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Synthesis of 2-substituted tetrahydroisoquinolin-6-ols: potential scaffolds for estrogen receptor modulation and/or microtubule degradation

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Dedicated to Prof. Stephen Hanessian on his 84th birthday - for the opportunity to be a postdoctoral fellow in his group and his continued support (and who further piqued our interest in the THIQ scaffold)[1]

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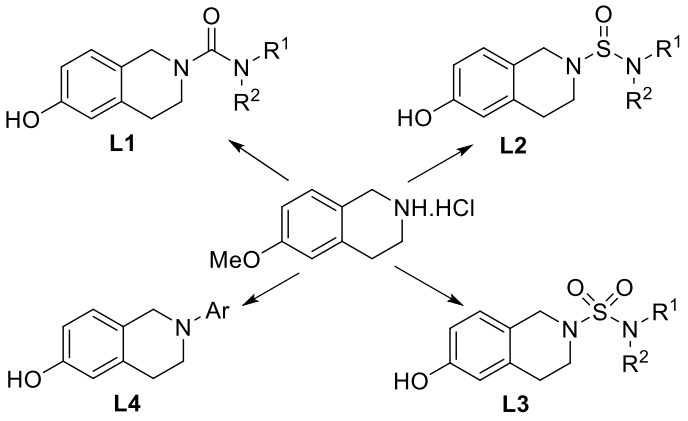
Abstract

6-Methoxytetrahydroisoquinoline hydrochloride was converted into four small libraries of substituted ureas, thioureas, sulfonamides and *N*-aryls, using the tetrahydroisoquinoline nitrogen as the scaffold-linking atom. Some of the compounds were evaluated for their ability to inhibit cell proliferation using the MCF7 (invasive ductal carcinoma) cell line.



Keywords: 6-Hydroxytetrahydroisoquinolines, estrogen modulators, ureas, thioureas, sulfonamides, anti-cancer

Introduction

The estrogen receptor (ER) is a critical component for the control of cellular processes in mammalian tissue.[2] Its ligands, including the hormone estradiol **1** (Figure 1, also written as oestradiol), are important for signal transduction processes crucial to many aspects of cellular life and death.[3] Cellular estrogenic activity is mediated by plasma membrane nuclear receptors which exist in two isoforms, ERα and ERβ, which further control a multitude of physiological responses and activities.[2,4,5] The two isoforms are differentially distributed within the tissue domains, with ERα being dominantly expressed in the uterus and mammary glands, while ERβ is more generally expressed throughout the body. Of specific significance is that the natural occurrence of estradiol in women affected with breast cancer may either worsen the disease, or a deficiency thereof could effect a cascade of hormonal related ailments. The importance of the relationship between estradiol and breast cancer has resulted in the development of a series of drugs termed selective estrogen receptor modulators (SERMs) and down-regulators/degraders (SERDs),[6] which are now regularly prescribed in therapies.[7]

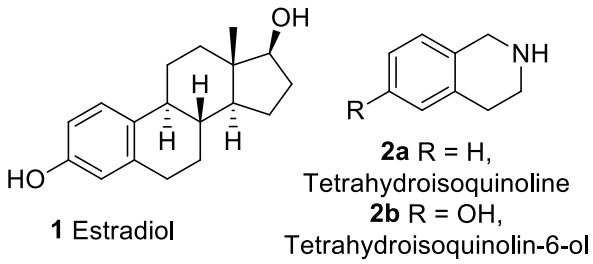


Figure 1. Structures of estradiol and THIQ motifs, including the tetrahydroisoquinolin-6-ol motif **2b** important in this study.

The tetrahydroisoquinoline (THIQ) scaffold **2a** (R = H, Figure 1) has been shown to be an extremely valuable motif in medicinal chemistry, and as a result has found regular application in pharmaceutical investigations.[8] In terms of a direct connection between THIQs and SERM-based breast cancer therapy, pharmaceutical companies were quick to pick up on this important association. In a series of studies, researchers from Novartis[9,10] and Pfizer[11] compared the well-known SERM used in the clinic, Lasofoxifene (**3**), to small libraries of THIQ-derived analogues, some examples (**4**) of which are shown in Figure 2.

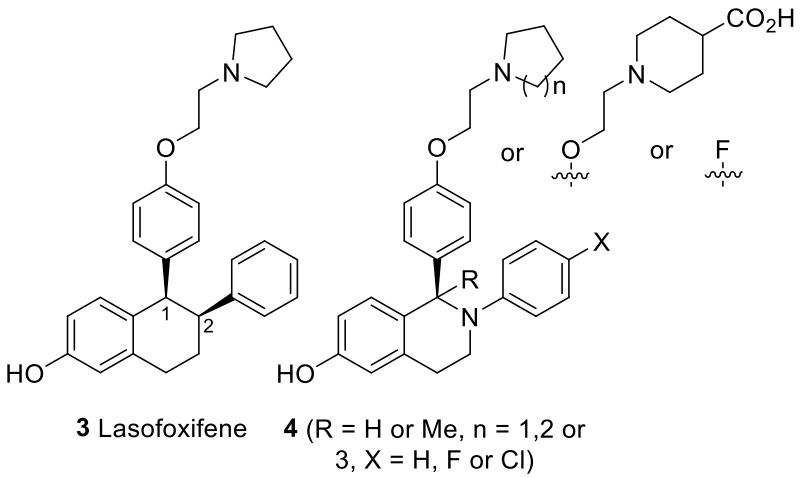


Figure 2. The clinical agent Lasofoxifene **3** and examples of THIQ analogues thereof.

The researchers from these companies determined that the THIQ ring system of Lasofoxifene **3** could readily be mimicked by the THIQ system, and importantly, it was noted that many of the THIQ analogues displayed an improved antagonistic/agonistic estrogen modulation effect compared to Lasofoxifene **3**.

A recent series of papers by Redda and co-workers describes their investigations into the utilization of THIQ scaffolds as potential agents applicable in anti-breast cancer therapies.[12-14] Redda's compounds comprised essentially mono- or un-substituted THIQs incorporating a hydrazine linker joining substituted benzamides to the THIQ core. Figure 3 illustrates the structures of some of these molecules **5** and Redda reported that their IC_{50} values (in the µg/mL range) suggested that the compounds were more active against the human ER+ (MCF7) and ER− (MDA-MB-231) breast cancers when compared to the standard Tamoxifen **6**, initially developed as a treatment for breast cancer.[15] It should be noted that these researchers observed that their compounds acted via microtubule destabilization, *i.e.* they were independent of the ER.[13] Other researchers, particularly Potter and co-workers, pioneered the concept of 2-substituted estratriene microtubule disruptors[16] and also found that the THIQ scaffold provided steroid mimics with excellent activities.[17-20]

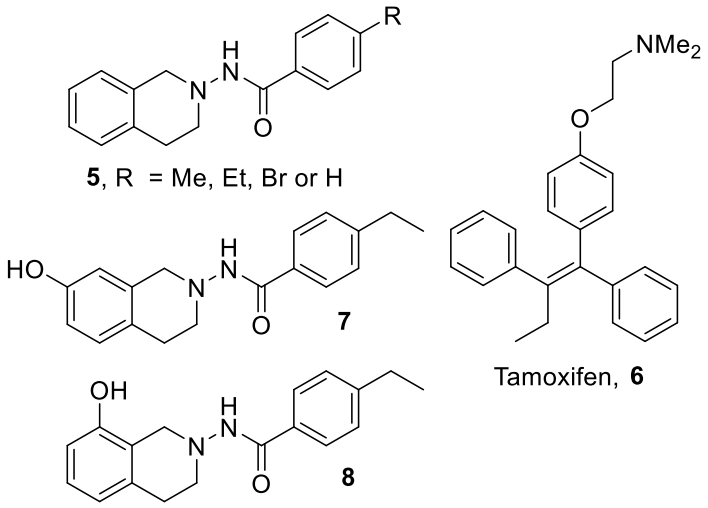


Figure 3. Compounds **5**, **7** and **8** compared to the clinical drug, Tamoxifen **6.**

Further active THIQ-based compounds from the Redda group demonstrated that phenolic groups on the THIQ skeleton, such as compounds **7** and **8** in Figure 3, resulted in some of the most active compounds.[13,14] However, what caught our attention was the fact that so few of the THIQ compounds prepared by Redda and co-workers had the phenolic OH group in the 6-position, as was demonstrated to be rather important by Chesworth and colleagues.[11] The importance of this phenolic group was also illustrated by our collaboration with the Brunsveld group, where it was demonstrated that the 6-OH group on compound **9** had a significant impact (up to 4 × lower EC_{50}) on the ERα and ERβ EC_{50} activity of the compounds (Figure 4, a).[21,22]

The importance of the phenolic group was further supported by a recent publication from AstraZeneca in which it was disclosed that the phenol group was critical for the potency of molecules such as **10** in SERD antagonist activity.[23] It should additionally be noted that in 2015 this company had the related THIQ-based AZD9486 **11** in clinical trials as an oral estrogen receptor inhibitor.[24,25] Mention should also be made here of the acrylic acid-based tetrahydroisoquinoline-6-ol **12** reported as a SERD by Novartis and their academic partners.[26]

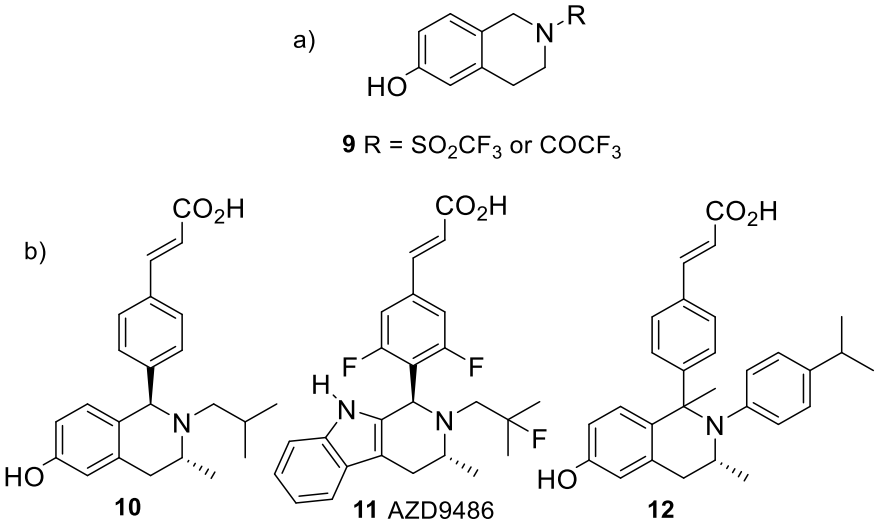
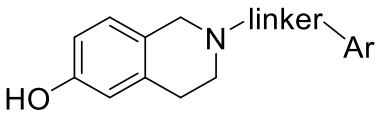


Figure 4. (a) THIQ-based fragment-like estrogen receptor ligands; (b) AstraZeneca and Novartis compounds.

Further inspection of the molecules synthesized and tested by Redda[12-15] indicated that firstly, most possess large aryl groups connected via hydrazine-themed linker groups to the nitrogen atom of the THIQ motif. Secondly, the aryl groups attached to the nitrogen atom were limited in terms of their number, type and position of functional groups on the aryl group (see earlier work regarding a series of tetrahydro-isoquinoline-*N*-phenylamide derivatives by Lin and co-workers[27]). This latter factor led to our interest and thus to the preparation of small libraries of, amongst others, *N*-aryl THIQ analogues to provide a more in-depth investigation into the importance of these aryl groups and their linkers.

Investigations by Redda,[12-15] together with our own unpublished docking studies, indicated a measure of uncertainty as to how THIQ analogues containing an *N*-aryl linker group would behave within the binding pocket of the ER protein (it should also be noted that we were willing to expand this paradigm to include the question as to whether the motifs were in fact targeting tubulin, rather than the ER). To extend our investigation into this area, a further library of THIQ analogues containing differently substituted aryl groups on nitrogen were designed and synthesized in order to discover whether any activity could be significantly associated with this group. The strategy adopted was to thus solely focus on changes at the nitrogen atom,

while retaining the phenolic moiety of estradiol (**2c** in Figure 5) based on the tetrahydroisoquinolin-6-ol motif **2b** shown in Figure 1, since we hoped this would essentially mimic estradiol as suggested by our initial docking studies.

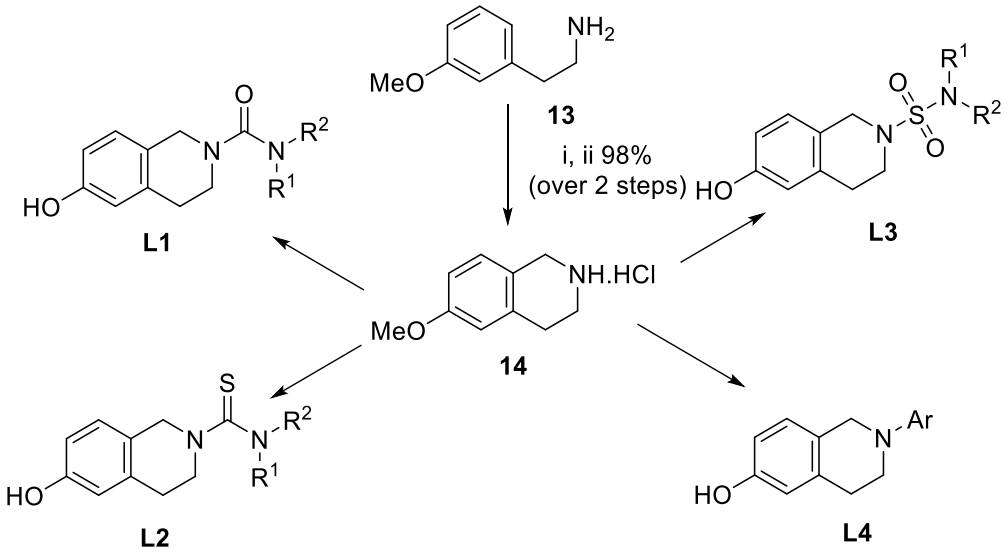


2c

Figure 5. Basic structure of THIQ-derived compounds synthesized for this project.

Results and Discussion

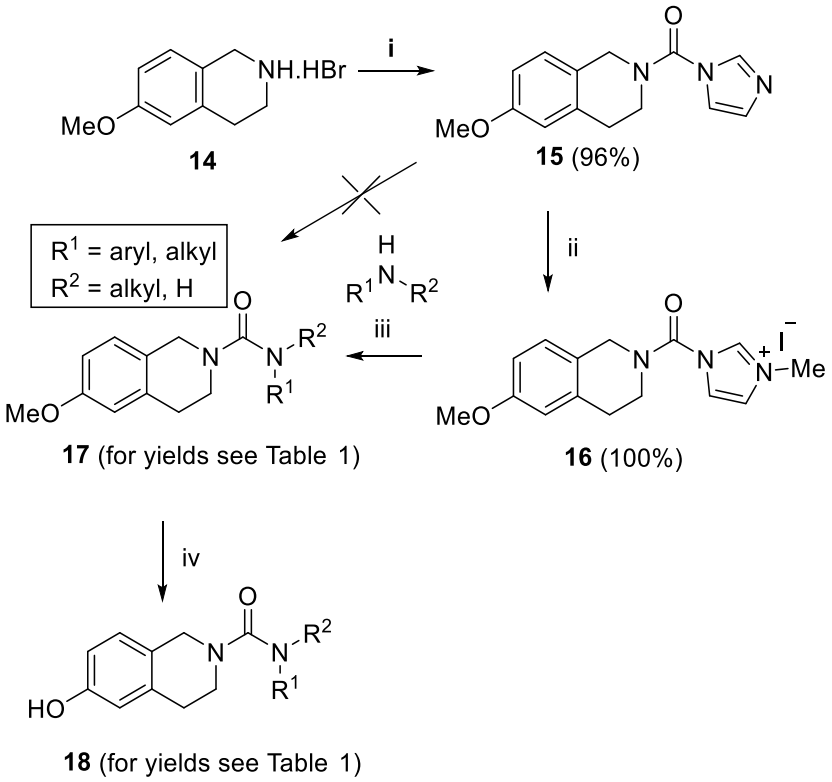
Based on our own interest in the synthesis and utilization of the THIQ skeleton,[28-32] it was thus decided to synthesize some tetrahydroisoquinolin-6-ol-based libraries. To this end, 6-methoxy-1,2,3,4-tetrahydro-isoquinoline was synthesized as the hydrobromide or hydrochloride salt **14** from commercially available 2-(3′-methoxyphenyl)ethylamine **13** according to the reliable procedure of Zhong and co-workers (Scheme 1).[33] From this central core we envisaged generating 4 small 6-OH-THIQ libraries **L1-4** illustrated in Scheme 1. It should be noted that initial investigations included working directly with the 1,2,3,4-tetrahydroisoquinolin-6-ol molecule **2b.** However, significant selectivity issues encountered in terms of differentiating between amine and phenolic chemoselectivity, persuaded us to avoid any lengthy protection-deprotection strategies[21] and to use the 6-methoxy THIQ scaffold throughout the protocols and demethylate the 6-MeO group at the last step of each synthesis.



Scheme 1. General approach to substituted THIQs. Reagents and conditions: (i) 37% CH_2O, 1 N HCl, 60 °C, 4 h; (ii) HCl, IPA, rt, 18 h.[33]

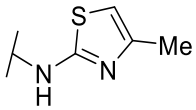
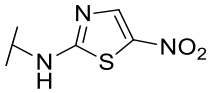
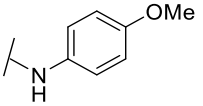
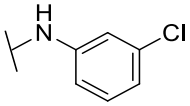
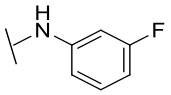
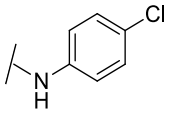
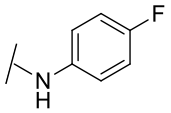
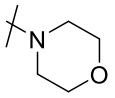
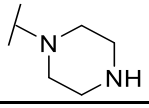
THIQ set L1: Urea-linked THIQs

Synthesis of the first small library of THIQ-derivatives involved treatment of the 6-methoxyTHIQ hydrobromide salt **14** with 1,1′-carbonyldiimidazole (CDI) to afford the urea analogue **15**.[34] However, direct treatment of compound **15** with the range of amines illustrated in Table 1, failed to displace the imidazole leaving group to provide the desired urea derivatives. In order to address this inactivity, methylation of the imidazole moiety of compound **15** with iodomethane in acetonitrile afforded the more active imidazolium iodide salt **16** in quantitative yield (Scheme 2).[34] Three base-mediated protocols were tested for the urea-formation (Et_3N, Cs_2CO_3 or *n*-BuLi), and in our hands treatment of the primary and secondary amines with *n*-BuLi, prior to addition of the THIQ salt **16**, proved to be the best protocol for obtaining compounds **17** (Table 1), essentially supporting the findings by Grzyb *et al.*[34] Apart from the substituted anilines utilized, and in order to expand the scope of the investigation, two substituted thiazoles (entries 1 and 2) were also chosen, as well as morpholine (entry 8) whose starting material, the corresponding 6-benzyloxy analogue of **16** was available from a different project in our laboratory. Piperazine (entry 9) was also used, but unfortunately, the piperazine derivative decomposed during its attempted synthesis. Finally, demethylation of compounds **17** into their corresponding free phenols **18** was achieved using either an excess of BBr_3 in dichloromethane or AlI_3 in toluene, as illustrated in Scheme 2 and described in Table 1.



Scheme 2. Synthesis of urea-linked THIQs. Reagents and conditions: (i) CDI, K_2CO_3, MeCN, rt , 12 h; (ii) MeI, MeCN, rt, 6 h; (iii) THIQ salt (1.1 equiv.), amine (2.0 equiv.): [a]Et_3N (2.0 equiv.), MeCN at rt, 12 h or [b]Cs_2CO_3 (2.0 equiv.), MeCN at rt, 12 h or [c]*n*-BuLi (3.0 equiv.), THF at −78 °C–rt , 12 h; (iv) [d]BBr_3 (3.0 equiv.), CH_2Cl_2 at 0 °C, 24 h or [e]AlI_3 (5.0 equiv.), PhMe at 110 °C, 24 h or [f]Pd/C, H_2, EtOH at 40 °C, 12 h.

Table 1. Results and conditions for the synthesis of ureas **17** and **18**

Entry	Nucleophile	Product structure	Yield step iii (%)[γ]	#	Yield step iv (%)[γ]	#
1	2-amino-4-methylthiazole		80[a]	**17a**	64[d]	**18a**
2	2-amino-5-nitrothiazole		90[b]	**17b**	-[α]	**18b**
3	4-anisidine		98[c]	**17c**	42[d]	**18c**[α,β]
4	3-chloroaniline		86[c]	**17d**	50[e]	**18d**
5	3-fluoroaniline		98[c]	**17e**	35[e]	**18e**
6	4-chloroaniline		44[c]	**17f**	50[e]	**18f**
7	4-fluoroaniline		81[c]	**17g**	3[e]	**18g**
8	morpholine		96[b]	**17h**	79[f]	**18h**
9	piperazine		Trace amounts[b]	**17i**	-	**18i**

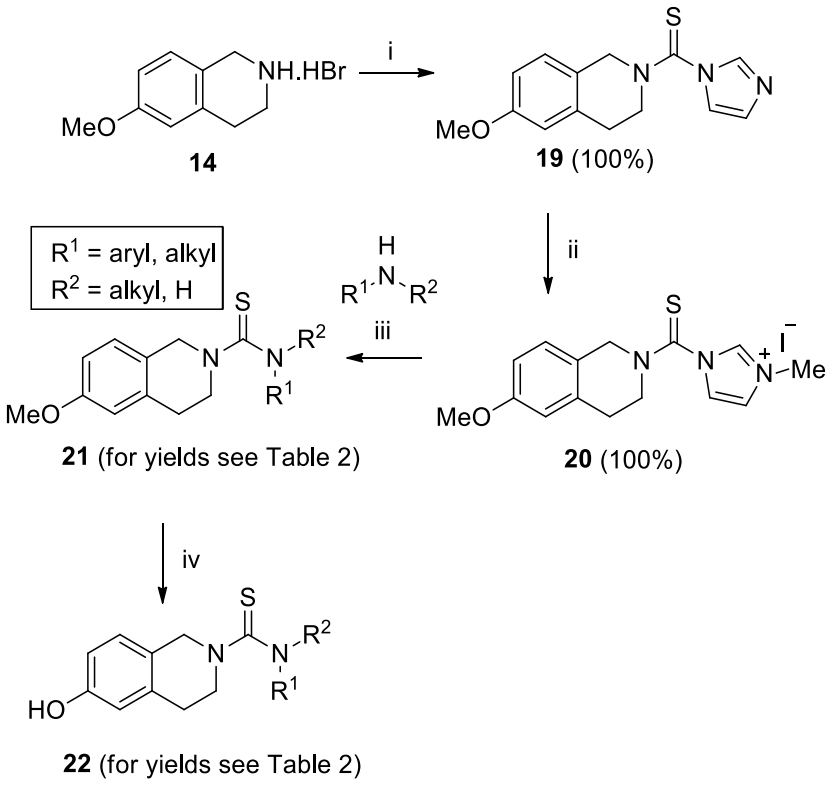
[α]Unstable molecule; [β]only HRMS was able to be determined ; [γ]letters refer to the experimental conditions described in the legend of Scheme 2.

THIQ Set L2: Thiourea-linked THIQs

The second small library of compounds comprised a thiourea linker that was synthesized through application of 1,1′-thiocarbonyldiimidazole (TCDI),[34] in an analogous manner to the first library of compounds. This second library was synthesized to establish whether the thiocarbonyl group could affect the bioactivity of the THIQ compounds. It might be envisaged that hydrogen bond interactions and/or the selectivity within the ER- or tubulin binding pocket could be differently impacted, due to the subtle differences in size and electronic nature of the thiocarbonyl group relative to the carbonyl group.

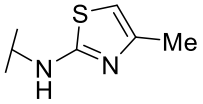
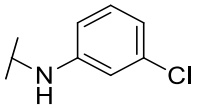
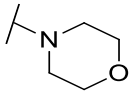
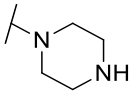
THIQ–thiocarbamoyl imidazole **19** was therefore prepared by treatment of the hydrobromide salt **14** with TCDI (Scheme 3). Subsequent methylation of **19** as described before, afforded the salt **20** in essentially quantitative yield, but this time as a foam, which proved to be too hygroscopic for isolation. Compound **20** was thus immediately treated with the amines listed in Table 2 as before, to afford thioureas **21**, albeit in poorer and more inconsistent yields than in the case for the carbonyl compounds illustrated in Table 1 (Scheme 3 and Table 2). As may also be noted in Table 2, yields in subsequent demethylations were not

acceptable and failed in one case (entry 2) after which alternative protocols needed to be sought to afford the desired members of THIQ set **L2**.



Scheme 3. Synthesis of thiourea-linked THIQs. Reagents and conditions: (i) TCDI, K_2CO_3, MeCN, 5 °C, 2 h, rt 18 h; (ii) MeI, MeCN, rt, 12 h; (iii) THIQ salt (1.1 equiv.), amine (1.0 equiv.): Cs_2CO_3 (3.0 equiv.), MeCN at rt, 12 h; (iv) BBr_3 (10.0 equiv.), CH_2Cl_2 at 0 °C. 24 h.

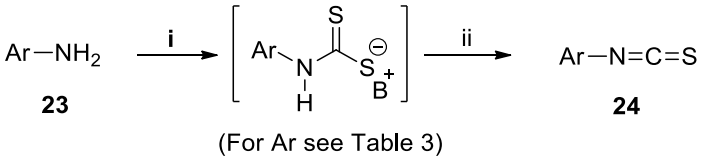
Table 2. Results and conditions for the procedures followed in Scheme 3

Entry	Nucleophile	Product	Yield for step iii (%)	#	Yield for step iv (%)	#
1	2-amino-4-methylthiazole		80	**21a**	36	**22a**
2	3-chloroaniline		8[α]	**21d**	-	**22d**
3	morpholine		65	**21h**	20	**22h**
4	piperazine		Trace amount	**21i**	-	**22i**

[α] 35% of THIQ dimer was also isolated.

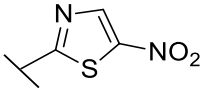
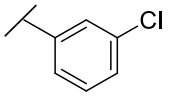
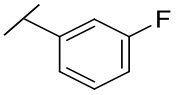
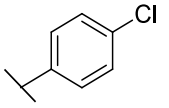
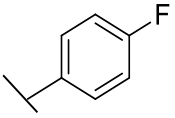
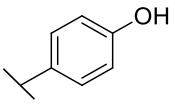
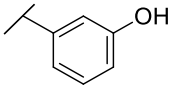
THIQ Set L2 – an alternative strategy

In an effort to improve yields of the THIQ compounds incorporating the thiourea linker **21**, reactions between 6-methoxy-THIQ hydrobromide salt **14** and suitably substituted isothiocyanates were undertaken since this protocol [35] is perceived to be a reliable synthetic approach to thioureas.[36,37] To this end, amines and anilines **23** were treated with an excess of carbon disulfide under basic conditions, followed by desulfurylation, to afford acceptable yields of the stable isothiocyanates **24** (Scheme 4, Table 3).



Scheme 4. Conversion of amines into isothiocyanates. Reaction conditions: (i) amine (1.2 equiv.), CS_2 (5.0 equiv.); (ii) Boc_2O, DMAP or TsCl. For details see Table 3.

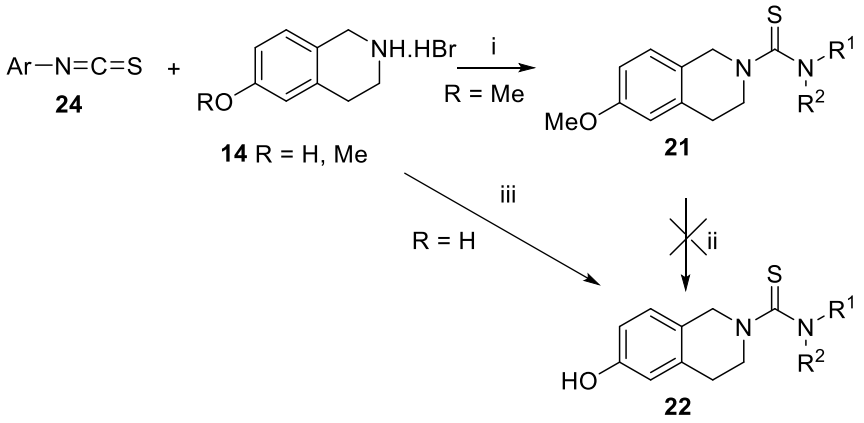
Table 3. Results and conditions for the syntheses of isothiocyanates **24** as depicted in Scheme 4

Entry	Substrate	Ar	Base	Desulfuryl-ating agent	Reaction time (h)	24 Yield (%)
1	**23b**		NaH, THF	Boc_2O, DMAP	36	-[α]
2	**23d**		NaH, THF	TsCl	48	34
3	**23e**		NaH, THF	TsCl	48	85
4	**23f**		NaH, THF	TsCl	48	77
5	**23g**		NaH, THF	TsCl	48	36
6	**23j**		Et_3N, EtOH	Boc_2O, DMAP	1.5	68
7	**23k**		Et_3N, EtOH	Boc_2O, DMAP	1.5	77

[α] Trace amounts isolated

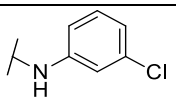
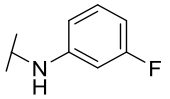
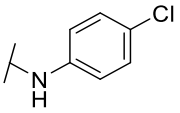
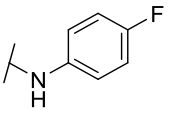
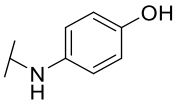
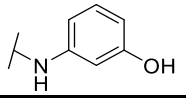
From a cursory look at Table 3 entry 1, it is clear that the relatively electron deficient 2-amino-5-nitrothiazole **23b** is unreactive towards carbon disulfide. Entries 6 and 7 illustrate a method described by Munch *et al*.[38] in which the phenolic amines **23j** and **23k** were treated with a base in ethanol prior to

treatment with CS_2. Apart from the use of Boc_2O, desulfurylation could also be effected by the use of tosyl chloride,[39] and in our hands the Boc_2O method only worked well for entries 6 and 7, while the tosyl chloride method worked best for entries 2-5, albeit with variable yields. With isothiocyanates **24d-g**, **24j** and **24k** in hand (not described in the experimental), they were treated with the THIQ hydrobromide salt **14** under basic conditions and readily afforded a new small library of thiourea products **21** in moderate yields illustrated in Scheme 5 and Table 4. It should be noted that **22j** and **22k** were produced directly from the 6-hydroxy-THIQ hydrobromide of **2b**.[40] Unfortunately, demethylation of the thiourea analogues **21d-g** once again proved to be problematic when using the protocols applied previously, and unfortunately the demethylation of the thioureas did not provide the desired phenolic THIQS **22** in sufficient quantities for further bioevaluation.



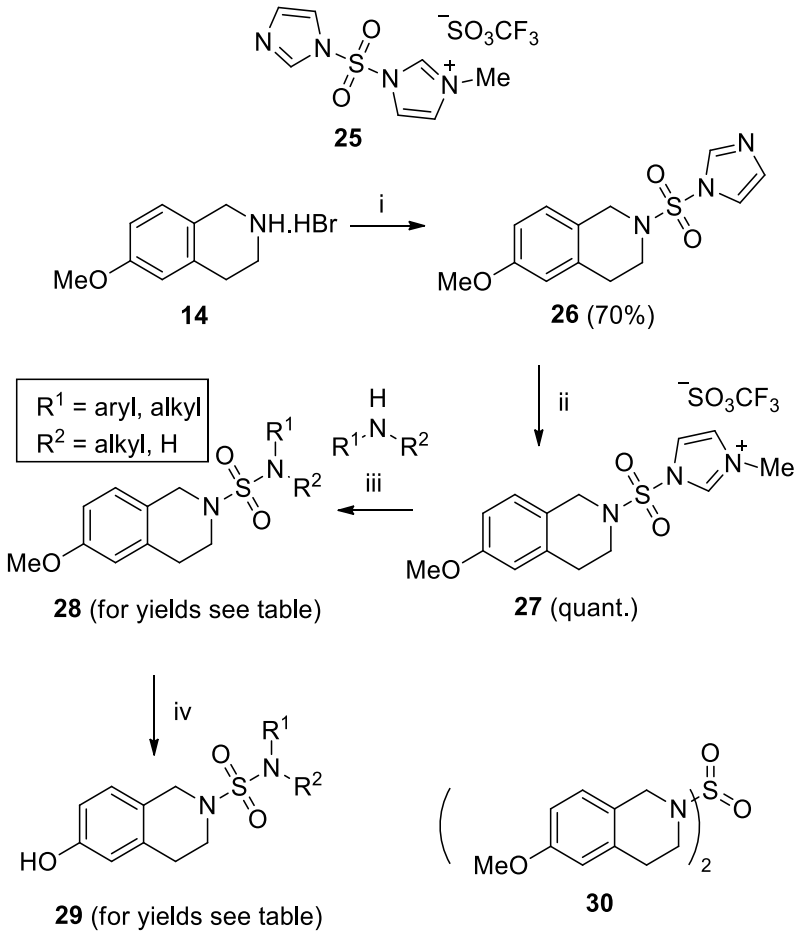
Scheme 5. Formation of the thiourea analogues. Reagents and conditions: (i) and (iii) Salt **14** (1.0 mmol), isocyanate **24** (1.2 mmol), MeCN and Et_3N under reflux 12 h, (ii) Methods as described in Scheme 2.

Table 4. Formation of thioureas **21** and **22** as depicted in Scheme 5

Entry	Ar-N=C=S, Ar =	R =	Product	Yield for step i or iii (%)	#
1	3-chlorophenyl	Me		(i) 40	**21d**
2	3-fluorophenyl	Me		(i) 56	**21e**
3	4-chlorophenyl	Me		(i) 79	**21f**
4	4-fluorophenyl	Me		(i) 62	**21g**
5	4-hydroxyphenyl	H		(iii) 41	**22j**
6	3-hydroxyphenyl	H		(iii) 39	**22k**

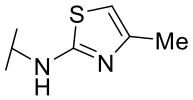
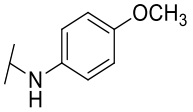
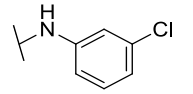
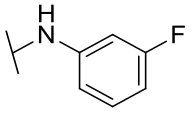
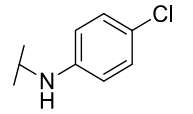
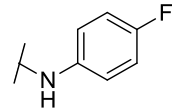
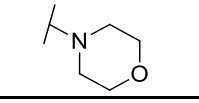
THIQ Set L3 – Sulfonamide-linked THIQs

The third library **L3** was comprised of coupled THIQ-aryl motifs joined by a sulfonamide functional group. In this instance, use of the 1,1′-sulfonylbis(1*H*-imidazolium) triflate salt **25** as described by Beaudoin *et al*.,[41] seemed to be a viable route. To this end, neutralization of THIQ hydrobromide **14** with a suitable base prior to addition of the sulfonyl imidazolium triflate salt **25** (Scheme 6) was essential for improving the homogeneity of the reaction, which in turn afforded a good yield of intermediate **26**. Activation of the imidazole ring of **26**, was again achieved by converting it into the corresponding imidazolium triflate salt **27** in quantitative yield upon treatment with methyl triflate at low temperature. This salt, **27**, as with the other salts prepared earlier, proved to be hygroscopic and thus amines **23** (shown in Table 5) were directly added to the vacuum dried **27** to afford the library of sulfonamides **28** listed in Table 5. Entry 1 in Table 5, illustrates that dimer **30** was the only product isolated from the reaction. Lowering the reaction temperature to 24 °C resulted in only starting material being recovered, which suggested that even 2-amino-4-methyl-thiazole was too weak a nucleophile to displace the imidazolium salt. However, stronger aniline nucleophiles (entries 2-7) afforded the desired products **28c-h** in moderate to good yields at either 24 °C or 80 °C.



Scheme 6. Synthesis of sulfonamide-linked THIQs. Reagents and conditions: (i) K_2CO_3, CH_2Cl_2, 0 °C–rt, 12 h; (ii) MeOTf, CH_2Cl_2, 0 °C, 6 h; (iii) **27** (1.1 equiv.), amine (1.0 equiv.): [a] Et_3N (2.0 equiv.), MeCN at 80 °C, 12 h or [b] K_2CO_3 (2.0 equiv.), MeCN at rt, 12 h or [c] Cs_2CO_3 (3.0 equiv.), MeCN at 80 °C, 12 h; (iv) [d] BBr_3 (3.0 equiv.), CH_2Cl_2 at 0 °C, 24 h or [e] AlI_3 (5.0 equiv.), PhMe at 110 °C, 24 h.

Table 5. Reaction conditions for the formation of sulfonamides **29** as depicted in Scheme 6

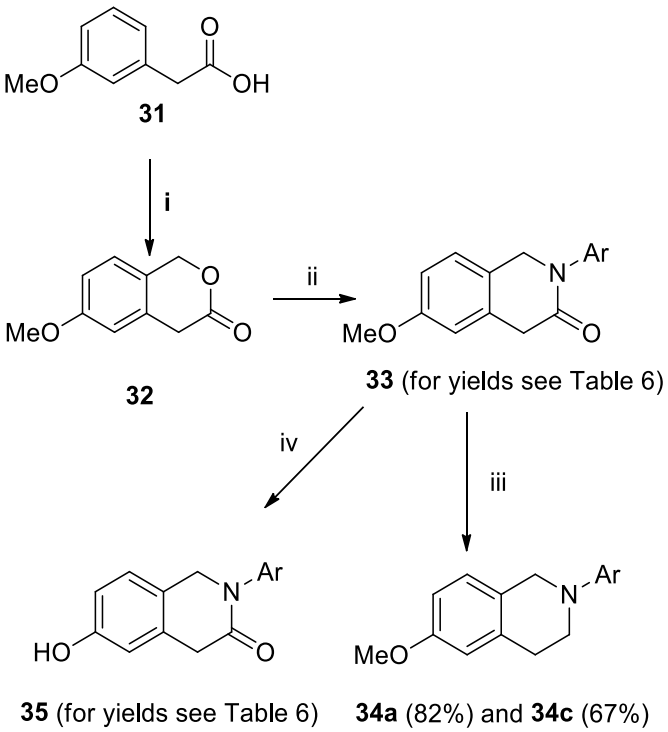
Entry	Nucleophile	Product	Yield for step iii (%)[γ]	#	Yield for step iv (%)[γ]	#
1	2-amino-4-methylthiazole		-[a,α]		-	
2	4-anisidine		87[b]	**28c**	32[e]	**29c**
3	3-chloroaniline		83[c]	**28d**	34[d]	**29d**
4	3-fluoroaniline		46[c]	**28e**	10[d]	**29e**
5	4-chloroaniline		54[c]	**28f**	41[d]	**29f**
6	4-fluoroaniline		94[c]	**28g**	33[d]	**29g**
7	morpholine		70[c]	**28h**	25[e]	**29h**

[α] Only dimer **30** was obtained; [γ] letters refer to the experimental conditions described in the legend of Scheme 6.

Demethylations were effected on all the molecules of this library using either BBr_3 or AlI_3 as indicated in Table 5, but again yields were generally on the low side, indicating that these systems are not easy to demethylate under the applied conditions.

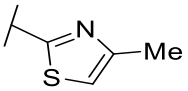
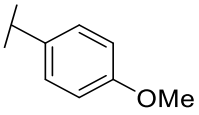
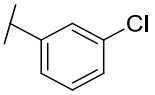
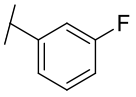
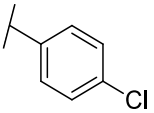
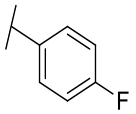
THIQ set L4: *N*-aryl THIQs

The next small library of THIQ-derivatives, **L4**, was designed to have the nitrogen atom of the THIQ directly attached to an aromatic ring. Our first attempts involved direct treatment of lactone **32**, synthesized from 3-methoxyphenyl acetic acid **31** via an Oxy-Pictet-Spengler protocol,[42] with various amines without solvent in a sealed tube containing $AlCl_3$ at 150 °C for 48 hours to produce a melt (Scheme 7).[43] The latter process also facilitated ring closure to afford lactams **33a**–**g** in variable yields ranging from 28–89% (Table 6). In terms of new structural features, the carbonyl at C3 was readily identified in the ^{13}C NMR spectra by a signal at approximately δ_C 170.0 for all the lactam analogues. However, attempts to reduce the C3 carbonyl group of **33** to afford **34** proved uncharacteristically challenging in our hands and only two of the lactams were successfully reduced by employing AlH_2Cl to afford **34a** (82%) and **34c** (67%). Thus, to finalise this library, the lactams **33** were demethylated under the AlI_3 conditions to provide a range of 6-hydroxy-2-phenyl-1,4-dihydroisoquinolin-3(2*H*)-ones **35**, once again in rather inconsistent and variable yields (Table 6). A new approach towards the direct *N*-aryl-THIQs was therefore sought, as described in the next section.



Scheme 7. Conversion of THIQ-based lactones into *N*-aryl lactams. Reagents and conditions: (i) CH_2O, AcOH, rt, 5 days, 45–70%; (ii) lactone (1.0 mmol), amine (1.5 mmol) $AlCl_3$ (0.2 mmol), sealed glass tube at 150 °C for 48 h; (iii) AlH_2Cl, THF, reflux, 12 h; (iv) AlI_3 (5.0 equiv.), PhMe, 110 °C. 10 h.

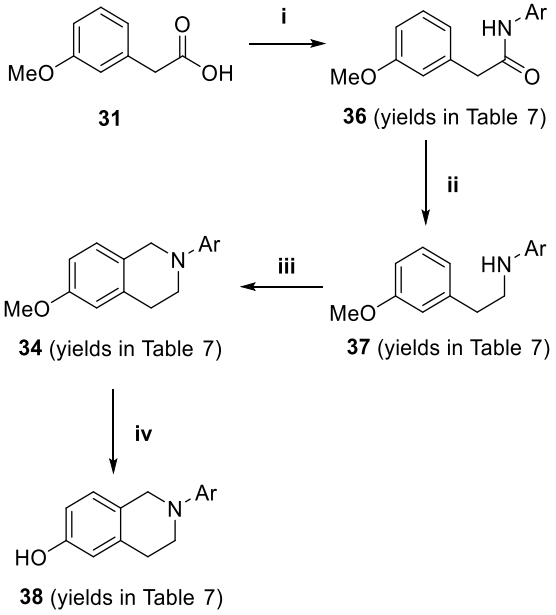
Table 6. Reagents and conditions for the formation of lactams **33** and **35** as depicted in Scheme 7

Entry	Nucleophile	Ar	Yield for step ii (%)	#	Yield for step iv (%)	#
1	2-amino-4-methylthiazole		35	**33a**	45	**35a**
2	4-anisidine		40	**33c**	78	**35c**[δ]
3	3-chloroaniline		57	**33d**	-[α]	**35d**
4	3-fluoroaniline		89	**33e**	89	**35e**
5	4-chloroaniline		37	**33f**	-[α]	**35f**
7	4-fluoroaniline		29	**33g**	24	**35g**

[α] No product obtained after work-up; [δ] product contains *N*-*p*-hydroxyphenyl.

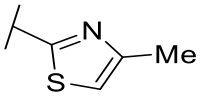
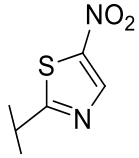
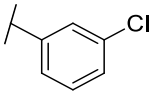
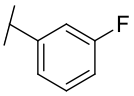
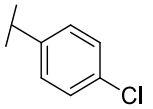
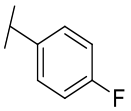
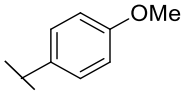
THIQ set 4: *N*-aryl THIQs – alternative approach to L4

An alternative approach to the THIQ library **L4**, also employing the classical Pictet-Spengler protocol, was developed for generating the desired THIQ analogues having a direct *N*-aryl link **34** (Scheme 8). In this approach, treatment of 3-methoxyphenyl acetic acid **31** with a cooled solution (0 °C) of amines/anilines **23b** and **23d**–**g** in dichloromethane containing catalytic amounts of DMAP, as well as the coupling agent, *N*,*N*'-dicyclohexylcarbodiimide (DCC)[44] afforded amides **36** in good yields (Table 7). The very poor yield for **36b** (16%, Table 7, entry 2) is undoubtedly due to both low solubility and poor nucleophilicity of amine **23b.** Generally, the other amide couplings proceeded successfully, providing the products **36d**–**g** for use in the next step. Reduction of the amides **36** was this time successfully accomplished by treatment with monochloroalane in tetrahydrofuran, followed by gentle heating at 80 °C. After work-up, amines **37d**–**g** were obtained in reasonable yields and their structures were confirmed by all having a set of two 2-proton triplets between δ 3.35–2.50 in their ^{1}H NMR spectra and the clear absence of a C=O signal at δ 169.0–171.0 in their ^{13}C NMR spectra. Failure of **36b** to undergo reduction is ascribed to the presence of the nitro group which appears to be chemically incompatible under the reaction conditions. Subsequent Pictet-Spengler ring-closure was effected by treatment of the amines **37d**–**g** with a mixture of paraformaldehyde in formic acid at 80 °C for 12 h,[45] to afford THIQs **34e** and **34g**, structurally confirmed by an intense 2-proton methylene bridge singlet at δ 4.00–4.50 in the ^{1}H NMR spectra for the new products. Unfortunately, in our hands the chloroaryl-substituted compounds **34d** and **34f** were found to be relatively unstable and decomposed in solution within hours of formation. Satisfyingly, despite this challenge, the two crude products **34d** and **34f** were successfully demethylated using AlI_3 in toluene to the corresponding desired phenols **38d** and **38f** in yields of 57 and 58% respectively. Finally, the two THIQ analogues **34e** and **34g**, as well as **34a** and **34c** (prepared earlier, Scheme 7), were demethylated with AlI_3 in toluene at 110 °C for the first two and BBr_3 in dichloromethane for the latter two, to afford no product for **34e,** but **38g, 38a** and **38j** in fair yield and thus five new *N*-aryl THIQ analogues (Table 7).



Scheme 8. Synthesis of *N*-aryl THIQs. Reagents and conditions: (i) amines (**23b**, **23d**–**g**), DCC, DMAP (cat.), CH_2Cl_2 , rt , 12 h; (ii) $LiAlH_4/AlCl_3$, THF, reflux 5 h; (iii) CH_2O, formic acid, 80 °C, 12 h; (iv) [a] BBr_3 (3.0 equiv.), CH_2Cl_2, 0 °C, 12 h or [b] AlI_3 (5.0 equiv.), PhMe, 110 °C, 10 h.

Table 7. Reaction conditions for the formation of 6-hydroxy *N*-arylTHIQs **38** as depicted in Scheme 8

Entry	Amine/aniline	Amide # Yield (%)	Amine # Yield (%)	6-OMe-THIQ # Yield (%)	6-OH-THIQ Yield (%)
1				**34a** (82)[α]	**38a**(45)
2		**36b** (16)	-	-	-
3		**36d** (66)	**37d** (98)	**34d**[β]	**38d** (57)
4		**36e** (94)	**37e** (73)	**34e** (75)	-[χ]
5		**36f** (87)	**37f** (88)	**34f**[β]	**38f** (58)
6		**36g** (56)	**37g** (96)	**34g** (98)	**38g** (55)
7				**34c**(67)[α]	**38j** (38)[δ]

[α] Obtained as shown in Scheme 7; [β] Compound proved difficult to purify and so utilized directly in next reaction; [χ] Product unstable; [δ] product contains *N*-*p*-hydroxyphenyl group.

Preliminary biological evaluations

In terms of a pre-screening of the compounds in hand, a selected set was sent to the Council for Scientific and Industrial Research (CSIR, Pretoria, South Africa) for cell proliferation inhibition assay using the MCF7 (invasive ductal carcinoma) cell line. The assay was performed by first printing or spotting the phenols **18d**, **18f**, **18g**, **18h**, **29h**, **35a**, **35c**, **35e**, **35g**, **38a**, **38g**, **38f** and **38j**, at the concentration of 2.5 mg/mL, on a 2.5 × 6.4 cm glass slide. The printing solution was prepared as described by Erfle and Pepperkok.[46] The slide was then placed in a tissue culture plate followed by the addition of MCF7 cells at the concentration of 1.5 x 10^6 cells / 10 mL of tissue culture media. The plate was placed in an incubator at 37 °C and 5% CO_2 for 4 days. Post cell culture, the cells were treated with immunofluorescent agents (sulforhodamine B, 568 nm; phalloidin, 488 nm and 4,6-diamidino-2-phenylindole, dihydrochloride (DAPI), 408 nm). Imaging was performed using a three channel Cytation3 cell imaging Multi-Mode Reader. The changes in blue (DAPI staining of cells nuclei) and green (phalloidin staining of cells cytoskeleton) fluorescence intensity at the spot representing each compound were taken to be indicative of changes in MCF7 viability (apoptosis or inhibition of cell proliferation) and experiments were performed in duplicate. Persomics analysis software was utilized to process images and data quantification was performed using Microsoft Excel. The results for the THIQ-based compounds are depicted in Figure 6.

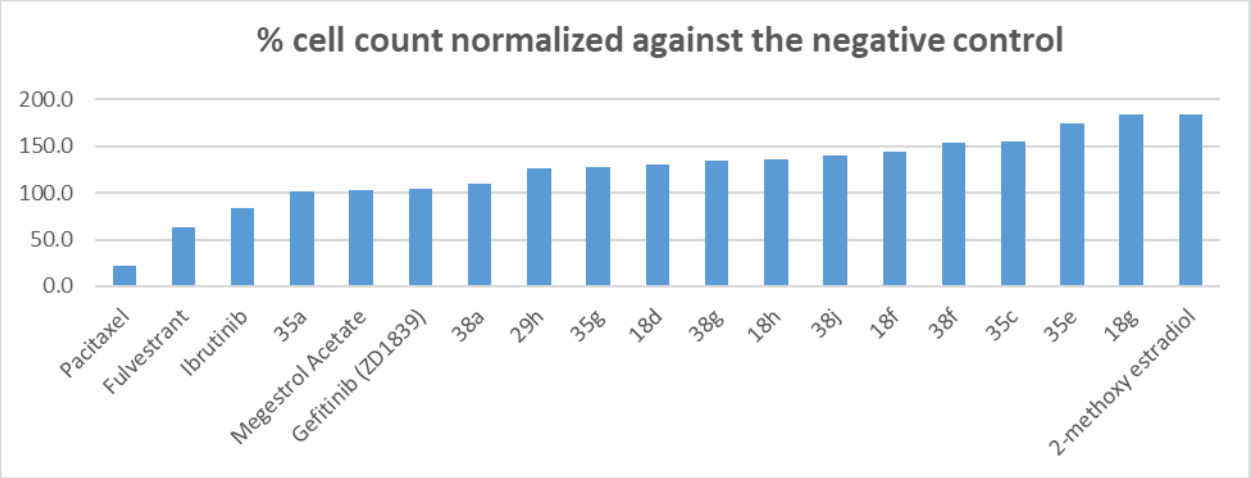


Figure 6: Percentage growth of MCF7 cells treated with selected compounds (2.50 mg/mL over 4 days).

Unfortunately, the small set of compounds tested were underwhelming in their ability to inhibit the proliferation of the MCF7 cells. As can be seen from Figure 6, the synthesized compounds had little effect. It should be noted that a number of reference compounds were included in the anti-proliferation assay, some of which provided better growth inhibition. The results of this initial screening indicate that a much larger set of compounds will need to be evaluated to note whether further compounds with higher activity can be identified – alternatively, other bio-testing strategies will be required to identify promising compounds.

Conclusions

Four small libraries of THIQ analogues, in which the nitrogen atom was employed as a linker group, were synthesized to reflect the urea-, thiourea- and sulfonamide-linked functional groups, as well as their direct *N*-Ar analogues. Initial observations revealed that the last step demethylation was problematic, frequently resulting in the final products in low yields only – the development of an alternative strategy making use of easier to remove phenol protecting groups is thus an ongoing concern in our laboratories. Initial evaluations of the compounds synthesized in an antiproliferative assay against the MCF7 carcinoma cell line revealed a lack of activities and thus a larger data set is required, or alternatively, other bioassay strategies should be attempted.

Experimental Section

General. Melting points were measured on a Gallenkamp melting point apparatus. Reaction times were determined using thin layer chromatography (TLC) on fluorescent silica gel plates HF_{254} (Merck) and viewed under UV radiation or employing reagents including potassium permanganate, ninhydrin, *p*-anisaldehyde, cerium ammonium molybdate, 2,4-dinitrophenylhydrazine and iodine vapors. Silica gel 60 (70-230 mesh) was used for gravity column chromatography and 230-400 mesh was used for flash chromatography. Silica sensitive compounds were purified using Aluminium oxide 90 active neutral 0.063-0.200 mm (70-230 mesh)(Merck). Nuclear magnetic resonance (NMR) spectra were recorded on Varian Gemini-300 (^{1}H NMR at

300 MHz and ^{13}C at 75 MHz) and Varian VXR-400 (^{1}H NMR at 400 MHz and ^{13}C at 101 MHz) spectrometers. Chemical shifts (δ) and coupling constants (*J*) are represented in ppm and Hertz units respectively. Positive electron spray impact (ESI+) high resolution mass spectra (HRMS) were recorded on a Unicam Automass mass spectrometer in conjunction with a gas chromatogram. All reactions were performed under a dry nitrogen atmosphere. The following compounds sent for biochemical evaluation were evaluated for purity by way of LCMS (% purity in parenthesis): **18h** (99%), **29h** (93%), **35a** (97%), **35c** (98%), **35e** (97%), **35g** (99%), **38a** (88%), **38g** (96%), **38f** (96%) and **38j** (92%).

THIQ set L1: General approach to the synthesis of THIQ–carbamoyl imidazoles[34]

(1*H*-Imidazol-1-yl)[6-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl]methanone (**15**)**.** To a cooled (0 °C) solution of 1,1′-carbonyldiimidazole (350 mg, 2.20 mmol) in anhydrous MeCN (25 mL) was added THIQ **14** (326 mg, 2.00 mmol) and K_2CO_3 (4.00 mmol). The resulting mixture was stirred at 24 °C for 18 h and then concentrated under reduced pressure to afford a residue which was purified by column chromatography (100% EtOAc) to give imidazole **15** (493 mg, 96%) as a colourless oil, R_f 0.31 (100% EtOAc). This intermediate was immediately used without further purification in the next synthetic step. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.86 (d, *J* 0.9 Hz, 1H, *imidazole*-H), 7.20 (d, *J* 1.4 Hz, 1H, *imidazole*-H), 7.05 (d, *J* 1.4 Hz, 1H, *imidazole*-H), 6.95–6.92 (m, 1H, ArH), 6.71–6.64 (m, 2H, ArH), 4.61 (s, 2H, Ar*CH*$_2$N), 3.78–3.67 (m, 5H, overlapping signals - NCH_2 and OMe), 2.90 (t, *J* 6.0 Hz, 2H, Ar*CH*$_2$CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 29.1 (Ar*C*H$_2$CH$_2$), 44.7 (CH$_2$*C*H$_2$N), 48.3 (Ar*CH*$_2$N), 55.6 (OMe), 113.3 (Ar*C*H), 113.9 (Ar*C*H), 118.2 (Ar*C*H), 124.1 (Ar*C*), 127.6 (Ar*C*H), 130.1 (Ar*C*H), 135.3 (Ar*C*), 137.1 (Ar*C*H), 151.4 (C-O), 159.0 (C=O).

1-(6-Methoxy-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-3′-methyl-1*H*-imidazol-3-ium iodide (**16**)**.** To a suspension of carbamoyl imidazole **15** (748 mg,2.91 mmol) in anhydrous MeCN (24 mL) was added iodomethane (0.960 mL, 15.5 mmol) and the resulting mixture stirred for 6 h to afford a precipitate which was filtered off to give **16** (1160 mg, 100%) as an off white solid, mp 172–173 °C, R_f 0.00 (100% EtOAc).This intermediate was used without further purification for the next step in the synthesis. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 9.62 (s, 1H, *imidazole*-H), 8.10–8.09 (m, 1H, *imidazole*-H), 7.89–7.88 (m, 1H, ArH), 7.13 (brs, 1H, ArH), 6.84–6.81 (m, 2H, ArH), 4.67 (s, 2H, Ar*CH*$_2$N), 3.94 (s, 3H, *imidazole*-Me), 3.75–3.68 (m, 5H, overlapping signals - OMe and CH_2), 2.95 (t, *J* 5.8 Hz, 2H, Ar*CH*$_2$CH$_2$). ^{13}C NMR (75 MHz, DMSO-d_6, some quaternary carbons not observed): δ_C 55.3 (OMe), 112.9 (Ar*C*H), 113.2 (Ar*C*H), 121.1 (Ar*C*), 123.8 (Ar*C*H), 127.6 (Ar*C*H), 135.7 (Ar*C*), 137.8 (Ar*C*H), 147.3 (C-O), 158.3 (C=O).

6-Methoxy-*N*-(4′-methylthiazol-2-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxamide (**17a**)**.** To a mixture of 2-amino-4-methylthiazole (120 mg, 1.08 mmol) and Et_3N (0.150 mL, 1.08 mmol) in anhydrous MeCN (15 mL) stirred at 24 °C for 30 min was added the imidazolium salt **16** (216 mg, 0.542 mmol) and the reaction mixture stirred for 18 h. The reaction mixture was washed with aqueous 1 N HCl solution (50 mL × 2) followed by extraction with EtOAc (20 mL × 2). The residue, obtained by reduction of the solvent volume, was purified by column chromatography (50:50 EtOAc/Hexane) to afford the amide **17a** (132 mg, 80%) as an orange oil, R_f 0.39 (50:50 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 6.95 (d, *J* 8.4 Hz, 1H, ArH), 6.75 (dd, *J* 8.4, 2.5 Hz, 1H, ArH), 6.66 (d, *J* 2.5 Hz, 1H, ArH), 6.39 (s, 1H, *thiazole*-ArH), 4.55 (s, 2H, Ar*CH*$_2$N), 3.78 (s, 3H, OMe), 3.70 (t, *J* 5.9 Hz, 2H, CH_2), 2.84 (t, *J* 5.9 Hz, 2H, Ar*CH*$_2$CH$_2$), 2.27 (s, 3H, *thiazole*-Me). ^{13}C NMR (75 MHz, $CDCl_3$, some quaternary carbons not observed): δ_C 16.8 (*thiazole*-Me), 29.1 (Ar*CH*$_2$CH$_2$), 41.5 (CH_2), 45.3 (Ar*CH*$_2$N), 55.4 (OMe), 107.1 (Ar*C*H), 112.8 (Ar*C*H), 113.4 (Ar*C*H), 124.8 (Ar*C*), 127.5 (Ar*C*H), 135.9 (Ar*C*NH), 154.5 (C-O), 158.5 (C=O). HRMS ESI$^+$: calcd for $C_{15}H_{18}N_3O_2S$ $[M+H]^+$ 304.1120, found 304.1111.

6-Methoxy-*N*-(5′-nitrothiazol-2-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxamide (**17b**)**.** To a suspension of 2-amino-5-nitrothiazole (100 mg, 0.714 mmol), and Cs_2CO_3 (310 mg, 0.952 mmol) in anhydrous MeCN (20 mL), which was stirred at 24 °C for 30 min, was added the salt **16** (190 mg, 0.476 mmol) and stirring was continued

for 12 h. Work-up as before afforded a solid residue which was purified using column chromatography (30:70 EtOAc/Hexane) to give **17b** (143 mg, 90%) as a yellow powder, R_f 0.50 (30:70 EtOAc/Hexane). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 12.17 (s, 1H, NH), 8.58 (s, 1H, *thiazole*-H), 7.10 (d, *J* 8.4 Hz, 1H, ArH), 6.89–6.67 (m, 2H, ArH), 4.64 (s, 2H, ArCH_2N), 3.89–3.62 (m, 5H, overlapping signals - OMe and CH_2), 2.84 (t, *J* 5.9 Hz, 2H, ArCH_2CH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 28.3 (ArCH_2CH_2), 41.5 (CH_2), 44.9 (ArCH_2N), 55.1 (OMe), 112.5 (Ar*C*H), 113.2 (Ar*C*H), 124.9 (Ar*C*H), 127.2 (Ar*C*H), 135.7 (Ar*C*), 140.5 (Ar*C*H), 142.1 (Ar*C*NH), 153.8 (C-O), 157.9 (C=O), 165.54 (Ar*C*NO_2). HRMS ESI$^+$: calcd for $C_{14}H_{15}N_4O_4S$ $[M+H]^+$ 335.0814, found 335.0805.

6-Methoxy-*N*-(4′-methoxyphenyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxamide (**17c**)**.** To a cooled (−78 °C) solution of anisole (80.0 mg, 0.649 mmol) in anhydrous THF (15 mL) was added *n*-BuLi (1.39 mL, 1.4 M, 1.94 mmol) and the mixture was stirred for 1 h at −78 °C. The temperature was gradually allowed to increase to 24 °C. Salt **16** (310 mg, 0.779 mmol) was then added and the reaction mixture was stirred at 24 °C for 12 h. Work-up as described before, followed by chromatography (30:70 EtOAc/Hexane) afforded **17c** as a brown oil (198 mg, 98%), R_f 0.50 (50:50 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.30–7.14 (m, 2H, ArH), 6.99 (d, *J* 8.4 Hz, 1H, ArH), 6.84–6.60 (m, 4H, ArH), 6.32 (s, 1H, NH), 4.52 (s, 2H, ArCH_2N), 3.73 (s, 3H, OMe), 3.74 (s, 3H, OMe), 3.63 (t, *J* 5.9 Hz, 2H, NCH_2), 2.82 (t, *J* 5.9 Hz, 2H, ArCH_2CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 29.7 (ArCH_2CH_2), 41.7 (CH_2), 45.6 (ArCH_2N), 55.7 (2 × OMe), 112.9 (Ar*C*H), 113.6 (Ar*C*H), 114.4 (Ar*C*H), 122.9 (Ar*C*H), 125.6 (Ar*C*H), 127.7 (Ar*C*), 132.4 (Ar*C*), 136.6 (Ar*C*NH), 155.8 (C-O), 156.2 (C-O), 158.69 (C=O). HRMS ESI$^+$: calcd for $C_{18}H_{21}N_2O_3$ $[M+H]^+$ 313.3638, found 313.3632.

***N*-(3′-Chlorophenyl)-6-methoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxamide** (**17d**)**.** In a similar way described for **17c** above, **17d** was obtained as a brown oil (178 mg, 86%) yield as a brown oil that waxified at low temperatures, R_f 0.50 (50:50 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.47 (d, *J* 1.9 Hz, 1H, ArH), 7.31–7.07 (m, 2H, ArH), 7.06–6.90 (m, 2H, ArH), 6.85–6.61 (m, 3H, ArH and NH), 4.55 (s, 2H, ArCH_2N), 3.77 (s, 3H, OMe), 3.65 (t, *J* 6.0 Hz, 2H, CH_2), 2.83 (t, *J* 6.0 Hz, 2H, ArCH_2CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 29.3 (ArCH_2CH_2), 41.6 (CH_2), 45.4 (ArCH_2N), 55.4 (OMe), 112.7 (Ar*C*H), 113.4 (Ar*C*H), 118.3 (Ar*C*H), 120.3 (Ar*C*H), 123.1 (Ar*C*H), 125.2 (Ar*C*H), 127.4 (Ar*C*), 129.8 (Ar*C*H), 134.4 (Ar*C*), 136.2 (Ar*C*Cl), 140.5 (Ar*C*NH), 154.9 (C-O), 158.5 (C=O). HRMS ESI$^+$ calcd for $C_{17}H_{18}ClN_2O_2$ $[M+H]^+$ 317.1057 (^{35}Cl), found 317.1052.

***N*-(3′-Fluorophenyl)-6-methoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxamide** (**17e**)**.** In a similar manner as described for **17c** above, **17e** was obtained as a brown oil (192 mg, 98%) that waxified at low temperature, R_f 0.50 (50:50 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.38–7.18 (m, 1H, ArH), 7.09–7.03 (m, 2H, ArH), 6.85–6.70 (m, 4H, ArH), 6.45 (s, 1H, NH), 4.62 (s, 2H, ArCH_2N), 3.83 (s, 3H, OMe), 3.70 (t, *J* 5.8 Hz, 2H, CH_2), 2.93 (t, *J* 5.8 Hz, 2H, ArCH_2CH_2). ^{13}C NMR (75 MHz, $CDCl_3$, some quaternary carbons not observed): δ_C 29.3 (ArCH_2CH_2), 41.5 (CH_2), 45.3 (ArCH_2N), 55.3 (OMe), 107.4 (Ar*C*H), 109.5 (Ar*C*H), 112.6 (Ar*C*H), 113.3 (Ar*C*H), 114.9 (Ar*C*), 127.3 (Ar*C*H), 136.2 (Ar*C*NH), 158.5 (C=O). HRMS ESI$^+$ calcd for $C_{17}H_{18}FN_2O_2$ $[M+H]^+$ 301.1352, found 301.1356.

***N*-(4′-Chlorophenyl)-6-methoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxamide** (**17f**)**.** In a similar manner as described for **17c** above, **17f** was obtained as a brown solid (91 mg, 44%), mp 105–107 °C, R_f 0.50 (50:50 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.40–7.19 (m, 4H, ArH), 7.06 (d, *J* 8.4 Hz, 1H, ArH), 6.88–6.65 (m, 2H, ArH), 6.45 (s, 1H, NH), 4.59 (s, 2H, ArCH_2N), 3.80 (s, 3H, OMe), 3.76–3.65 (m, 2H, CH_2), 2.90 (t, *J* 5.3 Hz, 2H, ArCH_2CH_2). ^{13}C NMR (75 MHz, $CDCl_3$, some quaternary carbons not observed): δ_C 29.7 (ArCH_2CH_2), 41.8 (CH_2), 45.6 (ArCH_2N), 55.7 (OMe), 113.0 (Ar*C*H), 113.7 (Ar*C*H), 121.5 (Ar*C*), 125.1 (Ar*C*H), 127.7 (Ar*C*H), 129.2 (Ar*C*), 136.4 (Ar*C*Cl), 138.1 (Ar*C*NH), 154.9 (Ar*C*H), 155.2 (C-O), 158.4 (C=O). HRMS ESI$^+$ calcd for $C_{17}H_{18}ClN_2O_2$ $[M+H]^+$ 317.1057 (^{35}Cl), found 317.1060.

***N*-(4′-Fluorophenyl)-6-methoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxamide** (**17g**)**.** In a similar manner as described for **17c** above, **17g** was obtained as a brown solid (159 mg, 81%), mp 136–137 °C, R_f 0.50 (50:50

EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.38–7.28 (m, 2H, ArH), 7.10–6.91 (m, 3H, ArH), 6.83–6.68 (m, 2H, ArH), 6.43 (s, 1H, NH), 4.59 (s, 2H, Ar*CH*$_2$N), 3.80 (s, 3H, OMe), 3.70 (t, *J* 5.9 Hz, 2H, CH_2), 2.89 (t, *J* 5.9 Hz, 2H, Ar*CH*$_2$$CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 29.7 (Ar*CH*$_2$$CH_2$), 41.8 ($CH_2$), 45.6 (Ar*CH*$_2$N), 55.7 (OMe), 113.0 (Ar*C*H), 113.7 (Ar*C*H), 115.8 (d, *J* 22.5 Hz, Ar*C*H-F), 122.5 (d, *J* 7.7 Hz, Ar*C*H-F), 125.5 (Ar*C*), 127.7 (Ar*C*H), 135.3 (Ar*C*), 136.6 (Ar*C*NH), 155.5 (C-O), 157.6 (d, *J* 67.5 Hz, Ar*C*-F), 158.8 (C=O). HRMS ESI$^+$ calcd for $C_{17}H_{18}FN_2O_2$ $[M+H]^+$ 301.1352, found, 301.1348.

6-[Benzyloxy-3,4-dihydroisoquinolin-2(1*H*)-yl(morpholino)]methanone (**17h**)**.** In a similar manner as described for **17c** above, **17h** was obtained as a thick white oil (220 mg, 96%) from the corresponding 6-benzyloxy imidazolium salt to **16** (donation from another project), R_f 0.48 (100% EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.39–7.15 (m, 5H, ArH), 6.93 (d, *J* 8.4 Hz, 1H, ArH), 6.80–6.62 (m, 2H, ArH), 4.96 (s, 2H, Ar*CH*$_2$O), 4.31 (s, 2H, Ar*CH*$_2$N), 3.74–3.53 (m, 4H, *morpholine* – 2 x OCH_2), 3.42 (t, *J* 5.8 Hz, 2H, CH_2), 3.29–3.13 (m, 4H, *morpholine* – 2 × NCH_2), 2.79 (t, *J* 5.8 Hz, 2H, Ar*CH*$_2$$CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 29.0 (Ar*CH*$_2$$CH_2$), 44.5 (*morpholine* – 2 × NCH_2), 47.4 (CH_2), 48.4 (Ar*CH*$_2$N), 66.8 (*morpholine* – 2 × CH_2O), 70.2 (Bn*CH*$_2$O), 113.5 (Ar*C*H), 114.7 (Ar*C*H), 126.1 (Ar*C*), 127.4 (Ar*C*H), 128.0 (Ar*C*H), 128.7 (Ar*C*H), 135.9 (Ar*C*), 137.1 (Bn*C*), 157.5 (C-O), 164.0 (C=O). HRMS ESI$^+$ calcd for $C_{21}H_{24}N_2O_3$ $[M+H]^+$ 353.1865, found 353.1866.

General procedure for demethylation using BBr_3 (Method A)[47]

To a mixture of 1 M BBr_3 in anhydrous CH_2Cl_2 (1.90 mL, 1.9 mmol) in a Schlenk tube cooled to −78 °C, was slowly added the MeO-THIQ analogues (0.66 mmol) in anhydrous CH_2Cl_2 (0.50 mL). The reaction mixture was stirred for 2 h at −60 °C, followed by stirring for an additional 4 h at 24 °C. Ethanol was then slowly added until fuming ceased, after which the reaction mixture was poured into a saturated $NaHCO_3$ solution (15 mL) and extracted with EtOAc (20 mL x 3). The solvent was dried and evaporated (rotary evaporator), to afford a residue which was purified by column chromatography (40:60 EtOAc/Hexane).

General procedure for demethylation using AlI_3 (Method B)[48]

To a cooled suspension of clean aluminium powder (180 mg, 6.66 mmol) in anhydrous toluene (20 mL) was added iodine (I_2) (1.31 g, 10.3 mmol) and the mixture was stirred at 110 °C, under nitrogen, until the red colour had disappeared. The reaction mixture was cooled to rt (~24 °C) and then the MeO-THIQ analogues (0.69 mmol) were added, after which the reactions were stirred at 60 °C for 12 h. The reaction mixture was cooled to 24 °C and the excess AlI_3 was quenched by the slow addition of water (20 mL). The reaction mixture was extracted with EtOAc (20 mL × 3), the organic solvent collected, dried and reduced (rotary evaporator) to afford a residue which was purified by column chromatography (40:60 EtOAc/Hexane).

6-Hydroxy-*N*-(4'-methylthiazol-2-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxamide (**18a**) was obtained as a yellow solid from **17a**, via Method A (123 mg, 64%), mp 199–200 °C, R_f 0.22 (50:50 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 6.36–6.33 (bs, 1H, ArH), 6.05–5.99 (m, 2H, ArH), 5.79 (bs, 1H, *thiazole*-H), 4.29 (brs, 2H, NH and OH), 3.98 (s, 2H, Ar*CH*$_2$N), 3.13–3.09 (m, 2H, NCH_2), 2.19 (t, *J* 5.9 Hz, 2H, Ar*CH*$_2$$CH_2$), 1.63 (d, *J* 1.1 Hz, 3H, *thiazole*-Me). ^{13}C NMR (75 MHz, DMSO-d_6, no C=O signal was visible): δ_C 6.8 (*thiazole*-Me), 20.6 (Ar*CH*$_2$$CH_2$), 33.4 ($CH_2$), 37.0 (Ar*CH*$_2$N), 70.1 (*thiazole*-*C*H), 97.5 (Ar*C*H), 105.4 (Ar*C*H), 106.4 (Ar*C*), 115.9 (Ar*C*H), 118.9 (Ar*C*), 127.8 (*thiazole*-Ar*C*), 134.5 (Ar*C*NH), 147.8 (C-O), 148.6 (C-O). HRMS ESI$^+$ calcd for $C_{14}H_{16}N_3O_2S$ $[M+H]^+$ 290.0963, found 290.0955.

6-Hydroxy-*N*-(4'-hydroxyphenyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxamide (**18c**) was obtained as a thick white oil from **17c**, via Method B (83 mg, 42%), R_f 0.14 (50:50 EtOAc/Hexane). The compound rapidly decomposed in solution as demonstrated by NMR spectroscopy. HRMS ESI$^+$ calcd for $C_{16}H_{17}N_2O_3$ $[M+H]^+$ 285.1239, found 285.1240.

***N*-(3'-Chlorophenyl)-6-hydroxy-3,4-dihydroisoquinoline-2(1*H*)-carboxamide** (**18d**) was obtained as a brown solid from **17d**, via Method B (105 mg, 50%), mp 188–190 °C, R_f 0.50 (50:50 EtOAc/Hexane). ^{1}H NMR (300

MHz, CD_3OD, OH and NH signals were not observed): δ_H 7.57–6.99 (m, 5H, ArH), 6.67–6.64 (m, 2H, ArH), 4.59 (s, 2H, Ar*CH*$_2$N), 3.71 (t, *J* 5.9 Hz, 2H, NCH_2), 2.86 (t, *J* 5.9 Hz, 2H, Ar*CH*$_2$$CH_2$). ^{13}C NMR (75 MHz, CD_3OD): δ_C 30.0 (Ar*CH*$_2$$CH_2$), 42.9 ($CH_2$), 46.5 (Ar*CH*$_2$N), 114.8 (Ar*C*H), 115.7 (Ar*C*H), 119.9 (Ar*C*H), 121.7 (Ar*C*), 123.7 (Ar*C*Cl), 125.4 (Ar*C*H), 128.3 (Ar*C*H), 130.7 (Ar*C*H), 135.0 (Ar*C*), 135.3 (Ar*C*HCl), 137.3 (Ar*C*NH), 157.1 (C-O), 157.4 (C=O). HRMS ESI$^+$ calcd for $C_{16}H_{16}ClN_2O_2$ $[M+H]^+$ 303.0900 (^{35}Cl), found 303.0910.

***N*-(3′-Fluorophenyl)-6-hydroxy-3,4-dihydroisoquinoline-2(1*H*)-carboxamide** (**18e**) was obtained as a white solid from **17e** via Method B (69 mg, 35%), mp 166–168 °C, R_f 0.33 (50:50 EtOAc/Hexane). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 9.25 (s, 1H, NH), 8.71 (brs, 1H, OH), 7.54–7.37 (m, 1H, ArH), 7.34–7.17 (m, 2H, ArH), 6.96 (d, *J* 8.2 Hz, 1H, ArH), 6.80–6.53 (m, 3H, ArH), 4.51 (s, 2H, Ar*CH*$_2$N), 3.63 (t, *J* 5.9 Hz, 2H, NCH_2), 2.75 (t, *J* 5.9 Hz, 2H, Ar*CH*$_2$$CH_2$). ^{13}C NMR (75 MHz, DMSO-d_6, no C-F coupling was observable): δ_C 28.7 (Ar*CH*$_2$$CH_2$), 41.6 ($CH_2$), 45.4 (Ar*CH*$_2$N), 106.1 (Ar*C*H), 106.5 (Ar*C*H), 108.0 (Ar*C*H), 108.3 (Ar*C*H), 113.8 (Ar*C*H), 115.0 (Ar*C*H), 115.3 (Ar*C*H), 124.2 (Ar*C*), [one extra signal 127.4 (ArCH)], 130.0 (Ar*C*), 136.1 (Ar*C*NH), 142.9 (Ar*C*-F), 154.9 (C-O), 156.0 (C=O). HRMS ESI$^+$ calcd for $C_{16}H_{16}FN_2O_2$ $[M+H]^+$ 287.1196, found 287.1197.

***N*-(4′-Chlorophenyl)-6-hydroxy-3,4-dihydroisoquinoline-2(1*H*)-carboxamide** (**18f**) was obtained as a brown oil from **17f**, via Method B (105 mg, 50%), R_f 0.50 (50:50 EtOAc/Hexane). ^{1}H NMR (300 MHz, CD_3OD, OH and NH signals not observed): δ_H 7.5–6.99 (m, 5H, ArH), 6.6–6.64 (m, 2H, ArH), 4.59 (s, 2H, Ar*CH*$_2$N), 3.72 (t, *J* 5.7 Hz, 2H, NCH_2), 2.86 (t, *J* 5.7 Hz, 2H, Ar*CH*$_2$$CH_2$). ^{13}C NMR (75 MHz, CD_3OD, some quaternary carbons not observed): δ_C 28.6 (Ar*CH*$_2$$CH_2$), 41.4 ($CH_2$), 45.0 (Ar*CH*$_2$N), 113.4 (Ar*C*H), 114.3 (Ar*C*H), 114.7 (Ar*C*), 123.1 (Ar*C*H), 123.6 (Ar*C*H), 124.1 (Ar*C*H), 126.8 (Ar*C*NH), 136.0 (Ar*C*Cl), 155.0 (C-O), 156.03 (C=O). HRMS ESI$^+$ calcd for $C_{16}H_{16}ClN_2O_2$ $[M+H]^+$ 303.0793 (^{35}Cl), found 303.0799.

***N*-(4′-Fluorophenyl)-6-hydroxy-3,4-dihydroisoquinoline-2(1*H*)-carboxamide** (**18g**) was obtained as a white solid from **17g**, via Method B (6 mg, 3%), mp 225–226 °C, R_f 0.33 (50:50 EtOAc/Hexane). ^{1}H NMR (300 MHz, CD_3OD, both OH and NH signals were not observed): δ_H 7.4–7.19 (m, 3H, ArH), 7.00 (d, *J* 7.9 Hz, 2H, ArH), 6.66 (d, *J* 7.9 Hz, 2H, ArH), 4.58 (s, 2H, ArC*H*$_2$N), 3.71 (t, *J* 5.7 Hz, 2H, CH_2), 2.85 (t, *J* 5.7 Hz, 2H, Ar$CH_2$$CH_2$). ^{13}C NMR (75 MHz, CD_3OD, C-F coupling was not observed): δ_C 30.0 (Ar*C*H$_2$$CH_2$), 42.9 ($CH_2$), 46.5 (Ar*C*H$_2$N), 114.8 (Ar*C*H), 115.7 (Ar*C*H), 123.5 (Ar*C*), 125.4 (Ar*C*), 128.3 (Ar*C*H), 129.0 (Ar*C*H), 129.5 (Ar*C*H), 137.3 (Ar*C*F), 139.9 (Ar*C*NH), 157.2 (C-O), 157.7 (C=O). HRMS ESI$^+$ calcd for $C_{16}H_{16}FN_2O_2$ $[M+H]^+$ 275.1196, found 275.1204.

[6-Hydroxy-3,4-dihydroisoquinolin-2(1*H*)-yl](morpholino)methanone (18h). To a stirred mixture of Pd (10% on activated charcoal) (81.0 mg, 0.075 mmol) in anhydrous MeOH (6.00 mL) containing a drop of acetic acid was added 17h (270 mg, 0.766 mmol) and then stirred under a hydrogen atmosphere (balloon) at 40 °C for 48 h. The mixture was filtered through celite and concentrated under reduced pressure. The residue was partitioned between EtOAc (30 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL × 3). Solvent reduction (rotary evaporator) afforded a residue which was purified by column chromatography (100% EtOAc) to afford 18h (158 mg, 79%) yield as a white solid mp 188–190 °C, R_f 0.21 (50:50 EtOAc/Hexane). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 9.02 (brs, 1H, OH), 6.90 (d, *J* 8.1 Hz, 1H, ArH), 6.67 (dd, *J* 8.1, 2.1 Hz, 1H, ArH), 6.55–6.46 (m, H, ArH), 3.58–3.48 (m, 4H, *morpholine* – 2 × OCH_2), 3.28–3.21 (m, 6H, *morpholine* – 2 × NCH_2 and NCH_2), 3.13 (dd, *J* 9.0, 3.8 Hz, 2H, CH_2), 2.59 (dd, *J* 9.0, 3.8 Hz, 2H, Ar*CH*$_2$$CH_2$). ^{13}C NMR (101 MHz, DMSO-d_6): δ_C 18.6 (Ar*CH*$_2$$CH_2$), 34.6 (*morpholine* – 2 x NCH_2), 41.5 (CH_2), 44.4 (Ar*C*H$_2$N), 66.6 (*morpholine* – 2 × OCH_2), 113.6 (Ar*C*H), 116.7 (Ar*C*H), 126.4 (Ar*C*), 131.4 (Ar*C*H), 139.4 (Ar*C*), 156.0 (C-O), 158.2 (C=O). HRMS ESI$^+$ calcd for $C_{14}H_{19}N_2O_3$ $[M+H]^+$ 263.1317, found 263.1320.

(1*H*-Imidazol-1-yl)[6-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl]methanethione (**19**). A cooled (5 °C) solution of 1,1′-thiocarbonyldiimidazole (215 mg, 1.20 mmol) in anhydrous MeCN (100 mL) containing K_2CO_3 (138 mg, 1.00 mm) was treated by the portion-wise addition of THIQ HBr 14 (244 mg,1.00 mmol), while maintaining the temperature of 5 °C for 2 h. The reaction mixture was allowed to warm to 24 °C and stirred for 18 h. The

reaction mixture was concentrated under reduced pressure to afford a residue which was purified with column chromatography (100% EtOAc). It is important to note that in order to prevent formation of the dimer, the portionwise addition of 14 was essential. In this way 19 (293 mg, 100%) was obtained a yellow oil, R_f 0.21 (100% EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.92–7.83 (m, 1H, *imidazole*-H), 7.26–7.19 (m, 1H, *imidazole*-H), 7.08 (dd, *J* 1.4, 0.9 Hz, 1H, *imidazole*-H), 6.98 (s, 1H, ArH), 6.84–6.67 (m, 2H, ArH), 4.85 (s, 2H, ArC*H*$_2$N), 4.00 (d, *J* 7.2 Hz, 2H, CH_2), 3.78 (s, 3H, OMe), 3.01 (t, *J* 5.6 Hz, 2H, ArC*H*$_2$CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, some quaternary carbons not observed): δ_C 50.0 (Ar*C*H$_2$CH$_2$), 53.3 (CH_2), 55.4 (OMe), 113.1 (Ar*C*H), 113.4 (Ar*C*H), 119.3 (*imidazole*-Ar*C*H), 123.5 (Ar*C*), 127.4 (Ar*C*H), 129.9 (Ar*C*), 137.2 (*imidazole*-Ar*C*H), 159.0 (C-O), 178.2 (C=S). HRMS ESI$^+$ calcd for $C_{14}H_{15}N_3OS$ [M]$^+$ 273.0936, found 273.0940.

6-Methoxy-[3,4 dihydroisoquinolin-2(1*H*)-yl]-3'-methyl-1*H*-imidazole-3-ium iodide (20). To a solution of 19 (110 mg, 0.403 mmol) in anhydrous MeCN (24.0 mL) was added MeI (0.200 mL, 3.32 mmol) and the resulting mixture stirred at 24 °C for 12 h. The reaction mixture was concentrated under reduced pressure affording 20 as a brown foam (184 mg, 100%) and used in the next step without further purification

6-Methoxy-*N*-(4'-methylthiazol-2-yl)-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (21a). To a mixture of 2-amino-4-methylthiazole (66.0 mg, 0.578 mmol) and Cs_2CO_3 (334 mg, 1.73 mmol) in anhydrous MeCN (15 mL), that had been stirring at 24 °C for 30 min, was added the salt 20 (184 mg, 0.403 mmol) and the reaction mixture was stirred at this temperature for 12 h. After the usual work-up the residue was purified with column chromatography (50:50 EtOAc/Hexane) and the desired product 21a was obtained as an orange oil (103 mg, 80%), R_f 0.63 (40:60 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 12.42 (s, 1H, NH), 7.08 (d, *J* 7.3 Hz, 1H, ArH), 6.86–6.67 (m, 2H, ArH), 6.30 (s, 1H, *thiazole*-H), 5.05 (s, 2H, ArC*H*$_2$N), 4.18 (t, *J* 5.9 Hz, 2H, CH_2), 3.72 (s, 3H, OMe), 2.83 (t, *J* 5.9 Hz, 2H, ArC*H*$_2$CH$_2$), 2.16 (s, 3H, *thiazole*-Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 29.2 (*thiazole*-Me), 46.7 (Ar*C*H$_2$CH$_2$), 50.0 (CH_2), 55.5 (Ar*C*H$_2$N), 55.6 (OMe), 112.7 (Ar*C*H), 113.1 (Ar*C*H), 114.1 (Ar*C*H), 125.0 (Ar*C*), 127.6 (Ar*C*H), 132.8 (Ar*C*H), 136.4 (Ar*C*), 157.7 (*thiazole*-Ar*C*NH), 158.7 (C-O), 182.3 (C=S). HRMS ESI$^+$ calcd for $C_{15}H_{18}N_3OS_2$ [M+H]$^+$ 320.0847, found 320.0887.

***N*-(3'-Chlorophenyl)-6-methoxy-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide** (**21d**)**.** By an analogous protocol employed for **21a, 21d** was obtained as a white solid (14.0 mg, 8%) from **20**, mp 184–186 °C, R_f 0.20 (10:90 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.30–7.21 (m, 3H, ArH), 7.19–7.00 (m, 3H, NH and ArH), 6.86–6.68 (m, 2H, ArH), 4.86 (s, 2H, ArC*H*$_2$N), 4.02 (t, *J* 5.7 Hz, 2H, ArC*H*$_2$N), 3.80 (s, 3H, OMe), 2.96 (t, *J* 5.7 Hz, 2H, ArC*H*$_2$CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, some quaternary carbons not observed): δ_C 29.3 (Ar*C*H$_2$CH$_2$), 47.5 (CH_2), 50.7 (Ar*C*H$_2$N), 55.7 (OMe), 113.1 (Ar*C*H), 113.4 (Ar*C*H), 122.4 (Ar*C*), 124.3 (Ar*C*H), 125.8 (Ar*C*H), 127.8 (Ar*C*H), 130.1 (Ar*C*Cl), 134.9 (Ar*C*H), 136.4 (Ar*C*H), 141.5 (Ar*C*NH), 159.0 (C-O), 183.5 (C=S). HRMS ESI$^+$ calcd for $C_{17}H_{18}N_2OSCl$ [M+H]$^+$ 333.0828 (^{35}Cl), found, 333.0821.

[6-Methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl](morpholino)methanethione (**21h**)**.** By an analogous protocol used for **21a** above, **21h** was obtained as a yellow oil (77 mg, 65%) from **20**, R_f 0.25 (30:70 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.01 (d, *J* 8.4 Hz, 1H, ArH), 6.84–6.63 (m, 2H, ArH), 4.66 (s, 2H, ArC*H*$_2$N), 3.91–3.82 (m, 4H, *morpholine*-CH_2N), 3.81–3.64 (m, 7H, overlapping signals- *morpholine*-OCH_2 and OMe), 3.62–3.50 (m, 2H, NCH_2), 2.98 (t, *J* 5.8 Hz, 2H, Ar*CH*$_2$CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, some quaternary carbons not observed): δ_C 28.6 (Ar*C*H$_2$CH$_2$), 49.1 (CH_2), 51.9 (*morpholine*-NCH_2), 52.8 (Ar*C*H$_2$N), 55.1 (OMe), 66.3 (*morpholine*-*C*H$_2$O), 112.6 (Ar*C*H), 113.2 (Ar*C*H), 124.9 (Ar*C*H), 127.0 (Ar*C*), 135.6 (Ar*C*), 158.3 (C-O), 193.69 (C=S). HRMS ESI$^+$ calcd for $C_{15}H_{21}N_2O_2S$ [M+H]$^+$ 293.1279, found, 293.1324.

6-Hydroxy-*N*-(4'-methylthiazol-2-yl)-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (**22a**) was obtained on demethylation via Method A as an orange oil (74 mg, 36%) from **20**, R_f 0.37 (40:60 EtOAc/Hexane). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 6.19–6.15 (m, 1H, ArH), 5.83–5.79 (m, 2H, ArH), 5.60 (s, 1H, *thiazole*-H), 3.79 (s, 2H,

ArC*H*$_2$N), 2.96–2.90 (m, 2H, NCH$_2$), 2.02–1.98 (m, 2H, ArC*H*$_2$CH$_2$), 1.43 (s, 3H, *thiazole*-Me). ^{13}C NMR (75 MHz, DMSO-d_6, some quaternary carbons not observed): δ_C 6.65 (*thiazole*-Me), 20.6 (Ar*C*H$_2$CH$_2$), 33.5 (CH$_2$), 37.0 (Ar*C*H$_2$N), 97.4 (*thiazole*-*C*H), 101.6 (Ar*C*H), 105.4 (Ar*C*H), 106.4 (Ar*C*), 115.9 (Ar*C*H), 118.8 (Ar*C*), 127.8 (*thiazole*-CN), 147.6 (C-O), 158.4 (*thiazole*-C), 170.1 (C=S). HRMS ESI$^+$ calcd for $C_{14}H_{16}N_3OS_2$ [M+H]$^+$, 306.0735, found, 306.0722.

[6-Hydroxy-3,4-dihydroisoquinolin-2(1*H*)-yl](morpholino)methanethione (**22h**) was obtained via demethylation Method B as a brown oil (34.0 mg, 20%) from **20**, R_f 0.32 (30:70 EtOAc/Hexane). ^{1}H NMR (300 MHz, CDCl$_3$): δ_H 6.94 (d, *J* 8.2 Hz, 1H, ArH), 6.76–6.53 (m, 2H, ArH), 4.64 (s, 2H, ArC*H*$_2$N), 3.90–3.71 (m, 4H, *morpholine*-2 × OCH$_2$), 3.64–3.44 (m, 6H, *morpholine*-2 × NCH$_2$ and NCH$_2$), 2.94 (t, *J* 5.8 Hz, 2H, ArC*H*$_2$CH$_2$), 1.21 (brs, 1H, OH). ^{13}C NMR (75 MHz, CDCl$_3$): δ_C 28.9 (Ar*C*H$_2$CH$_2$), 49.5 (CH$_2$), 52.3 (Ar*C*H$_2$N), 53.3 (*morpholine*-2 × CH$_2$O), 66.8 (*morpholine*-2 × NCH$_2$), 114.2 (Ar*C*H), 115.3 (Ar*C*H), 125.2 (Ar*C*), 127.6 (Ar*C*H), 136.2 (Ar*C*), 155.0 (C-O), 194.0 (C=S). HRMS ESI$^+$ calcd for $C_{14}H_{19}N_2O_2S$ [M+H]$^+$, 279.1167, found, 279.1166.

6-Hydroxy-*N*-(4'-hydroxyphenyl)-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (22j). A mixture of 6-hydroxy-THIQ hydrobromide 14 (191 mg, 0.782 mmol) and isothiocyanate 24j (142 mg, 0.939 mmol) containing Et$_3$N (0.330 mL, 0.26 mmol) in anhydrous MeCN (10 mL) was stirred and heated under reflux for 12 h. Saturated brine solution (5.0 mL) was added to the cooled solution which was extracted with EtOAc (20 mL x 2). The residue was purified using column chromatography (50:50 EtOAc/Hexane to afford 22j as a white solid (97 mg, 41%), mp 220–222 °C, R_f 0.43 (50:50 EtOAc/Hexane). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 9.30 and 9.32 (each s, each 1H, 2xOH), 9.04 (s, 1H, NH), 7.06–6.94 (m, 3H, ArH), 6.72–6.58 (m, 4H, ArH), 4.88 (s, 2H, ArC*H*$_2$N), 3.98 (t, *J* 6.0 Hz, 2H, CH$_2$), 2.85 (t, *J* 6.0 Hz, 2H, ArC*H*$_2$CH$_2$). ^{13}C NMR (75 MHz, DMSO-d_6,overlapping signals): δ_C 28.7 (Ar*C*H$_2$CH$_2$), 46.1 (CH$_2$), 49.6 (Ar*C*H$_2$N), 113.8 (Ar*C*H), 114.8 (Ar*C*H), 124.3 (Ar*C*NH), 127.4 (Ar*C*), 128.2 (Ar*C*H), 132.6 (Ar*C*H), 136.6 (Ar*C*), 155.0 (C-O), 156.3 (C-O), 181.3 (C=S). HRMS ESI$^+$ calcd for $C_{16}H_{17}N_2O_2S$ [M+H]$^+$ 301.1011, found, 301.1017.

6-Hydroxy-*N*-(3'-hydroxyphenyl)-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (**22k**)**.** By a similar protocol to the above for **22j**, **22k** was obtained from **24k** as a white solid (93 mg, 39%), mp 174–176 °C, R_f 0.68 (50:50 EtOAc/Hexane). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 9.31 (bs, 2H, 2xOH), 8.32 (s, 1H, NH), 7.44–7.29 (m, 2H, ArH), 7.16–7.02 (m, 3H, ArH), 6.66–6.61 (m, 2H, ArH), 4.68 (s, 2H, ArC*H*$_2$N), 3.83 (t, *J* 6.0 Hz, 2H, CH$_2$), 2.88 (t, *J* 6.0 Hz, 2H, ArC*H*$_2$CH$_2$). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 28.0 (Ar*C*H$_2$CH$_2$), 43.1 (CH$_2$), 46.6 (Ar*C*N), 109.2 (Ar*C*H), 114.0 (Ar*C*H), 115.1 (Ar*C*H), 116.0 (Ar*C*H), 120.7 (Ar*C*H), 123.0 (Ar*C*H), 124.3 (Ar*C*), 127.6 (Ar*C*H), 135.4 (Ar*C*), 143.4 (Ar*C*NH), 148.7 (C-O), 156.2 (C-O), 182.1 (C=S). HRMS ESI$^+$ calcd for $C_{16}H_{17}N_2O_2S$ [M+H]$^+$ 301.1011, found, 301.1023.

***N*-(3'-Chlorophenyl)-6-methoxy-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide** (**21d**)**.** By a similar protocol to the above for **22j**, 6-methoxyTHIQ hydrobromide **14** and isocyanate **24d** afforded the desired **21d** as a white solid (104 mg, 40%), mp 184–186 °C, R_f 0.20 (10:90 EtOAc/Hexane). ^{1}H NMR (300 MHz, CDCl$_3$): δ_H 7.30–7.21 (m, 3H, ArH), 7.19–7.00 (m, 3H, NH and ArH), 6.86–6.68 (m, 2H, ArH), 4.86 (s, 2H, ArC*H*$_2$N), 4.02 (t, *J* 5.7 Hz, 2H, ArC*H*$_2$N), 3.80 (s, 3H, OMe), 2.96 (t, *J* 5.7 Hz, 2H, Ar*CH*$_2$CH$_2$). ^{13}C NMR (75 MHz, CDCl$_3$, overlapping of signals): δ_C 29.3 (Ar*C*H$_2$CH$_2$), 47.5 (CH$_2$), 50.8 (Ar*C*H$_2$N), 55.7 (OMe), 113.1 (Ar*C*H), 113.4 (Ar*C*H), 122.4 (Ar*C*), 124.3 (Ar*C*H), 125.8 (Ar*C*H), 127.8 (Ar*C*H), 130.1 (Ar*C*Cl), 134.9 (Ar*C*H), 136.4 (Ar*C*H), 141.5 (Ar*C*NH), 159.0 (C-O), 183.5 (C=S). HRMS ESI$^+$ calcd for $C_{17}H_{18}ClN_2OS$ [M+H]$^+$, 333.0828 (^{35}Cl), found, 333.0821.

***N*-(3'-Fluorophenyl)-6-methoxy-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide** (**21e**)**.** By a similar protocol to the above for **22j**, and employing isocyanate **24e**, the desired thioanilide was obtained as a white solid (67 mg, 56%), mp 184–186 °C, R_f 0.53 (50:50 EtOAc/Hexane). ^{1}H NMR (300 MHz, CDCl$_3$): δ_H 7.31–7.28 (m, 2H, ArH), 7.14–6.75 (m, 6H, ArH and NH), 4.87 (s, 2H, ArC*H*$_2$N), 4.03 (t, *J* 5.9 Hz, 2H, CH$_2$), 3.82 (s, 3H, OMe), 2.98 (t, *J* 5.9

Hz, 2H, ArC*H*$_2$CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, overlapping signals): δ_C 29.3 (Ar*C*H$_2$CH$_2$), 47.5 (CH_2), 50.9 (Ar*C*H$_2$N), 55.7 (OMe), 111.3 (d, *J* 24.0 Hz, Ar*C*H-F), 112.4 (d, *J* 17.3 Hz, Ar*C*H-F), 113.2 (d, *J* 28.5 Hz, Ar*C*H-F), 119.3 (Ar*C*H), 127.7 (Ar*C*), 130.5 (Ar*C*H), 136.4 (Ar*C*), 157.3 (C-O), 182.8 (C=S). HRMS ESI$^+$ calcd for $C_{17}H_{18}FN_2OS$ $[M+H]^+$, 317.3949, found, 317.3942 .

***N*-(4'-Chlorophenyl)-6-methoxy-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide** (**21f**)**.** By a similar protocol to the above for **22j** and employing isocyanate **24f** the desired **21f** was obtained as a white solid (206 mg, 79%), mp 170–171 °C, R_f 0.33 (30:70 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.32–7.17 (m, 2H, ArH), 7.07–7.04 (m, 4H, NH and ArH), 6.80–6.75 (m, 3H, ArH), 4.88 (s, 2H, ArC*H*$_2$N), 4.02 (t, *J* 5.5 Hz, 2H, CH_2), 3.81 (s, 3H, OMe), 2.96 (t, *J* 5.5 Hz, 2H, ArC*H*$_2$CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 29.4 (Ar*C*H$_2$CH$_2$), 47.3 (CH_2), 50.6 (OMe), 55.7 (Ar*C*H$_2$N), 113.0 (Ar*C*H), 113.4 (Ar*C*H), 124.7 (Ar*C*), 126.1 (Ar*C*H), 127.8 (Ar*C*H), 129.4 (Ar*C*H), 131.1 (Ar*C*Cl), 137.95 (Ar*C*), 138.8 (Ar*C*NH), 159.1 (C-O), 182.7 (C=S). HRMS ESI$^+$ calcd for $C_{17}H_{18}ClN_2OS$ $[M+H]^+$, 333.0721 (^{35}Cl), found 333.0825.

***N*-(4'-Fluorophenyl)-6-methoxy-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide** (**21g**)**.** By a similar protocol to the above for **22j** and employing isocyanate **24g** the desired **21g** was obtained as a white solid (74 mg, 62%), mp 156–158 °C, R_f 0.44 (30:70 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.27–7.20 (m, 2H, ArH and NH), 7.08–7.01 (m, 4H, ArH), 6.81–6.75 (m, 2H, ArH), 4.89 (s, 2H, ArC*H*$_2$N), 4.03 (t, *J* 5.9 Hz, 2H, CH_2), 3.81 (s, 3H, OMe), 2.97 (t, *J* 5.9 Hz, 2H, ArC*H*$_2$CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, overlapping signals): δ_C 29.2 (Ar*C*H$_2$CH$_2$), 46.8 (CH_2), 50.1 (OMe), 55.4 (Ar*C*H$_2$N), 112.9 (d, *J* 28.5 Hz, Ar*C*H-F), 115.8 (d, *J* 22.5 Hz, Ar*C*H-F), 124.7 (Ar*C*H), 127.1 (Ar*C*H), 127.2 (Ar*C*), 135.5 (Ar*C*NH), 136.3 (Ar*C*H), 158.9 (C-O), 182.5 (C=S). HRMS ESI$^+$ calcd for $C_{17}H_{18}FN_2OS$ $[M+H]^+$, 317.3949, found, 317.3942.

2-[(1*H*-Imidazol-1-yl)sulfonyl]-6-methoxy-1,2,3,4-tetrahydroisoquinoline (26)

To a cooled (0˚C) mixture of **25** [41] (400 mg, 1.10 mmol) in anhydrous CH_2Cl_2 (50 mL) containing K_2CO_3 (276 mg, 2.00 mmol) was added 6-MeO-THIQ.HBr **14** (244 mg, 1.00 mmol) with stirring which was continued for 12 h during which time the temperature was allowed to reach 24 °C. The reaction mixture was concentrated under reduced pressure and the residue was purified by a short column chromatography (50:50 EtOAc/Hexane). Sulfone **26** was obtained as a transparent oil (206 mg, 70%) and utilized directly in the next reactions without further purification, R_f 0.58 (100% EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.93 (d, *J* 3.0 Hz, 1H, *imidazole*-H), 7.31 (d, *J* 3.0 Hz, 1H, *imidazole*-H), 7.15 (d, *J* 3.0 Hz, 1H, *imidazole*-H), 6.96 (d, *J* 8.5 Hz, 1H, ArH), 6.75 (dd, *J* 8.5, 2.5 Hz, 1H, ArH), 6.61 (d, *J* 2.5 Hz, 1H, ArH), 4.35 (s, 2H, ArC*H*$_2$N), 3.76 (s, 3H, OMe), 3.51 (t, *J* 6.0 Hz, 2H, CH_2), 2.88 (t, *J* 6.0 Hz, 2H, ArC*H*$_2$CH$_2$). HRMS ESI$^+$ calcd for $C_{13}H_{16}N_3O_3S$ $[M+H]^+$, 294.0914, found, 294.0908

1-[6-Methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl]sulfonyl-3'-methyl-1*H*-imidazol-3-ium trifluoromethane sulfonate (**27**)

To a cooled (0˚C) solution of **26** (735 mg, 2.50 mmol) in anhydrous CH_2Cl_2 (20 mL) was added methyl triflate (0.310 mL, 2.77 mmol) and stirring was continued for 4 h at 0 °C. The reaction mixture was concentrated under reduced pressure to afford **27** (1143 mg, 100%) as a beige semi-solid which was used without further purification. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 9.60 (m, 1H, *imidazole*-H), 8.04 (d, *J* 2.0 Hz, 1H, *imidazole*-H), 7.76–7.67 (m, 1H, *imidazole*-H), 7.11 (d, *J* 8.5 Hz, 1H, ArH), 6.82 (dd, *J* 8.5, 2.6 Hz, 1H, ArH), 6.75 (d, *J* 2.6 Hz, 1H, ArH), 4.64 (s, 2H, ArC*H*$_2$N), 3.98 (s, 3H, OMe), 3.86–3.74 (m, 5H, overlapping signals-CH_2 and NMe), 2.99 (t, *J* 6.2 Hz, 2H, ArC*H*$_2$CH$_2$). ^{13}C NMR (75 MHz, DMSO-d_6, overlapping signals): δ_C 29.0 (*imidazole*-Me), 37.4 (Ar*C*H$_2$CH$_2$), 46.4 (Ar*C*H$_2$N), 55.9 (OMe), 114.3 (Ar*C*H), 114.6 (Ar*C*H), 122.0 (Ar*C*), 123.3 (Ar*C*H), 126.5 (Ar*C*), 128.6 (*imidazole*-*C*H), 135.3 (*imidazole*-*C*H), 139.2 (*imidazole*-*C*H), 160.6 (C-O).

General procedure for the coupling of 27 with heteroaryl amines.[41] To a solution of the sulfamoyl imidazolium salt 27 (280 mg, 0.613 mmol) in anhydrous MeCN (25 mL) were added the various amine nucleophiles (c-h) (0.740 mmol) and the resultant mixture stirred under the conditions illustrated in Scheme 6.

After reactions were complete (tlc), solvent was removed and the residue purified by column chromatography (50:50 EtOAc/Hexane) to afford the following amino sulfones:

6-Methoxy-*N*-(4′-methoxyphenyl)-3,4-dihydroisoquinoline-2(1*H*)-sulfonamide (**28c**) was obtained as a brown oil (186 mg, 87%) by the general coupling procedure. R_f 0.41 (50:50 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.13 (dd, *J* 8.9, 0.9 Hz, 2H, ArH), 6.99–6.86 (m, 2H, ArH), 6.83–6.67 (m, 3H, ArH), 6.60 (s, 1H, NH), 4.39 (s, 2H, ArC*H*$_2$N), 3.86 (s, 3H, OMe), 3.65 (s, 3H, OMe), 3.49 (t, *J* 5.6 Hz, 2H, CH_2), 2.76 (t, *J* 5.6 Hz, 2H, ArC*H*$_2$$CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 29.3 (Ar*C*H_2CH_2), 44.2 (CH_2), 47.3 (Ar*C*H_2N), 55.5 (2xOMe), 112.8 (Ar*C*H), 113.6 (Ar*C*H), 114.6 (Ar*C*H), 124.2 (Ar*C*H), 124.6 (Ar*C*H), 127.4 (Ar*C*), 129.6 (Ar*C*NH), 134.7 (Ar*C*), 157.6 (C-O), 158.4 (C-O). HRMS (ESI$^+$) calcd for $C_{17}H_{21}N_2O_4S$ [M+H]$^+$, 349.1177, found, 349.1207.

***N*-(3′-Chlorophenyl)-6-methoxy-3,4-dihydroisoquinoline-2(1*H*)-sulfonamide** (**28d**) was obtained as an orange oil (179 mg, 83%) by the general coupling procedure. R_f 0.22 (15:85 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.37–6.86 (m, 4H, ArH), 6.84–6.48 (m, 3H, ArH), 4.43 (d, *J* 3.9 Hz, 2H, ArC*H*$_2$N), 3.68 (brm, 5H, overlapping signals-OMe and CH_2), 3.00–2.67 (m, 2H, ArC*H*$_2$$CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$, some quaternary carbons not observed): δ_C 29.0 (Ar*C*H_2CH_2), 44.3 (CH_2), 47.3 (Ar*C*H_2N), 55.4 (OMe), 113.0 (Ar*C*H), 113.6 (Ar*C*H), 118.0 (Ar*C*H), 120.0 (Ar*C*H), 123.8 (Ar*C*H), 124.7 (Ar*C*), 127.4 (Ar*C*H), 130.4 (Ar*C*), 134.5 (Ar*C*Cl), 135.0 (Ar*C*NH), 138.5 (C-O). HRMS ESI$^+$ calcd for $C_{16}H_{17}ClN_2O_3S$ [M]$^+$, 351.0570 (^{35}Cl), found, 351.0551.

***N*-(3′-Fluorophenyl)-6-methoxy-3,4-dihydroisoquinoline-2(1*H*)-sulfonamide** (**28e**) was obtained as a colourless oil (95 mg, 46%) by the general coupling procedure. R_f 0.37 (30:70 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.20 (m, 2H, ArH), 6.99–6.67 (m, 5H, NH and ArH), 6.60 (d, *J* 2.3 Hz, 1H, ArH), 4.42 (s, 2H, ArC*H*$_2$N), 3.80–3.51 (m, 5H, overlapping signals-OMe and CH_2), 2.81 (t, *J* 5.9 Hz, 2H, ArC*H*$_2$$CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$, no C-F coupling was observable): δ_C 29.0 (Ar*C*H_2CH_2), 44.2 (CH_2), 47.3 (Ar*C*H_2N), 55.4 (OMe), 107.0 (Ar*C*H), 107.4 (Ar*C*H), 111.2 (Ar*C*H), 111.4 (Ar*C*H), 113.0 (Ar*C*H), 113.6 (Ar*C*H), 115.3 (Ar*C*H), 123.8 (Ar*C*H), 127.4 (Ar*C*), 130.6 (Ar*C*H), 134.5 (Ar*C*), 138.9 (Ar*C*NH), 158.5 (C-O), 164.9 (Ar*C*F). HRMS ESI$^+$ calcd for $C_{16}H_{18}FN_2O_3S$ [M+H]$^+$, 337.1022 (^{18}F), found, 337.1024.

***N*-(4′-Chlorophenyl)-6-methoxy-3,4-dihydroisoquinoline-2(1*H*)-sulfonamide** (**28f**) was obtained as a translucent brown oil (118 mg, 54%) by the general coupling procedure. R_f 0.22 (15:85 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.22–7.19 (m, 3H, ArH), 7.10–7.06 (m, 2H, ArH), 6.94–6.91 (m, 1H, ArH), 6.73–6.70 (m, 1H, ArH), 6.60 (brs, 1H, NH), 4.48 (s, 2H, ArC*H*$_2$N), 3.84 (s, 3H, OMe), 3.61 (t, *J* 5.9 Hz, 2H, CH_2), 2.86 (t, *J* 5.9 Hz, 2H, ArC*H*$_2$$CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 29.2 (Ar*C*H_2CH_2), 44.4 (CH_2), 47.5 (Ar*C*H_2N), 55.6 (OMe), 113.1 (Ar*C*H), 113.8 (Ar*C*H), 121.9 (Ar*C*H), 124.0 (Ar*C*), 127.6 (Ar*C*H), 129.6 (Ar*C*), 130.3 (Ar*C*H), 134.7 (Ar*C*NH), 136.0 (Ar*C*Cl), 158.7 (C-O). HRMS ESI$^+$, calcd for $C_{16}H_{18}ClN_2O_3S$ [M+H]$^+$, 353.0727 (^{35}Cl), found, 353.0723.

***N*-(4′-Fluorophenyl)-6-methoxy-3,4-dihydroisoquinoline-2(1*H*)-sulfonamide** (**28g**) was obtained as a colourless oil (195 mg, 94%) by the general coupling procedure. R_f 0.37 (30:70 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.01–6.95 (m, 2H, ArH), 6.78 – 6.77 (m, 3H, ArH), 6.74–6.63 (m, 1H, ArH), 6.61 (m, 1H, ArH), 6.31 (brs, 1H, NH), 4.40 (s, 2H, ArC*H*$_2$N), 3.77 (s, 3H, OMe), 3.51 (t, *J* 5.9 Hz, 2H, CH_2), 2.78 (t, *J* 5.9 Hz, 2H, ArC*H*$_2$$CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 29.7 (Ar*C*H_2CH_2), 44.5 (CH_2), 47.6 (Ar CH_2), 55.6 (OMe), 113.2 (Ar*C*H), 115.0 (Ar*C*H), 117.3 (2xAr*C*H), 125.7 (Ar*C*), 128.9 (Ar*C*H), 131.8 (2xAr*C*H), 132.3 (Ar*C*), 135.0 (Ar*C*),156.4 (ArC-O) and 162.9 (Ar*C*-F). HRMS ESI$^+$ calcd for $C_{16}H_{18}FN_2O_3S$ [M+H]$^+$, 337.1022, found, 337.1016.

4-{[6-Methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl]sulfonyl}morpholine (**28h**) was obtained as a white amorphous solid (134 mg, 70%) as per the general coupling procedure, mp 119–121 °C, R_f 0.44 (40:60 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 6.99 (d, *J* 8.4 Hz, 1H, ArH), 6.82–6.71 (m, 1H, ArH), 6.67 (sharp s, 1H, ArH), 4.39 (s, 2H, ArC*H*$_2$N), 3.85–3.64 (m, 7H, overlapping signals-OMe and *morpholine*-2xOCH_2), 3.54 (t, *J* 5.9 Hz, 2H, CH_2), 3.28–3.15 (m, 4H, *morpholine*-2xNCH_2), 2.91 (t, *J* 5.9 Hz, 2H, ArC*H*$_2$$CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 29.3 (Ar*C*H_2CH_2), 44.1 (*morpholine*-2xNCH_2), 46.6 (CH_2), 47.6 (Ar*C*H_2N), 55.4 (OMe), 66.5

(*morpholine*-2xOCH$_2$), 113.0 (Ar*C*H), 113.7 (Ar*C*H), 124.4 (Ar*C*H), 127.4 (Ar*C*), 134.6 (Ar*C*), 158.5 (C-O). HRMS ESI$^+$ calcd for $C_{14}H_{21}N_2O_4S$ [M+H]$^+$, 313.1222, found, 313.1218.

6-Hydroxy-*N*-(4'-hydroxyphenyl)-3,4-dihydroisoquinoline-2(1*H*)-sulfonamide (**29c**) was obtained via demethylation Method B from **28c**, as a thick white oil (62 mg, 32%), R$_f$ 0.24 (50:50 EtOAc/Hexane). ^{1}H NMR (300 MHz, CD$_3$OD): δ_H 7.09–6.97 (m, 2H, ArH and NH), 6.85 (d, *J* 8.3 Hz, 1H, ArH), 6.77–6.54 (m, 3H, ArH), 6.50 (d, *J* 6.5 Hz, 2H, ArH), 4.59 (brs, 1H, OH), 4.26 (s, 2H, ArC*H*$_2$N), 3.38 (t, *J* 5.9 Hz, 2H, NCH$_2$), 2.65 (t, *J* 5.9 Hz, 2H, ArC*H*$_2$CH$_2$). ^{13}C NMR (75 MHz, CD$_3$OD): δ_C 20.7 (Ar*C*H$_2$CH$_2$), 36.1 (NCH$_2$), 39.1 (Ar*C*H$_2$N), 105.6 (Ar*C*H), 106.7 (Ar*C*H), 107.3 (Ar*C*), 115.2 (Ar*C*H), 115.3 (Ar*C*H), 116.2 (Ar*C*H), 119.0 (Ar*C*H), 121.3 (Ar*C*H), 121.5 (Ar*C*), 126.8 (Ar*C*NH), 146.8 (C-O), 147.7 (C-O). HRMS ESI$^+$ calcd for $C_{15}H_{16}N_2O_4S$ [M+H]$^+$, 321.0864, found, 321.0912.

***N*-(3'-Chlorophenyl)-6-hydroxy-3,4-dihydroisoquinoline-2(1*H*)-sulfonamide** (**29d**) was obtained via demethylation Method A from **28c**, as a colourless oil (77 mg, 34%), R$_f$ 0.41 (50:50 EtOAc/Hexane). ^{1}H NMR (300 MHz, CDCl$_3$): δ_H 7.28–7.24 (m, 1H, NH), 7.18 (d, *J* 8.0 Hz, 1H, ArH), 7.13–6.96 (m, 2H, ArH), 6.90 (d, *J* 8.3 Hz, 1H, ArH), 6.71–6.51 (m, 2H, ArH), 4.71 (brs, 1H, OH), 4.41 (s, 2H, ArC*H*$_2$N), 3.55 (t, *J* 6.0 Hz, 2H, NCH$_2$), 2.77 (t, *J* 6.0 Hz, 2H, ArC*H*$_2$CH$_2$). ^{13}C NMR (75 MHz, CDCl$_3$): δ_C 29.0 (Ar*C*H$_2$CH$_2$), 44.4 (CH$_2$), 47.5 (Ar*C*H$_2$N), 114.3 (Ar*C*H), 115.5 (Ar*C*H), 118.4 (Ar*C*H), 120.4 (Ar*C*H), 121.3 (Ar*C*), 124.1 (Ar*C*H), 125.0 (Ar*C*H), 127.8 (Ar*C*H), 130.6 (Ar*C*Cl), 135.0 (Ar*C*), 135.3 (Ar*C*NH), 154.6 (C-O). HRMS ESI$^+$ calcd for $C_{15}H_{16}ClN_2O_3S$ [M+H]$^+$, 339.0571 (^{35}Cl), found 339.0570.

***N*-(3'-Fluorophenyl)-6-hydroxy-3,4-dihydroisoquinoline-2(1*H*)-sulfonamide** (**29e**) was obtained via demethylation Method A from **28e**, as a brown oil (22 mg, 10%), R$_f$ 0.32 (50:50 EtOAc/Hexane). ^{1}H NMR (300 MHz, CDCl$_3$): δ_H 7.38–7.08 (m, 2H, ArH and NH), 7.01–6.44 (m, 6H, ArH), 4.87 (s, 1H, OH), 4.41 (d, *J* 6.0 Hz, 2H, ArC*H*$_2$N), 3.54 (t, *J* 6.0 Hz, 2H, NCH$_2$), 2.77 (t, *J* 6.0 Hz, 2H, ArC*H*$_2$CH$_2$). ^{13}C NMR (75 MHz, CDCl$_3$): δ_C 29.0 (Ar*C*H$_2$CH$_2$), 44.4 (CH$_2$), 47.6 (Ar*C*H$_2$N), 107.6 (d, *J* 25.5 Hz, Ar*C*H-F), 111.7 (d, *J* 30.75 Hz, Ar*C*H-F), 114.3 (Ar*C*H), 115.5 (Ar*C*H), 115.6 (Ar*C*H), 115.6 (Ar*C*), 124.1 (Ar*C*H), 127.8 (Ar*C*H), 130.8 (Ar*C*H), 130.9 (Ar*C*), 135.0 (Ar*C*H), 148.6 (Ar*C*NH), 154.6 (C-O). HRMS ESI$^+$ calcd for $C_{15}H_{16}FN_2O_3S$ [M+H]$^+$, 323.0866, found, 323.0854.

***N*-(4'-Chlorophenyl)-6-hydroxy-3,4-dihydroisoquinoline-2(1*H*)-sulfonamide** (**29f**) was obtained via demethylation Method A from **28f,** as a colourless oil (94 mg, 41%), R$_f$ 0.41 (50:50 EtOAc/Hexane). ^{1}H NMR (300 MHz, CDCl$_3$): δ_H 7.27–7.21 (m, 3H, ArH and NH), 7.09–7.06 (m, 2H, ArH), 6.90–6.56 (m, 3H, ArH), 4.39 (s, 2H, ArC*H*$_2$N), 3.71–3.35 (m, 2H, NCH$_2$), 2.76 (m, 2H, ArC*H*$_2$CH$_2$). ^{13}C NMR (75 MHz, CDCl$_3$, overlapping signals): δ_C 29.0 (Ar*C*H$_2$CH$_2$), 44.4 (CH$_2$), 47.5 (Ar*C*H$_2$N), 114.3 (Ar*C*H), 115.4 (Ar*C*H), 122.2 (Ar*C*), 127.8 (Ar*C*H), 129.7 (Ar*C*H), 130.4 (Ar*C*), 134.8 (Ar*C*Cl), 135.8 (Ar*C*NH), 154.6 (C-O). HRMS ESI$^+$ calcd for $C_{15}H_{16}ClN_2O_3S$ [M+H]$^+$, 339.0571 (^{35}Cl), found 339.0556.

***N*-(4'-Fluorophenyl)-6-hydroxy-3,4-dihydroisoquinoline-2(1*H*)-sulfonamide** (**29g**) was obtained via demethylation Method A from **28g**, as a brown oil (71.0 mg, 33%), R$_f$ 0.32 (50:50 EtOAc/Hexane). ^{1}H NMR (300 MHz, CDCl$_3$): δ_H 7.12–7.06 (m, 2H, ArH), 7.96–6.83 (m, 6H, ArH and NH), 4.36 (d, *J* 10.3 Hz, 2H, ArC*H*$_2$N), 3.51–3.47 (m, 2H, NCH$_2$), 2.71 (t, *J* 6.0 Hz, 2H, ArC*H*$_2$CH$_2$). ^{13}C NMR (75 MHz, CDCl$_3$): δ_C 29.8 (Ar*C*H$_2$CH$_2$), 44.0 (CH$_2$), 47.3 (Ar*C*H$_2$N), 112.9 (Ar*C*H), 114.2 (Ar*C*H), 116.0 (Ar*C*), 116.3 (Ar*C*H), 123.5 (d, *J* 8.2 Hz, Ar*C*H-F), 125.7 (Ar*C*), 126.6 (Ar*C*H), 133.5 (Ar*C*NH), 151.3 (Ar*C*-F), 161.8 (C-O). HRMS ESI$^+$ calcd for $C_{15}H_{16}FN_2O_3S$ [M+H]$^+$, 323.0866, found, 323.0858.

2-(Morpholinosulfonyl)-1,2,3,4-tetrahydroisoquinolin-6-ol (**29h**) was obtained via demethylation Method B from **28h** as a white solid (45.0 mg, 25%), mp 168–170 ^{o}C, R$_f$ 0.53 (100% EtOAc). ^{1}H NMR (300 MHz,CD$_3$OD): δ_C 6.94 (d, *J* 8.2 Hz, 1H, ArH), 6.72–6.51 (m, 2H, ArH), 4.37 (s, 2H, ArC*H*$_2$N), 3.69 (sharp m, 4H, *morpholine*-2xCH$_2$O), 3.54 (t, *J* 5.5 Hz, 2H, NCH$_2$), 3.22–3.18 (m, 4H, *morpholine*-2xNCH$_2$), 2.86 (t, *J* 5.5 Hz, 2H, ArC*H*$_2$CH$_2$). ^{13}C NMR (75 MHz, CD$_3$OD): δ_C 29.9 (Ar*C*H$_2$CH$_2$), 45.3 (*morpholine*-2xNCH$_2$), 47.7 (CH$_2$), 48.6 (Ar*C*H$_2$N), 67.4 (*morpholine*-2xCH$_2$O), 114.9 (Ar*C*H), 116.0 (Ar*C*H), 124.6 (Ar*C*), 128.3 (Ar*C*H), 135.9 (Ar*C*), 157.1 (C-O). HRMS ESI$^+$ calcd for $C_{13}H_{19}N_2O_4S$ [M+H]$^+$, 299.1066, found, 299.1055.

General procedure for the lactamization of lactone (32)

A mixture of 6-methoxyisochroman-3-one **32**[42] (300 mg, 1.68 mmol), amine analogues (**a** – **g**) (2.52 mmol) and $AlCl_3$ (45.0 mg, 0.340 mmol) were combined under anhydrous conditions in a sealed tube and heated at 150 °C for 48 h. The reaction mixture was poured into aqueous 1 N HCl (5.0 mL) and extracted with EtOAc (20 mL x 2) to afford a brown residue which was purified with column chromatography (30:70 EtOAc/Hexane).

6-Methoxy-2-(4′-methylthiazol-2-yl)-1,2-dihydroisoquinolin-3(4*H*)-one (**33a**) was obtained from **32** as a pale yellow residue (162 mg, 35%), R_f 0.76 (50:50 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.27–7.25 (m, 1H, ArH), 6.84–6.75 (m, 2H, ArH), 6.58 (s, 1H, *thiazole*-H), 5.29 (s, 2H, ArC*H*$_2$*N*), 3.83–3.80 (m, 5H, overlapping signals-OMe and CH_2), 2.33 (s, 3H, *thiazole*-Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 17.7 (*thiazole*-Me), 39.1 (Ar*C*H$_2$), 49.7 (Ar*C*H$_2$N), 55.7 (OMe), 110.0 (*thiazole*-*C*H), 112.5 (Ar*C*H), 113.3 (Ar*C*H), 123.7(Ar*C*H), 127.4 (Ar*C*), 132.8 (Ar*C*), 147.0 (*thiazole*-*C*Me), 158.7 (*thiazole*-Ar*C*N), 159.8 (C-O), 168.4 (C=O). HRMS ESI$^+$ calcd for $C_{14}H_{15}N_2O_2S$ $[M+H]^+$, 275.0854, found, 275.0855.

6-Methoxy-2-(4′-methoxyphenyl)-1,2-dihydroisoquinolin-3(4*H*)-one (**33c**) was obtained from **32** as a beige oily residue (191 mg, 40%), R_f 0.17 (50:50 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.26–7.19 (m, 2H, ArH), 7.09–7.07 (m, 1H, ArH), 6.93–6.90 (m, 2H, ArH), 6.81–6.75 (m, 2H, ArH), 4.75 (s, 2H, ArC*H*$_2$N), 3.81–3.73 (m, 8H, overlapping signals-2xOMe and ArCH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 39.2 (Ar*C*H$_2$), 54.3 (2xOMe), 55.8 (Ar*C*H$_2$N), 112.6 (Ar*C*H), 113.0 (Ar*C*H), 114.5 (Ar*C*H), 124.5 (Ar*C*H), 126.5 (Ar*C*H), 127.3 (Ar*C*H), 134.3 (Ar*C*), 135.6 (Ar*C*), 158.5 (Ar*C*N), 159.6 (2xC-O), 169.5 (C=O). HRMS ESI$^+$ calcd for $C_{17}H_{18}NO_3$ $[M+H]^+$, 284.1287, found, 284.1292.

2-(3′-Chlorophenyl)-6-methoxy-1,2-dihydroisoquinolin-3(4*H*)-one (**33d**) was obtained from **32** as a white solid (277 mg, 57%), mp 87–88 °C, R_f 0.36 (40:60 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.37–7.10 (m, 5H, ArH), 6.82–6.78 (m, 2H, ArH), 4.80 (d, *J* 6.0 Hz, 2H, ArC*H*$_2$N), 3.85–3.75 (m, 5H, overlapping signals-OMe and ArC*H*$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, overlapping signals): δ_C 39.1 (ArCH_2), 53.4 (OMe), 55.5 (Ar*C*H$_2$N), 112.4 (Ar*C*H), 112.7 (Ar*C*H), 123.8 (Ar*C*H), 125.8 (Ar*C*H), 126.3 (Ar*C*H), 126.8 (Ar*C*), 130.0 (Ar*C*Cl), 132.7 (Ar*C*H), 134.8 (Ar*C*N), 158.4 (C-O), 160.3 (C=O). HRMS ESI$^+$ calcd for $C_{16}H_{15}ClNO_2$ $[M+H]^+$, 288.0791 (^{35}Cl), found, 288.0785.

2-(3′-Fluorophenyl)-6-methoxy-1,2-dihydroisoquinolin-3(4*H*)-one (**33e**) was obtained from **32** as a white solid (407 mg, 89%), mp 108–110 °C, R_f 0.41 (50:50 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.38–6.78 (m, 7H, ArH), 4.79 (s, 2H, ArC*H*$_2$N), 4.01–3.55 (m, 5H, overlapping signals-ArCH_2 and OMe). ^{13}C NMR (75 MHz, $CDCl_3$, overlapping signals): δ_C 39.3 (ArCH_2), 53.5 (OMe), 55.6 (Ar*C*H$_2$N), 112.7 (d, *J* 28.50 Hz, Ar*C*H-F), 113.7 (d, *J* 21.00 Hz, Ar*C*H-F), 121.0 (Ar*C*H), 123.9 (Ar*C*H), 126.3 (Ar*C*H), 130.2 (Ar*C*), 133.7 (Ar*C*H), 159.3 (C-O), 169.8 (Ar*C*F), 172.9 (C=O). HRMS ESI$^+$ calcd for $C_{16}H_{15}FNO_2$ $[M+H]^+$, 272.1087, found, 272.1075.

2-(4′-Chlorophenyl)-6-methoxy-1,2-dihydroisoquinolin-3(4*H*)-one (**33f**) was obtained from **32** as a yellow solid (179 mg, 37%), mp 123–125 °C, R_f 0.38 (40:60 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.39–7.28 (m, 4H, ArH), 7.12–7.09 (m, 1H, ArH), 6.82–6.78 (m, 2H, ArH), 4.76 (s, 2H, ArC*H*$_2$N), 3.92–3.63 (m, 5H, overlapping signals-ArCH_2 and OMe). ^{13}C NMR (75 MHz, $CDCl_3$, overlapping signals): δ_C 39.2 (Ar*C*H$_2$), 53.6 (Ar*C*H$_2$N), 55.6 (OMe), 112.5 (Ar*C*H), 112.9 (Ar*C*H), 124.0 (Ar*C*), 126.4 (Ar*C*H), 127.0 (Ar*C*H), 129.4 (Ar*C*H), 132.2 (Ar*C*H), 133.9 (Ar*C*H), 140.7 (Ar*C*Cl), 157.2 (Ar*C*N), 159.6 (C-O), 169.3 (C=O). HRMS ESI$^+$ calcd for $C_{16}H_{15}ClNO_2$ $[M+H]^+$, 288.0684 (^{35}Cl), found, 288.0782.

2-(4′-Fluorophenyl)-6-methoxy-1,2-dihydroisoquinolin-3(4*H*)-one (**33g**) was obtained from **32** as a brown oil (133 mg, 29%), R_f 0.38 (40:60 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.47–7.23 (m, 5H, ArH), 7.00–6.95 (m, 2H, ArH), 4.93 (s, 2H, ArC*H*$_2$N), 3.97 (m, 5H, overlapping signals-OMe and CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 39.2 (Ar*C*H$_2$CH$_2$), 54.1 (Ar*C*H$_2$N), 55.8 (OMe), 112.8 (d, *J* 30.00 Hz, Ar*C*H-F), 116.2 (Ar*C*), 116.5 (Ar*C*H), 124.3 (Ar*C*), 126.6 (Ar*C*H), 127.7 (Ar*C*H), 127.8 (Ar*C*H), 134.1 (Ar*C*N), 159.7 (Ar*C*F), 162.9 (C-O), 169.5 (C=O). HRMS ESI$^+$ calcd for $C_{16}H_{15}FNO_2$ $[M+H]^+$, 272.1087, found, 272.1090.

6-Hydroxy-2-(4′-methylthiazol-2-yl)-1,2-dihydroisoquinolin-3(4*H*)-one (**35a**) was obtained from **33a** via demethylation Method A as a yellow solid (78 mg, 45%), mp 204–206 °C, R_f 0.79 (5:95 MeOH/CH_2Cl_2). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 9.58 (brs, 1H, OH), 7.25 (d, *J* 8.1 Hz, 1H, ArH), 6.86 (sharp m, 1H, *thiazole*-H), 6.69–6.66 (m, 2H, ArH), 5.23 (s, 2H, ArC*H*$_2$N), 3.83 (s, 2H, ArC*H*$_2$), 2.32 (d, *J* 1.0 Hz, 3H, *thiazole*-Me). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 17.0 (*thiazole*-Me), 38.1 (Ar*C*H$_2$O), 48.7 (Ar*C*H$_2$N), 109.6 (*thiazole*-Ar*C*H), 113.4 (Ar*C*H), 113.6 (Ar*C*H), 121.7 (Ar*C*H), 126.9 (Ar*C*), 132.9 (Ar*C*), 145.9 (*thiazole*-Ar*C*), 156.9 (C-O), 158.4 (*thiazole*-Ar*C*N), 168.5 (C=O). HRMS ESI$^+$ calcd for $C_{13}H_{13}N_2O_2S$ [M+H]$^+$, 261.0653, found, 261.0701.

6-Hydroxy-2-(4′-hydroxyphenyl)-1,2-dihydroisoquinolin-3(4*H*)-one (**35c**) was obtained from **33c** via demethylation Method A as a beige solid (132 mg, 78%), decomposition temperature 230–240 °C, R_f 0.21 (40:60 EtOAc/Hexane). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 9.45 (brs, 2H, 2xOH), 7.09–7.06 (m, 3H, ArH), 6.75 (d, *J* 8.6 Hz, 2H, ArH), 6.63 (d, *J* 8.6 Hz, 2H, ArH), 4.65 (s, 2H, ArC*H*$_2$N), 3.57 (s, 2H, ArC*H*$_2$). ^{13}C NMR (75 MHz, DMSO-d_6, overlapping signals): δ_C 38.5 (Ar*C*H$_2$), 53.1 (Ar*C*H$_2$N), 113.3 (Ar*C*H), 115.2 (Ar*C*H), 123.3 (Ar*C*H), 126.3 (Ar*C*), 126.8 (Ar*C*), 134.2 (Ar*C*N), 155.5 (C-O), 156.7 (C-O), 168.5 (C=O). HRMS ESI$^+$ calcd for $C_{15}H_{14}NO_3$ [M+H]$^+$, 256.0929, found, 256.0935.

2-(3′-Fluorophenyl)-6-hydroxy-1,2-dihydroisoquinolin-3(4*H*)-one (**35e**) was obtained from **33e** via demethylation Method B as a white solid (159 mg, 89%), mp 118–200 °C, R_f 0.41 (50:50 EtOAc/Hexane). ^{1}H NMR (300 MHz, CD_3OD): δ_H 7.56–7.33 (m, 1H, ArH), 7.23–6.96 (m, 4H, ArH), 6.84–6.58 (m, 2H, ArH), 4.81 (s, 2H, ArC*H*$_2$N), 3.70 (s, 2H, ArCH_2). ^{13}C NMR (75 MHz, CD_3OD): δ_C 39.7 (Ar*C*H$_2$), 54.8 (Ar*C*H$_2$N), 114.4 (d, *J* 21.8 Hz, Ar*C*H-F), 114.7 (d, *J* 24.0 Hz, Ar*C*H-F), 115.1 (Ar*C*H), 122.8 (Ar*C*H), 124.4 (Ar*C*H), 127.7 (Ar*C*H), 131.7 (Ar*C*H), 134.8 (Ar*C*), 145.5 (Ar*C*), 158.7 (C-O), 162.5 (Ar*C*N), 165.9 (Ar*C*F), 172.5 (C=O). HRMS ESI$^+$ calcd for $C_{15}H_{13}FNO_2$ [M+H]$^+$, 258.0930, found, 258.0919.

2-(4′-Fluorophenyl)-6-hydroxy-1,2-dihydroisoquinolin-3(4*H*)-one (**35g**) was obtained from **33g** via demethylation Method B as a brown solid (43 mg, 24%), mp 115–117 °C, R_f 0.41 (50:50 EtOAc/Hexane). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 6.53 (m, 2H, ArH), 6.42–6.22 (m, 3H, ArH), 5.88 (d, *J* 6.1 Hz, 2H, ArH), 3.97 (d, *J* 3.2 Hz, 2H, ArC*H*$_2$N), 3.77 (brs, 1H, OH), 2.88 (s, 2H, ArCH_2). ^{13}C NMR (75 MHz, DMSO-d_6, Ar*C* and C=O signals not detected): δ_C 30.0 (Ar*C*H$_2$CO), 45.7 (Ar*C*H$_2$N), 105.4 (d, *J* 31.5 Hz, Ar*C*H-F), 107.6 (d, *J* 23.0 Hz, Ar*C*H-F), 118.1 (Ar*C*H), 119.8 (Ar*C*H), 125.4 (Ar*C*H). HRMS ESI$^+$ calcd for $C_{15}H_{13}FNO_2$ [M+H]$^+$, 258.0930, found, 258.0934.

General procedure for the reduction of the acetamides 33.[49,50]

To a suspension of AlH_2Cl made by adding $AlCl_3$ (140 mg, 1.06 mmol) to a stirred suspension of $LiAlH_4$ (41.0 mg, 1.08 mmol) in anhydrous THF (30 mL) at −3 °C in small portions followed by stirring at 24 °C for 30 min, was added the amides (0.713 mmol) in THF (4.0 mL). The reaction mixture was then stirred under reflux for 5 h, cooled to 24 °C and carefully treated with water until no further effervescence occurred. The white solid (lithium aluminate) was separated by vacuum filtration and the filtrate extracted with EtOAc (20 mL × 2) to give the corresponding amines as pure oils.

2-[6-Methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl]-4′-methylthiazole (**34a**) was obtained from **33a** as a thick yellow oil (153 mg, 82%), R_f 0.33 (20:80 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.09 (d, *J* 8.4 Hz, 1H, ArH), 6.83–6.65 (m, 2H, ArH), 6.12 (s, 1H, *thiazole*-rH), 4.58 (s, 2H, ArC*H*$_2$N), 3.87–3.65 (m, 5H, overlapping signals-OMe and CH_2), 2.95 (t, *J* 5.8 Hz, 2H, ArC*H*$_2$CH$_2$), 2.28 (d, *J* 1.1 Hz, 3H, *thiazole*-Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 21.4 (*thiazole*-Me), 29.4 (Ar*C*H$_2$CH$_2$), 46.1 (CH_2), 49.6 (Ar*C*H$_2$N), 55.6 (OMe), 101.2 (Ar*C*H), 112.9 (Ar*C*H), 113.6 (Ar*C*H), 125.3 (Ar*C*), 127.7 (Ar*C*), 136.0 (Ar*C*), 149.8 (Ar*C*), 158.6 (C-O), 170.8 (Ar*C*N). HRMS ESI$^+$ calcd for $C_{14}H_{17}N_2OS$ [M+H]$^+$, 261.1062, found, 261.1070.

6-Methoxy-2-(4′-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**34c**) was obtained from **33a** as an off-white solid (129 mg, 67%), mp 116–118 °C, R_f 0.73 (50:50 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.12–7.11 (m, 1H, ArH), 6.93–6.90 (m, 2H, ArH), 6.78–6.69 (m, 3H, ArH), 6.58 (s, 1H, ArH), 4.38 (s, 2H, ArC*H*$_2$N), 3.80

and 3.82 (each s, each 3H, 2xOMe), 3.47 (t, *J* 5.7 Hz, 2H, CH_2), 2.75 (t, *J* 5.7 Hz, 2H, ArC*H*$_2$$CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 29.4 (Ar*C*$H_2$$CH_2$), 44.4 ($CH_2$), 47.5 (Ar*C*$H_2$N), 55.6 (OMe), 55.7 (OMe), 113.0 (Ar*C*H), 113.8 (Ar*C*H), 114.8 (Ar*C*H), 124.4 (Ar*C*H), 124.8 (Ar*C*H), 127.6 (Ar*C*), 129.8 (Ar*C*), 134.9 (Ar*C*N), 157.8 (C-O), 158.6 (C-O). HRMS ESI$^+$ calcd for $C_{17}H_{20}NO_2$ $[M+H]^+$, 270.1494, found, 270.1494.

General synthetic protocol for methoxyphenyl acetamides 36.[44]

To a mixture of *N*,*N*'-dicyclohexylcarbodimide (220 mg, 1.08 mmol), DMAP (11.1 mg, 9.03 × 10^{-5} mmol) and 3-methoxyphenylacetic acid **31** (150 mg, 0.903 mmol) at 0 °C were added the respective amines (**b**–**g**) (0.903 mmol) in anhydrous CH_2Cl_2 (5.0 mL) and the resultant reaction mixture was stirred at 24 °C for 12 h. The suspension was filtered and the eluent concentrated under reduced pressure to yield a solid residue which was purified by flash chromatography (15:85 EtOAc/Hexane) to afford the products described below. The compounds were characterized by NMR spectroscopy (for some compounds HRMS too) and utilized directly in the next reduction step).

2-(3-Methoxyphenyl)-*N*-(5'-nitrothiazol-2-yl)acetamide (**36b**) was obtained from **31** and 2-amino-5-nitro-thiazole as an orange solid (42 mg, 16%), mp 119–120 °C, R_f 0.29 (30:70 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 9.52 (brs, 1H, NH), 8.22 (s, 1H, *thiazole*-H), 7.29–7.19 (m, 1H, ArH), 6.85–6.76 (m, 3H, ArH), 4.17–3.55 (m, 5H, overlapping signals-OMe and CH_2). ^{13}C NMR (75 MHz, $CDCl_3$, overlapping signals): δ_C 43.4 (ArCH_2), 55.6 (OMe), 113.8 (*thiazole*-Ar*C*H), 115.78 (Ar*C*H), 121.8 (Ar*C*H), 131.0 (Ar*C*H), 133.4 (Ar*C*), 140.4 (*thiazole*-Ar*C*), 160.7 (*thiazole*-Ar*C*N), 161.2 (C-O), 169.5 (C=O). HRMS ESI$^+$ calcd for $C_{12}H_{12}N_3O_4S$ $[M+H]^+$, 294.0549, found, 294.0547.

***N*-(3'-Chlorophenyl)-2-(3-methoxyphenyl)acetamide** (**36d**) was obtained from **31** and 3-chloroaniline as a thick white oil (165 mg, 66%), R_f 0.66 (50:50 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.51 (d, *J* 1.8 Hz, 1H, ArH), 7.38–7.14 (m, 3H, ArH), 7.11–7.00 (m, 1H, ArH), 6.95–6.80 (m, 3H, ArH), 3.83 (s, 3H, OMe), 3.71 (s, 2H, ArC*H*$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 45.1 (ArCH_2), 55.4 (OMe), 113.4 (Ar*C*H), 115.3 (Ar*C*H), 117.9 (Ar*C*H), 120.0 (Ar*C*H), 121.8 (Ar*C*H), 124.6 (Ar*C*H), 130.0 (Ar*C*H), 130.5 (Ar*C*H), 134.7 (Ar*C*Cl), 135.6 (Ar*C*CH_2), 138.9 (Ar*C*N), 160.2 (C-O), 169.0 (C=O). HRMS ESI$^+$ calcd for $C_{15}H_{15}ClNO_2$ $[M+H]^+$, 276.0791 (^{35}Cl), found, 276.0780.

***N*-(3'-Fluorophenyl)-2-(3-methoxyphenyl)acetamide** (**36e**) was obtained from **31** and 3-fluoroaniline as a white solid (221 mg, 94%), mp 57–58 °C, R_f 0.46 (20:80 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$, NH signal was not detected): δ_H 7.45–7.11 (m, 3H, ArH), 7.06–6.69 (m, 5H, ArH), 3.80 (s, 3H, OMe), 3.69 (s, 2H, ArCH_2). ^{13}C NMR (75 MHz, $CDCl_3$, overlapping signals): δ_C 44.9 (ArCH_2), 55.5 (OMe), 107.8 (d, *J* 26.25 Hz, Ar*C*H-F), 111.4 (d, *J* 21.00 Hz, Ar*C*H-F), 113.3 (Ar*C*H), 115.5 (d, *J* 12.75 Hz, Ar*C*H-F)], 121.9 (Ar*C*H), 130.3 (d, *J* 9.00 Hz, Ar*C*H-F), 136.0 (Ar*C*N), 139.6 (d, *J* 10.50 Hz, Ar*C*H-F), 161.6 (C-O), 164.8 (Ar*C*F), 170.0 (C=O). HRMS ESI$^+$ calcd for $C_{15}H_{15}FNO_2$ $[M+H]^+$, 260.1087, found, 260.1083.

***N*-(4'-Chlorophenyl)-2-(3-methoxyphenyl)acetamide** (**36f**) was obtained from **31** and 4-chloroaniline a thick white oil (217 mg, 87%), R_f 0.41 (30:70 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$, NH signal was not observed): δ_H 7.51–7.50 (m, 5H, ArH), 7.11–6.80 (m, 3H, ArH), 3.83 (s, 3H, OMe), 3.71 (s, 2H, ArCH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 45.1 (ArCH_2), 55.4 (OMe), 113.4 (Ar*C*H), 115.3 (Ar*C*H), 117.8 (Ar*C*H), 120.0 (Ar*C*H), 121.8 (Ar*C*H), 124.6 (Ar*C*H), 130.1 (Ar*C*Cl), 130.8 (Ar*C*H), 130.4 (Ar*C*), 135.7 (Ar*C*NH), 158.5 (C-O), 168.2(C=O).

***N*-(4'-Fluorophenyl)-2-(3-methoxyphenyl)acetamide** (**36g**) was obtained from **31** and 4-fluoroaniline as a white solid (131 mg, 56%), mp 70–72 °C, R_f 0.46 (30:70 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.45–7.11 (m, 3H, ArH), 7.06–6.69 (m, 5H, ArH), 3.80 (s, 3H, OMe), 3.69 (s, 2H, ArCH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 44.7 (ArCH_2), 55.3 (OMe), 113.1 (Ar*C*H), 115.2 (Ar*C*H), 115.6 (d, *J* 22.5 Hz, Ar*C*H-F), 121.8 (d, *J* 7.50 Hz, Ar*C*H-F), 130.3 (Ar*C*H), 133.4 (Ar*C*H), 135.8 (Ar*C*N), 157.9 (Ar*C*CH_2), 160.20 (C-O), 161.1 (Ar*C*F), 169.0 (C=O).

Reduction of amides as described above for compounds 34a and 34c

3′-Chloro-*N*-(3-methoxyphenethyl)aniline (**37d**) was obtained from **36d** as a thick yellow oil (184 mg, 98%), R_f 0.82 (50:50 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 7.28-7.15 (m, 2H, ArH), 6.98-6.60 (m, 5H, ArH), 3.80 (3H, s, OMe), 3.46 (t, *J* 6.9 Hz, 2H, ArCH$_2$C*H*$_2$NH), 2.81 (t, *J* 6.9 Hz, ArC*H*$_2$CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 35.7 (ArCH$_2$), 45.0 (CH$_2$), 55.5 (OMe), 111.6 (Ar*C*H), 112.1 (Ar*C*H), 112.8 (Ar*C*H), 114.9 (Ar*C*H), 117.6 (Ar*C*H), 121.4 (Ar*C*H), 130.0 (Ar*C*H), 130.6 (Ar*C*H), 135.6 (Ar*C*Cl), 140.9 (Ar*C*NH), 149.5 (Ar*C*), 160.2 (C-O). HRMS ESI$^+$ calcd for $C_{15}H_{17}ClNO$ [M+H]$^+$, 262.0999 (^{35}Cl), found, 262.0988.

3′-Fluoro-*N*-(3-methoxyphenethyl)aniline (**37e**) was obtained from **36e** as a white oil (128 mg, 73%), R_f 0.63 (50:50 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$, NH signal was obscured): δ_H 7.77–7.29 (m, 5H, ArH), 6.42–6.28 (m, 3H, ArH), 3.80 (s, 3H, OMe), 3.38 (t, *J* 6.9 Hz, 2H, ArC*H*$_2$CH$_2$NH), 2.89 (t, *J* 6.9 Hz, 2H, ArC*H*$_2$CH$_2$NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 35.3 (Ar*C*H$_2$CH$_2$), 44.8 (CH$_2$*C*H$_2$NH), 55.2 (OMe), 99.6 (d, *J* 26.25 Hz, Ar*C*H-F), 103.9 (d, *J* 9.00 Hz, Ar*C*H-F), 108.8 (Ar*C*H), 111.8 (Ar*C*H), 114.6 (Ar*C*H), 121.1 (Ar*C*H), 120.0 (Ar*C*H), 130.2 (Ar*C*H), 130.4 (Ar*C*), 140.8 (Ar*C*NH), 160.0 (C-O). HRMS ESI$^+$ calcd for $C_{15}H_{17}FNO$ [M+H]$^+$, 246.1294, found, 246.1290.

4′-Chloro-*N*-(3-methoxyphenethyl)aniline (**37f**) was obtained from **36f** as a thick yellow oil (164 mg, 88%), R_f 0.80 (50:50 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.30–7.18 (m, 1H, ArH), 7.17–7.08 (m, 2H,ArH), 6.87–6.67 (m, 3H, ArH), 6.58–6.47 (m, 2H, ArH), 3.80 (s, 3H, OMe), 3.68 (brs, 1H, NH), 3.37 (t, *J* 6.8 Hz, 2H, ArCH$_2$C*H*$_2$), 2.88 (t, *J* 6.8 Hz, 2H, C*H*$_2$CH$_2$NH). ^{13}C NMR (75 MHz, $CDCl_3$, overlapping signals): δ_C 35.6 (Ar*C*H$_2$CH$_2$), 45.3 (CH$_2$*C*H$_2$NH), 55.5 (OMe), 112.0 (Ar*C*H), 114.3 (Ar*C*H), 114.9 (Ar*C*H), 121.4 (Ar*C*H), 122.5 (Ar*C*Cl), 129.4 (Ar*C*H), 130.0 (Ar*C*), 141.6 (Ar*C*NH), 159.8 (C-O). HRMS ESI$^+$ calcd for $C_{15}H_{17}ClNO$ [M+H]$^+$, 262.0999 (^{35}Cl), found, 262.0988.

4′-Fluoro-*N*-(3-methoxyphenethyl)aniline (**37g**) was obtained from **36g** as a translucent oil (168 mg, 96%), R_f 0.71 (50:50 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$, NH signal was obscured): δ_H 7.29–7.23 (s, 1H, ArH), 6.78–6.03 (m, 5H, ArH), 6.58–6.54 (m, 2H, ArH), 3.90 (s, 3H, OMe), 3.38 (t, *J* 6.0 Hz, 2H, CH$_2$C*H*$_2$NH), 2.90 (t, *J* 6.0 Hz, 2H, ArC*H*$_2$CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 35.5 (Ar*C*H$_2$CH$_2$), 45.6 (CH$_2$*C*H$_2$NH), 55.2 (OMe), 111.7 (Ar*C*H), 113.8 (d, *J* 7.50 Hz, Ar*C*H-F), 114.6 (Ar*C*H), 115.7 (d, *J* 21.75 Hz, Ar*C*H-F), 121.1 (Ar*C*H), 129.7 (Ar*C*H), 141.1 (Ar*C*), 144.1 (Ar*C*NH), 156.8 (Ar*C*F), 159.9 (C-O). HRMS ESI$^+$ calcd for $C_{15}H_{17}FNO$ [M+H]$^+$, 246.1294, found, 246.1292.

General procedure for the Pictet-Spengler cyclization of amines 37.[45]

A mixture of the amine substrates **37** (1.05 mmol) and paraformaldehyde (1.15 mmol) were heated in formic acid (5.0 mL) at 80 °C for 12 h. The reaction mixture was diluted with water (20 mL) and the pH adjusted to 5 with $NaHCO_3$ solution, followed by extraction with EtOAc (20 mL × 2). The residue was purified by chromatography in (20:80 EtOAc/Hexane).

2-(3′-Fluorophenyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**34e**) was obtained from **37e** as an orange oil (203 mg,75%), ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.28–7.00 (m, 2H, ArH), 6.87–6.37 (m, 5H, ArH), 4.36 (s, 2H, ArC*H*$_2$N), 3.80 (s, 3H, OMe), 3.55 (t, *J* 5.8 Hz, 2H, NHCH$_2$), 2.96 (t, *J* 5.8 Hz, 2H, ArC*H*$_2$CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, overlapping signals): δ_C 29.3 (Ar*C*H$_2$CH$_2$), 45.8 (CH$_2$), 49.6 (Ar*C*H$_2$N), 55.3 (OMe), 101.30 (d, *J* 25.5 Hz, Ar*C*H-F), 104.4 (d, *J* 21.75 Hz, Ar*C*H-F), 109.9 (Ar*C*H), 112.4 (Ar*C*H), 113.2 (Ar*C*H), 126.2 (Ar*C*H), 127.5 (Ar*C*H), 130.1 (Ar*C*), 136.0 (Ar*C*N), 157.2 (C-O), 159.3 (Ar*C*F). HRMS ESI$^+$ calcd for $C_{16}H_{17}FNO$ [M+H]$^+$, 258.1294 (^{18}F), found, 258.1288.

2-(4′-Fluorophenyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**34g**) was obtained from **37g** as a brown solid (266 mg, 98%), mp 75–78 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.12–6.87 (m, 5H, ArH), 6.82–6.66 (m, 2H, ArH), 4.28 (s, 2H, ArC*H*$_2$N), 3.81 (s, 3H, OMe), 3.48 (t, *J* 5.8 Hz, 2H, NCH$_2$), 2.97 (t, *J* 5.8 Hz, 2H, ArC*H*$_2$CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 29.6 (Ar*C*H$_2$CH$_2$), 48.1 (CH$_2$), 51.7 (Ar*C*H$_2$N), 55.6 (OMe), 112.7 (Ar*C*H), 113.6 (Ar*C*H), 115.9 (d, *J* 22.50 Hz, Ar*C*H-F), 117.5 (d, *J* 7.50 Hz, Ar*C*H-F), 126.8 (Ar*C*H), 127.8 (Ar*C*), 136.0 (Ar*C*), 147.5 (Ar*C*N), 155.2 (Ar*C*F), 158.4 (C-O). HRMS ESI$^+$ calcd. $C_{16}H_{17}NOF$ [M+H]$^+$, 258.1249 (^{18}F), found, 258.1292.

2-(4′-Methylthiazol-2-yl)-1,2,3,4-tetrahydroisoquinolin-6-ol (**38a**) was obtained from **34a** by demethylation Method A as a yellow solid (73 mg, 45%), mp 120–122 °C, R_f 0.24 (40:60 EtOAc/Hexane). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 6.34 (d, *J* 8.2 Hz, 1H, ArH), 6.10–5.94 (m, 2H, ArH), 5.78 (sharp m, 1H, *thiazole*-H), 4.29 (brs, 1H, OH), 3.97 (s, 2H, Ar*CH*$_2$N), 3.10 (t, *J* 6.0 Hz, 2H, CH_2), 2.18 (t, *J* 6.0 Hz, 2H, Ar*CH*$_2$$CH_2$), 1.63 (d, *J* 1.1 Hz, 3H, *thiazole*-Me). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 20.2 (*thiazole*-Me), 33.1 (Ar*C*H$_2$CH$_2$), 36.7 (CH_2), 69.8 (Ar*C*H$_2$N), 97.2 (*thiazole*-*C*H), 105.1 (Ar*C*H), 106.1 (Ar*C*H), 115.6 (Ar*C*H), 118.6 (Ar*C*), 127.5 (Ar*C*), 134.2 (*thiazole*-Ar*C*), 147.5 (C-O), 148.2 (*thiazole*-Ar*C*N). HRMS ESI$^+$ calcd for $C_{13}H_{15}N_2OS$ $[M+H]^+$, 247.0860, found, 247.0910.

2-(4′-Hydroxyphenyl)-1,2,3,4-tetrahydroisoquinolin-6-ol (**38j**) was obtained from **34c** via demethylation Method A as a yellow solid (61 mg, 38%), mp 178–180 °C ^{1}H NMR (300 MHz, CD_3OD): δ_H 7.05–6.89 (m, 3H, ArH), 6.83–6.69 (m, 2H, ArH), 6.67–6.53 (m, 2H, ArH), 4.12 (s, 2H, Ar*CH*$_2$N), 2.92 (t, *J* 5.8 Hz, 2H, Ar*CH*$_2$$CH_2$). ^{13}C NMR (75 MHz, CD_3OD, some quaternary carbons not observed): δ_C 30.0 (Ar*C*H$_2$CH$_2$), 51.1 (CH_2), 54.6 (Ar*C*H$_2$N), 114.5 (Ar*C*H), 115.7 (Ar*C*H), 116.7 (Ar*C*), 120.7 (Ar*C*H), 126.1 (Ar*C*), 126.8 (Ar*C*H), 135.8 (Ar*C*H), 136.7 (Ar*C*H). HRMS ESI$^+$ calcd for $C_{15}H_{16}NO_2$ $[M+H]^+$, 242.1181, found, 242.1185.

2-(3′-Chlorophenyl)-1,2,3,4-tetrahydroisoquinolin-6-ol (**38d**) was obtained via Method B from the transiently prepared **34d** (not isolated) as white crystals (103 mg, 57%), mp 128–130 °C, R_f 0.36 (40:60 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.27–7.06 (m, 1H, ArH), 6.99 (d, *J* 8.0 Hz, 1H, ArH), 6.87 (d, *J* 1.9 Hz, 1H, ArH), 6.82–6.51 (m, 4H, ArH), 4.30 (s, 2H, Ar*CH*$_2$N), 3.49 (t, *J* 5.3 Hz, 2H, CH_2), 2.87 (t, *J* 5.3 Hz, 2H, Ar*CH*$_2$$CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 29.4 (Ar*CH*$_2$$CH_2$), 46.3 ($CH_2$), 50.0 (Ar*CH*$_2$N), 113.0 (Ar*C*H), 114.1 (Ar*C*H), 114.8 (Ar*C*H), 115.2 (Ar*C*H), 118.4 (Ar*C*H), 126.3 (Ar*C*H), 128.0 (Ar*C*), 130.5 (Ar*C*H), 135.4 (Ar*C*), 136.6 (Ar*C*Cl), 151.8 (Ar*C*N), 154.8 (C-O). HRMS ESI$^+$ calcd for $C_{15}H_{15}ClNO$ $[M+H]^+$, 260.0842 (^{35}Cl), found, 260.0833.

2−(4′−Chlorophenyl)−1,2,3,4−tetrahydroisoquinolin−6−ol (**38f**) was obtained via Method B from the transiently prepared **34f** (not isolated) as a brown solid (104 mg, 58%), mp 116–117 °C; R_f 0.41 (50:50 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.27–7.15 (m, 2H, ArH), 7.00 (d, *J* 8.2 Hz, 1H, ArH), 6.90–6.81 (m, 2H, ArH), 6.71–6.58 (m, 2H, ArH), 4.28 (s, 2H, Ar*CH*$_2$N), 3.48 (t, *J* 5.9 Hz, 2H, CH_2), 2.89 (t, *J* 5.9 Hz, 2H, Ar*CH*$_2$$CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 29.1 (Ar*CH*$_2$$CH_2$), 46.6 ($CH_2$), 50.3 (Ar*CH*$_2$N), 113.7 (Ar*C*H), 115.0 (Ar*C*H), 116.4 (Ar*C*H), 123.2 (Ar*C*H), 124.0 (Ar*C*H), 126.5 (Ar*C*), 127.8 (Ar*C*Cl), 129.1 (Ar*C*H), 136.3 (Ar*C*H), 149.1 (Ar*C*), 149.6 (Ar*C*N), 154.8 (Ar*C*OH). HRMS ESI$^+$: calcd for $C_{15}H_{15}ClNO$ $[M+H]^+$, 260.0842, found, 260.0839.

2-(4-Fluorophenyl)-1,2,3,4-tetrahydroisoquinolin-6-ol (**38g**) was obtained from **34g** via demethylation Method B as an orange solid (93 mg, 55%), mp 105–107 °C, R_f 0.53 (50:50 EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.06–6.88 (m, 5H, ArH), 6.74–6.59 (m, 2H, ArH), 4.26 (s, 2H, ArC*H*$_2$N), 3.46 (t, *J* 5.7 Hz, 2H, NCH_2), 2.92 (t, *J* 5.7 Hz, 2H, ArC*H*$_2$$CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$, no C-F coupling detected): δ_C 29.4 (Ar*C*H$_2$CH$_2$), 48.2 (CH_2), 51.9 (Ar*C*H$_2$N), 113.9 (Ar*C*H), 115.3 (Ar*C*H), 115.8 (Ar*C*H), 116.1 (Ar*C*H), 117.7 (Ar*C*H), 126.1 (Ar*C*H), 126.8 (Ar*C*H), 128.0 (Ar*C*), 136.4 (Ar*C*), 154.4 (Ar*C*N), 157.8 (Ar*C*OH), 159.9 (Ar*C*F). HRMS ESI$^+$ calcd for $C_{15}H_{15}NOF$ $[M+H]^+$, 244.1138 (^{18}F), found, 244.1141.

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Supplementary Material

A selection of ^{1}H, ^{13}C and HRMS spectra are available as representative examples of the final substituted tetrahydroisoquinolin-6-ols (**18**, **22**, **29** and **38**) and 6-hydroxy-2-aryl-1,2-dihydroisoquinolin-3(4*H*)-ones (**35**) produced in this research.

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