N-Phenyl-1,2,3,4-tetrahydroisoquinoline: an alternative scaffold for design of 17β-hydroxysteroid dehydrogenase 1 inhibitors

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Abstract: 17β-Hydroxysteroid dehydrogenases catalyse interconversion at the C17 position between oxidized and reduced forms of steroidal nuclear receptor ligands. The type 1 enzyme, expressed in malignant cells, catalyses reduction of the less active estrone to estradiol and inhibitors have therapeutic potential in estrogen-dependent diseases such as breast and ovarian cancers and in endometriosis. Synthetic decoration of the nonsteroidal *N*-phenyl-1,2,3,4-tetrahydroisoquinoline (THIQ) template was pursued using Pomeranz-Fritsch-Bobbitt, Pictet-Spengler and Bischler-Napieralski approaches to explore the viability of this scaffold as a steroid mimic. Derivatives were evaluated biologically in vitro as type 1 enzyme inhibitors in a bacterial cell homogenate as source of recombinant protein. Structure-activity relationships are discussed. THIQs possessing a 6-hydroxyl group, lipophilic substitutions at the 1- or 4- positions in combination with *N*-4′-chlorophenyl substitution were most favourable for activity. Of these, one compound had an IC_{50} of ca. 350 nM as a racemate, testifying to the applicability of this novel approach.

Introduction

Breast cancer is the leading cause of death in women. Despite enormous progress in its diagnosis and treatment over recent years, more than 2 million new diagnoses and over 626,679 deaths worldwide occurred in 2018 in both men and women.[1] Multiple studies have highlighted an increment in estrogen receptor positive (ER+) breast cancer cases over estrogen receptor negative (ER−) ones.[2] ER− status is usually associated with poorer prognosis, whereas ER+ status allows exploitation of drugs targeting estrogen receptors to shrink tumour mass before surgical removal and to reduce recurrence post-removal.[3] ER-targeting therapies differ between women in pre- and postmenopausal stages. In premenopausal women, estrogens are mainly produced in the ovaries and then distributed through the body by the bloodstream, whereas in postmenopausal women estrogens are locally produced in many peripheral tissues.[4] Hence, the main treatment strategy for breast cancer in premenopausal women, apart from surgery and radiotherapy, is the use of selective ER modulators (SERMs) such as tamoxifen to block the stimulant effect on an ER+ tumour. Conversely, in postmenopausal women, the peripheral biosynthesis of estrogens can be targeted by using an aromatase inhibitor such as anastrozole and this is becoming the first line approach.[5] Recently, targeting other enzymes involved in the peripheral biosynthesis of estrogens, such as steroid sulfatase and 17β-hydroxysteroid dehydrogenase 1 (HSD17B1), has garnered increasing interest.[4b, 6]

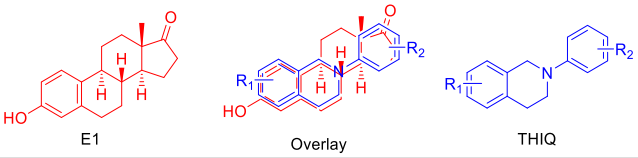


Figure 1. Structural analogies between E1 and the THIQ template

HSD17Bs are a class of enzymes belonging to the short-chain dehydrogenase/reductase (SDR) family comprising fifteen subtypes. The HSD17B enzymes are involved in the reduction and oxidation of hormones, fatty acids and bile acids. HSD17B subtypes differ in terms of substrate specificity, tissue distribution and regulation mechanisms, and they can be arbitrarily divided into androgenic or estrogenic, and oxidative or reductive. The oxidative HSDs depend on NAD^+/NADH and the reductive HSDs on $NADP^+$/NADPH. Due to higher cellular levels of NADPH and NAD^+, NAD^+/NADH-dependent enzymes act as oxidases and $NADP^+$/NADPH dependent enzymes as reductases.[7] HSD17B1 (EC 1.1.1.62) was originally isolated from human placenta in the 1950s and is a reducing enzyme which catalyses the NADPH dependent conversion of estrone (E1) into the more estrogenic estradiol (E2).[7a, 8] Although HSD17B1 is capable of converting E2 into E1 in vitro, this function in vivo is carried out exclusively by HSD17B2. This is due to the high intracellular concentration of the preferred cofactor NADPH versus $NADP^+$, which drives the reductive process.HSD17B1 is upregulated in breast cancer cells and is involved in maintaining high E2 intratumoral levels.[9] In addition, HSD17B1 expression has been associated with poorer prognoses in breast cancer patients.[10] Accordingly, HSD17B1 is a promising target for ER+ breast cancer.

Known inhibitors of HSD17B1 are based on e.g. modified steroids, biphenyl compounds, flavonoids, coumarins, benzothiazoles or thiophene.[7a, 11] Non-estrogenic, selective, steroidal HSD17B1 inhibitors such as the 2,16-di-substituted estrone derivative STX1040 have demonstrated potent inhibition of E1-stimulated breast tumour growth using a murine model.[11g, 12] STX1040 was observed to inhibit E1-stimulated proliferation of T47D cells in vitro and significantly decrease tumour volumes and plasma E2 levels in vivo.[13] In addition, designed multi-functional ligands targeting both HSD17B1 and estrogen receptors or HSD17B1 and the steroid sulphatase enzyme have been reported.[14] However, no HSD17B1 inhibitor has yet reached human clinical trials.

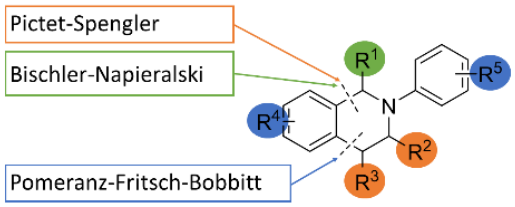


Figure 2. Different synthetic approaches were used to explore substitution at R^1 (Bischler-Napieralski), R^2 and R^3 (Pictet-Spengler) and at R^4 and R^5 (Pomeranz-Fritsch-Bobbitt) positions.

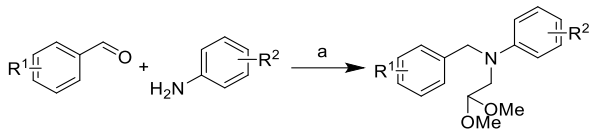
The nonsteroidal *N*-Phenyl-1,2,3,4-tetrahydroisoquinoline scaffold (THIQ) has structural similarities with steroidal E1 (**Figure 1**), the natural substrate of HSD17B1. Compounds based on a similar 1,2,3,4-tetrahydroisoquinoline scaffold have been reported in the literature as being steroidomimetic.[6g, 15] In addition, this THIQ framework allows for a wide range of substitutions that can be accessed in a rapid and convenient fashion. Thus, the THIQ core represents an interesting scaffold for constructing novel inhibitors of HSD17B1 as a potential ER+ breast cancer treatment. Moreover, the presence of a mildly basic nitrogen atom in the THIQ core allows for the formation of salts to aid solubility.

Herein we report the synthesis of a series of fully decorated THIQs and their biological activities as candidate HSD17B1 inhibitors. We identify a tractable THIQ derivative of nanomolar potency for further optimization.

Results and Discussion

Chemistry.

With the objective of introducing simple substituents at each possible position of the selected THIQ scaffold, synthetic approaches were designed around three well-established synthetic methodologies, namely the Pomeranz-Fritsch-Bobbitt, Pictet-Spengler and Bischler-Napieralski approaches (**Figure 2**).[16] These three robust and reliable key reactions delivered the desired final compounds in a short number of steps and starting from inexpensive, commercially available, compounds e.g. anilines and benzaldehydes.



1 **2** **3a-s**

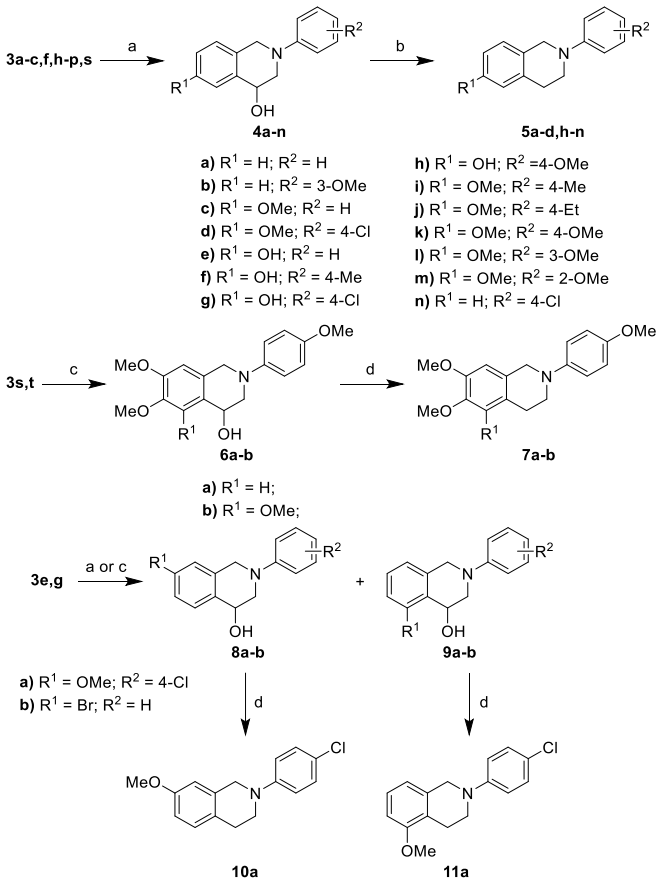
a) R^1 = H; R^2 = H
b) R^1 = H; R^2 = 3-OMe
c) R^1 = 4-OMe; R^2 = H
d) R^1 = 3-OMe; R^2 = H
e) R^1 = 3-Br; R^2 = H
f) R^1 = 4-OMe; R^2 = 4-Cl
g) R^1 = 3-OMe; R^2 = 4-Cl
h) R^1 = 4-OH; R^2 = H
i) R^1 = 4-OH; R^2 = 4-Me
j) R^1 = 4-OH; R^2 = 4-Cl
k) R^1 = 4-OH; R^2 =4-OMe
l) R^1 = 4-OMe; R^2 = 4-Me
m) R^1 = 4-OMe; R^2 = 4-Et
n) R^1 = 4-OMe; R^2 = 4-OMe
o) R^1 = 4-OMe; R^2 = 3-OMe
p) R^1 = 4-OMe; R^2 = 2-OMe
q) R^1 =3,4-$(OMe)_2$; R^2 = 4-OMe
r) R^1 =3,4,5-$(OMe)_3$; R^2 = 4-OMe
s) R^1 = H; R^2 = 4-Cl

Scheme 1. Double reductive amination. a) i) $NaBH(OAc)_3$, $CHCl_3$, rt, 1h ii) 2,2-dimethoxyacetaldehyde, rt, 8h (54-99%).

The first step of the Pomeranz-Fritsch-Bobbitt approach involves a double reductive amination (**Scheme 1**), followed by cyclization with standard or modified conditions (6M HCl or 70% $HClO_4$, respectively) as dictated by the substitution pattern (**Scheme 2**), as per literature precedent.[17] Cyclization of **3e** (**Scheme 2**) yielded a mixture of two regioisomers **8a** and **9a**, which could be directly separated. Similarly, the two regioisomers **8b** and **9b** were simultaneously obtained during the cyclization of **3g** (**Scheme 2**). Alternatively, the synthesis could be telescoped by reductive dehydroxylation of the crude mixture of **8a** and **9a** followed by purification to deliver **10a** and **11a** (**Scheme 2**). In general, the 4-hydroxy-THIQs intermediates (**4a-d,h-n**, **6a-b**, and the mixture of **8a** and **9a**) were subjected to a reductive dehydroxylation (**Scheme 2**) under conditions that were dictated by those controlling the cyclization step. The reduction could be achieved with $NaBH_4$ as a reducing agent in the presence of TFA where at least one electron-donating group was directly activating the position 4- of the THIQ ring (**6a-b**, **8a** and **9a**). If this was not the case, the $NaBH_4$ conditions proved ineffective and the desired THIQs **5a-d,h-n** were instead accessed via an ionic hydrogenation reaction with Et_3SiH in presence of $BF_3{\cdot}Et_2O$ as a Lewis acid (**Scheme 2**).

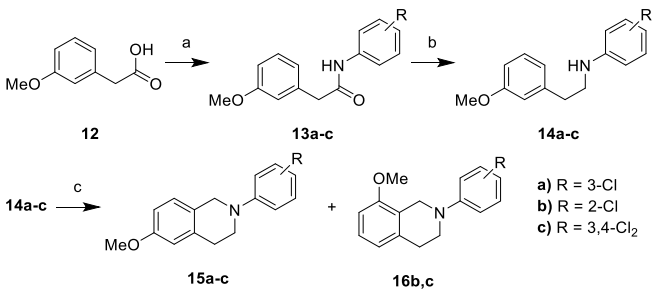
Due to their low nucleophilicity, 2- and 3-chloroaniline failed to deliver the double reductive amination products of **Scheme 1** (data not shown), and instead only yielded monoalkylated anilines. A Pictet-Spengler approach utilising phenylacetic acid starting material was adopted when the Pomeranz-Fritsch-Bobbitt approach proved impractical. In this case, the formation of amides **13a-c** from the commercial acid **12** via the acid chloride (**Scheme 3**) proceeded with decent yields. The resultant amides **13a-c**, were then be reduced with $LiAlH_4$ to the corresponding amines **14a-c** (**Scheme 3**).

Similarly to observations for the cyclization of compounds **3e,g** (**Scheme 2**), both regioisomers **15b,c** and **16b,c** (**Scheme 3**) were obtained in a ca. 10:1 ratio (ratio of isolated yields). Compound **15a** was isolated in only a 23% yield, but its expected regioisomer **16a** was not successfully isolated. This could be attributed to the very small amount formed on the scale at which the reaction was performed (**Scheme 3**). Thus, through the Pictet-Spengler approach, it was possible to obtain compounds **15a-c** that proved inaccessible through the Pomeranz-Fritsch-Bobbitt approach (**Scheme 3**). In addition, the respective regioisomers **16b,c** could be isolated from the same reaction (**Scheme 3**).



Scheme 2. Pomeranz-Fritsch-Bobbitt reaction and reductive dehydroxylation. a) 70% $HClO_4$, rt, 1h, 26-67%; b) Et_3SiH, $BF_3{\cdot}Et_2O$, DCM, reflux, 18h, 11-76%; c) 6M HCl, rt, 1h, 31-82; d) $NaBH_4$, TFA, DCM, rt, 6h, 11-85%.

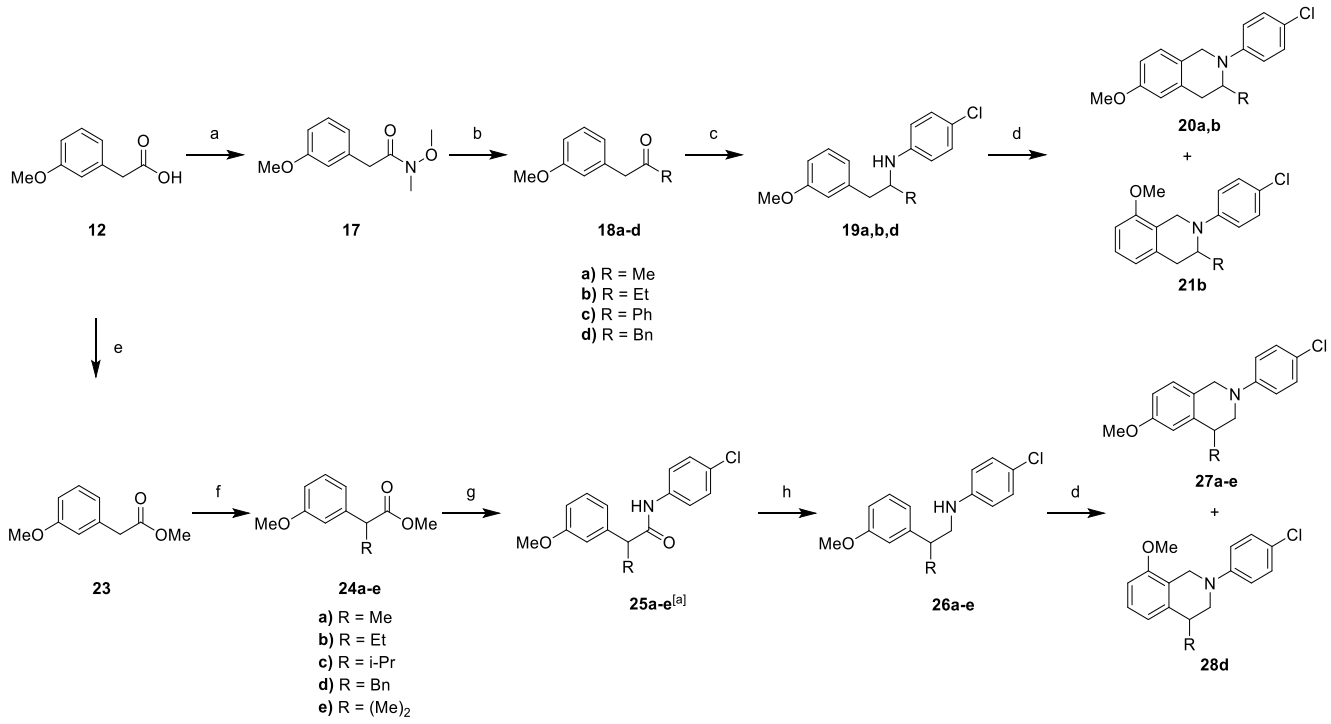
The Pictet-Spengler approach allowed direct access to 3- and 4- substituted THIQs devoid of substitution at the 1- position (**Scheme 4**). The introduction of substituents in position 3- of the final THIQs progressed through a Weinreb ketone synthesis followed by a reductive amination and Pictet-Spengler cyclization. The synthesis of the initial Weinreb amide **17** via coupling with acid chloride progressed with only 48% yield (data not shown), possibly due to the lower nucleophilicity of *N*,*O*-dimethylamine. However, pretreating the amine with PCl_3 to form a more reactive triaminophosphine intermediate that was then coupled directly with the acid **12** afforded the desired Weinreb amide **17** in a 64% yield (**Scheme 4**). Amide **17** was then alkylated with various Grignard reagents to yield, after acidic workup, the desired ketones (**Scheme 4**). Notably, upon treatment of **17** with *i*PrMgBr, a poorly nucleophilic Grignard reagent, none of the desired product could be recovered and only partial *N*-demethoxylation was observed. Ketones**18a-d** (**Scheme 4**) were subjected to reductive amination conditions to give amines **19a,b,d**; however, ketone **18c** proved unreactive under these conditions and no desired product could be isolated. Compounds **19a,b,d** (**Scheme 4**) were subjected to the Pictet-Spengler conditions but only compound **19b** afforded the two regioisomers **20b** and **21b** (**20b**/**21b** 10:1), whereas **19a** yielded only the 6-methoxy-THIQ **20a** with no detectable amount of the respective 8-methoxy derivative observed. In contrast to compounds **19a** and **19b**, the benzyl derivative **19d** proved unreactive in the experimental conditions used and none of the desired THIQs could be obtained (**Scheme 4**).



Scheme 3. Synthesis of THIQs from chloroanilines via Pictet-Spengler cyclization. a) i) $SOCl_2$, DCM, rt, 1h; ii) appropriately substituted aniline, Na_2CO_3, toluene, reflux, 12-16h, 66-80% b) $LiAlH_4$,THF, 80 °C, 4-6h, 74-97% c) paraformaldehyde, PTSA, toluene, reflux, 12-18h 23-57% (**15a-c**) and 4% (**16b,c**).

To obtain 4-substituted THIQs, acid **12** was converted, via classic Fischer esterification, into the respective methyl ester **23** (**Scheme 4**), which was then alkylated (LDA/requisite haloalkanes) to give compounds **24a-e**. Substituted amides **25a-e** (**Scheme 4**) were obtained directly from the corresponding ester by treating 4-chloroaniline first with bis(trimethylaluminum)-1,4-diazabicyclo-[2.2.2]octane adduct (DABAL-Me_3), a non-pyrophoric analogue of trimethylaluminum, followed by the appropriate esters **24a-e**. This reaction progressed cleanly and the amides **25a-e** (**Scheme 4**) were reduced without purification with $LiAlH_4$ to give the desired amines **26a-e**, which in turn were cyclized under Pictet-Spengler conditions to afford the desired 6-methoxy-THIQs **27a-e** in moderate yields (**Scheme 4**). Once more, the respective 8-methoxy regioisomers were relatively inaccessible with only **28d** being delivered in small amounts (**Scheme 4**).

The introduction of a substituent at position 1- of the desired THIQ could be easily achieved via a Bischler-Napieralski cyclization approach. The synthesis proceeded as previously seen for the synthesis of 1- unsubstituted THIQs that were not accessible through the Pomeranz-Fritsch-Bobbitt approach (**Scheme 3**). The synthesis commenced with conversion of the acid **12** into the corresponding amides **13d-f** (**Scheme 5**), which were in turn reduced to the respective amines **14d-f** in the presence of $LiAlH_4$. Amines **14d-f** (**Scheme 5**) were acylated with the appropriate acyl chloride to give the amides **29a-i**. The Bischler-Napieralski conditions traditionally involve secondary amides and yield 1,2-unsaturated THIQs.[18] In comparison, cyclization of the tertiary amides **29a-i** (**Scheme 5**) led to the formation of an iminium ion unstable to aqueous work up. Hence, after Bischler-Napieralski cyclization of amides **29a-i** (**Scheme 5**) with $POCl_3$ in anhydrous toluene, a solvent-switch from toluene to MeOH was performed followed by direct reduction of the product with $NaBH_4$. This eliminated the small excess of $POCl_3$ and allowed direct access to the desired final THIQs **30a-c,e-l** (**Scheme 5**).



Scheme 4. Synthesis of 3- and 4- substituted THIQs via Pictet-Spengler cyclization. a) i) *N*,*O*-dimethylamine, PCl_3, DIPEA, Et_2O, 0 °C, 1h then rt, 12 h; ii) **12**, toluene, 60 °C; b) appropriately substituted Grignard reagent, THF, rt, 1 h; c) 4-chloroaniline, $NaBH(OAc)_3$, DCE, AcOH, rt, 6-12 h; d) paraformaldehyde, PTSA, toluene, reflux, 12-18 h; e) conc. H_2SO_4, MeOH, reflux, 72 h; f) LDA, THF, −78 °C, 1h then appropriately substituted haloalkane, rt, 4-6 h; g) i) 4-chloroaniline, DABAL-Me_3, THF, 40 °C, 1 h; ii) **24a-f**, 12 h, reflux; h) $LiAlH_4$, THF, 80 °C, 6-12 h. [a]Compound **25e** was not purified by flash column chromatography and used as suc

As before (**Scheme 3** and **Scheme 4**), the corresponding 8-methoxy THIQs **31b,c,f,h,i** (**Scheme 5**) were isolable in some cases, albeit in low yield. However, the very sterically hindered **29d** showed very low reactivity under the experimental conditions used and no quantifiable amounts of the desired THIQ product could be identified in the reaction mixture.

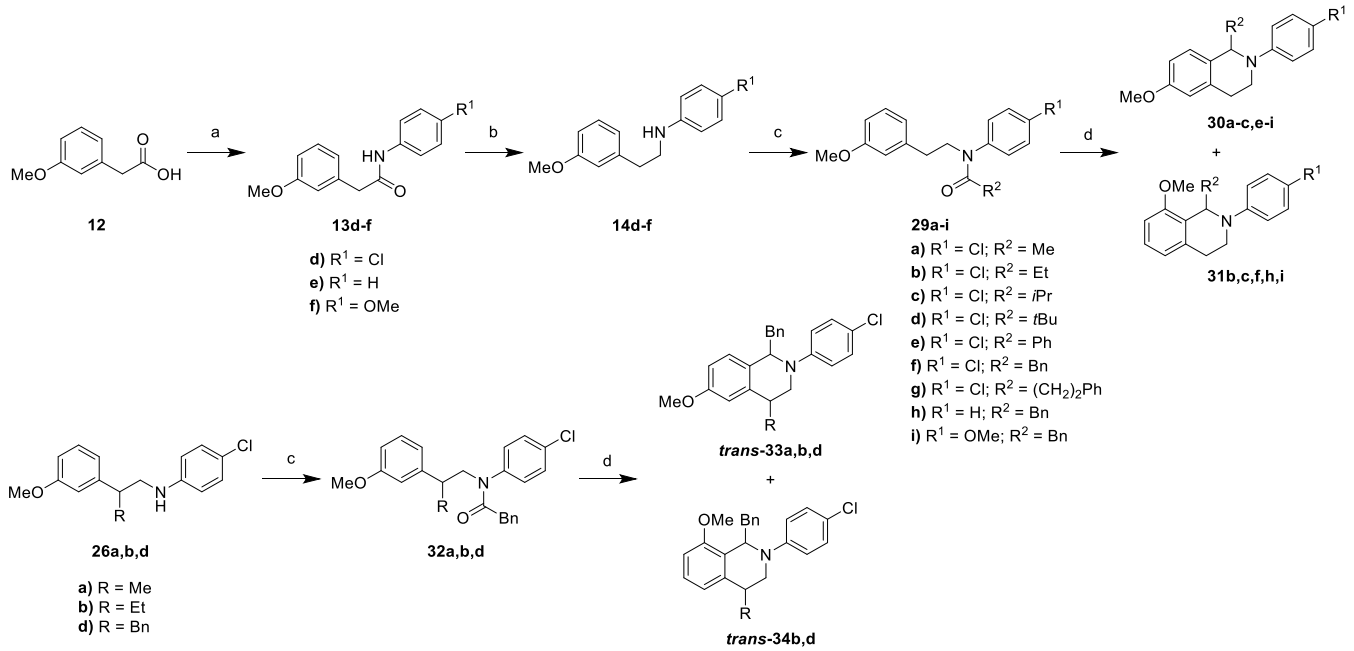
Branched amines **26a,b,d** were cyclized under Pictet-Spengler conditions to afford the 4- mono substituted THIQs **27a-e** and **28d** (**Scheme 4**), while the more linear amines **29a-c,e-i** could be cyclized under Bischler-Napieralski conditions to give the 1- mono substituted THIQs **30a-c,e-i** and **31b,c,f,h,l** (**Scheme 5**). 1,4- Disubstituted THIQs **33a,b,d** (**Scheme 5**) could be obtained by merging the two approaches for the synthesis of 1- and 4- monosubstituted THIQs. The synthesis started with the acylation of **26a,b,d** to give amides **32a,b,d** (**Scheme 5**), followed by the tandem Bischler-Napieralski cyclization and $NaBH_4$ reduction. Once more, small amount of the 8-methoxy regioisomers was formed and compounds **34b,d** could also be successfully isolated (**Scheme 5**).

Lastly, despite the hydroxy- derivatives being directly accessible through the Pomeranz-Fritsch-Bobbitt pathway, from a synthetic point of view, it proved expedient to derive them from their methoxy- counterparts by *O*-demethylation with BBr_3, affording the final compounds as the hydrobromide salts (**Scheme 6**). Naturally, compounds bearing both hydroxyl and methoxy groups, such as **5h** (**Scheme 2**), were accessed by the Pomeranz-Fritsch-Bobbitt approach.

Introduction of substituents in positions 1-, 2- or 3- of the final THIQs generated a chiral centre and led to the formation of a racemic mixture, considering that all the reactions presented in this work are expected to be non-stereoselective. Resolution of the enantiomeric mixture was not considered to be of value at this early stage of the work and thus the compounds were biologically evaluated as their racemates. Consequently, the generation of a second chiral centre during the cyclization of **32a,b,d** (**Scheme 5**) was expected to generate two diastereomeric pairs of enantiomers, 1,4-*cis*- and 1,4-*trans*- derivatives for the 6-methoxy and 8-methoxy regioisomers, **33a,b,d** and **34b,d**, respectively.

The two regioisomers (**33a,b,d** and **34a,b,d**, respectively) were easily separated by flash chromatography, but attempts to elucidate the diastereomeric composition of the two mixtures by ^{1}H-^{1}H NOESY NMR analysis were unsuccessful at this stage. However, the same experiment performed on the hydroxy- derivative **43b** (**Figure 3**), revealed that the compound was diastereomerically pure and that thus only an enantiomeric pair of a *trans*-diastereomer was present.

The protonation on the nitrogen probably increased the rigidity of the system and allowed more marked spatial interactions on the ^{1}H-^{1}H NOESY NMR timescale (**Figure 3**). Primarily, H^6 showed interaction with H^{3a}, which in turn correlated with H^4. However, no direct or extended interaction could be identified between H^5 or H^6 and H^7 or H^8, clearly leading to the interpretation that only enantiomers of the *trans*-diastereoisomers were present. The presence of only two such enantiomers was also confirmed by chiral HPLC and by ^{1}H and ^{1}H-^{13}C HSQC experiments with the chiral shift reagent Europium(III) tris[3-(heptafluoropropyl-hydroxymethylene)-*D*-camphorate] (see Supporting Information for the relevant spectra). Previous reports in the literature illustrated the stereoinduction of substituents in position 3- of the THIQ during the reduction of the 1,2-unsaturated bond.[18] The relative stereochemistry depended also on the reducing agents and the 1,3-*cis*- analogue was obtained using $NaBH_4$ while the 1,3-*trans*- one formed in presence of $LiAlH_4$. Consequently, it is plausible to expect that the same factors would induce the formation of 1,4-*trans* isomers in the experimental conditions described in



Scheme 5. Synthesis of 1- substituted and 1,4- disubstituted THIQs via Bischler-Napieralski cyclization. a) i) $SOCl_2$, DCM, rt, 1h; ii) appropriately substituted aniline, Na_2CO_3, toluene, reflux, 12-16h; b) $LiAlH_4$, THF, 80 °C, 4-6h; c) appropriately substituted acyl chloride, pyridine, DCM, rt, 12-18 h; d) i) $POCl_3$, toluene, reflux, 12-18 h; ii) $NaBH_4$, MeOH, rt, 6 h.

Scheme 5. In fact, due to the conformational constraints induced by the substituent in position 4 in the intermediate iminium ion, the hydrogen on the same carbon, and not the substituent itself, shields the face from which the corresponding nucleophilic attack would yield the cis-1,4 isomer (see page 206 of SI).

Biology.

Of the complete 73 compound library set only a fraction could be evaluated for their potential to inhibit HSD17B1 activity in vitro (**Table 1**). Compounds were thus selected based on substituent variety and compound availability, so that the viability of the THIQ scaffold for HSD17B1 inhibitor design could be assessed. Compounds were screened at an initial concentration of 6.0 µM, with active compounds (>70% inhibition) being re-evaluated at 0.6 µM. Finally, the most promising compound was selected for IC_{50} quantification.

Within the 6-methoxy- series, derivative **5d** that features an apolar electron-withdrawing 4′-chloro substituent showed the highest activity while **5k** that features an electron-donating 4′-methoxy substituent proved least active (**Table 1**). A similar trend could be observed among the 6-hydroxy series with compound **35d** showing 64% inhibition at 6.0 µM. The contribution of the chlorine atom at the 4′- position is also evident from comparison of 6-H, 4'-H THIQ **5a** with the corresponding 4′-chloro derivative **5n**, with a four-fold increase in activity at 6.0 µM being observed (**Table 1**). In addition, mono-substitution at position 4′- appears preferred over the corresponding 2′- and 3′- derivatives (**15b** and **15a** respectively) that showed somewhat lower inhibition. The 3′- and 4′-chloro substituted derivatives within the 6-hydroxy series (**36a** and **35d** respectively, **Table 1**) did not show enzyme inhibition differences at 6.0 µM. This may reflect a predomination of electronic effects on the inhibition activity over the steric effects.

The 6-hydroxy compounds were generally more active than their 6-methoxy analogues, while relocation of the hydroxyl substitution from position 6- to position 5- or 7- only led to a loss of inhibition, as is visible by comparing compounds **35d**, **38b** and **39b** (**Table 1**). Substitution of the 4′-chloro motif by a second hydroxyl group (**35k**) led to loss of inhibition, but shifting the second hydroxyl into position 3′- (**35l**) somewhat increased the activity compared to compound **35d** (**Table 1**). However, introduction of a second and/or a third hydroxyl group(s) to compound **35k**, giving compounds **37a** and **37b** respectively, led to drastic reduction or complete abolition of inhibitory activity (**Table 1**). In addition, these very electron-rich systems showed significant chemical stability issues, being prone to oxidation and would thus have eventually likely presented only a poor hit candidate. A separate observation can be made for compounds bearing a 4-hydroxyl group. While the 4-hydroxyl substituted series in general had only modest activity, as is evident from compounds **4g**-**35d**, **4n**-**5n**, and **6a**-**7a** (**Table 1**), introduction of a lipophilic electron-withdrawing bromine atom on the THIQ had a dramatic, positive, effect on activity. The 7-bromo derivative **8b** had comparable activity to the unsubstituted THIQ **5a**, whereas the 5-bromo compound **9b** showed a four-fold increased activity that was only marginally lower than that of compound **35d** (**Table 1**).

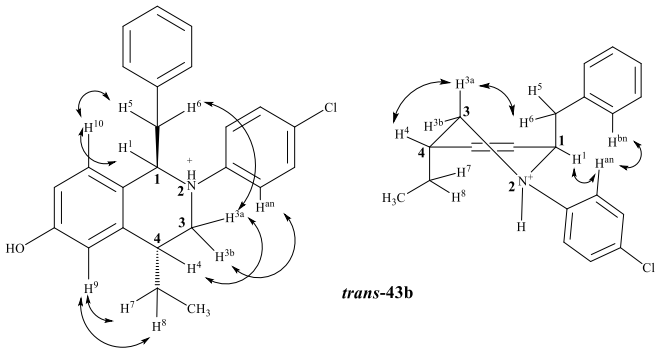
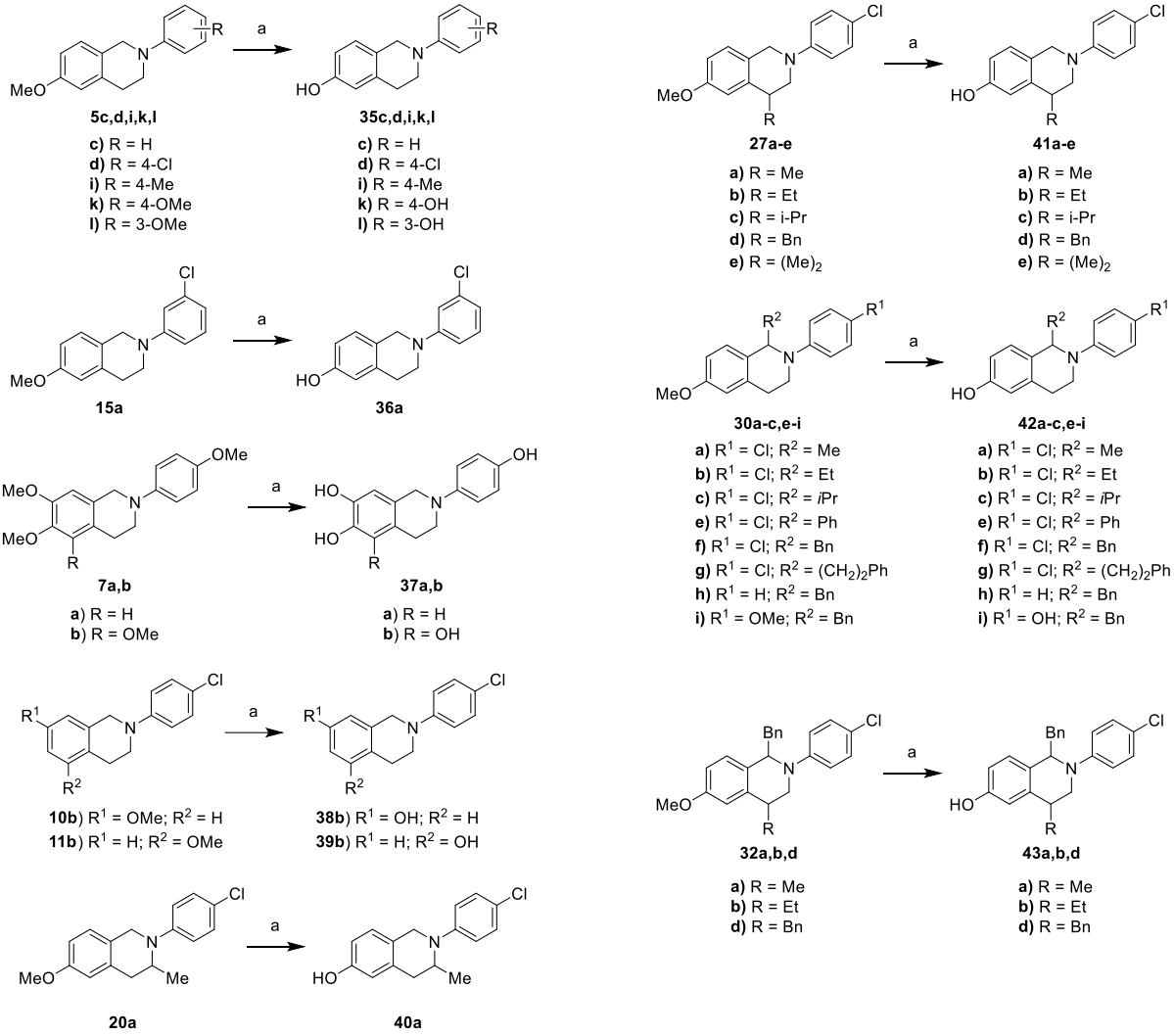


Figure 3. ^{1}H-^{1}H NOESY NMR interactions of compound **trans-43b**. Only the (1*R*,4*R*)-**43b** enantiomer is represented for simplicity. Please refer to Supporting Information for complete spectra.

Although a polar and hydrogen-bond-donor hydroxyl group was not tolerated in position 4-, lipophilic substitutions at the same position showed markedly positive effects that were size dependent (**41a**<**41b**<**41c, Table 1**). However, the 4-benzyl group in compound **41d** appears too large to be accommodated in the lipophilic binding pocket, leading to a lower inhibition value than the 4-*i*Pr derivative **41c** (**Table 1**). The 1,4- disubstituted compound **41e** showed a two-fold greater inhibition at 0.6 µM relative to 4- monosubstituted **41a** (**Table 1**). It may well be that one of the two enantiomers of **41e** is more active than the other but we have not had the opportunity to resolve the racemic mixture and test each enantiomer separately to date. Whereas substituents at position 4- had drastic effects on the inhibitory activity of the compounds, a methyl substituent at position 3- (**40a**) had only a mildly detrimental effect and this may possibly be due to the imposed change in dihedral angle between the tetrahydroisoquinoline and the phenyl rings (**Table 1**). A series of substitutions at position 1- (**42a-c,e**) showed a size-dependent effect on inhibition values, though with lower impact compared to the same substitutions in position 4- (**41a-c**) (**Table 1**). Activity plateaued with the phenyl group (**42e**) and somewhat decreased progressively with the benzyl (**42f**) and phenethyl (**42g**) groups (**Table 1**). Attempts to optimize compound **42f** by either removing the 4′-chloro substituent (**42h**) or replacing it with a 4′-hydroxyl group (**42i**) did not produce very significant changes (**Table 1**). However, the same changes on the 1- unsubstituted THIQ (**35d**) had more marked effects indicating that compound **42f** may bind in a different pose than the more simply substituted **35d** (**Table 1**).

Finally, further efforts to optimize compound **42f** by introducing substituents in position 4- (**43a,b,d**) produced significant effects, which were however less marked than in absence of the 1-benzyl substituent. In fact, the 1-benzyl-4-ethyl- THIQ **43b** was only comparable for activity with **41c** (52.7% and 60.3% at 0.6 µM respectively), despite the large increase in molecular weight **(Table 1).**



Scheme 6. Conversion of methoxy derivatives into the corresponding hydroxy compounds. a) BBr_3, DCM, −79 °C to rt, 2 h or aq. 48% HBr, 120 °C, 3 h.

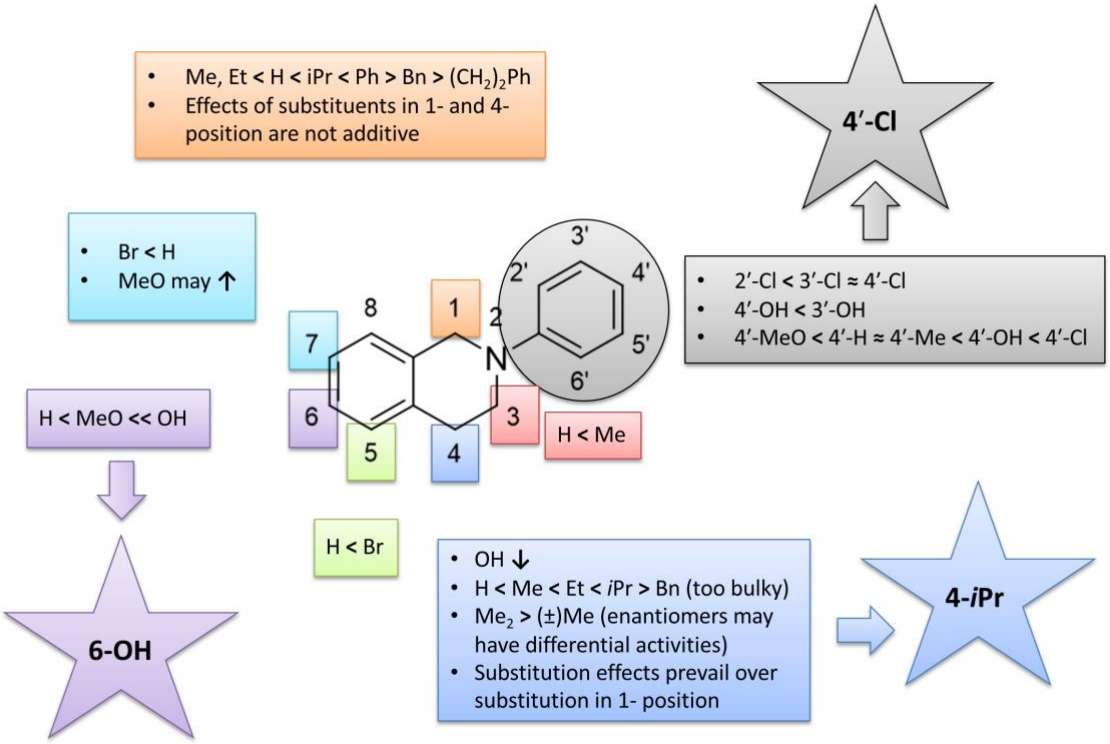
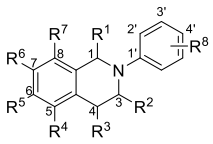


Figure 4. Summary of SAR result

Table 1. In vitro inhibition of HSD17B1 for selected THIQs.[a]



Cmpd.	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	% inh. (6.0 µM)[b]	% inh. (0.6 µM)[b]
4g[c]	H	H	OH	H	OH	H	H	4-Cl	22.3	NT
4n[c]	H	H	OH	H	H	H	H	4-Cl	15.7	NT
5a	H	H	H	H	H	H	H	H	9.3	NT
5c	H	H	H	H	MeO	H	H	H	27.0	NT
5d	H	H	H	H	MeO	H	H	4-Cl	38.0	NT
5h	H	H	H	H	OH	H	H	4-MeO	12.7	NT
5i	H	H	H	H	MeO	H	H	4-Me	27.0	NT
5k	H	H	H	H	MeO	H	H	4-MeO	13.0	NT
5n	H	H	H	H	H	H	H	4-Cl	40.9	NT
6a[c]	H	H	OH	H	MeO	MeO	H	4-MeO	12.6	NT
7a	H	H	H	H	MeO	MeO	H	4-MeO	25.4	NT
8b[c]	H	H	OH	H	H	Br	H	H	12.9	NT
9b[c]	H	H	OH	Br	H	H	H	H	47.1	NT
15a	H	H	H	H	MeO	H	H	3-Cl	33.5	NT
15b	H	H	H	H	MeO	H	H	2-Cl	25.3	NT
35c	H	H	H	H	OH	H	H	H	45.0	NT
Cmpd.	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	% inh. (6.0 µM)[b]	% inh. (0.6 µM)[b]
35d	H	H	H	H	OH	H	H	4-Cl	64.0	NT
35i	H	H	H	H	OH	H	H	4-Me	38.0	NT
35k	H	H	H	H	OH	H	H	4-OH	42.0	NT
35l	H	H	H	H	OH	H	H	3-OH	76.2	28.3
36a	H	H	H	H	OH	H	H	3-Cl	65.5	NT
37a	H	H	H	H	OH	OH	H	4-OH	0.0	NT
37b	H	H	H	OH	OH	OH	H	4-OH	21.1	NT
38b	H	H	H	H	H	OH	H	4-Cl	47.1	NT
39b	H	H	H	OH	H	H	H	4-Cl	45.4	NT
40a[c]	H	Me	H	H	OH	H	H	4-Cl	54.0	NT
41a[c]	H	H	Me	H	OH	H	H	4-Cl	77.2	19.9
41b[c]	H	H	Et	H	OH	H	H	4-Cl	91.5	45.9

41c[c]	H	H	*i*-Pr	H	OH	H	H	4-Cl	100.0	60.3
41d[c]	H	H	Bn	H	OH	H	H	4-Cl	84.3	0.0
41e	H	H	Me_2	H	OH	H	H	4-Cl	80.9	39.6
42a[c]	Me	H	H	H	OH	H	H	4-Cl	44.1	NT
42b[c]	Et	H	H	H	OH	H	H	4-Cl	40.7	NT
42c[c]	*i*-Pr	H	H	H	OH	H	H	4-Cl	73.1	10.8
42e[c]	Ph	H	H	H	OH	H	H	4-Cl	90.1	4.7
42f[c]	Bn	H	H	H	OH	H	H	4-Cl	81.0	0.0
42g[c]	$(CH_2)_2Ph$	H	H	H	OH	H	H	4-Cl	74.8	11.0
42h[c]	Bn	H	H	H	OH	H	H	H	73.7	10.6
42i[c]	Bn	H	H	H	OH	H	H	4-OH	68.8	24.1
43a[c]	Bn	H	Me	H	OH	H	H	4-Cl	69.8	23.5
43b[c]	Bn	H	Et	H	OH	H	H	4-Cl	95.1	52.7
43d[c]	Bn	H	Bn	H	OH	H	H	4-Cl	58.6	NT

[a] Cmpd. = compound; NT = not tested (<70% inhibition at 6.0 µM); [b] Values generated from a single experiment carried out in duplicate; [c] Compound was tested as a racemic mixture.

Compound **41c** (60% inhibition at 0.6 µM) possessed a marginally better enzyme inhibitory profile than **43b** (53% inhibition at 0.6 µM) making it the first choice candidate for an IC_{50} determination In terms of their ClogP parameters **41c** and **43b** exhibited values of 5.3 and 6.4 respectively (ChemDraw, Cambridge Soft) and **41c** was a preference. Compound **41c** showed an IC_{50} = 349.9 ± 34.7 nM (Table 1 and SI), making it an attractive candidate for further optimization. To assess suitability for potential future development and optimisation we also wished to compute physicochemical descriptors as well as predict outline ADME and pharmacokinetic properties, druglike nature and medicinal chemistry friendliness for our two best leads **41c** and **43b**. Thus, they were both evaluated computationally for druglikeness using the Swiss ADME programme.[19] Six physicochemical properties were considered: lipophilicity, size, polarity, solubility, flexibility and saturation. To be considered druglike these six properties of a molecule have to fall entirely within the pink area of the "Bioavailability Radar" plot shown (**Figure 4 (b)**). While this was entirely the case for **41c**, **43b** was borderline less favourable (see SI). Moreover, **41c** has a lower molecular weight, a consensus LogP of 4.11, TPSA 23.47Å and has predictions of moderate solubility and high GI absorption. We thus propose **41c** as the best candidate from this study for further progression. Clearly, (±)-**41c** is a racemate and thus a very important next step would be to resolve the two enantiomers and evaluate their individual biological properties. It may well be that one is more highly favoured as an inhibitor and its IC_{50} could be lower than 349.9nM.

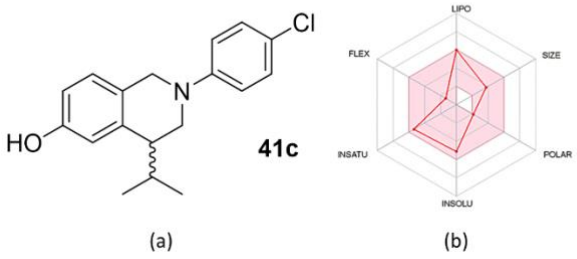
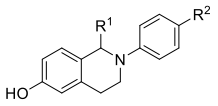


Figure 4. (a) Structure of lead inhibitor (±)-**41c** and (b) its druglike parameters as assessed by the "Bioavailability Radar" of the SwissADME programme.[19]

Three selected compounds, **35d**, **35k** and **42c**, possessing incremental structural changes, were tested in the DiscoverX PathHunter® assay against Estrogen Receptor α (ERα) at a concentration of 100 µM. Interestingly, changing the 4′-hydroxy group (**35k**) into a 4′-chloro (**35d**) drastically decreases the agonist activity at ERα while somewhat

increasing inhibitory activity at HSD17B1 (**Table 2**). Addition of a 1-*i*Pr group to compound **35d** gave **42c**, which showed further reduction in agonist activity at ERα accompanied by good inhibitory activity at ERα and a significant increase in inhibitory activity at HSD17B1 (**Table 2**). Altogether, even though these data cannot be directly correlated to our selected compound **41c**, it is still possible to infer that the core THIQ structure is indeed steroidomimetic and that simple substitution changes will modulate not only HSD17B1 activity but also agonist and antagonist activity at ERα. This gives considerable confidence that later-stage optimization will be able to fine-tune the desired activities.

Table 2. Agonist and antagonist activity of compounds **35d**, **35k** and **42c** at ERα.[a]



35d: R^1 = H; R^2 = Cl
35k: R^1 = H; R^2 = OH
42c: R^1 = *i*Pr; R^2 = Cl

Cmpd.	HSD17B1 (% inhibition) (6.0 μM)	HSD17B1 (% inhibition) (6.0 μM)	ERα Agonist mode (% activity) (100 μM)	ERα Antagonist mode (% inhibition) (100 μM)
35d	64.0	NT	60.7	-53.4[b]
35k	42.0	NT	114.7	-18.1[b]
	73.1	10.8	10.7	86.5

[a] Cmpd. = compound; NT = not tested (<70% inhibition at 6.0 μM); [b] Negative values in antagonist mode describe an agonist.

Conclusions

The literature shows that HSD17B1 is clearly involved in certain types of hormone-dependent cancers, as well as in endometriosis, and that it is an interesting and seemingly druggable target. At present, HSD17B1 inhibitors based on multiple chemical scaffolds, including steroidal, nonsteroidal and natural product templates have been reported, but no compound has yet reached the clinical trial stage. The present work reports exploration of the *N*-phenyl-1,2,3,4-tetrahydroisoquinoline (THIQ) template as a core steroidomimetic structure for the generation of new HSD17B1 inhibitors.

The three complementary synthetic approaches explored allowed generation of a series of fully-decorated THIQ-based inhibitory candidates that could be substituted with a variety of groups in most positions rendering this chosen new scaffold ideal for a structure-activity relationship investigation. A selection of the synthesized compounds was evaluated for in vitro inhibition of HSD17B1. These data allowed us to draw some initial structure-activity relationship (SAR) conclusions (**Figure 4**) and revealed how simple substitutions to the core structure could have important effects on biological activity. Initial results demonstrated how a hydroxyl group in position 6-, a chlorine in position 4′- of the *N*-phenyl group, and lipophilic substitutions in either position 1- or 4- of the THIQ core had the most marked effect. Compounds **35d**, **35k** and **42c** were also tested for agonist and antagonist activity at ERα, showing how also the activity at this receptor can be easily modulated by simple substitutions and further proving the steroidomimetic potential of the THIQ scaffold. Among the synthesised series of compounds, compound **41c** stood out for its relative simplicity, good druglike properties and promising activity (IC_{50} of 349.9 ± 34.7 nM), making it a good starting point for further optimization ideally to the low nM inhibitory level, as already achieved for the steroid-based inhibitor STX1040 and other non-steroidal thiophene and naphthalene based inhibitors and proving the scaffold as a viable alternative to those already reported in the literature.[11g, 12-13, 20]

Experimental Section

Chemistry.

All chemicals were purchased from Aldrich Chemical Co. or Alfa Aesar. Organic solvents of A. R. grade were supplied by Fisher Scientific. Thin-layer chromatography (TLC) was performed on precoated plates (Merck TLC aluminum sheets

silica gel 60 F254). Product(s) and starting material(s) were detected by either TLC and/or LC–MS. Flash column chromatography was performed on RediSep® prepacked columns (normal phase and reversed phase) with an Isco CombiFlash® Rf. NMR (400 MHz or 500 MHz) spectra were recorded with Bruker AMX systems and chemical shifts are reported in parts per million (ppm). HPLC and low-resolution mass spectra analyses were obtained on a Waters Micromass ZQ equipped with a Waters 996 PDA detector using either a Waters Radialpack C_{18} reversed-phase column (8 × 100 mm), or a Symmetry C_{18} reversed-phase column (4.6 × 150 mm) eluting with the solvent system specified at 1.0 mL/min. High-resolution mass spectra (HRMS) were recorded at the Mass Spectrometry Service Centre, University of Bath, on a Bruker microTOF. Meltingpoints were determined using an Optimelt block and are uncorrected.

General method for the double reductive amination reaction: Benzaldehyde (1.0 mL, 10 mmol) and aniline (1.1 mL, 12 mmol) were dissolved in $CHCl_3$ (60 mL) then treated with $NaBH_4(OAc)_3$ (3.3 g, 15 mmol). After stirring the mixture for 1 h at rt, 2,2-dimethoxyacetaldehyde (30 mmol) was introduced followed by $NaBH(OAc)_3$ (3.3 g, 15.0 mmol). After stirring for 8 h at rt the mixture was quenched with a saturated aqueous solution of K_2CO_3. The aqueous layer was extracted with $CHCl_3$ (30 mL). The combined organics were dried with $MgSO_4$, filtered and evaporated to give a pale yellow oil (3.87 g).

***N*-Benzyl-*N*-(2,2-dimethoxyethyl)aniline (3a)**
The crude compound was purified by column chromatography (eluent: from 0% to 30% EtOAc in pet. ether) to give a colorless oil (2.92 g, 99%) which showed as previously reported[17]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.41 (6H, s, OCH_3), 3.58 (2H, d, *J* = 5.1 Hz, NC*H*$_2$CH), 4.63 (1H, t, *J* = 5.1 Hz, CH(OR)$_2$), 4.67 (2H, s, CH_2Ar), 6.70 (1H, tt, *J* = 0.9, 7.4 Hz, ArH), 6.74 (2H, dd, *J* = 0.9, 8.9 Hz, ArH), 7.16 - 7.25 (5H, m, ArH) and 7.27 - 7.34 (2H, m, ArH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 53.9 (*C*H$_2$CH), 54.6 (CH_3), 54.9 (ArCH_2), 103.5 (*C*H(OR)$_2$), 112.3 (ArCH), 116.7 (ArCH), 126.6 (ArCH), 126.8 (ArCH), 128.7 (ArCH), 129.4 (ArCH), 138.9 (Ar*C*CH$_2$) and 148.7 (ArCN) ppm. LC/MS (ES+) t_r = 1.81 min (87%), m/z 226.0 (M^++H); HRMS (ES+) calcd. for $C_{17}H_{22}NO_2$ (M^++H) 272,16451, found 272.1651.

***N*-Benzyl-*N*-(2,2-dimethoxyethyl)-3-methoxyaniline (3b)**
The crude compound was purified by column chromatography (eluent: from 0% to 10% EtOAc in pet. ether) to give a colorless oil (2.21 g, 73%) which showed as previously reported[17]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.40 (6H, s, CH(OC*H*$_3$)$_2$), 3.55 (2H, d, *J* = 5.1 Hz, C*H*$_2$CH), 3.74 (3H, s, ArOC*H*$_3$), 4.62 (1H, t, *J* = 5.1 Hz, CH(OR)$_2$), 4.65 (2H, s, ArCH_2), 6.28 (1H, ddd, *J* = 0.6, 2.5, 8.2 Hz, ArH), 6.30 (1H, t, *J* = 2.5 Hz, ArH), 6.36 (1H, ddd, *J* = 0.6, 2.5, 8.2 Hz, ArH), 7.10 (1H, t, *J* = 8.2 Hz, ArH), 7.19 - 7.23 (3H, m, ArH) and 7.27 - 7.32 (2H, m, ArH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 53.9 (*C*H$_2$CH), 54.7 (CH(O*C*H$_3$)$_2$), 55.0 (ArCH_2), 55.2 (ArOCH_3), 99.0 (ArCH), 101.5 (ArCH), 103.5 (CH(OR)$_2$), 105.5 (ArCH), 126.6 (ArCH), 126.8 (ArCH), 128.7 (ArCH), 130.1 (ArCH), 138.8 (Ar*C*CH$_2$), 150.2 (ArCN) and 160.9 (Ar*C*OCH$_3$) ppm. LC/MS (ES^+) t_r = 2.48 min (96 %), m/z 301.5 (M^+); (RP, Isocratic, 90% MeOH). HRMS (ES+) calcd. for $C_{18}H_{24}NO_3$ (M^++H) 302.1751, found 302.1738.

***N*-(2,2-Dimethoxyethyl)-*N*-(4-methoxybenzyl)aniline (3c)**
The crude compound was purified by column chromatography (from 0% to 10% EtOAc in pet. ether) to give the product as a yellowish oil (2.09 g, 69%) which showed as previously reported[17]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.41 (6H, s, CHOC*H*$_3$), 3.56 (2H, d, *J* = 5.0 Hz, NC*H*$_2$CH), 3.79 (3H, s, ArOCH_3), 4.60 - 4.65 (3H, m, C*H*(OR)$_2$, ArCH_2), 6.61 - 6.73 (1H, m, ArH), 6.76 (2H, d, *J* = 8.3 Hz, ArH), 6.85 (2H, d, *J* = 8.3 Hz, ArH), 7.14 (2H, d, *J* = 8.4 Hz, ArH) and 7.20 (2H, t, *J* = 7.8 Hz, ArH) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 53.7 (N*C*H$_2$CH), 54.3 (ArOCH_3), 54.6 (CH(O*C*H$_3$)$_2$), 55.4 (ArCH2), 103.4 (CH(OR)$_2$), 112.4 (ArCH), 114.1 (ArCH), 116.6 (ArCH), 127.8 (ArCH), 129.3 (ArCH), 130.7 (Ar*C*CH$_2$), 148.7 (ArCN) and 158.6 (Ar*C*OCH$_3$) ppm. LC/MS (ES+) t_r = 2.46 min (70%), m/z 302.2 (M^++H); HRMS (ES+) calcd. for $C_{18}H_{24}NO_3$ (M^++H) 302.1751, found 302.1761.

***N*-(2,2-Dimethoxyethyl)-*N*-(3-methoxybenzyl)aniline (3d)**
The crude product was purified by column chromatography (from 0% to 10% EtOAc in pet. ether 40-60 °C) to give the product as a pale yellow oil (3.56 g, 79 %) which showed as previously reported[17]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.48 (6H, s, CHOC*H*$_3$), 3.65 (2H, d, *J* = 5.1 Hz, NC*H*$_2$CH), 3.84 (3H, s, ArOCH_3), 4.66 - 4.75 (3H, m, ArCH_2, CH(OR)$_2$), 6.67 - 6.92 (6H, m, ArH) and 7.21 - 7.35 (3H, m, ArH) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 53.86 (N*C*H$_2$CH), 54.60 (CH(O*C*H$_3$)$_2$), 54.93 (ArOCH_3), 55.27 (ArCH_2N), 103.38 (CH(OR)$_2$), 112.0 (ArCH), 112.3 (ArCH), 112.4 (ArCH), 116.7 (ArCH), 118.9 (ArCH), 129.3 (ArCH), 129.7 (ArCH), 140.8 (Ar*C*CH$_2$), 148.6 (ArCN) and 160.0 (Ar*C*OCH$_3$) ppm. LC/MS (ES^+) t_r = 2.51 min (98 %), m/z 302.2 (M^++H); (RP, Isocratic, 90% MeOH). HRMS (ES+) calcd. for $C_{18}H_{24}NO_3$ (M^++H) 302.1751, found 302.1739.

***N*-(3-Bromobenzyl)-*N*-(2,2-dimethoxyethyl)aniline (3e)**
The crude compound was purified by column chromatography (eluent: 0% to 10% EtOAc in pet. ether) to give the product as a colourless oil (1.9 g, 54%) which showed as previously reported[17]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.48 (6H, s, CHOC*H*$_3$), 3.65 (2H, d, *J* = 5.1 Hz, NC*H*$_2$CH), 3.84 (3H, s, ArOCH_3), 4.66 - 4.75 (3H, m, ArCH_2, CH(OR)$_2$), 6.67 - 6.92 (6H, m, ArH) and 7.21 - 7.35 (3H, m, ArH) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 53.9 (N*C*H$_2$CH), 54.6 (CH(O*C*H$_3$)$_2$), 54.9 (ArOCH_3), 55.3 (ArCH_2N), 103.4 (CH(OR)$_2$), 112.0 (ArCH), 112.3 (ArCH), 112.4 (ArCH), 116.7 (ArCH), 118.9 (ArCH),

129.3 (ArCH), 129.7 (ArCH), 140.8 (Ar*C*CH_2), 148.6 (ArCN) and 160.0 (ArCOCH_3) ppm. LC/MS (ES^+) t_r = 2.51 min (98 %), m/z 302.2 (M^++H); (RP, Isocratic, 90% MeOH). HRMS (ES+) calcd. for $C_{18}H_{24}NO_3$ (M^++H) 302.1751, found 302.1739.

4-Chloro-*N*-(2,2-dimethoxyethyl)-*N*-(4-methoxybenzyl)aniline (3f)
The crude compound was purified by column chromatography (eluent: from 0% to 20% EtOAc in pet. ether) to give the product as a yellow oil (9.16 g, 91%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.39 (6H, s, CH(OC*H*$_3$)$_2$), 3.52 (2H, d, *J* = 5.1 Hz, CHC*H*$_2$), 3.78 (3H, s, ArOCH_3), 4.55 (1H, t, *J* = 5.1 Hz, CH_2C*H*), 4.56 (2H, s, ArCH_2N), 6.65 (2H, d, *J* = 9.2 Hz, ArH, aniline), 6.84 (2H, d, *J* = 8.7 Hz, ArH, benzyl), 7.09 (2H, d, *J* = 8.7 Hz, ArH, benzyl) and 7.11 (2H, d, *J* = 9.2 Hz, ArH, aniline) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 54.0 (CH*C*H$_2$), 54.5 (ArCH_2), 54.7 (CH(O*C*H$_3$)$_2$), 55.4 (ArOCH_3), 103.3 (CH2*C*H), 113.7 (2 x ArCH, aniline), 114.2 (2 x ArCH, benzyl), 121.5 (ArCCl), 127.8 (ArCH, benzyl), 129.1 (ArCH, aniline), 130.1 (Ar*C*CH2), 147.4 (ArCN) and 158.7 (ArCO) ppm. LC/MS (ES+) t_r = 2.98 min (85 %), m/z 336.1 (M^++H). HRMS (ES+) calcd. for $C_{18}H_{23}{}^{35}ClNO_3$ (M^++H) 336.1361, found 336.1346; calcd. for $C_{18}H_{23}{}^{37}ClNO_3$ (M^++H) 338.1331, found 338.1346.

4-Chloro-*N*-(2,2-dimethoxyethyl)-*N*-(3-methoxybenzyl)aniline (3g)
The crude compound was purified by column chromatography (eluent: from 0% to 20% EtOAc in pet. ether) to give the product as a pale yellow oil (9.08 g, 90%) which showed as previously reported[17]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.40 (6H, s, CH(OC*H*$_3$)$_2$), 3.54 (2H, d, *J* = 5.1 Hz, CHC*H*$_2$), 3.76 (3H, s, ArOCH_3), 4.58 (1H, t, *J* = 5.1 Hz, C*H*CH_2), 4.60 (2H, s, ArCH_2N), 6.63 (2H, d, *J* = 9.2 Hz, ArH, aniline), 6.71 – 6.74 (1H, m, ArH, benzyl), 6.74 – 6.80 (2H, m, ArH, benzyl), 7.10 (2H, d, *J* = 9.2 Hz, ArH, aniline) and 7.22 (1H, t, *J* = 7.9 Hz, ArH, benzyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 54.2 (CH*C*H$_2$), 54.7 (CH(O*C*H$_3$)$_2$), 55.1 (ArCH_2N), 55.3(ArOCH_3), 103.3 (*C*H(OCH$_3$)$_2$), 112.0 (ArCH, benzyl), 112.4 (ArCH, benzyl), 113.6 (ArCH, aniline), 118.8 (ArCH, benzyl), 121.6 (ArCCl), 129.1 (ArCH, aniline), 129.8 (ArCH, benzyl), 140.2 (ArCCH_2), 147.2 (ArCN) and 160.1 (ArCO) ppm. LC/MS (ES^+) t_r = 2.91 min (98 %), m/z 336.0 (M^++H); (RP, Isocratic, 90% MeOH). HRMS (ES^+) calcd. $C_{18}H_{23}{}^{35}ClNO_3$ (M^++H) 336.1361, found 336.1353; calcd. $C_{18}H_{23}{}^{37}ClNO_3$ (M^++H) 338.1331, found 338.1353

4-(((2,2-Dimethoxyethyl)(phenyl)amino)methyl)phenol (3h)
The crude compound was purified by column chromatography (eluent: from 0% to 30% of EtOAc in pet. ether) to give the product as a colourless oil (2.5 g, 90%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.40 (6H, s, CH_3), 3.54 (2H, d, *J* = 5.1 Hz, C*H*$_2$CH), 4.58 (2H, s, ArCH_2), 4.61 (1H, t, *J* = 5.1 Hz, CH(OR)$_2$), 5.01 (1H, bs, OH), 6.70 (1H, t, *J* = 7.2 Hz, ArH), 6.74 (2H, d, *J* = 8.7 Hz, ArH) 6.74 (2H, d, *J* = 8.6 Hz, ArH), 7.06 (2H, d, *J* = 8.6 Hz, ArH) and 7.19 (2H, dd, *J* = 7.2, 8.7 Hz, ArH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 53.6 (*C*H_2CH), 54.3 (ArCH_2), 54.7 (CH_3), 103.5 (CH(OR)$_2$), 112.4 (ArCH), 115.5 (ArCH), 116.7 (ArCH), 128.0 (ArCH), 129.4 (ArCCH_2), 148.7 (ArCN) and 154.5 (ArCOH) ppm. LC/MS (ES^+) t_r = 2.91 min (65 %), m/z 287.5 (M^+); (RP, Isocratic, 80% MeOH). HRMS (ES+) calcd. for $C_{17}H_{22}NO_3$ (M^++H) 288.1600, found 288.1595; calcd. for $C_{17}H_{21}NNaO_3$ (M^++Na) 310.1419, found 310.1421.

4-(((2,2-Dimethoxyethyl)(*p*-tolyl)amino)methyl)phenol (3i)
The crude compound was purified by column chromatography (eluent: from 0% to 30% EtOAc in pet. ether) to give the product as a colourless oil (2.83 g, 94%) which showed as previously reported[17]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.24 (3H, s, ArC*H*$_3$), 3.40 (6H, s, CH(OC*H*$_3$)$_2$), 3.51 (2H, d, *J* = 5.1 Hz, C*H*$_2$CH), 4.54 (2H, s, ArCH_2), 4.59 (1H, t, *J* = 5.1 Hz, CH(OR)$_2$), 5.10 (1H, bs, OH), 6.66 (2H, d, *J* = 8.6 Hz, ArH), 6.74 (2H, d, *J* = 8.7 Hz, ArH), 7.00 (2H, d, *J* = 8.6 Hz, ArH) and 7.06 (2H, d, *J* = 8.7 Hz, ArH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.1 (ArCH_3), 53.7 (*C*H_2CH), 54.4 (ArCH_2), 54.5 (CH(O*C*H$_3$)$_2$), 103.4 (*C*H(OR)$_2$), 112.5 (ArCH), 115.3 (ArCH), 125.7 (Ar*C*CH$_3$), 127.9 (ArCH), 129.7 (ArCH), 130.8 (Ar*C*CH_2), 146.5 (ArCN) and 154.4 (ArCOH) ppm. LC/MS (ES^+) t_r = 1.92 min (>99 %), m/z 301.5 (M^+); (RP, Isocratic, 90% MeOH). HRMS (ES+) calcd. for $C_{18}H_{24}NO_3$ (M^++H) 302.1751, found 302.1757.

4-(((4-Chlorophenyl)(2,2-dimethoxyethyl)amino)methyl)-phenol (3j)
The crude compound was purified by column chromatography (eluent: from 0% to 30% EtOAc in pet. ether) to give the product as a colourless oil (2.12 g, 66%) which showed as previously reported[17]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.39 (6H, s, CH_3), 3.51 (2H, d, *J* = 5.1 Hz, C*H*$_2$CH), 4.54 (2H, s, ArCH_2), 4.56 (1H, t, *J* = 5.1 Hz, CH(OR)$_2$), 5.02 (1H, bs, OH), 6.64 (2H, d, *J* = 9.2 Hz, ArH), 6.76 (2H, d, *J* = 8.6 Hz, ArH), 7.03 (2H, d, *J* = 8.6 Hz, ArH) and 7.10 (2H, d, *J* = 9.1 Hz, ArH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 53.8 (*C*H_2CH), 54.4 (ArCH_2), 54.6 (CH_3), 103.2 (CH(OR)$_2$), 113.6 (ArCH), 115.4 (ArCH), 121.4 (ArCCl), 127.8 (ArCH), 128.9 (ArCH), 129.1 (Ar*C*CH_2), 147.2 (ArCN) and 154.5 (ArCOH) ppm. LC/MS (ES^+) t_r = 4.19 min (74 %), m/z 321.6 (M^+); (RP, Isocratic, 80% MeOH). HRMS (ES+) calcd. for $C_{17}H_{21}ClNO_3$ (M^++H) 322.1210, found 322.1201; calcd. for $C_{17}H_{20}ClNNaO_3$ (M^++Na) 344.1029, found 344.1043.

4-(((2,2-Dimethoxyethyl)(4-methoxyphenyl)amino)methyl)-phenol (3k)
The crude compound was purified by column chromatography (eluent 0% to 40% EtOAc in pet. ether) to give the product as a colourless oil (2.87 g, 90%) which showed as previously reported[17]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.38 (6H, s, CH(OC*H*$_3$)$_2$), 3.46 (2H, d, *J* = 5.1 Hz, C*H*$_2$CH)), 3.74 (3H, s, ArOC*H*$_3$), 4.48 (2H, s, ArCH_2), 4.55 (1H, t, *J* = 5.1 Hz, CH(OR)$_2$), 5.12 (1H, bs, OH), 6.71 (2H, d, *J* = 9.1 Hz, ArH), 6.74 (2H, d, *J* = 8.6 Hz, ArH), 6.79 (2H, d, *J* = 9.1 Hz, ArH) and 7.07 (2H, d, *J* = 8.6 Hz, ArH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 54.4 (*C*H_2CH), 54.5 (CH(O*C*H$_3$)$_2$), 55.3 (ArCH_2), 55.9 (ArOCH_3), 103.6 (CH(OR)$_2$), 114.6 (ArCH), 114.9 (ArCH), 115.4 (ArCH), 128.3 (ArCH), 131.0 (Ar*C*CH_2), 143.5

(ArCN), 151.7 (Ar*C*OCH$_3$) and 154.6 (ArCOH) ppm. LC/MS (ES$^+$) t_r = 1.56 min (97 %), m/z 317.5 (M$^+$); (RP, Isocratic, 90% MeOH). HRMS (ES+) calcd. for $C_{18}H_{24}NO_4$ (M$^+$+H) 318.1700, found 318.1698.

***N*-(2,2-Dimethoxyethyl)-*N*-(4-methoxybenzyl)-4-methylaniline (3l)**

The crude compound was purified by column chromatography (eluent: from 0% to 20% EtOAc in pet. ether) to give the product as a yellow oil (8.6 g, 91%) which showed: ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.23 (3H, s, ArC*H*$_3$), 3.39 (6H, s, CH(OC*H*$_3$)$_2$)), 3.51 (2H, d, *J* = 5.1 Hz, C*H*$_2$CH), 3.78 (3H, s, ArOC*H*$_3$), 4.56 (2H, s, ArC*H*$_2$), 4.58 (1H, t, *J* = 5.1 Hz, C*H*CH$_2$), 6.66 (2H, d, *J* = 8.7 Hz, ArH, aniline), 6.83 (2H, d, *J* = 8.7 Hz, ArH, benzyl), 7.00 (2H, d, *J* = 8.7 Hz, ArH, aniline) and 7.12 (2H, d, *J* = 8.7 Hz, ArH, benzyl) ppm. ^{13}C NMR (126 MHz, CDCl$_3$) δ 20.3 (Ar*C*H$_3$), 53.9 (CH*C*H$_2$), 54.5 (ArCH$_2$), 54.6 (CH(OCH$_3$)$_2$), 55.4 (ArOCH$_3$), 103.5 (*C*HCH$_2$), 112.6 (ArCH, aniline), 114.2 (ArCH, benzyl), 125.9 (Ar*C*CH$_3$), 128.0 (ArCH, benzyl), 130.0 (ArCH, aniline), 131.0 (Ar*C*CH$_2$), 146.7 (ArCN) and 158.6 (ArCO) ppm. LC/MS (ES+) t_r = 2.83 min (92 %), m/z 316.2 (M$^+$+H). HRMS (ES+) calcd. for $C_{19}H_{26}NO_3$ (M$^+$+H) 316.1907, found 316.1916.

***N*-(2,2-Dimethoxyethyl)-4-ethyl-*N*-(4-methoxybenzyl)aniline (3m)**

The crude compound was purified by column chromatography (eluent: from 0% to 10% EtOAc in pet. ether) to give the product as a yellow oil (3.42 g, 52%) which showed: ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.19 (3H, t, *J* = 7.6 Hz, CH$_2$C*H*$_3$), 2.54 (2H, q, *J* = 7.6 Hz, C*H*$_2$CH$_3$), 3.39 (6H, s, CH(OC*H*$_3$)$_2$), 3.52 (2H, d, *J* = 5.1 Hz, CHC*H*$_2$), 3.78 (3H, s, ArOC*H*$_3$), 4.56 (2H, s, ArCH$_2$N), 4.59 (1H, t, *J* = 5.1 Hz, C*H*CH$_2$), 6.68 (2H, d, *J* = 8.7 Hz, ArH, aniline), 6.83 (2H, d, *J* = 8.7 Hz, ArH, benzyl), 7.02 (2H, d, *J* = 8.7 Hz, ArH, aniline) and 7.13 (2H, d, *J* = 8.7 Hz, ArH, benzyl) ppm. ^{13}C NMR (126 MHz, CDCl$_3$) δ 15.9 (CH$_2$*C*H$_3$), 27.8 (*C*H$_2$CH$_3$), 53.9 (CH*C*H$_2$), 54.5 (ArCH$_2$N), 54.6 (CH(O*C*H$_3$)$_2$), 55.4 (ArOCH$_3$), 103.5 (*C*HCH$_2$), 112.5 (ArCH, aniline), 114.0 (ArCH, benzyl), 127.9 (ArCH, benzyl), 128.7 (ArCH, aniline), 131.0 (ArCCH$_2$N), 132.3 (ArCEt), 146.9 (ArCN) and 158.6 (ArCO) ppm. LC/MS (ES$^+$) t_r = 3.42 min (85 %), m/z 330.2 (M$^+$+H); (RP, Isocratic, 90% MeOH). HRMS (ES$^+$) calcd. $C_{20}H_{28}NO_3$ (M$^+$+H) 330.2064, found 330.2053.

***N*-(2,2-Dimethoxyethyl)-4-methoxy-*N*-(4-methoxybenzyl)-aniline (3n)**

The crude compound was purified by column chromatography (eluent: from 0% to 20% EtOAc in pet. ether) to give the product as a yellow oil (9.65 g, 97%) which showed: ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.38 (6H, s, CH(OC*H*$_3$)$_2$)), 3.47 (2H, d, *J* = 5.1 Hz, C*H*$_2$CH), 3.74 (3H, s, ArOCH$_3$), 3.78 (3H, s, ArOCH$_3$), 4.51 (2H, s, ArC*H*$_2$), 4.55 (1H, t, *J* = 5.1 Hz, C*H*CH$_2$), 6.72 (2H, d, *J* = 9.2 Hz, ArH, aniline), 6.79 (2H, d, *J* = 9.2 Hz, ArH, aniline), 6.83 (2H, d, *J* = 8.7 Hz, ArH, benzyl) and 7.13 (2H, d, *J* = 8.7 Hz, ArH, benzyl) ppm. ^{13}C NMR (126 MHz, CDCl$_3$) δ 54.4 (CH*C*H$_2$), 54.5 (CH(O*C*H$_3$)$_2$)), 55.2 (ArCH$_2$), 55.4 (ArOCH$_3$), 55.9 (ArOCH$_3$), 103.6 (*C*HCH$_2$), 114.0 (ArCH, benzyl), 114.5 (ArCH, aniline), 114.9 (ArCH, aniline), 128.1 (ArCH, benzyl), 131.1 (Ar*C*CH$_2$), 143.5 (ArCN), 151.7 (ArCO, aniline) and 158.6 (ArCO, benzyl) ppm. LC/MS (ES+) t_r = 1.99 min (92 %), m/z 332.2 (M$^+$+H). HRMS (ES+) calcd. for $C_{19}H_{26}NO_4$ (M$^+$+H) 332.1856, found 332.1859.

***N*-(2,2-Dimethoxyethyl)-3-methoxy-*N*-(4-methoxybenzyl)-aniline (3o)**

As described in the general method A except that after stirring for 12 h at rt the mixture was concentrated *in vacuo* into a slurry and stirred for further 6 h. The crude compound was purified by column chromatography (eluent: from 0% to 10% EtOAc in pet. ether) to give the product as an orange oil (5.93 g, 89%) which showed: ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.39 (6H, s, CH(OC*H*$_3$)$_2$), 3.52 (2H, d, *J* = 5.1 Hz, CHC*H*$_2$), 3.74 (3H, s, OCH$_3$, benzyl), 3.78 (3H, s, OCH$_3$, aniline), 4.58 (2H, s, ArCH$_2$N), 4.60 (1H, t, *J* = 5.1 Hz, C*H*CH$_2$), 6.27 (1H, ddd, *J* = 0.9, 2.5, 8.2 Hz, ArH, aniline), 6.30 (1H, t, *J* = 2.5 Hz, ArH, aniline), 6.36 (1H, ddd, *J* = 0.9, 2.5, 8.2 Hz, ArH aniline), 6.83 (2H, d, *J* = 8.9 Hz, ArH, benzyl), 7.09 (1H, t, *J* = 8.2 Hz, ArH, aniline) and 7.11 (2H, d, *J* = 8.9 Hz, ArH, benzyl) ppm. ^{13}C NMR (126 MHz, CDCl$_3$) δ 53.8 (CH*C*H$_2$), 54.4 (ArCH$_2$N), 54.7 (CH(O*C*H$_3$)$_2$), 55.2 (ArOCH$_3$, benzyl), 55.4 (ArOCH$_3$, aniline), 99.1 (ArCH, aniline), 101.5 (ArCH, aniline), 103.5 (*C*H(OCH$_3$)$_2$), 105.6 (ArCH, aniline), 114.1 (ArCH, benzyl), 127.8 (ArCH, benzyl), 130.0 (ArCH, aniline), 130.7 (Ar*C*CH$_2$), 150.2 (ArCN), 158.6 (ArCO, aniline) and 160.9 (ArCO, benzyl) ppm. LC/MS (ES$^+$) t_r = 2.30 min (96 %), m/z 332.1 (M$^+$+H); (RP, Isocratic, 90% MeOH). HRMS (ES$^+$) calcd. $C_{19}H_{26}NO_4$ (M$^+$+H) 332.1856, found 332.1840.

***N*-(2,2-Dimethoxyethyl)-2-methoxy-*N*-(4-methoxybenzyl)-aniline (3p)**

As described in the general method except that after stirring for 12 h at rt the mixture was concentrated *in vacuo* into a slurry and stirred for further 6 h. The crude compound was purified by column chromatography (eluent: from 0% to 10% EtOAc in pet. ether) to give the product as a yellow oil (5.34 g, 81%) which showed: ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.25 (6H, s, CH(OC*H*$_3$)$_2$), 3.26 (2H, d, *J* = 5.2 Hz, CHC*H*$_2$), 3.77 (3H, s, OCH$_3$, benzyl), 3.88 (3H, s, OCH$_3$, aniline), 4.33 (2H, s, ArCH$_2$N), 4.44 (1H, t, *J* = 5.2 Hz, C*H*CH$_2$), 6.80 (2H, d, *J* = 8.8 Hz, ArH, benzyl), 6.83 (1H, dd, *J* = 1.6, 8.0 Hz, ArH, aniline), 6.87 (1H, dd, *J* = 1.4, 7.9 Hz, ArH, aniline), 6.91 – 6.96 (2H, m, ArH, aniline) and 7.21 (2H, d, *J* = 8.8 Hz, ArH, benzyl) ppm. ^{13}C NMR (126 MHz, CDCl$_3$) δ 53.2 (CH*C*H$_2$), 53.7 (CH(O*C*H$_3$)$_2$), 55.4 (ArOCH$_3$, aniline), 55.7 (ArOCH$_3$, benzyl), 56.9 (ArCH$_2$N), 103.8 (*C*H(OCH$_3$)$_2$), 112.2 (ArCH, aniline), 113.6 (ArCH, benzyl), 120.9 (ArCH, aniline), 122.1 (ArCH, aniline), 122.6 (ArCH, aniline), 129.7 (ArCH, benzyl), 131.4 (ArCCH$_2$), 140.0 (ArCN), 153.4 (ArCO, benzyl) and 158.6 (ArCO, aniline) ppm. LC/MS (ES$^+$) t_r = 1.87 min (99 %), m/z 332.1 (M$^+$+H); (RP, Isocratic, 90% MeOH). HRMS (ES$^+$) calcd. $C_{19}H_{26}NO_4$ (M$^+$+H) 332.1856, found 332.1863.

***N*-(3,4-Dimethoxybenzyl)-*N*-(2,2-dimethoxyethyl)-4-methoxy-aniline (3q)**
The crude compound was purified by column chromatography (eluent: from 0% to 40% EtOAc in pet. ether) to give the product as an orange oil (6.58 g, 91%) which showed as previously reported[17]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.37 (6H, s), 3.45 (2H, t, *J* = 4.7 Hz), 3.73 (3H, s), 3.81 (3H, s), 3.84 (3H, s), 4.48 (2H, s), 4.56 (1H, bs) and 6.69 – 6.82 (7H, m) ppm. HRMS (ES^+) calcd. $C_{20}H_{28}NO_5$ (M^++H) 362.1962, found 362.1976.

***N*-(2,2-Dimethoxyethyl)-4-methoxy-*N*-(3,4,5-trimethoxyben-zyl)aniline (3r)**
The crude compound was purified by column chromatography (eluent: from 0% to 50% EtOAc in pet. ether) to give the product as an orange oil (7.71 g, 98%) which showed as previously reported[17]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.37 (6H, s), 3.47 (2H, d, *J* = 5.1 Hz), 3.74 (3H, s), 3.78 (6H, s), 3.81 (3H, s), 4.47 (2H, s), 4.56 (1H, t, *J* = 5.1 Hz), 6.46 (2H, s), 6.72 (2H, d, *J* = 9.2 Hz) and 6.79 (2H, d, *J* = 9.2 Hz) ppm. HRMS (ES^+) calcd. $C_{21}H_{30}NO_6$ (M^++H) 392.2068, found 392.2081.

4-Chloro-*N*-(2,2-dimethoxyethyl)-*N*-benzyl-aniline (3s)
The crude compound was purified by column chromatography (eluent: from 0% to 20% EtOAc in pet. ether) to give the product as a colourless oil (3.74 g, 82%) which solidified upon standing and showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.40 (6H, s, $CH(OC\mathit{H}_3)_2$), 3.55 (2H, d, *J* = 5.1 Hz, $CHC\mathit{H}_2$), 4.58 (1H, t, *J* = 5.1 Hz, $CHC\mathit{H}_2$), 4.63 (2H, s, $ArCH_2N$), 6.64 (2H, d, *J* = 9.2 Hz, ArH, aniline), 7.11 (2H, d, *J* = 9.2 Hz, ArH, aniline), 7.17 (2H, d, *J* = 7.0 Hz, ArH, benzyl), 7.23 (1H, t, *J* = 7.3 Hz, ArH, benzyl) and 7.30 (1H, t, *J* = 7.4 Hz, ArH, benzyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 54.2 ($CH\mathit{C}H_2$), 54.7 ($CH(OCH_3)_2$), 55.1 ($ArCH_2N$), 103.3 ($\mathit{C}HCH_2$), 113.6 (ArCH, aniline), 121.5 (ArCCl), 126.5 (ArCH, benzyl), 127.0 (ArCH, benzyl), 128.8 (ArCH, benzyl), 129.1 (ArCH, aniline), 138.3 ($Ar\mathit{C}CH_2$) and 147.3 (ArCN) ppm. LC/MS (ES^+) t_r = 3.08 min (96 %), m/z 305.9 (M^++H); (RP, Isocratic, 90% MeOH). HRMS (ES^+) calcd. $C_{17}H_{21}{}^{35}ClNO_2$ (M^++H) 306.1255, found 306.1244; calcd. $C_{17}H_{21}{}^{37}ClNO_2$ (M^++H) 308.1226, found 308.1244. Mp 61-63 °C (pet. ether).

General method for the Pomeranz-Fritsch-Bobbit cyclisation with $HClO_4$: Compound **3a** (3.0 g, 11.1 mmol) was dissolved in 70% $HClO_4$ (33 mL) and stirred for 1 h at rt. The mixture was then diluted with water (30 mL) and basified with Na_2CO_3. The aqueous layer was then extracted with EtOAc (3 x 30 mL). The combined organics were dried with $MgSO_4$, filtered and evaporated to give a brown foam (2.97 g).

2-Phenyl-1,2,3,4-tetrahydroisoquinolin-4-ol (4a)
A sample of crude compound was purified by column chromatography (eluent: from 0% to 10% EtOAc in pet. ether) to give a yellow oil which showed as previously reported[17]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.65 (1H, bs, OH), 3.39 (1H, dd, *J* = 2.6, 12.6 Hz, H_3-THIQ), 3.86 (1H, ddd, *J* = 1.1, 3.8, 12.6 Hz, H_3-THIQ), 4.20 (1H, d, *J* = 15.4 Hz, H_1-THIQ), 4.49 (1H, d, *J* = 15.4 Hz, H_1-THIQ), 4.79 (1H, bs, H_4-THIQ), 6.94 (1H, tt, *J* = 1.1, 7.4 Hz, ArH, phenyl), 7.09 (2H, dd, *J* = 1.0, 8.8 Hz, ArH, phenyl), 7.17 – 7.23 (1H, m), 7.29 – 7.32 (2H, m, H_6,H_7-THIQ), 7.34 (2H, dd, *J* = 7.3, 8.8 Hz, ArH, phenyl) and 7.47 – 7.51 (1H, m) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 51.4 (C_1-THIQ), 55.6 (C_3-THIQ), 67.3 (C_4-THIQ), 116.6 (ArCH, phenyl), 120.2 (ArCH, phenyl), 126.5, 127.2, 128.2, 129.3, 129.4 (ArCH, phenyl), 136.7, 134.3 and 151.1 (ArCN) ppm. LC/MS (ES^+) t_r = 1.75 min (66 %), m/z 226.0 (M^++H); (RP, Isocratic, 90% MeOH). HRMS (ES^+) calcd. for $C_{15}H_{16}NO$ (M^++H) 226.1226, found 226.1234.

2-(3-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-4-ol (4b)
The crude compound was obtained as a yellow oil (1.73 g) which showed as previously reported[17]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (1H, bs), 3.40 (1H, dd, *J* = 2.7, 12.6 Hz), 3.83 (3H, s), 3.85 (1H, ddd, *J* = 0.7, 3.9, 12.6 Hz), 4.21 (1H, d, *J* = 15.5 Hz), 4.50 (1H, d, *J* = 15.5 Hz), 4.79 (1H, s), 6.47 (1H, dd, *J* = 2.3, 8.2 Hz), 6.61 (1H, t, *J* = 2.3 Hz), 6.69 (1H, dd, *J* = 2.3, 8.2 Hz), 7.17 - 7.20 (1H, m), 7.23 (1H, t, *J* = 8.2 Hz), 7.28 - 7.32 (2H, m) and 7.45 - 7.53 (1H, m) ppm. LC/MS (ES^+) t_r = 1.78 min (87 %), m/z 256.1 (M^++H); (RP, Isocratic, 90% MeOH).

6-Methoxy-2-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ol (4c)
A sample of crude compound was purified by column chromatography (eluent: from 0% to 30% EtOAc in pet. ether) to give a yellow oil which showed as previously reported[17]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.54 (1H, bs, OH), 3.37 (1H, dd, *J* = 2.6, 12.6 Hz, H_3-THIQ), 3.83 (3H, s, $ArOCH_3$), 3.84 (4H, ddd, *J* = 1.1, 3.8, 12.6 Hz, H_3-THIQ), 4.14 (1H, d, *J* = 14.9 Hz, H_1-THIQ), 4.43 (1H, d, *J* = 14.9 Hz, H_1-THIQ), 4.74 (1H, bs, H_4-THIQ), 6.88 (1H, dd, *J* = 2.7, 8.4 Hz, H_7-THIQ), 6.91 (1H, tt, *J* = 0.8, 7.4 Hz, ArH, phenyl), 7.01 (1H, d, *J* = 2.7 Hz, H_5-THIQ), 7.07 (2H, dd, *J* = 0.8, 8.7 Hz, ArH, phenyl), 7.10 (1H, d, *J* = 8.4 Hz, H_8-THIQ) and 7.32 (2H, dd, *J* = 7.3, 8.7 Hz, ArH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 50.9 (C_1-THIQ), 55.5 ($ArOCH_3$), 55.5 (C_3-THIQ), 67.6 (C_4-THIQ), 113.1 (C_5-THIQ), 115.3 (C_7-THIQ), 116.6 (ArCH, phenyl), 120.2 (ArCH, phenyl), 126.4 ($C_1\mathit{C}C_8$-THIQ), 127.6 (C_8-THIQ), 129.4 (ArCH, phenyl), 137.8 ($C_4\mathit{C}C_5$-THIQ), 151.2 (ArCN) and 158.7 (C_6-THIQ) ppm. LC/MS (ES+) t_r = 1.77 min (56%), m/z 255.9 (M^++H). HRMS (ES+) calcd. for $C_{16}H_{18}NO_2$ (M^++H) 256.1332, found 256.1326.

2-(4-Chlorophenyl)-6-methoxy-1,2,3,4-tetrahydroisoquinolin-4-ol (4d)
A sample of crude compound was purified by column chromatography (eluent: from 0% to 30% EtOAc in pet. ether) to give a yellow oil which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.45 (1H, bs, OH), 3.36 (1H, dd, *J* = 2.7, 12.6 Hz, H_3-THIQ), 3.77 (1H, ddd, *J* = 0.9, 3.9, 12.6 Hz, H_3-THIQ), 3.83 (3H, s, $ArOCH_3$), 4.11 (1H, d, *J* = 14.8 Hz, H_1-THIQ), 4.38 (1H, d, *J*

= 14.8 Hz, H_1-THIQ), 4.74 (1H, bs, H_4-THIQ), 6.88 (1H, dd, *J* = 2.7, 8.5 Hz, H_7-THIQ), 6.97 (2H, d, *J* = 9.0 Hz, ArH, phenyl), 7.00 (1H, d, *J* = 2.6 Hz, , H_5-THIQ), 7.09 (1H, d, *J* = 8.5 Hz, H_8-THIQ) and 7.25 (2H, d, *J* = 9.0 Hz, ArH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 50.8 (C_1-THIQ), 55.5 (C_3-THIQ), 55.5 ($ArOCH_3$), 67.5 (C_4-THIQ), 113.15 (C_5-THIQ), 115.45 (C_7-THIQ), 117.7 (ArCH, phenyl), 125.0 (ArCCl), 126.0 (C_1CC_8), 127.65 (C_8-THIQ), 129.2 (ArCH, phenyl), 137.6 (C_4CC_5), 149.8 (ArCN) and 158.85 (C_6-THIQ) ppm. LC/MS (ES^+) t_r = 2.08 min (58 %), m/z 290.1 (M^++H); (RP, Isocratic, 90% MeOH). HRMS (ES^+) calcd. for $C_{16}H_{15}NO_2{}^{35}Cl$ (M^++H) 288.0786, found 288.0776. calcd. for $C_{16}H_{15}NO_2{}^{37}Cl$ (M^++H) 290.0756, found 290.0769.

2-Phenyl-1,2,3,4-tetrahydroisoquinoline-4,6-diol (4e)
The crude compound was obtained as a brown-yellow solid (2.15 g) which showed: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.42 (1H, ddd, *J* = 0.6, 2.9, 12.7 Hz), 3.85 (1H, ddd, *J* = 1.0, 4.0, 12.7 Hz), 4.17 (1H, d, *J* = 14.3 Hz), 4.46 (1H, d, *J* = 14.2 Hz), 4.76 (1H, s), 6.84 (1H, dd, *J* = 2.7, 8.4 Hz), 6.92 - 7.05 (2H, m), 7.08 - 7.13 (3H, m) and 7.31 - 7.39 (3H, m) ppm. LC/MS (ES^+) t_r = 1.22 min (81 %), m/z 242.1 (M^++H); (RP, Isocratic, 90% MeOH).

2-*p*-Tolyl-1,2,3,4-tetrahydroisoquinoline-4,6-diol (4f)
The crude compound was obtained as a brown-yellow solid (2.05 g) which showed as previously reported[17]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.31 (1H, dd, *J* = 2.5, 12.2 Hz), 3.76 (1H, dd, *J* = 3.5, 12.2 Hz), 4.07 (1H, d, *J* = 14.9 Hz), 4.36 (1H, d, *J* = 14.9 Hz), 4.69 (1H, s), 6.64 (1H, d, *J* = 8.7 Hz), 6.71 - 6.83 (2H, m) and 6.89 - 7.17 (4H, m) ppm. LC/MS (ES^+) t_r = 1.52 min (70 %), m/z 256.1 (M^++H); (RP, Isocratic, 90% MeOH).

2-(4-Chlorophenyl)-1,2,3,4-tetrahydroisoquinoline-4,6-diol (4g)
The crude compound was purified by column chromatography (eluent: 10% MeOH in DCM) to give a yellow-brown solid (1.88g, 95%) which showed as previously reported[17]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.63 (1H, bs, C_4OH), 3.37 (1H, dd, *J* = 2.2, 12.6 Hz, H_3-THIQ), 3.76 (1H, dd, *J* = 3.6, 12.6 Hz, H_3-THIQ), 4.11 (1H, d, *J* = 14.8 Hz, H_1-THIQ), 4.38 (1H, d, *J* = 14.8 Hz, H_1-THIQ), 4.72 (1H, s, H_4-THIQ), 5.30 (1H, bs, C_6OH), 6.81 (1H, dd, *J* = 2.3, 8.3 Hz, H_7-THIQ), 6.96 (1H, d, *J* = 2.2 Hz, H_5-THIQ), 6.99 (2H, d, *J* = 8.7 Hz, 2 x ArCH, phenyl), 7.05 (1H, d, *J* = 8.3 Hz, H_7-THIQ) and 7.27 (2H, d, *J* = 8.7 Hz, 2 x ArCH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 50.8 (C_1-THIQ), 55.3 (C_3-THIQ), 67.1 (C_4-THIQ), 115.1 (C_5-THIQ), 115.9 (C_7-THIQ), 117.6 (2 x ArCH, phenyl), 125.0 (ArCCl), 125.9 (C_1CC_8-THIQ), 127.7 (C_8-THIQ), 129.1 (2 x ArCH, phenyl), 137.6 (C_4CC_5-THIQ), 149.6 (ArCN) and 154.6 (C_6-THIQ) ppm. LC/MS (ES^+) t_r = 1.65 min (72 %), m/z 276.1 (M^++H); (RP, Isocratic, 90% MeOH). HRMS (ES^-) calcd. for $C_{15}H_{13}ClNO_2$ (M^--H) 274.0640, found 274.0629. Mp 168-171 °C.

2-(4-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-4,6-diol (4h)
The crude compound was obtained as a brown-yellow solid (2.17 g) which showed as previously reported[17]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.26 (1H, dd, *J* = 2.5, 12.4 Hz), 3.62 (1H, ddd, *J* = 1.1, 3.7, 12.2 Hz), 3.78 (3H, s), 4.00 (1H, d, *J* = 14.6 Hz), 4.25 (1H, d, *J* = 14.6 Hz), 4.66 (1H, t, *J* = 3.0 Hz), 6.77 (1H, dd, *J* = 2.7, 8.3 Hz), 6.87 (2H, d, *J* = 9.0 Hz), 6.90 (1H, d, *J* = 2.7 Hz), 6.99 (1H, d, *J* = 8.3 Hz) and 7.02 (2H, d, *J* = 9.0 Hz) ppm. LC/MS (ES^+) t_r = 1.35 min (98 %), m/z 271.8 (M^++H); (RP, Isocratic, 90% MeOH).

6-Methoxy-2-(*p*-tolyl)-1,2,3,4-tetrahydroisoquinolin-4-ol (4i)
A sample of crude compound was purified by column chromatography (eluent: from 0% to 30% EtOAc in pet. ether) to give a yellow oil which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.30 (3H, s, $ArCH_3$), 2.64 (1H, bs, OH), 3.31 (1H, dd, = 2.6, 12.5 Hz, H_3-THIQ), 3.77 (1H, ddd, *J* = 1.1, 3.8, 12.5 Hz, H_3-THIQ), 3.83 (3H, s, $ArOCH_3$), 4.08 (1H, d, *J* = 14.9 Hz, H_1-THIQ), 4.37 (1H, d, *J* = 14.8 Hz, H_1-THIQ), 4.72 (1H, bs, H_4-THIQ), 6.87 (1H, dd, *J* = 2.7, 8.5 Hz, H_7-THIQ), 6.98 (2H, d, *J* = 8.6 Hz, ArH, phenyl), 7.00 (1H, d, *J* = 2.7 Hz, H_5-THIQ), 7.09 (1H, d, *J* = 8.5 Hz, H_8-THIQ) and 7.13 (2H, d, *J* = 8.6 Hz, ArH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.6 ($ArCH_3$), 51.6 (C_1-THIQ), 55.5 ($ArOCH_3$), 56.2 (C_3-THIQ), 67.6 (C_4-THIQ), 113.1 (C_5-THIQ), 115.3 (C_7-THIQ), 117.1 (ArCH, phenyl), 126.6 (C_1CC_8), 127.6 (C_8-THIQ), 129.9 (ArCH, Ar*C*CH_3, phenyl), 137.9 (C_4CC_5), 149.1 (ArCN) and 158.7 (C_6-THIQ) ppm. LC/MS (ES^+) t_r = 1.82 min (70 %), m/z 270.2 (M^++H); (RP, Isocratic, 90% MeOH).

6-Methoxy-2-(4-ethylphenyl)-1,2,3,4-tetrahydroisoquinolin-4-ol (4j)
The crude compound was purified by column chromatography (eluent: from 0% to 20% EtOAc in pet. ether) to give the product as an orange wax (900 mg, 31%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (1H, t, *J* = 7.6 Hz, CH_2CH_3), 2.56 (1H, d, *J* = 10.8 Hz, OH), 2.61 (1H, q, *J* = 7.6 Hz, CH_2CH_3), 3.32 (1H, dd, *J* = 2.5, 12.5 Hz, H_3-THIQ), 3.81 (1H, ddd, *J* = 1.0, 3.7, 12.5 Hz, H_3-THIQ), 3.83 (1H, s, OCH_3), 4.09 (1H, d, *J* = 14.8 Hz, H_1-THIQ), 4.40 (1H, d, *J* = 14.8 Hz, H_1-THIQ), 4.73 (1H, dt, *J* = 3.1, 10.8 Hz, H_4-THIQ), 6.87 (1H, dd, *J* = 2.7, 8.5 Hz, H_7-THIQ), 7.00 (1H, d, *J* = 2.4 Hz, H_5-THIQ), 7.02 (1H, d, *J* = 8.8 Hz), 7.10 (1H, d, *J* = 8.5 Hz, H_8-THIQ) and 7.16 (1H, d, *J* = 8.6 Hz) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.8 (CH_2CH_3), 28.0 (CH_2CH_3), 51.3 (C_1-THIQ), 55.4 (OCH_3), 55.9 (C_3-THIQ), 67.5 (C_4-THIQ), 113.0 (C_5-THIQ), 115.1 (C_7-THIQ), 116.9 (ArCH, phenyl), 126.4 (C_1CC_8-THIQ), 127.5 (C_8-THIQ), 128.6 (ArCH, phenyl), 136.3 (ArCEt), 137.7 (C_4CC_6-THIQ), 149.1 (ArCN) and 158.5 (C_6-THIQ) ppm. LC/MS (ES^+) t_r = 2.19 min (48 %), m/z 284.2 (M^++H); (RP, Isocratic, 90% MeOH). HRMS (ES^+) calcd. $C_{18}H_{22}NO_2$ (M^++H) 284.1645, found 284.1636.

6-Methoxy-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-4-ol (4k)
A sample of crude compound was purified by column chromatography (eluent: from 0% to 30% EtOAc in pet. ether) to give a yellow oil which showed: 1H NMR (400 MHz, $CDCl_3$) δ 3.28 (1H, dd, *J* = 2.6, 12.2 Hz, H_3-THIQ), 3.75 (1H, dd, *J* = 4.5, 12.2 Hz), 3.79 (3H, s, OMe), 3.83 (3H, s, OMe), 4.04 (1H, d, *J* = 14.7 Hz, H_1-THIQ), 4.29 (1H, d, *J* = 14.7 Hz, H_1-THIQ), 4.71 (1H, m, H_4-THIQ), 6.86 (1H, dd, *J* = 2.5, 8.4 Hz, H_7-THIQ), 6.89 (2H, d, *J* = 9.0 Hz, 2 x ArH, phenyl), 7.01 (1H, d, *J* = 2.5 Hz, H_5-THIQ), 7.03 (2H, d, *J* = 9.0 Hz, 2 x ArH, phenyl) and 7.07 (1H, d, *J* = 8.4 Hz, H_8-THIQ) ppm. LC/MS (ES^+) t_r = 1.52 min (83 %), m/z 286.0 (M^++H); (RP, Isocratic, 90% MeOH). HRMS (ES^+) calcd. for $C_{17}H_{20}NO_3$ (M^++H) 286.1438, found 286.1445.

6-Methoxy-2-(3-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-4-ol (4l)
The crude compound was purified by column chromatography (eluent: from 0% to 50% EtOAc in pet. ether) to give a yellow oil (1.9 g, 36%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.48 (1H, d, *J* = 10.5 Hz, OH), 3.38 (1H, dd, *J* = 2.6, 12.6 Hz, H_3-THIQ), 3.83 (3H, s, OCH_3, THIQ), 3.83 (1H, ddd, *J* = 1.0, 3.9, 12.6 Hz, H_3-THIQ), 3.83 (3H, s, OCH3, phenyl), 4.14 (1H, d, *J* = 14.9 Hz, H_1-THIQ), 4.43 (1H, d, *J* = 14.9 Hz, H_1-THIQ), 4.74 (1H, dt, *J* = 3.1, 10.5 Hz, H_4-THIQ), 6.47 (1H, ddd, *J* = 0.5, 2.3, 8.2 Hz, ArH, phenyl), 6.60 (1H, t, *J* = 2.3 Hz, ArH, phenyl), 6.68 (1H, ddd, *J* = 0.5, 2.3, 8.2 Hz, ArH, phenyl), 6.88 (1H, dd, *J* = 2.7, 8.5 Hz, H_7-THIQ), 7.01 (1H, d, *J* = 2.6 Hz, H_5-THIQ), 7.10 (1H, d, *J* = 8.5 Hz, H_8-THIQ) and 7.23 (1H, t, *J* = 8.2 Hz, ArH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 50.8 (C_1-THIQ), 55.3 (C_3-THIQ), 55.4 (OCH_3, THIQ), 55.5 (OCH_3, phenyl), 67.6 (C_4-THIQ), 102.9 (ArCH, phenyl), 104.9 (ArCH, phenyl), 109.2 (ArCH, phenyl), 113.0 (C_5-THIQ), 115.3 (C_7-THIQ), 126.3 (C_1CC_8-THIQ), 127.6 (C_8-THIQ), 130.1 (ArCH, phenyl), 137.8 (C_4CC_5-THIQ), 152.6 (ArCN), 158.7 (ArCO) and 160.8 (C_6-THIQ) ppm. LC/MS (ES^+) t_r = 1.75 min (94 %), m/z 286.0 (M^++H); (RP, Isocratic, 90% MeOH). HRMS (ES^+) calcd. $C_{17}H_{20}NO_3$ (M^++H) 286.1438, found 286.1428.

6-Methoxy-2-(2-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-4-ol (4m)
The crude compound was purified by column chromatography (eluent: from 0% to 50% EtOAc in pet. ether) to give a yellow oil (1.4 g, 26%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.17 (1H, dd, *J* = 2.5, 12.3 Hz, H_3-THIQ), 3.49 (1H, d, *J* = 10.1 Hz, OH), 3.68 (1H, dd, *J* = 2.9, 12.1 Hz, H_3-THIQ), 3.83 (3H, s, OCH_3, THIQ), 3.88 (3H, s, OCH_3, phenyl), 4.12 – 4.25 (2H, m, , H_1-THIQ), 4.67 (1H, dt, *J* = 2.7, 9.9 Hz, H_4-THIQ), 6.85 (1H, dd, *J* = 2.8, 8.4 Hz, H_7-THIQ), 6.91 (1H, dd, *J* = 1.3, 8.0 Hz, ArH, phenyl), 6.97 (1H, td, *J* = 1.4, 7.6 Hz, ArH, phenyl), 7.01 (1H, d, *J* = 2.7 Hz, H_5-THIQ) and 7.04 – 7.11 (3H, m, H_8-THIQ, 2 x ArH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 52.4 (C_1-THIQ), 55.5 (OCH_3, THIQ), 55.5 (OCH_3, phenyl), 57.1 (C_3-THIQ), 67.9 (C_4-THIQ), 111.3 (ArCH, phenyl), 113.5 (C_5-THIQ), 114.9 (C_7-THIQ), 119.4 (ArCH, phenyl), 121.1 (ArCH, phenyl), 123.6 (ArCH, phenyl), 127.1 (C_1CC_8-THIQ), 127.4 (C_8-THIQ), 138.2 (C_4CC_5-THIQ), 140.9 (ArCN), 152.7 (ArCO, phenyl) and 158.6 (C_6-THIQ) ppm. LC/MS (ES^+) t_r = 1.59 min (68 %), m/z 285.9 (M^++H); (RP, Isocratic, 90% MeOH). HRMS (ES^+) calcd. $C_{17}H_{20}NO_3$ (M^++H) 286.1438, found 286.1443.

2-(4-Chlorophenyl)-1,2,3,4-tetrahydroisoquinolin-4-ol (4n)
The crude compound was purified by column chromatography (eluent: from 0% to 30% EtOAc in pet. ether) to give a white solid (1.9 g, 61%). The compound was recrystallised from Et_2O/pet. ether to give a white solid which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.43 (1H, d, *J* = 9.9 Hz, OH), 3.37 (1H, dd, *J* = 2.4, 12.6 Hz, H_3-THIQ), 3.81 (1H, ddd, *J* = 1.2, 3.7, 12.6 Hz, H_3-THIQ), 4.18 (1H, d, *J* = 15.3 Hz, H_1-THIQ), 4.45 (1H, d, *J* = 15.3 Hz, H_1-THIQ), 4.75 – 4.84 (1H, m, H_4-THIQ), 6.99 (2H, d, *J* = 9.0 Hz, ArH, phenyl), 7.17 – 7.21 (1H, m, H_5-THIQ), 7.26 (2H, d, *J* = 9.0 Hz, ArH, phenyl), 7.31 (2H, t, *J* = 3.5 Hz, H_6,H_7-THIQ) and 7.46 – 7.50 (1H, m, H_8-THIQ) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 51.3 (C_1-THIQ), 55.6 (C_3-THIQ), 67.3 (C_4-THIQ), 117.7 (ArCH, phenyl), 125.1 (ArCCl), 126.5 (C-THIQ), 127.3 (C-THIQ), 128.4 (C-THIQ), 129.3 (ArCH, phenyl), 129.3 (C_7,C_6-THIQ), 134.0 (C_1CC_8-THIQ), 136.5 (C_4CC_5-THIQ) and 149.7 (ArCN) ppm. LC/MS (ES^+) t_r = 2.01 min (99 %), m/z 259.9 (M^++H); (RP, Isocratic, 90% MeOH). HRMS (ES^+) calcd. $C_{15}H_{15}ClNO$ (M^++H) (^{35}Cl) 260.0837, found 260.0830; calcd. $C_{15}H_{15}ClNO$ (M^++H) (^{37}Cl) 262.0807, found 262.0830. Mp 98-100 °C (Et_2O/Pet). Anal. calcd. for $C_{15}H_{14}ClNO$: C 69.4, H 5.43, N 5.39% found C 69.4, H 5.43, N 5.28%.

General method for the reductive dihydroxylation with Et_3SiH: The crude compound **4a** (2.77 g) was dissolved in DCM (60 mL) and Et_3SiH (6.0 mL, 36.9 mmol) and $BF_3{\cdot}Et_2O$ (9.8 mL, 36.9 mmol) were introduced in the order. After refluxing for 18 h, the mixture was cooled to rt and quenched with a saturated aqueous solution of Na_2CO_3 (50 mL). The aqueous layer was then extracted with EtOAc (2 x 50 mL). The combined organics were dried with $MgSO_4$, filtered and evaporated to give a green oil (2.03 g).

2-Phenyl-1,2,3,4-tetrahydroisoquinoline (5a)
The crude product was purified by column chromatography (eluent: pet. ether) to yield the product as a pale yellow oil (1.72 g, 67%) which solidified upon standing and which showed:[21] ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.00 (2H, t, *J* = 5.8 Hz, H_4-THIQ), 3.57 (2H, t, *J* = 5.8 Hz, H_3-THIQ), 4.42 (2H, s, H_1-THIQ), 6.83 (1H, t, *J* = 7.3 Hz, ArH, phenyl), 6.99 (2H, d, *J* = 8.7 Hz, ArH, phenyl), 7.14 – 7.21 (4H, m, H_5,H_6,H_7,H_8-THIQ) and 7.30 (2H, dd, *J* = 7.3, 8.7 Hz, ArH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.27 (C_4-THIQ), 46.67 (C_3-THIQ), 50.89 (C_1-THIQ), 115.29 (ArCH, phenyl), 118.8 (ArCH, phenyl), 126.2 (ArCH, THIQ), 126.5 (ArCH, THIQ), 126.7 (ArCH, THIQ), 128.7 (ArCH, THIQ), 129.4 (ArCH, phenyl), 134.6 (C_1CC_8-THIQ), 135.0 (C_5CC_6-THIQ) and 150.7 (ArCN) ppm. LC/MS (ES^+) t_r = 2.79 min (97 %), m/z 209.9 (M^++H); (RP, Isocratic, 90% MeOH). HRMS (ES^+) calcd. for $C_{15}H_{16}N$ (M^++H) 210.1277, found 210.1284. Mp 44-45 °C (pet. ether).

2-(3-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (5b)
The crude product was purified by column chromatography (eluent 0% to 30% EtOAc in pet. ether) to yield the product as a dark yellow oil (152 mg, 11%) which showed:[21] ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.99 (2H, t, *J* = 5.9 Hz, ArC*H*$_2$CH$_2$), 3.56 (2H, t, *J* = 5.9 Hz, NC*H*$_2$CH$_2$), 3.82 (3H, s, ArOCH$_3$), 4.41 (2H, s, ArCH$_2$N), 6.39 (1H, dd, *J* = 2.4, 8.1 Hz, ArH), 6.52 (1H, t, *J* = 2.4 Hz, ArH), 6.60 (1H, dd, *J* = 2.4, 8.1 Hz, ArH) and 7.14 - 7.22 (5H, m, ArH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.3 (Ar*C*H$_2$CH$_2$), 46.5 (N*C*H$_2$CH$_2$), 50.8 (ArCH$_2$N), 55.3 (ArOCH$_3$), 101.6 (ArCH), 103.4 (ArCH), 108.0 (ArCH), 126.2 (ArCH), 126.5 (ArCH) 126.7 (ArCH), 128.6 (ArCH), 130.0 (ArCH), 134.6 (Ar*C*CH$_2$N), 135.1 (Ar*C*CH$_2$CH$_2$), 152.0 (ArCN) and 160.9 (Ar*C*OCH$_3$) ppm. LC/MS (ES$^+$) t_r = 2.84 min (84%), m/z 240.0 (M$^+$+H); (RP, Isocratic, 90% MeOH). HRMS (ES+) calcd. for $C_{16}H_{18}NO$ (M$^+$+H) 240.1383, found 240.1373.

6-Methoxy-2-phenyl-1,2,3,4-tetrahydroisoquinoline (5c)
The crude product was purified by column chromatography (eluent: from 0% to 0.5% EtOAc in pet. ether) to yield the product as a colourless oil (1.3 g, 25%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.96 (2H, t, *J* = 5.8 Hz, H$_4$-THIQ), 3.55 (2H, t, *J* = 5.8 Hz, H$_3$-THIQ), 3.80 (3H, s, ArOCH$_3$), 4.36 (2H, s, H$_1$-THIQ), 6.70 (1H, d, *J* = 2.6 Hz, H$_5$-THIQ), 6.77 (1H, dd, *J* = 2.6, 8.4 Hz, H$_7$-THIQ), 6.83 (1H, tt, *J* = 1.0, 7.3 Hz, ArH, phenyl), 6.98 (2H, dd, *J* = 1.0, 8.8 Hz, ArH, phenyl), 7.08 (1H, d, *J* = 8.4 Hz, H$_8$-THIQ) and 7.29 (2H, dd, *J* = 7.3, 8.8 Hz, ArH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.6 (C$_4$-THIQ), 46.6 (C$_3$-THIQ), 50.3 (C$_1$-THIQ), 55.4 (ArOCH$_3$), 112.5 (C$_7$-THIQ), 113.4 (C$_5$-THIQ), 115.3 (ArCH, phenyl), 118.8 (ArCH, phenyl), 126.8 (C$_1$*C*C$_8$-THIQ), 127.6 (C$_8$-THIQ), 129.3 (ArCH, phenyl), 136.2 (C$_5$*C*C$_6$-THIQ), 150.7 (ArCN) and 158.2 (C$_6$-THIQ) ppm. LC/MS (ES$^+$) t_r = 2.48 min (97 %), m/z 239.9 (M$^+$+H); (RP, Isocratic, 90% MeOH). HRMS (ES+) calcd. for $C_{16}H_{18}NO$ (M$^+$+H) 240.1383, found 240.1372. Mp 72-73 °C (pet. ether). Anal. calcd. for $C_{16}H_{17}NO$: C 80.3, H 7.16, N 5.85. Found: C 80.2, H 7.16, N 5.73%.

2-(4-Chlorophenyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (5d)
The crude product was purified by column chromatography (eluent: from 0% to 30% EtOAc in pet. ether) to yield the product as a white solid (1.41 g, 20%) which showed[22]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.95 (2H, t, *J* = 5.8 Hz, H$_4$-THIQ), 3.51 (2H, t, *J* = 5.9 Hz, H$_3$-THIQ), 3.80 (3H, s, ArOCH$_3$), 4.31 (2H, s, H$_1$-THIQ), 6.70 (1H, d, *J* = 2.6 Hz, H$_5$-THIQ), 6.77 (1H, dd, *J* = 2.7, 8.4 Hz, H$_7$-THIQ), 6.87 (2H, d, *J* = 9.1 Hz, ArH, phenyl), 7.06 (1H, d, *J* = 8.4 Hz, H$_8$-THIQ) and 7.21 (2H, d, *J* = 9.1 Hz, ArH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.4 (C$_4$-THIQ), 46.6 (C$_3$-THIQ), 50.3 (C$_1$-THIQ), 55.5 (ArOCH$_3$), 112.6 (C$_7$-THIQ), 113.4 (C$_5$-THIQ), 116.3 (ArCH, phenyl), 123.4 (ArCCl), 126.4 (C$_1$*C*C$_8$-THIQ), 127.6 (C$_8$-THIQ), 129.1 (ArCH, phenyl), 136.0 (C$_5$*C*C$_6$-THIQ), 149.3 (ArCN) and 158.3 (C$_6$-THIQ) ppm. LC/MS (ES$^+$) t_r = 3.56 min (96 %), m/z 274.0 (M$^+$+H) (^{35}Cl), 276.0 (M$^+$+H) (^{37}Cl); (RP, Isocratic, 90% MeOH). HRMS (ES+) calcd. for $C_{16}H_{17}{}^{35}ClNO$ (M$^+$+H) 274.0993, found 274.0980; calcd. for $C_{16}H_{17}{}^{37}ClNO$ (M$^+$+H) 276.0964, found 274.0980. Mp 99-100 °C (pet. ether).

2-(4-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-6-ol (5h)
The crude compound was purified by reversed phase column chromatography (eluent: from 5% to 100% MeOH in water) to get the compound as a yellow oil (503 mg, 20%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.93 (2H, t, *J* = 5.9 Hz, ArC*H*$_2$CH$_2$), 3.42 (2H, t, *J* = 5.9 Hz, ArCH$_2$C*H*$_2$), 3.78 (3H, s, ArOCH$_3$), 4.22 (2H, s, ArCH$_2$N), 6.62 (1H, d, *J* = 2.5 Hz, ArH), 6.67 (1H, dd, *J* = 2.5, 8.2 Hz, ArH), 6.86 (2H, d, *J* = 9.1 Hz, ArH), 6.97 (2H, d, *J* = 9.1 Hz, ArH) and 7.00 (1H, d, *J* = 8.2 Hz, ArH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.1 (Ar*C*H$_2$CH$_2$), 48.4 (N*C*H$_2$CH$_2$), 52.2 (ArCH$_2$N), 55.6 (ArOCH$_3$), 113.4 (ArCH), 114.6 (ArCH), 114.9 (ArCH), 118.1 (ArCH), 126.7 (ArCCH$_2$N), 127.6 (ArCH), 131.0 (Ar *C*CH$_2$CH$_2$), 145.5 (ArCN), 153.5 (Ar*C*OCH$_3$) and 154.0 (ArCOH) ppm. LC/MS (ES$^+$) t_r = 1.17 min (96%), m/z 255.7 (M$^+$+H); (RP, Isocratic, 90% MeOH). HRMS (ES+) calcd. for $C_{16}H_{18}NO_2$ (M$^+$+H) 256.1332, found 256.1336. Mp 192-194 °C (Hydrochloride from MeOH/Et$_2$O).

6-Methoxy-2-(*p*-tolyl)-1,2,3,4-tetrahydroisoquinoline (5i)
The crude product was purified by column chromatography (eluent: from 0% to 10% EtOAc in pet. ether) to yield the product as a white solid (1.65 g, 25%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.28 (3H, s, ArCH$_3$), 2.95 (2H, t, *J* = 5.8 Hz, H$_4$-THIQ), 3.49 (2H, t, *J* = 5.8 Hz, H$_3$-THIQ), 3.79 (3H, s, ArOCH$_3$), 4.30 (2H, s, H$_1$-THIQ), 6.69 (1H, d, *J* = 2.6 Hz, H$_5$-THIQ), 6.76 (1H, dd, *J* = 2.6, 8.4 Hz, H$_7$-THIQ), 6.91 (2H, d, *J* = 8.6 Hz, ArH, phenyl), 7.06 (1H, d, *J* = 8.4 Hz, H$_8$-THIQ) and 7.09 (2H, d, *J* = 8.6 Hz, ArH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.5 (ArCH$_3$), 29.5 (C$_4$-THIQ), 47.4 (C$_3$-THIQ), 51.1 (C$_1$-THIQ), 55.4 (ArOCH$_3$), 112.5 (C$_7$-THIQ), 113.4 (C$_5$-THIQ), 116.0 (ArCH, phenyl), 126.9 (C$_1$*C*C$_8$-THIQ), 127.6 (C$_8$-THIQ), 128.5 (Ar*C*CH$_3$), 129.8 (ArCH, phenyl), 136.1 (C$_5$*C*C$_6$-THIQ), 148.8 (ArCN) and 158.2 (C$_6$-THIQ) ppm. LC/MS (ES$^+$) t_r = 2.62 min (97 %), m/z 254.0 (M$^+$+H); (RP, Isocratic, 90% MeOH). HRMS (ES+) calcd. for $C_{17}H_{20}NO$ (M$^+$+H) 254.1539, found 254.1535. Mp 69-70 °C (pet. ether). Anal. calcd. for $C_{17}H_{19}NO$: C 80.6, H 7.56, N 5.53. Found: C 80.4, H 7.55, N 5.44 %.

2-(4-Ethylphenyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (5j)
The crude compound was purified by column chromatography (eluent: from 0% to 20% EtOAc in pet. ether) to get the product as a yellow solid (409 mg, 51%) which was recrystallised from pet. ether and showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (3H, t, *J* = 7.6 Hz, CH$_2$C*H*$_3$), 2.59 (2H, q, *J* = 7.6 Hz, C*H*$_2$CH$_3$), 2.97 (2H, t, *J* = 5.8 Hz, H$_4$-THIQ), 3.51 (2H, t, *J* = 5.8 Hz, H$_3$-THIQ), 3.80 (3H, s, OCH$_3$), 4.32 (2H, s, H$_1$-THIQ), 6.70 (1H, d, *J* = 2.5 Hz, H$_5$-THIQ), 6.77 (1H, dd, *J* = 2.5, 8.4

Hz, H_7-THIQ), 6.96 (2H, d, *J* = 8.3 Hz, 2 x ArCH, phenyl), 7.07 (1H, d, *J* = 8.4 Hz, H_8-THIQ) and 7.13 (2H, d, *J* = 8.6 Hz, 2 x ArCH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.8 (CH_2CH_3), 27.9 (CH_2CH_3), 29.3 (C_4-THIQ), 47.2 (C_3-THIQ), 50.9 (C_1-THIQ), 55.3 (OCH_3), 112.3 (C_7-THIQ), 113.2 (C_5-THIQ), 115.8 (2 x ArCH, phenyl), 126.6 (C_1CC_8-THIQ), 127.5 (C_8-THIQ), 128.5 (2 x ArCH, phenyl), 135.0 ($ArCCH_2CH_3$), 135.8 (C_4CC_5-THIQ), 148.6 (ArCN), 158.0 (C_6-THIQ) ppm. HRMS (ES$^+$) calcd. $C_{18}H_{22}NO$ (M^++H) 268.1696, found 268.1694. Mp 78-80 °C (pet. ether). Anal. calcd. for $C_{18}H_{21}NO$: C 80.86, H 7.92, N 5.24 %. Found: C 80.91, H 8.00, N 5.14 %.

6-Methoxy-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (5k)
The crude product was purified by column chromatography (eluent: from 0% to 15% EtOAc in pet. ether) to yield the product as a white solid (1.395 g, 21%) which showed:[23] ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.96 (2H, t, *J* = 5.8 Hz, H_4-THIQ), 3.43 (2H, t, *J* = 5.8 Hz, H_3-THIQ), 3.78 (3H, s, $ArOCH_3$), 3.79 (3H, s, $ArOCH_3$), 4.24 (2H, s, H_1-THIQ), 6.68 (1H, d, *J* = 2.6 Hz, H_5-THIQ), 6.75 (1H, dd, *J* = 2.6, 8.4 Hz, H_7-THIQ), 6.86 (2H, d, *J* = 9.1 Hz, ArH, phenyl), 6.97 (2H, d, *J* = 9.1 Hz, ArH, phenyl) and 7.04 (1H, d, *J* = 8.4 Hz, H_8-THIQ) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.5 (C_4-THIQ), 48.5 (C_3-THIQ), 52.3 (C_1-THIQ), 55.4 ($ArOCH_3$), 55.8 ($ArOCH_3$), 112.5 (C_7-THIQ), 113.4 (C_5-THIQ), 114.7 (ArCH, phenyl), 118.2 (ArCH, phenyl), 127.0 (C_1CC_8-THIQ), 127.6 (C_8-THIQ), 135.9 (C_5CC_6-THIQ), 145.6 (ArCN), 153.6 (ArCO, phenyl) and 158.2 (C_6-THIQ) ppm. LC/MS (ES$^+$) t_r = 1.47 min (90 %), m/z 270.0 (M^++H); (RP, Isocratic, 90% MeOH). HRMS (ES+) calcd. for $C_{17}H_{20}NO_2$ (M^++H) 270.1489, found 270.1477. Mp 124-125 °C (pet. ether). Anal. calcd. for $C_{17}H_{19}NO$: C 75.81, H 7.11, N 5.20. Found: C 75.5, H 7.16, N 5.10 %.

6-Methoxy-2-(3-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (5l)
The crude compound was purified by column chromatography (eluent: from 0% to 20% EtOAc in pet. ether) to get the compound as a yellow oil (761 mg, 44%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.95 (2H, t, *J* = 5.9 Hz, H_4-THIQ), 3.54 (2H, t, *J* = 5.9 Hz, H_3-THIQ), 3.80 (3H, s, $ArOCH_3$, THIQ), 3.81 (3H, s, $ArOCH_3$, phenyl), 4.35 (2H, s, H_1-THIQ), 6.39 (1H, ddd, *J* = 0.9, 2.5, 8.4 Hz, ArH, phenyl), 6.50 (1H, t, *J* = 2.5 Hz, ArH, phenyl), 6.59 (1H, ddd, *J* = 0.9, 2.5, 8.4 Hz, ArH, phenyl), 6.70 (1H, d, *J* = 2.6 Hz, H_5-THIQ), 6.76 (1H, dd, *J* = 2.7, 8.4 Hz, H_7-THIQ), 7.07 (1H, d, *J* = 8.4 Hz, H_8-THIQ) and 7.19 (1H, t, *J* = 8.4 Hz, ArH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.5 (C_4-THIQ), 46.4 (C_3-THIQ), 50.2 (C_1-THIQ), 55.3 (OCH_3, phenyl), 55.4 (OCH_3, THIQ), 101.6 (ArCH, phenyl), 103.4 (ArCH, phenyl), 108.0 (ArCH, phenyl), 112.5 (C_7-THIQ), 113.3 (C_5-THIQ), 126.7 (C_1CC_8-THIQ), 127.6 (C_8-THIQ), 130.0 (ArCH, phenyl), 136.2 (C_4CC_5-THIQ), 152.0 (ArCN), 158.2 (C_6-THIQ) and 160.8 (ArCO, phenyl) ppm. HRMS (ES$^+$) calcd. $C_{17}H_{20}NO_2$ (M^++H) 270.1489, found 270.1479. Mp 119-120 °C (pet. ether).

6-Methoxy-2-(2-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (5m)
The crude compound was purified by column chromatography (eluent: from 0% to 20% EtOAc in pet. ether) to get the product as a colourless oil (143 mg, 38%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.95 (2H, t, *J* = 5.8 Hz, H_4-THIQ), 3.39 (2H, t, *J* = 5.9 Hz, H_3-THIQ), 3.79 (3H, s, H_1-THIQ), 3.89 (3H, s, OCH_3), 4.23 (2H, s, OCH_3), 6.67 (1H, d, *J* = 2.3 Hz, H_5-THIQ), 6.74 (1H, dd, *J* = 2.6, 8.4 Hz, H_7-THIQ), 6.88 – 6.94 (2H, m, 2 x ArH, phenyl) and 6.98 – 7.05 (3H, m, H_8-THIQ and 2 x ArH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.1 (C_4-THIQ), 48.8 (C_3-THIQ), 52.5 (C_1-THIQ), 55.2 (CH_3O-), 55.4 (CH_3O-), 111.2 (ArCH, phenyl), 112.1 (C_7-THIQ), 113.4 (C_5-THIQ), 118.9 (ArCH, phenyl), 120.9 (ArCH, phenyl), 122.9 (ArCH, phenyl), 127.3 (C_6-THIQ), 127.4 (C_1CC_8-THIQ), 135.7 (C_4CC_5-THIQ), 141.1 (ArCN), 152.5 ($COCH_3$) and 157.9 ($COCH_3$) ppm. HRMS (ES$^+$) calcd. $C_{17}H_{20}NO_2$ (M^++H) 270.1489, found 270.1499. Mp 199-200 °C (as hydrochloride from Et_2O).

2-(4-Chlorophenyl)-1,2,3,4-tetrahydroisoquinoline (5n)
The crude compound was purified by column chromatography (eluent: from 0% to 20% EtOAc in pet. ether) to get the product as a white solid which was recrystallised from pet. ether (1.14 g, 76%) and showed:[24] ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.98 (2H, t, *J* = 5.9 Hz, H_4-THIQ), 3.53 (2H, t, *J* = 5.9 Hz, H_3-THIQ), 4.38 (2H, s, H_1-THIQ), 6.89 (2H, d, *J* = 9.1 Hz, ArH, phenyl), 7.12 – 7.21 (4H, m, H_5,H_6,H_7,H_8 -THIQ) and 7.22 (2H, d, *J* = 9.1 Hz, ArH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.1 (C_4-THIQ), 46.7 (C_3-THIQ), 50.8 (C_1-THIQ), 116.3 (ArCH, phenyl), 123.5, 126.3 (C_8-THIQ), 126.6 (ArCH-THIQ), 126.7 (ArCH-THIQ), 128.7 (C_5-THIQ), 129.2 (ArCH, phenyl), 134.2 (C_1CC_8-THIQ), 134.8 (C_4CC_5-THIQ) and 149.2 (ArCN) ppm. HRMS (ES$^+$) calcd. $C_{15}H_{15}{}^{35}ClN$ (M^++H) 244.0888, found 244.0896; calcd. $C_{15}H_{15}{}^{37}ClN$ (M^++H) 246.0858, found 246.0866.

General method for the Pomeranz-Fritsch-Bobbit cyclisation with HCl: Compound **3e** (500 mg, 1.66 mmol) was dissolved in conc. HCl (2 ml) and stirred at rt for 1 h during which time the mixture turned red. The reaction mixture was cooled to 0 °C and then quenched slowly with aq. 3 N NaOH (10 mL) (a white suspension with a yellow precipitate formed) and extracted with EtOAc (20 mL). The organic layer was dried with $MgSO_4$, filtered and evaporated to give a yellow-brown oil (445 mg).

6,7-Dimethoxy-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-4-ol (6a)
The crude compound was purified by column chromatography (eluent: from 0% to 50% EtOAc in pet. ether) to give the product as a white solid (3.54 g, 62%) which showed as previously reported[17]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.67 (1H, bs, OH), 3.23 (1H, dd, *J* = 2.3, 12.3 Hz, H_3-THIQ), 3.71 (1H, dd, *J* = 3.1, 12.3 Hz, H_3-THIQ), 3.79 (3H, s, OCH_3, phenyl),

3.88 (3H, s, C_6OCH_3-THIQ), 3.90 (3H, s, C_7OCH_3-THIQ), 4.01 (1H, d, *J* = 14.8 Hz, H_1-THIQ), 4.27 (1H, d, *J* = 14.8 Hz, H_1-THIQ), 4.67 (1H, bs, H_4-THIQ), 6.62 (1H, s, H_8-THIQ), 6.89 (2H, d, *J* = 9.0 Hz, 2 x ArCH, phenyl), 6.96 (1H, s, H_5-THIQ) and 7.03 (2H, d, *J* = 8.9 Hz, 2 x ArCH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 52.7 (C_1-THIQ), 55.6 (OCH_3, phenyl), 55.9(2 x OCH_3, THIQ), 57.2 (C_3-THIQ), 67.2 (C_4-THIQ), 108.6 (C_8-THIQ), 111.6 (C_5-THIQ), 114.5 (2 x ArCH, phenyl), 118.9 (2 x ArCH, phenyl), 126.8 (C_1CC_8-THIQ), 128.6 (C_4CC_5-THIQ), 145.3 (ArCN), 148.1 (C_7-THIQ), 148.9 (C_6-THIQ) and 154.2 (ArCO, phenyl) ppm. HRMS (ES^+) calcd. $C_{18}H_{22}NO_4$ (M^++H) 316.1543, found 316.1543. Mp 136-137 °C (DCM/Et_2O).

5,6,7-Trimethoxy-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-4-ol (6b)
The crude compound was purified by column chromatography (eluent: from 0% to 100% EtOAc in pet. ether) to give the product as a dark brown solid (5.49 g, 82%) which showed as previously reported[17]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.90 (1H, bs, OH), 3.18 (1H, dd, *J* = 2.7, 12.4 Hz, H_3-THIQ), 3.70 (1H, dd, *J* = 3.5, 12.6 Hz, H_3-THIQ), 3.79 (3H, s, OCH_3, phenyl), 3.86 (3H, s, C_6OCH_3-THIQ), 3.87 (3H, s, C_7OCH_3-THIQ), 3.98 (1H, d, *J* = 15.1 Hz, H_1-THIQ), 4.02 (3H, s, C_5OCH_3-THIQ), 4.29 (1H, d, *J* = 15.0 Hz, H_1-THIQ), 4.98 (1H, bs, H_4-THIQ), 6.45 (1H, s, H_8-THIQ), 6.88 (2H, d, *J* = 9.0 Hz, 2 x ArCH, phenyl) and 7.04 (2H, d, *J* = 9.0 Hz, 2 x ArCH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 53.2 (C_1-THIQ), 55.6 (OCH_3, phenyl), 56.0 (C_6OCH_3-THIQ), 56.9 (C_3-THIQ), 60.9 (C_7OCH_3-THIQ), 61.5(C_5OCH_3-THIQ), 62.7 (C_4-THIQ), 104.6 (C_8-THIQ), 114.5 (2 x ArCH, phenyl), 119.1 (2 x ArCH, phenyl), 123.0 (C_1CC_8-THIQ), 130.5 (C_4CC_5-THIQ), 140.6 (C_7-THIQ), 145.3 (ArCN), 152.2 (C_5-THIQ), 153.5 (C_6-THIQ) and 154.3 (ArCO, phenyl) ppm. HRMS (ES^+) calcd. $C_{19}H_{24}NO_5$ (M^++H) 346.1649, found 346.1638.

General method for the reductive dehydroxylation with $NaBH_4$: $NaBH_4$ (1.53 g, 39.7 mmol) was added to a stirring solution of **6a** (2.50 g, 7.93 mmol) in DCM (30 mL) followed by the dropwise addition of TFA (3.1 mL) and the mixture was stirred at rt for 3 h. The mixture was then diluted with DCM (30 mL) and washed with a sat. aq. solution of Na_2CO_3 (2 x 60 mL) and dried with MgSO4, filtered and evaporated to give a pale yellow solid (2.45 g).

6,7-Dimethoxy-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (7a)
The crude compound was purified by column chromatography (eluent: from 0% to 60% EtOAc in pet. ether) to give the product as a yellow solid (698 mg, 29%) which showed:[25] ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.89 (2H, t, *J* = 5.7 Hz, H_4-THIQ), 3.43 (2H, t, *J* = 5.7 Hz, H_3-THIQ), 3.78 (3H, s, OCH_3, phenyl), 3.86 (3H, s, OCH_3-THIQ), 3.87 (3H, s, OCH_3-THIQ), 4.22 (2H, s, H_1-THIQ), 6.62 (1H, s), 6.63 (1H, s), 6.86 (2H, d, *J* = 9.0 Hz, 2 x ArCH, phenyl) and 6.98 (2H, d, *J* = 9.0 Hz, 2 x ArCH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.5 (C_4-THIQ), 48.6 (C_3-THIQ), 52.4 (C_1-THIQ), 55.6 (OCH_3, phenyl), 55.9 (OCH_3-THIQ), 56.0 (OCH_3-THIQ), 109.3 (C_y-THIQ), 111.4 (C_y-THIQ), 114.5 (2 x ArCH, phenyl), 118.1 (2 x ArCH, phenyl), 126.3 (C_1CC_8-THIQ), 126.4 (C_4CC_5-THIQ), 145.3 (ArCN), 147.4 (C-THIQ), 147.6 (C-THIQ) and 153.5 (ArCO, phenyl) ppm. HRMS (ES^+) calcd. $C_{18}H_{22}NO_3$ (M^++H) 300.1594, found 300.1581. Mp 138-140 °C (DCM/Et_2O).

5,6,7-Trimethoxy-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (7b)
The crude compound was purified by column chromatography (eluent: form 0% to 70% EtOAc in pet. ether) to give the product as a white solid (1.13 g, 49%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.86 (2H, t, *J* = 5.9 Hz, H_4-THIQ), 3.39 (2H, t, *J* = 5.9 Hz, H_3-THIQ), 3.78 (3H, s, OCH_3, phenyl), 3.85 (3H, s, C_5OCH_3), 3.86 (3H, s, C_7OCH_3), 3.87 (3H, s, C_6OCH_3), 4.20 (2H, s, H_1-THIQ), 6.45 (1H, s, H_8-THIQ), 6.86 (2H, d, *J* = 9.1 Hz, 2 x ArCH, phenyl) and 6.98 (2H, d, *J* = 9.0 Hz, 2 x ArCH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.3 (C_4-THIQ), 48.5 (C_3-THIQ), 52.9 (C_1-THIQ), 55.6 (OCH_3, phenyl), 56.0 ($C_5O\mathit{C}H_3$), 60.5 ($C_7O\mathit{C}H_3$), 60.9 ($C_6O\mathit{C}H_3$), 105.2 (C_8-THIQ), 114.5 (2 x ArCH, phenyl), 118.4 (2 x ArCH, phenyl), 120.7 (C_4CC_5-THIQ), 130.1 (C_1CC_8-THIQ), 140.5 (C_7-THIQ), 145.4 (ArCN), 151.2 (C_6-THIQ), 151.9 (C_5-THIQ) and 153.7 (ArCO, phenyl) ppm. HRMS (ES^+) calcd. $C_{19}H_{24}NO_4$ (M^++H) 330.1700, found 330.1697. Mp 103-104 °C (DCM/Et_2O). Anal. calcd. for $C_{19}H_{23}NO_4$: C 69.28, H 7.04, N 4.25. Found: C 69.36, H 6.95, N 4.13 %.

2-(4-Clorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinolin-4-ol (8a)
Synthesized according to the general method for the Pomeranz-Fritsch-Bobbit cyclisation with HCl. The crude compound was purified by column chromatography (eluent: from 0% to 40% EtOAc in pet. ether) to give a dark yellow wax (2.39 g, 31%) which showed as previously reported[17]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.36 (1H, d, *J* = 8.6 Hz, OH), 3.32 (2H, dd, *J* = 2.5, 12.6 Hz, H_3-THIQ), 3.82 (3H, s, OCH_3), 3.82 (5H, ddd, *J* = 1.3, 3.5, 12.8 Hz, H_3-THIQ), 4.13 (2H, d, *J* = 15.3 Hz, H_1-THIQ), 4.42 (2H, d, *J* = 15.3 Hz, H_1-THIQ), 4.74 (1H, bs, H_4-THIQ), 6.69 (1H, d, *J* = 2.6 Hz, H_8-THIQ), 6.85 (1H, dd, *J* = 2.6, 8.5 Hz, H_6-THIQ), 6.98 (3H, d, *J* = 9.0 Hz, ArH, phenyl), 7.25 (4H, d, *J* = 9.0 Hz, ArH, phenyl) and 7.39 (1H, d, *J* = 8.5 Hz, H_5-THIQ) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 51.3 (C_1-THIQ), 55.3 (OCH_3), 55.7 (C_3-THIQ), 66.7 (C_4-THIQ), 110.9 (C_8-THIQ), 113.4 (C_6-THIQ), 117.6 (ArCH, phenyl), 124.9 (ArCCl), 129.0 (C_5CC_6-THIQ), 129.1 (ArCH, phenyl), 130.5 (C_5-THIQ), 135.3 (C_1CC_8-THIQ), 149.6 (ArCN) and 159.4 (C_7-THIQ) ppm. LC/MS (ES^+) t_r = 1.95 min (92 %), m/z 290.0 (M^++H); (RP, Isocratic, 90% MeOH). HRMS (ES^+) calcd. for $C_{16}H_{17}{}^{35}ClNO_2$ (M^++H) 290.0942, found 290.0935; calcd. $C_{16}H_{17}{}^{37}ClNO_2$ (M^++H) 292.0913, found 292.0935.

7-Bromo-2-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ol (8b)
Synthesized according to the general method for the Pomeranz-Fritsch-Bobbit cyclisation with HClO4. The crude compound was purified by column chromatography (eluant: from 0% to 30% EtOAc in pet. ether) to give a pale yellow oil

(250 mg, 48%) which showed as previously reported[17]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.19 (1H, dd, *J* = 2.1, 12.9 Hz, C*H*$_2$CH), 4.07 (1H, ddd, *J* = 1.6, 2.4, 12.9 Hz, C*H*$_2$CH), 4.11 (1H, d, *J* = 15.2 Hz, $ArCH_2$), 4.54 (1H, d, *J* = 15.5 Hz, $ArCH_2$), 5.03 (1H, t, *J* = 2.3 Hz, C*H*OH), 6.95 (1H, tt, *J* = 0.9, 7.4 Hz, ArH), 7.10 (2H, dd, *J* = 0.9, 8.7 Hz, ArH), 7.16 (1H, d, *J* = 2.0 Hz, ArH), 7.17 (1H, d, *J* = 7.2 Hz, ArH), 7.34 (2H, dd, *J* = 7.4, 8.7 Hz, ArH) and 7.52 (1H, dd, *J* = 2.0, 7.2 Hz, ArH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 51.5 ($ArCH_2$), 55.7 (*C*H_2CH), 66.7 (CHOH), 116.8 (ArCH), 117.0 (ArCH), 120.8 (ArCH), 125.8 (ArCBr), 126.0 (ArCH), 129.4 (ArCH), 131.4 (ArCH), 135.6 (Ar*C*CH), 137.1 (Ar*C*CH_2) and 150.9 (ArCN) ppm. LC/MS (ES^+) t_r = 1.97 min (61 %), m/z 303.4 (M^++H) (^{79}Br), 305.4 (M^++H) (^{81}Br); (RP, Isocratic, 90% MeOH). HRMS (ES^+) calcd. for $C_{15}H_{15}BrNO$ (M^++H) (^{79}Br) 304.0332, found 304.0335; calcd. for $C_{15}H_{15}BrNO$ (M^++H) (^{81}Br) 306.0311, found 306.0323.

5-Bromo-2-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ol (9b)
Synthesized according to the general method for the Pomeranz-Fritsch-Bobbit cyclisation with HClO4. The crude compound was purified by column chromatography (eluant: from 0% to 30% EtOAc in pet. ether) to give a pale yellow oil (50 mg, 10%) which showed as previously reported[17]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.35 (1H, dd, *J* = 2.7, 12.7 Hz, C*H*$_2$CH), 3.77 (1H, ddd, *J* = 1.0, 3.9, 12.7 Hz, C*H*$_2$CH), 3.89 (1H, bs, OH), 4.13 (1H, d, *J* = 15.6 Hz, $ArCH_2$), 4.37 (1H, d, *J* = 15.6 Hz, $ArCH_2$), 4.72 (1H, t, *J* = 3.3 Hz, C*H*OH), 6.93 (1H, tt, *J* = 0.9, 7.2 Hz, ArH), 7.03 (2H, dd, *J* = 0.9, 8.7 Hz, ArH), 7.29 - 7.35 (4H, m, ArH) and 7.39 (1H, dd, *J* = 2.0, 8.2 Hz, ArH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 51.0 ($ArCH_2$), 55.5 (*C*H_2CH), 66.6 (CHOH), 116.7 (ArCH), 120.6 (ArCH), 121.9 (ArCBr), 129.3 (ArCH), 129.4 (ArCH), 130.3 (ArCH), 131.0 (ArCH), 135.7 (Ar*C*CH), 136.5 (Ar*C*CH_2) and 150.7 (ArCN) ppm. LC/MS (ES^+) t_r = 2.20 min (86 %), m/z 303.4 (M^++H) (^{79}Br), 305.4 (M^++H) (^{81}Br); (RP, Isocratic, 90% MeOH). HRMS (ES+) calcd. for $C_{15}H_{15}{}^{79}BrNO$ (M^++H) 304.0332, found 304.0321; calcd. for $C_{15}H_{15}{}^{81}BrNO$ (M^++H) 306.0311, found 306.0320.

2-(4-Chlorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (10a)
Synthesized according to the general method for the reductive dehydroxylation with $NaBH_4$. The crude compound was purified by column chromatography (eluent: from 0% to 30% EtOAc in pet. ether) to get the product as a white solid (1.1 g, 51%) which was recrystallised from pet. ether and showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.90 (2H, t, *J* = 5.9 Hz, H_4-THIQ), 3.52 (2H, t, *J* = 5.9 Hz, H_3-THIQ), 3.80 (3H, s, OCH_3), 4.35 (2H, s, H_1-THIQ), 6.70 (1H, d, *J* = 2.6 Hz, H_8-THIQ), 6.76 (1H, dd, *J* = 2.6, 8.4 Hz, H_7-THIQ), 6.88 (2H, d, *J* = 9.1 Hz, ArH, phenyl), 7.07 (1H, d, *J* = 8.4 Hz, H_5-THIQ) and 7.22 (2H, d, *J* = 9.1 Hz, ArH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.1 (C_4-THIQ), 47.0 (C_3-THIQ), 51.0 (C_1-THIQ), 55.5 (OCH_3), 111.4 (C_8-THIQ), 112.8 (C_6-THIQ), 116.4 (ArCH, phenyl), 123.5 (ArCCl), 126.9 (C_5CC_6-THIQ), 129.1 (ArCH, phenyl), 129.6 (C_5-THIQ), 135.2 (C_1CC_8-THIQ), 149.2 (ArCN) and 158.1 (C_7-THIQ) ppm. LC/MS (ES^+) t_r = 3.49 min (99 %), m/z 273.9 (M^++H); (RP, Isocratic, 90% MeOH). HRMS (ES^+) calcd. $C_{16}H_{17}{}^{35}ClNO$ (M^++H) 274.0993, found 274.0987; calcd. $C_{16}H_{17}{}^{37}ClNO$ (M^++H) 276.0964, found 276.0987. Mp 79-80 °C (pet. ether).

2-(4-Chlorophenyl)-5-methoxy-1,2,3,4-tetrahydroisoquinoline (11a)
Synthesized according to the general method for the reductive dehydroxylation with $NaBH_4$. The crude compound was purified by column chromatography (eluent: from 0% to 30% EtOAc in pet. ether) to get the product as a white solid (230 mg, 11%) which was recrystallised from pet. ether and showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.87 (2H, t, *J* = 6.0 Hz, H_4-THIQ), 3.52 (2H, t, *J* = 6.0 Hz, H_3-THIQ), 3.83 (3H, s, OCH_3), 4.35 (2H, s, H_1-THIQ), 6.72 (1H, d, *J* = 8.1 Hz, H_6-THIQ), 6.77 (1H, d, *J* = 7.7 Hz, H_8-THIQ), 6.91 (2H, d, *J* = 9.0 Hz, ArH, phenyl), 7.17 (1H, t, *J* = 8.0 Hz, H_7-THIQ) and 7.21 (2H, d, *J* = 9.0 Hz, ArH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.0 (C_4-THIQ), 46.8 (C_3-THIQ), 51.0 (C_1-THIQ), 55.5 (OCH_3), 107.8 (C_6-THIQ), 116.8 (ArCH, phenyl), 118.8 (C_8-THIQ), 123.6 (C_5CC_6-THIQ), 123.7 (ArCCl), 126.8 (C_7-THIQ), 129.1 (ArCH, phenyl), 135.5 (C_1CC_8-THIQ), 149.4 (ArCN) and 157.2 (C_5-THIQ) ppm. HRMS (ES^+) calcd. $C_{16}H_{17}{}^{35}ClNO$ (M^++H) 274.0993, found 274.1015; Mp 75-78 °C (pet. ether).

General method for the synthesis of amides 13a-c: $SOCl_2$ (14.6 mL, 200 mmol) was added to a stirring solution of 3-methoxyphenylacetic acid (3.39 g, 20.0 mmol) in anhydrous DCM (40 mL) and the mixture was stirred at rt for 4 h. The mixture was then evaporated and the residue was dissolved in anhydrous toluene (40 mL) and *N,N*-diisopropylethylamine (7.0 mL, 40.0 mmol), aniline (2.7 mL, 30.0 mmol) and a catalytic amount of DMAP were introduced in the order. The mixture was refluxed under inert atmosphere overnight and the solvent was then evaporated. The residue was dissolved in EtOAc (150 mL) and washed with 1 N HCl (3 x 100 mL), 1 N NaOH (3 x 100 mL) and brine (2 x 100 mL) then dried with $MgSO_4$, filtered and evaporated to give a yellow solid (2.73 g).

***N*-(3-chlorophenyl)-2-(3-methoxyphenyl)acetamide (13a)**
A sample of the crude compound (100 mg) was recrystallised from EtOAc/pet. ether and showed:[26] ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.70 (2H, s, $ArCH_2$), 3.82 (3H, s, $ArOCH_3$), 6.84 – 6.86 (1H, m, ArCH, benzyl), 6.87 – 6.93 (2H, m, 2 x ArCH, benzyl), 7.05 (1H, dd, *J* = 1.7, 8.1 Hz, ArCH, aniline), 7.16 (1H, bs, NH), 7.19 (1H, t, *J* = 8.1 Hz, ArCH, aniline), 7.27 (1H, dd, *J* = 1.7, 8.1 Hz, ArCH, aniline), 7.32 (1H, t, *J* = 8.0 Hz, ArCH, benzyl) and 7.52 (1H, t, *J* = 1.7 Hz, ArCH, aniline) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 44.9 ($ArCH_2$), 55.3 ($ArOCH_3$), 113.2 (ArCH, benzyl), 115.2 (ArCH, benzyl), 117.7 (ArCH, aniline), 119.8 (ArCH, aniline), 121.6 (ArCH, benzyl), 124.4 (ArCH, benzyl), 129.9 (ArCH, aniline), 130.4 (ArCH, aniline), 134.6 (ArCCl), 135.5 (Ar*C*CH_2), 138.7 (ArCN), 160.2 (ArCO) and 168.9 (CH_2*C*ONH) ppm. HRMS (ES^+) calc. for $C_{15}H_{14}{}^{35}ClNNaO_2$ (M^++Na) 298.0605, found 298.0600. Calc. for $C_{15}H_{14}{}^{37}ClNNaO_2$ (M^++Na) 300.0576, found 300.0589. Mp 93-94 °C (EtOAc/pet. ether).

***N*-(2-Chlorophenyl)-2-(3-methoxyphenyl)acetamide (13b)**

The crude compound was obtained as a white solid (3.65 g, 66%) which showed:[27] ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.77 (2H, s, CH_2CO), 3.83 (3H, s, CH_3O), 6.88 – 6.92 (2H, m, phenyl), 6.95 (1H, d, *J* = 7.5 Hz, ArCH, phenyl), 7.00 (1H, td, *J* = 1.5, 7.9 Hz, aniline), 7.24 (1H, dd, *J* = 0.9, 8.2 Hz, aniline), 7.28 (1H, dd, *J* = 1.4, 8.0 Hz, aniline), 7.34 (1H, dd, *J* = 7.5, 9.0 Hz, ArCH, phenyl), 7.72 (1H, bs, NH), 8.36 (1H, d, *J* = 7.5 Hz, ArCH, aniline) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 45.4 (*C*CO), 55.4 (CH_3O), 113.7 (ArCH, phenyl), 115.2 (ArCH, phenyl), 121.4 (ArCH, aniline), 122.0 (ArCH, phenyl), 122.9 (ArCCl), 124.8 (ArCH, aniline), 127.8 (ArCH, aniline), 129.1 (ArCH, aniline), 130.6 (ArCH, phenyl), 134.6 (ArCN), 135.5 (Ar*C*CH_2), 160.4 (*C*OCH_3) and 169.1 (NCO) ppm. LC/MS (ES^+) t_r = 1.66 min (95 %), m/z 276.1 (M^++H); (RP, Isocratic, 90% MeOH) HRMS (ES^+) calc. for $C_{15}H_{14}{}^{35}ClNaNO_2$ (M^++Na) 298.0605, found 298.0599. Calc. for $C_{15}H_{14}{}^{37}ClNaNO_2$ (M^++Na) 300.0575, found 300.0590. Mp 109-110 °C (EtOAc/pet. ether).

***N*-(3,4-Dichlorophenyl)-2-(3-methoxyphenyl)acetamide (13c)**

The crude compound was obtained as a white solid (4.7 g, 76%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.71 (2H, s, CH_2CO), 3.83 (3H, s, CH_3O), 6.85 (1H, t, *J* = 2.1 Hz, ArH, phenyl), 6.89 (2H, dd, *J* = 2.1, 8.0 Hz, ArH, phenyl), 7.08 (1H, bs, NH), 7.25 (1H, dd, *J* = 2.4, 9.0 Hz, ArH, aniline), 7.32 (1H, d, *J* = 9.0 Hz, ArH, Aniline), 7.33 (1H, t, *J* = 8.0 Hz, ArH, phenyl) and 7.64 (1H, d, *J* = 2.4 Hz, ArH, aniline) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 44.8 (*C*H_2CO), 55.3 (CH_3O), 113.3 (ArCH, phenyl), 115.2 (ArCH, phenyl), 118.9 (ArCH, aniline), 121.4 (ArCH, aniline), 121.6 (ArCH, phenyl), 127.6 (ArCN), 130.4 (ArCH, phenyl), 130.5 (ArCH, aniline), 132.7 (ArCCl), 135.3 (Ar*C*CH_2), 137.0 (ArCCl), 160.3 (ArCO) and 168.9 (NCO) ppm. LC/MS (ES^+) t_r = 2.10 min (92 %), m/z (not ionised) (M^++H); (RP, Isocratic, 90% MeOH). HRMS (ES^+) calc. for $C_{15}H_{13}{}^{35}Cl_2NaNO_2$ (M^++Na) 332.0216, found 332.0219. Calc. for $C_{15}H_{13}{}^{35}Cl^{37}ClNaNO_2$ (M^++Na) 334.0238, found 334.0235. Mp 121-122 °C (EtOAc/pet. ether).

***N*-(4-Chlorophenyl)-2-(3-methoxyphenyl)acetamide (13d)**

The crude compound was recrystallised from EtOAc/pet. ether to give a white solid (2.51 g, 46%) showed:[22] ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.77 (2H, s, CH_2CO), 3.83 (3H, s, CH_3O), 6.88 – 6.92 (2H, m, phenyl), 6.95 (1H, d, *J* = 7.5 Hz, ArCH, phenyl), 7.00 (1H, td, *J* = 1.5, 7.9 Hz, aniline), 7.24 (1H, dd, *J* = 0.9, 8.2 Hz, aniline), 7.28 (1H, dd, *J* = 1.4, 8.0 Hz, aniline), 7.34 (1H, dd, *J* = 7.5, 9.0 Hz, ArCH, phenyl), 7.72 (1H, bs, NH) and 8.36 (1H, d, *J* = 7.5 Hz, ArCH, aniline) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 45.4 (*C*CO), 55.4 (CH_3O), 113.7 (ArCH, phenyl), 115.2 (ArCH, phenyl), 121.4 (ArCH, aniline), 122.0 (ArCH, phenyl), 122.9 (ArCCl), 124.8 (ArCH, aniline), 127.8 (ArCH, aniline), 129.1 (ArCH, aniline), 130.6 (ArCH, phenyl), 134.6 (ArCN), 135.5 (Ar*C*CH_2), 160.4 (*C*OCH_3) and 169.1 (NCO) ppm. LC/MS (ES^+) t_r = 1.66 min (95 %), m/z 276.1 (M^++H); (RP, Isocratic, 90% MeOH). HRMS (ES^+) calc. for $C_{15}H_{14}{}^{35}ClNaNO_2$ (M^++Na) 298.0605, found 298.0599. Calc. for $C_{15}H_{14}{}^{37}ClNaNO_2$ (M^++Na) 300.0575, found 300.0590. Mp 224-225 °C (EtOAc/pet. ether).

2-(3-Methoxyphenyl)-*N*-phenylacetamide (13e)

The crude compound was purified by column chromatography (eluent: from 0% to 80% EtOAc in pet. ether) to give the product as a pale yellow solid (2.20 g, 46 %) which showed:[28] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (2H, s), 3.82 (3H, s), 6.81 – 6.89 (2H, m), 6.91 (1H, d, *J* = 7.5 Hz), 7.08 (1H, dd, *J* = 4.2, 10.5 Hz), 7.14 (1H, bs), 7.26 – 7.35 (2H, m) and 7.41 (2H, dd, *J* = 1.0, 8.5 Hz) ppm. HRMS (ES^+) calcd. $C_{15}H_{16}NO_2$ (M^++H) 242.1176, found 242.1184. Mp 109-110 °C (as hydrochloride from Et_2O).

2-(3-Methoxyphenyl)-*N*-(4-methoxyphenyl)acetamide (13f)

The crude compound was purified by column chromatography (eluent: from 0% to 80% EtOAc in pet. ether) to give the product as a pale yellow solid (2.77 g, 51 %) which showed:[29] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (2H, s), 3.76 (3H, s), 3.81 (3H, s), 6.81 (2H, d, *J* = 9.0 Hz), 6.84 – 6.89 (2H, m), 6.91 (1H, d, *J* = 7.5 Hz), 7.07 (1H, bs) and 7.27 – 7.35 (3H, m) ppm. HRMS (ES^+) calcd. $C_{16}H_{18}NO_3$ (M^++H) 272.1281, found 272.1277. Mp 102-103 °C (as hydrochloride from Et_2O).

General method for the reduction of the amides 13a-f: A solution of **13e** (2.0 g, 8.29 mmol) in anhydrous THF (41 mL) was added to a stirring suspension of $LiAlH_4$ (521 mg, 12.4 mmol) in THF (10 mL) under inert atmosphere and the mixture was stirred at 80 °C for 4 h during which time the mixture turned green. The mixture was then cooled to 0 °C, diluted with Et_2O (50 mL) and carefully quenched with water (0.6 mL) under inert atmosphere. The mixture was stirred for 15 min, during which time a black precipitate formed. 15% NaOH (0.6 mL) was introduced and the mixture was stirred for 15 min, during which time the precipitate turned white. Water (1.2 mL) was added and after stirring for 15 min the mixture was dried with $MgSO_4$, filtered and evaporated to give a brown oil (1.7 g).

3-Chloro-*N*-(3-methoxyphenethyl)aniline (14a)

The crude compound was purified by column chromatography (from 0% to 20% EtOAc in pet. ether) to give the product as a yellow oil (1.32 g, 66%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.89 (2H, t, *J* = 6.9 Hz, ArC*H*$_2$$CH_2$), 3.38 (2H, t, *J* = 6.9 Hz, CH_2C*H*$_2$N), 3.76 (1H, bs, NH), 3.80 (3H, s, $ArOCH_3$), 6.46 (1H, ddd, *J* = 0.8, 2.1, 8.0 Hz, ArCH, aniline), 6.58 (1H, t, *J* = 2.1 Hz, ArCH, aniline), 6.66 (1H, ddd, *J* = 0.8, 2.1, 8.0 Hz, ArCH, aniline), 6.73 – 6.77 (1H, m, ArCH, phenethyl), 6.77 – 6.83 (2H, m, ArCH, phenethyl), 7.07 (1H, t, *J* = 8.0 Hz, ArCH, aniline) and 7.24 (1H, t, *J* = 7.9 Hz, ArCH, phenethyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 35.3 (Ar*C*$H_2$$CH_2$), 44.6 (Ar$CH_2$*C*$H_2$), 55.2 ($ArOCH_3$), 111.3 (ArCH, aniline), 111.8

(ArCH, phenethyl), 112.5 (ArCH, aniline), 114.6 (ArCH, phenethyl), 117.2 (ArCH, aniline), 121.1 (ArCH, phenethyl), 129.7 (ArCH, phenethyl), 130.2 (ArCH, aniline), 135.0 (ArCCl), 140.5 (Ar*C*CH_2), 149.1 (ArCN) and 159.8 (ArCO) ppm. HRMS (ES^+) calc. for $C_{15}H_{17}{}^{35}ClNO$ (M^++H) 262.0993, found 262.0988. Calc. for $C_{15}H_{17}{}^{37}ClNO$ (M^++H) 264.0964, found 264.0966. Mp 136-138 °C (as hydrochloride from Et_2O).

2-Chloro-*N*-(3-methoxyphenethyl)aniline (14b)
The filtrate was evaporated to give a yellow oil (1.5 g, 93%) which showed:[30] ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.93 (2H, t, *J* = 7.1 Hz, ArCH_2), 3.44 (2H, t, *J* = 7.1 Hz, CH_2N), 3.81 (3H, s), 4.38 (1H, bs, NH), 6.63 (1H, td, *J* = 1.5, 7.6 Hz, ArH, aniline), 6.70 (1H, dd, *J* = 1.3, 8.2 Hz, ArH, aniline), 6.76 – 6.78 (1H, m, ArH, benzyl), 6.80 (1H, ddd, *J* = 0.7, 2.5, 8.2 Hz, ArH, benzyl), 6.81 – 6.85 (1H, m, ArH, benzyl), 7.12 – 7.18 (1H, m, ArH, aniline) and 7.25 (2H, td, *J* = 1.3, 7.8 Hz, ArH, aniline and ArH, benzyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 35.4 (ArCH_2), 44.8 (CH_2N), 55.2 (OCH_3), 111.2 (ArCH, aniline), 111.9 (ArCH, benzyl), 114.4 (ArCH, benzyl), 117.2 (ArCH, aniline), 119.3 (ArCCl), 121.1 (ArCH, benzyl), 127.8 (ArCH, aniline), 129.2 (ArCH, aniline), 129.6 (ArCH, benzyl), 140.6 (Ar*C*CH_2), 143.7 (ArCN) and 159.8 (ArCO) ppm. LC/MS (ES^+) t_r = 3.12 min (85 %), m/z 262.1 (M^++H); (RP, Isocratic, 90% MeOH). HRMS (ES^+) calc. for $C_{15}H_{17}{}^{35}ClNO$ (M^++H) 262.0993, found 262.0990. Calc. for $C_{15}H_{17}{}^{37}Cl$ NO (M^++H) 264.0964, found 264.0976. Mp 127-129 °C (as hydrochloride from Et_2O).

3,4-Dichloro-*N*-(3-methoxyphenethyl)aniline (14c)
The crude compound was purified by column chromatography (eluent: from 0% to 30% EtOAc in pet. ether) to get the product as a yellow oil (1.6 g, 75%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.88 (2H, t, *J* = 6.9 Hz, Ar*C*$H_2$$CH_2$), 3.36 (2H, t, *J* = 6.9 Hz, CH_2*C*H_2N), 3.80 (3H, s, OCH_3), 6.42 (1H, dd, *J* = 2.7, 8.7 Hz, ArCH, aniline), 6.66 (1H, d, *J* = 2.7 Hz, ArCH, aniline), 6.75 (1H, t, *J* = 2.1, ArCH, phenethyl), 6.80 (2H, dd, *J* = 2.1, 7.9 Hz, 2 x ArCH, phenethyl), 7.17 (1H, d, *J* = 8.7 Hz, ArCH, aniline) and 7.25 (1H, t, *J* = 7.9 Hz, ArCH, phenethyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 35.2 (Ar*C*$H_2$$CH_2$), 44.7 ($CH_2$*C*$H_2$N), 55.2 ($OCH_3$), 111.8 (ArCH, phenethyl), 112.7 (ArCH, aniline), 113.9 (ArCH, aniline), 114.6 (ArCH, phenethyl), 119.8 (ArCCl), 121.0 (ArCH, phenethyl), 129.7 (ArCH, phenethyl), 130.6 (ArCH, aniline), 132.8 (ArCCl), 140.3 (Ar*C*CH_2), 147.4 (ArCN) and 159.9 (ArCO) ppm. LC/MS (ES^+) t_r = 3.09 min (89 %), m/z 296.1 (M^++H) (^{35}Cl), m/z 298.0 (M^++H) (^{37}Cl); (RP, Isocratic, 90% MeOH) HRMS (ES^+) calc. for $C_{15}H_{16}{}^{35}Cl_2NO$ (M^++H) 296.0609, found 296.0597; calc. for $C_{15}H_{16}{}^{35}Cl{}^{37}ClNO$ (M^++H) 298.0580, found 298.0592. Mp 134-136 °C (as hydrochloride from Et_2O).

4-Chloro-*N*-(3-methoxyphenethyl)aniline (14d)
The compound was precipitate as hydrochloride from Et_2O to give a pale yellow solid (1.38 g, 64%) which showed:[22] ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.87 (2H, t, *J* = 6.9 Hz), 3.36 (2H, t, *J* = 6.9 Hz), 3.79 (3H, s), 6.52 (2H, d, *J* = 8.8 Hz), 6.74 (1H, s), 6.76 – 6.82 (2H, m), 7.11 (2H, d, *J* = 8.8 Hz) and 7.23 (3H, t, *J* = 7.9 Hz) ppm. HRMS (ES^+) calcd. $C_{15}H_{17}ClNO$ (M^++H) 262.0993, found 262.1000. Mp 149-151 °C (EtOAc/pet. ether).

***N*-(3-Methoxyphenethyl)aniline (14e)**
The crude compound was purified by column chromatography (eluent: from 0% to 40% EtOAc in pet. ether) to give the product as a colourless oil (1.21 g, 64%) which showed:[31] ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.91 (2H, t, *J* = 7.1 Hz, C*H*$_2$$CH_2$N), 3.41 (2H, t, *J* = 7.1 Hz, CH_2C*H*$_2$N), 3.80 (3H, s, ArOCH_3), 6.67 (2H, d, *J* = 7.8 Hz, 2 x ArCH, aniline), 6.74 (1H, t, *J* = 7.8 Hz, ArCH, aniline), 6.76 – 6.80 (2H, m, 2 x ArCH, phenethyl), 6.82 (1H, d, *J* = 7.5 Hz, ArCH, phenethyl), 7.20 (2H, t, *J* = 7.8 Hz, 2 x ArCH, aniline) and 7.24 (1H, t, *J* = 7.9 Hz, ArCH, phenethyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 35.3 (*C*$H_2$$CH_2$N), 45.3 ($CH_2$*C*$H_2$N), 55.2 (Ar$OCH_3$), 111.7 (ArCH, phenethyl), 113.4 (2 x ArCH, aniline), 114.5 (ArCH, phenethyl), 118.0 (ArCH, aniline), 121.1 (ArCH, phenethyl), 129.3 (2 x ArCH, aniline), 129.6 (ArCH, phenethyl), 140.7 (Ar*C*CH_2), 147.4 (ArCN) and 159.7 (ArCO) ppm. HRMS (ES^+) calcd. $C_{15}H_{17}NNaO$ (M^++Na) 250.1208, found 250.1201. Mp 98-100 °C (as hydrochloride from Et_2O).

4-Methoxy-*N*-(3-methoxyphenethyl)aniline (14f)
The crude compound was purified by column chromatography (eluent: from 0% to 40% EtOAc in pet. ether) to give the product as a yellow oil (1.39 g, 59%) which showed:[32] ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.89 (2H, t, *J* = 7.0 Hz, C*H*$_2$$CH_2$N), 3.36 (2H, t, *J* = 7.0 Hz, CH_2C*H*$_2$N), 3.75 (3H, s, ArOCH_3, aniline), 3.80 (3H, s, ArOCH_3, phenethyl), 6.63 (2H, d, *J* = 8.8 Hz, 2 x ArCH, aniline), 6.74 – 6.83 (5H, m, 3 x ArCH, phenethyl, 2 x ArCH, aniline) and 7.23 (1H, t, *J* = 7.8 Hz, ArCH, phenethyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 35.4 (*C*$H_2$$CH_2$N), 46.2 ($CH_2$*C*$H_2$N), 55.2 (Ar$OCH_3$, phenethyl), 55.8 (Ar$OCH_3$, aniline), 111.7 (ArCH, phenethyl), 114.5 (ArCH, phenethyl), 114.8 (2 x ArCH, aniline), 114.9 (2 x ArCH, aniline), 121.1 (ArCH, phenethyl), 129.6 (ArCH, phenethyl), 140.8 (Ar*C*CH_2), 141.6 (ArCN), 152.4 (ArCO, aniline) and 159.7 (ArCO, phenethyl) ppm. HRMS (ES^+) calcd. $C_{16}H_{19}NNaO_2$ (M^++Na) 280.1308, found 280.1312. Mp 108-111 °C (as hydrochloride from Et_2O).

General method for the Pictect-Spengler cyclisation: Compound **14b** (1.0 g, 3.82 mmol) was dissolved in toluene (18 mL) and treated with paraformaldehyde (573 mg, 19.1 mmol) and PTSA (32 mg, 0.191 mmol). After stirring at 90 °C for 18 h, the mixture was cooled to rt and filtered. The solvent was evaporated and the residue was dissolved in DCM (30 mL). The organic layer was washed with 1 N NaOH (20 mL) then dried with $MgSO_4$, filtered and evaporated to give a yellow oil (996 mg).

2-(3-Chlorophenyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (15a)
The crude compound was purified by column chromatography (eluent: from 0% to 20% EtOAc in pet. ether) to get the product as a colourless oil (247 mg, 52%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.95 (1H, t, *J* = 5.8 Hz, H_4-THIQ), 3.54 (1H, t, *J* = 5.8 Hz, H_3-THIQ), 3.80 (1H, s, OCH_3), 4.35 (1H, s, H_1-THIQ), 6.71 (1H, d, *J* = 2.5 Hz, H_5-THIQ), 6.76 (1H, ddd, *J* = 0.9, 2.2, 8.1 Hz, ArH, phenyl), 6.77 (1H, dd, *J* = 2.5, 8.4 Hz, H_7-THIQ), 6.81 (1H, ddd, *J* = 0.9, 2.2, 8.1 Hz, ArH, phenyl), 6.90 (1H, t, *J* = 2.2 Hz, ArH, phenyl), 7.08 (1H, d, *J* = 8.4 Hz, H_8-THIQ) and 7.17 (1H, t, *J* = 8.1 Hz, ArH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.4 (C_4-THIQ), 46.0 (C_3-THIQ), 49.7 (C_1-THIQ), 55.5 (OCH_3), 112.6 (C_7-THIQ), 112.7 (ArCH, phenyl), 113.3 (C_5-THIQ), 114.5 (ArCH, phenyl), 118.1 (ArCH, phenyl), 126.3 (C_1CC_8-THIQ), 127.6 (C_8-THIQ), 130.2 (ArCH, phenyl), 135.2 (ArCCl), 136.1 (C_5CC_6-THIQ), 151.5 (ArCN) and 158.4 (C_6-THIQ). LC/MS (ES^+) t_r = 3.84 min (95 %), m/z 273.9 (M^++H); (RP, Isocratic, 90% MeOH). HRMS (ES^+) calcd. $C_{16}H_{17}{}^{35}ClNO$ (M^++H) 274.0993, found 274.0981; calcd. $C_{16}H_{17}{}^{37}ClNO$ (M^++H) 276.0964, found 276.0974. Mp 112-114 °C (as hydrochloride from Et_2O).

2-(2-Chlorophenyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (15b)
The crude compound was purified by column chromatography (eluent: from 0% to 10% EtOAc in pet. ether) to give a colourless oil (600 mg, 57%) which was crystallised as hydrochloride from Et_2O and showed (^{1}H and ^{13}C NMR data refer to the free base):
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.00 (2H, t, *J* = 5.8 Hz, H_4-THIQ), 3.38 (2H, t, *J* = 5.8 Hz, H_3-THIQ), 3.80 (3H, s, OCH_3), 4.22 (2H, s, H_1-THIQ), 6.71 (1H, d, *J* = 2.6 Hz, H_5-THIQ), 6.75 (1H, dd, *J* = 2.6, 8.4 Hz, H_7-THIQ), 6.98 (1H, ddd, *J* = 1.5, 7.4, 7.8 Hz, ArH, phenyl), 7.02 (1H, d, *J* = 8.4 Hz, H_8-THIQ), 7.12 (1H, dd, *J* = 1.5, 8.0 Hz, ArH, phenyl), 7.22 (1H, ddd, *J* = 1.5, 7.4, 8.0 Hz, ArH, phenyl) and 7.39 (1H, dd, *J* = 1.5, 7.8 Hz, ArH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.4 (C_4-THIQ), 49.8 (C_3-THIQ), 52.7 (C_2-THIQ), 55.3 (CH_3O), 112.2 (C_7-THIQ), 113.5 (C_5-THIQ), 120.6, 123.5, 126.9 (C_1CC_8-THIQ), 127.3, 127.5, 128.8 (ArCCl), 130.7, 135.7 (C_4CC_5-THIQ), 149.1 (ArCN), 158.1 (C_6-THIQ) ppm. HRMS (ES^+) calc. for $C_{16}H_{17}{}^{35}ClNO$ (M^++H) 274.0993, found 274.0980; Calc. for $C_{16}H_{17}{}^{37}ClNO$ (M^++H) 276.0964, found 276.0974. Mp 59-61 °C (pet. ether).

2-(3,4-Dichlorophenyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (15c)
The crude compound was purified by column chromatography (eluent: from 0% to 20% EtOAc in pet. ether) to give yellow solid (631 mg, 55%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.94 (2H, t, *J* = 5.9 Hz, H_4-THIQ), 3.51 (2H, t, *J* = 5.9 Hz, H_3-THIQ), 3.80 (3H, s, OCH_3), 4.32 (2H, s, H_1-THIQ), 6.70 (1H, d, *J* = 2.5 Hz), 6.75 (1H, dd, *J* = 2.9, 8.9 Hz), 6.77 (1H, dd, *J* = 2.3, 8.1 Hz), 6.97 (1H, d, *J* = 2.9 Hz), 7.07 (1H, d, *J* = 8.4 Hz) and 7.27 (1H, d, *J* = 8.9 Hz) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.1, 45.8, 49.5, 55.3, 112.5, 113.2, 113.9, 115.7, 120.6, 125.8, 127.5, 130.4, 132.8, 135.8 and 158.3 ppm. HRMS (ES^+) calc. for $C_{16}H_{17}{}^{35}Cl_2NO$ (M^++H) 306.0447, found 306.0406. Calc. for $C_{16}H_{17}{}^{37}Cl_2NO$ (M^++H) 310.0388, found 310.0394. Calc. for $C_{16}H_{17}{}^{35}Cl{}^{37}ClNO$ (M^++H) 308.0417, found 308.0390. Mp 81-82 °C (pet. ether).

2-(2-Chlorophenyl)-8-methoxy-1,2,3,4-tetrahydroisoquinoline (16b)
The crude compound was purified by column chromatography (eluent: from 0% to 10% EtOAc in pet. ether) to give a pale yellow oil (46 mg, 4%) which showed: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.01 (2H, t, *J* = 5.7 Hz), 3.36 (2H, t, *J* = 5.7 Hz), 3.82 (3H, s), 4.21 (2H, s), 6.70 (1H, d, *J* = 8.1 Hz), 6.78 (1H, d, *J* = 7.6 Hz), 6.94 – 7.00 (1H, m), 7.15 (1H, t, *J* = 7.9 Hz), 7.18 – 7.23 (2H, m) and 7.38 (1H, dd, *J* = 1.5, 7.9 Hz) ppm. LC/MS (ES^+) t_r = 4.13 min (82 %), m/z 274.1 (M^++H); (RP, Isocratic, 90% MeOH).

2-(3,4-Dichlorophenyl)-8-methoxy-1,2,3,4-tetrahydroisoquinoline (16c)
The crude compound was purified by column chromatography (eluent: from 0% to 20% EtOAc in pet. ether) to give pale yellow oil (36 mg, 4%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.95 (2H, t, *J* = 5.8 Hz, H_4-THIQ), 3.50 (2H, t, *J* = 5.8 Hz, H_3-THIQ), 3.87 (3H, s, OCH_3), 4.28 (2H, s, H_1-THIQ), 6.73 (1H, d, *J* = 8.1 Hz, H_7-THIQ), 6.78 (1H, d, *J* = 7.6 Hz, H_5-THIQ), 6.82 (1H, dd, *J* = 2.9, 9.0 Hz, ArCH, phenyl), 7.04 (1H, d, *J* = 2.9 Hz, ArCH, phenyl), 7.17 (1H, t, *J* = 7.9 Hz, H_6-THIQ) and 7.28 (1H, d, *J* = 9.0 Hz, ArCH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.1, 45.6, 45.7, 55.4, 107.5, 114.3, 116.1, 120.8, 122.5, 127.2, 130.6, 132.9, 135.9, 150.2 and 156.2 ppm. LC/MS (ES^+) t_r = 6.12 min (12 %), m/z 308.1 (M^++H); (RP, Isocratic, 90% MeOH).

***N*-Methoxy-2-(3-methoxyphenyl)-*N*-methylacetamide (17)**
A solution of PCl_3 (3.5 mL, 40.0 mmol) in anhydrous toluene (50 mL) was added to a stirring suspension of *N,O*-dimethylhydroxylamine hydrochloride (12.3 g, 124.0 mmol) and Et_3N (39 mL, 280 mmol) at 0 °C under inert atmosphere and the mixture was stirred at rt overnight. 3-Methoxyphenylacetic acid (13.7 g, 80.0 mmol) was added and the mixture was stirred overnight at 120 °C under inert atmosphere. The mixture was evaporated and the residue was dissolved with EtOAc (150 mL). The organic layer was washed with 1 N HCl (3 x 100 mL) and brine (3 x 100 mL), then dried with $MgSO_4$, filtered and evaporated to give a brown oil (6.40 g). The crude compound was purified by column chromatography (eluent: from 0% to 40% EtOAc in pet. ether) to give the product as a yellow oil (5.50 g, 21%) which showed:[33] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.19 (3H, s), 3.60 (3H, s), 3.74 (2H, s), 3.79 (3H, s), 6.78 (1H, dd, *J* = 2.3, 8.2 Hz), 6.83 – 6.91 (2H, m) and 7.22 (1H, t, *J* = 7.8 Hz) ppm. HRMS (ES^+) calcd. $C_{11}H_{16}NO_3$ (M^++H) 210.1125, found 210.1125.

General method for the Weinreb reaction: 1.4 M solution of MeMgBr (1.2 mL, 1.67 mmol) in toluene/THF (3:1) was added to a stirring solution of **17** (290 mg, 1.39 mmol) in anhydrous THF (14 mL) under inert atmosphere and the mixture was stirred at rt for 1 h. The mixture was quenched with 1N HCl (3 mL) and extracted with EtOAc (3 x 30 mL). The combined organics were dried with $MgSO_4$, filtered and evaporated to give the product as a yellow oil (211 mg, 93%).

1-(3-Methoxyphenyl)propan-2-one (18a)
The product was obtained as a yellow oil (211 mg, 93%) which showed:[34] ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.15 (3H, s, CH_3CO), 3.66 (2H, s, CH_2CO), 3.80 (3H, s, $ArOCH_3$), 6.73 – 6.76 (1H, m, ArCH), 6.77 – 6.80 (1H, m, ArCH), 6.80 – 6.84 (1H, m, ArCH) and 7.25 (1H, t, *J* = 7.9 Hz, ArCH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.2 (CH_3CO), 51.1 (CH_2CO), 55.2 ($ArOCH_3$), 112.5 (ArCH), 115.0 (ArCH), 121.7 (ArCH), 129.8 (ArCH), 135.7 (Ar*C*CH_2), 159.8 (ArCO) and 206.3 (CH_2*C*O) ppm. HRMS (ES^+) calcd. $C_{10}H_{13}O_2$ (M^++H) 165.0910, found 165.0923; calcd. $C_{10}H_{12}NaO_2$ (M^++Na) 187.0730, found 187.0737.

1-(3-Methoxyphenyl)butan-2-one (18b)
The crude compound was purified by column chromatography (eluent: from 0% to 15% EtOAc in pet. ether) to give a colourless oil (257 mg, 50%) which showed:[35] ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (3H, t, *J* = 7.3 Hz, CH_2CH_3), 2.47 (2H, q, *J* = 7.3 Hz, CH_2CH_3), 3.65 (2H, s, $ArCH_2$), 3.80 (3H, s, OCH_3), 6.73 – 6.77 (1H, m, ArCH), 6.77 – 6.84 (2H, m, 2 x ArCH) and 7.24 (1H, t, *J* = 8.0 Hz, ArCH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 7.8 (CH_2CH_3), 35.1 (CH_2CH_3), 49.9 ($ArCH_2$), 55.2 (OCH_3), 112.4 (ArCH), 115.0 (ArCH), 121.7 (ArCH), 129.7 (ArCH), 135.9 (Ar*C*CH_2), 159.8 (ArCO) and 208.9 (CH_2CO) ppm. HRMS (ES^+) calcd. $C_{11}H_{15}O_2$ (M^++H) 179.1067, found 179.1075.

2-(3-Methoxyphenyl)-1-phenylethanone (18c)
The crude compound was purified by column chromatography (eluent: pet. ether) to give the product as a yellow oil (356 mg, 66%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.79 (3H, s $ArOCH_3$), 4.26 (2H, s, CH_2), 6.80 (1H, d, *J* = 8.2 Hz, ArCH, methoxyphenyl), 6.82 (1H, s, ArCH, methoxyphenyl), 6.86 (1H, d, *J* = 7.5 Hz, ArCH, methoxyphenyl), 7.24 (1H, t, *J* = 8.0 Hz, ArCH, methoxyphenyl), 7.46 (2H, t, *J* = 7.7 Hz, 2 x ArCH, phenyl), 7.56 (1H, t, *J* = 7.7 Hz, ArCH, phenyl) and 8.01 (2H, d, *J* = 7.7 Hz, 2 x ArCH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 45.6 (CH_2), 55.2 ($ArOCH_3$), 112.4 (ArCH, methoxyphenyl), 115.1 (ArCH, methoxyphenyl), 121.8 (ArCH, methoxyphenyl), 128.6 (4 x ArCH, phenyl), 129.6 (ArCH, methoxyphenyl), 133.2 (ArCH, phenyl), 136.0 (Ar*C*CH_2), 136.6 (Ar*C*CO), 159.8 (ArCO) and 197.5 (CH_2*C*O) ppm. HRMS (ES^+) calcd. $C_{15}H_{15}O_2$ (M^++H) 227.1072, found 227.1082; calcd. $C_{15}H_{14}NaO_2$ (M^++Na) 249.0891, found 249.0901.

1-(3-Methoxyphenyl)-3-phenylpropan-2-one (18d)
The crude compound was purified by column chromatography (eluent: pet. ether) to give the product as a colourless oil (160 mg, 28%) which showed:[36] ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.69 (2H, s, CH_2, methoxyphenyl), 3.72 (2H, s, CH_2, phenyl), 3.78 (3H, s, $ArOCH_3$), 6.69 (1H, s, ArCH, methoxyphenyl), 6.75 (1H, d, *J* = 7.5 Hz, ArCH, methoxyphenyl), 6.81 (1H, dd, *J* = 1.9, 7.9 Hz, ArCH, methoxyphenyl), 7.15 (2H, d, *J* = 7.4 Hz, 2 x ArCH, phenyl), 7.24 (1H, t, *J* = 7.9 Hz, ArCH, methoxyphenyl), 7.26 – 7.29 (1H, m, ArCH, phenyl) and 7.32 (2H, t, *J* = 7.4 Hz, 2 x ArCH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 49.0 (CH_2, phenyl), 49.2 (CH_2, methoxyphenyl), 55.2 ($ArOCH_3$), 112.7 (ArCH, methoxyphenyl), 115.0 (ArCH, methoxyphenyl), 121.8 (ArCH, methoxyphenyl), 127.0 (ArCH, phenyl), 128.7 (2 x ArCH, phenyl), 129.5 (2 x ArCH, phenyl), 129.7 (ArCH, methoxyphenyl), 134.0 ($ArCCH_2$, phenyl), 135.4 ($ArCCH_2$, methoxyphenyl), 159.8 (ArCO) and 205.6 (CH_2*C*O) ppm.

4-Chloro-*N*-(1-(3-methoxyphenyl)propan-2-yl)aniline (19a)
$NaBH(OAc)_3$ (306 mg, 1.37 mmol) was added to a stirring solution of **18a** (105 mg, 0.914 mmol) and 4-chloroaniline (117 mg, 0.914 mmol) in $CHCl_3$ (5 mL) and the mixture was stirred at rt for 6 h. The mixture was diluted with $CHCl_3$ (15 mL) and washed with sat. aq. Na_2CO_3 (3 x 10 mL), then dried with $MgSO_4$, filtered and evaporated to give a yellow oil (205 mg). The crude compound was purified by column chromatography (eluent: from 0% to 30 % EtOAc in pet. ether) to get the product as a yellow oil (53 mg, 21%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16 (3H, d, *J* = 6.4 Hz, $CHCH_3$), 2.70 (1H, dd, *J* = 7.4, 13.4 Hz, CH_2CH), 2.91 (1H, dd, *J* = 4.7, 13.4 Hz, CH_2CH), 3.67 – 3.75 (1H, m, $CHCH_3$), 3.79 (3H, s, OCH_3), 6.61 (2H, d, *J* = 8.5 Hz, 2 x ArCH, aniline), 6.70 (1H, s, ArCH, phenyl), 6.73 – 6.81 (2H, m, 2 x ArCH, phenyl), 7.14 (2H, d, *J* = 8.7 Hz, 2 x ArCH, aniline) and 7.22 (1H, t, *J* = 7.9 Hz, ArCH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.8 ($CHCH_3$), 41.9 (CH_2CH), 50.2 ($CHCH_3$), 55.1 (OCH_3), 111.5 (ArCH, phenyl), 115.2 (2 x ArCH, aniline), 115.3 (ArCH, phenyl), 121.8 (ArCH, phenyl), 122.5 (ArCCl), 129.2 (2 x ArCH, aniline), 129.3 (ArCH, phenyl), 139.6 (Ar*C*CH_2), 144.9 (ArCN) and 159.6 (ArCO) ppm.

4-Chloro-*N*-(1-(3-methoxyphenyl)butan-2-yl)aniline (19b)
$NaBH(OAc)_3$ (445 mg, 2.10 mmol) was added to a stirring solution of **18b** (250 mg, 1.40 mmol) and 4-chloroaniline (268 mg, 2.10 mmol) in $CHCl_3$ (15 mL) and the mixture was stirred at rt overnight. The mixture was diluted with $CHCl_3$ (15 mL) and washed with sat. aq. Na_2CO_3 (2 x 30 mL) then dried with $MgSO_4$, filtered and evaporated to give a yellow oil (383 mg). the crude compound was purified by column chromatography (eluent: from 0% to 20% EtOAc in pet. ether) to give the product as a colourless oil (67 mg, 19%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (3H, t, *J* = 7.4 Hz, CH_2CH_3), 1.35 – 1.51 (1H, m, CH_2CH_3), 1.57 – 1.71 (1H, m, CH_2CH_3), 2.74 – 2.90 (2H, m, $ArCH_2$), 3.47 – 3.60 (1H, m, CHN), 3.80

(3H, s, OCH_3), 6.57 (2H, d, *J* = 8.7 Hz, 2 x ArCH, aniline), 6.72 (1H, s, ArCH, phenyl), 6.77 (1H, d, *J* = 8.7 Hz, ArCH, phenyl), 6.79 (1H, d, *J* = 8.7 Hz, ArCH, phenyl), 7.14 (2H, d, *J* = 8.7 Hz, ArCH, phenyl) and 7.23 (1H, t, *J* = 7.9 Hz) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 10.4 (CH_2CH_3), 26.6 (CH_2CH_3), 39.6 ($ArCH_2$), 55.1 (OCH_3), 55.5 (CHN), 111.4 (ArCH, phenyl), 114.5 (2 x ArCH, aniline), 115.4 (ArCH, phenyl), 121.8 (ArCCl), 121.9 (ArCH, phenyl), 129.2 (2 x ArCH, aniline), 129.3 (ArCH, phenyl), 139.8 ($ArCCH_2$), 145.9 (ArCN) and 159.6 (ArCO) ppm. HRMS (ES^-) calcd. $C_{17}H_{19}{}^{35}ClNO$ (M^--H) 288.1161, found 288.1159; calcd. $C_{17}H_{19}{}^{37}ClNO$ (M^--H) 290.1131, found 290.1119.

4-Chloro-*N*-(1-(3-methoxyphenyl)-3-phenylpropan-2-yl)aniline (19d)
$NaBH(OAc)_3$ (393 mg, 1.76 mmol) was added to a stirring solution of **18d** (280 mg, 1.17 mmol) and 4-chloroaniline (149 mg, 1.17 mmol) in dichloroethane (3.0 mL). Glacial acetic acid (67 µL, 1.17 mmol) was introduced and the mixture was stirred at rt overnight during which time the suspension turned into a solution. The mixture was diluted with DCM (10 mL) and washed with 1 N NaOH (1 x 10 mL) then dried with $MgSO_4$, filtered and evaporated to give a yellow oil (305 mg). The crude compound was purified by column chromatography (eluent: from 0% to 40 % EtOAc in pet. ether) to give the product as a yellow oil (116 mg, 28%) which showed: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64 – 2.95 (4H,z m), 3.77 (3H, m), 3.85 – 4.01 (1H, m), 6.51 (2H, d, *J* = 8.9 Hz), 6.69 – 6.72 (1H, m), 6.73 – 6.79 (2H, m), 7.09 (2H, d, *J* = 8.9 Hz), 7.15 – 7.19 (2H, m), 7.22 (2H, dd, *J* = 2.1, 7.7 Hz) and 7.26 – 7.30 (2H, m) ppm. HRMS (ES^+) calcd. $C_{22}H_{21}{}^{35}ClNO$ (M^--H) 350.1317, found 350.1328; calcd. $C_{22}H_{21}{}^{37}ClNO$ (M^--H) 352.1288, found 352.1301.

2-(4-Chlorophenyl)-6-methoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (20a)
Synthesized according to the general method for the Pictect-Spengler cyclisation. The crude compound was purified by column chromatography (eluent: from 0% to 20% EtOAc in pet. ether) to give the product as a white solid (120 mg, 28%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (3H, d, *J* = 6.6 Hz, $CHCH_3$), 2.66 (1H, dd, *J* = 2.0, 15.6 Hz, H_4-THIQ), 3.23 (1H, dd, *J* = 5.4, 15.6 Hz, H_4-THIQ), 3.81 (3H, s, OCH_3), 4.17 (1H, d, *J* = 15.0 Hz, H_1-THIQ), 4.24 – 4.32 (1H, m, H_3-THIQ), 4.35 (1H, d, *J* = 15.0 Hz, H_1-THIQ), 6.72 (1H, d, *J* = 2.6 Hz, H_5-THIQ), 6.79 (1H, dd, *J* = 2.6, 8.4 Hz, H_7-THIQ), 6.85 (2H, d, *J* = 9.0 Hz, 2 x ArCH, phenyl), 7.09 (1H, d, *J* = 8.4 Hz, H_8-THIQ) and 7.23 (2H, d, *J* = 9.0 Hz, 2 x ArCH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.5 ($CHCH_3$), 35.7 (C_4-THIQ), 45.7 (C_1-THIQ), 48.8 (C_3-THIQ), 55.2 (OCH_3), 112.2 (C_7-THIQ), 113.8 (C_5-THIQ), 115.4 (2 x ArCH, phenyl), 122.4 (ArCCl), 125.3 (C_1CC_8-THIQ), 127.3 (C_8-THIQ), 129.0 (2 x ArCH, phenyl), 134.3 (C_4CC_5-THIQ), 147.9 (ArCN) and 158.3 (C_6-THIQ) ppm. HRMS (ES^+) calcd. $C_{17}H_{19}{}^{35}ClNO$ (M^++H) 288.1150, found 288.1156. Mp 86-90 °C (pet. ether).

2-(4-Chlorophenyl)-3-ethyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (20b)
Synthesized according to the general method for the Pictect-Spengler cyclisation. The crude compound was purified by column chromatography (eluent: from 0% to 20% EtOAc in pet. ether) to give the product as a colourless oil (92 mg, 44%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, t, *J* = 7.4 Hz, CH_2CH_3), 1.27 – 1.37 (1H, m, CH_2CH_3), 1.49 – 1.60 (1H, m, CH_2CH_3), 2.78 (1H, dd, *J* = 1.5, 15.8 Hz, H_4-THIQ), 3.11 (1H, dd, *J* = 5.4, 15.7 Hz, H_4-THIQ), 3.81 (3H, s, OCH_3), 3.95 – 4.03 (1H, m, H_3-THIQ), 4.20 (1H, d, *J* = 15.2 Hz, H_1-THIQ), 4.35 (1H, d, *J* = 15.1 Hz, H_1-THIQ), 6.70 (1H, d, *J* = 2.2 Hz, H_5-THIQ), 6.78 (1H, dd, *J* = 2.5, 8.4 Hz, H_7-THIQ), 6.81 (2H, d, *J* = 9.0 Hz, 2 x ArCH, phenyl), 7.08 (1H, d, *J* = 8.4 Hz, H_8-THIQ) and 7.20 (2H, d, *J* = 9.0 Hz, 2 x ArCH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 11.4 (CH_2CH_3), 23.2 (CH_2CH_3), 32.3 (C_4-THIQ), 45.7 (C_1-THIQ), 55.1 (C_3-THIQ), 55.2 (OCH_3), 112.1 (C_7-THIQ), 113.9 (C_5-THIQ), 115.0 (2 x ArCH, phenyl), 121.9 (ArCCl), 125.6 (C_1CC_8-THIQ), 127.2 (C_8-THIQ), 129.0 (2 x ArCH, phenyl), 134.5 (C_4CC_5-THIQ), 148.3 (ArCN) and 158.2 (C_6-THIQ) ppm.

2-(4-Chlorophenyl)-3-ethyl-8-methoxy-1,2,3,4-tetrahydroisoquinoline (21b)
Synthesized according to the general method for the Pictect-Spengler cyclisation. The crude compound was purified by column chromatography (eluent: from 0% to 20% EtOAc in pet. ether) to give the product as a colourless oil (8 mg, 4%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (3H, t, *J* = 7.4 Hz, CH_2CH_3), 1.27 – 1.42 (1H, m, CH_2CH_3), 1.47 – 1.59 (1H, m, CH_2CH_3), 2.79 (1H, d, *J* = 15.9 Hz, H_4-THIQ), 3.13 (1H, dd, *J* = 5.4, 15.9 Hz, H_4-THIQ), 3.87 (3H, s, OCH_3), 3.99 – 4.06 (1H, m, H_3-THIQ), 4.09 (1H, d, *J* = 17.4 Hz, H_1-THIQ), 4.37 (1H, d, *J* = 16.8 Hz, H_1-THIQ), 6.73 (1H, d, *J* = 7.9 Hz, H_7-THIQ), 6.76 (1H, d, *J* = 7.9 Hz, H_5-THIQ), 6.88 (2H, d, *J* = 9.1 Hz, 2 x ArCH, phenyl), 7.17 (1H, t, *J* = 7.9 Hz, H_6-THIQ) and 7.20 (2H, d, *J* = 9.1 Hz, 2 x ArCH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 11.5 (CH_2CH_3), 22.6 (CH_2CH_3), 32.0 (C_4-THIQ), 41.5 (C_1-THIQ), 54.5 (C_3-THIQ), 55.2 (OCH_3), 107.2 (C_7-THIQ), 115.3 (2 x ArCH, phenyl), 121.3 (C_5-THIQ), 121.9 (ArCCl), 122.0 (C_1CC_8-THIQ), 126.9 (C_6-THIQ), 128.9 (2 x ArCH, phenyl), 134.2 (C_4CC_5-THIQ), 148.6 (ArCN) and 155.7 (C_8-THIQ) ppm.

Methyl 2-(3-methoxyphenyl)acetate (23)
Conc. H_2SO_4 (1.2 mL) was added dropwise to a stirring solution of 3-methoxyphenylacetic acid (6.78 g, 40.0 mmol) in MeOH (80 mL) and the mixture was refluxed for 3 days. Product did not form according to TLC. The mixture was then stirred for 3 h under reflux and inert atmosphere using a Soxhlet extractor containing CaH_2 as dehydrating agent. The mixture was then neutralised with Na_2CO_3, filtered and evaporated. The residue was dissolved in EtOAc (100 mL) and washed with 1 N NaOH (3 x 100 mL) and brine (100 mL) then dried with $MgSO_4$, filtered and evaporated to give the product as a colourless oil (6.36 g, 88%) which showed: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 (2H, s), 3.69 (3H, s), 3.80 (3H, s), 6.79 – 6.84 (2H, m), 6.86 (1H, d, *J* = 7.6 Hz) and 7.24 (1H, t, *J* = 7.8 Hz) ppm.

General method for the alkylation of the ester 23: 2.0 M LDA (3.3 mL, 6.66 mmol) was added to a stirring solution of **23** (1.0 g, 5.55 mmol) in anhydrous THF (50 mL) at -78 °C under inert atmosphere and the mixture was stirred for 1 h. Methyl iodide (384 µL, 6.11 mmol) was added and the mixture was stirred for 1 h at -78 °C then let reach rt and stirred for further 4 h. The mixture was cooled to 0 °C and carefully quenched with 1 N HCl (10 mL) then the organic solvent was evaporated. The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organics were washed with 1 N HCl (3 x 50 mL) and brine (3 x 50 mL) then dried with $MgSO_4$, filtered and evaporated to give a brown oil (1.11 g).

Methyl 2-(3-methoxyphenyl)propanoate (24a)
The crude compound was not purified and showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.49 (3H, d, *J* = 7.1 Hz, CHC*H*$_3$), 3.66 (3H, s, COOCH_3), 3.70 (1H, q, *J* = 7.1 Hz, C*H*CH$_3$), 3.80 (3H, s, ArOCH_3), 6.80 (1H, dd, *J* = 2.3, 8.2 Hz, ArCH), 6.84 (1H, t, *J* = 2.3 Hz, ArCH), 6.88 (1H, dd, *J* = 2.3, 8.2 Hz, ArCH) and 7.24 (1H, t, *J* = 8.0 Hz, ArCH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.5 (CH*C*H$_3$), 45.4 (*C*HCH$_3$), 52.0 (COO*C*H$_3$), 55.2 (ArOCH_3), 112.4 (ArCH), 113.2 (ArCH), 119.8 (ArCH), 129.6 (ArCH), 142.0 (Ar*C*CH), 159.7 (ArCO) and 174.8 (COO) ppm. HRMS (ES$^+$) calcd. $C_{11}H_{15}O_3$ (M^++H) 195.1021, found 195.1014; calcd. $C_{11}H_{14}NaO_3$ (M^++H) 217.0841, found 217.0831.

Methyl 2-(3-methoxyphenyl)butanoate (24b)
The crude compound was not purified and showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 7.4 Hz, CH$_2$C*H*$_3$), 1.72 – 1.86 (1H, m, CHC*H*$_2$), 2.03 – 2.14 (1H, m, CHC*H*$_2$), 3.42 (1H, t, *J* = 7.7 Hz, C*H*CH$_2$), 3.66 (3H, s, COOCH_3), 3.80 (3H, s, ArOCH_3), 6.80 (1H, ddd, *J* = 0.6, 2.5, 7.9 Hz, ArCH), 6.83 – 6.86 (1H, m, ArCH), 6.88 (1H, d, *J* = 7.9 Hz, ArCH) and 7.23 (1H, t, *J* = 7.9 Hz, ArCH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.1 (CH$_2$*C*H$_3$), 26.7 (CH*C*H$_2$), 51.9 (COO*C*H$_3$), 53.4 (*C*HCH$_2$), 55.2 (ArOCH$_3$), 112.5 (ArCH), 113.6 (ArCH), 120.4 (ArCH), 129.5 (ArCH), 140.6 (Ar*C*CH), 159.7 (ArCO) and 174.4 (COO) ppm. HRMS (ES$^+$) calcd. $C_{12}H_{17}O_3$ (M^++H) 209.1178, found 209.1163; calcd. $C_{12}H_{16}NaO_3$ (M^++H) 231.0997, found 231.0980.

Methyl 2-(3-methoxyphenyl)-3-methylbutanoate (24c)
The crude compound was purified by column chromatography (eluent: from 0% to 20% EtOAc in pet. ether) to give the product as a yellow oil (243mg, 20%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.71 (3H, d, *J* = 6.7 Hz, (C*H*$_3$)$_2$CH), 1.02 (3H, d, *J* = 6.5 Hz, (C*H*$_3$)$_2$CH), 2.24 – 2.41 (1H, m, (CH$_3$)$_2$C*H*), 3.12 (1H, d, *J* = 10.6 Hz, (CH$_3$)$_2$CHC*H*), 3.65 (3H, s, COOCH_3), 3.80 (3H, s, ArOCH_3), 6.80 (1H, dd, *J* = 1.7, 8.2 Hz, ArCH), 6.90 (2H, d, *J* = 7.8 Hz, 2 x ArCH) and 7.22 (1H, t, *J* = 7.8 Hz, ArCH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.2 ((*C*H$_3$)$_2$CH), 21.5 ((*C*H$_3$)$_2$CH), 31.9 ((CH$_3$)$_2$*C*H), 51.7 (COO*C*H$_3$), 55.2 (ArOCH$_3$), 60.0 ((CH$_3$)$_2$CH*C*H), 112.5 (ArCH), 114.1 (ArCH), 121.0 (ArCH), 129.3 (ArCH), 139.9 (Ar*C*CH), 159.6 (ArCO) and 174.3 (COO) ppm. HRMS (ES$^+$) calcd. $C_{13}H_{19}O_3$ (M^++H) 223.1334, found 223.1325; calcd. $C_{13}H_{18}NaO_3$ (M^++H) 245.1153, found 245.1133.

Methyl 2-(3-methoxyphenyl)-3-phenylpropanoate (24d)
The crude compound was purified by column chromatography (eluent: from 0% to 10% EtOAc in pet. ether) to give the product as a colourless oil (1.29 g, 86 %) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.02 (1H, dd, *J* = 6.7, 13.7 Hz, C*H*$_2$CH), 3.41 (1H, dd, *J* = 8.8, 13.7 Hz, C*H*$_2$CH), 3.61 (3H, s, COOCH_3), 3.79 (3H, s, ArOCH_3), 3.83 (1H, dd, *J* = 6.7, 8.8 Hz, CH$_2$C*H*), 6.81 (1H, dd, *J* = 2.4, 8.2 Hz, ArCH, methoxyphenyl), 6.84 – 6.88 (1H, m, ArCH, methoxyphenyl), 6.89 (1H, d, *J* = 7.7 Hz, ArCH, methoxyphenyl), 7.13 (2H, d, *J* = 7.1 Hz, 2 x ArCH, phenyl) and 7.16 – 7.26 (4H, m, 3 x ArCH, phenyl, ArCH, methoxyphenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 39.7 (*C*H$_2$CH), 52.0 (COO*C*H$_3$), 53.6 (CH$_2$*C*H), 55.2 (ArOCH$_3$), 112.8 (ArCH, methoxyphenyl), 113.6 (ArCH, methoxyphenyl), 120.3 (ArCH, methoxyphenyl), 126.4 (ArCH, phenyl), 128.3 (2 x ArCH, phenyl), 128.9 (2 x ArCH, phenyl), 129.6 (ArCH, methoxyphenyl), 139.0 (Ar*C*CH$_2$), 140.1 (Ar*C*CH), 159.7 (ArCO) and 173.7 (COO) ppm. HRMS (ES$^+$) calcd. $C_{17}H_{19}O_3$ (M^++H) 271.1334, found 271.1320; calcd. $C_{17}H_{18}NaO_3$ (M^++H) 293.1154, found 293.1149.

Methyl 2-(3-methoxyphenyl)-2-methylpropanoate (24e)
The crude compound was not purified and showed:[36] ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.57 (6H, s, C(C*H*$_3$)$_2$), 3.65 (3H, s, COOCH_3), 3.80 (3H, s, ArOCH_3), 6.78 (1H, dd, *J* = 2.2, 7.9 Hz, ArCH), 6.88 (1H, t, *J* = 2.2 Hz, ArCH), 6.92 (1H, dd, *J* = 2.2, 7.9 Hz, ArCH) and 7.25 (1H, t, *J* = 7.9 Hz, ArCH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.5 (C(*C*H$_3$)$_2$), 46.5 (*C*(CH$_3$)$_2$), 52.2 (COOCH$_3$), 55.2 (ArOCH$_3$), 111.4 (ArCH), 112.1 (ArCH), 118.0 (ArCH), 129.3 (ArCH), 146.3 (Ar*C*C(CH$_3$)$_2$), 159.5 (ArCO) and 177.1 (COO) ppm. HRMS (ES$^+$) calcd. $C_{12}H_{16}NaO_3$ (M^++H) 231.0997, found 231.0990.

General method for the direct conversion of ester into amide: 4-Chloroaniline (1.10 g, 8.49 mmol) was added to a stirring solution of bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane adduct (2.20 g, 8.49 mmol) in anhydrous THF (15 mL) under inert atmosphere and the mixture was stirred at 40 °C for 1 h. A solution of **24a** (1.10 g, 5.66 mmol) in anhydrous THF (3 mL) was added and the mixture was refluxed overnight. The mixture was then evaporated and the residue was dissolved in EtOAc (50 mL). The organic layer was then washed with 1 N HCl (3 x 50 mL) and brine (50 mL) then dried with $MgSO_4$, filtered and evaporated to give a brown oil (1.10 g).

***N*-(4-Chlorophenyl)-2-(3-methoxyphenyl)propanamide (25a)**
The crude compound was purified by column chromatography (eluent: from 0% to 40% EtOAc in pet. ether) to give the product as a yellow oil (418 mg, 25%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.58 (3H, d, *J* = 7.1 Hz, CHC*H*$_3$), 3.68 (1H, q, *J* = 7.1 Hz, C*H*CH_3), 3.81 (3H, s, OCH_3), 6.85 (1H, dd, *J* = 2.3, 7.9 Hz, ArCH, phenacetyl), 6.87 – 6.90 (1H, m, ArCH, phenacetyl), 6.93 (1H, d, *J* = 7.9 Hz, ArCH, phenacetyl), 7.08 (1H, bs, NH), 7.22 (2H, d, *J* = 8.8 Hz, ArCH, aniline), 7.30 (1H, t, *J* = 7.9 Hz, ArCH, phenacetyl) and 7.36 (2H, d, *J* = 8.8 Hz, ArCH, aniline) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.3 (CH*C*H_3), 48.1 (*C*HCH_3), 55.3 (OCH_3), 112.9 (ArCH, phenacetyl), 113.5 (ArCH, phenacetyl), 119.9 (ArCH, phenacetyl), 120.9 (2 x ArCH, aniline), 128.9 (2 x ArCH, aniline), 129.2 (ArCCl), 130.3 (ArCH, phenacetyl), 136.4 (ArCN), 142.2 (Ar*C*CH), 160.2 (ArCO) and 172.1 (CON) ppm. HRMS (ES^+) calcd. $C_{16}H_{17}{}^{35}ClNO_2$ (M^++H) 290.0942, found 290.0954; calcd. $C_{16}H_{17}{}^{37}ClNO_2$ (M^++H) 292.0913, found 292.0961.

***N*-(4-Chlorophenyl)-2-(3-methoxyphenyl)butanamide (25b)**
The crude compound was purified by column chromatography (eluent: from 0% to 40% EtOAc in pet. ether) to give the product as a yellow solid (400 mg, 24%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (3H, t, *J* = 7.4 Hz, CH_2CH_3), 1.77 – 1.96 (1H, m, CHCH_2), 2.16 – 2.35 (1H, m, CHCH_2), 3.35 (1H, t, *J* = 7.5 Hz, C*H*CH_2), 3.81 (3H, s OCH_3), 6.84 (1H, dd, *J* = 2.1, 8.2 Hz, ArCH, phenacetyl), 6.87 – 6.90 (1H, m, ArCH, phenacetyl), 6.92 (1H, d, *J* = 7.6 Hz, ArCH, phenacetyl), 7.08 (1H, bs, NH), 7.23 (2H, d, *J* = 8.8 Hz, ArCH, aniline), 7.29 (1H, t, *J* = 7.9 Hz, ArCH, phenacetyl) and 7.38 (2H, d, *J* = 8.8 Hz, ArCH, aniline) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.3 (CH_2*C*H_3), 26.2 (CH*C*H_2), 55.2 (OCH_3), 56.1 (*C*HCH_2), 112.8 (ArCH, phenacetyl), 113.8 (ArCH, phenacetyl), 120.3 (ArCH, phenacetyl), 120.9 (2 x ArCH, aniline), 128.9 (2 x ArCH, aniline), 129.2 (ArCCl), 130.1 (ArCH, phenacetyl), 136.4 (ArCN), 140.8 (Ar*C*CH), 160.1 (ArCO) and 171.5 (CON) ppm. HRMS (ES^+) calcd. $C_{17}H_{19}{}^{35}ClNO_2$ (M^++H) 304.1099, found 304.1116; calcd. $C_{17}H_{19}{}^{37}ClNO_2$ (M^++H) 306.1069, found 306.1098.

***N*-(4-Chlorophenyl)-2-(3-methoxyphenyl)-3-methylbutanamide (25c)**
The crude compound was purified by column chromatography (eluent: from 0% to 20 % EtOAc in pet. ether) to give the product as a yellow oil (212 mg, 42%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.76 (3H, d, *J* = 6.6 Hz, (C*H*$_3$)$_2$CH), 1.09 (3H, d, *J* = 6.5 Hz, (C*H*$_3$)$_2$CH), 2.40 – 2.56 (1H, m, , $(CH_3)_2$C*H*), 2.95 (1H, d, *J* = 10.0 Hz, $(CH_3)_2$CHC*H*), 3.80 (3H, s, OCH_3), 6.81 (1H, dd, *J* = 1.9, 8.2 Hz, ArCH, phenacetyl), 6.87 – 6.96 (2H, m, 2 x ArCH, phenacetyl), 7.18 (1H, bs, NH), 7.20 – 7.25 (3H, m, 2 x ArCH, aniline, ArCH, phenacetyl) and 7.42 (2H, d, *J* = 8.7 Hz m, 2 x ArCH, aniline) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.3 ((*C*H$_3$)$_2$CH), 21.7 ((*C*H$_3$)$_2$CH), 31.5 ((CH$_3$)$_2$*C*H), 55.2 (OCH_3), 62.8 ((CH$_3$)$_2$CH*C*H), 112.7 (ArCH, phenacetyl), 113.9 (ArCH, phenacetyl), 120.7 (ArCH, phenacetyl), 121.0 (2 x ArCH, aniline), 128.9 (2 x ArCH, aniline), 129.2 (ArCCl), 129.7 (ArCH, phenacetyl), 136.4 (ArCN), 140.2 (Ar*C*CH), 159.8 (ArCO) and 171.4 (CON) ppm.

***N*-(4-Chlorophenyl)-2-(3-methoxyphenyl)-3-phenylpropanamide (25d)**
The crude compound was purified by column chromatography (eluent: from 0% to 40% EtOAc in pet. ether) to give the product as a yellow oil (145 mg, 9%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.04 (1H, dd, *J* = 7.4, 13.6 Hz, CHCH_2), 3.60 (1H, dd, *J* = 7.4, 13.6 Hz, CHCH_2), 3.69 (1H, t, *J* = 7.4 Hz, C*H*CH_2), 3.78 (3H, s, OCH_3), 6.82 (1H, dd, *J* = 2.2, 8.2 Hz, ArCH, methoxyphenyl), 6.84 – 6.88 (1H, m, ArCH, methoxyphenyl), 6.90 (1H, d, *J* = 7.6 Hz, ArCH, methoxyphenyl) 6.98 (1H, bs, NH), 7.13 (2H, d, *J* = 7.3 Hz, 2 x ArCH, phenyl), 7.17 (1H, t, *J* = 7.3 Hz, ArCH, phenyl), 7.21 (3H, d, *J* = 8.8 Hz, 2 x ArCH, aniline), 7.23 (2H, d, *J* = 7.3 Hz, ArCH, phenyl), 7.26 (1H, d, *J* = 7.8 Hz, ArCH, methoxyphenyl) and 7.32 (2H, d, *J* = 8.7 Hz, ArCH, aniline) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 39.5 (CH*C*H_2), 55.3 (OCH_3), 56.5 (*C*HCH_2), 113.1 (ArCH, methoxyphenyl), 113.8 (ArCH, methoxyphenyl), 120.4 (ArCH, methoxyphenyl), 121.1 (2 x ArCH, aniline), 126.4 (ArCH, phenyl), 128.4 (2 x ArCH, aniline), 128.9 (2 x ArCH, phenyl), 129.0 (2 x ArCH, aniline), 129.3 (ArCCl), 130.0 (ArCH, methoxyphenyl), 136.2 (ArCN), 139.3 (Ar*C*CH$_2$), 140.4 (Ar*C*CH), 160.0 (ArCO) and 170.7 (CON) ppm. HRMS (ES^+) calcd. $C_{22}H_{21}{}^{35}ClNO_2$ (M^++H) 366.1255, found 366.1274; calcd. $C_{22}H_{21}{}^{37}ClNO_2$ (M^++H) 368.1226, found 368.1250.

***N*-(4-Chlorophenyl)-2-(3-methoxyphenyl)-2-methylpropanamide (25e)**
The crude compound was not purified and showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.64 (6H, s, (C*H*$_3$)$_2$C), 3.82 (3H, s, OCH_3), 6.81 (1H, bs, NH), 6.86 (1H, dd, *J* = 2.1, 7.9 Hz, ArCH, phenacetyl), 6.96 (1H, t, *J* = 2.1 Hz, ArCH, phenacetyl), 7.01 (1H, dd, *J* = 2.1, 7.9 Hz, ArCH, phenacetyl), 7.21 (2H, d, *J* = 8.8 Hz, 2 x ArCH, aniline), 7.31 (2H, d, *J* = 8.8 Hz, 2 x ArCH, aniline) and 7.33 (2H, t, *J* = 7.9 Hz, ArCH, phenacetyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.9 ((*C*H$_3$)$_2$C), 48.1 ((CH$_3$)$_2$*C*), 55.3 (OCH_3), 112.2 (ArCH, phenacetyl), 112.9 (ArCH, phenacetyl), 118.8 (ArCH, phenacetyl), 120.9 (2 x ArCH, aniline), 128.8 (2 x ArCH, aniline), 129.1 (ArCCl), 130.1 (ArCH, phenacetyl), 136.5 (ArCN), 146.0 (ArC(CH$_3$)$_2$), 160.0 (ArCO) and 175.5 (CON) ppm. HRMS (ES^+) calcd. $C_{18}H_{21}{}^{35}ClNO_2$ (M^++H) 334.1204, found 334.1215; calcd. $C_{18}H_{21}{}^{37}ClNO_2$ (M^++H) 336.1175, found 336.1190.

4-Chloro-*N*-(2-(3-methoxyphenyl)butyl)aniline (26b)
Synthesized according to the general method for the reduction of the amides **13a-f**. The crude compound was not purified and showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (3H, t, *J* = 7.4 Hz, CH_2CH_3), 1.56 – 1.67 (1H, m, C*H*$_2$CH$_3$), 1.73 – 1.85 (1H, m, C*H*$_2$CH$_3$), 2.70 – 2.83 (1H, m, C*H*CH_2CH_3), 3.18 (1H, dd, *J* = 9.1, 12.3 Hz, CH_2N), 3.41 (1H, dd, *J* = 5.6, 12.4 Hz, CH_2N), 3.80 (3H, s, OCH_3), 6.56 (2H, d, *J* = 8.8 Hz, 2 x ArCH, aniline), 6.69 – 6.72 (1H, m, ArCH, phenyl), 6.76 (1H, d, *J* = 8.0 Hz, ArCH, phenyl), 6.78 (1H, dd, *J* = 2.4, 8.0 Hz, ArCH, phenyl), 7.10 (2H, d, *J* = 8.8 Hz, 2 x ArCH, aniline) and 7.24

(1H, t, *J* = 8.0 Hz, ArCH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.0 ($CH_2\mathit{C}H_3$), 27.0 ($\mathit{C}H_2CH_3$), 46.8 ($\mathit{C}HCH_2CH_3$), 50.4 (CH_2N), 55.2 (OCH_3), 111.7 (ArCH, phenyl), 113.9 (ArCH, phenyl), 115.2 (2 x ArCH, aniline), 120.2 (ArCH, phenyl), 123.2 (ArCCl), 129.1 (2 x ArCH, aniline), 129.7 (ArCH, phenyl), 144.1 (Ar*C*CH), 145.2 (ArCN) and 159.9 (ArCO) ppm. HRMS (ES$^+$) calcd. $C_{17}H_{21}{}^{35}ClNO_2$ (M^++H) 290.1306, found 290.1322; calcd. $C_{17}H_{21}{}^{37}ClNO_2$ (M^++H) 292.1277, found 292.1268.

4-Chloro-*N*-(2-(3-methoxyphenyl)-3-methylbutyl)aniline (26c)
Synthesized according to the general method for the reduction of the amides **13a-f**. The crude compound was not purified and showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.77 (3H, d, *J* = 6.7 Hz, CH(CH_3)$_2$), 1.05 (3H, d, *J* = 6.6 Hz, CH(CH_3)$_2$), 1.84 – 1.99 (1H, m, C*H*(CH_3)$_2$), 2.55 (1H, ddd, *J* = 4.4, 8.4, 10.5 Hz, C*H*CH_2), 3.16 (1H, dd, *J* = 10.7, 11.8 Hz, CHC*H*$_2$), 3.37 (1H, bs, NH), 3.56 (1H, dd, *J* = 4.2, 11.9 Hz, CHC*H*$_2$), 3.79 (3H, s, OCH_3), 6.44 (2H, d, *J* = 8.9 Hz, 2 x ArCH, aniline), 6.68 – 6.70 (1H, m, ArCH, phenethyl), 6.72 – 6.76 (1H, m, ArCH, phenethyl), 6.79 (1H, ddd, *J* = 0.8, 2.6, 8.2 Hz, ArCH, phenethyl), 7.07 (2H, d, *J* = 8.9 Hz, 2 x ArCH, aniline) and 7.20 – 7.26 (1H, m, ArCH, phenethyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.1(CH($\mathit{C}H_3$)$_2$), 21.2(CH($\mathit{C}H_3$)$_2$), 31.9 (C*H*(CH_3)$_2$), 47.0 (CH*C*H_2), 52.6 (*C*HCH_2), 55.3 (OCH_3), 111.8 (ArCH, phenethyl), 114.3 (2 x ArCH, aniline), 114.7 (ArCH, phenethyl), 121.0 (ArCH, phenethyl), 121.9 (ArCCl), 129.1 (2 x ArCH, aniline), 129.6 (ArCH, phenethyl), 143.8 (Ar*C*CH_2), 147.0 (ArCN) and 159.9 (ArCO) ppm. HRMS (ES$^+$) calcd. $C_{18}H_{23}{}^{35}ClNO_2$ (M^++H) 304.1463, found 304.1465; calcd. $C_{18}H_{23}{}^{37}ClNO_2$ (M^++H) 306.1433, found 306.1465.

4-Chloro-*N*-(2-(3-methoxyphenyl)-3-phenylpropyl)aniline (26d)
Synthesized according to the general method for the reduction of the amides **13a-f**. The crude compound was not purified and showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.97 (2H, d, *J* = 7.3 Hz, ArCH_2, phenyl), 3.13 – 3.20 (1H, m, C*H*CH_2), 3.23 (1H, dd, *J* = 8.9, 12.2 Hz, CH_2N), 3.41 (1H, dd, *J* = 4.9, 12.2 Hz, CH_2N), 3.77 (3H, s, OCH_3), 6.43 (2H, d, *J* = 8.8 Hz, 2 x ArCH, aniline), 6.67 – 6.71 (1H, m, ArCH, methoxyphenyl), 6.74 – 6.80 (2H, m, 2 x ArCH, methoxyphenyl), 7.06 (2H, d, *J* = 8.8 Hz, 2 x ArCH, aniline), 7.09 (2H, d, *J* = 7.1 Hz, 2 x ArCH, phenyl) and 7.18 – 7.26 (4H, m, 3 x ArCH, phenyl, ArCH, methoxyphenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 40.8 (ArCH_2, phenyl), 46.6 (*C*HCH_2), 49.3 (CH_2N), 55.2 (OCH_3), 112.0 (ArCH, methoxyphenyl), 113.8 (ArCH, methoxyphenyl), 115.0 (2 x ArCH, aniline), 120.0 (ArCH, methoxyphenyl), 123.1 (ArCCl), 126.3 (ArCH, phenyl), 127.7, 128.3 (2 x ArCH, phenyl), 129.0 (2 x ArCH, phenyl), 129.1 (2 x ArCH, aniline), 129.7 (ArCH, methoxyphenyl), 139.5 (Ar*C*CH_2), 143.8 (Ar*C*CH), 145.3 (ArCN) and 159.8 (ArCO) ppm. HRMS (ES$^+$) calcd. $C_{22}H_{22}{}^{35}ClNO$ (M^--H) 350.1317, found 350.1330; calcd. $C_{22}H_{23}{}^{37}ClNO$ (M^--H) 352.1288, found 352.1275.

4-Chloro-*N*-(2-(3-methoxyphenyl)-2-methylpropyl)aniline (26e)
Synthesized according to the general method for the reduction of the amides **13a-f**. The crude compound was not purified and showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32 (6H, s, $(CH_3)_2$C), 3.15 (2H, s, CH_2N), 3.74 (3H, s, OCH_3), 6.40 (2H, d, *J* = 8.7 Hz, 2 x ArCH, aniline), 6.71 (1H, dd, *J* = 2.4, 8.0 Hz, ArCH, phenyl), 6.83 – 6.87 (1H, m, ArCH, phenyl), 6.89 (1H, d, *J* = 8.0 Hz, ArCH, phenyl), 6.99 (2H, d, *J* = 8.7 Hz, 2 x ArCH, aniline) and 7.20 (1H, t, *J* = 8.0 Hz, ArCH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 27.2 (($\mathit{C}H_3$)$_2$C), 38.8 ((CH$_3$)$_2$*C*), 55.2 (OCH_3), 57.9 (CH_2N), 111.0 (ArCH, phenyl), 112.9 (ArCH, phenyl), 116.3 (2 x ArCH, aniline), 118.4 (ArCH, phenyl), 124.2 (ArCCl), 129.1 (2 x ArCH, aniline), 129.6 (ArCH, phenyl), 147.4 (ArCN), 147.7 (Ar*C*C(CH$_3$)$_2$) and 159.8 (ArCO). HRMS (ES$^+$) calcd. $C_{17}H_{21}{}^{35}ClNO$ (M^++H) 290.1306, found 290.1320.

2-(4-Chlorophenyl)-6-methoxy-4-methyl-1,2,3,4-tetrahydroisoquinoline (27a)
Synthesized according to the general method for the Pictect-Spengler cyclisation. The crude compound was purified by column chromatography (eluent: from 0% to 20% EtOAc in pet. ether) to give the product as a white solid (302 mg, 58%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29 (3H, d, *J* = 6.9 Hz, CHC*H*$_3$), 2.96 – 3.06 (1H, m, H$_4$-THIQ), 3.19 (1H, dd, *J* = 6.2, 12.0 Hz, H$_3$-THIQ), 3.40 (1H, dd, *J* = 4.3, 12.0 Hz, H$_3$-THIQ), 3.74 (3H, s, OCH_3), 4.18 (1H, d, *J* = 14.7 Hz, H$_1$-THIQ), 4.27 (1H, d, *J* = 14.7 Hz, H$_1$-THIQ), 6.69 (1H, dd, *J* = 2.6, 8.3 Hz, H$_7$-THIQ), 6.72 (1H, d, *J* = 2.6 Hz, H$_5$-THIQ), 6.78 (2H, d, *J* = 9.0 Hz, 2 x ArCH, phenyl), 7.00 (1H, d, *J* = 8.3 Hz, H$_8$-THIQ) and 7.14 (2H, d, *J* = 9.0 Hz, 2 x ArCH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.6 (CH*C*H$_3$), 33.5 (C$_4$-THIQ), 50.0 (C$_1$-THIQ), 53.4 (C$_3$-THIQ), 55.3 (OCH_3), 112.0 (C$_5$-THIQ), 112.3 (C$_7$-THIQ), 115.7 (2 x ArCH, phenyl), 122.9 (ArCCl), 125.8 (C$_1$*C*C$_8$-THIQ), 127.4 (C$_8$-THIQ), 129.0 (2 x ArCH, phenyl), 141.2 (C$_4$*C*C$_5$-THIQ), 149.3 (ArCN) and 158.4 (C$_6$-THIQ) ppm. Mp 72-75 °C (pet. ether).

2-(4-Chlorophenyl)-4-ethyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (27b)
Synthesized according to the general method for the Pictect-Spengler cyclisation. The crude compound was purified by column chromatography (eluent: from 0% to 20% EtOAc in pet. ether) to give the product as a yellow oil (384 mg, 74%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (3H, t, *J* = 7.4 Hz, CH_2C*H*$_3$), 1.59 – 1.72 (2H, m, C*H*$_2$CH$_3$), 2.67 – 2.75 (1H, m, H$_4$-THIQ), 3.24 (1H, dd, *J* = 3.8, 12.1 Hz, H$_3$-THIQ), 3.53 (1H, dd, *J* = 4.1, 12.1 Hz, H$_3$-THIQ), 3.74 (3H, s, OCH_3), 4.10 (1H, d, *J* = 14.6 Hz, H$_1$-THIQ), 4.32 (1H, d, *J* = 14.7 Hz, H$_1$-THIQ), 6.68 (1H, d, *J* = 2.4 Hz, H$_5$-THIQ), 6.70 (1H, dd, *J* = 2.6, 8.3 Hz, H$_7$-THIQ), 6.77 (2H, d, *J* = 9.0 Hz, 2 x ArCH, phenyl), 7.00 (1H, d, *J* = 8.3 Hz, H$_8$-THIQ) and 7.15 (2H, d, *J* = 9.0 Hz, 2 x ArCH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.3 ($CH_2\mathit{C}H_3$), 27.2 ($\mathit{C}H_2CH_3$), 41.0 (C$_4$-THIQ), 49.5 (C$_3$-THIQ), 49.7(C$_1$-THIQ), 55.3 (OCH_3), 112.2 (C$_7$-THIQ), 113.1(C$_5$-THIQ), 115.2 (2 x ArCH, phenyl), 122.6 (ArCCl), 125.7 (C$_1$*C*C$_8$-THIQ), 127.5(C$_8$-THIQ), 129.0 (2 x ArCH, phenyl), 140.3 (C$_4$*C*C$_5$-THIQ), 149.4 (ArCN) and 158.1 (C$_6$-THIQ) ppm.

2-(4-Chlorophenyl)-4-isopropyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (27c)
Synthesized according to the general method for the Pictect-Spengler cyclisation. The crude compound was purified by column chromatography (eluent: from 0% to 20% EtOAc in pet. ether) to give the product as a colourless oil (53 mg, 36%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (3H, d, *J* = 6.8 Hz, $(CH_3)_2CH$), 0.98 (3H, d, *J* = 6.8 Hz, $(CH_3)_2CH$), 1.93 – 2.04 (1H, m, $(CH_3)_2CH$), 2.61 (1H, dt, *J* = 3.6, 7.2 Hz, H_4-THIQ), 3.23 (1H, dd, *J* = 3.6, 12.1 Hz, H_3-THIQ), 3.79 (1H, dd, *J* = 3.6, 12.1 Hz, H_3-THIQ), 3.81 (3H, s, OCH_3), 4.16 (1H, d, *J* = 14.6 Hz, H_1-THIQ), 4.44 (1H, d, *J* = 14.6 Hz, H_1-THIQ), 6.73 (1H, d, *J* = 2.6 Hz, H_5-THIQ), 6.79 (1H, dd, *J* = 2.6, 8.4 Hz, H_7-THIQ), 6.81 (2H, d, *J* = 9.1 Hz, 2 x ArCH, phenyl), 7.08 (1H, d, *J* = 8.4 Hz, H_8-THIQ) and 7.22 (2H, d, *J* = 9.0 Hz, 2 x ArCH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.1 ($(CH_3)_2CH$), 21.5 ($(CH_3)_2CH$), 30.7 ($(CH_3)_2CH$), 46.2 (C_4-THIQ), 46.4 (C_3-THIQ), 49.4 (C_1-THIQ), 55.3 (OCH_3), 112.1 (C_7-THIQ), 114.0 (C_5-THIQ), 114.3 (2 x ArCH, phenyl), 122.0 (ArCCl), 125.9 (C_1CC_8-THIQ), 127.6 (C_8-THIQ), 128.8, 129.0 (2 x ArCH, phenyl), 139.5 (C_4CC_5-THIQ), 148.7 (ArCN) and 157.8 (C_6-THIQ) ppm.

4-Benzyl-2-(4-chlorophenyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (27d)
Synthesized according to the general method for the Pictect-Spengler cyclisation. The crude compound was purified by column chromatography (eluent: from 0% to 20% EtOAc in pet. ether) to give the product as a white solid (327 mg, 63%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.86 (1H, dd, *J* = 10.1, 13.7 Hz, $ArCH_2CH$), 2.97 (1H, dd, *J* = 5.3, 13.7 Hz, $ArCH_2CH$), 3.03 (1H, dd, *J* = 3.4, 12.2 Hz, H_3-THIQ), 3.06 - 3.12 (1H, m, H_4-THIQ), 3.48 (1H, dd, *J* = 3.0, 12.2 Hz, H_3-THIQ), 3.68 (3H, s, OCH_3), 4.07 (1H, d, *J* = 14.8 Hz, H_1-THIQ), 4.44 (1H, d, *J* = 14.7 Hz, H_1-THIQ), 6.57 (1H, d, *J* = 2.5 Hz, H_5-THIQ), 6.70 (2H, d, *J* = 9.0 Hz, 2 x ArCH, *N*-phenyl), 6.73 (1H, dd, *J* = 2.6, 8.5 Hz, H_7-THIQ), 7.03 (1H, d, *J* = 8.4 Hz, H_8-THIQ), 7.08 - 7.15 (4H, m, 2 x ArCH, *N*-phenyl, 2 x ArCH, C_4-phenyl), 7.17 – 7.19 (1H, m, ArCH, C_4-phenyl) and 7.25 (2H, t, *J* = 7.3 Hz, 2 x ArCH, C_4-phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 41.3 ($ArCH_2CH$), 41.6 (C_4-THIQ), 48.5 (C_3-THIQ), 49.9 (C_1-THIQ), 55.3 (OCH_3), 112.9 (C_7-THIQ), 113.0 (C_5-THIQ), 115.4 (2 x ArCH, *N*-phenyl), 122.9 (ArCCl), 125.5 (C_1CC_8-THIQ), 126.4 (ArCH, C_4-phenyl), 127.6 (C_8-THIQ), 128.5 (2 x ArCH, C_4-phenyl), 128.9 (2 x ArCH), 129.4 (2 x ArCH), 139.4 (C_4CC_5-THIQ), 140.1 ($ArCCH_2$, C_4-phenyl), 149.3 (ArCN) and 158.1 (C_6-THIQ) ppm. Mp 84-87 °C (pet. ether).

2-(4-Chlorophenyl)-6-methoxy-4,4-dimethyl-1,2,3,4-tetra-hydroisoquinoline (27e)
Synthesized according to the general method for the Pictect-Spengler cyclisation. The crude compound was purified by column chromatography (eluent: from 0% to 20% EtOAc in pet. ether) to give the product as a white solid (94 mg, 23%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (6H, s, $(CH_3)_2C$), 3.14 (2H, s, H_3-THIQ), 3.74 (3H, s, OCH_3), 4.22 (2H, s, H_1-THIQ), 6.68 (1H, dd, *J* = 2.6, 8.4 Hz, H_7-THIQ), 6.79 (2H, d, *J* = 9.0 Hz, 2 x ArCH, phenyl), 6.83 (1H, d, *J* = 2.6 Hz, H_5-THIQ), 6.98 (1H, d, *J* = 8.4 Hz, H_8-THIQ) and 7.15 (2H, d, *J* = 9.0 Hz, 2 x ArCH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.1 ($(CH_3)_2C$), 35.8 (C_4-THIQ), 50.5 (C_1-THIQ), 55.3 (OCH_3), 59.9 (C_3-THIQ), 110.9 (C_5-THIQ), 111.6 (C_7-THIQ), 115.7 (2 x ArCH, phenyl), 123.0 (ArCCl), 125.1 (C_1CC_8-THIQ), 127.4 (C_8-THIQ), 129.0 (2 x ArCH, phenyl), 145.0 (C_4CC_5-THIQ), 149.5 (ArCN) and 158.4 (C_6-THIQ). Mp 90-93 °C (pet. ether) ppm.

4-Benzyl-2-(4-chlorophenyl)-8-methoxy-1,2,3,4-tetrahydroisoquinoline (28d)
Synthesized according to the general method for the Pictect-Spengler cyclisation. The crude compound was purified by column chromatography (eluent: from 0% to 20% EtOAc in pet. ether) to give the product as a colourless oil (19 mg, 4%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.81 – 2.88 (1H, m, $ArCH_2CH$), 2.93 – 2.99 (2H, m, $ArCH_2CH$, H_3-THIQ), 3.08 – 3.16 (1H, m, H_4-THIQ), 3.49 (1H, dd, *J* = 2.6, 12.3 Hz, H_3-THIQ), 3.81 (3H, s, OCH_3), 3.97 (1H, d, *J* = 16.4 Hz, H_1-THIQ), 4.44 (1H, d, *J* = 16.4 Hz, H_1-THIQ), 6.69 (1H, d, *J* = 8.1 Hz, H_5 or H_7-THIQ), 6.76 (3H, d, *J* = 8.9 Hz, 2 x ArCH, *N*-phenyl, H_5 or H_7-THIQ), 7.10 – 7.16 (5H, m, 2 x ArCH, *N*-phenyl, 2 x ArCH, C_4-phenyl, H_6-THIQ), 7.18 (1H, t, *J* = 7.2 Hz, ArCH, C_4-phenyl) and 7.25 (2H, t, *J* = 7.3 Hz, 2 x ArCH, C_4-phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 41.4 (C_3-THIQ), 41.5 ($ArCH_2CH$), 46.0 (C_1-THIQ), 47.7 (C_4-THIQ), 55.3 (OCH_3), 107.4 (C_7 or C_5-THIQ), 115.5 (2 x ArCH, *N*-phenyl), 120.4 (C_7 or C_5-THIQ), 122.3 (C_1CC_8-THIQ), 122.8 (ArCCl), 126.3 (ArCH), 126.9 (ArCH, C_4-phenyl), 128.5 (2 x ArCH), 128.9 (2 x ArCH), 129.4 (2 x ArCH), 139.7 (C_4CC_5-THIQ), 140.3 ($ArCCH_2$, C_4-phenyl), 149.5 (ArCN) and 156.0 (C_8-THIQ) ppm.

***N*-(4-Chlorophenyl)-N-(3-methoxyphenethyl)acetamide (29a)**
Compound **14d** (150 mg, 0.503 mmol) was dissolved in a mixture of EtOAc (2 mL) and Pyridine (123 µL, 1.51 mmol) and Acetylchloride (13.3 µL, 1.01 mmol) was added dropwise. The mixture was stirred for 1 h at rt during which time a white precipitate formed. The mixture was filtered and the filtrate was diluted with EtOAc (5 ml) washed with 1N HCl (5 mL) and 1N NaOH (5 mL). The organic layer was then dried with $MgSO_4$, filtered and evaporated to give a white solid (132 mg, 86%) which showed: ^{1}H NMR (500 MHz, CDCl3) δ 1.83 (3H, s, $COCH_3$), 2.83 (2H, t, *J* = 7.8 Hz, $ArCH_2CH_2$), 3.77 (3H, s, $ArOCH_3$), 3.90 (2H, t, *J* = 7.8 Hz, CH_2CH_2N), 6.70 (1H, s, ArCH, phenethyl), 6.74 (2H, d, *J* = 8.3 Hz, 2 x ArCH, phenethyl), 6.98 (2H, d, *J* = 8.5 Hz, 2 x ArCH, aniline), 7.17 (1H, t, *J* = 7.8 Hz, ArCH, phenethyl) and 7.36 (2H, d, *J* = 8.5 Hz, 2 x ArCH, aniline) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.9 ($NCOCH_3$), 34.0 ($ArCH_2CH_2$), 50.6 (CH_2CH_2N), 55.2 ($ArOCH_3$), 112.0 (ArCH, phenethyl), 114.3 (ArCH, phenethyl), 121.2 (ArCH, phenethyl), 129.4 (ArCH, aniline), 129.4 (ArCH, phenethyl), 129.9 (ArCH, aniline), 133.7 (ArCCl), 140.2 ($ArCCH_2$), 141.8 (ArCN), 159.7 (ArCO) and 170.1 (NCO) ppm. HRMS (ES^+) calcd. $C_{17}H_{18}{}^{35}ClNNaO_2$ (M^++Na) 326.0918, found 326.0924; calcd. $C_{17}H_{18}{}^{37}ClNNaO_2$ (M^++Na) 328.0889, found 328.0890.

***N*-(4-Chlorophenyl)-N-(3-methoxyphenethyl)propionamide (29b)**

Propanoyl chloride (90 µL, 1.01 mmol) was added to a stirring solution of **14d** (150 mg, 0.503 mmol) and pyridine (123 µL, 1.51 mmol) in DCM (2 mL) and the mixture was stirred at rt for 10 h. A white precipitate formed after the first ten minutes. The mixture was then diluted with DCM (10 mL) washed with a sat. aq. solution of $NaHCO_3$ (2 x 10 mL) and 1N HCl (2 x 10 mL) and the organic layer was dried with $MgSO_4$, filtered and evaporated to give the product as a pale yellow oil (114 mg, 71%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (3H, t, *J* = 7.4 Hz, CH_2CH_3), 2.02 (2H, q, *J* = 7.4 Hz, CH_2CH_3), 2.78 – 2.91 (2H, m, CH_2CH_2N), 3.77 (3H, s, OCH_3), 3.82 – 3.96 (2H, m, CH_2CH_2N), 6.69 – 6.72 (1H, m, ArCH, benzyl), 6.72 – 6.79 (2H, m, 2 x ArCH, benzyl), 6.97 (2H, d, *J* = 8.4 Hz, 2 x ArCH, aniline), 7.17 (1H, t, *J* = 7.9 Hz, ArCH, benzyl) and 7.36 (2H, d, *J* = 8.6 Hz, ArCH, aniline) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 9.5 (CH_2CH_3), 27.9 (CH_2CH_3), 34.1 (CH_2CH_2N), 50.9 (CH_2CH_2N), 55.2 (OCH_3), 112.0 (ArCH, phenethyl), 114.3 (ArCH, phenethyl), 121.2 (ArCH, phenethyl), 129.4 (ArCH, phenethyl), 129.6 (ArCH, aniline), 129.9 (ArCH, aniline), 133.7 (ArCCl), 140.2 ($ArCCH_2$), 141.5 (ArCN), 159.7 (ArCO) and 173.5 (NCO) ppm. HRMS (ES^+) calcd. $C_{18}H_{21}{}^{35}ClNO_2$ (M^++H) 318.1255, found 318.1255; calcd. $C_{18}H_{21}{}^{37}ClNO_2$ (M^++H) 320.1226, found 320.1237.

***N*-(4-Chlorophenyl)-N-(3-methoxyphenethyl)isobutyramide (29c)**

Isobutyryl chloride (108 µL, 1.01 mmol) was added to a stirring solution of **14d** (150 mg, 0.503 mmol) and pyridine (123 µL, 1.51 mmol) in DCM (2 mL) and the mixture was stirred at rt for 10 h. A white precipitate formed after the first ten minutes. The mixture was then diluted with DCM (10 mL) washed with a sat. aq. solution of $NaHCO_3$ (2 x 10 mL) and 1N HCl (2 x 10 mL) and the organic layer was dried with $MgSO_4$, filtered and evaporated to give the product as a pale yellow solid (113 mg, 68%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (6H, d, *J* = 6.7 Hz, $(CH_3)_2CH$), 2.38 (1H, septet, *J* = 6.7 Hz, $(CH_3)_2CH$), 2.85 (2H, t, *J* = 7.8 Hz, CH_2CH_2N), 3.77 (3H, s, OCH_3), 3.86 (2H, t, *J* = 7.8 Hz, CH_2CH_2N), 6.71 (1H, s, ArCH, phenethyl), 6.74 (2H, d, *J* = 8.0 Hz, 2 x ArCH, phenethyl), 6.95 (2H, d, *J* = 8.4 Hz, 2 x ArCH, aniline), 7.17 (1H, t, *J* = 7.8 Hz, ArCH, phenethyl) and 7.35 (2H, d, *J* = 8.6 Hz, 2 x ArCH, aniline) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.6 ($(CH_3)_2CH$), 31.3 ($(CH_3)_2CH$), 34.0 (CH_2CH_2N), 51.0 (CH_2CH_2N), 55.2 (CH_3O), 112.1 (ArCH, phenethyl), 114.3 (ArCH, phenethyl), 121.2 (ArCH, phenethyl), 129.4 (ArCH, phenethyl), 129.5 (2 x ArCH, aniline), 129.8 (2 x ArCH, aniline), 133.7 (ArCCl), 140.3 ($ArCCH_2$), 141.6 (ArCN), 159.7 (ArCO) and 177.0 (NCO) ppm. HRMS (ES^+) calcd. $C_{19}H_{23}{}^{35}ClNO_2$ (M^++H) 332.1412, found 332.1399; calcd. $C_{19}H_{23}{}^{37}ClNO_2$ (M^++H) 334.1382, found 334.1394.

***N*-(4-Chlorophenyl)-N-(3-methoxyphenethyl)pivalamide (29d)**

Pivaloyl chloride (126 µL, 1.01 mmol) was added to a stirring solution of **14d** (150 mg, 0.503 mmol) and pyridine (123 µL, 1.51 mmol) in DCM (2 mL) and the mixture was stirred at rt for 10 h. A white precipitate formed after the first ten minutes. The mixture was then diluted with DCM (10 mL) washed with a sat. aq. solution of $NaHCO_3$ (2 x 10 mL) and 1N HCl (2 x 10 mL) and the organic layer was dried with $MgSO_4$, filtered and evaporated to give the product as a yellow solid (122 mg, 70%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (9H, s, $C(CH_3)_3$), 2.79 – 2.92 (1H, m, CH_2CH_2N), 3.68 – 3.83 (2H, m, CH_2CH_2N), 3.77 (3H, s, CH_3O), 6.69 – 6.72 (1H, m, ArCH, phenethyl), 6.74 (1H, dd, *J* = 2.0, 8.0 Hz, 2 x ArCH, phenethyl), 6.99 (2H, d, *J* = 8.6 Hz, ArCH, aniline), 7.17 (1H, t, *J* = 7.9 Hz, ArCH, aniline) and 7.33 (2H, d, *J* = 8.6 Hz, ArCH, aniline) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.5 ($C(CH_3)_3$), 33.7 (CH_2CH_2N), 41.0 ($C(CH_3)_3$), 55.0 (CH_2CH_2N), 55.2 (OCH_3), 112.0 (ArCH, phenethyl), 114.4 (ArCH, phenethyl), 121.3 (ArCH, phenethyl), 129.3 (2 x ArCH, aniline), 129.4 (ArCH, phenethyl), 130.9 (2 x ArCH, aniline), 133.7 (ArCCl), 140.5 ($ArCCH_2$), 142.5 (ArCN), 159.7 (ArCO) and 177.6 (NCO) ppm. HRMS (ES^+) calcd. $C_{20}H_{25}{}^{35}ClNO_2$ (M^++H) 346.1568, found 346.1566; calcd. $C_{20}H_{25}{}^{37}ClNO_2$ (M^++H) 348.1539, found 348.1537.

***N*-(4-Chlorophenyl)-N-(3-methoxyphenethyl)benzamide (29e)**

Benzoyl chloride (118 µL, 1.01 mmol) was added to a stirring solution of **14d** (150 mg, 0.503 mmol) and pyridine (123 µL, 1.51 mmol) in DCM (2 mL) and the mixture was stirred at rt for 10 h. A white precipitate was formed after the first ten minutes. The mixture was then diluted with DCM (10 mL) washed with a sat. aq. solution of $NaHCO_3$ (2 x 10 mL) and 1N HCl (2 x 10 mL) and the organic layer was dried with $MgSO_4$, filtered and evaporated to give a yellow oil (263 mg). The crude compound was purified by column chromatography (from 0% to 30% EtOAc in pet. ether) to give the product as a pale yellow oil (89 mg, 48%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.98 (2H, t, *J* = 6.8 Hz, CH_2CH_2N), 3.77 (3H, s, OCH_3), 4.10 (2H, t, *J* = 6.8 Hz, CH_2CH_2N), 6.70 – 6.85 (5H, m), 7.14 (2H, d, *J* = 8.6 Hz), 7.20 (3H, td, *J* = 7.0, 14.4 Hz) and 7.25 – 7.31 (3H, m) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 33.8 (CH_2CH_2N), 52.4 (CH_2CH_2N), 55.1 (OCH_3), 112.1, 114.4, 121.3, 127.9, 128.6, 128.7, 129.2, 129.5, 129.8, 132.1 (ArCCl), 135.7 (ArCCO), 140.3 ($ArCCH_2$), 142.3 (ArCN), 159.7 (ArCO) and 170.3 (NCO) ppm. HRMS (ES^+) calcd. $C_{22}H_{21}{}^{35}ClNO_2$ (M^++H) 366.1255, found 366.1257; calcd. $C_{22}H_{21}{}^{37}ClNO_2$ (M^++H) 368.1226, found 368.1250.

***N*-(4-Chlorophenyl)-N-(3-methoxyphenethyl)-2-phenylacetamide (29f)**

Phenacetyl chloride (136 µL, 1.01 mmol) was added to a stirring solution of **14d** (150 mg, 0.503 mmol) and pyridine (123 µL, 1.51 mmol) in DCM (2 mL) and the mixture was stirred at rt for 10 h. A white precipitate was formed after the first ten minutes. The mixture was then diluted with DCM (10 mL) washed with a sat. aq. solution of $NaHCO_3$ (2 x 10 mL) and 1N HCl (2 x 10 mL) and the organic layer was dried with $MgSO_4$, filtered and evaporated to give a yellow oil (140 mg). The crude compound was purified by column chromatography (from 0% to 30% EtOAc in pet. ether) to give the product as a pale yellow oil (34 mg, 18%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.84 (2H, t, *J* = 7.7 Hz, CH_2CH_2N), 3.41 (2H, s,

$ArCH_2CO$), 3.75 (3H, s, OCH_3), 3.90 (2H, t, *J* = 7.7 Hz, CH_2CH_2N), 6.65 – 6.80 (3H, m, 3 x ArCH, phenethyl), 6.88 (2H, d, *J* = 8.5 Hz, 2 x ArCH, aniline), 7.02 (2H, d, *J* = 7.0 Hz, 2 x ArCH, phenacetyl), 7.15 (1H, t, *J* = 7.8 Hz, ArCH, phenethyl), 7.18 – 7.27 (3H, m, 3 x ArCH, phenacetyl) and 7.32 (2H, d, *J* = 8.5 Hz, 2 x ArCH, aniline) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 33.9 (CH_2CH_2N), 41.3 ($ArCH_2CO$), 51.1 (CH_2CH_2N), 55.1 (OCH_3), 112.0 (ArCH, phenethyl), 114.2 (ArCH, phenethyl), 121.2 (ArCH, phenethyl), 126.6 (ArCH, phenacetyl), 128.4 (2 x ArCH, phenacetyl), 128.9 (2 x ArCH, phenacetyl), 129.4 (ArCH, phenethyl), 129.7 (2 x ArCH, aniline), 129.8 (2 x ArCH, aniline), 133.8 (ArCCl), 135.0 ($ArCCH_2CO$), 140.0 ($ArCCH_2CH_2$), 141.1 (ArCN), 159.7 (ArCO) and 170.6 (NCO) ppm. HRMS (ES^+) calcd. $C_{23}H_{23}{}^{35}ClNO_2$ (M^++H) 380.1412, found 380.1408; calcd. $C_{23}H_{23}{}^{37}ClNO_2$ (M^++H) 382.1382, found 382.1383.

***N*-(4-Chlorophenyl)-*N*-(3-methoxyphenethyl)-3-phenylpropanamide (29g)**

3-Phenylpropanoyl chloride (153 µL, 1.01 mmol) was added to a stirring solution of **14d** (300 mg, 1.01 mmol) and Et_3N (353 µL, 2.53 mmol) in DCM (3 mL) and the mixture was stirred at rt overnight. The mixture was then diluted with DCM (10 mL) and washed with 1 N HCl (3 x 10 mL), 1 N NaOH (3 x 10 mL) and brine (3 x 10 mL) then dried with $MgSO_4$, filtered and evaporated to give a yellow oil (364 mg) which partly solidify upon standing. The crude compound was purified by column chromatography (eluent: from 0% to 30% EtOAc in pet. ether) to give the product as a pale yellow solid (301 mg, 76%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.31 (1H, t, *J* = 6.5 Hz, CH_2CH_2CO), 2.81 (1H, t, *J* = 7.8 Hz, CH_2CH_2N), 2.91 (1H, t, *J* = 6.5 Hz, CH_2CH_2CO), 3.77 (1H, s, $ArOCH_3$), 3.87 (1H, t, *J* = 7.6 Hz, CH_2CH_2N), 6.66 – 6.79 (2H, m), 7.04 – 7.10 (1H, m), 7.14 – 7.21 (1H, m), 7.21 – 7.25 (1H, m) and 7.26 – 7.33 (1H, m) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 31.7 (CH_2CH_2CO), 34.0 (CH_2CH_2N), 36.3 (CH_2CH_2CO), 51.0 (CH_2CH_2N), 55.2 ($ArOCH_3$), 112.0 (2 x ArCH), 114.3 (ArCH), 121.2 (ArCH), 126.1 (ArCH), 128.4 (2 x ArCH), 128.5 (2 x ArCH), 129.4 (ArCH), 129.6 (ArCH), 129.8 (2 x ArCH), 133.7 (ArCCl), 140.1 ($ArCCH_2CH_2N$), 141.0 ($ArCCH_2CH_2CO$), 141.1 (ArCN), 159.7 (ArCO) and 171.8 (CON) ppm. HRMS (ES^+) calcd. $C_{24}H_{25}{}^{35}ClNO_2$ (M^++H) 394.1568, found 394.1571; calcd. $C_{24}H_{25}{}^{37}ClNO_2$ (M^++H) 396.1539, found 396.1549.

***N*-(3-Methoxyphenethyl)-*N*,2-diphenylacetamide (29h)**

Phenacetyl chloride (154 µL, 1.14 mmol) was added to a stirring solution of **14e** (300 mg, 1.14 mmol) and Et_3N (398 µL, 2.85 mmol) in DCM (3 mL) and the mixture was stirred at rt overnight. The mixture was then diluted with DCM (10 mL) and washed with 1 N HCl (3 x 10 mL), 1 N NaOH (3 x 10 mL) and brine (3 x 10 mL) then dried with $MgSO_4$, filtered and evaporated to give a yellow oil (336 mg) which partly solidify upon standing. The crude compound was purified by column chromatography (eluent: from 0% to 30% EtOAc in pet. ether) to give the product as a pale yellow-brown oil (289 mg, 73%) which showed:[37] ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.87 (2H, t, *J* = 6.7 Hz, CH_2CH_2N), 3.42 (2H, s, CH_2CO), 3.75 (3H, s, $ArOCH_3$), 3.93 (2H, t, *J* = 6.7 Hz, CH_2CH_2N), 6.69 – 6.79 (3H, m, 3 x ArCH), 6.97 – 7.09 (3H, m, 3 x ArCH), 7.11 – 7.25 (5H, m, 5 x ArCH) and 7.33 – 7.42 (3H, m, 3 x ArCH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 34.0 (CH_2CH_2N), 41.4 (CH_2CO), 51.2 (CH_2CH_2N), 55.2 ($ArOCH_3$), 112.0 (ArCH), 114.2 (ArCH), 121.2 (ArCH), 126.5 (ArCH), 128.0 (ArCH), 128.3 (2 x ArCH), 128.6 (2 x ArCH), 129.1 (2 x ArCH), 129.4 (ArCH), 129.6 (2 x ArCH), 135.4 ($ArCCH_2CO$), 140.3 ($ArCCH_2CH_2$), 142.6 (ArCN), 159.7 (ArCO) and 170.8 (CON) ppm. HRMS (ES^+) calcd. $C_{23}H_{24}NO_2$ (M^++H) 346.1835, found 346.1832; $C_{23}H_{23}NNaO_2$ (M^++Na) 368.1621, found 368.1639.

***N*-(3-Methoxyphenethyl)-*N*-(4-methoxyphenyl)-2-phenylacetamide (29i)**

Phenacetyl chloride (138 µL, 1.02 mmol) was added to a stirring solution of **14f** (300 mg, 1.02 mmol) and Et_3N (356 µL, 2.55 mmol) in DCM (3 mL) and the mixture was stirred at rt overnight. The mixture was then diluted with DCM (10 mL) and washed with 1 N HCl (3 x 10 mL), 1 N NaOH (3 x 10 mL) and brine (3 x 10 mL) then dried with $MgSO_4$, filtered and evaporated to give a yellow oil (379 mg) which partly solidify upon standing. The crude compound was purified by column chromatography (eluent: from 0% to 30% EtOAc in pet. ether) to give the product as a pale yellow oil (320 mg, 87%) which showed:[23] ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.85 (2H, t, *J* = 7.9 Hz, CH_2CH_2N), 3.42 (2H, s, CH_2CO), 3.75 (3H, s, $ArOCH_3$, phenethyl), 3.84 (3H, s, $ArOCH_3$, aniline), 3.89 (2H, t, *J* = 7.9 Hz, CH_2CH_2N), 6.68 - 6.79 (3H, m, 3 x ArCH, phenethyl), 6.88 (2H, d, *J* = 17.4 Hz, 2 x ArCH, aniline), 6.90 (2H, d, *J* = 17.4 Hz, 2 x ArCH, aniline), 7.04 (2H, d, *J* = 7.2 Hz, 2 x ArCH, phenacetyl), 7.15 (1H, t, *J* = 7.8 Hz, ArCH, phenethyl), 7.21 (1H, t, *J* = 6.9 Hz, ArCH, phenacetyl) and 7.23 (2H, t, *J* = 6.9 Hz, 2 x ArCH, phenacetyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 33.9 (CH_2CH_2N), 41.1 (CH_2CO), 51.1 (CH_2CH_2N), 55.1 ($ArOCH_3$, phenethyl), 55.5 ($ArOCH_3$, aniline), 112.0 (ArCH, phenethyl), 114.2 (ArCH, phenethyl), 114.6 (2 x ArCH, aniline), 121.2 (ArCH, phenethyl), 126.5 (ArCH, phenacetyl), 128.3 (2 x ArCH, phenacetyl), 129.0 (2 x ArCH, phenacetyl), 129.3 (ArCH, phenethyl), 129.5 (2 x ArCH, aniline), 135.3 (ArCN), 135.5 ($ArCCH_2CO$), 140.3 ($ArCCH_2CH_2$), 159.0 (ArCO, aniline), 159.6 (ArCO, phenethyl) and 171.2 (CON) ppm. HRMS (ES^+) calcd. $C_{24}H_{26}NO_3$ (M^++H) 376.1907, found 376.1918.

General method for the Bischler-Napieralski cyclisation: $POCl_3$ (836 µl, 8.88 mmol) was added to a stirring solution of **29a** (450 mg, 1.48 mmol) in anhydrous toluene (15 mL) and the mixture was stirred at 100 °C overnight. The mixture was then cooled to rt and the solvent was evaporated. The residue was dissolved in MeOH (15 mL) and $NaBH_4$ (343 mg, 8.88 mmol) was added. The yellow solution started foaming and turned colourless. The mixture was stirred at rt for 1 h then the solvent was evaporated and the residue was dissolved in EtOAc (50 mL). The organic layer was washed with 1 N NaOH (2 x 50 mL) then dried with $MgSO_4$, filtered and evaporated to give a yellow oil (979 mg).

2-(4-Chlorophenyl)-6-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (30a)
The crude compound was purified by column chromatography (eluent: 100% pet. ether) to give white solid (292 mg, 69%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (3H, d, *J* = 6.6 Hz, CHC*H*$_3$), 2.77 – 2.93 (1H, m, H_4-THIQ), 2.93 – 3.06 (1H, m, H_4-THIQ), 3.41 – 3.50 (1H, m, H_3-THIQ), 3.50 – 3.62 (1H, m, H_3-THIQ), 3.79 (3H, s, OCH_3), 4.81 (1H, q, *J* = 6.6 Hz, C*H*CH_3), 6.68 (1H, d, *J* = 2.6 Hz, H_5-THIQ), 6.76 (1H, dd, *J* = 2.6, 8.4 Hz, H_7-THIQ), 6.84 (2H, bs, 2 x ArCH, phenyl), 7.04 (1H, d, *J* = 8.4 Hz, H_8-THIQ) and 7.19 (2H, d, *J* = 8.9 Hz, 2 x ArCH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.8 (C_1*C*H_3), 28.6 (C_4-THIQ), 41.2 (C_3-THIQ), 54.0 (C_1-THIQ), 55.3 (OCH_3), 112.4 (C_7-THIQ), 113.2 (C_5-THIQ), 115.8 (2 x ArCH, phenyl), 122.2 (ArCCl), 127.7 (C_8-THIQ), 129.0 (2 x ArCH, phenyl), 131.9 (C_8*C*C_1), 135.4 (C_5*C*C_4), 147.9 (ArCN) and 158.0 (C_6-THIQ) ppm. HRMS (ES$^+$) calcd. $C_{17}H_{19}{}^{35}ClNO$ (M^++H) 288.1150, found 288.1157; calcd. $C_{17}H_{19}{}^{37}ClNO$ (M^++H) 290.1120, found 290.1142. Mp 186-189 °C (as a hydrochloride from Et_2O).

2-(4-Chlorophenyl)-1-ethyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (30b)
The crude compound was purified by column chromatography (eluent: 100 % pet. ether) to give the product as a colourless oil (335 mg, 71%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (3H, t, *J* = 7.4 Hz, C*H*$_3$CH$_2$), 1.71 (1H, ddq, *J* = 7.0, 7.4, 14.2 Hz, CH$_3$C*H*$_2$), 1.94 (1H, ddq, *J* = 7.0, 7.4, 14.2 Hz, CH$_3$C*H*$_2$), 2.86 (1H, dd, *J* = 5.7, 15.8 Hz, H_4-THIQ), 2.97 (1H, ddd, *J* = 5.3, 7.8, 15.8 Hz, H_4-THIQ), 3.43 - 3.55 (1H, m, H_3-THIQ), 3.58 (1H, ddd, *J* = 5.0, 7.8, 12.6 Hz, H_4-THIQ), 3.80 (3H, s, OCH_3), 4.45 (1H, t, *J* = 7.0 Hz, H_1-THIQ), 6.71 (1H, d, *J* = 2.6 Hz, H_5-THIQ), 6.75 (1H, dd, *J* = 2.6, 8.4 Hz, H_7-THIQ), 6.78 (2H, d, *J* = 9.1 Hz, 2 x ARCH, phenyl), 7.04 (1H, d, *J* = 8.4 Hz, H_8-THIQ) and 7.18 (2H, d, *J* = 9.1 Hz, 2 x ARCH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 11.3 (*C*H$_3$CH$_2$), 27.5 (C_4-THIQ), 29.5 (CH$_3$*C*H$_2$), 42.1 (C_3-THIQ), 55.2 (OCH_3), 60.2 (C_1-THIQ), 111.7 (C_7-THIQ), 113.3 (C_5-THIQ), 114.6 (2 x ArCH, phenyl), 121.4 (ArCCl), 128.3 (C_8-THIQ), 128.9 (2 x ArCH, phenyl), 130.7 (C_1CC_8-THIQ), 136.0 (C_4CC_5-THIQ), 148.3 (ArCN) and 158.1 (C_6-THIQ) ppm. HRMS (ES$^+$) calcd. $C_{18}H_{21}{}^{35}ClNO$ (M^++H) 302.1306, found 302.1292; calcd. $C_{18}H_{21}{}^{37}ClNO$ (M^++H) 304.1277, found 304.1287. Mp 142-144 °C (pet. ether).

2-(4-Chlorophenyl)-1-isopropyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (30c)
The crude compound was purified by column chromatography (eluent: 100% pet. ether) to give a colourless oil (267 mg, 56%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (3H, d, *J* = 6.6 Hz, (C*H*$_3$)$_2$CH), 1.03 (3H, d, *J* = 6.9 Hz, (C*H*$_3$)$_2$CH)), 2.03 – 2.13 (1H, m, (CH$_3$)$_2$C*H*)), 2.92 – 3.01 (2H, m, H_4-THIQ), 3.36 – 3.46 (1H, m, H_3-THIQ), 3.68 (1H, dt, *J* = 6.1, 12.2 Hz, H_3-THIQ), 3.79 (3H, s, OCH_3), 4.26 (1H, d, *J* = 8.1 Hz, H_1-THIQ), 6.68 – 6.72 (2H, m, H_5,H_7-THIQ), 6.76 (2H, d, *J* = 9.1 Hz, 2 x ArCH, phenyl), 7.02 (1H, d, *J* = 7.9 Hz, H_8-THIQ) and 7.14 (2H, d, *J* = 9.1 Hz, 2 x ArCH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.0 ((*C*H$_3$)$_2$CH), 20.5 ((CH$_3$)$_2$CH), 27.5 (C_4-THIQ), 34.4 ((CH$_3$)$_2$*C*H), 42.9 (C_3-THIQ), 55.2 (OCH_3), 64.2 (C_1-THIQ), 111.0 (C_7-THIQ), 113.4 (C_5-THIQ), 114.3 (2 x ArCH, phenyl), 121.1 (ArCCl), 128.8 (2 x ArCH, phenyl), 129.2 (C_8-THIQ), 129.6 (C_1CC_8-THIQ), 136.3 (C_5CC_4-THIQ), 148.6 (ArCN) and 158.3 (C_6-THIQ) ppm. HRMS (ES$^+$) calcd. $C_{19}H_{23}{}^{35}ClNO$ (M^++H) 316.1463, found 316.1460; calcd. $C_{19}H_{23}{}^{37}ClNO$ (M^++H) 318.1433, found 318.1448.

2-(4-Chlorophenyl)-6-methoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (30e)
The crude compound was purified by column chromatography (eluent: 100% pet. ether) to give a colourless oil (342 mg, 68%) which showed: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.80 – 2.97 (2H, m, H_4-THIQ), 3.45 (1H, ddd, *J* = 5.7, 8.0, 11.4 Hz, H_3-THIQ), 3.66 (1H, dt, *J* = 5.5, 11.2 Hz, H_3-THIQ), 3.79 (3H, s, OCH_3), 5.71 (1H, s, H_1-THIQ), 6.71 (1H, d, *J* = 2.6 Hz, H_5-THIQ), 6.74 (2H, d, *J* = 9.1 Hz, 2 x ArCH, *N*-phenyl), 6.77 (2H, dd, *J* = 2.5, 8.3 Hz, H_7-THIQ), 7.14 (2H, d, *J* = 9.1 Hz, 2 x ArCH, *N*-phenyl) and 7.16 – 7.25 (6H, m, H_8-THIQ, 5 x ArCH, C_1-phenyl) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 28.2 (C_4-THIQ), 43.8 (C_3-THIQ), 55.2 (OCH_3), 62.3 (C_1-THIQ), 111.9 (C_7-THIQ), 113.2 (C_5-THIQ), 115.1 (2 x ArCH, *N*-phenyl), 122.2 (ArCCl), 126.8 (ArCH), 127.1 (2 x ArCH, C_1-phenyl), 128.2 (2 x ArCH, C_1-phenyl), 128.7 (ArCH), 128.9 (2 x ArCH, *N*-phenyl), 129.9 (C_1CC_8-THIQ), 136.7 (C_4CC_5-THIQ), 143.0 (ArCC_1, C_1-phenyl), 148.1 (ArCN) and 158.6 (C_6-THIQ) ppm. Mp 188-191 °C (pet. ether)

1-Benzyl-2-(4-chlorophenyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (30f)
The crude compound was purified by column chromatography (eluent: 100% pet. ether) to give a yellow oil (437 mg, 78%) which showed: ^{1}H NMR (500 MHz, CDCl3) δ 2.92 – 3.05 (1H, m), 3.05 – 3.19 (1H, m), 3.29 – 3.43 (1H, m), 3.67 – 3.78 (1H, m), 3.80 (3H, s), 3.83 – 3.92 (1H, m), 3.92 – 4.03 (1H, m), 4.86 – 4.96 (1H, m), 6.57 (1H, d, *J* = 7.8 Hz), 6.66 (1H, dd, *J* = 2.6, 8.6 Hz), 6.74 (1H, d, *J* = 2.5 Hz), 7.03 – 7.12 (2H, m), 7.19 – 7.25 (3H, m), 7.32 – 7.40 (2H, m) and 7.61 (2H, d, *J* = 8.4 Hz) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.2, 40.1, 51.4, 55.3, 66.2, 107.0, 113.2, 113.5, 123.5, 123.9, 127.1, 128.4, 128.7, 129.6, 130.1, 134.8, 136.0, 140.4, 142.2 and 159.5 ppm. Mp 149-151 °C (pet. ether).

2-(4-Chlorophenyl)-6-methoxy-1-phenethyl-1,2,3,4-tetrahydroisoquinoline (30g)
The crude compound was purified by column chromatography (eluent: from 0% to 20% EtOAc in pet. ether) to give a yellow oil (194 mg, 67%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.94 - 2.05 (1H, m, CH*H*$_2$CH$_2$), 2.17 - 2.34 (1H, m, CHC*H*$_2$CH$_2$), 2.66 - 2.79 (2H, m, CHCH$_2$C*H*$_2$), 2.80 - 2.90 (1H, m, H_4-THIQ), 2.90 - 3.03 (1H, m H_4-THIQ), 3.52 -3.68 (2H, m H_3-THIQ), 3.79 (3H, s, OCH_3), 4.55 (1H, t, *J* = 6.9 Hz, H_1-THIQ), 6.68 (1H, d, *J* = 2.4 Hz, H_5-THIQ), 6.71 - 6.83 (3H, m, H_7-THIQ, 2 x ArCH, *N*-phenyl), 7.05 (1H, d, *J* = 8.4 Hz, H_8-THIQ), 7.10 - 7.22 (5H, m, 3 x ArCH, phenethyl, 2 x ArCH, *N*-phenyl) and 7.25 - 7.31 (2H, m, 2 x ArCH, phenethyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.9 (C_4-THIQ), 32.7 (CHCH$_2$*C*H$_2$), 38.0 (CH*C*H$_2$CH$_2$), 43.2 (C_3-THIQ), 55.3 (OCH_3), 59.0 (C_1-THIQ), 112.1, 113.5 (C_5-THIQ), 121.0, 125.9,

128.2 (C_8-THIQ), 128.4 (2 x ArCH), 128.5 (2 x ArCH), 129.0, 135.9 (C_1CC_8-THIQ), 141.6 (Ar*C*CH_2, phenethyl), 147.7 (ArCN) and 158.3 (C_6-THIQ) ppm. HRMS (ES^+) calcd. $C_{24}H_{25}{}^{37}ClNO$ (M^++H) 380.1590, found 380.1615.

1-Benzyl-6-methoxy-2-phenyl-1,2,3,4-tetrahydroisoquinoline (30h)
The crude compound was purified by column chromatography (eluent: from 0% to 20% EtOAc in pet. ether) to give a yellow oil (155 mg, 58%) which showed:[37] ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.64 – 2.83 (1H, m, 1 x H_4-THIQ), 2.87 – 3.06 (2H, m, 1 x H_4-THIQ, 1 x CHC*H*$_2$), 3.11 – 3.34 (1H, m, 1 x CHC*H*$_2$), 3.44 – 3.58 (1H, m, H_3-THIQ), 3.58 – 3.70 (1H, m, H_3-THIQ), 3.78 (3H, s, OCH_3), 4.86 (1H, t, *J* = 6.5 Hz, H_1-THIQ), 6.60 (1H, dd, *J* = 2.4, 8.4 Hz, H_7-THIQ), 6.63 (1H, d, *J* = 8.4 Hz, H_8-THIQ), 6.67 (1H, d, *J* = 1.8 Hz, H_5-THIQ), 6.70 – 6.79 (1H, m), 6.79 - 6.94 (2H, m), 7.02 (2H, d, *J* = 6.5 Hz) and 7.15 – 7.25 (5H, m) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 27.8 (C_4-THIQ), 42.1 (C_3-THIQ), 42.4 (CH*C*H_2), 55.2 (OCH_3), 61.0 (C_1-THIQ), 111.5 (C_7-THIQ), 113.0 (C_5-THIQ), 113.7 (2 x ArCH), 117.3 (ArCH), 126.2 (ArCH), 128.1 (2 x ArCH), 128.6 (C_8-THIQ), 129.2 (2 x ArCH), 129.6 (C_1CC_8-THIQ), 129.8 (2 x ArCH), 136.2 (C_4CC_5-THIQ), 138.7 (Ar*C*CH_2CH), 149.1 (ArCN) and 158.1 (C_6-THIQ) ppm.

1-Benzyl-6-methoxy-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (30i)
The crude compound was purified by column chromatography (eluent: from 0% to 20% EtOAc in pet. ether) to give a yellow oil (182 mg, 61%) which showed:[23] ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.62 – 2.79 (1H, m, 1 x H_4-THIQ), 2.86 – 3.05 (2H, m, 1 x H_4-THIQ, 1 x CHC*H*$_2$), 3.20 (1H, dd, *J* = 5.4, 13.5 Hz, 1 x CHC*H*$_2$), 3.43 - 3.55 (1H, m, H_3-THIQ), 3.60 (1H, ddd, *J* = 4.5, 9.0, 13.5 Hz, H_3-THIQ), 3.77 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 4.76 (1H, t, *J* = 6.5 Hz, H_1-THIQ), 6.59 – 6.66 (2H, m, H_7-THIQ, H_8-THIQ), 6.67 (1H, d, *J* = 1.7 Hz, H_5-THIQ), 6.78 – 6.92 (4H, m), 7.04 (2H, d, *J* = 6.8 Hz) and 7.15 – 7.29 (3H, m) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 27.5 (C_4-THIQ), 42.0 (CH*C*H_2), 42.4 (C_3-THIQ), 55.1 (OCH_3), 55.6 (OCH_3), 61.8 (C_1-THIQ), 111.5 (C_7-THIQ), 113.1 (C_5-THIQ), 114.6 (2 x ArCH), 116.8 (2 x ArCH), 126.0 (ArCH), 128.0 (2 x ArCH), 128.6 (C_8-THIQ), 129.7 (2 x ArCH), 130.0 (C_1CC_8-THIQ), 136.0 (C_4CC_5-THIQ), 139.3 (Ar*C*CH_2CH), 144.2 (ArCN), 152.4 (ArCO, phenyl) and 158.0 (C_6-THIQ) ppm.

2-(4-Chlorophenyl)-1-ethyl-8-methoxy-1,2,3,4-tetrahydroisoquinoline (31b)
The crude compound was purified by column chromatography (eluent: 100% pet. ether) to give a colourless oil (24 mg, 5%) which showed: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, t, *J* = 7.4 Hz, C*H*$_3$CH$_2$), 1.74 – 1.91 (2H, m, CH$_3$C*H*$_2$), 2.78 (1H, dt, *J* = 5.1, 16.2 Hz, H_4-THIQ), 2.97 (1H, ddd, *J* = 5.9, 8.8, 15.0 Hz, H_4-THIQ), 3.49 – 3.68 (2H, m, H_3-THIQ), 3.83 (3H, s, OCH_3), 4.87 (1H, dd, *J* = 5.7, 8.0 Hz, H_1-THIQ), 6.71 (1H, d, *J* = 7.9 Hz, H_5 or H_7-THIQ), 6.72 (1H, d, *J* = 7.9 Hz, H_5 or H_7-THIQ), 6.80 (2H, d, *J* = 9.1 Hz, 2 x ArCH, phenyl), 7.11 (1H, t, *J* = 7.9 Hz, H_6-THIQ) and 7.13 (2H, d, *J* = 9.2 Hz, 2 x ArCH, phenyl) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 11.3 (*C*H$_3$CH$_2$), 26.3 (C_4-THIQ), 27.6 (CH$_3$*C*H$_2$), 41.1 (C_3-THIQ), 54.6 (C_1-THIQ), 55.2 (OCH_3), 107.8 (C_5 or C_7-THIQ), 115.0 (2 x ArCH, phenyl), 120.8 (C_5 or C_7-THIQ), 121.3 (ArCCl), 126.9 (C_6-THIQ), 127.7 (C_1CC_8-THIQ), 128.8 (2 x ArCH, phenyl), 135.9 (C_4CC_5-THIQ), 148.7 (ArCN) and 155.7 (C_8-THIQ) ppm.

2-(4-Chlorophenyl)-1-isopropyl-8-methoxy-1,2,3,4-tetrahydroisoquinoline (31c)
The crude compound was purified by column chromatography (eluent: 100% pet. ether) to give a white solid (57 mg, 12%) which showed: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (3H, d, *J* = 6.7 Hz, (C*H*$_3$)$_2$CH), 1.02 (3H, d, *J* = 6.8 Hz, (C*H*$_3$)$_2$CH), 2.08 (1H, ddt, *J* = 6.8, 9.4, 13.6 Hz, (CH$_3$)$_2$C*H*), 2.92 (1H, ddd, *J* = 4.5, 6.3, 15.8 Hz, H_4-THIQ), 3.02 – 3.18 (1H, m, H_4-THIQ), 3.31 (1H, ddd, *J* = 6.3, 9.3, 11.4 Hz, H_3-THIQ), 3.68 (1H, ddd, *J* = 4.5, 6.8, 11.4 Hz, H_4-THIQ), 3.81 (3H, s, OCH_3), 4.95 (1H, d, *J* = 9.3 Hz, H_1-THIQ), 6.72 (1H, d, *J* = 7.4 Hz, H_5 or H_7-THIQ), 6.75 (1H, d, *J* = 7.4 Hz, H_5 or H_7-THIQ), 6.76 (2H, d, *J* = 9.2 Hz, 2 x ArCH, phenyl), 7.12 (2H, d, *J* = 9.2 Hz, 2 x ArCH, phenyl) and 7.13 (1H, t, *J* = 7.4 Hz, H_6-THIQ) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 19.8 ((*C*H$_3$)$_2$CH), 20.9 ((*C*H$_3$)$_2$CH), 27.2 (C_4-THIQ), 34.9 ((CH$_3$)$_2$*C*H), 43.3 (C_3-THIQ), 55.1 (OCH_3), 56.5 (C_1-THIQ), 108.0 (C_5 or C_7-THIQ), 113.8 (2 x ArCH, phenyl), 120.3 (C_5 or C_7-THIQ), 120.5 (ArCCl), 127.2 (C_6-THIQ), 127.6 (C_1CC_8-THIQ), 128.6 (2 x ArCH, phenyl), 136.3 (C_4CC_5-THIQ), 148.8 (ArCN) and 155.6 (C_8-THIQ) ppm. HRMS (ES^+) calcd. $C_{19}H_{23}ClNO$ (M^++H) 316.1463, found 316.1475.

1-Benzyl-2-(4-chlorophenyl)-8-methoxy-1,2,3,4-tetrahydroisoquinoline (31f)
The crude compound was purified by column chromatography (eluent: 100% pet. ether) to give a colourless oil (62 mg, 11%) which showed: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.55 (1H, dt, *J* = 5.1, 16.2 Hz), 2.87 – 2.99 (1H, m), 3.04 (1H, dd, *J* = 7.8, 13.5 Hz), 3.15 (1H, dd, *J* = 4.5, 13.5 Hz), 3.51 – 3.60 (1H, m), 3.66 – 3.74 (1H, m), 3.78 (3H, s), 5.15 (1H, dd, *J* = 4.5, 7.7 Hz), 6.60 (2H, d, *J* = 9.1 Hz), 6.66 – 6.75 (2H, m), 7.04 (2H, d, *J* = 9.1 Hz) and 7.09 – 7.24 (6H, m) ppm.

1-Benzyl-8-methoxy-2-phenyl-1,2,3,4-tetrahydroisoquinoline (31h)
The crude compound was purified by column chromatography (eluent: from 0% to 20% EtOAc in pet. ether) to give a white solid (16 mg, 6%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.46 - 2.73 (1H, m, H_4-THIQ), 2.89 - 3.03 (1H, m, H_4-THIQ), 3.03 - 3.24 (2H, m, CHC*H*$_2$), 3.53 - 3.64 (1H, m, H_3-THIQ), 3.67 - 3.82 (4H, m, OCH_3, H_3-THIQ), 5.23 (1H, t, *J* = 6.1 Hz, H_1-THIQ), 6.69 (2H, d, *J* = 8.1 Hz), 6.72 (1H, d, *J* = 7.6 Hz), 6.74 – 6.85 (2H, m), 7.09 - 7.17 (6H, m) and 7.17 - 7.23 (2H, m) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.3 (C_4-THIQ), 40.2 (CH*C*H_2), 41.1 (C_3-THIQ), 55.1 (OCH_3), 56.5 (C_1-THIQ), 107.7 (ArCH), 114.1 (2 x ArCH), 120.7 (2 x ArCH), 125.9 (ArCH), 126.8 (C_q), 127.9 (2 x ArCH), 129.0 (ArCH),

129.5 (2 x ArCH), 129.7 (ArCH), 130.9 (ArCH), 136.1 (C_4CC_5-THIQ), 139.8 (C_q), 149.4 (C_q) and 155.6 (C_8-THIQ) ppm. HRMS (ES^+) calcd. $C_{23}H_{24}NO$ (M^++H) 330.1858, found 330.1842. Mp 126-128 °C (pet. ether).

1-Benzyl-8-methoxy-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (31i)
The crude compound was purified by column chromatography (eluent: from 0% to 20% EtOAc in pet. ether) to give a yellow oil (25 mg, 8%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.41 – 2.65 (1H, m, H_4-THIQ), 2.84 – 2.99 (1H, m, H_4-THIQ), 2.99 – 3.23 (2H, m, CHC*H*$_2$), 3.44 – 3.63 (1H, m, H_3-THIQ), 3.70 (3H, s, OCH_3), 3.71 – 3.75 (1H, m, H_3-THIQ), 3.78 (3H, s, *J* = 30.7 Hz, OCH_3), 5.05 (1H, bs, H_1-THIQ), 6.61 – 6.77 (6H, m), 7.09 – 7.18(4H, m) and 7.18 – 7.25 (2H, m) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.8 (C_4-THIQ), 40.2 (CH*C*H$_2$), 41.6 (C_3-THIQ), 55.1 (OCH_3), 55.7 (OCH_3), 57.1 (H_1-THIQ), 107.5 (ArCH), 114.4 (2 x ArCH), 116.5 (ArCH), 120.9 (2 x ArCH), 125.8 (ArCH), 127.0 (ArCH), 127.9 (2 x ArCH), 129.6 (2 x ArCH), 136.2 (C_q), 140.5 (C_q), 144.5 (C_q), 146.9 (ArCN), 151.9 (ArCO) and 155.7 (ArCO) ppm. HRMS (ES^+) calcd. $C_{24}H_{26}NO_2$ (M^++H) 360.1964, found 360.1973. Mp 114-118 °C (pet. ether).

***N*-(4-Chlorophenyl)-*N*-(2-(3-methoxyphenyl)propyl)-2-phenylacetamide (32a)**
Phenacetyl chloride (162 µL, 1.20 mmol) was added to a stirring solution of **26a** (300 mg, 1.09 mmol) and Et_3N (229 µL, 1.64 mmol) in DCM (3 mL) and the mixture was stirred overnight at rt under inert atmosphere. The mixture was then diluted with DCM (25 mL) washed with 1 N NaOH (3 x 25 mL), 1 N HCl (3 x 25 mL) and brine (25 mL), then dried with $MgSO_4$, filtered and evaporated to give a yellow oil (403 mg). The crude compound was purified by column chromatography (eluent: from 0% to 40% EtOAc in pet. ether) to give the product as a colourless oil (223 mg, 52%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (3H, d, *J* = 7.0 Hz, CHC*H*$_3$), 2.89 – 3.01 (1H, m, C*H*CH_3), 3.27 (2H, s, CH_2CO), 3.67 (3H, s, OCH_3), 3.68 – 3.73 (1H, m, CH_2N), 3.93 (1H, dd, *J* = 6.9, 13.5 Hz, CH_2N), 6.58 (2H, d, *J* = 7.4 Hz, 2 x ArCH, aniline), 6.59 – 6.61 (1H, m, ArCH, methoxyphenyl), 6.63 (1H, d, *J* = 7.9 Hz, ArCH, methoxyphenyl), 6.67 (1H, dd, *J* = 2.0, 7.9 Hz, ArCH, methoxyphenyl), 6.85 (2H, d, *J* = 7.4 Hz, 2 x ArCH, aniline), 7.08 (1H, t, *J* = 7.9 Hz, ArCH, methoxyphenyl) and 7.10 – 7.17 (5H, m, 5 x ArCH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.9 (CH*C*H$_3$), 38.3 (*C*HCH_3), 41.4 (*C*H$_2$CO), 55.2 (OCH_3), 55.9 (CH_2N), 112.1 (ArCH, methoxyphenyl), 113.1 (ArCH, methoxyphenyl), 120.0 (ArCH, methoxyphenyl), 126.6 (ArCH, phenyl), 128.4 (2 x ArCH, phenyl), 128.8 (2 x ArCH, aniline), 129.4 (ArCH, methoxyphenyl), 129.5 (ArCH, phenyl), 129.7 (2 x ArCH, aniline), 133.6 (ArCCl), 135.2 (Ar*C*CH$_2$), 141.3 (ArCN), 145.7 (Ar*C*CH), 159.7 (ArCO) and 170.9 (CON) ppm.

***N*-(4-Chlorophenyl)-*N*-(2-(3-methoxyphenyl)butyl)-2-phenylacetamide (32b)**
Phenacetyl chloride (154 µL, 1.14 mmol) was added to a stirring solution of **26b** (300 mg, 1.04 mmol) and Et_3N (218 µL, 1.56 mmol) in DCM (3 mL) and the mixture was stirred overnight at rt under inert atmosphere. The mixture was then diluted with DCM (25 mL) washed with 1 N NaOH (3 x 25 mL), 1 N HCl (3 x 25 mL) and brine (25 mL), then dried with $MgSO_4$, filtered and evaporated to give a yellow oil (426 mg). The crude compound was purified by column chromatography (eluent: from 0% to 40% EtOAc in pet. ether) to give the product as a colourless oil (361 mg, 85%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.68 (3H, t, *J* = 7.4 Hz, CH_2CH_3), 1.36 – 1.48 (1H, m, C*H*$_2$CH$_3$), 1.54 – 1.63 (1H, m, C*H*$_2$CH$_3$), 2.64 – 2.79 (1H, m, C*H*CH_2), 3.24 (2H, s, CH_2CO), 3.66 (3H, s, OCH_3), 3.72 (1H, dd, *J* = 9.9, 13.5 Hz, CH_2N), 3.98 (1H, dd, *J* = 6.1, 13.5 Hz, CH_2N), 6.44 - 6.53 (2H, m, 2 x ArCH, aniline), 6.53 – 6.57 (1H, m, ArCH, methoxyphenyl), 6.58 (1H, d, *J* = 7.8 Hz, ArCH, methoxyphenyl), 6.68 (1H, dd, *J* = 2.1, 7.8 Hz, ArCH, methoxyphenyl), 6.80 – 6.85 (2H, m, 2 x ArCH, phenyl), 7.07 (2H, t, *J* = 7.8 Hz, ArCH, methoxyphenyl) and 7.09 – 7.15 (5H, m, 3 x ArCH, phenyl, 2 x ArCH, aniline) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 11.8 (CH_2CH_3), 27.1 (*C*H$_2$CH$_3$), 41.4 (*C*H$_2$CO), 45.8 (*C*HCH$_2$), 54.8 (CH_2N), 55.2 (OCH_3), 112.1 (ArCH, methoxyphenyl), 113.8 (ArCH, methoxyphenyl), 120.9 (ArCH, methoxyphenyl), 126.5 (ArCH, phenyl), 128.3 (2 x ArCH), 128.8 (2 x ArCH), 129.2 (ArCH, methoxyphenyl), 129.4 (2 x ArCH), 129.7 (2 x ArCH), 133.5 (ArCCl), 135.2 (Ar*C*CH$_2$), 141.4 (ArCN), 144.0 (Ar*C*CH), 159.6 (ArCO) and 170.8 (CON) ppm.

***N*-(4-Chlorophenyl)-*N*-(2-(3-methoxyphenyl)-3-phenylprop-yl)-2-phenylacetamide (32d)**
Phenacetyl chloride (127 µL, 0.938 mmol) was added to a stirring solution of **26d** (300 mg, 0.853 mmol) and Et_3N (179 µL, 1.28 mmol) in DCM (3 mL) and the mixture was stirred overnight at rt under inert atmosphere. The mixture was then diluted with DCM (25 mL) washed with 1 N NaOH (3 x 25 mL), 1 N HCl (3 x 25 mL) and brine (25 mL), then dried with $MgSO_4$, filtered and evaporated to give a yellow oil (387 mg). The crude compound was purified by column chromatography (eluent: from 0% to 40% EtOAc in pet. ether) to give the product as a colourless oil (153 mg, 38%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.77 (2H, dd, *J* = 8.4, 13.8 Hz, ArC*H*$_2$CH), 2.83 (2H, dd, *J* = 6.5, 13.8 Hz, ArC*H*$_2$CH), 3.07 – 3.17 (1H, m, ArCH$_2$C*H*), 3.23 (2H, s, ArCH$_2$CO), 3.62 (3H, s, OCH_3), 3.86 (1H, dd, *J* = 9.9, 13.6 Hz, CH_2N), 4.00 (1H, dd, *J* = 6.1, 13.6 Hz, CH_2N), 6.48 (2H, d, *J* = 7.4 Hz, 2 x ArCH, aniline), 6.49 – 6.52 (1H, m, ArCH, methoxyphenyl), 6.54 (1H, d, *J* = 7.8 Hz, ArCH, methoxyphenyl), 6.66 (1H, dd, *J* = 2.1, 7.8 Hz, ArCH, methoxyphenyl), 6.78 – 6.84 (2H, m, 2 x ArCH), 6.88 (2H, d, *J* = 7.0 Hz, 2 x ArCH), 7.03 (1H, t, *J* = 7.8 Hz, ArCH, methoxyphenyl) and 7.05 - 7.15 (8H, m, 8 x ArCH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 41.0 (Ar*C*H$_2$CH), 41.4 (Ar*C*H$_2$CO), 45.6 (ArCH$_2$*C*H), 54.0 (CH_2N), 55.2 (OCH_3), 112.4 (ArCH, methoxyphenyl), 113.7 (ArCH, methoxyphenyl), 120.8 (ArCH, methoxyphenyl), 126.0 (ArCH), 126.6 (ArCH), 128.1 (2 x ArCH), 128.3 (2 x ArCH), 128.8 (2 x ArCH), 129.0 (2 x ArCH), 129.3 (ArCH, methoxyphenyl), 129.4 (2 x ArCH), 129.7 (2 x ArCH), 133.6 (ArCCl), 135.1 (Ar*C*CH$_2$CO), 139.4 (Ar*C*CH$_2$CH), 141.1 (ArCN), 143.3 (Ar*C*CH), 159.6 (ArCO) and 170.9 (CON) ppm.

***trans*-1-Benzyl-2-(4-chlorophenyl)-6-methoxy-4-methyl-1,2,3,4-tetrahydroisoquinoline (33a)**
Synthesized according to the general method for the Bischler-Napieralski cyclisation. The crude compound was purified by column chromatography (eluent: from 0% to 10% EtOAc in pet. ether) to give the product as a yellow oil (22 mg, 36%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32 (3H, d, *J* = 6.8 Hz, CHC*H*$_3$), 3.02 (1H, dd, *J* = 5.5, 13.7 Hz, ArC*H*$_2$CH), 3.04 – 3.14 (1H, m, H_4-THIQ), 3.14 – 3.26 (2H, m, 1 x ArC*H*$_2$CH, 1 x H_3-THIQ), 3.66 – 3.74 (1H, m, 1 x H_3-THIQ), 3.79 (3H, s, OCH_3), 4.78 – 4.87 (1H, m, H_1-THIQ), 6.61 (2H, d, *J* = 9.1 Hz, 2 x ArCH, *N*-phenyl), 6.68 (1H, dd, *J* = 2.6, 8.5 Hz, H_7-THIQ), 6.82 (H, d, *J* = 2.6 Hz, H_5-THIQ), 6.86 (H, d, *J* = 8.5 Hz, H_8-THIQ), 7.05 (2H, d, *J* = 9.1 Hz, 2 x ArCH, *N*-phenyl), 7.10 – 7.15 (2H, m, 2 x ArCH, benzyl), 7.18 – 7.22 (2H, m, 2 x ArCH, benzyl) and 7.22 – 7.25 (1H, m, ArCH, benzyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.0 (CH*C*H$_3$), 29.5 (C_4-THIQ), 41.9 (Ar*C*H$_2$CH), 48.0 (C_3-THIQ), 55.2 (OCH_3), 61.9 (C_1-THIQ), 111.4 (C_7-THIQ), 112.1 (C_5-THIQ), 116.5 (2 x ArCH, *N*-phenyl), 122.5 (ArCCl), 126.3(2 x ArCH, benzyl), 128.3(ArCH, benzyl), 128.4(2 x ArCH, *N*-phenyl), 128.8(C_8-THIQ), 129.0 (C_1*C*C$_8$-THIQ), 129.6 (2 x ArCH, benzyl), 139.2 (Ar*C*CH$_2$), 140.9 (C_4*C*C$_5$-THIQ), 148.6 (ArCN) and 158.3 (C_6-THIQ) ppm.

***trans*-1-Benzyl-2-(4-chlorophenyl)-4-ethyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (33b)**
Synthesized according to the general method for the Bischler-Napieralski cyclisation. The crude compound was purified by column chromatography (eluent: from 0% to 10% EtOAc in pet. ether) to give the product as a yellow oil (87 mg, 46%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (3H, t, *J* = 7.4 Hz, CH$_2$C*H*$_3$), 1.59 – 1.78 (1H, m, C*H*$_2$CH$_3$), 1.90 – 2.04 (1H, m, C*H*$_2$CH$_3$), 2.92 – 3.05 (2H, m, H_4-THIQ, ArC*H*$_2$CH), 3.19 (1H, dd, *J* = 7.2, 13.4 Hz, ArC*H*$_2$CH), 3.32 (1H, dd, *J* = 10.5, 13.6 Hz, H_3-THIQ), 3.73 (1H, dd, *J* = 5.8, 13.6 Hz, H_3-THIQ), 3.78 (3H, s, OCH_3), 4.80 (1H, t, *J* = 6.5 Hz, H_1-THIQ), 6.65 (1H, dd, *J* = 2.6, 8.6 Hz, H_7-THIQ), 6.67 (2H, d, *J* = 8.8 Hz, 2 x ArCH, *N*-phenyl), 6.77 (1H, d, *J* = 8.5 Hz, H_8-THIQ), 6.81 (1H, d, *J* = 2.2 Hz, H_5-THIQ), 7.02 – 7.14 (4H, m, 2 x ArCH, *N*-phenyl, 2 x ArCH, phenyl), 7.15 – 7.21 (1H, m, ArCH, phenyl) and 7.21 – 7.25 (2H, m, 2 x ArCH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 10.9 (CH$_2$*C*H$_3$), 25.8 (*C*H$_2$CH$_3$), 35.9 (C_4-THIQ), 41.7 (Ar*C*H$_2$CH), 45.8 (C_3-THIQ), 55.2 (OCH_3), 61.8 (C_1-THIQ), 111.3 (C_7-THIQ), 112.3 (C_5-THIQ), 116.9 (2 x ArCH, *N*-phenyl), 120.9 (ArCCl), 126.3 (ArCH, phenyl), 128.3 (2 x ArCH, phenyl), 128.6 (C_8-THIQ), 128.9 (2 x ArCH, *N*-phenyl), 129.3 (C_1*C*C$_8$-THIQ), 129.7 (2 x ArCH, phenyl), 138.9 (Ar*C*CH$_2$CH), 139.4 (C_4*C*C$_5$-THIQ), 148.5 (ArCN) and 158.3 (C_6-THIQ) ppm.

***trans*-1,4-Dibenzyl-2-(4-chlorophenyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (33d)**
Synthesized according to the general method for the Bischler-Napieralski cyclisation. The crude compound was purified by column chromatography (eluent: from 0% to 10% EtOAc in pet. ether) to give the product as a colourless oil (11 mg, 46%) which showed: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68 (1H, dd, *J* = 8.5, 13.5 Hz), 2.94 (1H, dd, *J* = 6.6, 13.6 Hz), 3.29 (4H, t, *J* = 10.7 Hz), 3.47 (1H, d, *J* = 7.6 Hz), 3.76 (3H, s), 4.80 (1H, t, *J* = 6.3 Hz), 6.63 – 6.73 (3H, m), 6.78 (1H, d, *J* = 8.6 Hz), 6.85 (1H, d, *J* = 2.5 Hz), 7.01 (2H, d, *J* = 6.4 Hz), 7.07 (2H, d, *J* = 8.9 Hz), 7.14 – 7.24 (6H, m) and 7.29 – 7.37 (2H, m) ppm.

***trans*-1-Benzyl-4-ethyl-8-methoxy-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (34b)**
Synthesized according to the general method for the Bischler-Napieralski cyclisation. The crude compound was purified by column chromatography (eluent: from 0% to 10% EtOAc in pet. ether) to give the product as a white solid (22mg, 12%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (3H, t, *J* = 7.4 Hz, CH$_2$C*H*$_3$), 1.60 – 1.74 (1H, m, C*H*$_2$CH$_3$), 1.97 – 2.13 (1H, m, C*H*$_2$CH$_3$), 2.99 – 3.12 (2H, m, ArC*H*$_2$CH, H_4-THIQ), 3.19 (1H, dd, *J* = 3.0, 13.8 Hz, ArC*H*$_2$CH), 3.51 (1H, dd, *J* = 11.5, 14.3 Hz, H_3-THIQ), 3.82 (1H, dd, *J* = 6.6, 14.3 Hz, H_3-THIQ), 3.89 (3H, s, OCH_3), 5.05 (1H, d, *J* = 8.1 Hz, H_1-THIQ), 6.50 (2H, d, *J* = 9.0 Hz, 2 x ArCH, *N*-phenyl), 6.72 (1H, d, *J* = 8.1 Hz, H_7-THIQ), 6.92 (1H, d, *J* = 7.8 Hz, H_5-THIQ), 6.95 (2H, d, *J* = 9.0 Hz, 2 x ArCH, *N*-phenyl), 7.15 – 7.22 (2H, m, 1 x ArCH, phenyl, H_6-THIQ) and 7.22 - 7.29 (4H, m, 4 x ArCH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 10.8 (CH$_2$*C*H$_3$), 25.9 (*C*H$_2$CH$_3$), 34.1 (C_4-THIQ), 39.4 (Ar*C*H$_2$CH), 44.5 (C_3-THIQ), 55.3 (OCH_3), 58.0 (C_1-THIQ), 107.3 (C_7-THIQ), 116.2 (2 x ArCH, *N*-phenyl), 119.5 (C_5-THIQ), 122.0 (ArCCl), 126.0 (ArCH, phenyl), 127.3 (C_6-THIQ), 127.5 (C_1CC_8-THIQ), 128.2 (2 x ArCH, phenyl), 128.6 (2 x ArCH, *N*-phenyl), 129.4 (2 x ArCH, phenyl), 139.5 (C_4CC_5-THIQ), 140.5 (Ar*C*CH$_2$CH), 148.9 (ArCN) and 155.6 (C_8-THIQ) ppm.

***trans*-1,4-Dibenzyl-8-methoxy-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (34d)**
Synthesized according to the general method for the Bischler-Napieralski cyclisation. The crude compound was purified by column chromatography (eluent: from 0% to 10% EtOAc in pet. ether) to give the product as a colourless oil (2 mg, 8%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.64 (1H, dd, *J* = 9.5, 13.8 Hz), 2.96 (1H, dd, *J* = 9.5, 13.7 Hz), 3.15 (1H, dd, *J* = 3.1, 13.8 Hz), 3.34 – 3.54 (3H, m), 3.90 (3H, s), 5.03 (1H, d, *J* = 7.5 Hz), 6.25 – 6.34 (2H, m), 6.76 (1H, d, *J* = 8.1 Hz), 6.86 – 6.91 (2H, m), 7.05 (1H, d, *J* = 7.4 Hz), 7.24 (6H, s), 7.24 – 7.29 (3H, m) and 7.35 (2H, dd, *J* = 6.4, 13.9 Hz) ppm.

General method for methoxy deprotection with HBr: **5c** (200 mg, 836 µmol) was suspended in 46% HBr (3 mL) and stirred for 3 h at 120 °C. The mixture became a solution upon heating. The mixture was then cooled to rt and filtered to give the product as a white precipitate (230 mg, 90%).

General method for methoxy deprotection with BBr_3: 1.0 M solution of BBr_3 (6.7 mL, 6.68 mmol) in DCM was added to a stirring solution of **7a** (200 mg, 0.668 mmol) in anhydrous DCM (1 mL) at 0 °C under inert atmosphere. The mixture

was stirred for 2 h letting it reach rt then quenched with a minimum amount of ice and stirred for 10 min. The mixture was filtered and the precipitate was washed with DCM then dried to give the product as a yellow solid (168 mg, 74%).

2-Phenyl-1,2,3,4-tetrahydroisoquinolin-6-ol hydrobromide (35c)
Synthesized according to the general method for methoxy deprotection with HBr. The product was obtained as a white precipitate (230 mg, 90%) which showed (^{1}H and ^{13}C NMR data refer to the free base): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.93 (2H, t, *J* = 5.8 Hz, H_4-THIQ), 3.54 (2H, t, *J* = 5.8 Hz, H_3-THIQ), 4.34 (2H, s, H_1-THIQ), 4.75 (1H, bs, OH), 6.63 (1H, d, *J* = 2.6 Hz, H_5-THIQ), 6.68 (1H, dd, *J* = 2.6, 8.2 Hz, H_7-THIQ), 6.83 (1H, t, *J* = 7.3 Hz, ArH, phenyl), 6.97 (2H, d, *J* = 8.8 Hz, ArH, phenyl), 7.03 (1H, d, *J* = 8.2 Hz, H_8-THIQ) and 7.29 (2H, dd, *J* = 7.3, 8.8 Hz, ArH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.3 (C_4-THIQ), 46.6 (C_3-THIQ), 50.4 (C_1-THIQ), 113.6 (C_7-THIQ), 115.0 (C_5-THIQ), 115.4 (ArCH, phenyl), 118.9 (ArCH, phenyl), 126.9 (C_1CC_8-THIQ), 127.9 (C_8-THIQ), 129.3 (ArCH, phenyl), 136.5 (C_5CC_6-THIQ), 150.7 (ArCN) and 154.1 (C_6-THIQ) ppm. LC/MS (ES^+) t_r = 2.14 min (98 %), m/z 225.9 (M^++H); (RP, Isocratic, 80% MeOH). HRMS (ES^+) calcd. for $C_{15}H_{16}NO$ (M^++H) 226.1226, found 226.1258. Mp 220-221 °C (aqueous HBr). Anal. calcd. for $C_{15}H_{16}BrNO$: C 58.54, H 5.27, N 4.57. Found: C 58.6, H 5.25, N 4.44 %.

2-(4-Chlorophenyl)-1,2,3,4-tetrahydroisoquinolin-6-ol hydrobromide (35d)
Synthesized according to the general method for methoxy deprotection with HBr. The product was obtained as a yellow precipitate (196 mg, 79%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.92 (2H, t, *J* = 5.9 Hz, H_4-THIQ), 3.50 (2H, t, *J* = 5.9 Hz, H_3-THIQ), 4.30 (2H, s, H_1-THIQ), 4.79 (1H, bs, OH), 6.64 (1H, d, *J* = 2.6 Hz, H_5-THIQ), 6.68 (1H, dd, *J* = 2.6, 8.2 Hz, H_7-THIQ), 6.87 (2H, d, *J* = 9.1 Hz, ArH, phenyl), 7.02 (1H, d, *J* = 8.2 Hz, H_8-THIQ) and 7.21 (2H, d, *J* = 9.1 Hz, ArH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.2 (C_4-THIQ), 46.6 (C_3-THIQ), 50.3 (C_1-THIQ), 113.7 (C_7-THIQ), 115.0 (C_5-THIQ), 116.3 (ArCH, phenyl), 123.5 (ArCCl), 126.5 (C_1CC_8-THIQ), 127.8 (C_8-THIQ), 129.1 (ArCH, phenyl), 136.3 (C_5CC_6-THIQ), 149.2 (ArCN) and 154.2 (C_6-THIQ) ppm. LC/MS (ES^+) t_r = 4.39 min (97 %), m/z 259.8 (M^++H); (RP, Isocratic, 80% MeOH). HRMS (ES^+) calcd. $C_{15}H_{15}{}^{35}ClNO$ (M^++H) 260.0837, found 260.0845, calcd. $C_{15}H_{15}{}^{37}ClNO$ (M^++H) 262.0807, found 262.0845. Mp 196-197 °C (aqueous HBr).

2-(*p*-Tolyl)-1,2,3,4-tetrahydroisoquinolin-6-ol hydrobromide (35i)
Synthesized according to the general method for methoxy deprotection with HBr. The product was obtained as a yellow precipitate (240 mg, 95%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.28 (3H, s, CH_3), 2.92 (2H, t, *J* = 5.8 Hz, H_4-THIQ), 3.48 (2H, t, *J* = 5.9 Hz, H_3-THIQ), 4.28 (2H, s, H_1-THIQ), 4.77 (1H, bs), 6.62 (1H, d, *J* = 2.5 Hz, H_5-THIQ), 6.67 (1H, dd, *J* = 2.5, 8.2 Hz, H_7-THIQ), 6.91 (2H, d, *J* = 8.6 Hz, ArH, phenyl), 7.01 (1H, d, *J* = 8.2 Hz, H_8-THIQ) and 7.09 (2H, d, *J* = 8.6 Hz, ArH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.5 (CH_3), 29.3 (C_4-THIQ), 47.4 (C_3-THIQ), 51.2 (C_1-THIQ), 113.5 (C_7-THIQ), 115.0 (C_5-THIQ), 116.1 (ArCH, phenyl), 127.0 (C_1CC_8-THIQ), 127.8 (C_8-THIQ), 128.6 (Ar*C*CH_3), 129.8 (ArCH, phenyl), 136.4 (C_5CC_6-THIQ), 148.8 (ArCN) and 154.0 (C_6-THIQ) ppm. LC/MS (ES^+) t_r = 1.73 min (97 %), m/z 239.9 (M^++H); (RP, Isocratic, 80% MeOH). HRMS (ES^+) calcd. $C_{16}H_{17}NO$ (M^++H) 240.1383, found 240.1380. Mp 224-225 °C (aqueous HBr). Anal. calcd. for $C_{16}H_{18}BrClNO$: C 60.0, H 5.67, N 4.37. Found: C 59.5, H 5.69, N 4.32 %.

2-(4-Hydroxyphenyl)-1,2,3,4-tetrahydroisoquinolin-6-ol hydrobromide (35k)
Synthesized according to the general method for methoxy deprotection with HBr. The product was obtained as a yellow precipitate (217 mg, 91%) which showed:[23] ^{1}H NMR (500 MHz, D_6-DMSO) δ 2.78 (2H, t, *J* = 5.7 Hz, H_4-THIQ), 3.27 (2H, t, *J* = 5.9 Hz, H_3-THIQ), 4.05 (2H, s, H_1-THIQ), 6.52 (1H, d, *J* = 2.5 Hz, H_5-THIQ), 6.56 (1H, dd, *J* = 2.5, 8.2 Hz, H_7-THIQ), 6.66 (2H, d, *J* = 8.9 Hz, ArH, phenyl), 6.84 (2H, d, *J* = 8.9 Hz, ArH, phenyl), 6.94 (1H, d, *J* = 8.2 Hz, H_8-THIQ), 8.80 (1H, bs, OH, phenyl) and 9.15 (1H, bs, OH-THIQ) ppm. ^{13}C NMR (126 MHz, D_6-DMSO) δ 28.6 (C_4-THIQ), 47.8 (C_3-THIQ), 51.7 (C_1-THIQ), 113.3 (C_7-THIQ), 114.6 (C_5-THIQ), 115.6 (ArCH, phenyl), 117.7 (ArCH, phenyl), 125.0 (C_1CC_8-THIQ), 127.4 (C_8-THIQ), 135.3 (C_5CC_6-THIQ), 143.9 (ArCN), 150.6 (ArCO, phenyl) and 155.5 (C_6-THIQ) ppm. LC/MS (ES^+) t_r = 1.96 min (95 %), m/z 241.8 (M^++H); (RP, Isocratic, 70% MeOH). HRMS (ES^+) calcd. $C_{15}H_{15}NO_2$ (M^++H) 242.1176, found 242.1178. Mp 245-246 °C (aqueous HBr). Anal. calcd. for $C_{15}H_{16}BrNO_2$: C 55.9, H 5.01, N 4.35. Found: C 55.7, H 4.99, N 4.17 %.

2-(3-Hydroxyphenyl)-1,2,3,4-tetrahydroisoquinolin-6-ol hydrobromide (35l)
Synthesized according to the general method for methoxy deprotection with HBr. The product was obtained as a black solid (20 mg, 67%) which showed: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.90 (2H, t, *J* = 5.8 Hz), 3.51 (2H, t, *J* = 5.9 Hz), 4.32 (2H, s), 4.66 (2H, bs), 6.27 (1H, ddd, *J* = 0.7, 2.3, 8.0 Hz), 6.42 (1H, t, *J* = 2.3 Hz), 6.54 (1H, dd, *J* = 2.1, 8.0 Hz), 6.63 (1H, d, *J* = 2.6 Hz), 6.67 (1H, dd, *J* = 2.7, 8.2 Hz), 7.01 (1H, d, *J* = 8.3 Hz) and 7.12 (1H, t, *J* = 8.1 Hz) ppm. HRMS (ES^+) calcd. $C_{15}H_{16}NO_2$ (M^++H) 242.1176, found 242.1187.

2-(3-Chlorophenyl)-1,2,3,4-tetrahydroisoquinolin-6-ol hydrobromide (36a)
Synthesized according to the general method for methoxy deprotection with HBr. The product was obtained as a yellow solid (35 mg, 64%) which showed: ^{1}H NMR (500 MHz, D_6-DMSO) δ 2.79 (2H, t, *J* = 5.7 Hz, H_4-THIQ), 3.48 (9H, t, *J* = 5.7 Hz, H_3-THIQ), 4.27 (2H, s, H_1-THIQ), 6.57 (1H, s, H_5-THIQ), 6.60 (1H, dd, *J* = 2.3, 8.2 Hz, H_7-THIQ), 6.70 (1H, d, *J* = 7.8 Hz, ArCH, phenyl), 6.89 (1H, dd, *J* = 2.2, 8.4 Hz, ArCH, phenyl), 6.92 (1H, s, ArCH, phenyl), 7.01 (1H, d, *J* = 8.2 Hz, H_8-THIQ), 7.20 (1H, t, *J* = 8.1 Hz, ArCH, phenyl) and 9.29 (1H, bs, OH) ppm. ^{13}C NMR (126 MHz, D_6-DMSO) δ 28.2 (C_4-

THIQ), 45.1 (C_3-THIQ), 48.7 (C_1-THIQ), 112.6 (ArCH, phenyl), 113.4 (ArCH, phenyl), 113.5 (C_7-THIQ), 114.5 (C_5-THIQ), 116.8 (ArCH, phenyl), 124.4 (C_1CC_8-THIQ), 127.5 (C_8-THIQ), 130.5 (ArCH, phenyl), 134.0 (ArCCl), 135.7 (C_4CC_5-THIQ), 151.3 (ArCN) and 155.8 (C_6-THIQ) ppm. HRMS (ES^+) calcd. $C_{15}H_{15}{}^{35}ClNO$ (M^++H) 260.0837, found 260.0825; calcd. $C_{15}H_{15}{}^{37}ClNO$ (M^++H) 262.0807, found 262.0805. Mp 211-215 °C.

2-(4-Hydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline-6,7-diol hydrobromide (37a)
Synthesized according to the general method for methoxy deprotection with BBr_3. The product was obtained as a yellow solid (168 mg, 74%) which showed: ^{1}H NMR (500 MHz, D_2O) δ 3.18 (2H, t, *J* = 6.0 Hz, H_4-THIQ), 3.93 (2H, t, *J* = 6.0 Hz, H_3-THIQ), 4.63 (2H, s, H_1-THIQ), 6.74 (1H, s, H_8-THIQ), 6.84 (1H, s, H_5-THIQ), 7.06 (2H, d, *J* = 8.3 Hz, 2 x ArCH, phenyl) and 7.50 (2H, d, *J* = 8.3 Hz, 2 x ArCH, phenyl) ppm. ^{13}C NMR (126 MHz, D_2O) δ 24.9 (C_4-THIQ), 53.4 (C_3-THIQ), 56.5 (C_1-THIQ), 113.4 (C_8-THIQ), 115.7 (C_5-THIQ), 116.8 (2 x ArCH, phenyl), 120.0 (C_1CC_8-THIQ), 122.5 (2 x ArCH, phenyl), 122.9 (C_4CC_5-THIQ), 133.5 (ArCN), 143.2 (C_6-THIQ), 144.2 (C_7-THIQ) and 156.9 (ArCO, phenyl) ppm. HRMS (ES^+) calcd. $C_{15}H_{16}NO_3$ (M^++H) 258.1125, found 258.1127. Compound degraded before melting.

2-(4-Hydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline-5,6,7-triol hydrobromide (37b)
Synthesized according to the general method for methoxy deprotection with BBr_3. The product was obtained as a yellow solid (245 mg, 99%) which showed: ^{1}H NMR (500 MHz, D2O) δ 3.10 (2H, t, *J* = 6.3 Hz, H_4-THIQ), 3.94 (2H, t, *J* = 6.4 Hz, H_3-THIQ), 4.61 (2H, s, H_1-THIQ), 6.40 (1H, s, H_8-THIQ), 7.07 (2H, d, *J* = 9.1 Hz, 2 x ArCH, phenyl) and 7.49 (2H, d, *J* = 9.1 Hz, 2 x ArCH, phenyl) ppm. ^{13}C NMR (126 MHz, D_2O) δ 20.6 (C_4-THIQ), 53.1 (C_3-THIQ), 56.4 (C_1-THIQ), 105.5 (C_8-THIQ), 111.4 (C_4CC_5-THIQ), 116.8 (2 x ArCH, phenyl), 120.4 (C_1CC_8-THIQ), 122.4 (2 x ArCH, phenyl), 132.3 (C_6-THIQ), 133.6 (ArCN), 143.0 (C_5-THIQ), 144.5 (C_7-THIQ) and 156.8 (ArCO, phenyl) ppm. Mp 178-181 °C.

2-(4-Chlorophenyl)-1,2,3,4-tetrahydroisoquinolin-7-ol hydrobromide (38b)
Synthesized according to the general method for methoxy deprotection with HBr. The product was obtained as a yellow precipitate (92 mg, 74%) which showed: ^{1}H NMR (500 MHz, D_6-DMSO) δ 2.75 (2H, t, *J* = 5.9 Hz, H_4-THIQ), 3.48 (2H, t, *J* = 5.9 Hz, H_3-THIQ), 4.27 (2H, s, H_1-THIQ), 6.58 (1H, dd, *J* = 2.4, 8.2 Hz, H_6-THIQ), 6.60 (1H, d, *J* = 2.4 Hz, H_8-THIQ), 6.94 (1H, d, *J* = 8.2 Hz, H_5-THIQ), 6.97 (2H, d, *J* = 9.1 Hz, ArH, phenyl), 7.22 (2H, d, *J* = 9.1 Hz, ArH, phenyl) and 9.20 (1H, bs, OH) ppm. ^{13}C NMR (126 MHz, D_6-DMSO) δ 27.0 (C_4-THIQ), 45.9 (C_3-THIQ), 49.7 (C_1-THIQ), 112.8 (C_8-THIQ), 113.8 (C_6-THIQ), 116.0 (ArCH, phenyl), 121.2 (ArCCl), 124.6 (C_4CC_5-THIQ), 128.7 (ArCH, phenyl), 129.2 (C_5-THIQ), 135.0 (C_1CC_8-THIQ), 148.9 (ArCN) and 155.4 (C_7-THIQ) ppm. HRMS (ES^+) calcd. $C_{15}H_{15}{}^{35}ClNO$ (M^++H) 260.0837, found 260.0827; calcd. $C_{15}H_{15}{}^{37}ClNO$ (M^++H) 262.0807, found 262.0831. Mp 225-228 °C.

2-(4-Chlorophenyl)-1,2,3,4-tetrahydroisoquinolin-5-ol hydrobromide (39b)
Synthesized according to the general method for methoxy deprotection with HBr. The product was obtained as a brown precipitate (47 mg, 75%) which showed: ^{1}H NMR (500 MHz, D_6-DMSO) δ 2.69 (2H, t, *J* = 5.9 Hz, H_4-THIQ), 3.51 (2H, t, *J* = 5.9 Hz, H_3-THIQ), 4.31 (2H, s, H_1-THIQ), 6.64 (1H, d, *J* = 7.9 Hz, H_6-THIQ), 6.65 (1H, d, *J* = 7.9 Hz, H_8-THIQ), 6.97 (1H, t, *J* = 7.9 Hz, H_7-THIQ), 7.00 (2H, d, *J* = 9.1 Hz, ArH, phenyl), 7.22 (2H, d, *J* = 9.1 Hz, ArH, phenyl) and 9.37 (1H, bs, OH) ppm. ^{13}C NMR (126 MHz, D_6-DMSO) δ 22.2 (C_4-THIQ), 45.6 (C_3-THIQ), 49.9 (C_1-THIQ), 112.2 (C_6-THIQ), 116.4 (ArCH, phenyl), 117.1 (C_8-THIQ), 121.3 (C_4CC_5-THIQ), 121.4 (ArCCl), 126.3 (C_7-THIQ), 128.7 (ArCH, phenyl), 135.4 (C_1CC_8-THIQ), 149.0 (ArCN) and 154.7(C_5-THIQ) ppm. HRMS (ES^+) calcd. $C_{15}H_{15}{}^{35}ClNO$ (M^++H) 260.0837, found 260.0826; calcd. $C_{15}H_{15}{}^{37}ClNO$ (M^++H) 262.0807, found 262.0830. Mp 271-274 °C (as hydrobromide).

2-(4-Chlorophenyl)-3-methyl-1,2,3,4-tetrahydroisoquinolin-6-ol hydrobromide (40a)
Synthesized according to the general method for methoxy deprotection with BBr_3. Filtration afforded the product as a white precipitate (429 mg, 87%) which showed: ^{1}H NMR (500 MHz, D_6-DMSO) δ 0.91 (3H, d, *J* = 6.5 Hz, CHC*H*$_3$), 2.59 (1H, dd, *J* = 1.6, 15.7 Hz, H_4-THIQ), 3.06 (1H, dd, *J* = 5.3, 15.7 Hz, H_4-THIQ), 4.03 (1H, d, *J* = 15.3 Hz, H_1-THIQ), 4.29 – 4.31 (1H, m, H_3-THIQ), 4.32 (1H, d, *J* = 15.3 Hz, H_1-THIQ), 6.60 (1H, d, *J* = 2.2 Hz, H_5-THIQ), 6.63 (1H, dd, *J* = 2.2, 8.2 Hz, H_7-THIQ), 6.93 (2H, d, *J* = 9.1 Hz, 2 x ArCH, phenyl), 7.04 (1H, d, *J* = 8.2 Hz, H_8-THIQ), 7.23 (2H, d, *J* = 9.0 Hz, 2 x ArCH, phenyl) and 9.26 (1H, bs, OH) ppm. ^{13}C NMR (126 MHz, D_6-DMSO) δ 15.3 (CH*C*H$_3$), 34.9 (C_4-THIQ), 44.9 (C_1-THIQ), 47.5 (C_3-THIQ), 113.3 (C_7-THIQ), 115.0 (C_5-THIQ), 115.1 (2 x ArCH, phenyl), 120.4 (ArCCl), 123.3 (C_1CC_8-THIQ), 127.2 (C_8-THIQ), 128.7 (2 x ArCH, phenyl), 133.8 (C_1CC_4-THI), 147.8 (ArCN) and 155.8 (C_6-THIQ) ppm. Mp 240-242 °C.

2-(4-Chlorophenyl)-4-methyl-1,2,3,4-tetrahydroisoquinolin-6-ol hydrobromide (41a)
Synthesized according to the general method for methoxy deprotection with BBr_3. Filtration afforded the product as a yellow precipitate (178 mg, 58%) which showed: ^{1}H NMR (500 MHz, D_6-DMSO) δ 1.25 (3H, d, *J* = 6.9 Hz, CHC*H*$_3$), 2.92 – 3.04 (1H, m, H_4-THIQ), 3.21 (1H, dd, *J* = 6.6, 12.2 Hz, H_3-THIQ), 3.47 (1H, dd, *J* = 4.4, 12.2 Hz, H_3-THIQ), 4.20 (1H, d, *J* = 15.0 Hz, H_1-THIQ), 4.28 (1H, d, *J* = 15.0 Hz, H_1-THIQ), 6.61 (1H, dd, *J* = 2.3, 8.3 Hz, H_7-THIQ), 6.66 (1H, d, *J* = 2.3 Hz, H_5-THIQ), 6.95 (2H, d, *J* = 9.0 Hz, 2 x ArCH, phenyl), 7.00 (1H, d, *J* = 8.3 Hz, H_8-THIQ), 7.23 (2H, d, *J* = 9.0 Hz, 2 x ArCH, phenyl) and 9.25 (1H, bs, OH) ppm. ^{13}C NMR (126 MHz, D_6-DMSO) δ 19.3 (CH*C*H$_3$), 32.3 (C_4-THIQ), 49.0 (C_1-THIQ), 52.2 (C_3-THIQ), 113.2 (C_5-THIQ), 113.3 (C_7-THIQ), 115.5 (2 x ArCH, phenyl), 120.8 (ArCCl), 123.7 (C_1CC_8-THIQ), 127.3 (C_8-THIQ), 128.6 (2 x Arch, phenyl), 140.7 (C_4CC_5-THIQ), 149.1 (ArCN) and 155.8 (C_6-THIQ) ppm. HRMS (ES^+)

calcd. $C_{16}H_{17}{}^{35}ClNO$ (M^++H) 274.0993, found 274.0956; calcd. $C_{16}H_{17}{}^{37}ClNO$ (M^++H) 276.0965, found 276.0967. Mp 205-209 °C.

2-(4-Chlorophenyl)-4-ethyl-1,2,3,4-tetrahydroisoquinolin-6-ol hydrobromide (41b)
Synthesized according to the general method for methoxy deprotection with BBr_3. Filtration afforded the product as a yellow precipitate (161 mg, 47%) which showed: ^{1}H NMR (500 MHz, D_6-DMSO) δ 0.97 (3H, t, *J* = 7.4 Hz, CH_2CH_3), 1.50 – 1.70 (2H, m, CH_2CH_3), 2.66 – 2.78 (1H, m, H_4-THIQ), 3.27 (1H, dd, *J* = 3.9, 12.3 Hz, H_3-THIQ), 3.56 (1H, dd, *J* = 4.4, 12.3 Hz, H_3-THIQ), 4.11 (1H, d, *J* = 15.0 Hz, H_1-THIQ), 4.35 (1H, d, *J* = 15.0 Hz, H_1-THIQ), 6.58 – 6.67 (2H, m, H_5, H_7-THIQ), 6.94 (2H, d, *J* = 9.0 Hz, 2 x ArCH, phenyl), 7.01 (1H, d, *J* = 8.9 Hz, H_8-THIQ), 7.24 (2H, d, *J* = 9.0 Hz, 2 x ArCH, phenyl) and 9.25 (1H, bs, OH) ppm. ^{13}C NMR (126 MHz, D_6-DMSO) δ 11.8 (CH_2CH_3), 26.6 (CH_2CH_3), 39.6 (C_4-THIQ), 48.7 (C_3-THIQ), 48.8 (C_1-THIQ), 113.4 (C_5 or C_7-THIQ), 114.0 (C_5 or C_7-THIQ), 115.1 (2 x ArCH, phenyl), 120.6 (ArCCl), 123.7 (C_1CC_8-THIQ), 127.4 (C_8-THIQ), 128.6 (2 x ArCH, phenyl), 139.6 (C_4CC_5-THIQ), 149.1 (ArCN) and 155.6 (C_6-THIQ) ppm. HRMS (ES^+) calcd. $C_{17}H_{19}{}^{35}ClNO$ (M^++H) 288.1150, found 288.1148; calcd. $C_{17}H_{19}{}^{37}ClNO$ (M^++H) 290.1120, found 290.1150. Mp 119-123 °C.

2-(4-Chlorophenyl)-4-isopropyl-1,2,3,4-tetrahydroiso-quinolin-6-ol hydrobromide (41c)
Synthesized according to the general method for methoxy deprotection with BBr_3. Filtration afforded the product as a pale yellow precipitate (12 mg, 31%) which showed: ^{1}H NMR (500 MHz, D_6-DMSO) δ 0.86 (3H, d, *J* = 6.7 Hz, $(CH_3)_2CH$), 0.92 (3H, d, *J* = 6.8 Hz, $(CH_3)_2CH$), 1.80 – 1.97 (1H, m, $(CH_3)_2CH$), 2.57 (1H, dt, *J* = 3.6, 7.1 Hz, H_4-THIQ), 3.15 (1H, dd, *J* = 3.7, 12.4 Hz, H_3-THIQ), 3.75 (1H, dd, *J* = 3.9, 12.4 Hz, H_3-THIQ), 4.11 (1H, d, *J* = 15.1 Hz, H_1-THIQ), 4.37 (1H, d, *J* = 15.0 Hz, H_1-THIQ), 6.62 (1H, d, *J* = 2.1 Hz, H_5-THIQ), 6.64 (1H, dd, *J* = 2.4, 8.2 Hz, H_7-THIQ), 6.91 (2H, d, *J* = 9.0 Hz, 2 x ArCH, phenyl), 7.03 (1H, d, *J* = 8.2 Hz, H_8-THIQ), 7.23 (2H, d, *J* = 9.0 Hz, 2 x ArCH, phenyl) and 9.27 (1H, bs, OH) ppm. ^{13}C NMR (126 MHz, D_6-DMSO) δ 19.7 ($(CH_3)_2CH$), 21.1 ($(CH_3)_2CH$), 30.1 ($(CH_3)_2CH$), 44.8 (C_4-THIQ), 45.7 (C_3-THIQ), 48.6 (C_{14}-THIQ), 113.5 (C_7-THIQ), 114.3 (2 x ArCH, phenyl), 114.8 (C_5-THIQ), 120.1 (ArCCl), 123.9 (C_1CC_8-THIQ), 127.5 (C_8-THIQ), 128.6 (2 x ArCH, phenyl), 138.9 (C_1CC_4-THIQ), 148.5 (ArCN) and 155.3 (C_6-THIQ) ppm. Mp 190-193 °C.

4-Benzyl-2-(4-chlorophenyl)-1,2,3,4-tetrahydroisoquinolin-6-ol hydrobromide (41d)
Synthesized according to the general method for methoxy deprotection with BBr_3. The crude compound was purified by reversed phase column chromatography (eluent: from 10% to 100% MeOH in water) to give the desired product as a yellow solid (201 mg, 66%) which showed: ^{1}H NMR (500 MHz, D_6-DMSO) δ 2.78 (1H, dd, *J* = 10.2, 13.3 Hz, $ArCH_2$, benzyl), 2.96 (1H, dd, *J* = 4.9, 13.5 Hz, $ArCH_2$, benzyl), 3.05 (1H, dd, *J* = 3.2, 12.1 Hz, H_3-THIQ), 3.11 – 3.20 (1H, m, H_4-THIQ), 3.38 (3H, dd, *J* = 4.3, 12.1 Hz, H_3-THIQ), 4.08 (1H, d, *J* = 15.0 Hz, H_1-THIQ), 4.45 (1H, d, *J* = 15.0 Hz, H_4-THIQ), 6.60 – 6.69 (2H, m, H_5, H_7-THIQ), 6.80 (2H, d, *J* = 8.9 Hz, 2 x ArCH, phenyl), 7.04 (1H, d, *J* = 8.9 Hz, H_8-THIQ), 7.18 – 7.28 (5H, m, 3 x ArCH, benzyl, 2 x ArCH, phenyl), 7.32 (2H, t, *J* = 7.4 Hz, 2 x ArCH, benzyl) and 9.30 (1H, bs, OH) ppm. Mp 172-175 °C.

2-(4-Chlorophenyl)-4,4-dimethyl-1,2,3,4-tetrahydroiso-quinolin-6-ol hydrobromide (41f)
Synthesized according to the general method for methoxy deprotection with BBr_3. Filtration afforded the product as a white precipitate (81 mg, 85%) which showed: ^{1}H NMR (500 MHz, D_6-DMSO) δ 1.26 (6H, s, $(CH_3)_2C$), 3.22 (2H, s, H_3-THIQ), 4.23 (2H, s, H_1-THIQ), 6.61 (1H, dd, *J* = 2.3, 8.3 Hz, H_7-THIQ), 6.77 (1H, d, *J* = 2.3 Hz, H_5-THIQ), 6.98 (1H, d, *J* = 8.3 Hz), 6.98 (2H, d, *J* = 9.1 Hz, 2 x ArCH, phenyl), 7.25 (2H, d, *J* = 9.1 Hz, 2 x ArCH, phenyl) and 9.20 (1H, bs, OH) ppm. ^{13}C NMR (126 MHz, D_6-DMSO) δ 27.7 ($(CH_3)_2C$), 35.2 (C_4-THIQ), 49.6 (C_1-THIQ), 58.5 (C_3-THIQ), 111.4 (C_5-THIQ), 113.4 (C_7-THIQ), 115.6 (2 x ArCH, phenyl), 121.0 (ArCCl), 122.8 (C_1CC_8-THIQ), 127.3 (C_8-THIQ), 128.6 (2 x ArCH, phenyl), 144.5 (C_4CC_5-THIQ), 149.3 (ArCN) and 155.9 (C_6-THIQ) ppm. HRMS (ES^+) calcd. $C_{17}H_{19}{}^{35}ClNO$ (M^++H) 288.1150, found 288.1137; calcd. $C_{17}H_{19}{}^{37}ClNO$ (M^++H) 290.1120, found 290.1141. Mp 207-211 °C.

2-(4-Chlorophenyl)-1-methyl-1,2,3,4-tetrahydroisoquinolin-6-ol hydrobromide (42a)
Synthesized according to the general method for methoxy deprotection with BBr_3. The product was obtained as a white solid (130 mg, 41%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (3H, d, *J* = 6.7 Hz, CH_3), 2.81 (1H, dt, *J* = 4.6, 16.0 Hz, H_4-THIQ), 2.88 – 3.05 (1H, m, H_4-THIQ), 3.35 – 3.49 (1H, m, H_3-THIQ), 3.54 (1H, dt, *J* = 5.2, 12.2 Hz, H_3-THIQ), 4.79 (1H, q, *J* = 6.7 Hz, H_1THIQ), 6.63 (1H, d, *J* = 2.5 Hz, H_5-THIQ), 6.68 (1H, dd, *J* = 2.6, 8.3 Hz, H_7-THIQ), 6.81 (2H, d, *J* = 9.1 Hz, 2 x ArCH, phenyl), 6.99 (1H, d, *J* = 8.3 Hz, H_8-THIQ) and 7.19 (2H, d, *J* = 9.1 Hz, 2 x ArCH, phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.8 (CH_3), 28.4 (C_4-THIQ), 41.0 (C_3-THIQ), 54.0 (C_1-THIQ), 113.5 (C_7-THIQ), 114.8 (C_5-THIQ), 115.8 (2 x ArCH, phenyl), 122.3 (ArCCl), 128.0 (C_8-THIQ), 129.0 (2 x ArCH, phenyl), 132.0 (C_1CC_8-THIQ), 135.8 (C_4CC_5-THIQ), 148.1 (ArCN) and 153.9 (C_6-THIQ) ppm. HRMS (ES^+) calcd. $C_{16}H_{17}{}^{35}ClNO$ (M^++H) 274.0993, found 274.0979; calcd. $C_{16}H_{17}{}^{37}ClNO$ (M^++H) 276.0964, found 276.0981. Mp 210-213 °C.

2-(4-Chlorophenyl)-1-ethyl-1,2,3,4-tetrahydroisoquinolin-6-ol hydrobromide (42b)
Synthesized according to the general method for methoxy deprotection with BBr_3. The product was obtained as a white solid (57 mg, 61%) which showed: ^{1}H NMR (500 MHz, D_6-DMSO) δ 0.88 (3H, t, *J* = 7.3 Hz, CH_3), 1.52 – 1.68 (1H, m, CH_3CH_2), 1.72 – 1.87 (1H, m, CH_3CH_2), 2.73 (1H, dt, *J* = 5.5, 16.0 Hz, H_4-THIQ), 2.83 (1H, dt, *J* = 6.5, 13.3 Hz, H_4-THIQ), 3.43 – 3.50 (2H, m, H_3-THIQ), 4.49 (1H, t, *J* = 7.0 Hz, H_1-THIQ), 6.48 – 6.63 (2H, m, H_5, H_7-THIQ), 6.84 (2H, d, *J* = 8.8

Hz, 2 x ArCH, phenyl), 6.96 (1H, d, *J* = 8.0 Hz, H_8-THIQ), 7.17 (2H, d, *J* = 8.8 Hz, 2 x ArCH, phenyl) and 9.33 (1H, bs, OH) ppm. ^{13}C NMR (126 MHz, D_6-DMSO) δ 11.1 (CH_3), 26.4 (C_4-THIQ), 28.9 (CH_3CH_2), 41.0 (C_3-THIQ), 58.9 (C_1-THIQ), 112.9 (C_5 or C_7-THIQ), 114.4 (2 x ArCH, phenyl), 114.6 (C_5 or C_7-THIQ), 119.5 (ArCCl), 128.3 (C_8-THIQ), 128.6 (C_1CC_8-THIQ), 128.7 (2 x ArCH, phenyl), 135.6 (C_4CC_5-THIQ), 148.1 (ArCN) and 155.8 (C_6-THIQ) ppm. HRMS (ES^+) calcd. $C_{17}H_{19}{}^{35}ClNO$ (M^++H) 290.1120, found 290.1107. Mp 184-187 °C.

2-(4-Chlorophenyl)-1-isopropyl-1,2,3,4-tetrahydroiso-quinolin-6-ol hydrobromide (42c)
Synthesized according to the general method for methoxy deprotection with BBr_3. The product was obtained as a pale grey solid (37 mg, 58%) which showed: ^{1}H NMR (500 MHz, D_6-DMSO) δ 0.86 (3H, d, *J* = 6.3 Hz, $(CH_3)_2CH$), 0.93 (3H, d, *J* = 6.9 Hz, $(CH_3)_2CH$), 1.98 (1H, td, *J* = 6.8, 13.8 Hz, $(CH_3)_2CH$), 2.76 – 2.94 (2H, m, H_4-THIQ), 3.37 – 3.40 (1H, m, H_3-THIQ), 3.58 (1H, dt, *J* = 6.1, 12.4 Hz, H_3-THIQ), 4.31 (1H, d, *J* = 8.6 Hz, H_1-THIQ), 6.54 (1H, d, *J* = 8.2 Hz, H_7-THIQ), 6.56 (1H, s, H_5-THIQ), 6.86 (2H, d, *J* = 8.6 Hz, 2 x ArCH, phenyl), 6.95 (1H, d, *J* = 8.2 Hz, H_8-THIQ), 7.14 (2H, d, *J* = 8.0 Hz, 2 x ArCH, phenyl) and 9.30 (1H, bs, OH) ppm. ^{13}C NMR (126 MHz, D_6-DMSO) δ 19.9 ($(CH_3)_2CH$), 20.3 ($(CH_3)_2CH$), 26.4 (C_4-THIQ), 33.6 ($(CH_3)_2CH$), 41.9 (C_3-THIQ), 62.9 (C_1-THIQ), 112.2 (C_7-THIQ), 114.2 (2 x ArCH, phenyl), 114.7 (C_5-THIQ), 119.2 (ArCCl), 127.7 (C_1CC_8-THIQ), 128.5 (2 x ArCH, phenyl), 129.1 (C_8-THIQ), 135.8 (C_4CC_5-THIQ), 148.5 (ArCN) and 156.0 (C_6-THIQ) ppm. HRMS (ES^-) calcd. $C_{18}H_{19}{}^{35}ClNO$ (M^--H) 300.1155, found 300.1151; calcd. $C_{18}H_{19}{}^{37}ClNO$ (M^--H) 302.1131, found 302.1135. Mp 111-115 °C.

2-(4-Chlorophenyl)-1-phenyl-1,2,3,4-tetrahydroisoquinolin-6-ol hydrobromide (42e)
Synthesized according to the general method for methoxy deprotection with BBr_3. The product was obtained as a white solid (247 mg, 79%) which showed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.80 – 2.94 (2H, m, H_4-THIQ), 3.44 (1H, ddd, *J* = 5.7, 8.1, 11.4 Hz, H_3-THIQ), 3.65 (1H, dt, *J* = 5.5, 11.2 Hz, H_3-THIQ), 4.69 (1H, bs, OH), 5.70 (1H, s, H_1-THIQ), 6.65 (1H, d, *J* = 2.5 H, H_5-THIQ), 6.70 (1H, dd, *J* = 2.5, 8.2 Hz, H_7-THIQ), 6.74 (2H, d, *J* = 9.0 Hz, 2 x ArCH, *N*-phenyl), 7.14 (1H, d, *J* = 8.2 Hz, H_8-THIQ), 7.15 (2H, d, *J* = 9.0 Hz, 2 x ArCH, *N*-phenyl), 7.19 (2H, d, *J* = 6.9 Hz, 2 x ArCH, C_1-phenyl) and 7.22 – 7.27 (3H, m, 3 x ArCH, C_1-phenyl) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.0 (C_4-THIQ), 43.8 (C_3-THIQ), 62.3 (C_1-THIQ), 113.3 (C_7-THIQ), 114.7 (C_5-THIQ), 115.1 (2 x ArCH, *N*-phenyl), 122.3 (ArCCl), 126.9 (ArCH, C_1-phenyl), 127.2 (2 x ArCH, C_1-phenyl), 128.3 (2 x ArCH, C_1-phenyl), 128.9 (2 x ArCH, *N*-phenyl), 129.0 (C_8-THIQ), 130.1 (C_1CC_8-THIQ), 137.1 (C_4CC_5-THIQ), 142.9 ($ArCCH_2$, C_1-phenyl), 148.1 (ArCN) and 154.5 (C_6-THIQ) ppm. HRMS (ES^+) calcd. $C_{21}H_{19}{}^{35}ClNO$ (M^++H) 336.1150, found 336.1133; calcd. $C_{16}H_{17}{}^{37}ClNO$ (M^++H) 338.1120, found 338.1140. Mp 227-228 °C.

1-Benzyl-2-(4-chlorophenyl)-1,2,3,4-tetrahydroisoquinolin-6-ol hydrobromide (42f)
Synthesized according to the general method for methoxy deprotection with BBr_3. The product was obtained as a yellow precipitate (62 mg, 44%) which showed:[38] ^{1}H NMR (400 MHz, CDCl3) δ 2.64 (1H, dt, *J* = 5.7, 15.9 Hz), 2.80 – 2.91 (1H, m), 2.94 (1H, dd, *J* = 7.1, 13.3 Hz), 3.15 (1H, dd, *J* = 6.0, 13.3 Hz), 3.38 – 3.49 (1H, m), 3.50 - 3.61 (1H, m), 4.75 (1H, t, *J* = 6.5 Hz), 6.53 – 6.62 (2H, m), 6.64 (1H, d, *J* = 2.1 Hz), 6.69 (2H, d, *J* = 9.1 Hz), 6.99 (2H, dd, *J* = 1.8, 7.5 Hz), 7.13 (2H, d, *J* = 9.1 Hz) and 7.16 – 7.23 (3H, m) ppm. HRMS (ES^+) calcd. $C_{22}H_{21}{}^{35}ClNO$ (M^++H) 350.1306, found 350.1296; calcd. $C_{21}H_{19}{}^{37}ClNO$ (M^++H) 352.1277, found 352.1331. Mp 143-147 °C.

2-(4-Chlorophenyl)-1-phenethyl-1,2,3,4-tetrahydroiso-quinolin-6-ol hydrobromide (42g)
Synthesized according to the general method for methoxy deprotection with BBr_3. The product was obtained as a white precipitate (98 mg, 61%) which showed: ^{1}H NMR (500 MHz, D_6-DMSO) δ 1.85 – 2.01 (1H, m, $ArCH_2CH_2CH$), 2.01 – 2.13 (1H, m, $ArCH_2CH_2CH$), 2.58 – 2.70 (2H, m, $ArCH_2CH_2CH$), 2.74 (1H, dt, *J* = 6.1, 14.0 Hz, H_4-THIQ), 2.85 (1H, dt, *J* = 6.1, 14.0 Hz, H_4-THIQ), 3.53 (2H, t, *J* = 6.1 Hz, H_3-THIQ), 4.62 (1H, t, *J* = 7.0 Hz, H_1-THIQ), 6.56 (1H, d, *J* = 2.3 Hz, H_5-THIQ), 6.59 (1H, dd, *J* = 2.3, 8.3 Hz, H_5-THIQ), 6.82 (2H, d, *J* = 9.1 Hz, 2 x ArCH, *N*-phenyl), 7.02 (1H, d, *J* = 8.3 Hz, H_8-THIQ), 7.12 – 7.18 (3H, m, 2 x ArCH, *N*-phenyl, ArCH, phenyl), 7.19 (2H, d, *J* = 7.4 Hz, 2 x ArCH, phenyl), 7.27 (2H, t, *J* = 7.5 Hz, 2 x ArCH, phenyl) and 9.27 (1H, bs, OH) ppm. ^{13}C NMR (126 MHz, D_6-DMSO) δ 26.1 (C_4-THIQ), 32.2 ($ArCH_2CH_2CH$), 37.9 ($ArCH_2CH_2CH$), 40.8 (C_3-THIQ), 57.1 (C_1-THIQ), 113.0 (C_7-THIQ), 114.6 (C_5-THIQ), 114.7 (2 x ArCH, *N*-phenyl), 119.8 (ArCCl), 125.7 (ArCH, phenyl), 128.1 (C_8-THIQ), 128.2 (2 x ArCH, phenyl), 128.3 (2 x ArCH, phenyl), 128.6 (C_1CC_8-THIQ), 128.7 (2 x ArCH, *N*-phenyl), 135.7 (C_4CC_5-THIQ), 141.7 ($ArCCH_2$, phenyl), 148.0 (ArCN) and 155.8 (C_6-THIQ) ppm. HRMS (ES^+) calcd. $C_{23}H_{23}{}^{35}ClNO$ (M^++H) 364.1463, found 364.1456; calcd. $C_{23}H_{23}{}^{37}ClNO$ (M^++H) 366.1433, found 366.1465. Mp 190-192 °C.

1-Benzyl-2-phenyl-1,2,3,4-tetrahydroisoquinolin-6-ol hydrobromide (42h)
Synthesized according to the general method for methoxy deprotection with BBr_3. The product was obtained as a dark green precipitate (118 mg, 87%) which showed:[31] ^{1}H NMR (500 MHz, D_6-DMSO) δ 2.62 (1H, dt, *J* = 4.7, 16.2 Hz, H_4-THIQ), 2.78 – 2.90 (1H, m, H_4-THIQ), 2.95 (1H, dd, *J* = 6.8, 13.4 Hz, CH_2CH), 3.11 (1H, dd, *J* = 6.8, 13.4 Hz, CH_2CH), 3.49 – 3.64 (2H, m, H_3-THIQ), 4.87 (1H, t, *J* = 6.8 Hz, H_1-THIQ), 6.48 (1H, dd, *J* = 2.2, 8.2 Hz, H_7-THIQ), 6.53 (1H, d, *J* = 2.2 Hz, H_5-THIQ), 6.59 (1H, t, *J* = 7.2 Hz, ArCH), 6.72 – 6.81 (3H, m, 2 x ArCH, H_8-THIQ), 7.11 (2H, t, *J* = 7.9 Hz, 2 x ArCH), 7.13 – 7.19 (3H, m, 3 x ArCH), 7.23 (2H, t, *J* = 7.3 Hz, 2 x ArCH) and 9.21 (1H, bs, OH) ppm. ^{13}C NMR (126 MHz, D_6-DMSO) δ 26.1 (C_4-THIQ), 40.3 (C_3-THIQ), 41.7 (CH_2CH), 59.8 (C_1-THIQ), 112.7 (C_7-THIQ), 113.3 (2 x ArCH), 114.5 (C_5-THIQ), 116.5 (ArCH), 125.9 (ArCH), 127.9 (2 x ArCH), 128.1 (C_1CC_8-THIQ), 128.3 (C_8-THIQ), 129.0 (2 x ArCH), 129.5 (2 x ArCH), 135.8 (C_4CC_5-THIQ), 139.1 ($ArCCH_2CH$), 149.1 (ArCN) and 155.6 (C_6-THIQ) ppm. Mp 137-141 °C.

1-benzyl-2-(4-hydroxyphenyl)-1,2,3,4-tetrahydroisoquinolin-6-ol hydrobromide (42i)
Synthesized according to the general method for methoxy deprotection with BBr_3. The product was obtained as a pale yellow precipitate (104 mg, 96%) which showed:[23] ^{1}H NMR (500 MHz, D_6-DMSO) δ 2.51 – 2.57 (1H, m, H_4-THIQ), 2.79 (1H, ddd, *J* = 6.0, 10.0, 16.0 Hz, H_4-THIQ), 2.86 (1H, dd, *J* = 6.1, 13.5 Hz, C*H*$_2$CH), 3.04 (1H, dd, *J* = 7.6, 13.5 Hz, C*H*$_2$CH), 3.39 – 3.47 (1H, m, H_3-THIQ), 3.47 – 3.56 (1H, m, H_3-THIQ), 4.66 (1H, t, *J* = 6.7 Hz, H_1-THIQ), 6.47 (1H, dd, *J* = 2.2, 8.3 Hz, H_7-THIQ), 6.49 (1H, d, *J* = 2.2 Hz, H_5-THIQ), 6.57 (2H, d, *J* = 8.9 Hz, 2 x ArCH, *N*-phenyl), 6.64 (2H, d, *J* = 8.9 Hz, 2 x ArCH, *N*-phenyl), 6.71 (1H, d, *J* = 8.3 Hz, H_8-THIQ), 7.12 (2H, d, *J* = 7.3 Hz, 2 x ArCH, phenyl), 7.15 (1H, t, *J* = 7.3 Hz, 2 x ArCH, phenyl), 7.22 (2H, t, *J* = 7.3 Hz, ArCH, phenyl), 8.66 (1H, bs, OH) and 9.16 (1H, bs, OH) ppm. ^{13}C NMR (126 MHz, D_6-DMSO) δ 25.9 (C_4-THIQ), 41.1 (C_3-THIQ), 41.5 (*C*H_2CH), 60.7 (C_1-THIQ), 112.7 (C_7-THIQ), 114.6 (C_5-THIQ), 115.5 (2 x ArCH, *N*-phenyl), 116.7 (2 x ArCH, *N*-phenyl), 125.8 (ArCH, phenyl), 127.8 (2 x ArCH, phenyl), 128.3 (C_8-THIQ), 128.4 (C_1CC_8-THIQ), 129.4 (2 x ArCH, phenyl), 135.6 (C_4CC_5-THIQ), 139.6 (Ar*C*CH_2CH), 142.7 (ArCN), 149.5 (ArCO, *N*-phenyl) and 155.4 (C_6-THIQ) ppm. HRMS (ES$^+$) calcd. $C_{22}H_{21}{}^{35}$ClNNaO (M^++Na) 354.1465, found 354.1481. Degraded before melting.

***trans*-1-Benzyl-2-(4-methoxyphenyl)-4-methyl-1,2,3,4-tetra-hydroisoquinolin-6-ol hydrobromide (43a)**
Synthesized according to the general method for methoxy deprotection with BBr_3. Filtration afforded the product as a pale yellow precipitate (19 mg, 63%) which showed: ^{1}H NMR (500 MHz, D_6-DMSO) δ 1.15 (3H, d, *J* = 6.6 Hz, CHC*H*$_3$), 2.74 – 2.88 (1H, m, H_4-THIQ), 2.91 (1H, dd, *J* = 4.5, 13.7 Hz, C*H*$_2$CH), 3.03 (1H, dd, *J* = 9.4, 13.7 Hz, C*H*$_2$CH), 3.08 – 3.18 (1H, m, H_3-THIQ), 3.65 (1H, dd, *J* = 5.5, 14.4 Hz, H_3-THIQ), 4.77 – 4.90 (1H, m, H_1-THIQ), 6.44 – 6.53 (3H, m), 6.59 (2H, d, *J* = 8.9 Hz), 6.88 – 6.96 (2H, m), 7.08 (2H, dd, *J* = 4.6, 10.9 Hz), 7.16 (3H, q, *J* = 7.3 Hz) and 9.19 (2H, bs, OH) ppm. ^{13}C NMR (126 MHz, D_6-DMSO) δ 17.8 (CH*C*H$_3$), 28.2 (C_4-THIQ), 41.5 (*C*H_2CH), 46.2 (C_3-THIQ), 60.4 (C_1-THIQ), 113.0 (ArCH), 115.5 (2 x ArCH), 120.1 (ArCCl), 126.0 (ArCH), 127.9 (C_1CC_8-THIQ), 128.0 (2 x ArCH), 128.3 (ArCH), 128.5 (2 x ArCH), 128.6 (ArCH), 129.4 (2 x ArCH), 139.4 (ArCH_2CH), 140.4 (C_4CC_5-THIQ), 148.4 (ArCN) and 155.9 (C_6-THIQ) ppm. HRMS (ES$^+$) calcd. $C_{23}H_{21}{}^{35}$ClNO (M^++H) 362.1317, found 362.1335. Mp 133-137 °C.

***trans*-1-Benzyl-4-ethyl-2-(4-methoxyphenyl)-1,2,3,4-tetra-hydroisoquinolin-6-ol hydrobromide (43b)**
Synthesized according to the general method for methoxy deprotection with BBr_3. Filtration afforded the product as a pale yellow precipitate (88 mg, 86%) which showed: ^{1}H NMR (500 MHz, D_6-DMSO) δ 0.97 (3H, t, *J* = 7.4 Hz, CH_2C*H*$_3$), 1.47 – 1.72 (1H, m, C*H*$_2$CH$_3$), 1.82 – 2.01 (1H, m, C*H*$_2$CH$_3$), 2.80 – 2.93 (1H, m, H_4-THIQ), 2.99 (1H, dd, *J* = 5.0, 13.7 Hz, ArC*H*$_2$CH), 3.10 (1H, dd, *J* = 9.2, 13.7 Hz, ArC*H*$_2$CH), 3.32 (1H, dd, *J* = 11.6, 14.2 Hz, H_3-THIQ), 3.76 (1H, dd, *J* = 5.8, 14.2 Hz, H_3-THIQ), 4.91 (1H, dd, *J* = 5.0, 8.6 Hz, H_1-THIQ), 6.54 (1H, dd, *J* = 1.9, 8.3 Hz, H_7-THIQ), 6.68 (1H, d, *J* = 1.9 Hz, H_5-THIQ), 6.71 (2H, d, *J* = 9.0 Hz, 2 x ArCH, *N*-phenyl), 6.95 (1H, d, *J* = 8.4 Hz, H_8-THIQ), 7.05 (2H, d, *J* = 9.0 Hz, 2 x ArCH, *N*-phenyl), 7.12 - 7.19 (1H, m, ArCH, phenyl), 7.20 – 7.28 (4H, m, 4 x ArCH, phenyl) and 9.22 (1H, bs, OH) ppm. ^{13}C NMR (126 MHz, D_6-DMSO) δ 10.4 (CH_2C*H*$_3$), 25.0 (*C*H_2CH$_3$), 34.0 (C_4-THIQ), 41.3 (Ar*C*H_2CH), 43.6 (C_3-THIQ), 60.2 (C_1-THIQ), 112.8 (C_7-THIQ), 113.0 (C_5-THIQ), 115.8 (2 x ArCH, *N*-phenyl), 120.2 (ArCCl), 126.0 (ArCH), 128.0 (2 x ArCH, phenyl), 128.3 (C_1CC_8-THIQ), 128.4 (C_8-THIQ), 128.5 (2 x ArCH, *N*-phenyl), 129.4 (2 x ArCH, phenyl), 138.8 (C_4CC_5-THIQ), 139.2 (Ar*C*CH_2CH), 148.5 (ArCN) and 155.8 (C_6-THIQ) ppm. HRMS (ES$^+$) calcd. $C_{24}H_{25}{}^{35}$ClNO (M^++H) 378.1619, found 378.1632; calcd. $C_{24}H_{25}{}^{37}$ClNO (M^++H) 380.1590, found 380.1616; calcd. $C_{24}H_{24}{}^{35}$ClNNaO (M^++H) 400.1439, found 400.1466. Mp 179-181 °C.

***trans*-1,4-Dibenzyl-2-(4-methoxyphenyl)-1,2,3,4-tetrahydro-isoquinolin-6-ol hydrobromide (43d)**
Synthesized according to the general method for methoxy deprotection with BBr_3. Filtration afforded the product as a white precipitate (12 mg, 45%) which showed: ^{1}H NMR (500 MHz, D_6-DMSO) δ 2.60 – 2.77 (1H, m, H_3-THIQ), 2.95 (2H, ddd, *J* = 7.2, 13.7, 18.8 Hz, C*H*$_2$C$_1$), 3.15 – 3.32 (4H, m, H_3, H_4-THIQ, CH_2C_4), 4.84 – 4.95 (1H, m, H_1-THIQ), 6.50 (2H, d, *J* = 8.9 Hz, 2 x ArCH, *N*-phenyl), 6.57 (1H, d, *J* = 8.4 Hz, H_7-THIQ), 6.85 (1H, s, H_5-THIQ), 6.96 (1H, d, *J* = 8.4 Hz, H_8-THIQ), 7.01 (2H, d, *J* = 8.9 Hz, 2 x ArCH, *N*-phenyl), 7.12 – 7.17 (3H, d, *J* = 7.5 Hz), 7.22 (2H, t, *J* = 7.4 Hz), 7.26 (1H, dd, *J* = 6.0, 13.5 Hz), 7.32 (2H, d, *J* = 7.2 Hz), 7.36 (2H, t, *J* = 7.4 Hz) and 9.28 (1H, bs, OH) ppm. ^{13}C NMR (126 MHz, D_6-DMSO) δ 34.6 (C_4-THIQ), 38.8 (C_3-THIQ), 41.1 (*C*H_2C_4), 44.2 (*C*H_2C_1), 60.2 (C_1-THIQ), 113.1 (C_7-THIQ), 113.4 (C_5-THIQ), 115.7 (2 x ArCH), 120.4 (ArCCl), 126.0 (ArCH), 126.2 (ArCH), 127.9 (2 x ArCH), 128.2 (C_1CC_8-THIQ), 128.3 (2 x ArCH), 128.4 (C_8-THIQ), 128.5 (2 x ArCH), 129.1 (2 x ArCH), 129.4 (2 x ArCH), 138.7 (C_4CC_5-THIQ), 139.0 (Ar*C*CH_2CH), 139.6 (Ar*C*CH_2CH), 148.4 (ArCN) and 155.8 (C_6-THIQ) ppm. HRMS (ES$^+$) calcd. $C_{29}H_{27}{}^{35}$ClNO (M^++H) 440.1776, found 440.1768; calcd. $C_{24}H_{25}{}^{37}$ClNO (M^++H) 442.1746, found 442.1762; calcd. $C_{24}H_{24}{}^{35}$ClNNaO (M^++H) 400.1439, found 400.1466. Mp 148-151 °C.

Biology.

Inhibition assay

Human HSD17B1 was overexpressed in the BL21-CodonPlus (DE3)-RIL strain of *Escherichia coli* containing pQE30-type construct (provided by Dr. Jerzy Adamski). The cells were then grown in 2YT medium containing 100 µg/ml ampicilin, at 37 °C in a rotary shaker, until an OD_{600} of 1.0 had been reached. Expression of HSD17B1 was induced by IPTG at a

final concentration 0.5 mM, and the incubation was continued for 2 hours at 37 °C. Bacteria were resuspended in PBS and sonicated; the resultant cell homogenate was used as the source of the recombinant protein. Inhibition assays were carried out in 100 mM phosphate buffer (pH 6.5) in the presence of 1% acetonitrile as the co-solvent. The inhibitor stock solutions were prepared in DMSO, and diluted with acetonitrile prior to the assays. The concentration of the substrate ([^{3}H]-labelled E1 [2,4,6,7-^{3}H(N)] and unlabelled E1) in the reaction solution was 62 nM, and the concentration of NADPH was 100 µM. The reactions were carried out at 37 °C and stopped with ice cold ethyl acetate after the time needed to convert approximately 30% of the substrate in a control assay (in the absence of inhibitor). Substrate and product were extracted from the reaction mixture in ethyl acetate. The organic phase was removed, the residue was dissolved in acetonitrile and separated on a reverse-phase (C18) HPLC column with a mobile phase of acetonitrile and water (45:55, v/v) at 1mL/min. The screening assays were performed in duplicates and the measurement for IC_{50} in triplicates; the results are expressed as the mean values.

DiscoverX PathHunter® assay

PathHunter NHRPro cell lines were seeded into white-walled, clear-bottom 384-well microplates at a density of 10,000 cells per well in a total volume of 20 µL and were allowed to adhere and recover overnight prior to compound addition.

Agonist format: Intermediate dilution of compound stocks were generated such that 5 µL of 5X compound could be added to each well with a final vehicle concentration of 1% of the total volume. Cells were incubated in the presence of compound at 37 °C for 5 hours.

Antagonist format: For antagonist determination, cells were preincubated with antagonist followed by agonist (17β-estradiol) challenge at the EC_{80} concentration: 5 µL of 5X compound was added to the cells and incubated at 37°C for 1 hour. 5 µL of 6X EC_{80} agonist was added to the cells and incubated at 37°C for 5 hours.

Assay signal was generated through a single addition of 12.5 or 15 µL (50% v/v) of PathHunter Detection reagent cocktail for agonist and antagonist assays respectively, followed by a one hour incubation at room temperature. Microplates were read following signal generation with a PerkinElmer EnvisionTM instrument for chemiluminescent signal detection.

Compound activity was analyzed using CBIS data analysis suite (ChemInnovation, CA).

For agonist mode:

% Activity = 100% x (Mean RLU of test sample — mean RLU of vehicle control) / (mean MAX RLU control ligand — mean RLU of vehicle control).

For antagonist mode:

% Inhibition =100% x (1 — (Mean RLU of test sample — mean RLU of vehicle control) / (mean RLU of EC80 control — mean RLU of vehicle control)).

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Supporting Information for this article is provided.

Keywords: 17β-hydroxysteroid dehydrogenase 1 • breast cancer • tetrahydroisoquinoline • inhibition • SAR

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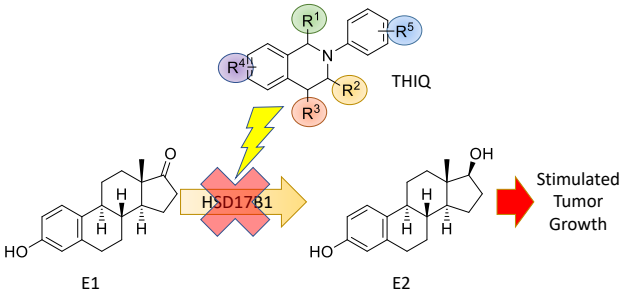

Type 1 17β-Hydroxysteroid dehydrogenase reduces steroidal estrone to estradiol that can drive hormone-sensitive diseases. The non-steroidal *N*-phenyl-1,2,3,4-tetrahydroisoquinoline template is a candidate non-steroidal mimic and synthetic decoration of all three ring systems gave candidate enzyme inhibitors that were evaluated biologically to explore SAR. Sub-micromolar potency was achieved validating the applicability of this novel approach.