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SAR studies of capsazepinoid bronchodilators. Part 1: The importance of the catechol moiety and aspects of the B-ring structure

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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 part concerns the catechol moiety of the A-ring as well as the 2,3,4,5-tetrahydro-1*H*-2-azepine moiety (the B-ring) of capsazepine. It is revealed that a conformational constrain (as a fused ring) is important and that compounds with a six-membered B-ring (as a 1,2,3,4-tetrahydroisoquinoline) in general are more potent than the corresponding isoindoline, 2,3,4,5-tetrahydro-1*H*-2-benzazepine and 2,3,4,5-tetrahydro-1*H*-3-benzazepine derivatives.

1. Introduction

The first competitive capsaicin (**1**) antagonist, capsazepine (**2**, Fig. 1), was discovered in 1992, before the identification and cloning of its target.[1,2] TRPV1 (transient receptor potential vanilloid channel subfamily member 1) agonists as well as antagonists have been studied as plausible analgesics and candidate drugs modulating TRPV1 have entered clinical phases.[3] Some studies also have addressed the possible role of capsazepine as inhibitor of TRPV1 mediated bronchoconstriction.[4–6] However, none of those have revealed the general bronchodilatory properties of capsazepine and some close related derivatives such as compound **3**, recently described by us. Capsazepine is a general inhibitor of agonist evoked (leukotriene D_4, histamine, acetylcholine, prostaglandin D_2) constriction of human small bronchi (0.5–1.5 mm in diameter).[7] Small airways play an important role in airway obstruction in diseases such as asthma and chronic obstructive pulmonary disease (COPD) since they are specially sensitive to contractile agents such as the ones mentioned above.[8] Although the mechanism of action remains to be elucidated, established bronchodilator principles, for example, β_2-adrenoceptor agonism as well as TRPV1 antagonism, have been excluded.[7,9] Analogues of capsazepine, capsazepinoids, share this bronchodilatory effect and compound **4**, developed from capsazepine, was shown to be approximately 10 times more potent.[9]

Mimicking the approach in an earlier SAR study of capsaicin,[10] the structure of capsazepine was divided into the four regions (shown in Fig. 2) in order to systematically study the effect on the activity of structural variations of each region. In this paper, we show the importance of a catechol moiety in the A-ring and explore how structural differences in the B-ring affect the bronchodilating ability of the capsazepinoids. In the two following papers, SAR studies of the A-ring, the coupling region as well as the C-region are reported.[11,12] To facilitate the comparison of the results from the complete study, a continuous numbering of the compounds has been used in all three papers. Compounds discussed in more than one paper consequently have the same number everywhere.

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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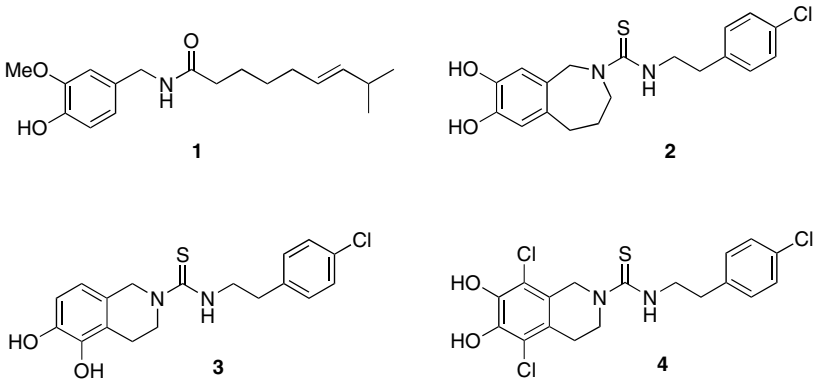


Figure 1.

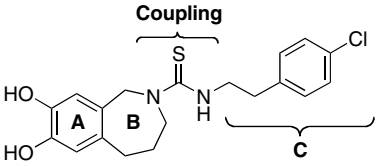


Figure 2.

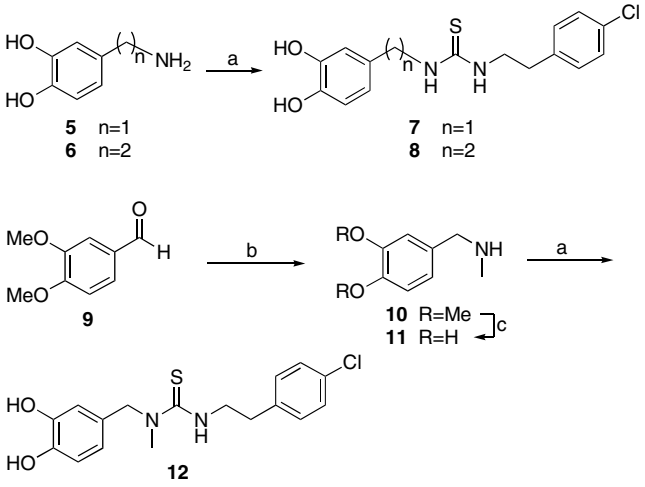
Experiments to confirm the class effect of capsazepinoids as bronchodilators showed that the size of the saturated ring strongly influences the potency. In addition, the substitution pattern of the catechol moiety and replacement of the phenylethyl substituent with an octyl group affected the potency considerably.[11,12] Here, the activities of compounds lacking the B-ring, having different B-rings, and B-rings substituted with methyl/benzyl groups in various positions, are compared. In order to facilitate a comparison, the coupling region was a thiourea while the C-region was a 2-(4-chlorophenyl)ethyl group in all compounds reported in this paper.

2. Chemistry

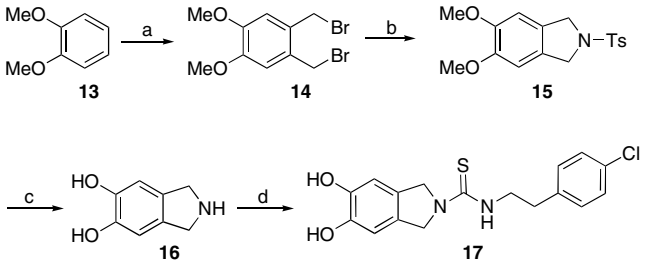
Capsazepinoids with no B-ring, and compounds with a conformationally constrained B-ring as in isoindolines (5-membered B-ring), tetrahydroisoquinolines (6-membered B-ring) and tetrahydro-1*H*-2-benzazepines as well as tetrahydro-1*H*-3-benzazepines (7-membered B-ring) were synthesized by coupling with 2-(4-chlorophenyl)ethyl isothiocyanate.

The open chain thiourea derivatives shown in Scheme 1 were synthesized by coupling of commercially available amines **5** and **6** with 2-(4-chlorophenyl)ethyl isothiocyanate. Reductive amination of **9** afforded **10**,[13] which was demethylated and coupled with 2-(4-chlorophenyl)ethyl isothiocyanate to afford **12**.

The synthesis of the isoindoline analogue **17** is outlined in Scheme 2. Bis-bromomethylation of 1,2-dimethoxybenzene (**13**) afforded **14**,[14] which was coupled with TsNHNa to afford **15**.[15] Demethylation and detosylation of **15** was done by treatment with a mixture of hydrobromic acid (48% in H_2O), phenol and propionic



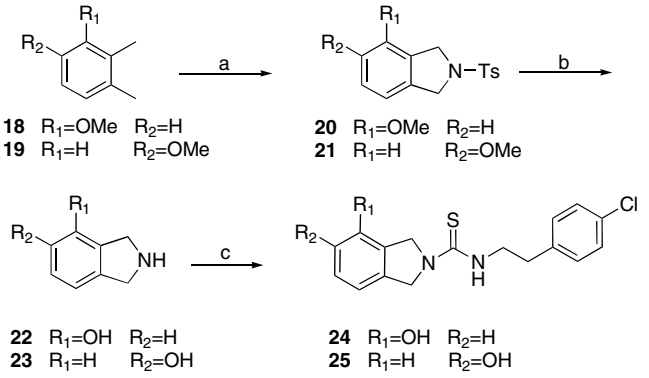
Scheme 1. Reagents and conditions: (a) Et_3N, 2-(4-chlorophenyl)ethyl isothiocyanate, DMF, rt, 4 h; (b) 1—Me–NH_2, MeOH, 40 °C, 5 h; 2—$NaBH_4$, 0 °C to rt, o.n., 64%; (c) HBr (48% in H_2O), reflux, 4.5 h, quant.



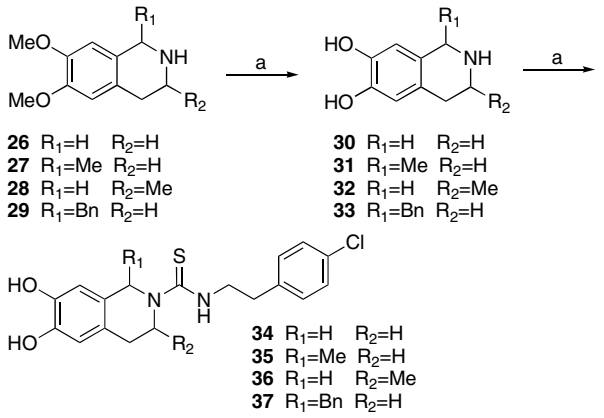
Scheme 2. Reagents and conditions: (a) 1—paraformaldehyde, HBr (33% in AcOH), rt, 20h; 2—65 °C, 1h, 58%; (b) TsNHNa, DMF, 80 °C, 5 h, 75%; (c) 1—HBr (48% in H_2O), phenol, propionic acid, reflux, 4 h; 2—HBr (48% in H_2O), reflux, 3h, 67%; (d) Et_3N, 2-(4-chlorophenyl)ethyl isothiocyanate, DMF, rt, 4 h, 86%.

acid to give the hydrobromic salt of **16**,[16] which was coupled with 2-(4-chlorophenyl)ethyl isothiocyanate to afford **17**.

The synthesis of the isoindoline analogues **24** and **25** is outlined in Scheme 3. Dimethylanisoles **18** and **19** were brominated with *N*-bromosuccinimide in the presence of



Scheme 3. Reagents and conditions: (a) 1—NBS, benzoyl peroxide, CCl_4, reflux, 20h; 2—TsNHNa, DMF, 80°, 5 h; (b) 1—HBr (48% in H_2O), phenol, propionic acid, reflux, 4 h; 2—HBr (48% in H_2O), reflux, 3 h; (c) Et_3N, 2-(4-chlorophenyl)ethyl isothiocyanate, DMF, rt, 4 h.



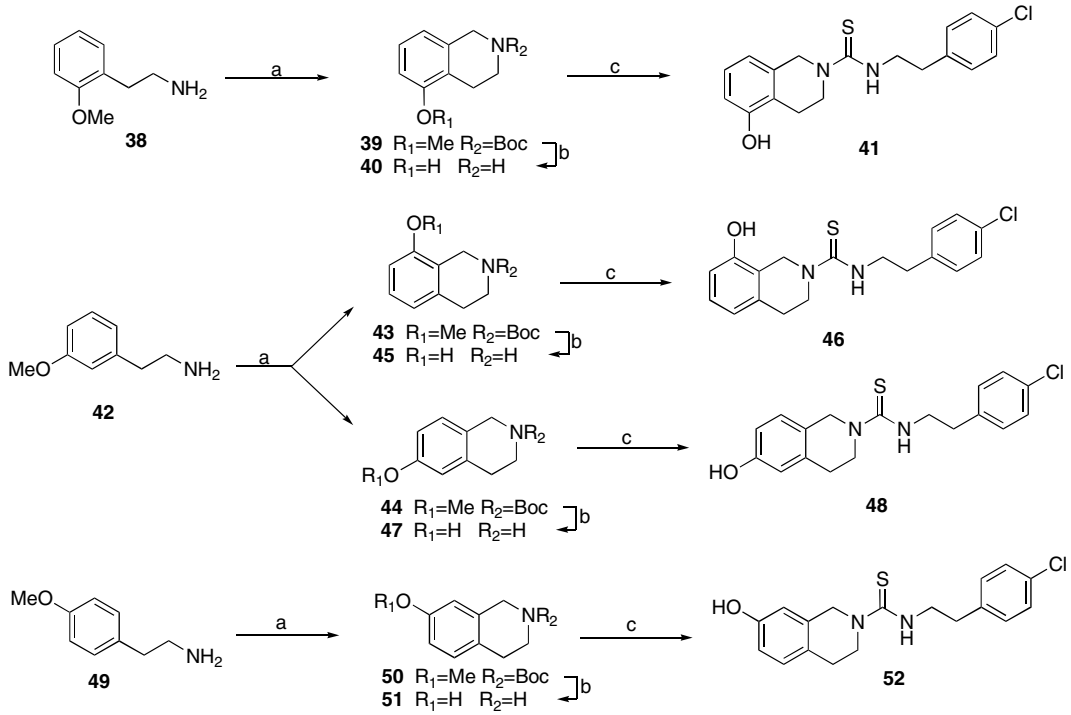
Scheme 4. Reagents and conditions: (a) HBr (48% in H_2O), reflux, 5 h; (b) Et_3N, 2-(4-chlorophenyl)ethyl isothiocyanate, DMF, rt, 4 h.

benzoyl peroxide,[17] followed by coupling with TsNHNa affording **20** and **21**. Demethylation and detosylation of **20** and **21** was carried out by treatment with a mixture of hydrobromic acid (48% in H_2O), phenol and propionic acid, giving the hydrobromic salts of **22** and **23**. Coupling with 2-(4-chlorophenyl)ethyl isothiocyanate afforded products **24** and **25**.

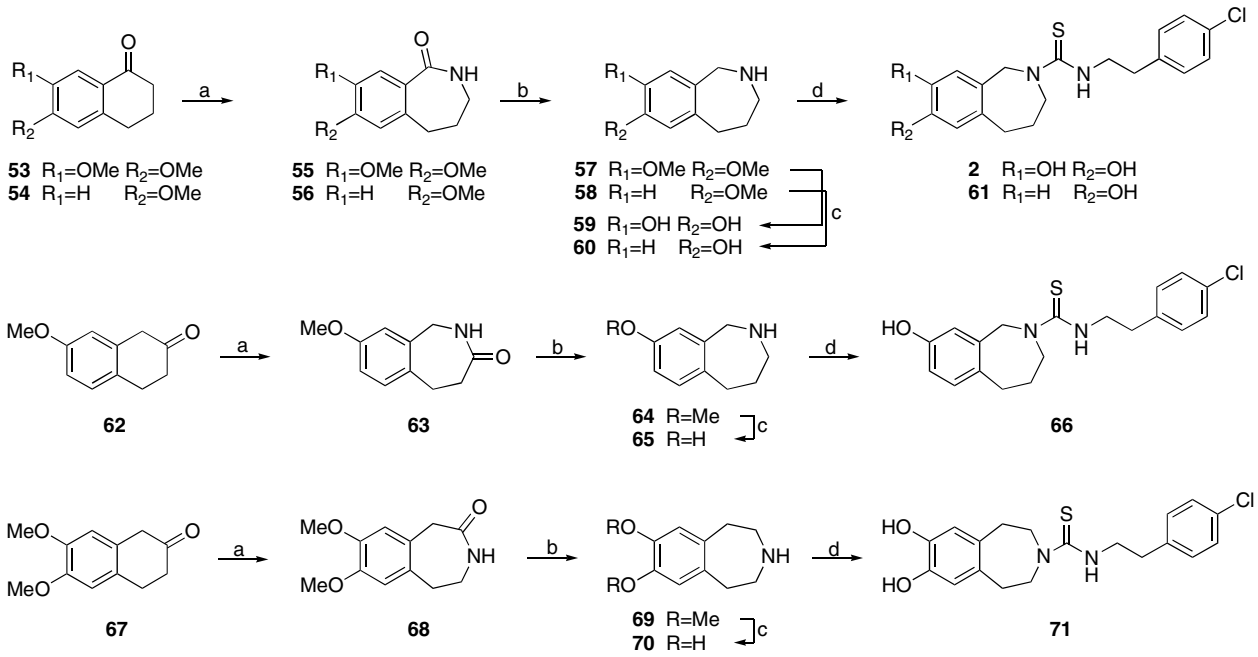
Dihydroxy-1,2,3,4-tetrahydroisoquinoline analogues were synthesized as illustrated in Scheme 4. Demethylation of the commercially available 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines **26**–**29** with HBr (48% in H_2O) acid afforded the hydrobromic salts of 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolines **30**–**33**, which subsequently were coupled with 2-(4-chlorophenyl)ethyl isothiocyanate to yield analogues **34**–**37**.

Monohydroxy-1,2,3,4-tetrahydroisoquinoline derivatives **41**, **46**, **48** and **52** were prepared as shown in Scheme 5. Starting from the amines **38**, **42** and **49**, a prototype Pictet-Spengler reaction using paraformaldehyde and trifluoroacetic acid yielded intermediates **39**, **43**, **44** and **50**,[18] after *N*-Boc protection to facilitate purification. Demethylation, deprotection and coupling afforded compounds **41**, **46**, **48** and **52**.

The general synthesis of the capsazepine derivatives is shown in Scheme 6. Nitrogen insertion into the tetralones **53**, **54**, **62** and **67** via a Schmidt reaction yielded the lactams **55**, **56**, **63** and **68** as the major products.[19] Reduction with borane in THF afforded the hydrochloric salt of **57**, **58**, **64** and **69**. Demethylation and coupling with commercially available 2-(4-chlorophenyl)ethyl isothiocyanate yielded **2**, **61**, **66** and **71**.



Scheme 5. Reagents and conditions: (a) 1—paraformaldehyde, $MgSO_4$, CH_2Cl_2, rt, 2 h; 2—TFA, reflux, 15 h; 3—di-*tert*-butyl dicarbonate, Et_3N, DMF, rt, 2 h; (b) HBr (48% in H_2O), reflux, 5 h; (c) Et_3N, 2-(4-chlorophenyl)ethyl isothiocyanate, DMF, rt, 4 h.



Scheme 6. Reagents and conditions: (a) NaN_3, $MeSO_3H$, rt, 18 h; (b) 1—BH_3, THF, reflux, 18 h; 2—HCl, MeOH, reflux, 2 h; (c) HBr (48% in H_2O), reflux, 5 h; (d) Et_3N, 2-(4-chlorophenyl)ethyl isothiocyanate, DMF, rt, 4 h.

3. Results and discussion

The bronchorelaxing effect of the compounds reported here was evaluated in human small airways (0.5–1.5 mm in diameter) in an organ bath as previously described.[7,20] The constriction evoked by 10 nM leukotriene D_4 in untreated preparations and on the same preparations exposed to 10 μM of the test compound for 1.5 h was compared. The results (Table 1) 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, same concentration and same time of exposure, in order to get comparable values. The effects can vary between 0% relaxation (=100% remaining contraction) for an inactive compound and 100% relaxation (=0% remaining contraction) for a compound with maximal activity. It should be remembered that 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 physiochemical 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 based on the chemical structure only. In the case of the chiral compounds, they were prepared and assayed as the racemic mixtures. The data are summarised in Table 1.

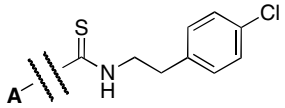
This investigation is part of a series in which the various parts of the capsazepine structure (see Fig. 2) were systematically varied.[11,12] Obviously, it has not been in our power to prepare all compounds considered interesting to assay as we, for example, have been limited by synthetic constrictions. While varying the hydroxylation pattern of the A-ring as well as the structure and substituents of the B-ring, the structures of the remaining parts were essentially retained as they are in the potent derivative **4**, with the B-ring and the C-region coupled with a thiourea moiety and the C-region consisting of a 2-(4-chlorophenyl)ethyl group.

Starting with the monohydroxylated derivatives, it is obvious that hydroxyl groups in different positions will affect the activity differently. For the isoindolines (A = II), a 5/6-hydroxyl is considerably better than a 4/7-hydroxyl (**25** vs **24**), while the good positions for a hydroxyl group in the 1,2,3,4-tetrahydroisoquinolines (A = III) are 5 and 6 (as indicated by the superior activity of **48** and **41** compared to that of **46** and **52**) (see Fig. 3 for atom numbering). The two monohydroxylated tetrahydro-1*H*-2-benzazepines (A = IV) **66** and **61** are comparably active, although the former is slightly more potent.

Including also the dihydroxylated (catechol) derivatives in the discussion, the results show that the 5,6-dihydroxylated isoindoline **17**, the 5,6-dihydroxylated tetrahydroisoquinoline **1** and the 5,6-dihydroxylated tetrahydro-1*H*-2-benzazepine (**2**) are not better than their best monohydroxylated analogues. However, the 6,7-dihydroxylated tetrahydroisoquinoline **34** is considerably more potent, indicating that it is not the number but more the spatial arrangement of the hydroxyl groups what is important for activity, presumably due to specific interactions with the target protein.

To find the low-energy conformers of **2**, **17**, **34** and **71**, with the 2-(4-chlorophenyl)ethyl moiety replaced with

Table 1.



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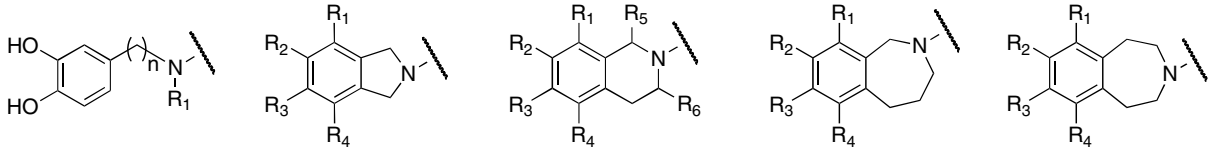

I **II** **III** **IV** **V**

Compound	A	R_1	R_2	R_3	R_4	R_5	R_6	Remaining contraction[a]
7	I, $n = 1$	H	—	—	—	—	—	69 ± 8.5 (4)
8	I, $n = 2$	H	—	—	—	—	—	72 ± 7.8 (4)
12	I, $n = 1$	Me	—	—	—	—	—	69 ± 8.5 (4)
17	II	H	OH	OH	H	—	—	56 ± 10.0 (5)
24	II	OH	H	H	H	—	—	82 ± 2.9 (4)
25	II	H	OH	H	H	—	—	41 ± 10.0 (5)
34	III	H	OH	OH	H	H	H	36 ± 6.5 (5)
35	III	H	OH	OH	H	Me	H	58 ± 11.7 (5)
36	III	H	OH	OH	H	H	Me	70 ± 10.1 (4)
37	III	H	OH	OH	H	Bn	H	79 ± 5.4 (4)
41	III	H	H	H	OH	H	H	48 ± 4.8 (4)
46	III	OH	H	H	H	H	H	73 ± 3.5 (4)
48	III	H	H	OH	H	H	H	52 ± 6.8 (4)
52	III	H	OH	H	H	H	H	75 ± 7.0 (4)
3	III	H	H	OH	OH	H	H	63 ± 7.5 (4)
2	IV	H	OH	OH	H	—	—	55 ± 3.0 (24)
61	IV	H	H	OH	H	—	—	53 ± 4.7 (3)
66	IV	H	OH	H	H	—	—	40 ± 9.9 (4)
71	V	H	OH	OH	H	—	—	54 ± 5.5 (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.

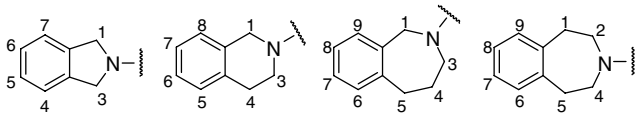

Figure 3.

a methyl group for simplicity, Monte-Carlo Multiple Minimum (MCMM) conformational searches (MacroModel, version 8.5, Schrödinger, LLC, New York, NY, 2006) were performed using the MMFF force field with the Generalized Born/Surface Area (GB/SA) solvation model for water. The smaller rings (**17** and **34**) were searched in 500 steps, while the larger and more flexible 7-membered rings (**2** and **71**) were searched in 2000 steps. Only one conformer (if its enantio-conformer is omitted) was found for **17**, in contrast to **2**, **34** and **71** for which several were found. In Figure 4 the representative conformers are shown.

As seen in Figure 4 the low-energy conformers of **17** and **34** are fairly stretched out and planar while the low-energy conformer of **2** is more folded. The conformers of **71** are either folded or twisted with respect to the aromatic plane and the plane of the thiourea moiety. This was used as the point of reference for the superimposition since it has been reported that the strength of hydrogen bonds to thiocarbonyls is sensitive to the relative orientation of the donor and the acceptor.[21] In Figure 5, the low-energy conformer of the most active compound, **34** is superimposed on the low-energy conformer of **17** (top), the planar high-energy (+13.5 kJ/mol) conformer of **2** (middle), and the low-energy conformer of **71** (bottom) (the selected conformers are indicated in blue in Figure 4). The planar high-energy conformer of **2** was chosen and assumed to be the active conformer because of its resemblance to the low-energy conformer of **34**.

As seen from the superimposed conformers of **2**, **17**, and **71** on **34**, shown in Figure 5, the spatial orientation of

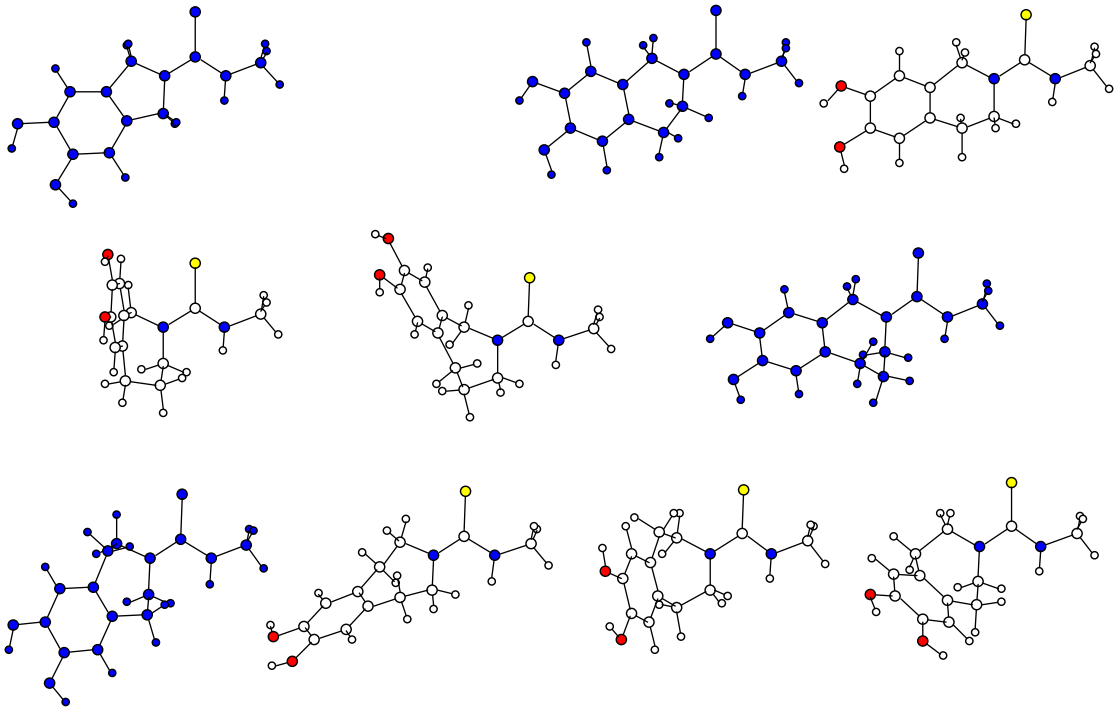

Figure 4. Representative conformers of **17** (top, left), **34** (top, middle and right, 0, +4.5 kJ/mol, respectively), **2** (middle row, 0, +9.9, +13.5 kJ/mol, respectively) and **71** (bottom row, 0, +9.6, +10.8, +12.2 kJ/mol, respectively). Only conformers within 20 kJ/mol were regarded as relevant and only one of the enantio-conformers is shown. Although both *E*/*Z*-isomers were found of each type of conformer, only the *Z*-isomers are shown. The conformations chosen for comparisons are shown in blue.

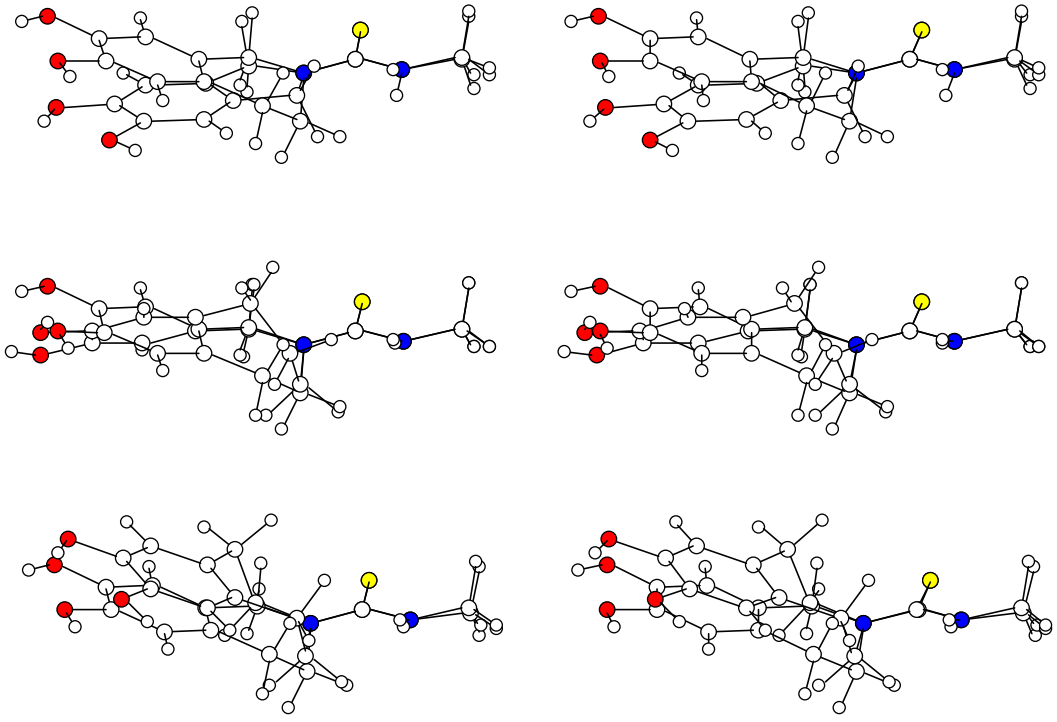

Figure 5. Stereoview (crossed) of the superimpositions **17** (top), **2** (middle) and **71** (bottom) on **34**. The superimpositions show that the catechol and thiourea are differently orientated with respect to each other in the different ring systems.

the thiourea and the catechol moiety differs between the different ring systems. These findings are in agreement with the SAR findings discussed above.

Assuming that such interactions together with those of the B-ring, the coupling region and the C-region of the capsazepinoids together determine how the compounds

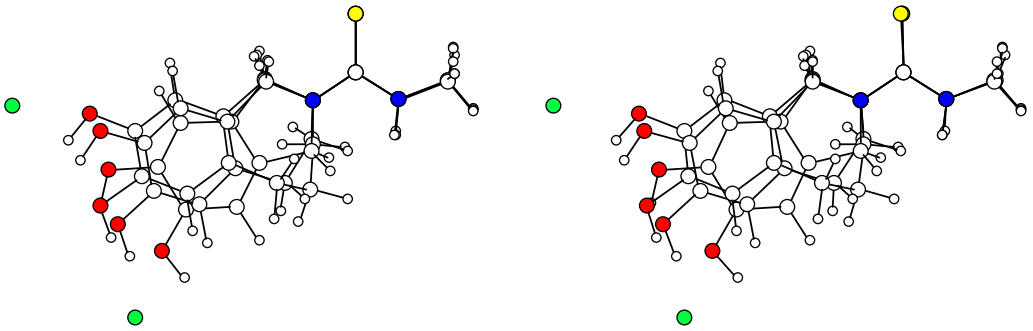

Figure 6. Stereoview (crossed) of a superposition of **17**, **34** and **2**. The two suggested interactions between the catechol moiety of **17**, **34** and **2** (positioned in suitable hydrogen bond distances to the catechol moiety of the 1,2,3,4-tetrahydroisoquinoline derivative (**34**)) and the target are shown in green.

can bind to the target and exert an effect, it would be interesting to compare how the different sizes of the B-ring affect the spatial arrangement of the substituents of the A-ring. The planar conformers of the three dihydroxylated compounds **17**, **34** and **2** (shown in blue in Fig. 4) were therefore compared by, again, superimposing the thiourea moiety (see Fig. 6).

When assessing the SARs of the hydroxylated derivatives, the presence of two specific interactions (shown in green in Fig. 6) is suggested. One is close to C-6 and C-5 (of the 1,2,3,4-tetrahydroisoquinoline system) and seems to be more important for the activity, while the other is close to C-7 and of less importance. Compounds **41** and **48** both show moderately good activities that are similar or even slightly better than that of compound **1**. This suggests that both hydroxyl groups participate in the interaction with the same target atom and there is no benefit for the presence of two hydroxyl groups. This point would also be available for the hydroxyl groups of the monohydroxylated **25** and **61**. None of the hydroxyls of **41**, **48** and **1** reaches the upper point of interaction, however, if the tetrahydroisoquinoline aromatic ring is substituted with hydroxyl groups in C-6 and C-7, as in **34**, each group participates in a separate interaction and the activity is enhanced. A similar reasoning would explain the differences observed between the isoindolines **24**, **25** and **17**. In the tetrahydro-2-benzazepine and tetrahydro-3-benzazepine series (A = IV and A = V, respectively, in Table 1) derivatives, the most important interaction seems to be in the region around C-8, accompanied by a weaker interaction around C-7 (upper and lower points in Fig. 6, respectively). This is indicated by the relative potencies of **66** and **71**, but, in contrast to **34** which seems to be favoured from both interactions, **2** is not more potent than either **66** or **71**. This might be due to an unsuitable positioning of the C-7 hydroxyl group for binding.

The three first entries, **7**, **8** and **12**, in Table 1 lack a B-ring, and although they are not completely inactive it is evident that some sort of conformational restraint is important. This is clearly demonstrated by the comparison of **7**, **8** and **12** with **2**, **17**, **34** and **71**, revealing that all variants having a conformational restriction in the B-ring are considerably more active than the opened-chain analogues. The most obvious explanation for this is that the ring helps to place the catechol hydroxyls, the thiourea moiety and the 4-chlorophenyl in positions relative to each other so that they all can interact with the target in a favourable way. There is obviously no effect from altering the possibility for a hydrogen bond from the left nitrogen in the thiourea, as **12** is equipotent to **7**. When the size and nature of the B-ring is investigated, it is obvious from the comparison of the isoindoline **17** with the tetrahydroisoquinoline **34** and the 2-benzazepine **2** as well as the 3-benzazepine **71** that the tetrahydroisoquinoline is markedly more active.

Both **17** and **34** have been reported as TRPV1-agonists in a Ca^{2+}-influx assay based on the use of neonatal rat cultured spinal sensory neurons.[22] In contradiction to this, both show similar properties as capsazepine in dilating constricted human bronchi, an effect that has been suggested not to be mediated by TRPV1.[7] The isoindoline derivative **17** as well as the benzazepine derivatives **2** and **71** possess similar potency. If the activity depends on the interaction of the compounds with a binding site of a receptor, which is reasonable to assume, the hydroxyl groups and the thiourea moiety are presumably positioned in less favourable conformations in the isoindoline derivatives and the benzazepine derivatives compared to the 1,2,3,4-tetrahydroisoquinoline derivatives.

The investigation of the effects of substituents in the B-ring was consequently limited to the 1,2,3,4-tetrahydroisoquinolines, and only methyl and benzyl substituents in position 1 and 3. Compared to the unsubstituted tetrahydroisoquinoline **34**, a methyl group in position 1 (**35**) or in position 3 (**36**) clearly results in a lower activity. The benzyl group, which only was evaluated in position 1, is strongly deactivating and the benzylated derivative **37** is almost inactive. Alkyl/aryl substituents in the B-ring would increase the lipophilicity of the compounds, which should be expected to facilitate their ability to reach and bind to the target, but they also increase the size, which may be critical for the interaction with a specific binding site. The latter fact appears to be particularly true for the benzylated derivative **37**, which is considerably less active compared with its methylated counterpart **35**. Steric hindrance by substituents in the B-ring therefore appears to be a major obstacle, and should be avoided.

4. Conclusions

Capsazepinoids have been shown to possess a unique and potentially useful relaxing effect in small human airways in vitro. The relaxation is dose-dependent and stronger than any of the agents used to treat the airway obstruction caused by asthma or COPD today. Although the mechanism of action initially was believed to involve the TRPV1 channel, as capsazepine is a TRPV1 antagonist, it has been shown that this is probably not the case and the cellular target for the bronchorelaxing effect of the capsazepinoids is not yet known. The capsazepinoids prepared and assayed here, which were used to discuss and explain SARs of the hydroxylation pattern in the A-ring and the size and substitution of the B-ring (according to Fig. 2), clearly show that their activities depend on their structures. The following conclusions concerning the SARs could be made:

1. The presence of a B-ring is important; derivatives with no B-ring are less active even if they in principle could adopt the same conformation as the potent derivatives.
2. While isoindoline, tetrahydro-2-benzazepine and tetrahydro-3-benzazepine derivatives bearing a catechol in the A-ring are comparably active, the corresponding tetrahydroisoquinoline derivatives are considerably better.
3. The presence of two specific interactions, presumably hydrogen bonds or another strong dipole–dipole interaction at the site where the derivatives bind (shown in Fig. 6), is suggested. The positions of the hydroxyl groups relative to each other as well as the size of the saturated B-ring influence the strength of these interactions and thereby the potency of the compounds.
4. Substituents in the B-ring of the tetrahydroisoquinoline derivatives decrease the activity, presumably because this part is sensitive to steric hindrance.

In the absence of a characterized target for the effects studied here, there can only be direct comparison of the effect on the activity of variations in the structure. Assuming that the phenolic groups as well as the thiourea moiety of capsazepine are involved in the intermolecular bonds between the ligand to the binding site of a receptor, the differences observed between the different B-ring derivatives discussed in this investigation can be explained by the effect the B-ring has on the conformation and general structure of the compounds. Since capsazepinoids most likely represent a novel class of bronchodilators, which might find use in treatment of restricted airflow caused by asthma and COPD, further studies of the capsazepinoids are of importance. Work is now in progress to verify this by identifying novel bronchorelaxing compounds, whose structures comply with the confinement indicated here.

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. HR-MS (ESI) spectra were recorded with a Micromass Q-TOF Micro spectrometer. NMR spectra (in $CDCl_3$, CD_3OD or DMSO-d_6) 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 or the residual CD_3SOCD_2H peak in $(CD_3)_2SO$ solution as internal standard (7.26, 3.32 or 2.50 and 77.2, 49.0 or 39.5 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. 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.

5.2.2.1. *N*-[2-(4-Chlorophenyl)ethyl]-5,6-dihydroxy-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (1). Compound **1** was synthesized as described previously.[22]

5.2.2.2. *N*-[2-(4-Chlorophenyl)ethyl]-*N*′-(3,4-dihydroxybenzyl)thiourea (7). Compound **7** was prepared from 4-(aminomethyl)benzene-1,2-diol hydrobromide (**5**) as described in the general procedure for coupling and purified by flash column chromatography (silica, Pet. Ether/EtOAc 3:2) (59%). ^1H NMR (CD_3OD 400 MHz) δ 2.86 (t, $J = 7.2$ Hz, 2H), 3.71 (br s, 2H), 4.48 (br s, 2H), 6.65 (dd, $J = 8.1$ Hz, $J = 1.8$ Hz, 1H), 6.71 (d, $J = 8.1$ Hz, 1H), 6.75 (d, $J = 1.8$ Hz, 1H), 7.18 (d, $J = 8.2$ Hz, 2H), 7.26 (d, $J = 8.2$ Hz, 2H). ^{13}C NMR (CD_3OD 100 MHz) δ 35.8, 46.6, 48.6, 116.1, 116.5, 120.3, 129.6, 129.6, 131.2, 131.6, 131.6, 133.3, 139.4, 145.9, 146.6, 183.5. HR-MS (ESI) calculated for $C_{16}H_{18}ClN_2O_2S$ (M+H) 337.0778, found 337.0766.

5.2.2.3. *N*-[2-(4-Chlorophenyl)ethyl]-*N*′-[2-(3,4-dihydroxyphenyl)ethyl]thiourea (8). Compound **8** was prepared from 4-(2-aminoethyl)benzene-1,2-diol hydrochloride (**6**) as described in the general procedure for cou-

pling and purified by flash column chromatography (silica, Pet. Ether/EtOAc 1:1) (61%). ^{1}H NMR (CD_3OD 400 MHz) δ 2.70 (t, J = 7.1 Hz, 2H), 2.84 (t, J = 7.2 Hz, 2H), 3.65 (br s, 4H), 6.54 (dd, J = 2.0 Hz, J = 8.0 Hz, 1H), 6.68 (d, J = 2.0 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 7.20 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H). ^{13}C NMR (CD_3OD 100 MHz) δ 35.6, 35.6, 46.4, 46.6, 116.4, 116.9, 121.1, 129.5, 129.5, 131.5, 131.5, 131.9, 133.1, 139.3, 144.8, 146.3, 182.7. HR-MS (ESI) calculated for $C_{17}H_{20}N_2O_2SCl$ (M+H) 351.0934, found 351.0927.

5.2.2.4. *N*-(3,4-Dimethoxybenzyl)-*N*-methylamine (10). 3,4-Dimethoxybenzaldehyde (**9**) (1.0 equiv) was dissolved in MeOH, then a 2.3 M solution of $MeNH_2$ in MeOH (1.0 equiv) was added. The mixture was stirred at 40 °C for 5 h. The reaction mixture was cooled in an ice bath and $NaBH_4$ (5.0 equiv) was added in small portions. Once addition was finished, the ice bath was removed and the mixture stirred at room temperature overnight. A hydrochloric acid solution in ice-water was added until acidic pH. The MeOH was evaporated and the aqueous residue was adjusted to pH 10 with a solution of NaOH, then it was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (silica, EtOAc) to afford **10** (64%). ^{1}H NMR (CD_3OD 300 MHz) δ 2.34 (s, 3H), 3.61 (s, 2H), 3.79 (s, 3H), 3.82 (s, 3H), 6.83 (d, J = 8.4 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 6.95 (s, 1H).

5.2.2.5. 4-[(Methylamino)methyl]benzene-1,2-diol hydrobromide (11). Compound **11** was prepared from **10** using the general procedure for demethylation (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 2.67 (s, 3H), 4.01 (s, 2H), 6.81 (m, 2H), 6.90 (s, 1H).

5.2.2.6. *N*′-[2-(4-Chlorophenyl)ethyl]-*N*-(3,4-dihydroxybenzyl)-*N*-methylthiourea (12). Compound **12** was prepared from **11** as described in the general procedure for coupling and purified by flash column chromatography (silica, Pet. Ether/EtOAc 3:2) (64%). ^{1}H NMR (CD_3OD 400 MHz) δ 2.92 (t, J = 7.4 Hz, 2H), 2.97 (s, 3H), 3.81 (t, J = 7.4 Hz, 2H), 4.91 (s, 2H), 6.56 (dd, J = 8.1 Hz, J = 1.9 Hz, 1H), 6.72 (m, 2H), 7.19 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H). ^{13}C NMR (CD_3OD 100 MHz) δ 35.8, 37.2, 48.1, 56.9, 115.5, 116.3, 120.0, 129.4, 129.4, 129.9, 131.5, 131.5, 133.0, 139.6, 145.8, 146.5, 182.9. HR-MS (ESI) calculated for $C_{17}H_{19}ClN_2O_2S$ (M+H) 350.0856, found 350.0843.

5.2.2.7. 1,2-Bis(bromomethyl)-4,5-dimethoxybenzene (14). Thirty-three percentages HBr in AcOH (about 3.1 ml/g of 1,2-dimethoxybenzene) was added to a solution of **13** (1.0 equiv) and paraformaldehyde (2.0 equiv) in acetic acid, while the temperature was kept at 17 °C. After stirring at room temperature for 20 h, the mixture was heated to 65 °C for 1 h. The mixture was concentrated. Purification was done by flash column chromatography (silica, Pet. Ether/EtOAc 4:1) affording **14** (58%) as white crystals. ^{1}H NMR ($CDCl_3$ 300 MHz) δ 3.90 (s, 6H), 4.64 (s, 4H), 6.85 (s, 2H).

5.2.2.8. 5,6-Dimethoxy-2-[(4-methylphenyl)sulfonyl]isoindoline (15). To a stirred refluxing solution of freshly prepared NaOEt (1.0 equiv) in absolute EtOH, tosylamide (1.0 equiv) was added. The mixture was refluxed for 2 h and then cooled. The insoluble TsNHNa was filtered off, washed with absolute ethanol and dried in vacuo. To a stirred solution of TsNHNa (1.0 equiv) in anhydrous DMF at 80 °C under a N_2 atmosphere, a solution of **14** (1.0 equiv) in anhydrous DMF was added dropwise. After 1 h, solid TsNHNa (1.0 equiv) was added all at once and the mixture was stirred at 80 °C for 4 h. The mixture was concentrated and the residue extracted with CH_2Cl_2. The organic phase was washed with 1 N NaOH, dried ($MgSO_4$) and concentrated. The crystals formed were washed with MeOH. The product still remaining in the MeOH was purified by flash column chromatography (silica, Pet. Ether/EtOAc 7:3) affording **15** (75%). ^{1}H NMR ($CDCl_3$ 300 MHz) δ 2.41 (s, 3H), 3.83 (s, 6H), 4.57 (s, 4H), 6.66 (s, 2H), 7.31 (d, J = 8.1 Hz, 2H), 7.76 (d, J = 8.1 Hz, 2H).

5.2.2.9. 5,6-Dihydroxyisoindoline hydrobromide (16). Forty-eight percentages HBr in H_2O, phenol, propionic acid and **15** (6 ml:0.75 ml:1 ml:1 g) were mixed together and refluxed for 4 h under N_2 atmosphere. The reaction solution was evaporated under reduced pressure to dryness, and 48% HBr (2 ml/g of **15**) was added to the residue. The mixture was again refluxed under a N_2 atmosphere for 3 h. The reaction solution was cooled down; H_2O and $CHCl_3$ were added thereto. The water phase was treated with active carbon and evaporated under reduced pressure to dryness, the crystalline residue was washed with ether/ethanol (1:1) to afford **16** (67%). ^{1}H NMR (CD_3OD 300 MHz) δ 4.45 (s, 4H), 6.79 (s, 2H).

5.2.2.10. *N*-[2-(4-Chlorophenyl)ethyl]-5,6-dihydroxy-1,3-dihydro-2*H*-isoindole-2-carbothioamide (17). Compound **17** was prepared from **16** as described in the general procedure for coupling and purified by flash column chromatography (silica, Pet. Ether/EtOAc 1:1) (86%). Spectroscopic data as described previously.[22]

5.2.2.11. 4-Methoxy-2-[(4-methylphenyl)sulfonyl]isoindoline (20). A mixture of 2,3-dimethylanisole, **18** (1.0 equiv), *N*-bromosuccinimide (2.0 equiv) and benzoyl peroxide (50 mg/g of **18**) was refluxed in CCl_4 for 20 h. After cooling, the insoluble material was filtered off and extracted with a small amount of CCl_4. The filtrate and CCl_4 used for the extraction were mixed and concentrated to give an oily residue containing 2,3-bis(bromomethyl)anisole which was used without further purification.

To a stirred solution of TsNHNa (1.0 equiv) in anhydrous DMF at 80 °C was added dropwise under a N_2 atmosphere a solution of 2,3-bis(bromomethyl)anisol (1.0 equiv) in anhydrous DMF. After 1 h, solid TsNHNa (1.0 equiv) was added all at once, and the mixture was stirred at 80 °C for 4 h. The mixture was concentrated. The residue was extracted with CH_2Cl_2, thoroughly washed with 1 N NaOH, dried ($MgSO_4$) and concentrated. Purification was done by flash column chromatography (silica, gradient elution, 20–30% EtOAc in Pet. Ether) and by crystallization from etha-

nol, affording **20**. ^{1}H NMR ($CDCl_3$ 300 MHz) δ 2.40 (s, 3H), 3.79 (s, 3H), 4.57 (s, 2H), 4.62 (s, 2H), 6.70 (d, J = 7.9 Hz, 1H), 6.75 (d, J = 7.9 Hz, 1H), 7.20 (t, J = 7.9 Hz, 1H), 7.30 (d, J = 8.2 Hz, 2H), 7.77 (d, J = 8.2 Hz, 2H).

5.2.2.12. 5-Methoxy-2-[(4-methylphenyl)sulfonyl]isoindoline (21). This compound was prepared as described for **20** from 3,4-dimethylanisole, **19**, purification was done by flash column chromatography (silica, gradient elution 20–50% EtOAc in Pet. Ether) affording **21**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 2.45 (s, 3H), 3.76 (s, 3H), 4.55 (s, 2H), 4.59 (s, 2H), 6.69 (br s, 1H), 6.78 (dd, J = 8.4 Hz, J = 2.3 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 8.2 Hz, 2H), 7.76 (d, J = 8.2 Hz, 2H).

5.2.2.13. Isoindolin-4-ol hydrobromide (22). Forty-eight percentages HBr in H_2O, phenol, propionic acid and **20** (6 ml:0.75 ml:1 ml:1 g), were mixed together. The mixture was refluxed for 4 h under N_2 atmosphere. The reaction solution was evaporated under reduced pressure to dryness, and 48% HBr in H_2O (2 ml/g of **20**) was added to the residue. The mixture was again refluxed under a N_2 atmosphere for 3 h. The reaction solution was cooled down; H_2O and $CHCl_3$ were added thereto. The water layer was separated, treated with active carbon and evaporated under reduced pressure to dryness; the crystalline residue was washed with di-ethyl ether/ethanol (1:1) to afford **22** (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 4.54 (s, 2H), 4.61 (s, 2H), 6.77 (br s, 1H), 6.88 (br s, 1H), 7.21 (br s, 1H).

5.2.2.14. Isoindolin-5-ol hydrobromide (23). This compound was prepared as described for **22** from **21**, affording **23** (24%). ^{1}H NMR (CD_3OD 300 MHz) δ 4.51 (s, 2H), 4.54 (s, 2H) 6.80 (m, 2H), 7.21 (d, J = 8.2 Hz, 1H).

5.2.2.15. *N*-[2-(4-chlorophenyl)ethyl]-4-hydroxy-1,3-dihydro-2*H*-isoindole-2-carbothioamide (24). This compound was prepared from **22** as described in the general procedure for coupling, the crude product was washed several times with CH_2Cl_2 and with cold MeOH affording **24** (35%). ^{1}H NMR (DMSO-d_6 400 MHz) δ 2.89 (t, J = 7.4 Hz, 2H), 3.70 (m, 2H), 4.75 (br s, 4H), 6.71 (d, J = 7.7 Hz, 1H), 6.77 (d, J = 7.7 Hz, 1H), 7.12 (t, J = 7.7 Hz, 1H), 7.27 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.3 Hz, 2H), 7.62 (br s, 1H), 9.85 (s, 1H). ^{13}C NMR (DMSO-d_6 100 MHz) δ 34.2, 46.2, 48.6, 54.9, 113.2, 113.5, 122.4, 128.3, 128.3, 129.0, 130.6, 130.6, 130.7, 137.8, 138.6, 152.4, 178.5. HR-MS (ESI) calculated for $C_{17}H_{18}ClN_2OS$ (M+H) 333.0828, found 333.0824.

5.2.2.16. *N*-[2-(4-Chlorophenyl)ethyl]-5-hydroxy-1,3-dihydro-2*H*-isoindole-2-carbothioamide (25). This compound was prepared from **23** as described in the general procedure for coupling. Purification was done by flash column chromatography (silica, gradient elution 20–60% EtOAc in Pet. Ether + 1% AcOH) affording **25** (31%). ^{1}H NMR (CD_3OD 400 MHz) δ 2.94 (t, J = 7.5 Hz, 2H), 3.80 (t, J = 7.5 Hz, 2H), 4.63 (br s, 4H), 6.73 (m, 2H), 7.10 (d, J = 8.2 Hz, 1H), 7.25 (m, 4H). ^{13}C NMR (CD_3OD 100 MHz) δ 35.9, 47.7, 54.5, 57.9, 110.1, 116.2, 124.4, 127.6, 129.5, 129.5, 131.5, 131.5, 133.0, 138.5, 139.6, 158.6, 179.9. HR-MS (ESI) calculated for $C_{17}H_{18}ClN_2OS$ (M+H) 333.0828, found 333.0837.

5.2.2.17. 1,2,3,4-Tetrahydroisoquinoline-6,7-diol hydrobromide (30). Compound **30** was prepared from 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (**26**) using the general procedure for demethylation (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 2.96 (t, J = 6.4 Hz, 2H), 3.44 (t, J = 6.4 Hz, 2H), 4.19 (s, 2H), 6.59 (s, 1H), 6.63 (s, 1H).

5.2.2.18. 1-Methyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol hydrobromide (31). Compound **31** was prepared from 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (**27**) using the general procedure for demethylation (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 1.62 (d, J = 6.7 Hz, 3H), 2.95 (m, 2H), 3.32 (m, 1H), 3.49 (m, 1H), 4.45 (d, J = 6.7 Hz, 1H), 4.49 (d, J = 6.7 Hz, 1H), 6.57 (s, 1H), 6.66 (s, 1H).

5.2.2.19. 3-Methyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol hydrobromide (32). Compound **32** was prepared from 6,7-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (**28**) using the general procedure for demethylation (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 1.47 (d, J = 6.5 Hz, 3H), 2.76 (dd, J = 17.0 Hz, J = 11.0 Hz, 1H), 2.98 (dd, J = 17.0 Hz, J = 4.9 Hz, 1H), 3.57 (m, 1H), 4.19 (d, J = 15.4 Hz, 1H), 4.26 (d, J = 15.4 Hz, 1H), 6.60 (s, 2H).

5.2.2.20. 1-Benzyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol hydrobromide (33). Compound **33** was prepared from 1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (**29**) using the general procedure for demethylation (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 3.11 (m, 3H), 3.30 (m, 1H), 3.47 (m, 2H), 4.68 (m, 1H), 6.60 (s, 1H), 6.64 (s, 1H), 7.36 (m, 5H).

5.2.2.21. *N*-[2-(4-Chlorophenyl)ethyl]-6,7-dihydroxy-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (34). Compound **34** was prepared from **30** as described in the general procedure for coupling, and purified by flash column chromatography (silica, Pet. Ether/EtOAc 1:1 + 1% AcOH) (69%). Spectroscopic data as described previously.[22]

5.2.2.22. *N*-[2-(4-Chlorophenyl)ethyl]-6,7-dihydroxy-1-methyl-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (35). Compound **35** was prepared from **31** as described in the general procedure for coupling and purified by flash column chromatography (silica, Pet. Ether/EtOAc 2:1 + 1% AcOH) (87%). ^{1}H NMR (CD_3OD 400 MHz) δ 1.40 (d, J = 6.7 Hz, 3H), 2.69 (m, 2H), 2.91 (t, J = 7.4 Hz, 2H), 3.39 (m, 1H), 3.81 (t, J = 7.4 Hz, 2H), 4.40 (br s, 1H), 5.64 (br s, 1H), 6.53 (s, 1H), 6.54 (s, 1H), 7.16 (d, J = 8.1 Hz, 2H), 7.21 (d, J = 8.1 Hz, 2H). ^{13}C NMR (CD_3OD 100 MHz) δ 21.5, 28.7, 35.7, 43.0, 47.9, 55.4, 114.2, 115.9, 126.4, 129.4, 129.4, 130.7, 131.5, 131.5, 132.9, 139.6, 145.0, 145.1, 175.3. HR-MS (ESI) calculated for $C_{19}H_{22}ClN_2O_2S$ (M+H) 377.1091, found 377.1085.

5.2.2.23. *N*-[2-(4-Chlorophenyl)ethyl]-6,7-dihydroxy-3-methyl-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (36). Compound **36** was prepared from **32** as described in the general procedure for coupling and purified by flash column chromatography (silica, Pet. Ether/EtOAc 1:1 + 1% AcOH) (91%). ^{1}H NMR (CD_3OD 400 MHz) δ 1.02 (d, J = 6.6 Hz, 3H) 2.50 (dd, J = 15.6 Hz, J = 2.2 Hz, 1H), 2.95 (m, 3H), 3.85 (m, 2H), 4.32 (d, J = 15.3 Hz, 1H), 4.73 (d, J = 15.3 Hz, 1H), 5.39 (br s, 1H), 6.58 (s, 1H), 6.59 (s, 1H), 7.22 (d, J = 8.5 Hz, 2H), 7.27 (t, J = 8.5 Hz, 2H). ^{1}3C NMR (CD_3OD 100 MHz) δ 17.5, 35.1, 35.7, 47.1, 47.9, 51.1, 113.7, 116.6, 123.8, 125.2, 129.4, 129.4, 131.6, 131.6, 133.0, 139.6, 145.1, 145.6, 181.4. HR-MS (ESI) calculated for $C_{19}H_{22}ClN_2O_2S$ (M+H) 377.1091, found 377.1084.

5.2.2.24. 1-Benzyl-*N*-[2-(4-chlorophenyl)ethyl]-6,7-dihydroxy-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (37). Compound **37** was prepared from **33** as described in the general procedure for coupling and purified by flash column chromatography (silica, Pet. Ether/EtOAc 4:1 + 1% AcOH) (97%). ^{1}H NMR (CD_3OD 400 MHz) δ 2.75 (br s, 4H), 2.97 (m, 1H), 3.26 (br s, 1H), 3.49 (m, 1H), 3.87 (br s, 3H), 5.90 (br s, 1H), 6.22 (br s, 1H), 6.58 (s, 1H), 7.15 (m, 9H). ^{13}C NMR (CD_3OD 100 MHz) δ 28.1, 35.6, 43.0, 44.4, 47.8, 62.1, 115.5, 115.6, 126.9, 127.4, 128.8, 129.2, 129.2, 129.4, 129.4, 130.8, 130.8, 131.4, 131.4, 132.9, 139.5, 139.7, 144.4, 145.4, 181.6. HR-MS (ESI) calculated for $C_{25}H_{26}ClN_2O_2S$ (M+H) 453.1404, found 453.1394.

5.2.2.25. *tert*-Butyl 5-methoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (39). 2-(2-Methoxyphenyl)ethylamine, **38** (1.0 equiv), paraformaldehyde (5.0 equiv) and $MgSO_4$ (3.0 equiv) were suspended in anhydrous CH_2Cl_2. After stirring for 2 h the solid was filtered off. The filtrate was concentrated. The residue was dissolved in anhydrous trifluoroacetic acid and refluxed under nitrogen overnight. The mixture was poured into a mixture of ice and water. The water phase was made basic with NaOH (6 M) and extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated. The remaining oil was dissolved in THF. To this solution were added di-*tert*-butyl dicarbonate (1.2 equiv) and triethylamine (3.0 equiv). The mixture was stirred for 3 h and then concentrated. The residue was dissolved in EtOAc and washed with a saturated solution of Na_2CO_3. The organic phase was dried ($MgSO_4$) and concentrated. Purification was done by flash column chromatography (silica, Pet. Ether/EtOAc 6:1) (26%). ^{1}H NMR ($CDCl_3$ 400 MHz) δ 1.47 (s, 9H), 2.74 (br s, 2H), 3.62 (br s, 2H), 3.81 (s, 3H), 4.55 (s, 2H), 6.70 (m, 2H), 7.14 (t, J = 8.0 Hz, 1H).

5.2.2.26. 1,2,3,4-Tetrahydroisoquinolin-5-ol hydrobromide (40). This compound was prepared from **39** using the general procedure for demethylation (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 2.98 (t, J = 6.5 Hz, 2H), 3.50 (t, J = 6.5 Hz, 2H), 4.31 (s, 2H), 6.70 (d, J = 7.7 Hz, 1H), 6.75 (d, J = 7.7 Hz, 1H), 7.09 (t, J = 7.7 Hz, 1H).

5.2.2.27. *N*-[2-(4-Chlorophenyl)ethyl]-5-hydroxy-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (41). This compound was prepared from **40** as described in the general procedure for coupling and purified by flash column chromatography (silica, gradient elution 0–3% MeOH in CH_2Cl_2) (65%). ^{1}H NMR (CD_3OD 400 MHz) δ 2.81 (t, J = 6.0 Hz, 2H), 2.94 (t, J = 7.4 Hz, 2H), 3.83 (t, J = 7.4 Hz, 2H), 3.96 (t, J = 6.0 Hz, 2H), 4.84 (s, 2H), 6.62 (d, J = 7.8 Hz, 1H), 6.67 (d, J = 7.8 Hz, 1H), 7.01 (t, J = 7.8 Hz, 1H), 7.23 (m, 4H). ^{13}C NMR (CD_3OD 100 MHz) δ 23.6, 35.7, 46.6, 47.9, 50.7, 113.8, 118.3, 123.1, 128.0, 129.4, 129.4, 131.5, 131.5, 133.0, 135.8, 139.6, 155.8, 182.0. HR-MS (ESI) calculated for $C_{18}H_{20}ClN_2OS$ (M+H) 347.0985, found 347.0980.

5.2.2.28. 1,2,3,4-*tert*-Butyl 8-methoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (43) and *tert*-butyl 6-methoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (44). These compounds were prepared from 2-(3-methoxyphenyl)ethylamine, **42**, by the procedure described for **39**, affording **43** and **44** in a 1:5 ratio. Purification was done by flash column chromatography (silica, gradient elution, 10–30% EtOAc in Pet. Ether) (47%).

Compound **43**: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 1.50 (s, 9H), 2.82 (br s, 2H), 3.64 (br s, 2H), 3.83 (s, 3H), 4.49 (s, 2H), 6.70 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H).

Compound **44**: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 1.49 (s, 9H), 2.81 (br s, 2H), 3.62 (br s, 2H), 3.78 (s, 3H), 4.50 (s, 2H), 6.67 (s, 1H), 6.75 (d, J = 8.3 Hz, 1H), 7.02 (d, J = 8.3 Hz, 1H).

5.2.2.29. 1,2,3,4-Tetrahydroisoquinolin-8-ol hydrobromide (45). This compound was prepared from **43** using the general procedure for demethylation (quantitative), ^{1}H NMR (CD_3OD 300 MHz) δ 3.08 (t, J = 6.3 Hz, 2H), 3.47 (t, J = 6.3 Hz, 2H), 4.25 (s, 2H), 6.72 (m, 2H), 7.12 (t, J = 7.9 Hz, 1H).

5.2.2.30. *N*-[2-(4-Chlorophenyl)ethyl]-8-hydroxy-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (46). This compound was prepared from **45** as described in the general procedure for coupling and purified by flash column chromatography (silica, Pet. Ether/EtOAc/AcOH 70:30:1) (55%). ^{1}H NMR (CD_3OD 400 MHz) δ 2.74 (t, J = 5.7 Hz, 2H), 2.85 (t, J = 7.4 Hz, 2H), 3.75 (t, J = 7.4 Hz, 2H), 3.94 (t, J = 5.7 Hz, 2H), 4.63 (s, 2H), 6.55 (d, J = 7.8 Hz, 1H), 6.56 (d, J = 7.8 Hz, 1H), 6.92 (t, J = 7.8 Hz, 1H), 7.14 (m, 4H). ^{13}C NMR (CD_3OD 100 MHz) δ 29.7, 35.8, 46.1, 47.0, 48.0, 113.2, 120.2, 120.9, 128.3, 129.4, 129.4, 131.6, 131.6, 133.0, 137.6, 139.7, 154.9, 182.3. HR-MS (ESI) calculated for $C_{18}H_{20}ClN_2OS$ (M+H) 347.0985, found 347.0993.

5.2.2.31. 1,2,3,4-Tetrahydroisoquinolin-6-ol hydrobromide (47). This compound was prepared from **44** using the general procedure for demethylation (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 3.06 (t, J = 6.4 Hz, 2H), 3.47 (t, J = 6.4 Hz, 2H), 4.26 (s, 2H), 6.67 (s, 2H), 6.71 (d, J = 8.3 Hz, 1H), 7.04 (d, J = 8.3 Hz, 1H).

5.2.2.32. *N*-[2-(4-Chlorophenyl)ethyl]-6-hydroxy-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (48). This compound was prepared from **47** as described in the

general procedure for coupling and purified by flash column chromatography (silica, Pet. Ether/EtOAc/AcOH 50:50:1) (74%). ^{1}H NMR (CD_3OD 300 MHz) δ 2.82 (t, J = 5.9 Hz, 2H), 2.92 (t, J = 7.5 Hz, 2H), 3.83 (t, J = 7.5 Hz, 2H), 3.89 (t, J = 5.9 Hz, 2H), 4.73 (s, 2H), 6.64 (m, 2H), 6.95 (d, J = 8.1 Hz, 1H), 7.19 (m, 4H). ^{13}C NMR (CD_3OD 75 MHz) δ 29.5, 35.3, 46.3, 47.4, 49.4, 114.3, 114.9, 124.7, 127.9, 129.0, 129.0, 130.8, 130.8, 132.5, 137.2, 138.6, 156.5, 181.0. HR-MS (ESI) calculated for $C_{18}H_{20}ClN_2OS$ (M+H) 347.0985, found 347.0988.

5.2.2.33. *tert*-Butyl 7-methoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (50). This compound was prepared from 2-(4-methoxyphenyl)ethylamine, **49**, by the procedure described for **39**. Purification was done by flash column chromatography (silica, gradient elution, 14–33% EtOAc in Pet. Ether) (47%). ^{1}H NMR ($CDCl_3$ 300 MHz) δ 1.48 (s, 9H), 2.75 (t, J = 5.5 Hz, 2H), 3.62 (t, J = 5.5 Hz, 2H), 3.77 (s, 3H), 4.53 (s, 2H), 6.63 (br s, 1H), 6.73 (dd, J = 8.4 Hz, J = 2.5 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H).

5.2.2.34. 1,2,3,4-Tetrahydroisoquinolin-7-ol hydrobromide (51). This compound was prepared from **50** using the general procedure for demethylation (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 3.02 (t, J = 6.3 Hz, 2H), 3.45 (t, J = 6.3 Hz, 2H), 4.29 (s, 2H), 6.63 (d, J = 2.4 Hz, 1H), 6.74 (dd, J = 8.4 Hz, J = 2.4 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H).

5.2.2.35. *N*-[2-(4-Chlorophenyl)ethyl]-7-hydroxy-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (52). This compound was prepared from **51** as described in the general procedure for coupling and purified by flash column chromatography (silica, Pet. Ether/EtOAc/AcOH 50:50:1) (22%). ^{1}H NMR (CD_3OD 300 MHz) δ 2.80 (t, J = 6.0 Hz, 2H), 2.93 (t, J = 7.6 Hz, 2H), 3.84 (t, J = 7.6 Hz, 2H), 3.89 (t, J = 6.0 Hz, 2H), 4.80 (s, 2H), 6.61 (d, J = 2.4 Hz, 1H), 6.66 (dd, J = 8.2 Hz, 2.4 Hz, 1H), 6.99 (d, J = 8.2 Hz, 1H), 7.21 (m, 4H). ^{13}C NMR (CD_3OD 75 MHz) δ 28.5, 35.3, 46.6, 47.5, 50.2, 113.3, 114.8, 126.7, 129.0, 129.0, 129.5, 130.9, 130.9, 132.6, 134.8, 138.6, 156.1, 181.1. HR-MS (ESI) calculated for $C_{18}H_{20}ClN_2OS$ (M+H) 347.0985, found 347.1000.

5.2.2.36. 7,8-Dimethoxy-2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one (55). 6,7-Dimethoxy-3,4-dihydronaphthalen-1(2*H*)-one, **53** (1.0 equiv) was dissolved in methanesulfonic acid. The solution was cooled on an ice bath and NaN_3 (1.3 equiv) was added over a period of 30 min. The mixture was stirred at room temperature for 18 h. It was then cooled on an ice bath and a saturated solution of $NaHCO_3$ was added until slight basicity. The aqueous phase was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (silica, gradient elution, 40–100% EtOAc in CH_2Cl_2), affording compound **55** (65%) as a white solid. ^{1}H NMR ($CDCl_3$ 300 MHz) δ 2.03 (quint, J = 7.0 Hz, 2H), 2.84 (t, J = 7.0 Hz, 2H), 3.16 (q, J = 7.0 Hz, 2H), 3.93 (s, 3H), 3.95 (s, 3H), 6.30 (br s, 1H), 6.70 (s, 1H), 7.28 (s, 1H).

5.2.2.37. 7,8-Dimethoxy-2,3,4,5-tetrahydro-1*H*-2-benzazepine hydrochloride (57). Compound **55** (1.0 equiv) was suspended in anhydrous THF; the suspension was cooled on an ice bath under nitrogen. A 1M solution of borane in THF (3.0 equiv) was added dropwise to this suspension. The reaction mixture was then refluxed (70 °C) overnight. The mixture was then cooled on an ice bath. MeOH (15 ml/g of **55**) and 5 M HCl solution (15 ml/g of **55**) were added. The solution was heated to 90 °C for 2 h. Solvents were then evaporated. Purification was done by re-crystallization of the hydrochloride from EtOAc, affording compound **57** (85%) as a white solid. ^{1}H NMR (CD_3OD 300 MHz) δ 1.96 (m, 2H), 3.00 (m, 2H), 3.45 (m, 2H), 3.83 (s, 3H), 3.84 (s, 3H), 4.31 (s, 2H), 6.90 (s, 1H), 6.99 (s, 1H).

5.2.2.38. 2,3,4,5-Tetrahydro-1*H*-2-benzazepine-7,8-diol hydrobromide (59). This compound was prepared from **57** using the general procedure for demethylation (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 1.94 (m, 2H), 2.89 (m, 2H), 3.41 (t, J = 5.7 Hz, 2H), 4.20 (s, 2H), 6.70 (s, 1H), 6.78 (s, 1H).

5.2.2.39. *N*-[2-(4-Chlorophenyl)ethyl]-7,8-dihydroxy-1,3,4,5-tetrahydro-2*H*-2-benzazepine-2-carbothioamide (2). Compound **2** was prepared from **59** as described in the general procedure for coupling and purified by flash column chromatography (silica, Pet. Ether/EtOAc 1:1) (70%). Spectroscopic data as described previously.[22]

5.2.2.40. 7-Methoxy-2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one (56). This compound was prepared as described for **55** from **54** and purified by flash column chromatography (silica, gradient elution 40–100% EtOAc in CH_2Cl_2) yielding **56** and 7-methoxy-1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-one in 7:1 ratio (60%). ^{1}H NMR ($CDCl_3$ 300 MHz) δ 2.03 (quint, J = 7.0 Hz, 2H), 2.86 (t, J = 7.0 Hz, 2H), 3.15 (q, J = 7.0 Hz, 2H), 3.86 (s, 3H), 6.42 (br s, 1H), 6.73 (d, J = 2.5 Hz, 1H), 6.87 (dd, J = 8.5 Hz, J = 2.5 Hz, 1H), 7.70 (d, J = 8.5 Hz, 1H).

5.2.2.41. 7-Methoxy-2,3,4,5-tetrahydro-1*H*-2-benzazepine hydrochloride (58). This compound was prepared as described for **57** from **56** and purified by flash column chromatography (silica, gradient elution 0–50% MeOH in EtOAc) (94%). ^{1}H NMR (CD_3OD 300 MHz) δ 1.98 (m, 2H), 3.02 (m, 2H), 3.45 (m, 2H), 3.80 (s, 3H), 4.30 (s, 2H), 6.79 (dd, J = 8.3 Hz, J = 2.6 Hz, 1H), 6.86 (d, J = 2.6 Hz, 1H), 7.27 (d, J = 8.3 Hz, 1H).

5.2.2.42. 2,3,4,5-Tetrahydro-1*H*-2-benzazepin-7-ol hydrobromide (60). This compound was prepared from **58** using the general procedure for demethylation (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 1.99 (m, 2H), 2.98 (m, 2H), 3.44 (m, 2H), 4.28 (s, 2H), 6.65 (dd, J = 8.2 Hz, J = 2.5 Hz, 1H), 6.72 (d, J = 2.5 Hz, 1H), 7.18 (d, J = 8.2 Hz, 1H).

5.2.2.43. *N*-[2-(4-Chlorophenyl)ethyl]-7-hydroxy-1,3,4,5-tetrahydro-2*H*-2-benzazepine-2-carbothioamide (61). This compound was prepared from **60** as described in the general procedure for coupling and purified by flash

column chromatography (silica, Pet. Ether/EtOAc 1:1) (63%). ^{1}H NMR (CD_3OD 400 MHz) δ 1.77 (m, 2H), 2.85 (m, 2H), 2.85 (t, J = 7.0 Hz, 2H), 3.75 (t, J = 7.0 Hz, 2H), 4.07 (br s, 2H), 4.70 (s, 2H), 6.50 (dd, J = 8.1 Hz, 2.5 Hz, 1H), 6.61 (d, J = 2.5 Hz, 1H), 7.06 (d, J = 8.1 Hz, 1H), 7.10 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H). ^{13}C NMR (CD_3OD 100 MHz) δ 28.6, 35.6, 36.7, 47.8, 49.6, 54.5, 113.1, 117.8, 128.5, 129.4, 129.4, 131.5, 131.5, 131.6, 132.9, 139.5, 144.3, 158.1, 181.2. HR-MS (ESI) calculated for $C_{19}H_{22}ClN_2OS$ (M+H) 361.1141, found 361.1139.

5.2.2.44. 8-Methoxy-1,2,4,5-tetrahydro-3*H*-2-benzazepin-3-one (63). This compound was prepared from **62** as described for **55**. Purification was done by flash chromatography (silica, gradient elution 40–100% EtOAc in CH_2Cl_2), yielding **63** and 8-methoxy-1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-one in 1:2 ratio (65%). ^{1}H NMR (CD_3OD 300 MHz) δ 2.73 (m, 2H), 3.03 (m, 2H), 3.78 (s, 3H), 4.33 (s, 2H), 6.76 (d, J = 2.7 Hz, 1H), 6.81 (dd, J = 8.4 Hz, J = 2.7 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H).

5.2.2.45. 8-Methoxy-2,3,4,5-tetrahydro-1*H*-2-benzazepine hydrochloride (64). This compound was prepared as described for **57** from **63** (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 1.97 (m, 2H), 3.01 (m, 2H), 3.47 (m, 2H), 3.80 (s, 3H), 4.34 (s, 2H), 6.89 (dd, J = 8.2 Hz, J = 2.7 Hz, 1H), 6.97 (d, J = 2.7 Hz, 1H), 7.21 (d, J = 8.2 Hz, 1H).

5.2.2.46. 2,3,4,5-Tetrahydro-1*H*-2-benzazepin-8-ol hydrobromide (65). This compound was prepared from **64** using the general procedure for demethylation (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 1.94 (m, 2H), 2.98 (m, 2H), 3.46 (m, 2H), 4.29 (s, 2H), 6.74 (dd, J = 8.2 Hz, J = 2.6 Hz, 1H), 6.82 (d, J = 2.6 Hz, 1H), 7.10 (d, J = 8.2 Hz, 1H).

5.2.2.47. *N*-[2-(4-Chlorophenyl)ethyl]-8-hydroxy-1,3,4,5-tetrahydro-2*H*-2-benzazepine-2-carbothioamide (66). This compound was prepared from **65** as described in the general procedure for coupling and purified by flash column chromatography (silica, Pet. Ether/EtOAc 6:4) (62%). ^{1}H NMR (CD_3OD 400 MHz) δ 1.74 (m, 2H), 2.83 (m, 2H), 2.85 (t, J = 7.4 Hz, 2H) 3.75 (t, J = 7.4 Hz, 2H), 4.02 (br s, 2H), 4.78 (s, 2H), 6.60 (dd, J = 8.1 Hz, 2.6 Hz, 1H), 6.82 (d, J = 2.6 Hz, 1H), 6.96 (d, J = 8.1 Hz, 1H), 7.10 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H). ^{13}C NMR (CD_3OD 100 MHz) δ 28.7, 34.6, 35.6, 47.9, 54.5, 55.7, 115.0, 118.0, 129.4, 129.4, 131.5, 131.5, 131.7, 132.9, 133.4, 138.6, 139.5, 156.5, 181.4. HR-MS (ESI) calculated for $C_{19}H_{22}ClN_2OS$ (M+H) 361.1141, found 361.1155.

5.2.2.48. 7,8-Dimethoxy-1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-one (68). Compound **68** was prepared as described for **55** from 6,7-dimethoxy-3,4-dihydronaphthalen-2(1*H*)-one (**67**) and purified by flash column chromatography (silica, gradient elution, 0–5% MeOH in EtOAc). (65%). ^{1}H NMR (CD_3OD 300 MHz) δ 3.08 (t, J = 6.0 Hz, 2H), 3.61 (q, J = 6.0 Hz, 2H), 3.80 (s, 2H), 3.88 (s, 6H), 5.96 (br s, 1H), 6.63 (s, 1H), 6.66 (s, 1H).

5.2.2.49. 7,8-Dimethoxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride (69). Compound **69** was prepared as described for **57** from **68** and purified by flash column chromatography (silica, gradient elution, 5–10% MeOH in CH_2Cl_2) (44%). ^{1}H NMR (CD_3OD 300 MHz) δ 3.08 (m, 4H), 3.26 (m, 4H), 3.81 (s, 6H), 6.84 (s, 2H).

5.2.2.50. 2,3,4,5-Tetrahydro-1*H*-3-benzazepine-7,8-diol hydrobromide (70). Compound **70** was prepared from **69** using the general procedure for demethylation (quantitative). ^{1}H NMR (CD_3OD 300 MHz) δ 2.99 (m, 4H), 3.23 (m, 4H), 6.64 (s, 2H).

5.2.2.51. *N*-[2-(4-Chlorophenyl)ethyl]-7,8-dihydroxy-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carbothioamide (71). Compound **71** was prepared from **70** as described in the general procedure for coupling, and purified by flash column chromatography (silica, CH_2Cl_2/MeOH 98:2) (60%). ^{1}H NMR (CD_3OD 400 MHz) δ 2.76 (br s, 4H), 2.93 (t, J = 7.4 Hz, 2H), 3.82 (t, J = 7.4 Hz, 2H), 3.92 (br s, 4H), 6.55 (s, 2H), 7.19 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H). ^{13}C NMR (CD_3OD 100 MHz) δ 35.7, 36.6, 36.6, 48.0, 51.9, 51.9, 118.5, 118.5, 129.4, 129.4, 131.6, 131.6, 132.4, 132.4, 133.0, 139.8, 144.2, 144.2, 181.5. HR-MS (ESI) calculated for $C_{19}H_{20}ClN_2O_2S$ (M−H) 475.0934, found 475.0931.

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