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SAR studies of capsazepinoid bronchodilators. Part 2: Chlorination and catechol replacement in the A-ring

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Abstract—Capsazepine as well as its derivatives and analogues are general inhibitors of constriction of human small airways. From a systematic variation of the capsazepine structure, divided into four regions, SARs were established. This paper concerns the chlorination of the A-ring as well as the replacement of the catechol with bioisosteric groups. It is revealed that chlorination of the A-ring has a profound effect on activity. Moreover, di-chlorination of the 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline structure results in a 10-fold increase in potency compared to capsazepine.

1. Introduction

β_2-Agonists, among other bronchodilators, constitute the mainstay of the symptomatic treatment of asthma and chronic obstructive pulmonary disease (COPD).[1–3] They act as functional antagonists, reversing and preventing bronchoconstriction from the various bronchoconstrictor mechanisms that operate in these diseases.[4] We have recently reported that capsazepine (**2**), a transient receptor potential vanilloid channel subfamily member 1 (TRPV1) antagonist,[5–7] induces in vitro bronchodilation of human small bronchi constricted with various agents such as leukotriene D_4 (LTD_4), histamine, prostaglandin D_2 and acetylcholine.[8]

A systematic SAR study of the bronchorelaxing activity of capsazepinoids, partly reported in this paper, eventually led to the synthesis of **4**, which has superior potency compared to **2**.[9] Additionally, its duration of action is longer than the one of **2**.[9] The ability of **4** to inhibit the induction of constriction in human small airway smooth muscle has been compared to that of known β_2-agonists such as formoterol (**72**) and salbutamol (**73**) (Fig. 1). The results show that **4** not only has a higher efficacy but also that it acts through a different and possibly novel mechanism,[9] making it interesting as a lead structure for the development of new drugs to treat asthma and COPD.

Compounds containing phenol and catechol moieties can be attractive candidates for drug development due to their ability to take part in electrostatic interactions, such as hydrogen bonds. A characteristic of these types of compounds is their rapid metabolism by conjugation

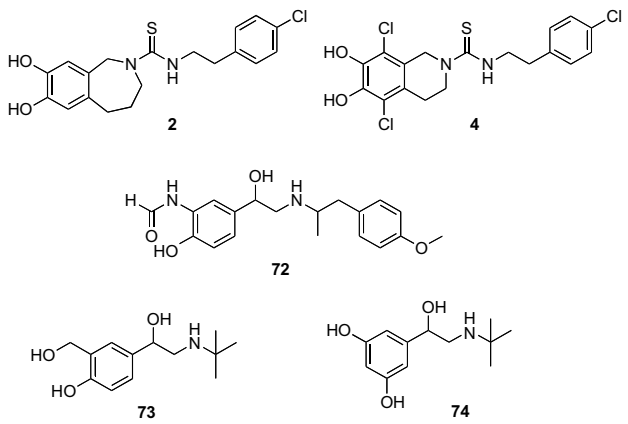

Figure 1.

Keywords: Capsazepine; SAR; A-ring catechol; B-ring; Isoindoline; 1,2,3,4-Tetrahydroisoquinoline; 2,3,4,5-Tetrahydro-1*H*-2-azepine; 2,3,4,5-Tetrahydro-1*H*-3-benzazepine; Bronchodilator; Small human airways; Asthma; COPD.
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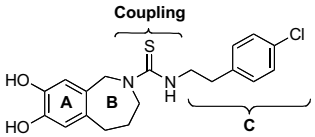


Figure 2.

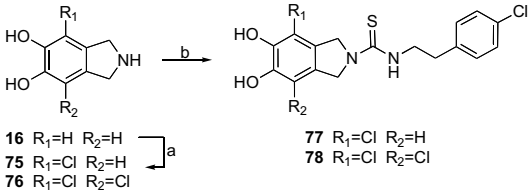
with glucuronic acid and, in the case of catechols, methylation catalyzed by catechol-*O*-methyltransferase (COMT). This is a major drawback when the drug is intended for oral use,[10] but it may be seen as an advantage for inhaled drugs as the risk of side effects is diminished. For example, phenol-containing bronchodilator agents such as the β_2-agonists **73** and **74** (Fig. 1) are distributed directly to the target organ, that is, the airways, by inhalation.

However, since the progressive deterioration of the airways in diseases, such as chronic obstructive pulmonary disease (COPD), greatly reduces the respiratory capacity, inhalation is less suitable as administration route when such diseases are to be treated.[11] Consequently, drugs directed against diseases such as COPD should preferably not comprise hydroxyl groups, and attempts have therefore been made to replace the hydroxyls in the A-ring (Fig. 2).

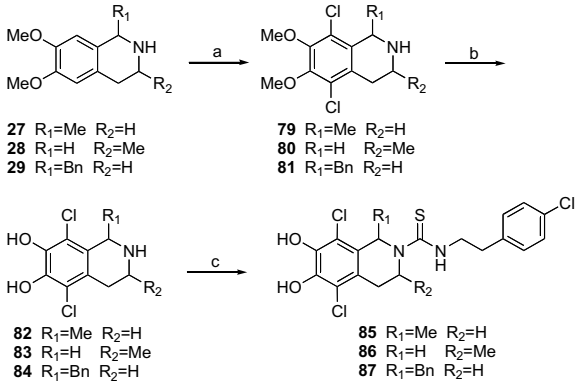
The structure of capsazepine has been divided into four regions, which are shown in Figure 2, in order to systematically study the effect on the activity of structural variations of each region. In this paper, we investigate the effect of chlorination of the A-ring in phenolic and catecholic derivatives having different B-rings, and in B-rings substituted with methyl/benzyl groups in various positions. In addition, the effect of alternative A-ring substituents is studied in 1,2,3,4-tetrahydroisoquinoline derivatives. In the preceding paper,[12] the importance of a catechol moiety in the A-ring and how structural differences in the B-ring affect the bronchodilating ability of the capsazepinoids is discussed, while the following paper discusses the coupling region as well as the C-region.[13] To facilitate the comparison of the results from the complete study, a continuous numbering of the compounds has been used. Compounds discussed in more than one paper consequently have the same number everywhere. The preparation of compounds having numbers below **72** is described in the preceding paper.[12]

2. Chemistry

Synthetic routes to mono- and dichlorinated capsazepinoids with a conformationally constrained B-ring as in isoindolines (5-membered B-ring), tetrahydroisoquinolines (6-membered B-ring), and tetrahydro-1*H*-2-benzazepines as well as tetrahydro-1*H*-3-benzazepines (7-membered B-ring) were developed as this modification was found to have a particularly strong effect on the activity (Schemes 1–4 and Table 1). In addition, the effect of replacing the catechol or phenol moiety of the 1,2,3,4-tetrahydroisoquinoline ring system with an aniline, a methylsulfonyl amide, a phthalic acid, a phthalic acid methylester or a phthalonitrile was investigated (Schemes 5–7 and Table 2).



Scheme 1. Reagents and conditions: (a) 1—di-*tert*-butyl dicarbonate, Et_3N, DMF rt, 2 h; 2—trifluoroacetic acid, CH_2Cl_2, anisol, rt, 1 h; 3—SO_2Cl_2, AcOH, rt, 2.5 h; (b) Et_3N, 2-(4-chlorophenyl)ethyl isothiocyanate, DMF, rt, 4 h.

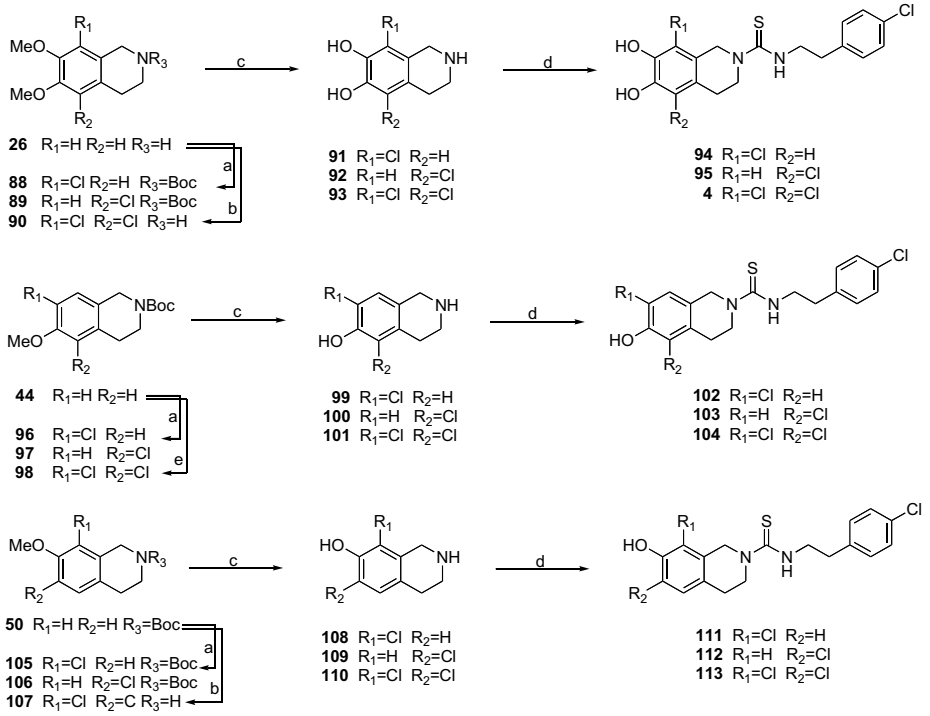


Scheme 2. Reagents and conditions: (a) SO_2Cl_2, AcOH, rt, 2.5 h; (b) HBr (48% in H_2O), reflux, 5 h; (c) Et_3N, 2-(4-chlorophenyl)ethyl isothiocyanate, DMF, rt, 4 h.

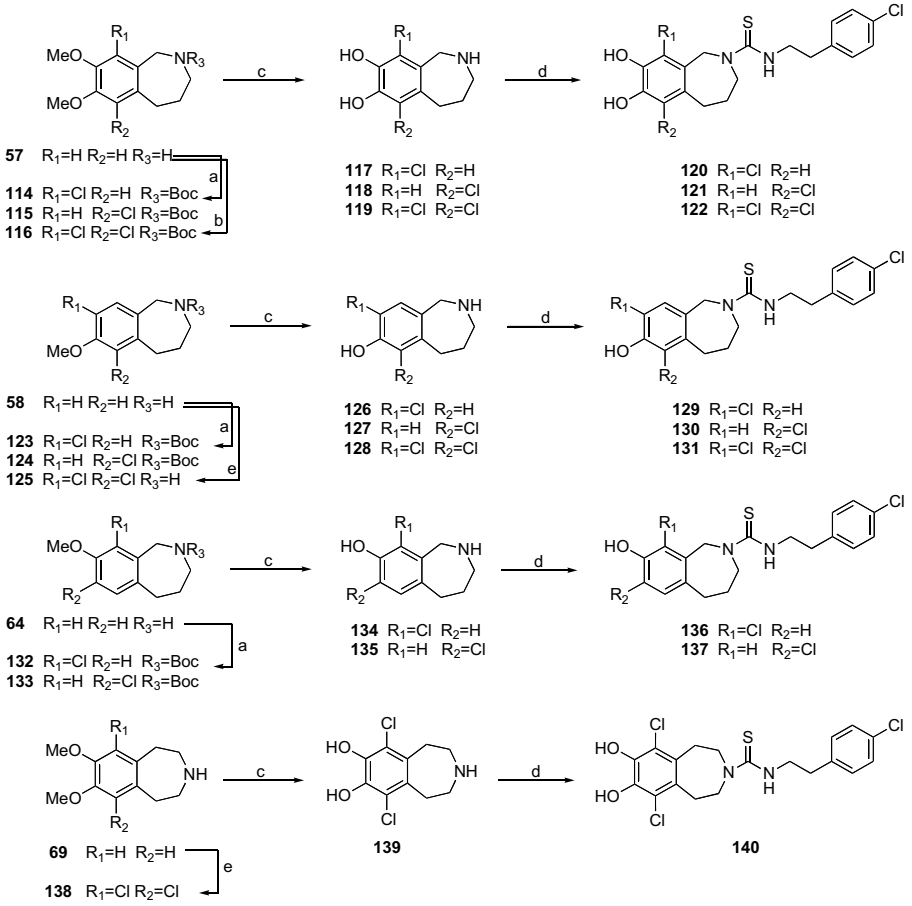
The synthesis of chlorinated isoindoline analogues is outlined in Scheme 1. Attempts to chlorinate the hydrobromic salt of **16**[14] with sulfuryl chloride in acetic acid[15] failed, a complex mixture of chlorinated and brominated products was formed. This problem was overcome by changing the counterion by *N*-Boc protection and deprotection with trifluoroacetic acid, yielding the trifluoroacetic salt of **16** which was chlorinated without problems to the intermediates **75** and **76**. In general, monochlorinations were achieved with 1.2 equivalents of sulfuryl chloride while dichlorinations were accomplished with 2.2 equivalents of sulfuryl chloride. Coupling with 2-(4-chlorophenyl)ethyl isothiocyanate afforded the mono- and dichlorinated products **77** and **78**.

1,2,3,4-Tetrahydroisoquinoline analogues having a substituted B-ring, **85**–**87**, were synthesized as illustrated in Scheme 2. Dichlorination of the commercially available 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines **27**-**29** was carried out with sulfuryl chloride in acetic acid, to yield **79**-**81**, which were demethylated in HBr (48% in H_2O) to give **82**–**84**. Coupling of these intermediates with 2-(4-chlorophenyl)ethyl isothiocyanate afforded **85**–**87**.

The chlorinated 1,2,3,4-tetrahydroisoquinoline derivatives **94**, **95**, **4**, **102**–**104** and **111**–**113** were prepared as

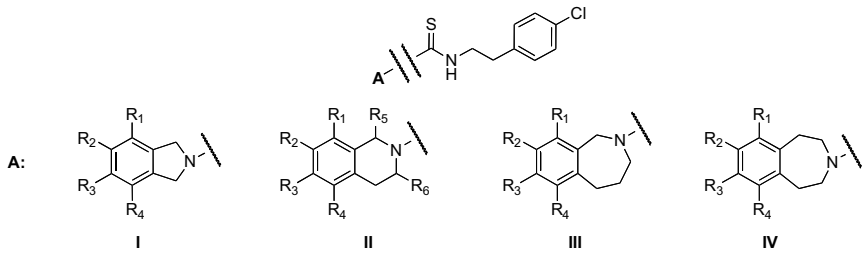


Scheme 3. Reagents and conditions: (a) 1—SO_2Cl_2 (1.1 equiv), AcOH, rt, 2.5 h; 2—di-*tert*-butyl dicarbonate, Et_3N, DMF, rt, 2 h; (b) SO_2Cl_2 (2.1 equiv), AcOH, rt, 2.5 h; (c) HBr (48% in H_2O), reflux, 5 h; (d) Et_3N, 2-(4-chlorophenyl)ethyl isothiocyanate, DMF, rt, 4 h; (e) 1—SO_2Cl_2 (2.1 equiv), AcOH, rt, 2.5 h; 2—di-*tert*-butyl dicarbonate, Et_3N, DMF, rt, 2 h.



Scheme 4. Reagents and conditions: (a) 1—SO_2Cl_2 (1.1 equiv), AcOH, rt, 2.5 h; 2—di-*tert*-butyl dicarbonate, Et_3N, DMF, rt, 2 h; (b) (1) SO_2Cl_2 (2.1 equiv), AcOH, rt, 2.5 h; 2—di-*tert*-butyl dicarbonate, Et_3N, DMF, rt, 2 h; (c) HBr (48% in H_2O), reflux, 5 h; (d) Et_3N, 2-(4-chlorophenyl)ethyl isothiocyanate, DMF, rt, 4 h; (e) 1—SO_2Cl_2 (2.1 equiv), AcOH, rt, 2.5 h.

Table 1. Remaining contraction after pretreatment with different capszepinoids (10 μM)

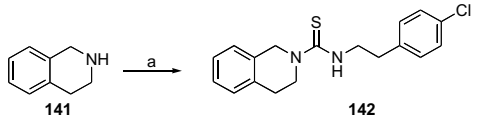


Compound	A	R_1	R_2	R_3	R_4	R_5	R_6	Remaining contraction[a]
17[b]	**I**	H	OH	OH	H			56 ± 10.0 (5)
77	**I**	Cl	OH	OH	H	—	—	65 ± 13.1 (4)
78	**I**	Cl	OH	OH	Cl	—	—	31 ± 7.7 (4)
35[b]	**II**	H	OH	OH	H	Me	H	58 ± 11.7 (5)
85	**II**	Cl	OH	OH	Cl	Me	H	48 ± 8.4 (4)
36[b]	**II**	H	OH	OH	H	H	Me	70 ± 10.1 (4)
86	**II**	Cl	OH	OH	Cl	H	Me	31 ± 7.6 (4)
37[b]	**II**	H	OH	OH	H	Bn	H	79 ± 5.4 (4)
87	**II**	Cl	OH	OH	Cl	Bn	H	84 ± 5.8 (4)
34[b]	**II**	H	OH	OH	H	H	H	36 ± 6.5 (5)
94	**II**	Cl	OH	OH	H	H	H	49 ± 1.2 (5)
95	**II**	H	OH	OH	Cl	H	H	40 ± 10.5 (4)
4[c]	**II**	Cl	OH	OH	Cl	H	H	14 ± 2.7 (16)
48[b]	**II**	H	H	OH	H	H	H	52 ± 6.8 (4)
102	**II**	H	Cl	OH	H	H	H	73 ± 3.2 (4)
103	**II**	H	H	OH	Cl	H	H	69 ± 4.8 (4)
104	**II**	H	Cl	OH	Cl	H	H	55 ± 4.3 (4)
52[b]	**II**	H	OH	H	H	H	H	75 ± 7.0 (4)
111	**II**	Cl	OH	H	H	H	H	47 ± 9.2 (4)
112	**II**	H	OH	Cl	H	H	H	69 ± 6.5 (4)
113	**II**	Cl	OH	Cl	H	H	H	57 ± 11.4 (3)
2[b]	**III**	H	OH	OH	H	—	—	55 ± 3.0 (24)
120	**III**	Cl	OH	OH	H	—	—	63 ± 14.8 (3)
121	**III**	H	OH	OH	Cl	—	—	64 ± 7.0 (2)
122	**III**	Cl	OH	OH	Cl	—	—	38 ± 10.0 (4)
61[b]	**III**	H	H	OH	H	—	—	53 ± 4.7 (3)
129	**III**	H	Cl	OH	H	—	—	49 ± 5.7 (4)
130	**III**	H	H	OH	Cl	—	—	67 ± 10.3 (3)
131	**III**	H	Cl	OH	Cl	—	—	30 ± 2.4 (3)
66[b]	**III**	H	OH	H	H	—	—	40 ± 9.9 (4)
136	**III**	Cl	OH	H	H	—	—	46 ± 6.6 (4)
137	**III**	H	OH	Cl	H	—	—	56 ± 11.9 (3)
71[b]	**IV**	H	OH	OH	H	—	—	54 ± 5.5 (4)
140	**IV**	Cl	OH	OH	Cl	—	—	29 ± 3.0 (2)

[a] Arithmetic mean ± the standard error of the mean of the percent remaining contraction in small human airways contracted with LTD4 in the presence of 10 μM test substance compared to a full contraction evoked by LTD4 in the absence of test compound. Number of times tested in parentheses.

[b] Compounds reported previously.[12]

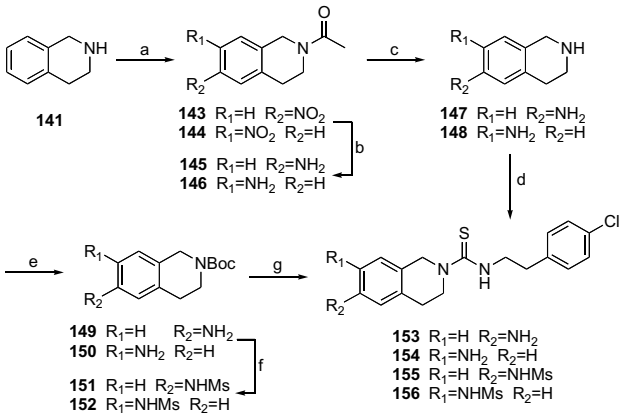
[c] A detailed study of the pharmacological effects of **4** has been reported.[9]



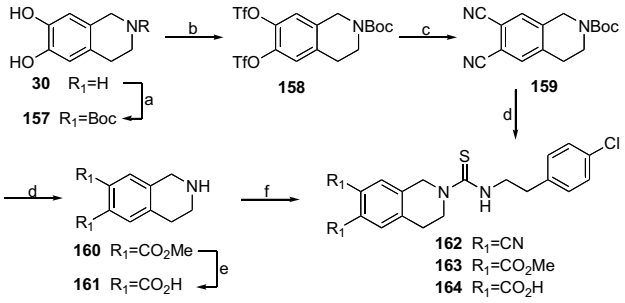
Scheme 5. Reagents and condition: (a) Et_3N, 2-(4-chlorophenyl)ethyl isothiocyanate, DMF, rt, 4 h.

described in Scheme 3. Chlorination of intermediates **26**, **44** and **50**[14] with sulfuryl chloride followed by Boc-protection of the mixtures to facilitate purification yielded **88**, **89**, **96–98** and **105–107**. Intermediate **90** was obtained as the only product and Boc-protection was not required. Deprotection and coupling with 2-(4-chlorophenyl)ethyl isothiocyanate was carried out as described above.

The general synthesis of the capsazepine derivatives **120–122**, **129–131**, **136–137** and **140** is outlined in Scheme 4. The preparation of the dichlorinated deriva-



Scheme 6. Reagents and conditions: (a) 1—Ac_2O, 0 °C, 3 h; 2—HNO_3/H_2SO_4, 0 °C, 4 h; (b) H_2 (1 atm), Pd/C, HCl, MeOH, rt, 1 h; (c) HBr (aq), reflux, 4 h; (d) Et_3N, 2-(4-chlorophenyl)ethyl isothiocyanate, DMF, rt, 4 h; (e) Boc_2O, THF, H_2O, rt, 3 h; (f) MsCl, Et_3N, CH_2Cl_2, 0 °C–rt, 2 h; (g) 1—trifluoroacetic acid, CH_2Cl_2, anisol, rt, 1 h; 2—Et_3N, 2-(4-chlorophenyl)ethyl isothiocyanate, DMF, rt, 4 h.



Scheme 7. Reagents and conditions: (a) Boc_2O, Et_3N, THF, H_2O, rt, 17 h, 68%; (b) Tf_2O, Et_3N, CH_2Cl_2, 0 °C–rt, 3 h, 95%; (c) $Zn(CN)_2$, $Pd_2(dba)_3$, dppf, DMF 80 °C, 2 h, 42%; (d) 1—trifluoroacetic acid, CH_2Cl_2, anisol, rt, 1 h; 2—Et_3N, 2-(4-chlorophenyl)ethyl isothiocyanate, DMF, rt, 4 h; (e) 1–NaOH, H_2O, reflux, 48 h; 2—H_2SO_4, MeOH, reflux, 17 h, 35%; (e) LiOH·H_2O, THF, H_2O, rt, 48 h; (f) Et_3N, 2-(4-chlorophenyl)ethyl isothiocyanate, DMF, rt, 4 h.

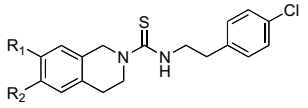
tive of **64** failed, even with up to 5 equivalents of sulfuryl chloride. Only the monochlorinated products were obtained.

The effect of substituting the hydroxyl groups in the A-ring with other functional groups that also can participate in hydrogen bonds was investigated. As indicated in the preceding paper,[12] the 1,2,3,4-tetrahydroisoquinolines are considered to be the most interesting of the capsazepinoids and consequently this part of the study was limited to 1,2,3,4-tetrahydroisoquinolines. For reference, the non-substituted 1,2,3,4-tetrahydroisoquinoline **142** was prepared, according to Scheme 5, by coupling of **141** with 2-(4-chlorophenyl)ethyl isothiocyanate.

In Scheme 6, the syntheses of the derivatives in which the hydroxyl groups in the A-ring are replaced by an amino group or a methylsulfonyl amide moiety are shown. Acylation of **141** and subsequent nitration afforded a mixture of **143** and **144**, which were isolated by chromatography. Hydrogenation and hydrolysis of **143** and **144** afforded **147** and **148**, which after coupling with 2-(4-chlorophenyl)ethyl isothiocyanate gave **153** and **154**. Selective *N*-Boc protection of the secondary amine of **147** and **148** afforded **149** and **150**, which could be mesylated to afford **151** and **152**. Deprotection of **151** and **152** with trifluoroacetic acid and coupling with 2-(4-chlorophenyl)ethyl isothiocyanate afforded **155** and **156**.

The preparation of additional analogues with cyano, carboxylic acid and methyl carboxylate groups in the A-ring is described in Scheme 7. The *N*-Boc protection of **30** yielded **157**, which was converted to **158** with triflic anhydride. Aromatic triflates have been reported to be converted nitriles in a palladium (0) catalyzed reaction,[14] but this method did not yield **159** from **158**. However, changing the ligand from triphenylphoshine to the strongly chelating ligand 1,1′-bis(diphenylphosphino)ferrocene and the palladium source from palladium tetrakistriphenylphoshine to tris(dibenzylideneacetone) dipalladium, and adding the $Zn(CN)_2$ in portions as previously suggested for catechols,[15] enabled us to prepare **159**, which was deprotected and coupled with 2-(4-chlorophenyl)ethyl isothiocyanate to yield **162**. Basic hydrolysis of the phthalonitrile **159** and in situ Fischer esterification produced the phthalic acid methylester **160**. The esterification was necessary to facilitate isolation of **160**, and basic hydrolysis of **160** afforded the phthalic acid **161**. Coupling of **160** and **161** with 2-(4-chlorophenyl)ethyl isothiocyanate afforded **163** and **164**.

Table 2. Remaining contraction after pretreatment with different capszepinoids (10 μM) with various substitution of the A-ring



Compound	R_1	R_2	Remaining contraction[a]
48[b]	H	OH	52 ± 6.8 (4)
153	H	NH_2	62 ± 6.0 (4)
155	H	$NHSO_2Me$	75 ± 6.7 (4)
52[b]	OH	H	75 ± 7.0 (4)
154	NH_2	H	79 ± 4.6 (4)
156	$NHSO_2Me$	H	72 ± 7.5 (4)
142	H	H	83 ± 2.2 (4)
34[b]	OH	OH	36 ± 6.5 (5)
162	CN	CN	84 ± 10.6 (4)
163	CO_2Me	CO_2Me	87 ± 1.8 (4)
164	CO_2H	CO_2H	99 ± 4.3 (4)

[a] Arithmetic mean ± the standard error of the mean of the percent remaining contraction in small human airways contracted with LTD4 in the presence of 10 μM test substance compared to a full contraction evoked by LTD4 in the absence of test compound. Number of times tested in parentheses.

[b] Compounds synthesized previously.[12]

3. Results and discussion

The bronchorelaxing effect of the derivatives synthesized was evaluated in vitro, as previously described,[8,16] in

human small airways (0.5–1.5 mm in diameter). The constriction evoked by 10 nM LTD_4 on untreated preparations and on the same preparations exposed to 10 μM of the test compound for 1.5 h was compared. The results, summarized in Tables 1 and 2, are shown as the percentage of the remaining contraction after 1.5 h exposure to the test substance compared to the full contraction. All compounds were assayed in the same way, in the same concentration and for the same time of exposure, in order to get comparable values. The effects can vary between 100% remaining contraction for an inactive compound and 0% remaining contraction for a compound with a maximal effect. This is a functional assay that is carried out with human tissue obtained from lung cancer patients. Until the target has been characterized and its function understood it is not possible to assess how the lipophilicity and other physicochemical properties of the compounds may affect their ability to reach and interact with the target. Two compounds reported to be equally active in this investigation may therefore differ if the concentration or time of exposure is changed. The SARs discussed here are consequently limited to the activities recorded in the assay used in this investigation.

The importance of hydroxyl groups in various positions in the different structure types has been discussed in the preceding paper,[12] where it was suggested that the hydroxyls participate in intermolecular bonds with the target protein. In an effort to investigate how the interactions of the hydroxyl groups may be modulated by other substituents in the A-ring, a number of chlorinated derivatives were prepared and assayed (results shown in Table 1). In an effort to investigate the necessity of the hydroxyl groups for the activity of the isoquinolines, a number of derivatives having other substituents in positions 6 and 7 were prepared and assayed (results are shown in Table 2). Both tables also contain the activity of a few derivatives reported in the preceding paper,[12] in order to facilitate comparison.

The monochlorination of the phenolic derivatives does not result in a clear effect. For the isoquinolines, **102** and **103** are both less potent compared to their non-chlorinated analogue **48**, while **111** is more potent and **112** equally potent compared to **52**. For the 1*H*-2-benzazepines, **129** is equally potent while **130** less potent compared to **61**, and **136** is equally potent while **137** is less potent compared to **66**. Dichlorination of the phenols has a clearer effect. **113** and **131** are both significantly more potent compared to **52** and **61**, while **104** is equally potent as **48**. The dichlorinated phenolic tetrahydro-1*H*-2-benzazepine **131** is also considerably better than the corresponding monochlorinated phenols **129** and **130**, and this could be seen as an electronic effect facilitating the interaction of the hydroxyl group of **131** with the target. However, as the catechols in general are more potent than the phenols,[12] adding chlorine to one or both remaining positions in the catechols may be more interesting. For the three B-ring systems isoindoline, 1,2,3,4-tetrahydroisoquinoline and 2,3,4,5-tetrahydro-1*H*-2-benzazepine, the general trend for monochlorination of a catechol is decreased activity (**17** vs **77**, **34** vs **94** and **95**, **2** vs **120** and **121**). On the other hand, dichlorination of the same derivatives resulted in considerably more potent compounds (**78**, **4** and **122**). The effect of chlorination on the bronchorelaxing properties of the capsazepinoids can be expected to be due to a combination of steric hindrance and changes in the electronic properties of the molecules. It is interesting to note that dichlorination of the 6,7-dihydroxylated isoquinolines **35** and **37**, that are substituted in position 1 with a methyl group (**35**) or a benzyl group (**37**), does not result in potent derivatives. As already suggested,[12] substituents in the B-ring appear to be unfavourable for steric reasons, and dichlorination will not affect the potency of compounds having a big group (e.g., benzyl) in position 1. However, position 3 appears to be less critical as the dichlorination of **36**, having a methyl group in position 3, results in **86** that is rather potent. The disparity of the results suggests that depending on the relative position of the hydroxyl group and chlorine with respect to each other, either steric or electronic factors will determine the strength of the interactions, presumably hydrogen bonds, of the hydroxyl group and hence the activity of the specific compound. In addition, the lipophilicity will increase upon addition of chlorines, which in general would be expected to facilitate the approach of the compound to the target, especially if it is intracellular. However, as mentioned above, no solid information about the target is available.

In an effort to investigate the necessity of the hydroxyl groups for the activity of the isoquinolines, a number of derivatives having other substituents in positions 6 and 7 were prepared (Schemes 5–7) and assayed (Table 2).

Compared to the corresponding phenol **48**, the aniline **153** displayed a somewhat lower potency, which may be explained by the lower hydrogen bond donating ability of the amino group compared to the hydroxyl group.[17] An amino group at C-7 (**154**) instead of a hydroxyl group (**52**) did not increase the potency, even compared to the non-substituted **142**. These findings support our suggestion that the hydroxyl group of **48** acts as a hydrogen bond donor.[12] Like phenols, anilines are known to be glucuronidated, although less rapidly, and altogether they are not attractive as a bioisostere to phenols in capsazepinoids. **2** was originally reported as a capsaicin and TRPV1 antagonist.[7] Replacement of the hydroxyl group with the biosteric methylsulfonylamido group and removal of the methoxy group converts vanilloids displaying TRPV1-agonism into antagonists, especially if the methoxy group is replaced with fluorine.[18] Inspired by this, the methylsulfonyl amides **155** and **156** were prepared. However, mesylation of the aniline **154** did not enhance its low potency, instead mesylation of the aniline **153** resulted in a drop in potency. Although metabolically more stable, the methylsulfonylamido group does seem less interesting as a bioisostere to the hydroxyl group in capsazepinoids. Previous findings have indicated that the binding site has limited volume around C-6, which may explain the drop in potency from the aniline **153** to the methylsulfo-

nyl amide **155**.[12] The catechol **34** is more potent than either of the phenols **48** or **52**. We have argued that this might be caused by both hydroxyl groups of the catechol moiety taking part in specific interactions, for example, hydrogen bonds.[12] The phthalic acid derivative **164** and derivatives thereof, **162** and **163**, are all possible hydrogen bond donors/acceptors. Unfortunately neither of them is potent, which might be because of the limited volume in the binding site where the A-ring binds. The phthalic acid derivative **164** is devoid of activity, possibly because it is charged at physiological pH and cannot pass cell membranes. The localization of the binding site of capsazepinoids acting as inhibitors of bronchoconstriction, as discussed above, is unknown, but if intracellularly located, as the capsaicin binding site of TRPV1, the complete lack of activity of **164** is explainable.[19,20]

4. Conclusions

Capsazepinoids, a novel class of bronchodilators, have been shown to be potent in vitro inhibitors of bronchoconstriction in human small airways. If similar effects are at hand also in vivo, they constitute a promising novel pharmaceutical principle to prevent and revoke airway obstruction caused by asthma or COPD. SAR studies of the capsazepinoids have revealed the importance of a phenol, or even better, a catechol moiety in the A-ring for the activity, and the effect of chlorination of the A-ring was studied. In addition, in an attempt to counteract the metabolic instability of phenols and catechols, alternatives to the hydroxyl groups in the A-ring were evaluated. The following conclusions could be drawn:

1. Monochlorination of the phenol derivatives does not provide any clear SARs, while dichlorination of the phenols in general enhances the activity.
2. Monochlorination of the catechol derivatives gives less potent compounds, while dichlorination of the catechols gives more potent compounds.
3. All the compounds with amino, (methylsulfonyl)amido, carboxy, methoxycarbonyl and cyano substituents instead of hydroxyl groups in the A-ring were less active compared to the corresponding phenols and catechols.
4. The two evaluated anilines (**153** and **154**) displayed a similar activity pattern as the corresponding phenols (**48** and **52**), supporting the suggestion that these groups interact with the target protein by donating a hydrogen bond.

5. Experimental

5.1. Materials

Materials were obtained from commercial suppliers and were used without further purification unless otherwise noted. DMF was distilled under reduced pressure. All moisture- and air-sensitive reactions were carried out under an atmosphere of dry nitrogen using oven-dried glassware. HRMS (ESI) spectra were recorded with a Micromass Q-TOF Micro spectrometer. NMR spectra (in $CDCl_3$ or CD_3OD) were recorded with a Bruker ARX 300 spectrometer at 300 MHz (^1H) and at 75 MHz (^{13}C) and with a Bruker DRX 400 spectrometer at 400 MHz (^1H) and at 100 MHz (^{13}C). Chemical shifts are given in ppm relative to TMS using the residual $CHCl_3$ peak in $CDCl_3$ or the residual CD_2HOD peak in CD_3OD solution as internal standard (7.26 or 3.32 and 77.2 or 49.0 ppm, respectively, relative to TMS). All flash chromatography was performed on 60 Å 35–70 μm Matrex silica gel (Grace Amicon). TLC analyses were made on Silica Gel 60 F_{254} (Merck) plates and visualized with ninhydrin/acetic acid and heating. The purity of the assayed compounds was verified with ^1H NMR and HPLC, and only used if more than 98% pure.

5.2. Synthesis

5.2.1. General procedure for demethylation. The corresponding amine was dissolved in HBr (48% in H_2O). The mixture was heated to 105 °C for 5 h and then concentrated. The residue was suspended in EtOAc and concentrated again.

5.2.2. Procedure A for chlorinations. The corresponding amine (1.0 equiv) was suspended in glacial acetic acid, SO_2Cl_2 (2.2 equiv for dichlorinations) was added dropwise. After stirring for 2.5 h the mixture was concentrated.

5.2.3. Procedure B for chlorinations. The corresponding amine (1.0 equiv) was suspended in glacial acetic acid, SO_2Cl_2 (1.2 equiv for monochlorinations and 2.2 equiv for dichlorinations) was added dropwise. After stirring for 2.5 h the mixture was concentrated. The crude mixture was dissolved in anhydrous DMF, triethylamine (3.0 equiv) and di-*tert*-butyl dicarbonate (1.5 equiv) were added. The reaction mixture was stirred for 2 h at room temperature, then it was concentrated under vacuum, H_2O was added to the residue and several extractions were made with EtOAc. The combined organic phases were dried ($MgSO_4$) and concentrated.

5.2.4. General procedure for coupling of amines with 2-(4-chlorophenyl)ethyl isothiocyanate. The corresponding amine (usually as a salt) (1.0 equiv) was dissolved in anhydrous DMF and triethylamine (3.0 equiv) was added. This mixture was stirred for 15 min and then 2-(4-chlorophenyl)ethyl isothiocyanate (1.2 equiv) was added. This mixture was stirred for additional 4 h and then concentrated. The residue was dissolved in EtOAc and washed with water. The organic phase was dried ($MgSO_4$) and concentrated.

5.2.4.1. 4,7-Dichloroisoindoline-5,6-diol hydrochloride (76). Compound **16** (1.0 equiv) was dissolved in anhydrous DMF, di-*tert*-butyldicarbonate (1.2 equiv) and triethylamine (2.0 equiv) were added. The mixture was stirred for 1 h and then concentrated. The residue was dissolved in EtOAc and washed with water. The organic phase was dried ($MgSO_4$) and concentrated. The residue was dissolved in a mixture of 80% trifluoroacetic acid, 19% dichloromethane and 1% anisol and stirred for 1 h. After evaporation a grey solid of 5,6-dihydroxyiso-

indoline trifluoroacetic acid salt remained. The salt was suspended in glacial acetic acid and SO_2Cl_2 (3.0 equiv) was added dropwise. After stirring for 2.5 h the mixture was concentrated. Toluene was added and the mixture concentrated again, to afford **76** (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 4.62 (s, 4H).

5.2.4.2. 4-Chloro-*N*-[2-(4-chlorophenyl)ethyl]-5,6-dihydroxy-1,3-dihydro-2*H*-isoindole-2-carbothioamide (77). Compound **16** (1.0 equiv) was dissolved in anhydrous DMF, di-*tert*-butyldicarbonate (1.2 equiv) and triethylamine (2.0 equiv) were added. The mixture was stirred for 1 h and then concentrated. The residue was dissolved in EtOAc and washed with water. The organic phase was dried ($MgSO_4$) and concentrated. The residue was dissolved in a mixture of 80% trifluoroacetic acid, 19% dichloromethane and 1% anisol and stirred for 1 h. After evaporation a grey solid of 5,6-dihydroxyisoindoline trifluoroacetic acid salt remained. This salt was suspended in glacial acetic acid and SO_2Cl_2 (2.0 equiv) was added dropwise. After stirring for 2.5 h, the mixture was concentrated. H_2O was added and extractions were made with EtOAc. The organic phases were dried ($MgSO_4$) and concentrated affording **75** which was used for the next step without further purification. **75** was dissolved in anhydrous DMF and triethylamine (3.0 equiv) was added. This mixture was stirred for 15 min and then 2-(4-chlorophenyl)ethyl isothiocyanate (1.2 equiv) was added. This mixture was stirred for additional 3 h and then concentrated. The residue was dissolved in EtOAc and washed with water. The organic phase was dried ($MgSO_4$) and concentrated. **77** was purified by flash column chromatography (silica, pet. ether/EtOAc 7:3) (27%). ^{1}H NMR (CD_3OD 400 MHz) δ 2.92 (t, J = 7.6 Hz, 2H), 3.78 (t, J = 7.6 Hz, 2H), 4.68 (br s, 4H), 6.64 (s, 1H), 7.21 (d, J = 8.5 Hz, 2H), 7.26 (d, J = 8.5 Hz, 2H). ^{13}C NMR (CD_3OD 100 MHz) δ 35.9, 47.7, 53.5, 58.8, 108.5, 116.1, 126.5, 128.2, 129.4, 129.4, 131.5, 131.5, 133.0, 139.5, 142.8, 147.9, 179.8. HRMS (ESI) calculated for $C_{17}H_{17}Cl_2N_2O_2S$ (M+H) 383.0388, found 383.0371.

5.2.4.3. 4,7-Dichloro-*N*-[2-(4-chlorophenyl)ethyl]-5,6-dihydroxy-1,3-dihydro-2*H*-isoindole-2-carbothioamide (78). Compound **78** was prepared from **76** as described in the general procedure for coupling and purified by flash column chromatography (silica, pet. ether/EtOAc 6:4) (78%). ^{1}H NMR (CD_3OD 400 MHz) δ 2.93 (t, J = 7.6 Hz, 2H), 3.78 (t, J = 7.6 Hz, 2H), 4.76 (br s, 4H), 7.22 (d, J = 8.6 Hz, 2H), 7.27 (d, J = 8.6 Hz, 2H). ^{13}C NMR (CD_3OD 100 MHz) δ 35.8, 47.8, 54.0, 58.5, 115.0, 115.0, 126.8, 126.8, 129.5, 129.5, 131.5, 131.5, 133.0, 139.5, 144.2, 144.2, 180.0. HRMS (ESI) calculated for $C_{17}H_{16}Cl_3N_2O_2S$ (M+H) 416.9998, found 416.9994.

5.2.4.4. 5,8-Dichloro-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (79). Compound **79** was synthesized from **27**, using the procedure A for chlorinations (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 1.67 (d, J = 6.8 Hz, 3H), 3.00 (m, 1H), 3.18 (m, 1H), 3.60 (m, 2H), 3.91 (s, 3H), 3.92 (s, 6H), 4.89 (m, 1H).

5.2.4.5. 5,8-Dichloro-6,7-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (80). Compound **80** was synthesized from **28**, using the procedure A for chlorinations (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 1.54 (d, J = 6.4 Hz, 3H), 2.76 (m, 1H), 3.26 (m, 1H), 3.61 (m, 1H), 3.92 (s, 6H), 4.30 (d, J = 16.4 Hz, 1H), 4.40 (d, J = 16.4 Hz, 1H).

5.2.4.6. 1-Benzyl-5,8-dichloro-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (81). Compound **81** was synthesized from **29**, using the procedure A for chlorinations (quantitative). ^{1}H NMR ($CDCl_3$ 300 MHz) δ 3.21 (m, 5H), 3.86 (m, 1H), 3.89 (s, 3H), 3.93 (s, 3H), 5.06 (s, 1H), 7.25 (m, 5H).

5.2.4.7. 5,8-Dichloro-1-methyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol hydrobromide (82). Compound **82** was prepared from **79** using the general procedure for demethylation (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 1.65 (d, J = 6.8 Hz, 3H), 3.00 (m, 1H), 3.12 (m, 1H), 3.58 (m, 2H), 4.80 (q, J = 6.8 Hz, 1H).

5.2.4.8. 5,8-Dichloro-3-methyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol hydrobromide (83). Compound **83** was prepared from **80** using the general procedure for demethylation (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 1.53 (d, J = 6.5 Hz, 3H), 2.68 (dd, J = 17.6 Hz, J = 11.0 Hz, 1H), 3.17 (dd, J = 17.6 Hz, J = 4.5 Hz, 1H), 3.63 (m, 1H), 4.22 (d, J = 16.4 Hz, 1H), 4.41 (d, J = 16.4 Hz, 1H).

5.2.4.9. 1-Benzyl-5,8-dichloro-1,2,3,4-tetrahydroisoquinoline-6,7-diol hydrobromide (84). Compound **84** was prepared from **81** using the general procedure for demethylation (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 3.08 (m, 3H), 3.47 (m, 2H), 3.71 (m, 1H), 5.01 (m, 1H), 7.41 (m, 5H).

5.2.4.10. 5,8-Dichloro-*N*-[2-(4-chlorophenyl)ethyl]-6,7-dihydroxy-1-methyl-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (85). Compound **85** was prepared from **82** as described in the general procedure for coupling and purified by flash column chromatography (silica, pet. ether/EtOAc 3:2+1%AcOH) (58%). ^{1}H NMR (CD_3OD 300 MHz) δ 1.48 (d, J = 6.6 Hz, 3H), 2.85 (m, 2H), 2.94 (t, J = 6.9 Hz, 2H), 3.56 (m, 1H), 3.83 (m, 2H), 4.23 (br s, 1H), 6.29 (br s, 1H), 7.19 (d, J = 8.6 Hz, 2H), 7.23 (t, J = 8.6 Hz, 2H). ^{13}C NMR (CD_3OD 75 MHz) δ 19.4, 26.6, 35.6, 41.5, 47.9, 53.8, 118.4, 120.2, 122.3, 125.1, 129.4, 129.4, 131.5, 131.5, 133.0, 139.6, 142.8, 143.1, 181.7. HRMS (ESI) calculated for $C_{19}H_{20}Cl_3N_2O_2S$ (M+H) 445.0311, found 445.0302.

5.2.4.11. 5,8-Dichloro-*N*-[2-(4-chlorophenyl)ethyl]-6,7-dihydroxy-3-methyl-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (86). Compound **86** was prepared from **83** as described in the general procedure for coupling and purified by flash column chromatography (silica, pet. ether/EtOAc 3:2+1%AcOH) (52%). ^{1}H NMR (CD_3OD 300 MHz) δ 1.05 (d, J = 6.7 Hz, 3H), 2.85 (d, J = 3.3 Hz, 2H), 2.96 (dt, J = 1.8 Hz, J = 7.5 Hz, 2H), 3.86 (m, 2H), 4.29 (d, J = 17.1 Hz, 1H), 5.04 (d, J = 17.1 Hz, 1H), 5.46 (br s, 1H), 7.22 (d, J = 8.8 Hz,

2H), 7.26 (t, $J = 8.8$ Hz, 2H). ^{13}C NMR (CD_3OD 75 MHz) δ 17.0, 32.7, 35.6, 45.2, 47.9, 49.8, 119.6, 120.8, 122.6, 123.6, 129.4, 129.4, 131.5, 131.5, 133.0, 139.6, 143.0, 143.2, 182. HRMS (ESI) calculated for $C_{19}H_{20}Cl_3N_2O_2S$ (M+H) 445.0311, found 445.0296.

5.2.4.12. 1-Benzyl-5,8-dichloro-*N*-[2-(4-chlorophenyl) ethyl]-6,7-dihydroxy-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (87). Compound **87** was prepared from **84** as described in the general procedure for coupling and purified by flash column chromatography (silica, pet. ether/EtOAc 4:1+1%AcOH) (75%). ^{1}H NMR (CD_3OD 400 MHz) δ 2.60 (m, 1H), 2.81 (m, 3H), 3.08 (m, 1H), 3.32 (m, 1H), 3.67 (m, 3H), 4.17 (br s, 1H), 6.48 (br s, 1H), 7.20 (m, 9H). ^{13}C NMR (CD_3OD 100 MHz) δ 26.0, 35.4, 40.4, 42.3, 47.8, 59.1, 119.0, 125.8, 127.6, 129.3, 129.3, 129.5, 129.5, 130.7, 130.7, 131.5, 131.5, 133.0, 139.3, 139.6, 142.7, 143.3, 152.5, 153.8, 182.9. HRMS (ESI) calculated for $C_{25}H_{24}Cl_3N_2O_2S$ (M+H) 521.0624, found 521.0619.

5.2.4.13. *tert*-Butyl 8-chloro-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (88) and *tert*-butyl 5-chloro-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (89). These compounds were synthesized from compound **26**, using procedure B for chlorinations (1.1 equiv of SO_2Cl_2) affording **88** and **89** in 1:1.7 ratio. Purification was done by flash column chromatography (silica, gradient elution, 15–20% EtOAc in pet. ether) (51%).

Compound **88**: ^{1}H NMR ($CDCl_3$ 300 MHz) δ 1.49 (s, 9H), 2.76 (t, $J = 5.6$ Hz, 2H), 3.61 (t, $J = 5.6$ Hz, 2H), 3.84 (s, 3H), 3.85 (s, 3H), 4.49 (s, 2H), 6.60 (s, 1H).

Compound **89**: ^{1}H NMR ($CDCl_3$ 300 MHz) δ 1.48 (s, 9H), 2.77 (t, $J = 6.0$ Hz, 2H), 3.63 (t, $J = 6.0$ Hz, 2H), 3.83 (s, 3H), 3.84 (s, 3H), 4.50 (s, 2H), 6.56 (s, 1H).

5.2.4.14. 5,8-Dichloro-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (90). Compound **90** was synthesized from compound **26**, using procedure A for chlorinations (quantitative). ^{1}HNMR ($CDCl_3$ 300 MHz) δ 3.10 (t, $J = 6.3$ Hz, 2H), 3.53 (t, $J = 6.3$ Hz, 2H), 3.91 (s, 3H), 3.92 (s, 3H), 4.36 (s, 2H)

5.2.4.15. 8-Chloro-1,2,3,4-tetrahydroisoquinoline-6,7-diol hydrobromide (91). This compound was prepared from **88** using the general procedure for demethylation (quantitative). ^{1}H (CD_3OD 300 MHz) δ 2.98 (t, $J = 6.2$ Hz, 2H), 3.44 (t, $J = 6.2$ Hz, 2H), 4.24 (s, 2H), 6.64 (s, 1H).

5.2.4.16. 5-Chloro-1,2,3,4-tetrahydroisoquinoline-6,7-diol hydrobromide (92). This compound was prepared from **89** using the general procedure for demethylation (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 3.00 (t, $J = 6.5$ Hz, 2H), 3.50 (t, $J = 6.5$ Hz, 2H), 4.21 (s, 2H), 6.60 (s, 1H).

5.2.4.17. 5,8-Dichloro-1,2,3,4-tetrahydroisoquinoline-6,7-diol hydrobromide (93). This compound was prepared from **90** using the general procedure for demethylation (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 3.02 (t, $J = 6.3$ Hz, 2H), 3.51 (t, $J = 6.3$ Hz, 2H), 4.28 (s, 2H).

5.2.4.18. 8-Chloro-*N*-[2-(4-chlorophenyl)ethyl]-6,7-dihydroxy-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (94). This compound was prepared from **91** as described in the general procedure for coupling and purified by flash column chromatography (silica, pet. ether/EtOAc/AcOH 50:50:1) (53%). ^{1}H NMR (CD_3OD 300 MHz) δ 2.72 (t, $J = 5.5$ Hz, 2H), 2.93 (t, $J = 7.2$ Hz, 2H), 3.83 (t, $J = 7.2$ Hz, 2H), 3.93 (t, $J = 5.5$ Hz, 2H), 4.79 (s, 2H), 6.57 (s, 1H), 7.20 (d, $J = 8.6$ Hz, 2H), 7.24 (t, $J = 8.6$ Hz, 2H). ^{13}C NMR (CD_3OD 75 MHz) δ 29.1, 35.6, 46.6, 47.9, 48.9, 114.3, 119.5, 122.9, 128.1, 129.4, 129.4, 131.5, 131.5, 133.0, 139.6, 141.7, 146.2, 182.3. HRMS (ESI) calculated for $C_{18}H_{19}Cl_2N_2O_2S$ (M+H) 397.0544, found 397.0531.

5.2.4.19. 5-Chloro-*N*-[2-(4-chlorophenyl)ethyl]-6,7-dihydroxy-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (95). This compound was prepared from **92** as described in the general procedure for coupling and purified by flash column chromatography (silica, pet. ether/EtOAc/AcOH 50:50:1) (24%). ^{1}H NMR (CD_3OD 400 MHz) δ 2.81 (t, $J = 6.0$ Hz, 2H), 2.93 (t, $J = 7.4$ Hz, 2H), 3.82 (t, $J = 7.4$ Hz, 2H), 3.95 (t, $J = 6.0$ Hz, 2H), 4.77 (s, 2H), 6.55 (s, 1H), 7.23 (m, 4H). ^{13}C NMR (CD_3OD 100 MHz) δ 26.9, 35.6, 46.5, 47.9, 50.3, 112.2, 121.2, 125.0, 126.4, 129.4, 129.4, 131.5, 131.5, 133.0, 139.6, 142.1, 146.0, 182.0. HRMS (ESI) calculated for $C_{18}H_{19}Cl_2N_2O_2S$ (M+H) 397.0544, found 397.0585.

5.2.4.20. 5,8-Dichloro-*N*-[2-(4-chlorophenyl)ethyl]-6,7-dihydroxy-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (4). This compound was prepared from **93** as described in the general procedure for coupling and purified by flash column chromatography (silica, pet. ether/EtOAc 60:40+1%AcOH) (51%). ^{1}H NMR (CD_3OD 400 MHz) δ 2.77 (t, $J = 5.8$ Hz, 2H), 2.93 (t, $J = 7.4$ Hz, 2H), 3.82 (t, $J = 7.4$ Hz, 2H), 3.95 (t, $J = 5.8$ Hz, 2H), 4.85 (s, 2H), 7.20 (m, 4H). ^{13}C NMR (CD_3OD 100 MHz) δ 27.1, 35.5, 45.8, 47.9, 49.3, 118.4, 120.2, 124.2, 125.8, 129.4, 129.4, 131.5, 131.5, 133.0, 139.5, 142.6, 142.9, 182.5. HRMS (ESI) calculated for $C_{18}H_{18}Cl_3N_2OS$ (M+H) 431.0154, found 431.0210.

5.2.4.21. *tert*-Butyl 7-chloro-6-methoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (96) and *tert*-butyl 5-chloro-6-methoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (97). These compounds were synthesized from **44**, using procedure B for chlorinations (1.1 equiv of SO_2Cl_2) affording *tert*-butyl 7-chloro-6-methoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate and *tert*-butyl 5-chloro-6-methoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate in a 2:11 ratio. Purification was done by flash column chromatography (silica, gradient elution 10–90% EtOAc in pet. ether) (35%).

Compound **96**: ^{1}H NMR ($CDCl_3$ 300 MHz) δ 1.48 (s, 9H), 2.78 (t, $J = 5.7$ Hz, 2H), 3.62 (t, $J = 5.7$ Hz, 2H), 3.87 (s, 3H), 4.47 (s, 2H), 6.67 (s, 1H), 7.10 (s, 1H).

Compound **97**: ^{1}H NMR ($CDCl_3$ 300 MHz) δ 1.48 (s, 9H), 2.87 (t, J = 6.0 Hz, 2H), 3.64 (t, J = 6.0 Hz, 2H), 3.88 (s, 3H), 4.51 (s, 2H), 6.81 (d, J = 8.4 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H).

5.2.4.22. *tert*-Butyl 5,7-dichloro-6-methoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (98). This compound was synthesized from **44**, using procedure B for chlorinations (2.2 equiv of SO_2Cl_2). Purification was done by flash column chromatography (silica, pet. ether/EtOAc 8:1) to afford *tert*-butyl 5,7-dichloro-6-methoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (29%). ^{1}H NMR ($CDCl_3$ 400 MHz) δ 1.47 (s, 9H), 2.81 (t, J = 6.0 Hz, 2H), 3.64 (t, J = 6.0 Hz, 2H), 3.86 (s, 3H), 4.49 (s, 2H), 7.06 (s, 1H).

5.2.4.23. 7-Chloro-1,2,3,4-tetrahydroisoquinolin-6-ol hydrobromide (99). This compound was prepared from **96** using the general procedure for demethylation (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 3.05 (t, J = 6.4 Hz, 2H), 3.48 (t, J = 6.4 Hz, 2H), 4.27 (s, 2H), 6.80 (s, 1H), 7.20 (s, 1H).

5.2.4.24. 5-Chloro-1,2,3,4-tetrahydroisoquinolin-6-ol hydrobromide (100). This compound was prepared from **97** using the general procedure for demethylation (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 3.11 (t, J = 6.6 Hz, 2H), 3.54 (t, J = 6.6 Hz, 2H), 4.29 (s, 2H), 6.90 (d, J = 8.5 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H).

5.2.4.25. 5,7-Dichloro-1,2,3,4-tetrahydroisoquinolin-6-ol hydrobromide (101). This compound was prepared from **98** using the general procedure for demethylation (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 3.08 (t, J = 6.5 Hz, 2H), 3.56 (t, J = 6.5 Hz, 2H), 4.31 (s, 2H), 7.24 (s, 1H).

5.2.4.26. 7-Chloro-*N*-[2-(4-chlorophenyl)ethyl]-6-hydroxy-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (102). This compound was prepared from **99** as described in the general procedure for coupling and purified by flash column chromatography (silica, pet. ether/EtOAc/AcOH 50:50:1) (53%). ^{1}H NMR ($CDCl_3$:CD_3OD, 5:1, 300 MHz) δ 2.68 (t, J = 5.8 Hz, 2H), 2.82 (t, J = 7.3 Hz, 2H), 3.75 (m, 4H), 3.89 (br s, 1H), 4.60 (s, 2H), 6.63 (s, 1H), 6.86 (s, 1H), 7.05 (d, J = 8.3 Hz, 2H), 7.13 (d, J = 8.3 Hz, 2H). ^{13}C NMR ($CDCl_3$:CD_3OD, 5:1, 75 MHz) δ 28.3, 34.6, 45.3, 46.7, 48.2, 115.5, 118.5, 125.1, 127.3, 128.5, 128.5, 130.1, 130.1, 132.0, 135.0, 137.6, 151.3, 180.6. HRMS (ESI) calculated for $C_{18}H_{19}Cl_2N_2OS$ (M+H) 381.0595, found 381.0588.

5.2.4.27. 5-Chloro-*N*-[2-(4-chlorophenyl)ethyl]-6-hydroxy-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (103). This compound was prepared from **100** as described in the general procedure for coupling and purified by flash column chromatography (silica, pet. ether/EtOAc/AcOH 50:50:1) (80%). ^{1}H NMR (CD_3OD 300 MHz) δ 2.92 (t, J = 5.9 Hz, 2H), 2.94 (t, J = 7.6 Hz, 2H), 3.83 (t, J = 7.6 Hz, 2H), 3.99 (t, J = 5.9 Hz, 2H), 4.81 (s, 2H), 6.82 (d, J = 8.3 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 7.23 (m, 4H). ^{13}C NMR (CD_3OD 75 MHz) δ 27.6, 35.6, 46.2, 47.9, 50.2, 115.5, 121.7, 126.3, 127.1, 129.4, 129.4, 131.6, 131.6, 133.0, 135.2, 139.6, 153.2, 182.2. HRMS (ESI) calculated for $C_{18}H_{19}Cl_2N_2OS$ (M+H) 381.0595, found 381.0609.

5.2.4.28. 5,7-Dichloro-*N*-[2-(4-chlorophenyl)ethyl]-6-hydroxy-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (104). This compound was prepared from **101** as described in the general procedure for coupling and purified by flash column chromatography (silica, LC, pet. ether/EtOAc/AcOH 40:10:1) (58%). ^{1}H NMR (CD_3OD 300 MHz) δ 2.84 (t, J = 6.0 Hz, 2H), 2.92 (t, J = 7.4 Hz, 2H), 3.81 (t, J = 7.4 Hz, 2H), 3.98 (t, J = 6.0 Hz, 2H), 4.79 (s, 2H), 7.05 (s, 1H), 7.17 (d, J = 8.6 Hz, 2H), 7.22 (d, J = 8.6 Hz, 2H). ^{13}C NMR (CD_3OD 75 MHz) δ 27.5, 35.6, 46.0, 47.9, 49.8, 121.1, 122.8, 126.6, 127.7, 129.4, 129.4, 131.5, 131.5, 133.0, 133.9, 139.5, 149.2, 182.2. HRMS (ESI) calculated for $C_{18}H_{18}Cl_3N_2OS$ (M+H) 415.0205, found 415.0195.

5.2.4.29. *tert*-Butyl 8-chloro-7-methoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (105) and *tert*-butyl 6-chloro-7-methoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (106). These compounds were synthesized from **50**, using procedure B for chlorinations (1.1 equiv of SO_2Cl_2) to yield a mixture containing both compounds. Purification was not possible, so the mixture was used for further synthesis.

5.2.4.30. *tert*-Butyl 6,8-dichloro-7-methoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (107). This compound was synthesized from **50**, using procedure B for chlorinations (2.2 equiv of SO_2Cl_2). Purification was done by flash column chromatography (silica, pet. ether/EtOAc 5:1) to afford **107** along with the **105** in a 1:2.2 ratio (57%). ^{1}H NMR ($CDCl_3$ 300 MHz) δ 1.50 (s, 9H), 2.77 (br s, 2H), 3.65 (br s, 2H), 3.87 (s, 3H), 4.53 (s, 2H), 7.10 (s, 1H).

5.2.4.31. 8-Chloro-1,2,3,4-tetrahydroisoquinolin-7-ol hydrobromide (108) and 6-chloro-1,2,3,4-tetrahydroisoquinolin-7-ol hydrobromide (109). The mixture containing **105** and **106** was treated as described in the general method for demethylation affording a mixture containing **105** and **106** which was used for further synthesis without purification.

5.2.4.32. 6,8-Dichloro-1,2,3,4-tetrahydroisoquinolin-7-ol hydrobromide (110). This compound was prepared from **107**, using the general procedure for demethylation (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 2.77 (t, J = 5.8 Hz, 2H), 3.49 (t, J = 5.8 Hz, 2H), 4.35 (s, 2H), 7.28 (s, 1H).

5.2.4.33. 8-Chloro-*N*-[2-(4-chlorophenyl)ethyl]-7-hydroxy-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (111) and 6-chloro-*N*-[2-(4-chlorophenyl)ethyl]-7-hydroxy-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (112). These compounds were prepared from the mixture containing **108** and **109** as described in the general procedure for coupling. Purification was done first by flash column chromatography (silica, pet. ether/EtOAc/ AcOH 50:50:1) and then with normal phase HPLC (Microsorb,

silica 5 μm, 250 × 10 mm, 4.0 ml/min of 28 % EtOAc in petroleum ether, detection at 280 nm) (55%).

Compound **111**: ^{1}H NMR ($CDCl_3$ 300 MHz) δ 2.74 (t, J = 5.7 Hz, 2H), 2.89 (t, J = 7.1 Hz, 2H), 3.11, (br s, 2H), 3.85 (t, J = 7.1 Hz, 2H), 3.93 (t, J = 5.7 Hz, 2H), 4.66 (s, 2H), 6.76 (d, J = 8.3 Hz, 1H), 6.86 (d, J = 8.3 Hz, 1H), 7.11 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$ 75 MHz) δ 27.9, 34.5, 45.7, 46.7, 47.4, 114.1, 117.9, 127.2, 127.5, 128.6, 128.6, 130.1, 130.1, 130.6, 132.2, 137.5, 150.8, 181.2. HRMS (ESI) calculated for $C_{18}H_{19}Cl_2N_2OS$ (M+H) 381.0595, found 381.0612.

Compound **112**: ^{1}H NMR ($CDCl_3$ 300 MHz) δ 2.77 (t, J = 5.9 Hz, 2H), 2.84 (br s, 2H), 2.92 (t, J = 7.2 Hz, 2H), 3.77 (t, J = 7.2 Hz, 2H), 3.87 (t, J = 5.9 Hz, 2H), 4.76 (s, 2H), 6.71 (s, 1H), 7.08 (s, 1H), 7.14 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$ 75 MHz) δ 27.6, 34.6, 45.3, 46.7, 49.0, 114.0, 118.9, 127.3, 128.5, 128.6, 128.6, 130.1, 130.1, 132.2, 132.8, 137.5, 150.8, 180.9. HRMS (ESI) calculated for $C_{18}H_{19}Cl_2N_2OS$ (M+H) 381.0595, found 381.0591.

5.2.4.34. 6,8-Dichloro-*N*-[2-(4-chlorophenyl)ethyl]-7-hydroxy-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (113). This compound was prepared from **110** as described in the general procedure for coupling and purified by flash chromatography (silica, heptane/EtOAc/AcOH 66:33:1) (56%). ^{1}H NMR (CD_3OD 400 MHz) δ 2.78 (t, J = 5.7 Hz, 2H), 2.94 (t, J = 7.4 Hz, 2H), 3.84 (t, J = 7.4 Hz, 2H), 3.93 (t, J = 5.7 Hz, 2H), 4.89 (s, 2H), 7.12 (s, 1H), 7.22 (m, 4H). ^{13}C NMR (CD_3OD 100 MHz) δ 28.6, 35.6, 46.1, 48.0, 49.5, 121.1, 121.5, 128.7, 129.3, 129.4, 131.5, 131.5, 132.0, 133.0, 139.5, 139.6, 148.9, 182.8. HRMS (ESI) calculated for $C_{18}H_{18}Cl_3N_2O_2S$ (M+H) 415.0205, found 415.0214.

5.2.4.35. *tert*-Butyl 9-chloro-7,8-dimethoxy-1,3,4,5-tetrahydro-2*H*-2-benzazepine-2-carboxylate (114) and *tert*-butyl 6-chloro-7,8-dimethoxy-1,3,4,5-tetrahydro-2*H*-2-benzazepine-2-carboxylate (115). These compounds were synthesized from compound**57**, using procedure B for chlorinations (1.1 equiv of SO_2Cl_2), affording a mixture of **114** and **115** in 1:1 ratio. Purification was done by flash column chromatography (silica, pet. ether/EtOAc 6:1) (45%).

Compound **114**: ^{1}H NMR ($CDCl_3$ 300 MHz) δ 1.43 (s, 9H), 1.85 (m, 2H), 2.90 (m, 2H), 3.69 (m, 2H), 3.84 (s, 3H), 3.87 (s, 3H), 4.66 (s, 2H), 6.64 (s, 1H).

Compound **115**: ^{1}H NMR ($CDCl_3$ 300 MHz) δ 1.43 (s, 9H), 1.75 (m, 2H), 3.12 (m, 2H), 3.65 (m, 2H), 3.85 (s, 3H), 3.88 (s, 3H), 4.35 (s, 2H), 6.72 (s, 1H).

5.2.4.36. *tert*-Butyl 6,9-dichloro-7,8-dimethoxy-1,3,4,5-tetrahydro-2*H*-2-benzazepine-2-carboxylate (116). This compound was synthesized from **57**, using procedure B for chlorinations (2.2 equiv of SO_2Cl_2). Purification was done by flash column chromatography (silica, pet. ether/EtOAc 6:1) to afford **116** (45%). ^{1}H NMR ($CDCl_3$ 300 MHz) δ 1.43 (s, 9H), 1.85 (m, 2H), 3.15 (m, 2H), 3.69 (m, 2H), 3.90 (s, 3H), 3.91 (s, 3H), 4.73 (s, 2H).

5.2.4.37. 9-Chloro-2,3,4,5-tetrahydro-1*H*-2-benzazepine-7,8-diol hydrobromide (117). This compound was prepared from **114** using the general procedure for demethylation (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 1.95 (m, 2H), 2.95 (m, 2H), 3.46 (m, 2H), 4.54 (s, 2H), 6.68 (s, 1H).

5.2.4.38. 6-Chloro-2,3,4,5-tetrahydro-1*H*-2-benzazepine-7,8-diol hydrobromide (118). This compound was prepared from **115** using the general procedure for demethylation (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 1.93 (m, 2H), 3.21 (m, 2H), 3.44 (m, 2H), 4.27 (s, 2H), 6.79 (s, 1H).

5.2.4.39. 6,9-Dichloro-2,3,4,5-tetrahydro-1*H*-2-benzazepine-7,8-diol hydrobromide (119). This compound was prepared from **116** using the general procedure for demethylation, to afford **119** (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 1.96 (m, 2H), 3.31 (m, 2H), 3.46 (m, 2H), 4.61 (s, 2H).

5.2.4.40. 9-Chloro-*N*-[2-(4-chlorophenyl)ethyl]-7,8-dihydroxy-1,3,4,5-tetrahydro-2*H*-2-benzazepine-2-carbothioamide (120). This compound was prepared from **117** as described in the general procedure for coupling and purified by flash column chromatography (silica, CH_2Cl_2) (48%). ^{1}H NMR (CD_3OD 400 MHz) δ 1.80 (m, 2H), 2.80 (m, 2H), 2.87 (t, J = 7.0 Hz, 2H), 3.82 (t, J = 7.0 Hz, 2H), 4.21 (br s, 2H), 4.80 (s, 2H), 6.60 (s, 1H), 7.13 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H). ^{13}C NMR (CD_3OD 100 MHz) δ 28.7, 35.5, 35.5, 47.9, 50.7, 55.4, 116.8, 121.1, 125.4, 129.5, 129.5, 131.5, 131.5, 133.1, 135.2, 139.4, 141.0, 146.6, 181.3. HRMS (ESI) calculated for $C_{19}H_{21}Cl_2N_2O_2S$ (M+H) 411.0701, found 411.0690.

5.2.4.41. 6-Chloro-*N*-[2-(4-chlorophenyl)ethyl]-7,8-dihydroxy-1,3,4,5-tetrahydro-2*H*-2-benzazepine-2-carbothioamide (121). This compound was prepared from **118** as described in the general procedure for coupling and purified by flash column chromatography (silica, CH_2Cl_2) (31%). ^{1}H NMR (CD_3OD 500 MHz) δ 1.75 (m, 2H), 2.87 (t, J = 7.3 Hz, 2H), 3.03 (m, 2H), 3.75 (t, J = 7.3 Hz, 2H), 4.93 (br s, 2H), 4.77 (s, 2H), 6.82 (s, 1H), 7.01 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H). ^{13}C NMR (CD_3OD 125 MHz) δ 27.6, 29.6, 35.6, 47.8, 52.8, 55.5, 116.8, 122.1, 129.4, 129.4, 129.6, 130.7, 131.6, 131.6, 133.0, 139.6, 142.3, 144.7, 181.4. HRMS (ESI) calculated for $C_{19}H_{19}Cl_2N_2O_2S$ (M−H) 409.0545, found 409.0557.

5.2.4.42. 6,9-Dichloro-*N*-[2-(4-chlorophenyl)ethyl]-7,8-dihydroxy-1,3,4,5-tetrahydro-2*H*-2-benzazepine-2-carbothioamide (122). This compound was prepared from **119** as described in the general procedure for coupling and purified by flash column chromatography (silica, CH_2Cl_2) (44%). ^{1}H NMR (CD_3OD 400 MHz) δ 1.82 (m, 2H), 2.88 (t, J = 7.2 Hz, 2H), 3.06 (m, 2H), 3.82 (t, J = 7.2 Hz, 2H), 4.07 (br s, 2H), 4.92 (s, 2H), 7.14 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H). ^{13}C NMR

(CD_3OD 100 MHz) δ 27.2, 29.9, 35.5, 47.9, 51.1, 53.1, 120.2, 121.3, 126.3, 129.5, 129.5, 131.5, 131.5, 131.8, 133.1, 139.4, 142.1, 143.7, 181.7. HRMS (ESI) calculated for $C_{19}H_{20}Cl_3N_2O_2S$ (M+H) 445.0311, found 445.0313.

5.2.4.43. *tert*-Butyl 8-chloro-7-methoxy-1,3,4,5-tetrahydro-2*H*-2-benzazepine-2-carboxylate (123) and *tert*-butyl 6-chloro-7-methoxy-1,3,4,5-tetrahydro-2*H*-2-benzazepine-2-carboxylate (124). These compounds were synthesized from **58** using procedure B for chlorinations (1.1 equiv of SO_2Cl_2), affording **123** and **124** along with the 6,8-dichloro derivative **125** in a 4.2:1:2.2 ratio. Purification was done by flash column chromatography (silica, gradient elution 10–20% EtOAc in pet. ether), (70%).

Compound **123**: ^{1}H NMR ($CDCl_3$ 300 MHz) δ 1.39 (s, 9H), 1.76 (m, 2H), 2.90 (m, 2H), 3.66 (m, 2H), 3.87 (s, 3H), 4,26 (s, 2H), 6.72 (s, 1H), 7.16 (s, 1H).

Compound **124**: ^{1}H NMR ($CDCl_3$ 300 MHz) δ 1.40 (s, 9H), 1.76 (m, 2H), 3.20 (m, 2H), 3.67 (m, 2H), 3.89 (s, 3H), 4,35 (s, 2H), 6.71 (d, J = 8.2 Hz, 1H), 7.05 (d, J = 8.2 Hz, 1H).

5.2.4.44. *tert*-Butyl 6,8-dichloro-7-methoxy-1,3,4,5-tetrahydro-2*H*-2-benzazepine-2-carboxylate (125). This compound was synthesized from **58** using procedure B for chlorinations (2.2 equiv SO_2Cl_2). Purification was done by flash column chromatography (silica, gradient elution 12.5–20 EtOAc in pet. ether) affording **125** (58%). ^{1}H NMR ($CDCl_3$ 300 MHz) δ 1.40 (s, 9H), 1.75 (m, 2H), 3.14 (m, 2H), 3.68 (m, 2H), 3.86 (s, 3H), 4.31 (s, 2H), 7.12 (s, 1H).

5.2.4.45. 8-Chloro-2,3,4,5-tetrahydro-1*H*-2-benzazepin-7-ol hydrobromide (126). This compound was prepared from **123** using the general procedure for demethylation (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 1.97 (m, 2H), 2.96 (m, 2H), 3.44 (m, 2H), 4.28 (s, 2H), 6.85 (s, 1H), 7.34 (s, 1H).

5.2.4.46. 6-Chloro-2,3,4,5-tetrahydro-1*H*-2-benzazepin-7-ol hydrobromide (127). This compound was prepared from **124** using the general procedure for demethylation (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 1.97 (m, 2H), 3.31 (m, 2H), 3.45 (m, 2H), 4.35 (s, 2H), 6.81 (d, J = 8.2 Hz, 1H), 7.17 (d, J = 8.2 Hz, 1H).

5.2.4.47. 6,8-Dichloro-2,3,4,5-tetrahydro-1*H*-2-benzazepin-7-ol hydrobromide (128). This compound was prepared from **125**, using the general procedure for demethylation (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 1.97 (m, 2H), 3.31 (m, 2H), 3.46 (m, 2H), 4.36 (s, 2H), 7.38 (s, 1H).

5.2.4.48. 8-Chloro-*N*-[2-(4-chlorophenyl)ethyl]-7-hydroxy-1,3,4,5-tetrahydro-2*H*-2-benzazepine-2-carbothioamide (129). This compound was prepared from **126** as described in the general procedure for coupling and purified by flash column chromatography (silica, CH_2Cl_2/MeOH 99:1) (38%). ^{1}H NMR (CD_3OD 400 MHz) δ 1.75 (m, 2H), 2.84 (m, 4H), 3.75 (t, J = 7.2 Hz, 2H), 4.02 (br s, 2H), 4.73 (s, 2H), 6.73 (s, 1H), 7.08 (d, J = 8.1 Hz, 2H), 7.19 (d, J = 8.1 Hz, 2H). 7.29 (s, 1H). ^{13}C NMR (CD_3OD, 100 MHz) δ 28.5, 35.3, 35.6, 47.8, 49.7, 54.5, 118.1, 119.0, 129.4, 129.4, 130.1, 131.5, 131.5, 132.0, 132.9, 139.4, 142.0, 153.4, 181.3. HRMS (ESI) calculated for $C_{19}H_{21}Cl_2N_2OS$ (M+H) 395.0752, found 395.0761.

5.2.4.49. 6-Chloro-*N*-[2-(4-chlorophenyl)ethyl]-7-hydroxy-1,3,4,5-tetrahydro-2*H*-2-benzazepine-2-carbothioamide (130). This compound was prepared from **127** as described in the general procedure for coupling and purified by flash column chromatography (silica, CH_2Cl_2/MeOH 99:1) (36%). ^{1}H NMR (CD_3OD 300 MHz) δ 1.78 (br s, 2H), 2.86 (t, J = 7.3 Hz, 2H), 3.12 (br s, 2H), 3.75 (t, J = 7.3 Hz, 2H), 3.97 (br s, 2H), 4.77 (s, 2H), 6.66 (d, J = 8.2 Hz, 1H), 7.08 (m, 3H), 7.21 (d, J = 7.4 Hz, 2H). ^{13}C NMR (CD_3OD 75 MHz) δ 27.2, 30.2, 35.5, 47.7, 53.0, 55.0, 114.0, 121.9, 129.4, 129.4, 129.6, 129.9, 131.5, 131.5, 133.0, 139.5, 140.9, 154.0, 181.3. HRMS (ESI) calculated for $C_{19}H_{21}Cl_2N_2OS$ (M+H) 395.0752, found 395.0749.

5.2.4.50. 6,8-Dichloro-*N*-[2-(4-chlorophenyl)ethyl]-7-hydroxy-1,3,4,5-tetrahydro-2*H*-2-benzazepine-2-carbothioamide (131). This compound was prepared from **128** as described in the general procedure for coupling and purified by flash column chromatography (silica, CH_2Cl_2) (71%). ^{1}H NMR (CD_3OD 400 MHz) δ 1.78 (m, 2H), 2.85 (t, J = 7.3 Hz, 2H) 3.13 (m, 2H), 3.75 (t, J = 7.3 Hz, 2H), 3.97 (br s, 2H), 4.83 (s, 2H), 7.09 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 8.5 Hz, 2H), 7.33 (s, 1H). ^{13}C NMR (CD_3OD 100 MHz) δ 27.2, 30.6, 35.5, 47.8, 53.23, 54.68, 119.5, 123.5, 129.4, 129.4, 130.3, 131.0, 131.5, 131.5, 133.0, 139.5, 139.9, 150.0, 181.7. HRMS (ESI) calculated for $C_{19}H_{19}Cl_3N_2OSNa$ (M+Na) 451.0182, found 451.0182.

5.2.4.51. *tert*-Butyl 9-chloro-8-methoxy-1,3,4,5-tetrahydro-2*H*-2-benzazepine-2-carboxylate (132) and *tert*-butyl 7-chloro-8-methoxy-1,3,4,5-tetrahydro-2*H*-2-benzazepine-2-carboxylate (133). These compounds were synthesized from **64**, using procedure B for chlorinations (1.1 equiv of SO_2Cl_2) to yield a mixture containing both compounds. Purification was not possible, so the mixture was used for further synthesis.

5.2.4.52. 9-Chloro-2,3,4,5-tetrahydro-1*H*-2-benzazepin-8-ol hydrobromide (134) and 7-chloro-2,3,4,5-tetrahydro-1*H*-2-benzazepin-8-ol hydrobromide (135). The mixture containing **132** and **133** was treated as described in the general method for demethylation affording a mixture containing **134** and **135**. The mixture was used for further synthesis without purification.

5.2.4.53. 9-Chloro-*N*-[2-(4-chlorophenyl)ethyl]-8-hydroxy-1,3,4,5-tetrahydro-2*H*-2-benzazepine-2-carbothioamide (136) and 7-chloro-*N*-[2-(4-chlorophenyl)ethyl]-8-hydroxy-1,3,4,5-tetrahydro-2*H*-2-benzazepine-2-carbothioamide (137). These compounds were prepared from the mixture containing **134** and **135**, as described in the general procedure for coupling. Purification was done

by flash column chromatography (silica, CH_2Cl_2/MeOH 99:1) affording **136** and **137** (23%, 1:1).

Compound **136**: ^{1}H NMR (CD_3OD 400 MHz) δ 2.82 (m, 2H), 2.86 (m, 4H), 3.81 (t, J = 7.1 Hz, 2H), 4.19 (br s, 2H), 4.94 (s, 2H), 6.75 (d, J = 8.2 Hz, 1H), 6.94 (d, J = 8.2 Hz, 1H), 7.12 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H). ^{13}C NMR (CD_3OD 100 MHz) δ 28.5, 35.0, 35.4, 47.9, 51.4, 54.9, 116.1, 120.8, 129.5, 129.5, 130.3, 131.5, 131.5, 133.1, 135.1, 135.6, 139.3, 152.8, 181.6. HRMS (ESI) calculated for $C_{19}H_{21}Cl_2N_2OS$ (M+H) 395.0751, found 395.0757.

Compound **137**: ^{1}H NMR (CD_3OD 400 MHz) δ 1.74 (m, 2H), 2.82 (m, 2H), 2.86 (t, J = 7.4 Hz, 2H), 3.74 (t, J = 7.4 Hz, 2H), 3.95 (br s, 2H), 4.83 (s, 2H), 6.98 (s, 1H), 7.08 (s, 1H), 7.10 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H). ^{13}C NMR (CD_3OD 100 MHz) δ 28.6, 34.5, 35.5, 47.8, 53.9, 55.6, 119.7, 119.9, 129.4, 129.4, 131.5, 131.6, 131.6, 132.9, 134.9, 137.9, 139.5, 151.9, 181.6. HRMS (ESI) calculated for $C_{19}H_{21}Cl_2N_2OS$ (M+H) 395.0765, found 395.0765.

5.2.4.54. 6,9-Dichloro-7,8-dimethoxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride (138). This compound was synthesized from **69** using procedure A for chlorinations (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 3.33 (m, 4H), 3.46 (m, 4H), 3.89 (s, 6H).

5.2.4.55. 6,9-Dichloro-2,3,4,5-tetrahydro-1*H*-3-benzazepine-7,8-diol hydrobromide (139). This compound was prepared from **138** using the general procedure for demethylation (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 3.14 (br s, 4H), 3.24 (br s, 4H).

5.2.4.56. 6,9-Dichloro-*N*-[2-(4-chlorophenyl)ethyl]-7,8-dihydroxy-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carbothioamide (140). This compound was prepared from **139** as described in the general procedure for coupling and purified by flash column chromatography (silica, CH_2Cl_2/MeOH 99:1) (24%). ^{1}H NMR (CD_3OD 400 MHz) δ 2.85 (t, J = 7.4 Hz, 2H), 3.21 (t, J = 5.8 Hz, 4H), 3.74 (t, J = 7.4 Hz, 2H), 3.95 (t, J = 5.8 Hz, 4H), 7.14 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H). ^{13}C NMR (CD_3OD 100 MHz) δ 31.5, 31.5, 35.6, 48.0, 49.0, 49.0, 121.0, 121.0, 129.5, 129.5, 129.7, 129.7, 131.5, 131.5, 133.0, 139.7, 142.4, 142.4, 182.6. HRMS (ESI) calculated for $C_{19}H_{20}Cl_3N_2O_2S$ (M+H) 445.0311, found 445.0294.

5.2.4.57. *N*-[2-(4-Chlorophenyl)ethyl]-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (142). This compound was prepared from **141** as described in the general procedure for coupling and purified by flash chromatography (silica, pet. ether/etoac 4:1) affording **142** (96%) spectroscopic data. ^{1}H NMR ($CDCl_3$ 300 MHz) δ 2.95 (m, 4H), 3.86 (t, J = 6.0 Hz, 2H), 3.97 (m, 2H), 4.85 (s, 2H), 5.34 (br s, 1H), 7.22 (m, 8H). ^{13}C NMR ($CDCl_3$ 75 MHz) δ 29.0, 34.8, 45.5, 46.8, 49.4, 126.6, 126.9, 127.4, 127.9, 128.9, 128.9, 130.3. 130.3, 132.5, 133.0, 135.3, 137.5, 181.5. HRMS (ESI) calculated for $C_{18}H_{20}ClN_2O$ (M+H) 331.1036, found 331.1022.

5.2.4.58. 1-(3,4-Dihydro-6-nitroisoquinolin-2(1*H*)-yl) ethanone (143) and 1-(3,4-dihydro-7-nitroisoquinolin-2(1*H*)-yl)ethanone (144). 1,2,3,4-Tetrahydroisoquinoline, **141** (2.0 g, 15 mmol), was cooled on ice and acetic anhydride (2.3 g, 22 mmol) was added dropwise. The mixture was stirred for 2 h and then diluted with EtOAc. The organic phase was washed with $NaHCO_3$ (satd), dried ($MgSO_4$) and concentrated to give 1-(3,4-dihydroisoquinolin-2(1*H*)-yl)ethanone (2.1 g, 81%). Without further purification 1-(3,4-dihydroisoquinolin-2(1*H*)-yl)ethanone (1.5 g, 8.7 mmol) was cooled on ice and a 20 ml of mixture of concentrated nitric and concentrated sulfuric acid (1:1) was added dropwise. The mixture was stirred on ice for 4 h and then poured into a mixture of ice and water. The water phase was extracted with EtOAc. The combined organic phases were washed with $NaHCO_3$ (satd), dried ($MgSO_4$) and concentrated to give 1-(3,4-dihydro-mononitroisoquinolin-2(1*H*)-yl)ethanone as a crude mixture of regioisomers. Pure isomers were obtained by HPLC (Microsorb, silica 5 μm, 250 × 21.4 mm, 20 ml/min of 100% EtOAc, detection at 300 nm), **143** (409 mg, 21%) and **144** (210 mg, 11%).

Compound **143**: ^{1}H NMR ($CDCl_3$) δ (rotameric mixture) 2.19 (ma) (s, 3H), 2.21 (mi) (s, 3H), 2.94 (mi) (t, J = 5.9 Hz, 2H), 3.01 (ma) (t, J = 5.9 Hz, 2H), 3,73 (ma) (t, J = 5.9 Hz, 2H), 3.86 (mi) (t, J = 5.9 Hz, 2H), 4.72 (mi) (s, 2H), 4.82 (ma) (s, 2H), 7.32 (m, 1H), 8.02 (m, 2H).

Compound **144**: ^{1}H NMR ($CDCl_3$) δ (rotameric mixture) 2.20 (s, 3H), 2.95 (mi) (t, J = 5.9 Hz, 2H), 3.02 (ma) (t, J = 5.9 Hz, 2H), 3,74 (ma) (t, J = 5.9 Hz, 2H), 3.87 (mi) (t, J = 5.9 Hz, 2H), 4.72 (mi) (s, 2H), 4.83 (ma) (s, 2H), 7.32 (m, 1H), 8.04 (m, 2H).

5.2.4.59. 1-(6-Amino-3,4-dihydroisoquinolin-2(1*H*)-yl) ethanone hydrochloride (145). To a solution of **143** (253 mg, 1.15 mmol) in MeOH and some HCl (10% in water), palladium on carbon (5%) was added. The mixture was stirred under hydrogen atmosphere for 1 h, filtered through Celite and concentrated to give **145** (265 mg, quant.). ^{1}H NMR (CD_3OD) δ (rotameric mixture) 2.24 (ma) (s, 3H), 2.25 (mi) (s, 3H), 2.94 (mi) (t, J = 5.6 Hz, 2H), 3.03 (ma) (t, J = 5.9 Hz, 2H), 3.81 (m, 2H), 4.76 (ma) (s, 2H), 4.79 (mi) (s, 2H), 7.27 (m, 2H), 7.38 (m, 1H).

5.2.4.60. 1-(7-Amino-3,4-dihydroisoquinolin-2(1*H*)-yl) ethanone hydrochloride (146). Compound **146** was synthesized as described for**145** from **144** (89%). ^{1}H NMR (CD_3OD) δ (rotameric mixture) 2.27 (ma) (s, 3H), 2.30 (mi) (s, 3H), 2.94 (mi) (br s, 2H), 3.02 (ma) (br s, 2H), 3.84 (m, 2H), 4.79 (ma) (s, 2H), 4.84 (mi) (s, 2H), 7.25 (m, 2H), 7.38 (m, 1H).

5.2.4.61. 1,2,3,4-Tetrahydroisoquinolin-6-amine dihydrobromide (147). Compound **145** (265 mg, 1.2 mmol) was dissolved in concentrated HBr (48% in H_2O) and heated to reflux for 4 hours. The mixture was then concentrated to give **147** (289 mg, 80%). ^{1}H NMR (CD_3OD) δ 3.21 (t, J = 6.4 Hz, 2H), 3.56 (t, J = 6.4 Hz, 2H), 3.84 (s, 2H), 6.44 (d, J = 2.1 Hz, 1H), 6.56 (dd, J = 2.1, 8.2 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H).

5.2.4.62. 1,2,3,4-Tetrahydroisoquinolin-7-amine dihydrobromide (148). Compound **148** was synthesized as described for **147** from **146** (91%). ^{1}H NMR (CD_3OD) δ2.69 (t, J = 5.9 Hz, 2H), 3.02 (t, J = 5.9 Hz, 2H), 4.45 (s, 2H), 7.34 (m, 2H), 7.45 (d, J = 9.0 Hz, 1H).

5.2.4.63. *tert*-Butyl 6-amino-3,4-dihydro-isoquinoline-2(1*H*)-carboxylate (149). To a suspension of the free amine of **147** (83 mg, 0.56 mmol) in THF, water and di-*tert*-butyldicarbonate (116 mg, 0.53 mmol) were added. The solution was stirred at room temperature for 3 h. The reaction mixture was concentrated, dissolved in H_2O and extracted with EtOAc. The organic phase was dried ($MgSO_4$), filtered and concentrated. The residue was chromatographed on silica gel (pet. ether/EtOAc 1:1) to afford **149** (101 mg, 73%). ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 9H), 2.71 (t, J = 5.7 Hz, 2H), 3.59 (br s, 4H), 4.47 (s, 2H), 6.44 (d, J = 2.3 Hz, 1H), 6.52 (dd, J = 2.3, 8.1 Hz, 1H), 6.92 (d, J = 8.1 Hz, 1H).

5.2.4.64. *tert*-Butyl 7-amino-3,4-dihydro-isoquinoline-2(1*H*)-carboxylate (150). Compound **150** was synthesized as described for **149** from **148** (47%). ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 9H), 2.71 (t, J = 5.8 Hz, 2H), 3.59 (br s, 2H), 3.66 (br s, 2H), 4.45 (s, 2H), 6.45 (d, J = 2.0 Hz, 1H), 6.52 (dd, J = 2.0, 8.1 Hz, 1H), 6.87 (d, J = 8.1 Hz, 1H).

5.2.4.65. *tert*-Butyl 6-[(methylsulfonyl)-amino]-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (151). To a solution of **149** (101 mg, 0.41 mmol) in CH_2Cl_2 cooled on ice, methanesulfonyl chloride (49 mg, 0.43 mmol) and triethylamine (47 mg, 0.47 mmol) were added. The solution was stirred for 2 h, then diluted with H_2O and extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (pet. ether/EtOAc 3:2) to afford **151** (96 mg, 72%). ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 9H), 2.80 (t, J = 5.8 Hz, 2H), 2.99 (s, 3H), 3.62 (t, J = 5.8 Hz, 2H), 4.53 (s, 2H), 7.02 (m, 4H).

5.2.4.66. *tert*-Butyl 7-[(methylsulfonyl)-amino]-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (152). Compound **152** was synthesized as described for **151** from **150** (46%). ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 9H), 2.79 (t, J = 5.7 Hz, 2H), 2.99 (s, 3H), 3.63 (t, J = 5.7 Hz, 2H), 4.54 (s, 2H), 7.07 (m, 4H).

5.2.4.67. 6-Amino-*N*-[2-(4-chlorophenyl)ethyl]-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (153). This compound was prepared from **147** as described in the general procedure for coupling and purified by flash column chromatography (pet. ether/EtOAc 1:2) to give **153** (72%). ^{1}H NMR (CD_3OD) δ 2.77 (t, J = 6.0 Hz, 2H), 2.93 (t, J = 7.5 Hz, 2H), 3.82 (t, J = 7.5 Hz, 2H), 3.89 (t, J = 6.0 Hz, 2H), 4.71 (s, 2H), 6.57 (d, J = 2.3 Hz, 1H), 6.60 (dd, J = 8.0, 2.3 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 7.20 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 8.6 Hz, 2H). ^{13}C NMR (CD_3OD) δ 29.9, 35.8, 47.1, 47.9, 50.1, 115.2, 115.7, 124.1, 128.0, 129.4, 129.4, 131.5, 131.5, 133.0, 137.4, 139.7, 147.6, 181.8. HRMS (ESI) calculated for $C_{18}H_{21}ClN_3S$ (M+H) 346.1145, found 346.1140.

5.2.4.68. 7-Amino-*N*-[2-(4-chlorophenyl)ethyl]-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (154). This compound was prepared from **148** as described in the general procedure for coupling. The crude product was recrystallized from EtOAc to give **154** (80%). ^{1}H NMR ($(CD_3)_2SO$) δ 2.67 (t, J = 5.7 Hz, 2H), 2.86 (t, J = 7.4 Hz, 2H), 3.69 (m, 2H), 3.85 (t, J = 5.7 Hz, 2H), 4.73 (s, 2H), 4.93 (s, 2H), 6.34 (d, J = 2.0 Hz, 1H), 6.42 (dd, J = 8.0, 2.0 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 7.72 (t, J = 5.0 Hz, 1H). ^{13}C NMR ($(CD_3)_2SO$) δ 27.2, 34.2, 45.7, 46.5, 49.3, 111.0, 112.9, 121.2, 128.3, 128.3, 128.5, 130.5, 130.5, 130.7, 133.9, 138.6, 146.9, 180.6. HRMS (ESI) calculated for $C_{18}H_{21}ClN_3S$ (M+H) 346.1145, found 346.1135.

5.2.4.69. *N*-[2-(4-Chlorophenyl)ethyl]-6-[(methylsulfonyl)amino]-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (155). Compound **151** was stirred for 40 min in trifluoroacetic acid/CH_2Cl_2/anisol (80:19:1) and then concentrated. The residue was coupled with 2-(4-chlorophenyl)ethyl isothiocyanate as described in the general procedure for coupling. The crude product was chromatographed on silica (pet. ether/EtOAc+AcOH 2:3+1%) (65%). ^{1}H NMR ($CDCl_3$) δ 2.89 (t, J = 5.9 Hz, 2H), 2.96 (t, J = 6.9 Hz, 2H), 3.00 (s, 3H), 3.82 (t, J = 5.9 Hz, 2H), 3.95 (dt, J = 6.9, J = 5.5 Hz, 2H), 4.85 (s, 2H), 5.54 (br s, 1H), 6.89 (s, 1H), 7.09 (m, 3H), 7.16 (d, J = 8.3 Hz, 1H), 7.27 (d, J = 8.3 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 29.0, 34.8, 39.6, 45.1, 46.9, 49.1, 119.5, 120.3, 127.9, 128.9, 128.9, 130.3, 130.3, 130.5, 132.6, 135.9, 137.0, 137.5, 181.5. HRMS (ESI) calculated for $C_{19}H_{23}N_3O_2S_2Cl$ (M+H) 424.0920, found 424.0929.

5.2.4.70. *N*-[2-(4-Chlorophenyl)ethyl]-7-[(methylsulfonyl)amino]-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (156). Compound **156** was synthesized as described for **155** from **152**. The crude product was chromatographed on silica (pet. ether/EtOAc+AcOH 2:3+1%) (56%). ^{1}H NMR ($CDCl_3$) δ 2.86 (t, J = 5.7 Hz, 2H), 2.94 (t, J = 7.1 Hz, 2H), 2.97 (s, 3H), 3.87 (t, J = 5.7 Hz, 2H), 3.94 (m, 2H), 4.85 (s, 2H), 5.81 (t, J = 5.2 Hz, 1H), 7.09 (m, 3H), 7.18 (d, J = 8.3 Hz, 1H), 7.27 (d, J = 8.3 Hz, 1H), 7.38 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 28.3, 34.8, 39.4, 45.4, 47.0, 49.3, 119.2, 120.2, 128.8, 128.8, 129.2, 130.3, 130.3, 132.3, 132.5, 134.5, 135.4, 137.5, 181.2. HRMS (ESI) calculated for $C_{19}H_{23}N_3O_2S_2Cl$ (M+H) 424.0920, found 424.0918.

5.2.4.71. *tert*-Butyl 6,7-dihydroxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (157). To a suspension of **30** (3.77 g, 15.3 mmol) in H_2O (15 ml), di-*tert*-butyldicarbonate (3.51 g, 16.1 mmol) and triethylamine (3.26 g, 32.2 mmol) in 40 ml THF were added dropwise. The mixture was stirred overnight. The mixture was concentrated, dissolved in EtOAc and washed with water. The organic phase was dried ($MgSO_4$), concentrated and chromatographed on silica gel (pet. ether/EtOAc 3:2) to give **157** (2.8 g, 68%). ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 9H), 2.70 (t, J = 5.9 Hz, 2H), 3.60 (t, J = 5.9 Hz, 2H), 4.44 (s, 3H), 6.65 (s, 2H).

5.2.4.72. *tert*-Butyl 6,7-bis{[(trifluoromethyl)sulfonyl]oxy}-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (158). Trifluoromethanesulfonic anhydride (2.6 g, 9.1 mmol) was added slowly to an ice-cold solution of **157** (1.17 g, 4.4 mmol) and triethylamine (1.1 g, 11.1 mmol) in dry CH_2Cl_2 (25 ml). The mixture was allowed to reach room temperature. After 2 h the mixture was poured into $NaHCO_3$ (satd). The water phase was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated to give **158** (2.2 g, 95%). ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 9H), 2.88 (t, J = 5.7 Hz, 2H), 3.68 (t, J = 5.7 Hz, 2H), 4.61 (s, 3H), 7.21 (s, 1H), 7.24 (s, 1H).

5.2.4.73. *tert*-Butyl 6,7-dicyano-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (159). To a mixture of **158** (2.2 g, 4.3 mmol), tris(dibenzylideneacetone)dipalladium (156 mg, 0.17 mmol) and 1,1′-bis(diphenylphosphino)ferrocene (371 mg, 0.67 mmol) in DMF heated to 80 °C, $Zn(CN)_2$ (30 mg, 0.25 mmol) was added every 6th minute over 2 h (600 mg. 5.0 mmol in total). The mixture was poured into aqueous Na_2CO_3 (satd), and the water phase was extracted with CH_2Cl_2. The combined organic phases were washed with water, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (pet. ether/EtOAc 14:1 to 1:1) to give **159** (500 mg, 42%). ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 9H), 2.93 (t, J = 5.7 Hz, 2H), 3.69 (t, J = 5.7 Hz, 2H), 4.66 (s, 3H), 7.56 (s, 1H), 7.59 (s, 1H).

5.2.4.74. Dimethyl 1,2,3,4-tetrahydroisoquinoline-6,7-dicarboxylate (160). A suspension of compound **159** (112 mg) in 50% aqueous NaOH was heated to reflux for 15 h. The mixture was concentrated and the residue extracted with MeOH. H_2SO_4 was added to the organic phase, which then was refluxed for 15 h. The mixture was concentrated and the residue suspended in aqueous $NaHCO_3$. The water phase was extracted with EtOAc. The combined organic phases were dried ($MgSO_4$) and concentrated to give **160** (44 mg, 35% over two steps). ^{1}H NMR ($CDCl_3$) δ 2.87 (br s, 2H), 3.20 (br s, 2H), 3.88 (s, 6H), 4.10 (br s, 2H), 7.40 (s, 1H), 7.46 (s, 1H) MS (ESI) calculated for $C_{13}H_{16}NO_4$ (M+H) 250.1, found 250.1.

5.2.4.75. 1,2,3,4-Tetrahydroisoquinoline-6,7-dicarboxylic acid hydrochloride (161). To a solution of the di-ester **160** (39 mg) in 10 ml THF/H_2O, $LiOH{\cdot}H_2O$ (33 mg, 5 equiv) was added. The mixture was stirred at room temperature for 3 days and then HCl (10% in H_2O) was added. The resulting acidic mixture was concentrated to give **161** (used in the synthesis of **164** without further purification). ^{1}H NMR ($CDCl_3$) δ 3.24 (br s, 2H), 3.58 (br s, 2H), 4.48 (s, 2H), 7.69 (s, 1H), 7.71 (s, 1H) HRMS (ESI) calculated for $C_{11}H_{12}NO_4$ (M+H) 222.0766, found 222.0764.

5.2.4.76. *N*-[2-(4-Chlorophenyl)ethyl]-6,7-dicyano-3,4-dihydro-isoquinoline-2(1*H*)-carbothioamide (162). Compound **162** was synthesized as described for **155** from **159**. The crude product was chromatographed on silica (pet. ether/EtOAc 2:5) (56%). ^{1}H NMR ($CDCl_3$) δ 2.95 (t, J = 7.0 Hz, 2H), 3.03 (t, J = 5.9 Hz, 2H), 3.85 (t, J = 5.9 Hz, 2H), 3.93 (m, 2H), 5.07 (s, 2H), 5.68 (br s, 1H), 7.15 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.61 (s, 1H), 7.64 (s, 1H). ^{13}C NMR (CD_3OD) δ 28.9, 34.5, 44.0, 47.0, 49.3, 114.0, 114.3, 115.3, 115.3, 129.0, 129.0, 130.3, 130.3, 131.8, 132.6, 133.4, 137.3, 140.0, 141.7, 182.1. HRMS (ESI) calculated for $C_{20}H_{18}ClN_4S$ (M+H) 381.0941, found 381.0943.

5.2.4.77. Dimethyl 2-({[2-(4-chlorophenyl)ethyl]amino-carbono-thioyl)-1,2,3,4-tetrahydroisoquinoline-6,7-dicarboxylate (163). Compound **163** was synthesized as described in the general procedure for coupling from **160**. The crude product was chromatographed on silica (pet. ether/EtOAc 2:1) (56%). ^{1}H NMR ($CDCl_3$) δ 2.95 (m, 4H), 3.88 (m, 2H), 3.89 (s, 3H), 3.90 (s, 3H), 3.94 (m, 2H), 4.91 (s, 2H), 5.59 (br s, 1H), 7.15 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.52 (s, 1H), 7.53 (s, 1H). ^{13}C NMR (CD_3OD) δ 28.8, 34.7, 44.9, 46.9, 49.1, 53.8, 53.8, 127.4, 128.8, 129.0, 129.0, 130.3, 130.3, 131.1, 131.1, 132.6, 136.4, 137.4, 138.8, 167.6, 167.9, 181.9. HRMS (ESI) calculated for $C_{22}H_{23}ClN_2NaO_4S$ (M+Na) 469.0965, found 469.0974.

5.2.4.78. 2-({[2-(4-Chlorophenyl)ethyl]amino}carbonothioyl)-1,2,3,4-tetrahydroisoquinoline-6,7-dicarboxylic acid (164). Compound **164** was synthesized as described in the general procedure for coupling from **161**. The crude mixture was washed with diethyl ether to give **164** (28% over two steps). ^{1}H NMR (CD_3OD 300 MHz) δ 2.96 (m, 4H), 3.84 (t, J = 7.4 Hz, 2H), 4.03 (t, J = 5.7 Hz, 2H), 4.96 (s, 2H), 7.21 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.60 (s, 1H), 7.62 (s, 1H). ^{13}C NMR (CD_3OD 75 MHz) δ 29.4, 35.6, 46.3, 48.0, 50.3, 128.5, 129.5, 129.5, 130.3, 131.5, 131.5, 132.1, 132.9, 133.0, 137.8, 139.6, 140.0, 170.0, 171.3, 182.6. HRMS (ESI) calculated for $C_{20}H_{20}ClN_2O_4S$ (M+H) 419.0832, found 419.0819.

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