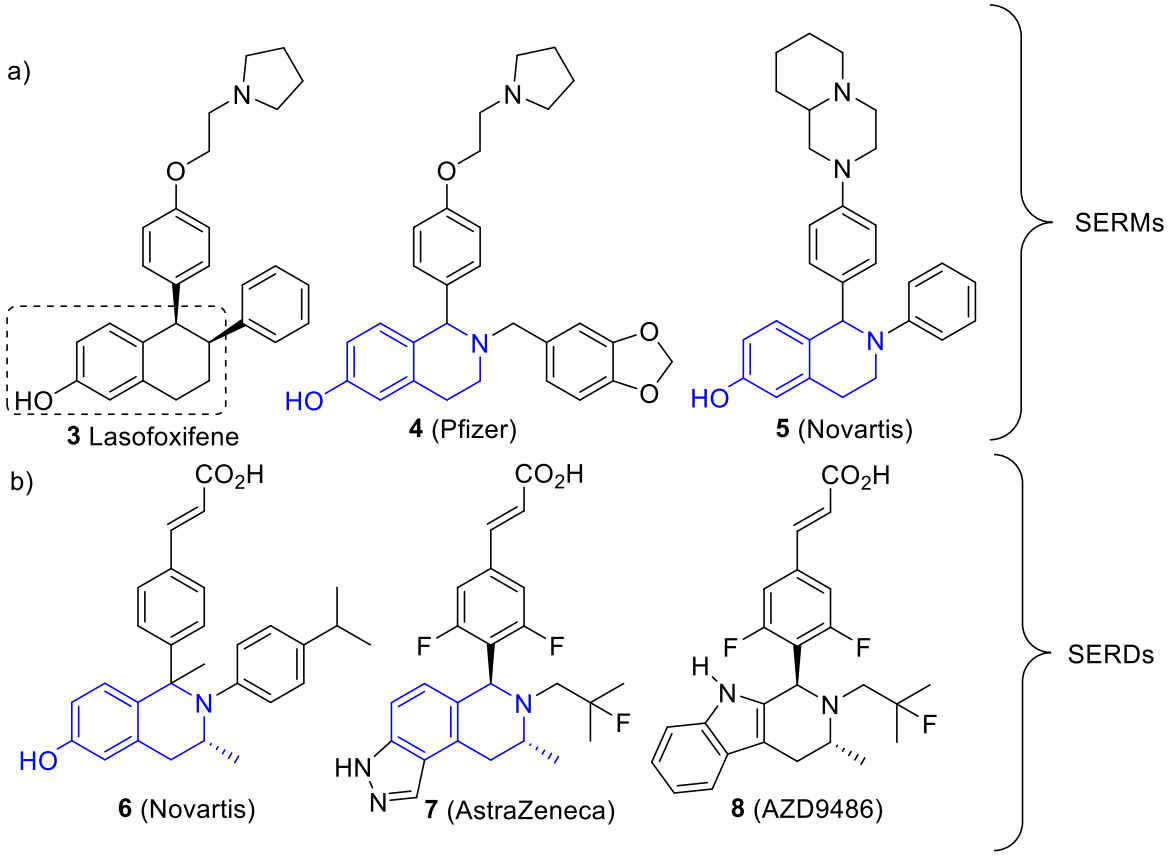


Figure 2. a) Examples of THIQ-based SERMs (core of Lasofoxifene highlighted); b) Examples of THIQ-based and -inspired SERDs.

In 2009 and 2011, work by Brunsveld and collaborators, highlighted the notion that the THIQ skeleton was indeed a privileged scaffold for ER modulation,[5] and secondly, based on a small set of nitrogen-substituted compounds, established that the trifluoromethylsulfonamide analogue **9a**, displayed an impressive ER-binding capability for a fragment of such small size [EC_{50} (μM) 3.0 ± 0.3 for ERα and 0.6 ± 0.3 for ERβ], while also demonstrating about *ca.* 4-5 fold selectivity for ERβ over ERα.[4] Further evaluation of the crystal structure of **9a** (PDB code: 3OMQ) prompted the idea that by adding steric bulk at position C-4 of the THIQ skeleton, this would deliver THIQ analogues **9b-e**, potentially with an even higher selectivity for ERβ. It was reasoned that differences in amino acid residues within the binding sites for the two ER proteins – Leu384 & Met421 (ERα) *versus* Met335 & Ile373 (ERβ) could allow for steric factors to play an important role. This suggested that THIQ skeletons with more steric bulk at C-4 would possibly prefer the ERβ receptor. Based on preliminary molecular modelling, it was decided to add small 1-3 carbon substituents on position C-4 of the 6-hydroxy-tetrahydroisoquinoline scaffold by utilizing a dialkylation strategy to obviate any anticipated complexity that would be introduced by the generation of stereochemical centers at this position (for earlier THIQ-based work see ref. 3). The purpose of synthesizing analogues **9b-e** was therefore to compare their biochemical activities with respect to **9a** and to determine the effect (potency and selectivity) the alkyl groups at this position might have.

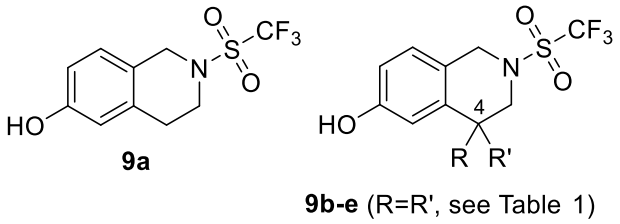
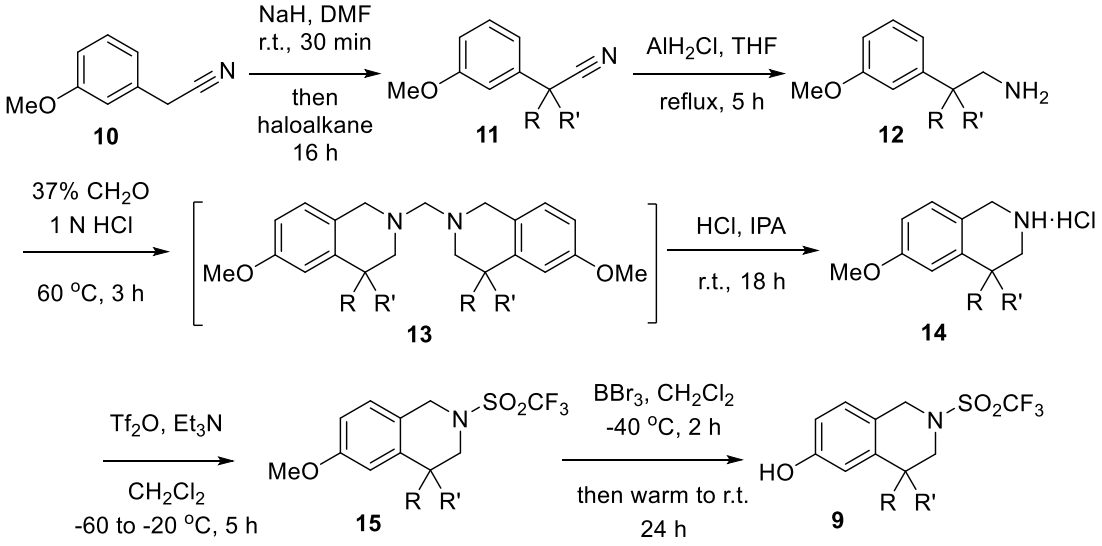


Figure 3. Structures of 2-[(trifluoromethyl)sulfonyl]-1,2,3,4-tetrahydroisoquinolin-6-ol (**9a**) and C-4 modified analogues **9b-e.**

Results and Discussion

Synthesis: After careful evaluation of the desired C-4 substituted 1,2,3,4-tetrahydroisoquinolin-6-ol scaffolds it was decided to synthesize them by making use of the well-known Pictet-Spengler ring-closing reaction approach – for earlier research by our group involving substituted isoquinolines,[27] dihydroisoquinolines[28] and THIQs[29-33] see the references listed. Firstly, the basic THIQ skeleton of the known reference compound **9a** (R,R'=H) was synthesized from 2-(3-methoxyphenyl)ethan-1-amine (**12a**) (R,R'=H), closely following a protocol described by Zhong *et al*.[34] In summary, compound **14a** (R,R'=H) was first obtained from **12a** (R,R'=H) over two steps in a moderate yield of 50%, after which the THIQ nitrogen atom of **14a** was converted into the trifluoromethylsulfonamide group of **15a** (R,R'=H) by reaction with triflic anhydride (87%). Demethylation with BBr_3 then afforded **9a** (R,R'=H) (Scheme 1), with spectroscopic characteristics in agreement with that produced in previous syntheses,[4,5,34] and in a good yield of 90%.



Scheme 1. Synthesis of 4-substituted analogues of THIQ **9a** – for yields and definitions of R and R' see Table 1.

Table 1. Yields for individual steps described in Scheme 1

Variant	a	b	c	d	e
R, R' =	H, H	Me, Me	Et, Et	$-CH_2CH_2-$	$-CH_2CH_2CH_2-$
Step 10→11	-	100%	77%	86%	81%
Step 11→12	-[b]	81%	100%	93%	54%
Step 12→[13][a]→14	50%	53%	60%	62%	50%
Step 14→15	87%	100%	81%	82%[c]	81%
Step 15→9	90%	86%	36%	-	65%

[a] Bis(6-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)methanes **13a–e** used directly in next step – yield listed based on crude mass of intermediate obtained; [b] 2-(3-methoxyphenyl)ethan-1-amine commercially available; [c] Compound **15d** unstable.

The general strategy for the C-4 alkylated THIQ analogues commenced with the starting material 2-(3-methoxyphenyl)acetonitrile (**10**).[35] Chemoselective α-alkylation of this commercially available material by initial treatment with NaH in DMF at room temperature for 30 min produced a red-coloured solution, to which the small set of di- or mono-halogenated alkanes were individually added.[36] The reaction mixtures were then stirred for 18 h, affording after work-up and chromatography alkylated acetonitriles **11b-e** in reasonable yields of 77-100%. Amongst other spectroscopic evidence, the alkylations were confirmed by ^{1}H NMR spectroscopy by additional signals of the new aliphatic groups in the region of δ_H 2.8-0.8.

The nitrile functional group in substrates **11b-e** was next efficiently reduced by the drop-wise addition of a solution of these compounds to a monochloroalane suspension in THF.[37,38] The reaction mixture was subsequently stirred under reflux for 5 h, followed by the addition of water to the cooled mixture until effervescence ceased. After work-up, product amines **12b-e** were isolated as thick oils in yields of 54-100%. The additional singlets integrating for 2-protons at δ_H ~2.8 in the ^{1}H NMR spectra confirmed the expected presence of the new methylene group. The amines **12b-e** were next treated with formaldehyde under acidic conditions, i.e., under the classic Pictet-Spengler reaction conditions, to initially afford the dimeric intermediates **13b-e** as oils,[34] and used without further purification. Compounds **13b-e** were subsequently suspended in acidified isopropanol to afford the THIQs **14b-e** as their hydrochlorides in moderate yields of 50-62% based on the aminal dimers **13**.[34] Common identifying signals in the ^{1}H NMR spectra for the monomeric THIQ-scaffolds were a broad 1-proton downfield singlet at δ_H 9.78-9.62 for the amine (NH) and an intense 2-proton singlet in the region of δ_H 4.25-4.11 for the new benzylic methylene group.

The corresponding trifluoromethylsulfonamides **15b**,**c** & **e** were next efficiently generated by treatment of **14b-e** with triflic anhydride at -40 °C under basic conditions.[39] The products so obtained were purified by column chromatography providing **15b**,**c** & **e** as thick oils in good yields ranging between 81-100%. The ^{1}H NMR spectra of these compounds illustrated an absence of the amine N-H signal previously noted for the precursor compounds, and in some cases the C-F coupling for the CF_3 group was evident in the ^{13}C NMR spectra. Unfortunately, whilst cyclopropyl compound **15d** could be obtained in 81%, its instability unexpectedly proved to be an issue and regretfully it could not be carried forward (although it should be noted that related aromatic structures have been listed in the patent literature – see for example the following ref. 40). Finally, deprotection of the aryl methyl ethers in hand was accomplished by treatment of substrates **15b**,**c** & **e** with boron tribromide (BBr_3) in dichloromethane at low temperature, which afforded the desired three corresponding phenol analogues **9b**,**c** & **e** as oils in varying yields of 86%, 36% and 65%,

respectively.[4] All three new compounds were fully characterized by spectroscopy and spectrometry to confirm their structures.

Computational and bio-evaluation of compounds: The trifluoromethylsulfonamide-decorated THIQs **9a-c** & **e** were evaluated in terms of molecular modelling by generation of a "Ligand efficiency score" for each of the receptors, but unfortunately the computational results indicated that the modelling was unable to distinguish any subtleties concerning the synthesized THIQ's ability to differentiate between ERα and ERβ (results not shown). Since the ligand efficiency scores did not demonstrate much difference between ERα/ERβ affinity for the library of compounds **9**, as a proof of concept, two members of this library of 4-substituted THIQ compounds were evaluated for their ability to interact with ERα to establish whether substitution in the C-4 region of the THIQ compounds would affect the inhibition. Compounds **9b** (4,4-dimethyl substituents) and **9e** (4-spirobutane substituent) were chosen for testing, versus the use of estradiol as a positive control. The three compounds were therefore evaluated in a fluorescence polarization cofactor recruitment assay with SUMO-tagged ERα, using a protocol similar to the study previously described by Brunsveld and co-workers.[4] Compounds **9b** and **9e** rather disappointedly appeared to only induce a partial response, i.e., at a fraction of the maximum response induced by estradiol, at concentrations above 1 μM (See Figure S1 in Supplementary Information file). Due to the weak response, an accurate determination of an EC_{50} for the two THIQ-based compounds was not possible.

Conclusions

A small library of 4,4-disubstituted 6-hydroxy-tetrahydroisoquinolines (**9a-c** & **e**) was readily synthesized. Due to the disappointing results by **9b** and **9e** in the SUMO-tagged ERα cofactor recruitment assays it was decided not to further evaluate this set of 4-C substituted 1,2,3,4-tetrahydroisoquinolin-6-ols. Potter and co-workers recently demonstrated that methyl substitution at the C-3 position of the THIQ skeleton in the development of microtubule disrupters was essential for good anti-proliferative activities.[41] These researchers suggest that this modification of the THIQ scaffold allows for their small THIQ-based molecules to adopt a more steroid-like conformation.[42,43] It was interesting to note that THIQ compounds featuring *gem* dimethylation at C-3 gave compounds which were devoid of activity, pointing out the subtleties involved in determining the scaffold functionalization/activity relationships. Future studies from our group could thus involve the generation of variably substituted 1,2,3,4-tetrahydroisoquinolin-6-ols with potential ERα/ERβ selectivity and thus as starting points for compounds with application as SERMs or SERDs.

Experimental Section

Experimental details below extracted from PhD thesis of Dr T. Mabank.[44]

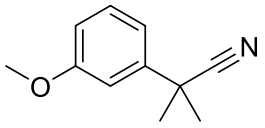
Synthesis – General:
Silica gel 60 (70-230 mesh) was used for gravity column chromatography and 230-400 mesh was used for flash chromatography. Silica sensitive compounds were purified using aluminium oxide 90 active neutral 0.063-0.200 mm (70-230 mesh). Nuclear magnetic resonance (NMR) spectra were recorded as follows: Varian Gemini-300 (^{1}H NMR at 300 MHz and ^{13}C at 75 MHz) or Varian VXR-400 (^{1}H NMR at 400 MHz and ^{13}C at 101

MHz) spectrometers. Chemical shifts (δ) and coupling constants (J) are reported in ppm and Hz units respectively. Positive electron spray impact (ESI^+) high resolution mass spectra (HRMS) were recorded on a Unicam Automass mass spectrometer in conjunction with a gas chromatogram. All reactions were performed under a anhydrous N_2 atmosphere.

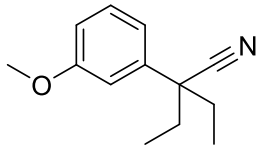
General procedure A – alkylation of 2-(3-methoxyphenyl)acetonitrile (10) to afford 11b–e

According to a procedure described by Melvin and co-workers,[36] a solution of 2-(3-methoxyphenyl)acetonitrile (**10**) (0.263 g, 0.250 mL, 1.79 mmol) in anhydrous DMF (5.0 mL) was added to a cooled (3 °C) 60% suspension of NaH in mineral oil (0.18 g, 7.5 mmol) in anhydrous DMF (5.0 mL). The resulting mixture was stirred for 30 min. providing a red coloured solution. The haloalkanes, *viz*., iodomethane (1.3 mL, 21 mmol), bromoethane (1.3 mL, 17 mmol), 1,2-dibromoethane (0.23 mL, 2.7 mmol) or 1,3-dibromopropane (0.23 mL, 2.3 mmol) were added individually, followed by stirring at r.t. for 16 h. Once the reaction was deemed complete (TLC), the mixture was treated with an aqueous saturated NH_4Cl solution (20 mL) and extracted with EtOAc (3 × 20 mL). The organic layers were combined, dried with $MgSO_4$, filtered and concentrated under reduced pressure to provide a residue which was purified by flash chromatography (EtOAc/Hexane 5:95), yielding products **11b–e** as oils. Structure of compounds was checked by NMR spectroscopy and they were then used directly in the next synthetic step without further characterization.

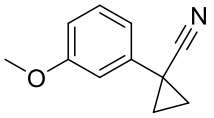
2-(3-Methoxyphenyl)-2-methylpropanenitrile (11b) was obtained as a colourless oil (0.313 g, quantitative) R_f 0.60 (50:50 EtOAc/Hexane). **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H 7.29–7.21 (m, 1H, ArH), 7.02–6.95 (m, 2H, 2 × ArH), 6.82–6.78 (m, 1H, ArH), 3.78 (s, 3H, OCH_3), 1.67 (s, 6H, 2 × CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$): δ_C 29.3 (2 × CH_3), 37.3 (C), 55.5 (OCH_3), 111.6 (ArCH), 112.9 (ArCH), 117.5 (ArCH), 124.6 (CN), 130.1 (ArCH), 143.2 (ArC), 160.1 (ArCOMe). The experimental spectroscopic information corresponded well with that reported by Kündig and co-workers.[45]



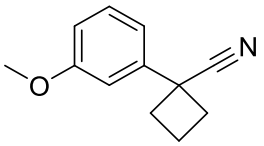
2-Ethyl-2-(3-methoxyphenyl)butanenitrile (11c) was obtained as a translucent oil (0.280 g, 77%); R_f 0.57 (20:80 CH_2Cl_2/Hexane). **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H 7.29–7.22 (m, 1H, ArH), 6.95–6.78 (m, 3H, 3 × ArH), 3.79 (s, 3H, OCH_3), 2.03–1.82 (m, 4H, 2 × CH_2), 0.88 (t, J 7.5 Hz, 6H, 2 × CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$): δ_C 10.0 (CH_3), 34.1 (CH_2), 50.2 (C), 55.6 (OCH_3), 112.8 (ArCH), 112.8 (ArCH), 118.7 (ArCH), 122.6 (CN), 130.1 (ArCH), 140.1 (ArC), 160.2 (ArCOMe).



1-(3-Methoxyphenyl)cyclopropanecarbonitrile (11d) was obtained as a yellow oil (0.266 g, 86%); R_f 0.30 (20:80 EtOAc/Hexane). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.48–7.43 (m, 1H, ArH), 7.07–7.00 (m, 3H, 3 × ArH), 4.01 (s, 3H, OCH_3), 1.93–1.88 (m, 2H, CH_2), 1.62–1.57 (m, 2H, CH_2). **^{13}C NMR** (75 MHz, $CDCl_3$): δ_C 14.0 (C), 18.3 (2 × CH_2), 55.5 (OCH_3), 112.0 (ArCH), 113.0 (ArCH), 118.0 (ArCH), 122.7 (CN), 130.1 (ArCH), 137.7 (ArC), 160.1 (ArCOMe). The experimental spectroscopic information was similar to that reported by Arava *et al*.[46]



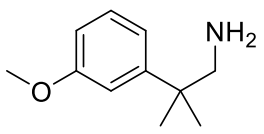
1-(3-Methoxyphenyl)cyclobutanecarbonitrile (11e) was obtained as a yellow oil (0.271 g, 81%); R_f 0.52 (100% Hexane). Sample contains some contaminant in the aliphatic region. **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H 7.23–7.16 (m, 1H, ArH), 6.91–6.83 (m, 2H, 2 × ArH), 6.76–6.73 (m, 1H, ArH), 3.73 (brs, 3H, OCH_3), 2.72–2.66 (m, 2H, CH_2), 2.56–2.46 (m, 2H, CH_2), 2.32–2.28 (m, 2H, CH_2). **^{13}C NMR** (75 MHz, $CDCl_3$): δ_C 17.2 (CH_2), 34.7 (2 × CH_2), 40.3 (C), 55.4 (OCH_3), 111.8 (ArCH), 113.1 (ArCH), 117.9 (ArCH), 124.4 (CN), 130.1 (ArCH), 141.4 (ArC), 160.1 (ArCOMe).



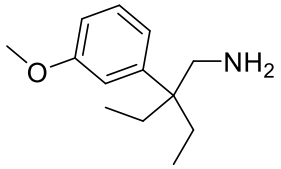
General procedure B for reduction of nitriles 11b–e to amines 12b–e

The general reduction procedure described by Nystrom,[38] Davis and Brown,[37] was applied as follows - lithium aluminium hydride ($LiAlH_4$) (41.0 mg, 1.07 mmol) was suspended in anhydrous THF (30 mL) and cooled to −3 °C in an ice bath. Aluminium chloride ($AlCl_3$) (140 mg, 1.07 mmol) was then carefully added in small portions while maintaining the temperature at −3 °C. The resulting hydride (AlH_2Cl) suspension was stirred at r.t. for 30 min., to which the nitriles **11b**–**e** (~0.125 g, ~0.7 mmol) in THF (4.0 mL) were added. The reaction mixture was stirred under reflux for 5 h, cooled to r.t. and carefully treated with water until no further effervescence occurred. The resultant colourless solid was separated by vacuum filtration and the filtrate extracted with EtOAc (2 × 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the corresponding amines **12b**–**e**, as oils which were utilized directly in the next reaction. The structures of the synthesized compounds were checked by NMR spectroscopy and then used directly in the next synthetic step without further characterization.

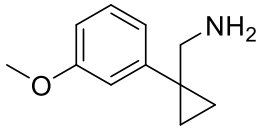
2-(3-Methoxyphenyl)-2-methylpropan-1-amine (12b) was obtained from starting material **11b** (0.125 g) as a yellow oil (0.103 g, 81%). **^{1}H NMR** (300MHz, $CDCl_3$, amine NH_2 not detected): δ_H 7.29-7.23 (m, 1H, ArH), 6.95-6.89 (m, 2H, 2 × ArH), 6.77-6.73 (m, 1H, ArH), 3.81 (s, 3H, OCH_3), 2.79 (s, 2H, CH_2), 1.29 (s, 6H, 2 × CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$): δ_C 26.5 (CH_3), 39.4 (C), 55.0 (NCH_2), 55.2 (OCH_3), 110.4 (ArCH), 113.1 (ArCH), 118.8 (ArCH), 129.3 (ArCH), 149.2 (ArC), 159.7 (ArCOMe).



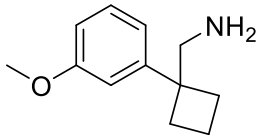
2-Ethyl-2-(3-methoxyphenyl)butan-1-amine (12c) was obtained from starting material **11c** (0.145 g) as a yellow oil (0.148 g, quantitative). **^{1}H NMR** (300 MHz, $CDCl_3$, amine NH_2 not detected): δ_H 7.29–7.23 (m, 1H, ArH), 6.93–6.87 (m, 2H, 2 × ArH), 6.77-6.73 (m, 1H, ArH), 3.82 (s, 3H, OCH_3), 2.86 (s, 2H, NCH_2), 1.70 (q, *J* 7.4 Hz, 4H, 2 × CH_2), 0.76 (t, *J* 7.4 Hz, 6H, 2 × CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$): δ_C 8.0 (CH_3), 26.5 (CH_2), 45.9 (C), 48.3 (NCH_2), 55.3 (OCH_3), 110.2 (ArCH), 114.0 (ArCH), 119.6 (ArCH), 129.2 (ArCH), 147.6 (ArC), 159.7 (ArCOMe).



1-[(3-Methoxyphenyl)cyclopropyl]methanamine (12d) was obtained from starting material **11d** (0.123 g) as a yellow oil (0.117 g, 93%). **^{1}H NMR** (300MHz, $CDCl_3$, amine NH_2 not detected): δ_H 7.28–7.22 (m, 1H, ArH), 6.96–6.89 (m, 2H, 2 × ArH), 6.80-6.76 (m, 1H, ArH), 3.82 (s, 3H, OCH_3), 2.79 (s, 2H, NCH_2), 0.87–0.83 (m, 2H, CH_2), 0.76–0.73 (m, 2H, CH_2). **^{13}C NMR** (75 MHz, $CDCl_3$): δ_C 12.0 (CH_2), 29.7 (C), 52.2 (NCH_2), 55.5 (OCH_3), 111.8 (ArCH), 115.5 (ArCH), 121.9 (ArCH), 129.6 (ArCH), 145.5 (ArC), 159.9 (ArCOMe).



1-[(3-Methoxyphenyl)cyclobutyl]methanamine (12e) was obtained from starting material **11e** (0.133 g) as a yellow translucent oil (0.074 g, 54%). **^{1}H NMR** (300 MHz, $CDCl_3$, amine NH_2 not detected: δ_H 7.20–7.15 (m, 1H, ArH), 6.69-6.57 (m, 3H, 3 × ArH), 3.75 (s, 3H, OCH_3), 2.85 (s, 2H, NCH_2), 2.27-2.24 (m, 2H, CH_2), 2.08-2.01 (m, 4H, 2 × CH_2). **^{13}C NMR** (75 MHz, $CDCl_3$, quaternary, aliphatic C not clearly shown in spectrum): δ_C 15.9 (CH_2), 30.5 (CH_2), 52.7 (NCH_2), 55.3 (OCH_3), 110.7 (ArCH), 112.2 (ArCH), 118.5 (ArCH), 129.2 (ArCH), 144.2 (ArC), 159.6 (ArCOMe).



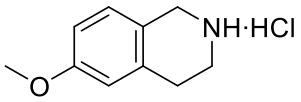
The synthesis of 4-substituted 6-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochlorides 14a–e, by way of intermediate bis(6-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)methanes 13a–e

General procedure C. The procedure by Zhong and co-workers[34] was followed for the synthesis of the aminal dimers **13a**–**e**. In this experimental process, a solution of 37% aqueous formaldehyde (1.0 mL, 13 mmol) was added to a solution of the substituted 2-(3-methoxyphenyl)ethylamines **12a**–**e** (0.50 mL, ~3.3 mmol) in 1 N aqueous HCl solution (5.0 mL, 5.0 mmol). The mixtures were heated and stirred at 60 °C for 4 h, resulting in yellow translucent solutions which were cooled to 0 °C and neutralized by the slow addition of a 50% aqueous NaOH solution (~1.0 mL, 5.6 mmol). The resulting thick suspension was extracted using EtOAc (2 × 20 mL) providing compounds **13a**–**e** after drying and removal of solvent. These compounds were directly used in the subsequent reactions with no further purification. In some cases, neutralization with NaOH solution resulted in the formation of a colourless sticky gum-like residue, which solidified on further stirring and was pulverized very carefully before extraction with the EtOAc. In all cases, compounds **13a**–**e** were obtained in near quantitative yields (based on mass) and utilized directly in the next reaction without spectroscopic characterization.

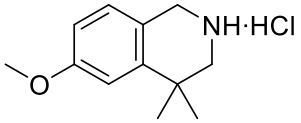
General procedure D. The procedure described by Zhong and co−workers,[34] was utilized for the synthesis of the THIQs **14a**–**e**. Thus, the aminal dimers **13a**–**e** (~2.0 mmol) were suspended in IPA (10 mL), to which an 11 M HCl solution (2.5 mol equiv.) was slowly added, resulting in a yellow translucent solution and with a slight

exotherm being noted. After stirring for 6 h, a precipitate started to develop. The resulting suspension was stirred at r.t. for a further 18 h. MTBE (1.0 mL per mmol of dimer) was added, and the resulting mixture was left to stir for an additional 4 h. The precipitates were collected by vacuum filtration providing solid products which were washed with IPA/MTBE (1:1) and air dried to yield amorphous hydrochloride powders, **14a–e** described below. These compounds were fully characterized.

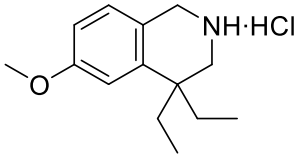
6-Methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (14a) was obtained in (0.348 g, 50%) from starting material **13a** (0.590 g) as a colourless amorphous powder; **mp** 238–239 °C. **^{1}H NMR** (400 MHz, DMSO−d_6): δ_H 9.80 (brs, 2H, NH), 7.13 (d, *J* 8.4 Hz, 1H, H-8), 6.83-6.78 (m, 2H, H-5 and H-7), 4.12 (s, 2H, $ArCH_2N$), 3.73 (s, 3H, OCH_3), 3.28 (t, *J* 4.4 Hz, 2H, NCH_2CH_2), 2.98 (t, *J* 4.4 Hz, 2H, $ArCH_2$). **^{13}C NMR** (101 MHz, DMSO-d_6): δ_C 24.9 ($ArCH_2$), 40.3 (NCH_2), 42.9 ($ArCH_2N$), 55.2 (OCH_3), 113.1 (ArCH), 113.1 (ArCH), 120.8 (ArCH), 127.9 (ArC), 133.4 (ArC), 158.4 (ArCOMe). The experimental spectroscopic information corresponded well with that reported in the literature.[34]



6-Methoxy-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (14b) was obtained (0.48 g, 53%) from starting material **13b** (0.79 g) as a colourless semi-solid. **^{1}H NMR** (300 MHz, DMSO-d_6): δ_H 9.63 (brs, 2H, NH_2), 7.12 (d, *J* 8.6 Hz, 1H, H-8), 6.97 (d, *J* 2.5 Hz, 1H, H-5), 6.83 (dd, *J* 8.6, 2.5 Hz, 1H, H-7), 4.15 (s, 2H, $ArCH_2N$), 3.76 (s, 3H, OCH_3), 3.14 (s, 2H, NCH_2), 1.35 (s, 6H, 2 × CH_3). **^{13}C NMR** (75 MHz, DMSO−d_6): δ_C 28.8 (CH_3), 32.9 (C), 52.0 ($ArCH_2N$), 55.3 (OCH_3), 62.3 (NCH_2), 111.3 (ArCH), 112.8 (ArCH), 119.5 (ArC), 128.0 (ArCH), 142.7 (ArC), 159.1 (ArCOMe). **HRMS ESI$^+$**: *m/z* $[M+H]^+$ calcd for $C_{12}H_{18}NO$, 192.1388; found, 192.1388. Only ^{1}H NMR and MS previously reported in the patent literature.[47]

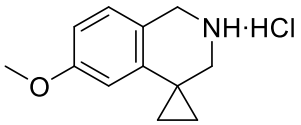


4,4-Diethyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (14c) was obtained in (0.54 g, 60%) yield from starting material **13c** (0.79 g) as a light-brown coloured powder. **^{1}H NMR** (300 MHz, DMSO−d_6): δ_H 9.62 (brs, 2H, NH_2), 7.15 (d, *J* 7.5 Hz, 1H, H-8), 6.86–6.83 (m, 2H, H-5 and H-7), 4.13 (s, 2H, $ArCH_2N$), 3.75 (s, 3H, OCH_3), 3.14 (s, 2H, NCH_2), 1.89–1.82 (m, 2H, CH_2), 1.68–1.60 (m, 2H, CH_2), 0.74 (t, *J* 7.4 Hz, 6H, 2 × CH_3). **^{13}C NMR** (75 MHz, DMSO−d_6): δ_C 8.3 (CH_3), 30.4 (CH_2), 43.7 (C), 45.3 ($ArCH_2N$), 55.2 (OCH_3), 62.2 (NCH_2), 111.8 (ArCH), 112.5 (ArCH), 120.7 (ArC), 128.0 (ArCH), 140.2 (ArC), 158.7 (ArCOMe). **HRMS ESI$^+$**: *m/z* $[M+H]^+$ calcd for $C_{14}H_{22}NO$, 220.1701; found, 220.1693.

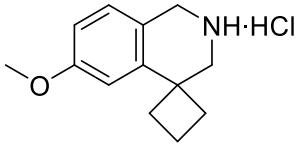


6'-Methoxy-2',3'-dihydro-1'*H*-spiro(cyclopropane-1,4'-isoquinoline) hydrochloride (14d) was obtained (0.86 g, 62%) from starting material **13d** (1.16 g) as a colourless semi-solid. **^{1}H NMR** (300 MHz, DMSO−d_6): δ_H 9.78 (brs, 2H, NH_2), 7.12 (d, *J* 8.5 Hz, 1H, H-8), 6.78 (dd, *J* 8.5, 2.5 Hz, 1H, H-7), 6.34 (d, *J* 2.5 Hz, 1H, H-5), 4.25 (s, 2H, $ArCH_2N$), 3.72 (s, 3H, OCH_3), 3.17 (s, 2H, NCH_2), 1.11–1.07 (m, 4H, CH_2–CH_2). **^{13}C NMR** (75 MHz, DMSO−d_6): δ_C

16.5 (C), 17.0 (CH_2), 44.4 ($ArCH_2$), 48.8 (NCH_2), 55.3 (OCH_3), 106.9 (ArCH), 112.1 (ArCH), 121.3 (ArCH), 127.8 (ArC), 138.9 (ArC), 159.3 (ArCOMe). **HRMS ESI$^+$**: *m/z* $[M+H]^+$ calcd for $C_{12}H_{16}NO$, 190.1232; found, 190.1243.



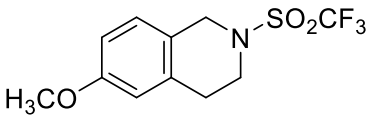
6'-Methoxy-2',3'-dihydro-1'*H*-spiro(cyclobutane-1,4'-isoquinoline) hydrochloride (14e) was obtained (0.166 g, 50%) from starting material **13e** (0.29 g) as a yellow oil. **^{1}H NMR** (300 MHz, DMSO−d_6): δ_H 9.73 (brs, 2H, NH_2), 7.21–7.20 (m, 1H, ArH), 7.13-7.10 (m, 1H, ArH), 6.87-6.83 (m, 1H, ArH), 4.11 (s, 2H, $ArCH_2$), 3.80 (s, 3H, OCH_3), 3.43 -0(brs, 2H, NCH_2), 2.40–2.36 (m, 2H, CH_2), 2.19–1.80 (m, 4H, 2 × CH_2). **^{13}C NMR** (75 MHz, DMSO−d_6): δ_C 14.4 (CH_2), 33.3 (CH_2), 43.6 (C), 49.4 ($ArCH_2$), 55.3 (OCH_3), 62.0 (NCH_2), 111.1 (ArCH), 112.9 (ArCH), 119.9 (ArCH), 127.6 (ArC), 141.3 (ArC), 159.2 (ArCOMe). **HRMS ESI$^+$**: *m/z* $[M+H]^+$ calcd for $C_{13}H_{18}NO$, 204.1388; found, 204.1384.



General procedure E - synthesis of trifluoromethylsulfonamide analogues 15a-e

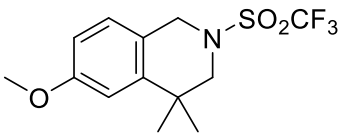
The procedures by Ho and Broka,[39] and Bailey *et al*.[48] were implemented for the trifluoromethylsulfonylation of **14a**–**e**. To this end, a mixture of the individual hydrochlorides **14a**–**e** (~1.0 mmol) and Et_3N (3.5–4 mmol) in anhydrous CH_2Cl_2 (20 mL) was stirred at r.t. for 30 min to ensure complete solubilization of the reagents. The resulting mixtures were cooled to −60 °C, to which trifluoromethanesulfonic anhydride (1.5 mmol) was slowly added. The mixtures were stirred at −20 °C for an additional 2 h, followed by stirring at r.t. for 3 h. The reaction mixtures were partitioned between an aqueous saturated $NaHCO_3$ solution and CH_2Cl_2, and further extracted with CH_2Cl_2 (3 × 25 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure, affording brown residues which were purified by flash chromatography (EtOAc/Hexane 5:95).

6-Methoxy-2-[(trifluoromethyl)sulfonyl]-1,2,3,4-tetrahydroisoquinoline (15a) was obtained (0.258 g, 87%) from starting material **14a** (0.200 g) as a yellow/orange oil; Rf 0.46 (30:70, EtOAc/Hexane). **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H 7.01 (d, *J* 8.5 Hz, 1H, H-8), 6.80 (dd, *J* 8.5, 2.6 Hz, 1H, H-7), 6.70 (d, *J* 2.6 Hz, 1H, H-5), 4.61 (s, 2H, $ArCH_2N$), 3.80–3.74 (m, 5H, overlapping signals−OCH_3 and NCH_2), 2.96 (t, *J* 6.0 Hz, 2H, $ArCH_2CH_2$). **^{13}C NMR** (75 MHz, $CDCl_3$, C−F coupled CF_3 peak was not clearly visible in spectrum): δ_C 29.4 ($ArCH_2CH_2$), 44.6 (NCH_2), 47.5 ($ArCH_2N$), 55.6 (OCH_3), 113.5 (ArCH), 114.0 (ArCH), 122.6 (ArCH), 123.1 (ArC), 134.2 (ArC), 159.0 (ArCOMe). Compound was used without further characterization directly in next reaction to synthesize **9a**.

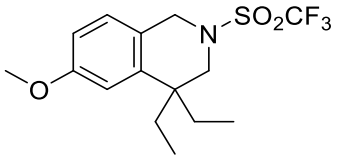


6-Methoxy-4,4-dimethyl-2-[(trifluoromethyl)sulfonyl]-1,2,3,4-tetrahydroisoquinoline (15b) was obtained (0.129 g, quantitative) from starting material **14b** (0.0892 g) as an orange oil; R_f 0.55 (20:80 EtOAc/Hexane). **^{1}H**

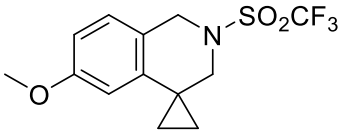
NMR (300 MHz, $CDCl_3$): δ_H 6.98 (d, *J* 8.5 Hz, 1H, H-8), 6.88 (d, *J* 2.6 Hz, 1H, H-5), 6.77 (dd, *J* 8.5 Hz, 2.6 Hz, 1H, H-7), 4.62 (brs, 2H, $ArCH_2N$), 3.81 (s, 3H, OCH_3), 3.44 (brs, 2H, NCH_2), 1.35 (s, 6H, 2 × CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$, C–F coupled CF_3 and quaternary aliphatic C-4 peaks not clearly visible in spectrum): δ_C 35.9 (CH_3), 55.7 (OCH_3 and $ArCH_2$), 65.6 (NCH_2), 109.3 (ArCH), 119.3 (ArCH), 130.0 (Ar*C*H), 132.5 (Ar*C*), 155.3 (ArCOMe), 171.1 (ArC). Compound was used without further characterization directly in the next reaction to synthesize **9b**.



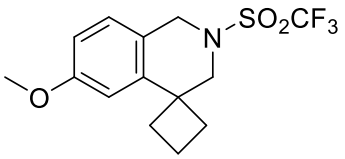
4,4-Diethyl-6-methoxy-2-[(trifluoromethyl)sulfonyl]-1,2,3,4-tetrahydroisoquinoline (15c) was obtained (0.239 g, 81%) from starting material **14c** (0.214 g) as an orange oil; R_f 0.75 (30:70 EtOAc/Hexane). **^{1}H NMR** (300 MHz, DMSO-d_6): δ_H 7.14–7.11 (m, 1H, ArH), 6.85–6.82 (m, 2H, 2 × ArH), 4.11 (brs, 2H, $ArCH_2N$), 3.75 (s, 3H, OCH_3), 3.13 (s, 2H, NCH_2), 1.86–1.78 (m, 2H, CH_2), 1.66–1.59 (m, 2H, CH_2), 0.74 (t, *J* 6.0 Hz, 6H, 2 × CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$, C–F coupled CF_3 peak was not clearly visible in spectrum): δ_C 8.4 (CH_3), 29.8 (CH_2), 41.3 (C), 47.9 ($ArCH_2$), 50.8 (NCH_2), 55.4 (OCH_3), 112.0 (ArCH), 112.7 (ArCH), 122.7 (ArC), 127.2 (ArCH), 140.8 (ArC), 158.7 (ArCOMe). **HRMS ESI$^+$**: *m/z* $[M-H]^+$ calcd for $C_{15}H_{19}F_3NO_3S$, 350.1038; found, 350.1046.



6'-Methoxy-2'-[(trifluoromethyl)sulfonyl]-2',3'-dihydro-1'*H*-spirocyclopropane-1,4'-isoquinoline (15d) was obtained (0.195 g, 82%) from starting material **14d** (0.167 g) as a brown-coloured oil; R_f 0.62 (20:80 EtOAc/Hexane). **^{1}H NMR** (400 MHz, $CDCl_3$, quaternary aliphatic carbon not observable in spectrum): δ_H 7.00 (d, *J* 8.5 Hz, 1H, H-8), 6.74 (dd, *J* 8.5, 2.5 Hz, 1H, H-7), 6.30 (d, *J* 2.5 Hz, 1H, H-5), 4.70 (brs, 2H, $ArCH_2N$), 3.76 (s, 3H, OCH_3), 3.51 (brs, 2H, NCH_2), 1.09–1.04 (m, 4H, 2 × CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 20.2 (CH_2), 20.3 (C), 48.7 ($ArCH_2$), 53.5 (NCH_2), 55.8 (OCH_3), 108.2 (ArCH), 112.0 (ArCH) 121.0 (q, *J* 336 Hz, CF_3), 123.9 (ArC), 127.3 (ArCH), 139.8 (ArC), 159.8 (ArCOMe). Compound unstable and degraded within days.



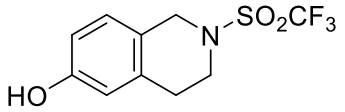
6'-Methoxy-2'-[(trifluoromethyl)sulfonyl]-2',3'-dihydro-1'*H*-spirocyclobutane-1,4'-isoquinoline (15e) was obtained (0.194 g, 81%) from of starting material **14e** (0.171 g) as an orange oil; R_f 0.76 (30:70 EtOAc/Hexane). **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H 7.14 (d, *J* 2.6 Hz, 1H, H-5), 6.98 (d, *J* 8.5 Hz, 1H, H-8), 6.80 (dd, *J* 8.5, 2.6 Hz, 1H, H-7), 4.58 (brs, 2H, $ArCH_2N$), 3.86 (s, 3H, OCH_3), 3.68-3.60 (m, 2H, NCH_2), 2.38–2.07 (m, 6H, 3 × CH_2). **^{13}C NMR** (75 MHz, $CDCl_3$): δ_C 15.1 (CH_2), 41.8 (CH_2), 48.1 (ArC), 53.8 ($ArCH_2$), 55.7 (OCH_3 and NCH_2), 111.9 (ArCH), 112.6 (ArCH) 118.6 (CF_3), 120.8 (q, *J* 325 Hz, CF_3), 122.2 (ArC), 127.2 (ArCH), 142.4 (ArC), 159.6 (ArCOMe). **MS ESI$^+$**: *m/z* $[M+H]^+$ calcd for $C_{14}H_{17}F_3NO_3S$, 336.08; found, 336.19.



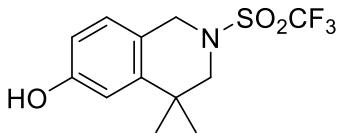
General procedure F - demethylation of aryl ethers 15a-c & e to afford compounds 9a-c & e

The general procedure by McOmie and co−workers,[49] was implemented for the demethylation of aryl methyl ethers **15a-c** & **e**. To a cooled (-40 °C) solution of 1 M BBr_3 (~10 mmol equiv.) in anhydrous CH_2Cl_2 (6.0 mL) was slowly added the sulfonamide derivatives **15a-c** & **e** (0.4-0.8 mmol) dissolved in anhydrous CH_2Cl_2 (1 mL) and stirred at −40 °C for 2 h. The mixtures were allowed to warm to r.t. and stirred for an additional 24 h. The reactions were quenched with water (15 mL) at 0 °C and the product was obtained by extracting the aqueous mixture with CH_2Cl_2 (3 × 25 mL) to produce after drying ($MgSO_4$) and evaporation a residue which was purified by flash chromatography using EtOAc/Hexane 30:70 as eluent to afford the products described below:

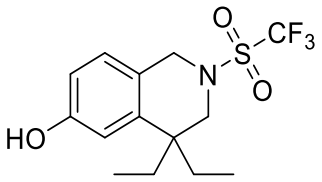
2-[(Trifluoromethyl)sulfonyl]-1,2,3,4-tetrahydroisoquinolin-6-ol (9a) was obtained as an orange-brown oil (0.202 g, 90%) from starting material **15a** (0.236 g); R_f 0.20 (100% EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 6.94-6.92 (m, 1H, ArH), 6.74-6.65 (m, 2H, 2 × ArH), 6.33 (s, 1H, ArOH), 4.57 (brs, 2H, $ArCH_2N$), 3.72 (s, 2H, NCH_2), 2.93-2.98 (m, 2H, $ArCH_2$). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 29.2 ($ArCH_2$), 44.6 (CH_2CH_2N), 47.5 ($ArCH_2N$), 114.7 (ArCH*),* 115.7 (ArCH), 120.5 (q, *J* 330 Hz, CF_3), 122.8 (ArC), 127.5 (ArCH), 134.3 (ArC), 155.3 (ArCOH). The experimental spectroscopic information corresponded well with that reported in the literature.[4]



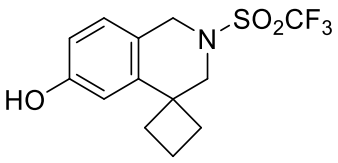
4,4-Dimethyl-2-[(trifluoromethyl)sulfonyl]-1,2,3,4-tetrahydroisoquinolin-6-ol (9b) was obtained as a yellow oil) (0.104 g, 86%) from starting material **15b** (0.127 g); R_f 0.43 (30:70 EtOAc/Hexane). **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H 6.92 (d, *J* 8.4 Hz, 1H, H-8), 6.83 (d, *J* 2.6 Hz, 1H, H-5), 6.70 (dd, *J* 8.4, 2.6 Hz, 1H, H-7), 4.89 (brs, 1H, OH), 4.61 (br s, 2H, $ArCH_2N$), 3.44 (br s, 2H, NCH_2), 1.34 (s, 6H, 2 × CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$, aliphatic quaternary C not visible): δ_C (ppm) 35.4 (CH_3), 48.2 ($ArCH_2$), 56.1 (NCH_2), 112.7 (ArCH), 114.5 (ArCH), 120.3 (CF_3, *J* 331 Hz), 121.7 (ArC), 127.5 (ArCH), 144.1 (ArC), 155.2 (ArCOH). **HRMS ESI$^+$**: *m/z* $[M+H]^+$ calcd for $C_{12}H_{15}F_3NO_3S$, 310.0725; found, 310.0721.



4,4-Diethyl-2-[(trifluoromethyl)sulfonyl]-1,2,3,4-tetrahydroisoquinolin-6-ol (9c) was obtained as an orange oil) (0.084 g, 36%) from starting material **15c** (0.242 g); R_f 0.55 (30:70 EtOAc/Hexane). **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H 6.89 (d, *J* 8.2 Hz, 1H, H-8), 6.73-6.68 (m, 2H, 2 × ArH), 5.70 (brs, 1H, OH), 4.55 (brs, 2H, $ArCH_2N$), 3.51 (brs, 2H, NCH_2), 1.78-1.59 (m, 4H, 2 × CH_2), 0.79 (t, *J* 7.5 Hz, 6H, 2 × CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$,): δ_C (ppm) 8.3 (CH_3), 31.0 (br C), 41.2 (CH_2), 48.0 ($ArCH_2$), 50.8 (NCH_2), 113.6 (ArCH) 114.1 (ArCH), 120.3 (q, *J* 323 Hz, CF_3), 122.7 (ArC), 127.4 (ArCH), 141.1 (ArC), 154.6 (ArCOH). **HRMS ESI$^+$**: *m/z* $[M-H]^+$ calcd for $C_{14}H_{17}F_3NO_3S$, 336.0881; found, 336.0881.



2'-[(Trifluoromethyl)sulfonyl]-2',3'-dihydro-1'*H*-spirocyclobutane-1,4'-isoquinolin-6'-ol (9e) was obtained as a colourless oil) (0.109 g, 65%) from starting material **15e** (0.175 g); R_f 0.53 (30:70 EtOAc/Hexane). **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H 7.08 (d, *J* 2.5 Hz, 1H, H-5), 6.90 (d, *J* 8.3 Hz, 1H, H-8), 6.70 (dd, *J* 8.3, 2.5 Hz, 1H, H-7), 5.02 (brs, 1H, OH), 4.55 (brs, 2H, $ArCH_2N$), 3.69 (bs, 2H, NCH_2), 2.33-2.02 (m, 6H, 3 × CH_2). **^{13}C NMR** (75 MHz, $CDCl_3$): δ_C 15.1 (CH_2), 32.5 (br C), 41.7 (CH_2), 48.1 ($ArCH_2N$), 53.8 (NCH_2), 112.9 (ArCH), 114.4 (ArCH), 120.5 (q, *J* 323 Hz, CF_3), 122.2 (ArC), 127.4 (ArCH), 142.8 (ArC), 155.5 (ArCOH). **HRMS ESI$^+$:** *m/z* $[M-H]^+$ calcd for $C_{13}H_{13}F_3NO_3S$, 320.0568; found, 320.0568.



Bioevaluations: For experimental procedures related to the fluorescence polarization cofactor recruitment assay with SUMO-tagged ERα, see the following references for detailed experimental descriptions.[4,50,51]

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Supplementary Material

NMR spectroscopic and HRMS spectrometry data for compounds synthesized in this work are available in the Supplementary Information (SI) file.

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