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SAR studies of capsazepinoid bronchodilators 3: The thiourea part (coupling region) and the 2-(4-chlorophenyl)ethyl moiety (C-region)

Magnus Berglund,[a] María F. Dalence-Guzmán,[a,b] Staffan Skogvall[c] and Olov Sterner[a,*]

[a]*Division of Organic Chemistry, Lund University, PO Box 124, SE-221 00 Lund, Sweden*
[b]*Centro de Tecnologia Agroindustrial, Facultad de Ciencias y Tecnologia, Universidad Mayor de San Simón, Cochabamba, Bolivia*
[c]*Respiratorius AB, Magistratsvägen 10, 226 43 Lund, Sweden*

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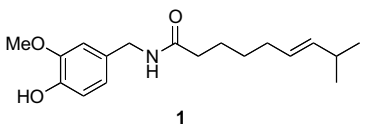
Abstract—Certain derivatives and analogues of capsazepine are potent in vitro inhibitors of bronchoconstriction in human small airways. During an investigation of the dependency of the potency on the structural features of the capsazepinoids in the thiourea moiety (coupling region) and the 2-(4-chlorophenyl)ethyl moiety (C-region), it was revealed that capsazepinoids with a thiourea or an amide link between the B-ring and the C-region in general have a good bronchorelaxing activity, while urea is a less attractive choice. Further, it was shown that 1,2,3,4-tetrahydroisoquinolines with a 2-(phenyl)ethyl derivative as the C-region are considerably more potent than those with an octyl group, while 2,3,4,5-tetrahydro-1*H*-2-benzazepines were found to be more insensitive to the nature of the C-region.

1. Introduction

Exposure to capsaicin, the major pungent agent isolated from chili pepper, is known to cause pain and cough, but also bronchoconstriction in experimental animals.[1] The receptor of capsaicin, TRPV1, was suggested by Szolcsanyi and Jansco-Gaber in 1975 and cloned for the first time in 1997.[2,3] The bronchoconstricting potency of capsaicin (**1**) and olvanil (**165**) (Fig. 1), a capsaicin analogue with reduced pungency and analgesic properties,[4] has been compared, and it was found that olvanil (**165**) was markedly less bronchoconstricting than capsaicin (**1**) in guinea pigs.[5] Previous studies have shown that the constricting effect of capsaicin (**1**) in guinea pig trachea is inhibited by the TRPV1-antagonist capsazepine (**2**),[6] but that capsazepine does not inhibit bronchoconstriction evoked in guinea pig by histamine.[7,8] Recently, we have described that capsazepine (**2**) is a general in vitro inhibitor of agonist evoked (leukotriene D_4, histamine, acetylcholine, prostaglandin D_2) contraction of human small airway preparations.[9] This inhibitory activity is a class effect and analogues of capsazepine, capsazepinoids, also are more or less potent bronchodilators. One of the most potent class members, the 1,2,3,4-tetrahydroisoquinoline **4**, which is approximately 10 times as potent compared to capsazepine (**2**), was identified after a systematic variation of the structure of capsazepine (**2**) (Fig. 2).[10]

The SAR study is described in a series of three parallel papers dealing with the different regions of the molecule,



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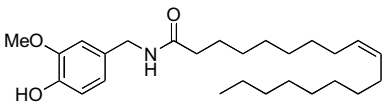

165

Figure 1.

Keywords: Capsazepine; Coupling region; Thiourea; C-region; 2-(Phenyl)ethyl; SAR; Bronchodilator; Small human airways; Asthma; COPD.
* Corresponding author. Tel.: +46 462228213; fax: +46 462228209; e-mail: Olov.Sterner@organic.lu.se

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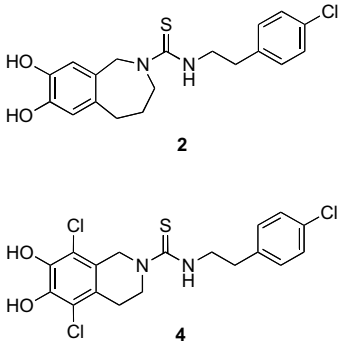


Figure 2.

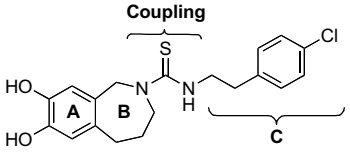
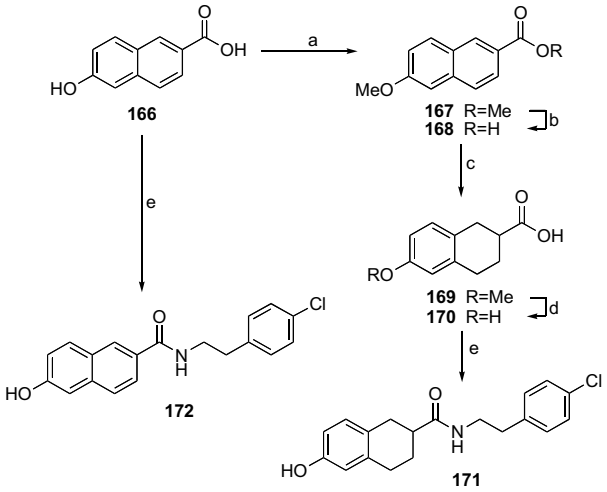


Figure 3.



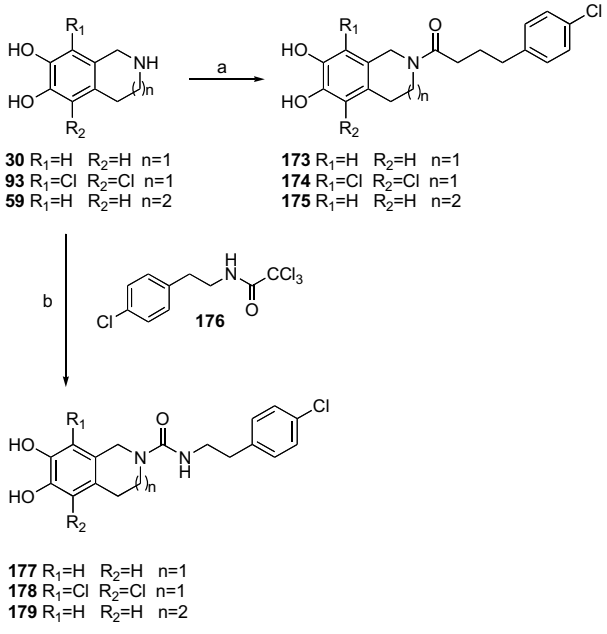
Scheme 1. Reagents and conditions: (a) MeI, K_2CO_3, DMF, rt, overnight, 83%; (b) LiOH·H_2O, THF, reflux, overnight, 79%; (c) 1—Li, NH_3, THF, −33 °C, 1.5 h; 2—NH_4Cl 46%; (d) HBr (48% in H_2O), reflux, 5 h quant.; (e) 2-(4-chlorophenyl)ethylamine, HOBt, EDC, DMF, rt, 45 h.

as defined in Fig. 3, which were adopted from a previous study of capsaicin.[11–13] The current paper discusses how structural variations in the coupling region and the C-region affect the activity. In the preceding papers, 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[12] as well as 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[13] is discussed. For the coupling region, the focus of the study was to determine the importance of the sulfur and nitrogen atoms as well as the effect of conformational changes. Both derivatives having six-membered (tetrahydroisoquinoline) and seven-membered (tetrahydro-2-benzazepine) B-rings were included since the size of this saturated ring will influence the relative position of the coupling region and the other functionalities present in the molecules. In the part studying the effect of various C-regions, the A-ring, the B-ring and the coupling region were retained as in the relatively potent compounds **2** and **4**. 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 **165** is described in the preceding papers.[12,13]

2. Chemistry

The synthesis of the amide **171** is shown in Scheme 1. 6-Hydroxy-2-naphthoic acid (**166**) was methylated with methyl iodide to afford **167**, followed by hydrolysis of the methyl ester to **168**. Partial reduction of **168** yielded the 1,2,3,4-tetrahydronaphthalene derivative **169**,[14] which was demethylated with hydrobromic acid to give 6-hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (**170**), and coupled with 2-(4-chlorophenyl)ethylamine to afford **171**. Compound **172** was prepared by the direct coupling of **166** with 2-(4-chlorophenyl)ethylamine.

The preparation of amides **173**, **174** and **175**, described in Scheme 2, was accomplished by the coupling of 4-(4-chlorophenyl)butanoic acid[15] with the amines **30**, **93** and **59** (prepared as reported)[12,13] using EDC as coupling reagent and HOBt as additive for the reaction. The synthesis of the urea derivatives **177**, **178** and **179** was carried out by the coupling of the amines **30, 59**



Scheme 2. Reagents and conditions: (a) 4-(4-chlorophenyl)butanoic acid, HOBt, EDC, *N*-methyl-morpholine, DMF, rt, 18 h; (b) DBU, DMSO, 80 °C, 48 h.

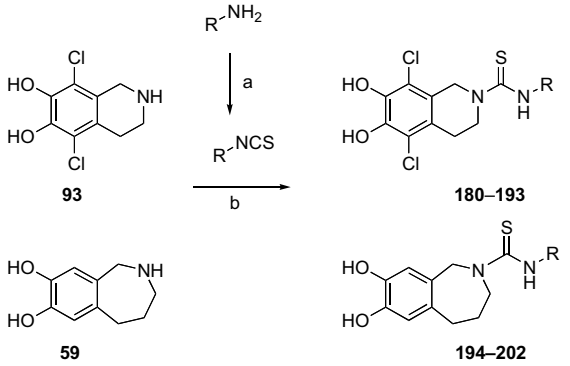
and **93** with 2-(4-chlorophenyl)ethyl isocyanate, generated in situ by β-elimination of chloroform from **176** in the presence of DBU.[16]

The derivatives **180–202** were prepared as indicated in Scheme 3, by the coupling of either of the two amines **59** and **93** with different isothiocyanates, commercially available or synthesized from different arylalkylamines by the reaction with 1,1′-thiocarbonyldiimidazole.[17]

3. Results and discussion

The bronchorelaxing effect of the synthesized derivatives was evaluated in small (0.5–1.5 mm in diameter) human airway preparations, as previously described.[9,18] In short, the constriction evoked by 10 nM leukotriene D_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 (Tables 1 and 3) are shown as the percentage of the remaining contraction compared to the full contraction (100% not active and 0% maximal inhibition). In addition, the effect of the most potent compounds (**4**, **174** and **178**) was also assayed at 1 μM (Table 2), in four consecutive cycles. The constriction evoked by 10 nM leukotriene D_4 on untreated preparations and on the same preparations exposed to leukotriene D_4-free physiological solution for one hour followed by 10 nM leukotriene D_4 for 30 min, in the continuous presence of 1 μM of the test compounds, was compared. The results are shown in Table 2 as the percentage of the remaining contraction after each cycle, that takes 1.5 h, compared to the control contraction.

The target of capsazepinoids and its localization are unknown, but established bronchodilatory principles as well as TRPV1-antagonism have been excluded as mechanism of action.[9,10] As the target and its localization are unknown, it is not possible to assess how physicochemical properties, for example, lipophilicity, will affect the observed potency of the substances tested. Consequently the SARs discussed here are only based on the activity of the compounds in the assay. Variations in concentration or time of exposure might result in altered relative potencies. Nevertheless, in order to get an impression of the solubility properties, the relative lipophilicity of some of the more hydrophilic capsazepinoids was estimated (calculated $\log D_{7.4}$ (ACD/Log D v8.02 using ACD-I-lab service) values and retention factors determined by HPLC)[19] and compared with that of capsazepine (**2**) and **4** (see Table 4).



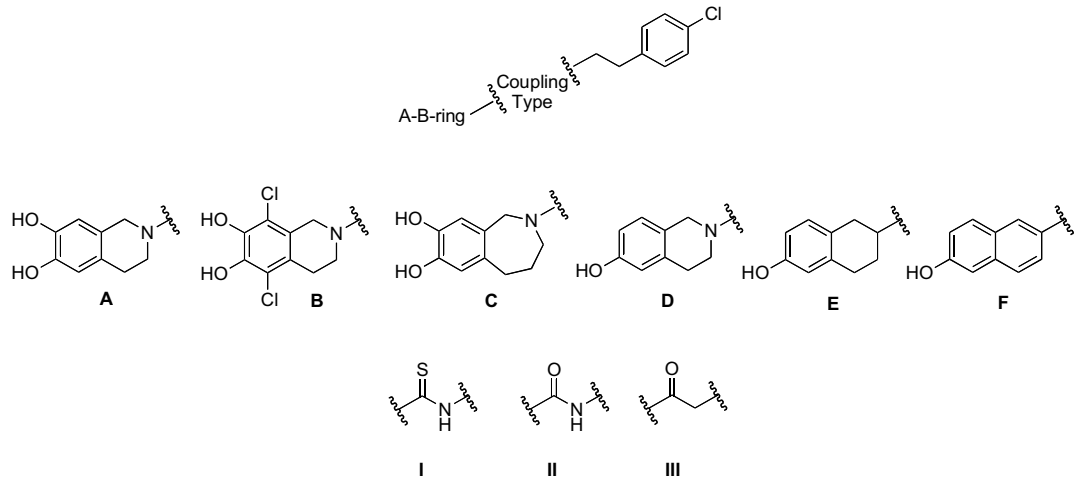
Scheme 3. Reagents and conditions: (a) 1,1′-thiocarbonyldiimidazole, triethylamine, DMF, 50 °C, 2 h; (b) triethylamine, DMF, rt.

Among the nonchlorinated 1,2,3,4-tetrahydroiosquinoline-6,7-diols, the thiourea **34** is slightly more active compared to the amide **173**, while the urea **177** is only weakly active. However, in the case of the 5,8-dichloro-1,2,3,4-tetrahydroiosquinoline-6,7-diols both the urea **178** and the amide **174** have the same potency as the thiourea **4**. Although unexpected, this could depend on limitations in the bioassay to differentiate very potent compounds from each other. Those compounds were therefore reassayed at lower concentrations (1 μM) and the results are shown in Table 2 (vide infra).

Amides **175** and **173** show somewhat disparate activities compared to thioureas **2** and **34**, although both are significantly more active than the corresponding urea derivatives. The only difference between urea and amide derivatives, **179** and **177** compared with **175** and **173**, respectively, is the nitrogen linking the coupling and the C-region. The conformational restrictions induced by this second nitrogen in the urea derivatives (the nitrogen lone pair lobe should preferably be perpendicular to the plane of the amide moiety) will not be present in the more flexible propyl chain of the amide derivatives, thereby possibly allowing **175** and **173** to adopt more suitable conformations for binding. The difference in activity between **175** and **173** compared to each other was expected, as a similar difference was observed for the corresponding thiourea derivatives.[12]

The evaluation of compounds **48**, **171** and **172** addresses the question of the anchorage of the coupling part in the B-ring. As demonstrated in the study of the B-ring,[12] this should preferably be six-membered. As is discussed above, a thiourea, urea or amide moiety may be used for the coupling of the B-ring with the C-region, however, the necessity of a nitrogen atom in the B-ring needs to be assesed. The 6-hydroxy-1,2,3,4-tetrahydroiosquinoline **48** is as potent as capsazepine (**2**), as the 6-hydroxyl group appears to be critical for the interaction of tetrahydroiosquinolines and tetrahydro-2-benzazepines with the target.[12] However, exchanging the B-ring nitrogen for a carbon (to compound **171**) diminishes the activity, an effect that cannot be explained by the change of the thiocarbonyl in **48** for a carbonyl group in **171**. The drop in activity seen for **171** could, however, be due to other factors: (a) The compound was tested as a racemic mixture. (b) The rotational barrier of the bond formed between the nitrogen in the B-ring and the thiocarbonyl carbon in **48** is bigger than the corresponding bond in **170**. (c) The nitrogen atom might be involved in a specific interaction with the target, exchanging it for a carbon will interupt such an interaction. Full planarity of the B-ring does not enhance activity as the naphthamide **172** is even less active compared to **48** and **170**. Although a constrained B-ring is important for activity,[12] the result obtained with **172** suggests that the angle induced by the limited flexibility of saturated B-ring between

Table 1.



Compound	A-B-ring	Coupling type	Remaining contraction[a]
34[b]	A	I	36 ± 6.5 (5)
177	A	II	69 ± 3.7 (4)
173	A	III	47 ± 6.1 (4)
4[c]	B	I	14 ± 2.7 (16)
178	B	II	16 ± 1.7 (5)
174	B	III	16 ± 4.3 (4)
2[b]	C	I	55 ± 3.0 (24)
179	C	II	73 ± 6.6 (3)
175	C	III	54 ± 8.9 (6)
48[b]	D	I	52 ± 6.8 (4)
171	E	II	78 ± 1.9 (4)
172	F	II	90 ± 2.6 (4)

[a] Arithmetic means ± standard error of the mean of the percentage of remaining contraction in small human airways contracted with LTD_4 in the presence of 10 μM test substance compared to a full contraction evoked by LTD_4 in the absence of test compound. Number of times tested in parentheses.
[b] Compound reported in Ref. 12.
[c] Compound reported in Ref. 13.

Table 2. Remaining contraction after treatment with 1 μM of **4**, **178** and **174**

Compound	Remaining contraction ± SEM[a]				*N*[b]
	1.5 h	3 h	4.5 h	6 h	
4	79 ± 6.8	57 ± 11.0	44 ± 10.2	32 ± 7.2	5
178	91 ± 1.8	81 ± 3.9	78 ± 4.2	71 ± 3.9	4
174	80 ± 4.4	65 ± 3.6	55 ± 3.7	45 ± 5.7	5

See text for details.
[a] Standard error of the mean.
[b] Number of experiments performed.

the aromatic A-ring and the plane of the coupling region is critical for activity. A similar hypothesis was suggested by Walpole et al. in their study of constrained capsaicin derivatives.[20]

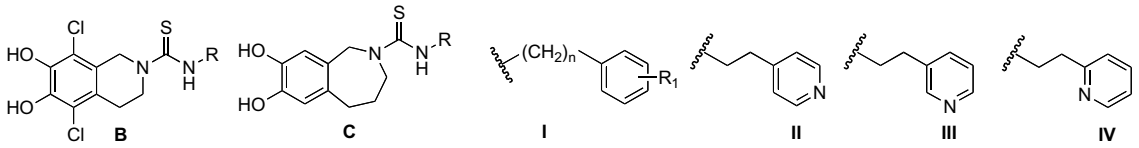
In the standard assay used throughout this investigation, the 5,8-dichloro-1,2,3,4-tetrahydroiosquinoline-6,7-diols **4**, **178** and **174**, differing only in the coupling type, are equipotent. As all three are very potent and relax the preparations almost completely, this result might be due to a limitation in the bioassay. All three compounds were therefore reassayed at a lower concentration (1 μM) for four test cycles, and the results are shown in Table 2. At this concentration the activity correlates with the results discussed above with **34**, **173** and **177**, especially after 6 h, showing that the thiourea in fact is slightly more potent than the amide, while the urea is significantly less bronchorelaxing.

If the substitution of the aromatic A-ring is as that of **4**, **174** and **178**, the binding of the molecule to the receptor seems to be optimal and activity increases dramatically as seen in studies concerning the A- and B-rings.[12,13] In this case, changes in the coupling region do not have that dramatical affect on the activity. On the other hand, when the substitution pattern in the A-ring is as in **2** or **34**, differences in the coupling region enhance or decrease the activity significantly. Sulfur and oxygen atoms in the coupling region are likely to act as hydrogen bond acceptors or in dipole interactions. In carbonyl groups the oxygen lone pair lobes are in the $R_2C{=}O$ plane and form angles of about 120° with the C=O bond. Hydrogen bonding to a carbonyl oxygen is at its strongest at this angle, although

it also takes place at any other angle between 115° and 180°. On the other hand, the acceptor directionality of the thiocarbonyl group is much more pronounced, with the lone pair directions forming an angle of only 105° with $R_2C{=}S$.[21] Angles between 130° and 180° will not be suitable for hydrogen bonding to a thiocarbonyl. For **2** and **34**, the sulfur atom seems to be placed in the right position for binding, but once the sulfur atom is changed to oxygen both the directionality and the size of the acceptor will change, offering a possible explanation for the decrease in activity of the urea derivatives. However, the amides (**173**, **174** and **175**) are almost as active as the thioureas (**2**, **4** and **34**), and also significantly more active than the corresponding urea derivatives. The only difference between urea and amide derivatives (**177**, **178** and **179**) is the nitrogen linking the coupling and the C-region. As discussed above, the conformational restrictions induced by this second nitrogen in the urea derivatives (the nitrogen lone pair lobe should preferably be perpendicular to the plane of the amide moiety) will not be present in the amide derivatives.

Interestingly, the bronchodilating activity of the capsazepine derivatives depends differently on variations in the C-region if they are based on A-B–ring type **B** or **C** (see Tables 1 and 3). For those based on **C**, that is, capsazepine (**2**) analogues, **2** itself with a 2-(4-chlorophenyl)ethyl moeity is actually the most potent of all compounds of this type tested. Only the 2-(2-chlorophenyl)ethyl variant (**197**) has a similar potency. The octyl derivative **202** is as active as several of the 2-phenylethyl derivatives. This indicates strongly that the C-region is less important for the binding of capsazepine (**2**) and its closely related analogues, presumably because the C-region is not positioned in a way to optimize the interactions with the binding site. As discussed,[12] the B-ring will affect how the A-ring, coupling and C-region are orientated relative to each other and the B-ring in **4** was shown to be better in this sense.[12] In contrast, the 1,2,3,4-tetrahydroisoquinoline derivatives, based on structure **B** in Table 3, show a larger dependency on the C-region. Here it is obvious that an alkyl substituent (compound **190**) is poor compared to the phenylethyl analogues, even if the size is comparable. This indicates that some kind of aromatic π-interaction between the target and the C-region is facilitated for this type of structure. The length of the link between the thiourea and the aromatic C-ring (*n* in Table 3) does not appear to be critical, as the phenylmethylene **180**, the 2-phenyl-

Table 3.



Compound	A-B-ring	R	*n*	R_1	Remaining contraction[a]
180	B	I	1	H	10 ± 2.8 (5)
181	B	I	1	4-Cl	19 ± 2.3 (4)
194	C	I	1	4-Cl	70 ± 8.2 (4)
182	B	I	2	H	8 ± 4.3 (4)
195	C	I	2	H	71 ± 9.5 (4)
183	B	I	2	4-*t*-Bu	69 ± 7.0 (4)
196	C	I	2	4-*t*-Bu	80 ± 2.5 (4)
184	B	I	2	2-Cl	10 ± 3.3 (5)
197	C	I	2	2-Cl	56 ± 8.3 (4)
185	B	I	2	3-Cl	27 ± 6.4 (4)
198	C	I	2	3-Cl	76 ± 3.5 (4)
4[b]	B	I	2	4-Cl	14 ± 2.7 (16)
2[c]	C	I	2	4-Cl	55 ± 3.0 (24)
186	B	I	2	4-F	6 ± 1.4 (4)
199	C	I	2	4-F	68 ± 5.4 (4)
187	B	I	2	4-Br	17 ± 4.6 (4)
200	C	I	2	4-Br	67 ± 3.7 (4)
188	B	I	2	4-OH	22 ± 5.3 (4)
189	B	I	3	H	11 ± 3.6 (4)
201	C	I	3	H	84 ± 2.9 (4)
190	B	*n*-C_8H_{17}	—	—	69 ± 1.6 (4)
202	C	*n*-C_8H_{17}	—	—	69 ± 8.0 (5)
191	B	II	—	—	33 ± 5.1 (4)
192	B	III	—	—	30 ± 4.5 (4)
193	B	IV	—	—	26 ± 6.2 (7)

[a] Arithmetic mean ± the standard error of the mean of the percentage of remaining contraction in small human airways contracted with LTD_4 in the presence of 10 μM test substance compared to a full contraction evoked by LTD_4 in the absence of test compound. Number of times tested in parentheses.

[b] Compound reported in Ref. 13.

[c] Compound reported in Ref. 12.

ethylene **182** and the 3-phenylpropylene **189** are approximately equally active, and also comparable with the 2-(4-chlorophenyl)ethylene derivative **4**. In addition, the shorter (4-chlorophenyl)methylene derivative **181** is approximately as active as **4**. The different potency of the three 2-(chlorophenyl)ethylene derivatives **184**, **185** and **4** suggests that the volume of the part of the binding site where the C-region interacts is limited for a substituent in the *meta* position, and the same trend is also seen for the corresponding benzazepines **197**, **198** and **2**. Steric interactions that hamper binding are definitely indicated in the case of the 2-(4-*tert*-butylphenyl)ethyl derivatives **183** and **196**, suggesting that the binding pocket has a limited size also in the *para* direction. In addition it should be noted that the 4-fluoro derivative **186** actually is better than the 4-chloro, while the 4-bromo (**187**) is comparable. This may also be due to steric interactions, although electronic effects or a combination of both may not be excluded.

The dependency of the bronchodilating effect of the capsazepine derivatives (Table 3) on the C-region differs compared to the effect of variations of the phenylethyl moiety for the TRPV1 antagonist activity. Recent studies in $^{45}Ca^{2+}$-influx models to assay TRPV1-antagonism have reported that a *tert*-butyl group is the optimum *para*-substituent in the region corresponding to the C-region.[22] This is in accordance with the low bronchodilating activity of established TRPV1-antagonists, for example, iodo-resiniferatoxin, ruthenium red, JYL1421 and SB366791, previously reported by us,[10] and supports the suggestion that the bronchodilating effect observed in our assay is not mediated by TRPV1.

Since most of the compounds discussed here are rather lipophilic and would probably suffer from extensive protein binding and poor solubility in plasma in vitro,[23] the more hydrophilic pyridine derivatives **191**, **192** and **193**, and the 4-hydroxyl derivative **188**, were therefore prepared. They all have a similar potency, slightly lower that of **4**, and as can be seen in Table 4, the lipophilicity of **191**, **192**, **193** and **188** is considerably lower compared to compounds **2** and **4**. It is at this stage not possible to draw any conclusions about whether the small difference in activity between **4** and **191/192/193/188** is caused by poorer binding or by other factors. Still, it is interesting to note that the properties of these compounds can be modulated in the C-region while retaining the bronchodilating activity. Similarly the amide **174**, although being almost as potent as the thiourea **4**, is more hydrophilic, as judged by the experimentally determined retention factor.

Table 4. The lipophilicity of selected capsazepinoids

Compound	Log$D_{7.4}$[a]	Retention factor[b]
2	3.5	8.9
4	4.0	8.6
188	2.7	1.8
191	1.9	0.9
192	2.0	0.9
193	1.9	1.1
174	4.6	5.2

See text for details.

[a] The result of ACD/Log D v8.02 was obtained using the ACD/I-lab service and is given at pH 7.4.

[b] HPLC, symmetry shield RP8 2.1 × 150 mm, 0.3 ml/min 40% acetonitrile in 20 mM NaH_2PO_4, pH 7.4.

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 vitro, they constitute a promising novel pharmaceutical principle to prevent and revoke airway obstruction caused by asthma or COPD. The capsazepinoids prepared, assayed and discussed in part of the study focus on the coupling region and the C-region (according to Fig. 3), and it is obvious that their activities depend on their structures.

The following conclusions could be drawn concerning the coupling region:

1. The amide derivatives **173**, **174** and **175** show similar bronchorelaxing properties as the corresponding thioureas, suggesting that the nitrogen atom linking the coupling unit and the C-region is not of great importance for the activity. The inverse amides with no nitrogen in the B-ring (**171** and **172**) are considerably less active, especially if the B-ring is aromatic.
2. The urea derivatives **177**, **176** and **178** are less potent compared to the corresponding thioureas.

Additional conclusions could be drawn concerning the C-region:

1. The importance of the C-region for the binding appears to be different for capsazepine and 1,2,3,4-tetrahydroisoquinoline derivatives, suggesting that the two compound types present the C-region to the binding site differently.
2. An aromatic π-interaction between the target and the C-region is indicated, at least for the 1,2,3,4-tetrahydroisoquinoline derivatives.
3. The volume in the binding site where the C-region of capsazepinoids binds is limited and bigger substituents in the C-region lower the activity. This also restricts how long the linker between the thiourea and the aromatic C-ring can be.
4. Several different C-regions, for example, 2-(2-chlorophenyl)ethyl, 2-(4-chlorophenyl)ethyl, 2-(4-fluorophenyl)ethyl, and 2-(phenyl)ethyl are all approximately equally potent, suggesting that the interaction between the binding site and the C-region in general is weak.
5. The finding that the 2-(4-*tert*-butylphenyl)ethyl derivatives are impotent support the suggestion that the bronchodilating effect of the capsazepinoids is not mediated by TRPV1.

Work is now in progress to investigate the in vitro activity of the capsazepinoids as bronchodilators. In this respect, the more hydrophilic derivatives described here, for example, **174** and **193**, might prove useful.

5. Experimental

5.1. Materials

Materials were obtained from commercial suppliers and were used without further purification unless otherwise noted. DMF were 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. Methyl 6-methoxy-2-naphthoate (167). To a solution of 6-hydroxy-2-naphthoic acid, **166** (1.0 equiv) and K_2CO_3 (2.5 equiv) in anhydrous DMF, MeI (2.2 equiv) was added. The mixture was stirred overnight, concentrated and dissolved in EtOAc. The organic phase was washed with Na_2CO_3 (saturated solution), dried ($MgSO_4$) and concentrated. Recrystallization (heptane/EtOAc 1:1) of the crude gave **167** (83%). ^1H NMR ($CDCl_3$ 300 MHz) δ 3.95 (s, 3H), 3.97 (s, 3H), 7.16 (d, J = 2.5 Hz, 1H), 7.20 (dd, J = 8.9 Hz, J = 2.5 Hz, 1H), 7.76 (d, J = 8.7 Hz, 1H), 7.84 (d, J = 8.9 Hz, 1H), 8.03 (dd, J = 8.7 Hz, J = 1.8 Hz, 1H), 8.54 (d, J = 1.8 Hz, 1H).

5.2.2. 6-Methoxy-2-naphthoic acid (168). Compound **167** (1.0 equiv) and $LiOH{\cdot}H_2O$ (10.0 equiv) were suspended in THF. The slurry was heated to reflux overnight. The reaction mixture was concentrated and HCl (1% in H_2O) was added. The water phase was extracted with EtOAc. The combined organic phases were dried ($MgSO_4$) and concentrated. Recrystallization from EtOAc afforded **168** (79%). ^1H NMR ($CDCl_3$ 300 MHz) δ 3.96 (s, 3H), 7.17 (d, J = 2.5 Hz, 1H), 7.22 (dd, J = 8.9 Hz, J = 2.5 Hz, 1H), 7.80 (d, J = 8.6 Hz, 1H), 7.88 (d, J = 8.9 Hz, 1H), 8.09 (dd, J = 8.6 Hz, J = 1.6 Hz, 1H), 8.54 (bs, 1H).

5.2.3. 6-Methoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (169). Compound 169 was prepared from 168. Spectroscopic data as described previously.[14]

5.2.4. 6-Hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (170). Compound **169** 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 affording **170** (quantitative). ^1H NMR ($CDCl_3$ 300 MHz) δ 1.86 (m, 1H), 2.22 (m, 1H), 2.76 (m, 1H), 2.84 (m, 2H), 2.96 (m, 2H), 6.57 (d, J = 2.8 Hz, 1H), 6.63 (dd, J = 8.2 Hz, J = 2.8 Hz, 1H), 6.54 (d, J = 8.2 Hz, 1H).

5.2.5. *N*-[2-(4-Chlorophenyl)ethyl]-6-hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxamide (171). EDC (1.1 equiv) and HOBt (1.1 equiv) were dissolved in anhydrous DMF. Compound **170** (1.0 equiv) and 2-(4-chlorophenyl)ethylamine (1.0 equiv) were added to this solution. The mixture was stirred for 45 h. Purification was done by flash column chromatography (silica, Pet. ether/EtOAc/AcOH 33:77:1) affording **7** (65%). ^1H NMR (CD_3OD, 400 MHz) δ 1.75 (m, 1H), 1.92 (m, 1H), 2.47 (m, 1H), 2.75 (m, 4H), 2.81 (t, J = 7.2 Hz, 2H), 3.44 (t, J = 7.2 Hz, 2H), 6.50 (d, J = 2.3 Hz, 1H), 6.54 (dd, J = 8.2 Hz, J = 2.3 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 7.21 (d,J = 8.4 Hz, 2H), 7.29 (d,J = 8.4 Hz, 2H). ^{13}C NMR (CD_3OD, 100 MHz) δ 27.8, 29.4, 32.7, 35.8, 41.6, 43.3, 114.3, 115.8, 127.1, 129.5, 129.5, 130.8, 131.5, 131.5, 133.2, 137.8, 139.4, 156.3, 178.6. ESI-MS calculated for $C_{19}H_{21}NO_2Cl$ (M+H) 330.1261, found 330.1247.

5.2.6. *N*-[2-(4-Chlorophenyl)ethyl]-6-hydroxy-2-naphthamide (172). Compound **171** was prepared from **166**, using the method described for **170**. Purification was done by flash column chromatography (silica, Pet. ether/EtOAc/AcOH 33:77:1) (38%). ^1H NMR (DMSO-d_6, 400 MHz) δ 2.87 (t, J = 7.1 Hz, 2H), 3.51 (dd, J = 5.7 Hz, J = 7.1 Hz, 2H), 7.14 (m, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 8.6 Hz, 1H), 7.79 (dd, J = 1.7 Hz, J = 8.6 Hz, 1H), 7.85 (d, J = 8.6 Hz, 1H), 8.27 (bs, 1H), 8.58 (t, J = 5.7 Hz, 1H).^{13}C NMR (DMSO-d_6, 100 MHz) δ 34.5, 40.7, 108.7, 119.5, 124.4, 126.0, 126.7, 127.4, 128.3, 128.3, 128.7, 130.6, 130.7, 130.7, 130.8, 136.1, 138.7, 156.9, 166.5. ESI-MS calculated for $C_{19}H_{17}NO_2Cl$ (M+H) 326.0948, found 326.0943.

5.2.7. 2-[4-(4-Chlorophenyl)butanoyl]-1,2,3,4-tetrahydroisoquinoline-6,7-diol (173). 4-(4-chlorophenyl)butanoic acid (1.0 equiv) and 1,2,3,4-tetrahydroisoquinoline-6,7-diol hydrobromide, **30** (1.0 equiv) were dissolved in anhydrous DMF, then 1-hydroxy-benzotriazole, HOBt (1.0 equiv), *N*′-(3-dimethyl-aminopropyl)-N-ethylcarbodiimide hydrochloride, EDC (1.05 equiv) and N-methyl-morpholine (3.0 equiv) were added. The reaction mixture was stirred at room temperature for 18 h and then it was concentrated. Purification was done by flash column chromatography (silica, gradient elution: 60–100% EtOAc in Pet. ether) affording **173** (rotameric mixture), (48%). ^1H NMR (CD_3OD 400 MHz) δ 1.92 (m, 2H), 2.45 (t, J = 7.1 Hz, 2H), 2.67 (m, 4H), 2.62 (ma) (t, J = 6.0 Hz, 2H), 3.71 (mi) (t, J = 6.0 Hz, 2H), 4.45 (mi) (s, 2H), 4.50 (ma) (s, 2H), 6.55 (m, 2H), 7.20 (m, 4H). ^{13}C NMR (CD_3OD 100 MHz) δ 28.0, 28.7 (mi), 29.6 (ma), 33.5, 35.5, 41.7 (mi), 45.0 (ma), 45.0(ma), 48.0 (mi), 113.7 (mi), 113.9

(ma), 115.9 (mi), 116.1 (ma), 124.9, 126.3, 129.4, 129.4, 129.5, 131.1, 131.1, 132.3, 141.9, 145.0, 174.0. ESI-MS calculated for $C_{19}H_{20}ClN_2O_3$ (M+H) 347.1162, found 347.1148.

5.2.8. 5,8-Dichloro-2-[4-(4-chlorophenyl)butanoyl]-1,2,3,4-tetrahydroisoquinoline-6,7-diol (174). Compound **174** was prepared as described for 173 from 5,8-dichloro-1,2,3,4-tetrahydroisoquinoline-6,7-diol hydrobromide 93. Purification was done by flash column chromatography (Pet. ether/EtOAc 1:1) affording 174 (rotameric mixture) (21%). ^{1}H NMR (CD_3OD 400 MHz) δ 1.93 (m, 2H), 2.48 (m, 2H), 2.66 (m, 2H), 2.73 (mi) (t, J = 6.0 Hz, 2H), 2.79 (ma) (t, J = 6.0 Hz, 2H), 3.69 (ma) (t, J = 6.0 Hz, 2H), 3.78 (mi) (t, J = 6.0 Hz, 2H), 4.51 (mi) (s, 2H), 4.60 (ma) (s, 2H), 7.19 (m, 4H). ^{13}C NMR (CD_3OD 100 MHz) δ 27.0 (mi), 27.9, 28.1 (ma), 33.1 (ma), 33.6 (mi), 35.4 (mi), 35.5 (ma), 40.4 (mi), 43.6 (ma), 43.9 (ma), 46.9 (mi), 118.7, 124.01, 125.17, 129.4, 129.4, 131.0, 131.1, 131.1, 132.8, 141.6, 141.9, 142.8, 173.9. ESI-MS calculated for $C_{19}H_{19}Cl_3NO_3$ (M+H) 414.0431, found 414.0417.

5.2.9. 2-[4-(4-Chlorophenyl)butanoyl]-2,3,4,5-tetrahydro-1*H*-2-benzazepine-7,8-diol (175). Compound **175** was prepared as described for **173** from 2,3,4,5-tetrahydro-1*H*-3-benzazepine-7,8-diol hydrobromide **59**. Purification was done by flash column chromatography (silica, CH_2Cl_2/MeOH 98:2) (19%). ^{1}H NMR ($CDCl_3$400 MHz) δ 1.74 (m, 2H), 1.91 (m, 2H), 2.31 (t, J = 7.4 Hz, 2H), 2.59 (t, J = 7.4 Hz, 2H), 2.90 (m, 2H), 3.69 (bs, 2H), 4.48 (s, 2H), 6.71 (s, 1H), 7.03 (d, J = 8.3 Hz, 2H), 7.17 (s, 1H), 7.20 (d, J = 8.3 Hz, 2H). ^{13}C NMR ($CDCl_3$ 100 MHz) δ 26.3, 29.6, 32.2, 34.4, 34.5, 51.0, 52.5, 116.0, 117.0, 128.4, 128.4, 129.1, 129.7, 129.7, 132.5, 132.8, 139.8, 142.0, 143.6, 172.5. ESI-MS calculated for $C_{20}H_{23}ClN_2O_3$ (M+H) 360.1366, found 360.1375.

5.2.10. *N*-[2-(4-Chlorophenyl)ethyl]-6,7-dihydroxy-3,4-dihydroisoquinoline-2(1*H*)-carboxamide (177). 1,2,3,4-tetrahydroisoquinoline-6,7-diol hydrobromide, **30** (1.0 equiv) was dissolved in anhydrous DMSO, DBU (1.0 equiv) was added and the solution was stirred for 15 min. Then **176** (1.0 equiv) and DBU (1.0 equiv) were added. The intermediate 2-(4-chlorophenyl)ethyl isocyanate is formed in situ. The reaction mixture was stirred at 80 °C for 48 h. CH_2Cl_2 was added to the solution and the organic phase was washed with HCl (3% in H_2O) and $NaHCO_3$ (saturated solution). The organic phase was dried ($MgSO_4$) and concentrated. Purification was done by flash column chromatography (silica, CH_2Cl_2/MeOH 98:2) yielding **177** (23%). ^{1}H NMR (CD_3OD 400 MHz) δ 2.64 (t, J = 5.9 Hz, 2H), 2.77 (t, J = 7.3 Hz, 2H), 3.37 (t, J = 7.3 Hz, 2H), 3.51 (t, J = 5.9 Hz, 2H), 4.33 (s, 2H), 6.53 (s, 1H), 6.56 (s, 1H), 7.15 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H). ^{13}C NMR (CD_3OD 100 MHz) δ 29.0, 36.8, 42.7, 43.3, 46.2, 113.8, 116.0, 125.6, 127.1, 129.4, 129.4, 131.5, 131.5, 132.9, 139.7, 145.0, 145.2, 160.0. ESI-MS calculated for $C_{18}H_{20}N_2O_3Cl$ (M+H) 347.1162, found 347.1148.

5.2.11. 5,8-Dichloro-*N*-[2-(4-chlorophenyl)ethyl]-6,7-dihydroxy-3,4-dihydroisoquinoline-2(1*H*)-carboxamide (178). Compound **178** was prepared as described for **177** from 5,8-dichloro-1,2,3,4-tetrahydroisoquinoline-6,7-diol hydrobromide **93**. Purification was done by flash column chromatography (silica, gradient elution: 0.5-2% MeOH in CH_2Cl_2) (38%). ^{1}H NMR (CD_3OD 400 MHz) δ 2.68 (t, J = 5.8 Hz, 2H), 2.77 (t, J = 7.3 Hz, 2H), 3.38 (t, J = 7.3 Hz, 2H), 3.55 (t, J = 5.8 Hz, 2H), 4.43 (s, 2H), 7.13 (d, J = 8.3 Hz, 2H), 7.20 (d, J = 8.3 Hz, 2H). ^{13}C NMR (CD_3OD 100 MHz) δ 27.1, 36.7, 42.0, 43.2, 45.3, 118.5, 120.5, 124.6, 125.7, 129.4, 129.4, 131.5, 131.5, 133.0, 139.7, 142.5, 142.8, 159.8. ESI-MS calculated for $C_{18}H_{18}N_2O_3Cl_3$ (M+H) 415.0383, found 415.0395.

5.2.12. *N*-[2-(4-Chlorophenyl)ethyl]-7,8-dihydroxy-1,3,4,5-tetrahydro-2*H*-2-benzazepine-2-carboxamide (178). Compound **179** was prepared as described for **177** from 2,3,4,5-tetrahydro-1*H*-3-benzazepine-7,8-diol hydrobromide **59**. Purification was done by flash column chromatography (silica, CH_2Cl_2/MeOH 98:2) (29%). ^{1}H NMR (CD_3OD 400 MHz) δ 1.46 (m, 2H), 2.50 (t, J = 7.3 Hz, 2H), 2.60 (m, 2H), 3.12 (t, J = 7.3 Hz, 2H), 3.40 (m, 2H), 4.11 (s, 2H), 6.43 (s, 1H), 6.54 (s, 1H), 6.83 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 8.4 Hz, 2H) ^{13}C NMR (CD_3OD, 100 MHz) δ 24.4, 34.3, 35.6, 41.9, 49.9, 51.2, 116.8, 117.1, 128.2, 128.2, 128.4, 130.3, 130.3, 131.7, 133.3, 138.5, 142.5, 143.8, 158.3 ESI-MS calculated for $C_{19}H_{21}ClN_2O_3$ (M+H) 360.1241, found 360.1241.

The isothiocyanates were purchased from commercial suppliers (1-isothiocyanatooctane and 1-chloro-4-(isothiocyanatomethyl)-benzene) or synthesized from commercially available amines.

Isothiocyanate synthesis, general method: 1,1′-thiocarbonyldiimidazole (1.2 equiv) was dissolved in DMF at 50 °C. To this solution a solution of the amine (1 equiv) and triethylamine (1 equiv) in DMF was added dropwise. When the amine was available as a protonated salt, 3 equivalent of triethylamine was used. The mixture was stirred at room temperature for 2 h, diluted with water and extracted with EtOAc. The combined organic phases were washed with water, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (heptane:EtOAc). All isothiocyanates were obtained as pale yellow liquids.

5.2.13. Isothiocyanatomethylbenzene. ^{1}H NMR (CDCl3 300 MHz) δ 4.70 (s, 2H), 7.33 (m, 5H).

5.2.14. 1-*tert*-Butyl-4-(2-isothiocyanatoethyl)-benzene. ^{1}H NMR ($CDCl_3$ 300 MHz) δ 1.32 (s, 9H), 2.97 (t, J = 7.0 Hz, 2H), 3.72 (t, J = 7.0 Hz, 2H), 7.15 (d, J = 8.2, 2H), 7.37 (d, J = 8.2, 2H).

5.2.15. 1-Chloro-2-(2-isothiocyanatoethyl)-benzene. ^{1}H NMR ($CDCl_3$ 300 MHz) δ 2.96 (t, J = 6.8 Hz, 2H), 3.73 (t, J = 6.8 Hz, 2H), 7.14 (m, 1H), 7.22 (m, 1H), 7.27 (m, 2H).

5.2.16. 1-Chloro-3-(2-isothiocyanatoethyl)-benzene. ^{1}H NMR ($CDCl_3$ 300 MHz) δ 3.13 (t, J = 6.8 Hz, 2H), 3.78 (t, J = 6.8 Hz, 2H), 7.26 (m, 3H), 7.39 (m, 1H).

5.2.17. 1-Fluoro-4-(2-isothiocyanatoethyl)-benzene. ^{1}H NMR ($CDCl_3$ 300 MHz) δ 2.95 (t, J = 6.8 Hz, 2H), 3.70 (t, J = 6.8 Hz, 2H), 7.02 (dd, J = 8.7, J_F = 8.7 Hz, 2H), 7.18 (dd, J = 8.7, J_F=5.4 Hz, 2H).

5.2.18. 1-Bromo-4-(2-isothiocyanatoethyl)-benzene. ^{1}H NMR ($CDCl_3$ 300 MHz) δ 2.94 (t, J = 6.8 Hz, 2H), 3.72 (t, J = 6.8 Hz, 2H), 7.10 (d, J = 8.3 Hz, 2H), 7.47 (d, J = 8.3 Hz, 2H).

5.2.19. 4-(2-Isothiocyanatoethyl)-phenol. ^{1}H NMR ($CDCl_3$ 300 MHz) δ 2.91 (t, J = 6.9 Hz, 2H), 3.67 (t, J = 6.9 Hz, 2H), 5.33 (s, 1H), 6.81 (d, J = 8.5 Hz, 2H), 7.08 (d, J = 8.5 Hz, 2H).

5.2.20. (3-Isothiocyanatopropyl)-benzene. ^{1}H NMR ($CDCl_3$ 300 MHz) δ 2.02 (m, 2H), 2.76 (t, J = 7.5 Hz, 2H), 3.50 (t, J = 6.5 Hz, 2H), 7.21 (m, 3H), 7.31 (m, 2H).

5.2.21. 4-(2-Isothiocyanatoethyl)-pyridine. ^{1}H NMR ($CDCl_3$ 300 MHz) δ 2.95 (t, J = 6.7 Hz, 2H), 3.75 (t, J = 6.7 Hz, 2H), 7.13 (t, J = 5.9 Hz, 2H), 8.54 (t, J = 5.9 Hz, 2H).

5.2.22. 3-(2-Isothiocyanatoethyl)-pyridine. ^{1}H NMR ($CDCl_3$ 300 MHz) δ 3.00 (t, J = 6.7 Hz, 2H), 3.92 (t, J = 6.7 Hz, 2H), 7.30 (dd, J = 7.7, 4.8 Hz, 1H), 7.58 (dt, J = 7.7, 1.7 Hz 1H), 8.52 (d, J = 1.7 Hz, 1H), 8.55 (dd, J = 4.8, 1.7 Hz, 1H).

5.2.23. 2-(2-Isothiocyanatoethyl)-pyridine. ^{1}H NMR ($CDCl_3$ 300 MHz) δ 3.31 (t, J = 6.7 Hz, 2H), 3.78 (t, J = 6.7 Hz, 2H), 7.18 (m, 2H), 7.62 (td, J = 7.7, 1.8 Hz 1H), 8.54 (dq, J = 4.8, 0.9 Hz, 1H).

Coupling method, general method: 5,8-dichloro-1,2,3,4-tetrahydroisoquinoline-6,7-diol hydrobromide or 2,3,4,5-tetrahydro-1*H*-2-benzazepine-7,8-diol hydrobromide (1 equiv) was dissolved in DMF and triethylamine (3 equiv) was added. This mixture was stirred for 15–30 min and then the corresponding 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 to give the crude product, typically as a yellow oil. The thiourea was purified by chromatography on silica gel (heptane:EtOAc + 1% AcOH).

5.2.24. *N*-Benzyl-5,8-dichloro-6,7-dihydroxy-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (180). Yield: 24%. ^{1}H NMR (CD_3OD 400 MHz) δ 2.81 (t, J = 5.8 Hz, 2H), 4.00 (t, J = 5.8 Hz, 2H), 4.90 (s, 2H), 4.94 (s, 2H), 7.18 (m, 1H), 7.28 (m, 4H). ^{13}C NMR (CD_3OD 100 MHz) δ 27.3, 46.0, 49.6, 50.2, 118.5, 120.2, 124.3, 125.9, 127.9, 128.4, 128.4, 129.3, 129.3, 140.5, 142.6, 142.9, 183.1. HRMS (ESI) calculated for $C_{17}H_{17}Cl_2N_2O_2S$ (M+H) 383.0388, found 383.0379.

5.2.25. 5,8-Dichloro-*N*-(4-chlorobenzyl)-6,7-dihydroxy-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (181). Yield: 65%. ^{1}H NMR (CD_3OD 400 MHz) δ 2.82 (t, J = 5.8 Hz, 2H), 4.01 (t, J = 5.8 Hz, 2H), 4.88 (s, 2H), 4.91 (s, 2H), 7.25 (d, J = 8.6 Hz, 2H), 7.3 (d, J = 8.6 Hz, 2H). ^{13}C NMR (CD_3OD 100 MHz) δ 27.3, 46.1, 49.6, 49.8, 118.4, 120.2, 124.2, 125.9, 129.3, 129.3, 130.1, 130.1, 133.5, 139.5, 142.6, 142.9, 183.6. HRMS (ESI) calculated for $C_{17}H_{16}Cl_3N_2O_2S$ (M+H) 416.9998, found 417.0004.

5.2.26. 5,8-Dichloro-6,7-dihydroxy-*N*-(2-phenylethyl)-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (182). Yield: 66%. ^{1}H NMR (CD_3OD 400 MHz) δ 2.84 (t, J = 5.9 Hz, 2H), 2.93 (t, J = 7.4 Hz, 2H), 3.83 (t, J = 7.4 Hz, 2H), 3.94 (t, J = 5.9 Hz, 2H), 4.84 (s, 2H), 7.20 (m, 5H), ^{13}C NMR (CD_3OD 100 MHz) δ 27.1, 36.3, 45.3, 48.3, 49.3, 118.4, 120.2, 124.2, 125.9, 127.2, 129.4, 129.4, 129.9, 129.9, 140.7, 142.6, 142.9, 182.4. HRMS (ESI) calculated for $C_{18}Cl_2H_{19}N_2O_2S$ (M+H) 397.0544, found 397.0532.

5.2.27. *N*-[2-(4-*tert*-Butylphenyl)ethyl]-5,8-dichloro-6,7-dihydroxy-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (183). Yield: 25%. ^{1}H NMR (CD_3OD 400 MHz) δ 1.27, (s, 9H), 2.77 (t, J = 5.8 Hz, 2H), 2.90 (t, J = 7.4 Hz, 2H), 3.82 (t, J = 7.4 Hz, 2H), 3.96 (t, J = 5.8 Hz, 2H), 4.84 (s, 2H), 7.12 (d, J = 8.4, 2H), 7.27 (d, J = 8.4 Hz, 2H). ^{13}C NMR (CD_3OD 100 MHz) δ 27.1, 31.8, 31,8, 31.8, 35.2, 35.7, 45.9, 48.3, 49.3, 118.4, 120.3, 124.3, 125.9, 126.3, 126.3, 129.7, 129.7, 137.7, 142.7, 142.9, 150.1, 182.5. HRMS (ESI) calculated for $C_{22}H_{27}Cl_2N_2O_2S$ (M+H) 453.1170, found 453.1161.

5.2.28. 5,8-Dichloro-*N*-[2-(2-chlorophenyl)ethyl]-6,7-dihydroxy-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (184). Yield: 67%. ^{1}H NMR (CD_3OD 400 MHz) δ 2.76 (t, J = 5.8 Hz, 2H), 3.10 (t, J = 7.2 Hz, 2H), 3.87 (t, J = 7.2 Hz, 2H), 3.95 (t, J = 5.8 Hz, 2H), 4.83 (s, 2H), 7.13 (m, 2H), 7.23 (m, 1H), 7.31 (m, 1H). ^{13}C NMR (CD_3OD 100 MHz) δ 27.1, 33.8, 45.8, 46.3, 49.3, 118.4, 120.2, 124.2, 125.9, 128.0, 129.0, 130.4, 132.4, 135.1, 138.4, 142.5, 142.8, 182.6. HRMS (ESI) calculated for $C_{18}H_{18}Cl_3N_2O_2S$ (M+H) 431.0155, found 431.0149.

5.2.29. 5,8-Dichloro-*N*-[2-(3-chlorophenyl)ethyl]-6,7-dihydroxy-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (185). Yield: 65%. ^{1}H NMR (CD_3OD 400 MHz) δ 2.79 (t, J = 5.8 Hz, 2H), 2.95 (t, J = 7.3 Hz, 2H), 3.83 (t, J = 7.3 Hz, 2H), 3.96 (t, J = 5.8 Hz, 2H), 4.85 (s, 2H), 7.18 (m, 4H). ^{13}C NMR (CD_3OD 100 MHz) δ 27.1, 35.8, 45.8, 47.8, 49.3, 118.5, 120.3, 124.3, 125.9, 127.3, 128.4, 130.0, 130.9, 135.2, 142.7, 142.9, 143.2, 182.7. HRMS (ESI) calculated for $C_{18}H_{18}Cl_3N_2O_2S$ (M+H) 431.0155, found 431.0152.

5.2.30. *N*-[2-(4-Fluorophenyl)ethyl]-5,8-dichloro-6,7-dihydroxy-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (186). Yield: 75%. ^{1}H NMR (CD_3OD 400 MHz) δ 2.76 (t, J = 5.8 Hz, 2H), 2.91 (t, J = 7.4 Hz, 2H), 3.80 (t, J = 7.4 Hz, 2H), 3.94 (t, J = 5.8 Hz, 2H), 4.84 (s, 2H), 6.93 (m, 2H), 7.19 (m, 2H). ^{13}C NMR (CD_3OD 100

MHz) δ 27.1, 35.4, 45.8, 48.2, 49.3, 115.9 (d, J = 21 Hz), 115.9 (d, J = 21 Hz), 118.4, 120.2, 124.2, 125.8, 131.5 (d, J_F=8 Hz), 131.5 (d, J_F=8 Hz), 136.6 (d, J_F=3 Hz), 142.5, 142.8, 162.9 (d, J_F=241 Hz), 182.4. HRMS (ESI) calculated for $C_{18}H_{18}Cl_2FN_2O_2S$ (M+H) 415.0450, found 415.0446.

5.2.31. *N*-[2-(4-Bromophenyl)ethyl]-5,8-dichloro-6,7-dihydroxy-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (187). Yield: 40%. ^{1}H NMR (CD_3OD 400 MHz) δ 2.77 (t, J = 5.8 Hz, 2H), 2.90 (t, J = 7.3 Hz, 2H), 3.81 (t, J = 7.3 Hz, 2H), 3.94 (t, J = 5.8 Hz, 2H), 4.84 (s, 2H), 7.11 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H). ^{13}C NMR (CD_3OD 100 MHz) δ 27.1, 35.6, 45.8, 47.8, 49.3, 118.4, 120.3, 120.9, 124.2, 125.8, 131.9, 131.9, 132.4, 132.4, 140.0, 142.6, 142.9, 182.5. HRMS (ESI) calculated for $C_{18}H_{18}Cl_2BrN_2O_2S$ (M+H) 474.9649, found 474.9658.

5.2.32. 5,8-Dichloro-6,7-dihydroxy-*N*-[2-(4-hydroxyphenyl)-ethyl]-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (188). Yield: 20%. ^{1}H NMR (CD_3OD 400 MHz) δ 2.80 (t, J = 5.9 Hz, 2H), 2.84 (t, J = 7.3 Hz, 2H), 3.78 (t, J = 7.3 Hz, 2H), 3.96 (t, J = 5.9 Hz, 2H), 4.87 (s, 2H), 6.69 (dd, J = 6.5, 2.0 Hz, 2H), 7.03 (dd, J = 6.5, 2.0 Hz, 2H). ^{13}C NMR (CD_3OD 100 MHz) δ 27.2, 35.4, 45.8, 47.9, 49.3, 116.2, 116.2, 118.5, 120.3, 124.3, 125.9, 130.8, 130.8, 131.6, 142.7, 142.9, 156.8, 182.5. HRMS (ESI) calculated for $C_{18}H_{19}Cl_2N_2O_3S$ (M+H) 413.0493, found 431.0503.

5.2.33. 5,8-Dichloro-6,7-dihydroxy-*N*-(3-phenylpropyl)-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (189). Yield: 50%. ^{1}H NMR (CD_3OD 400 MHz) δ 1.96 (m, 2H), 2.64 (t, J = 5.8 Hz, 2H), 2.79 (t, J = 7.4 Hz, 2H), 3.67 (t, J = 7.4 Hz, 2H), 3.93 (t, J = 5.8 Hz, 2H), 4.83 (s, 2H), 7.10 (m, 1H), 7.21 (m, 4H). ^{13}C NMR (CD_3OD 100 MHz) δ 27.2, 32.0, 34.4, 45.8, 46.8, 49.3, 118.5, 120.2, 124.3, 125.9, 126.8, 129.3, 129.3, 129.4, 129.4, 142.6, 142.9, 143.2, 182.4. HRMS (ESI) calculated for $C_{19}H_{21}Cl_2N_2O_2S$ (M+H) 411.0701, found 411.0692.

5.2.34. 5,8-Dichloro-6,7-dihydroxy-*N*-octyl-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (190). Yield: 59%. ^{1}H NMR (CD_3OD 400 MHz) δ 0.88 (t, J = 7.0 Hz, 3H), 1.30 (m, 10H), 1.62 (bs, 2H), 2.81 (t, J = 5.8 Hz, 2H), 3.61 (t, J = 7.4 Hz, 2H), 3.98 (t, J = 5.8 Hz, 2H), 4.89 (s, 2H). ^{13}C NMR (CD_3OD 100 MHz) δ 14.4, 23.7, 27.2, 28.0, 30.3, 30.4, 30.5, 33.0, 45.8, 47.1, 49.4, 118.4, 120.2, 124.3, 125.9, 142.6, 142.9, 182.4. HRMS (ESI) calculated for $C_{18}H_{27}Cl_2N_2O_2S$ (M+H) 405.1170, found 405.1162.

5.2.35. 5,8-Dichloro-6,7-dihydroxy-*N*-(2-pyridin-4-ylethyl)-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (191). Yield: 13%. ^{1}H NMR (CD_3OD 400 MHz) δ 2.79 (t, J = 5.8 Hz, 2H), 3.03 (t, J = 7.0 Hz, 2H), 3.90 (t, J = 7.0 Hz, 2H), 3.97 (t, J = 5.8 Hz, 2H), 4.85 (s, 2H), 7.30 (d, J = 6.0 Hz, 2H), 8.38 (d, J = 6.0 Hz, 2H). ^{13}C NMR (CD_3OD 100 MHz) δ 27.1, 35.6, 45.9, 46.9, 49.3, 118.5, 120.3, 124.2, 125.9, 126.2, 126.2, 142.7, 143.03, 149.8, 149.8, 151.7, 182.8. HRMS (ESI) calculated for $C_{17}H_{18}Cl_2N_3O_2S$ (M+H) 498.0497, found 498.0514.

5.2.36. 5,8-Dichloro-6,7-dihydroxy-*N*-(2-pyridin-3-ylethyl)-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (192). Yield: 39%. ^{1}H NMR (CD_3OD 400 MHz) δ 2.77 (t, J = 5.8 Hz, 2H), 3.01 (t, J = 7.1 Hz, 2H), 3.87 (t, J = 7.1 Hz, 2H), 4.08 (t, J = 5.8 Hz, 2H), 4.84 (s, 2H), 7.31 (dd, J = 7.8, 4.9 Hz, 1H), 7.70 (ddd, J = 7.8, 1.8, 1.6 Hz, 1H), 8.35 (dd, J = 4.9, 1.6 Hz, 1H), 8.41 (d, J = 1.8 Hz, 1H). ^{13}C NMR (CD_3OD 100 MHz) δ 27.1, 33.3, 45.8, 47.4, 49.3, 118.4, 120.2, 124.2, 125.1, 125.8, 137.4, 138.9, 142.6, 142.9, 147.7, 150.3, 182.7. HRMS (ESI) calculated for $C_{17}H_{18}Cl_2N_3O_2S$ (M+H) 398.0497, found 398.0511.

5.2.37. 5,8-Dichloro-6,7-dihydroxy-*N*-(2-pyridin-2-ylethyl)-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (193). Yield: 14%. ^{1}H NMR ($(CD_3)_2SO$ 400 MHz) δ 2.69 (t, J = 5.7 Hz, 2H), 3.02 (t, J = 7.5 Hz, 2H), 3.83 (m, 2H), 3.91 (t, J = 5.7 Hz, 2H), 4.89 (s, 2H), 7.23 (m, 2H), 7.68 (dt, J= 7.7, 1.8 Hz, 1H), 8.04 (t, J = 5.0 Hz, 1H), 8.49 (d, J = 4.2 Hz, 1H). ^{13}C NMR ($(CD_3)_2SO$ 100 MHz) δ 25.8, 36.8, 43.8, 45.2, 48.2, 117.5, 119.4, 121.5, 123.2, 123.4, 124.4, 136.5, 141.5, 141.8, 149.0, 159.3, 180.1. HRMS (ESI) calculated for $C_{17}H_{18}Cl_2N_3O_2S$ (M+H) 398.0497, found 398.0478.

5.2.38. *N*-(4-Chlorobenzyl)-7,8-dihydroxy-1,3,4,5-tetrahydro-2*H*-2-benzazepine-2-carbothioamide (194). Yield: 63%. ^{1}H NMR (CD_3OD 400 MHz) δ 1.82 (m, 2H), 2.80 (m, 2H), 4.12 (bs, 2H), 4.73 (s, 2H), 4.80 (s, 2H), 6.61 (s, 1H), 6.81 (s, 1H), 7.11 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H). ^{13}C NMR (CD_3OD 100 MHz) δ 28.8, 34.9, 49.3, 49.8, 55.0, 118.3, 118.5, 128.7, 129.3, 129.3, 129.8, 129.8, 133.4, 134.3, 139.4, 143.7, 145.3, 181.9. HRMS (ESI) calculated for $C_{18}H_{20}ClN_2O_2S$ (M+H) 363.0934, found 363.0935.

5.2.39. 7,8-Dihydroxy-*N*-(2-phenylethyl)-1,3,4,5-tetrahydro-2*H*-2-benzazepine-2-carbothioamide (195). Yield: 58%. ^{1}H NMR (CD_3OD 400 MHz) δ 1.76 (m, 2H), 2.77 (m, 2H), 2.87 (t, J = 7.5 Hz, 2H), 3.76 (t, J = 7.5 Hz, 2H), 4.03 (bs, 2H), 4.67 (s, 2H), 6.59 (s, 1H), 6.78 (s, 1H), 7.15 (m, 3H), 7.24 (m, 2H). ^{13}C NMR (CD_3OD 100 MHz) δ 28.8, 34.7, 36.4, 48.2, 54.2, 58.3, 118.2, 118.3, 127.2, 128.8, 129.4, 129.4, 129.9, 129.9, 134.1, 140.7, 143.8, 145.4, 181.2. HRMS (ESI) calculated for $C_{19}H_{23}N_2O_2S$ (M+H) 343.1480, found 343.1493.

5.2.40. *N*-[2-(4-tert-Butylphenyl)ethyl]-7,8-dihydroxy-1,3,4,5-tetrahydro-2*H*-2-benzazepine-2-carbothioamide (196). Yield: 72%. ^{1}H NMR (CD_3OD 400 MHz) δ 1.28 (s, 9H), 1.72 (m, 2H), 2.74 (m, 2H), 2.83 (t, J = 7.5 Hz, 2H), 3.74 (t, J = 7.5 Hz, 2H), 4.00 (bs, 2H), 4.66 (s, 2H), 6.60 (s, 1H), 6.79 (s, 1H), 7.07 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 8.3 Hz, 2H). ^{13}C NMR (CD_3OD 100 MHz) δ 28.8, 31.8, 31.8, 31.8, 34.7, 35.2, 35.8, 48.2, 54.5, 55.3, 118.2, 118.4, 126.3, 126.31, 128.5, 129.6, 129.6, 134.1, 137.6, 143.7, 145.3, 150.1, 181.1. HRMS (ESI) calculated for $C_{23}H_{31}N_2O_2S$ (M+H) 399.2107 found 399.2108.

5.2.41. *N*-[2-(2-Chlorophenyl)ethyl]-7,8-dihydroxy-1,3,4,5-tetrahydro-2*H*-2-benzazepine-2-carbothioamide (197). Yield: 22%. ^{1}H NMR (CD_3OD 400 MHz) δ 1.75 (m,

2H), 2.77 (m, 2H), 3.15 (t, J = 7.0 Hz, 2H), 3.80 (t, J = 7.0 Hz, 2H), 4.02 (bs, 2H), 4.70 (s, 2H), 6.60 (s, 1H), 6.78 (s, 1H), 7.15 (m, 3H), 7.30 (m, 1H). ^{13}C NMR (CD_3OD 100 MHz) δ 28.8, 33.9, 34.7, 46.2, 54.1, 55.2, 118.2, 118.3, 128.1, 129.0, 130.0, 130.3, 132.5, 132.7, 134.1, 138.3, 143.8, 145.3, 181.4. HRMS (ESI) calculated for $C_{19}H_{22}ClN_2O_2S$ (M+H) 377.1090, found 377.1089.

5.2.42. *N*-[2-(3-Chlorophenyl)ethyl]-7,8-dihydroxy-1,3,4,5-tetrahydro-2*H*-2-benzazepine-2-carbothioamide (198). Yield: 66%. ^{1}H NMR (CD_3OD 400 MHz) δ 1.76 (m, 2H), 2.76 (m, 2H), 2.87 (t, J = 7.3 Hz, 2H), 3.75 (t, J = 7.3 Hz, 2H), 4.01 (bs, 2H), 4.68 (s, 2H), 6.59 (s, 1H), 6.79 (s, 1H), 7.05 (dd, J = 7.1, 1.7 Hz, 1H), 7.18 (m, 3H). ^{13}C NMR (CD_3OD 100 MHz) δ 28.8, 34.7, 36.0, 47.8, 54.3, 55.5, 118.2, 118.3, 127.3, 128.4, 128.6, 129.9, 130.9, 134.1, 135.1, 143.1, 143.7, 145.3, 181.2. HRMS (ESI) calculated for $C_{19}H_{22}ClN_2O_2S$ (M+H) 377.1090, found 377.1086.

5.2.43. *N*-[2-(4-Fluorophenyl)ethyl]-7,8-dihydroxy-1,3,4,5-tetrahydro-2*H*-2-benzazepine-2-carbothioamide (199). Yield: 26.4%. ^{1}H NMR (CD_3OD 400 MHz) δ 1.75 (m, 2H), 2.77 (m, 2H), 2.85 (t, J = 7.4 Hz, 2H), 3.75 (t, J = 7.4 Hz, 2H), 4.03 (bs, 2H), 4.68 (s, 2H), 6.60 (s, 1H), 6.80 (s, 1H), 6.95 (m, 2H), 7.13 (m, 2H). ^{13}C NMR (CD_3OD 100 MHz) δ 28.8, 34.8, 35.5, 48.1, 54.3, 55.2, 116.0 (d, J_F=21 Hz), 116.0 (d, J_F=21 Hz), 118.2, 118.4, 128.8, 131.5 (d, J_F=8 Hz), 131.5 (d, J_F=8 Hz), 134.1, 136.6 (d, J_F=3 Hz), 143.8, 154.4, 163.0 (d, J_F=251 Hz), 181.2. HRMS (ESI) calculated for $C_{19}H_{22}FN_2O_2S$ (M+H) 361.1386, found 361.1373.

5.2.44. *N*-[2-(4-Bromophenyl)ethyl]-7,8-dihydroxy-1,3,4,5-tetrahydro-2*H*-2-benzazepine-2-carbothioamide (200). Yield: 32%. ^{1}H NMR (CD_3OD 400 MHz) δ 1.74 (m, 2H), 2.76 (m, 2H), 2.84 (t, J = 7.3 Hz, 2H), 3.75 (t, J = 7.3 Hz, 2H), 4.02 (bs, 2H), 4.69 (s, 2H), 6.60 (s, 1H), 6.81 (s, 1H), 7.05 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H). ^{13}C NMR (CD_3OD 100 MHz) δ 28.8, 34.8, 35.8, 47.8, 54.5, 55.6, 118.2, 118.4, 120.9, 128.8, 131.9, 131.9, 132.4, 132.4, 134.1, 140.1, 143.7, 145.3, 181.2. HRMS (ESI) calculated for $C_{19}H_{20}BrN_2O_2S$ (M-H) 419.0429, found 419.0413.

5.2.45. 7,8-Dihydroxy-*N*-(3-phenylpropyl)-1,3,4,5-tetrahydro-2*H*-2-benzazepine-2-carbothioamide (201). Yield: 37%. ^{1}H NMR (CD_3OD 400 MHz) δ 1.79 (m, 2H), 1.88 (dd, J = 7.0 Hz, 7.0 Hz, 2H), 2.55 (t, J = 7.0 Hz, 2H), 2.79 (m, 2H), 3.60 (t, J = 7.0 Hz, 2H), 4.08 (bs, 2H), 4.65 (s, 2H), 6.60 (s, 1H), 6.84 (s, 1H), 7.13 (m, 3H), 7.24 (m, 2H). ^{13}C NMR (CD_3OD 100 MHz) δ 28.9, 32.3, 34.2, 34.8, 46.6, 54.7, 54.7, 118.3, 118.3, 126.7, 128.8, 129.3, 129.3, 129.4, 129.4, 134.2, 143.3, 143.8, 145.4, 181.1. HRMS (ESI) calculated for $C_{20}H_{25}N_2O_2S$ (M+H) 357.1636, found 357.1641.

5.2.46. 7,8-Dihydroxy-*N*-octyl-1,3,4,5-tetrahydro-2*H*-2-benzazepine-2-carbothioamide (202). Spectroscopic data as prevoiusly reported.[20]

5.3. Test procedure

The bronchorelaxing effect of the compounds reported here was evaluated in human small airways. Human lung tissue was obtained from patients undergoing lobectomy due to lung carcinoma in accordance with procedures approved by Lund Ethical Committee, and treated as described in Refs. 9,17 In short, lung tissue was placed in a dissection bowl, an airway was identified and a bronchial preparation from a bronchus with a diameter of 0.5–1.5 mm was obtained. This was mounted in the experimental chamber for force measurements. The experimental chamber was kept at 37 °C and was continuously perfused with physiological saline solution. The force development of the preparation was registered on a computer. After mounting in the chamber and a period of adjustment, the preparation was contracted with LTD_4 and stretched repeatedly until it exerted a force of 1.2 mN. This was followed by 2 cycles with control contractions consisting of 60 min relaxation with LTD_4-free physiological saline solution and 30 min contraction with LTD_4. If these two consecutive LTD_4 contractions differed by less than 10%, the preparations were considered to be stable and the experiments begun. The inhibitory potency of the different substances was evaluated by having 10 μM of the test-substance present during one whole cycle (1 h of LTD_4-free PSS followed by 30 min of contraction with 10 nM LTD_4). This contraction was then compared to the previous one and the potency is expressed as the arithmetic mean (± standard error of the mean) of the contraction remaining, expressed as percentage, after exposure to test-substance. Noteworthy, often each test-chamber contained two preparations from the same patient. The mean of the observed contractions was then regarded as a single value. At the end of the experiments, the preparations were exposed to 0 Ca^{2+} -solution, to establish the baseline tension level.

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