A Synthetic Route to Benzothiazocines with Two or Three Carbon Stereocenters via Copper-Catalyzed Intramolecular N-Arylation

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A new structural family of benzothiazocines bearing two or three carbon stereogenic centers on the 8-membered ring was synthesized by intramolecular Cu-catalyzed *N*-arylation. The chiral racemic 1,3-aminothioethers precursors have been prepared from easily available starting materials. An ionic organic base was used for the first time in an intramolecular C–N

coupling, in medium-ring series, leading to higher yields than those obtained with an inorganic base, and a partial epimerization in some cases. The synthetic sequence was successfully performed on one example in asymmetric version, demonstrating the accessibility of enantioenriched benzothiazocines.

Introduction

Among the large diversity of heterocyclic compounds, medium-sized heterocycles (8 to 11 atoms) represent a class of increasing interest due not only to their presence in bioactive natural products and pharmaceuticals but also because their syntheses still have challenges. Several reviews dealt with these aspects and the different approaches for the synthesis of these compounds.^[1] In particular, when intramolecular cyclizations are employed, enthalpic and entropic factors make the closing process difficult. In this context, we focused our recent research on benzothiazocines which are benzene-fused 8-membered ring *N,S*-heterocycles belonging to the class of medium-sized heterocycles. Although these scaffolds are present in some bioactive molecules,^[2] they are much less studied than their 5-, 6- and 7-membered *N,S*-heterocyclic counterparts (i.e. benzothiazoles, benzothiazines, benzothiazepines), which can be found in the list of the 362 sulfur-containing drugs approved by the FDA.^[3] One of the reasons may be the limited synthetic accessibility of these heterocycles and as a consequence their scarcity in chemical libraries for screening. The main methods to access benzothiazocines (Figure 1) include inter or intramolecular cyclization with *N*- and/or *S*-nucleophiles (i.e. *S*_N2 reactions, amide formation),^[4] or intramolecular Friedel-Crafts reaction.^[5] Some structures have been synthesized by benzyne ring closure,^[6] ring-enlargement,^[7] or by Pd-catalyzed carbonylation reactions.^[8] Our group has recently reported the use of reductive carbopalladation to access benzimidazole-fused benzothiazocines.^[9,10] On the other hand, most of the

Figure 1. Structural diversity of benzothiazocines and key-step reactions for their synthesis (the corresponding formed bond is indicated in red).

published benzothiazocine structures are either achiral or racemic possessing one stereogenic carbon (Figure 1, I–VII).

This state-of-the-art of literature review prompted us to develop a method to access variously substituted benzothiazocines bearing two or three stereogenic carbons on the 8-membered ring, thus increasing their bioactivity potential.^[10] We describe herein the synthesis of such benzothiazocines using intramolecular copper-catalyzed *N*-arylation as the key-step (Figure 1, VIII).

The intramolecular Cu-catalyzed *N*-arylation represents a straightforward synthetic strategy to access a wide range of 5- and 6-membered *N*-heterocycles,^[11] however, to our knowledge, only very few examples have been described to obtain 8-membered *N*-heterocycles.^[12,2h] The use of this approach for the cyclization of substrates such as substituted 1,3-aminothioethers is therefore not trivial. We can also mention that our

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previous attempts using intramolecular *N*-arylation under palladium-catalysis have all failed.

The synthesis of the target 5,1-benzothiazocines could be achieved starting from 1,3-aminothioethers having two or three controlled stereogenic centers (Scheme 1). Based on methodologies previously developed by some of us,^[13] the suitable precursors may be accessible via ring-opening and subsequent *S*-benzylation from 1,3-thiazin-2-ones, which can be obtained in turn by a three-component hetero-Diels-Alder reaction.

Results and Discussion

We first prepared the racemic 1,3-aminothioether **3a** bearing on sulfur a 2-iodobenzyl group, as the model study substrate for the copper-catalyzed *N*-arylation (Scheme 2).

The synthesis started with the three-component cycloaddition using *O*-cyclohexyl thiocarbamate, benzaldehyde, and styrene. The major *cis*-cycloadduct **1a** was isolated, then transformed into its *N*-Boc derivative **2a**. This was necessary to activate the 1,3-thiazin-2-one for the ring-opening step, preventing also the *N*-alkylation during the next step. From **2a** the transformation was achieved in three steps, ethanolysis, *S*-alkylation, and Boc-deprotection. The desired product **3a** was obtained in a satisfactory overall yield of 55% as a single *syn*-stereoisomer.

Scheme 1. Proposed retrosynthetic route to 5,1-benzothiazocines with 2 or 3 stereogenic centers via intramolecular *N*-arylation.

Scheme 2. Our general sequence accessing substrates **3**; synthesis of **3a**.

We started with the optimization of the Cu-catalyzed intramolecular *N*-arylation using substrate **3a** to obtain benzothiazocine **4a** (Table 1). A screening was conducted to identify the most suitable ligand/base combination.

The experiments were performed with copper iodide as the catalyst, in dimethylformamide, at 110 °C, for 40 hours. First, commonly used ligands **L1–L7** in copper-catalyzed C–N bond formation have been tested, keeping K_3PO_4 as the base (Table 1, entries 1–7). With 1,10-phenanthroline (**L1**) and *N,N'*-dimethylethane-1,2-diamine (**L2**) the conversion was low, and the desired product **4a** was obtained along with the hydrodehalogenated side-product **5a**,^[14,15] and isolated with yields below 10% (Table 1, entries 1 and 2). With *N,N'*-dimethylcyclohexane-1,2-diamine (**L3**) the conversion was increased, but more undesired **5a** was formed and the yield in **4a** was not improved (Table 1, entry 3). Ethylene glycol (**L4**) was used as both ligand and solvent leading to **4a** in 17% yield (Table 1, entry 4). A good result was obtained with *L*-proline (**L5**) (Table 1, entry 5). Under these conditions the conversion was total and although the formation of side-product **5a** was not avoided (ratio **4a**/**5a** 2:1), the desired product **4a** was isolated in 44% yield. Diketone-type ligands such 2-isobutyryl-cyclohexanone (**L6**) or pentane-2,4-dione (**L7**) did not give better results (Table 1, entries 6 and 7). A low conversion of 24% was obtained under ligand-free reaction conditions (Table 1, entry 8). Working with

Table 1. Optimization of the Cu-catalyzed intramolecular *N*-arylation to obtain **4a**.

Entry	Ligand	Base	3a / 4a / 5a [%] ^[a]	Yield [%] ^[b]
1	L1	K_3PO_4	72/14/14	9
2	L2	K_3PO_4	56/22/22	9
3	L3	K_3PO_4	19/32/59	10
4 ^[c]	L4	K_3PO_4	6/47/47	17
5	L5	K_3PO_4	0/66/34	44
6	L6	K_3PO_4	0/50/50	nd ^[d]
7	L7	K_3PO_4	nd	23
8	–	K_3PO_4	76/12/12	nd
9	L5	Cs_2CO_3	20/66/14	nd
10	L5	K_2CO_3	0/65/35	30
11	–	TBPM	0/1/0	(58) ^[e]
12 ^[f]	–	TBPM	0/1/0	49 (12) ^[g]

[a] Ratio measured by 1H NMR in the crude mixture; [b] Iso-lated yield of **4a**; [c] **L4** was used as the solvent instead of DMF; [d] Not determined; [e] Combined isolated yield of diastereomers **4a** and **4'a**, ratio **4a**/**4'a** 4:1; [f] Performed with CuI (10 mol%); [g] In brackets, isolated yield of **4'a**.

L5 using another base (Cs_2CO_3 or K_2CO_3 , Table 1, entries 9 and 10), temperature (80°C , 130°C), solvent (MeCN), or concentration, the yield dropped.

In 2009 Fu, Liu, and co-workers published a highly effective Cu-catalyzed coupling of aryl iodides with amines by using tetrabutylphosphonium malonate (TBPM) as an organic ionic soluble base.^[16] Then, in-depth mechanistic studies carried out by Davies and co-workers showed the ability of TBPM to serve as both base and ancillary Cu-ligand for intermolecular *N*-arylation.^[17] These interesting results prompted us to test TBPM in our reaction. Thus, under the same reaction conditions, TBPM was used as the base instead of the inorganic one, without adding a ligand (Table 1, entry 11). Two significant results were obtained: the competitive hydrodeiodination was suppressed (no trace of **5a** was observed) and the desired product **4a** was obtained along with its diastereomer **4'a** (phenyl substituents in *trans*), in a **4a/4'a** ratio of 4:1 (measured by ^1H NMR in the crude mixture). The combined isolated yield of benzothiazocines **4a** and **4'a** was higher than the best result obtained previously (58% vs 44%). We then decreased the catalytic charge to 10 mol% CuI (Table 1, entry 12) and the diastereomeric products could be separated by column chromatography leading to **4a** and **4'a** in 49% and 12% yield, respectively (combined yield: 61%).

To explore the substrate scope and limitations, a range of 1,3-aminothioethers **3b–r** (Figure 2) was synthesized similarly to **3a** using different aldehydes and alkenes partners. Experimental details are given in SI. Styrene and norbornene have been selected due to their highly stereoselective cycloaddition, affording the corresponding 1,3-thiazin-2-ones **1** as major *cis*-cycloadducts (**1a–l**) or *trans*-cycloadducts (**1n–r**), respectively. As the *cis/trans* stereoisomers of either from precursors **3** or **2** were separable, the corresponding aminothioethers **3** were obtained as a single stereoisomer, except the NO_2 -derivative **3g** (ratio *syn/anti* 83:17). Cyclohexene led to a 60:40 *cis/trans* mixture of cycloadducts **1m/1'm** from which we were able to obtain only the *syn*-product **3m**. We did not exemplify on substrates having only alkyl substituents as the stereoselectivity

of the three-component reaction is low, making the stereoisomers separation difficult.

Considering the best results obtained in the optimization phase, we decided to use on the prepared substrates two sets of reaction conditions: one using *L*-proline (**L5**) as the ligand and K_3PO_4 as the base (Table 2, conditions A, in green) and the other using TBPM as both ligand and base (Table 2, conditions B, in red). We first examined the influence of the electronic nature and position of the substituents on the aromatics in the cyclization of aminothioethers **3b–j** under conditions A. The substrates bearing in para or in meta positions electron donating (i.e. Me) or electron-withdrawing groups (i.e. Cl, F, CF_3), led to the desired products **4** accompanied by the corresponding by-products **5** in a ratio **4/5** close to 2:1, however, we were able to isolate them with yields ranging from 18% to 47%.

In the experiments involving substrates **3d** and **3g**, we were not able to detect any of the known compounds (i.e. the starting material, the benzothiazocine, or the hydrodeiodinated product) in the crude mixture analyzed by ^1H NMR, but only unidentified products. Then, substrates **3k** and **3n** bearing alkyl substituents have been placed under conditions A, leading to the expected products in respectively 40% and 64% yield. In these cases, we did not observe the corresponding undesired products **5k** and **5n**. We next performed the reaction under conditions B for all synthesized substrates **3**. The set of results obtained showed the total suppression of the hydrodeiodination in all cases. As a consequence, benzothiazocines with two aryl substituents were obtained in higher yields than under conditions A. In these cases, the isolated yields represent the mixture of *cis*-**4**/*trans*-**4'** diastereomers with ratios ranging from 4:1 to 0.5/1, but which are separable by column chromatography. With substrates **3d** and **3g** the reaction, unfortunately, failed again, with results similar to those obtained previously. Interestingly, starting from substrates bearing an isopropyl or a benzyl group next to the N-atom (i.e. **3k**, **3l**), as well as from those containing a cycloalkane (i.e. **3m–r**), the expected products **4k–r** were obtained as a single diastereomer. In particular, norbornane benzothiazocines **4n–r** were isolated in good to excellent yields, with again a higher yield for **4n** than that obtained under conditions A (98% vs. 64%).

Noticeable, conditions B allowed obtaining product **4r** having a bromophenyl substituent, without hydrodeiodination. We also noticed that the cyclization of the aminothioethers with cycloalkane substituents (**3m–r**) took place faster than the others (18 vs 40 hours). This could also explain the absence of hydrodeiodination under conditions A in the case of **3n**. An additional experiment was performed on substrate **3b**, keeping the ligand **L5**, but replacing the inorganic base with the ionic organic one. In this case, neither the hydrodeiodinated product **5b** nor the epimer **4'b** was formed, and **4b** was isolated in 50% yield (see in Table 2). In some cases (**4h**, **4j**, **4l**, **4m**), despite a total conversion, the isolated yields remained around 30%. The crude mixture contained in these cases unidentified products and we could not explain this fact and improve the yields.

Figure 2. 1,3-Aminothioether substrates **3a–r**.

Table 2. Scope of the Cu-catalyzed intramolecular *N*-arylation accessing 5,1-benzothiazocines.^[a,b]

<p>[a] In green are given the isolated yields of products 4 obtained under conditions A; [b] In red are given the combined yields of 4 and 4' obtained under conditions B; ratios refer to the isolated mixture of 4 and 4', measured by ¹H NMR. [c] Product 5 was present in the crude mixture in a ratio 4/5 of 2:1, measured by ¹H NMR. [d] Reaction performed with CuI (20 mol%), L5 (40 mol%), TBPM (2 equiv).</p>

Crystals obtained from **4b** (CCDC 2042277), **4e** (CCDC 2056458), **4f** (CCDC 2042276), and **4n** (CCDC 2042275) allowed to unambiguously assign their relative stereochemistry by X-ray crystallographic analysis (Figure 3 and SI).

A proposed reaction mechanism involving TBPM, based on the relevant literature,^[17b] is given in Scheme 3. The catalytic cycle may be similar to the general Ullmann-type C–N coupling, with the dianionic malonate from TBPM acting as both the ancillary Cu-ligand (in **i1** intermediate) and base (for the N–H deprotonation of **i1**). The resulting species **i2** represents the key catalytic intermediate and gives, via oxidative addition of the aryl iodide, species **i3**. Final reductive elimination affords

arylamine product **4** and regenerates the Cu(I) catalytic complex.

On another hand, we wondered if the formation of **4'** under conditions B took place before the cyclization, or after by partial epimerization of **4**. To check this, we first placed pure **4a** in the reaction conditions (Scheme 3, Eq. 1). After 16 hours, the crude reaction mixture contained diastereomers **4a** and **4'a** in a ratio of 2:1. When pure **4'a** was submitted to the same test the starting material was recovered without epimerization (Scheme 3, Eq. 2). In the presence of TBPM, without copper iodide, **4a** was also epimerized, giving a **4a/4'a** ratio of 4:1 (Scheme 3, Eq. 3). Modification of the reaction time, of the temperature, or of the CuI or base charge, did not make significant changes to these results. We supposed that under the reaction conditions, a deprotonation/reprotonation occurred at one of the stereogenic centers leading to the more stable *trans*-isomer. In order to get more information, we placed the *cis*-isomer **4b** under conditions B but using as the solvent a 9/1 mixture of DMF/D₂O (Scheme 4, Eq. 4). The epimerization took place leading to a mixture of **4b** and **4'b** in 4:1 ratio, with a 50% deuterium incorporation on the formed *trans*-isomer **4'b**, while **4b** was recovered non-deuterated. The deuterium labeling was observed only at the 4-position (SCHPh), indicating that the stereogenic carbon next to the sulfur atom is the one, which epimerizes. In-depth studies will certainly be necessary to rationalize the epimerization induced by the use of TBPM.

Figure 3. X-ray structures of benzothiazocines **4b** and **4n** (50% probability ellipsoids).

Scheme 3. Proposed reaction mechanism

Scheme 4. Control experiments.

Scheme 5. Toward chiral non-racemic benzothiazocines (the major stereoisomers are illustrated)

We finally envisaged potential access to non-racemic benzothiazocines (Scheme 5). Starting from *O*-(*L*-menthyl) thiocarbamate, styrene, and para-tolyl aldehyde, 1,3-thiazin-2-one *cis*-**1b*** was obtained with an enantiomeric ratio (er) of 80:20 (measured by chiral HPLC).^[18] It should be noticed that 1,3-thiazin-2-ones with higher er (up to 97:3) can be prepared by using (–)-8-(2-naphthyl)menthol as the chiral auxiliary.^[13a] Then,

the same synthetic sequence previously used to access **3b** enabled the transformation of **1b*** into **3b*** with preservation of the initial er (measured by derivatization using the Mosher's method^[19]). The cyclization was performed under conditions A, leading to the enantioenriched benzothiazocine **4b*** with an unchanged er of 80:20 (measured utilizing the *R*-(+)-tert-butylphenylphosphinothioic acid as a chiral solvating agent^[20]). The *N*-arylation using the *L*-proline/TBPM combination led to a similar result.

Conclusion

In summary, we have developed a Cu-catalyzed *N*-arylation to synthesize chiral racemic benzothiazocines bearing two or three stereogenic carbons on the 8-membered ring. Higher yields have been obtained when the reaction was performed using an ionic organic base (TBPM) instead of an inorganic base (K₃PO₄). This represents also the first example of the use of an ionic organic base in Cu-catalyzed intramolecular C–N bond formation, moreover in the difficult case of medium-sized heterocycle series. In some cases, the use of TBPM prevented the undesired hydrodehalogenation, but induced a partial epimerization at the stereogenic carbon next to the sulfur atom of the heterocycle. Further studies will be conducted to rationalize this result. The example performed in non-racemic series allows us to validate the feasibility of the asymmetric synthesis of this new family of benzothiazocines. The overall synthetic sequence enables access to a large variety of new potentially active compounds, rare in chemical libraries.

Experimental Section

General Information: Reagents and dry solvents were obtained from commercial sources and used without further purification. Thin-layer chromatography (TLC) was performed on silica gel 60 F254 plates and was visualized under UV light and revealed with KMnO₄ stain. Crude products were purified by flash column chromatography on Merck silica gel Si 60 (40–63 μm) or by using a CombiFlash Rf (Teledyne Isco) system. NMR spectra were recorded at 400 or 500 MHz for ¹H, at 100 or 125 MHz for ¹³C, and at 376 MHz for ¹⁹F. Chemical shifts (δ) were reported in ppm relative to residual solvent. Coupling constants (J) were reported in hertz (Hz). Assignments of ¹H and ¹³C signal were made by DEPT, COSY, HSQC, HMBC, and NOESY-2D experiments. The following abbreviations were adopted in reporting NMR data: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), broad signal (bs), doublet of doublets (dd), doublet of doublet of doublets (ddd), doublet of triplets (dt), doublet of quartets (dq), triplet of doublets (td), triplet of triplets (tt), quartet of triplets (qt) or multiplet (m). HRMS were performed with a Q-TOF analyzer using electrospray ionization (ESI). Melting points were determined in open capillary tubes and were uncorrected. High-performance liquid chromatography (HPLC) separation of the enantioenriched **1b*** was achieved using a chromatograph constructed with the following components: a Waters 2795 pump, a Waters 996 photodiode array detector and Empower Software. The following column has been used: Chiralpak® IB, a 3,5-dimethylphenylcarbamate derivative of cellulose, immobilized on 5 μm silica gel.

Typical procedures for the Cu-catalyzed cyclization; Synthesis of benzothiazocine 4a

General Procedure A. Under argon, substrate **3a** (50 mg, 0.11 mmol, 1 equiv) was placed in a pressure tube. K_3PO_4 (46 mg, 0.22 mmol, 2 equiv), *L*-proline (5 mg, 0.044 mmol, 0.4 equiv), and CuI (4 mg, 0.022 mmol, 0.2 equiv) were added. DMF (0.04 M, 2.7 mL) was added, the tube was sealed, and three freeze-thaw cycles are performed under stirring to degas the solvent. Under argon, the tube is heated in a 110 °C oil-bath for 18 to 40 h. After reaching room temperature, volatiles were removed by vacuum, the crude was diluted with AcOEt, filtered through basic alumina, then the solvent was removed. The crude mixture (containing **4a** and **5a** in a ratio of 2:1) was purified by flash chromatography with heptane/AcOEt (95/5) to give product **4a** (16 mg, 0.05 mmol, 44%) as a white amorphous solid.

General Procedure B. Under argon, substrate **3a** (60 mg, 0.13 mmol, 1 equiv) was placed in a pressure tube. TBPM (161 mg, 0.2 mmol, 2 equiv) and CuI (2.5 mg, 0.013 mmol, 0.1 equiv) were added. DMF (0.04 M, 3.2 mL) was added, the tube was sealed, and three freeze-thaw cycles are performed under stirring to degas the solvent. Under argon, the tube is heated in a 110 °C oil-bath for 18 to 40 h. The work-up was identical to that of procedure A. Products **4a** (21 mg, 0.064 mmol, 49%) and **4'a** (5 mg, 0.016 mmol, 12%) have been obtained as white amorphous solids.

2,4-diphenyl-1,3,4,6-tetrahydro-2H-benzo[c][1,5]thiazocine (4a)

Following the general procedure A, starting from substrate **3a** (50 mg, 0.11 mmol), product **4a** (16 mg, 0.05 mmol, 44%) has been obtained as a white amorphous solid. TLC (heptane/AcOEt 95/05, R_f =0.20).

Following the general procedure B, starting from substrate **3a** (60 mg, 0.13 mmol), products **4a** (21 mg, 0.064 mmol, 49%) and **4'a** (5 mg, 0.016 mmol, 12%) have been obtained as white amorphous solids.

4a: 1H NMR (400 MHz, $CDCl_3$) δ 7.47–7.10 (m, 13H), 6.98–6.71 (m, 1H), 4.60 (d, J =13.2 Hz, 1H, SCH_2), 4.10 (dd, J =11.3, 2.1 Hz, 1H, NCH), 3.76 (d, J =13.2 Hz, 1H, SCH_2), 3.63 (dd, J =7.0, 2.1 Hz, 1H, SCH), 2.85 (ddd, J =15.3, 11.2, 7.0 Hz, 1H, CH_2), 2.58 (dt, J =15.3, 2.1 Hz, 1H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.3, 145.0, 142.3, 134.2, 132.8, 130.2, 129.0, 128.8 (2C), 128.7 (2C), 128.6 (2C), 128.2, 127.7, 126.5 (2C), 125.6, 125.5, 66.1 (NCH), 49.4 (CH_2), 46.1 (SCH), 32.7 (SCH_2). HRMS (ESI-Q-TOF) m/z calcd for $C_{22}H_{22}NS$ $[M+H]^+$: 332.1467, found: 332.1468.

4'a: 1H NMR (400 MHz, $CDCl_3$) δ 7.50–7.45 (m, 2H), 7.41–7.35 (m, 2H), 7.34–7.28 (m, 1H), 7.24–7.12 (m, 5H), 7.10–7.06 (m, 2H), 6.99 (td, J =7.4, 1.3 Hz, 1H), 6.82 (dd, J =7.8, 1.4 Hz, 1H), 5.11 (t, J =5.8 Hz, 1H, NCH), 4.38 (t, J =6.5 Hz, 1H, SCH), 4.23 (s, 2H, SCH_2), 2.75–2.29 (m, 2H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.3, 143.3, 143.2, 131.4, 128.8 (2C), 128.6 (2C), 128.2, 127.6, 127.3 (2C), 127.0, 126.9 (2C), 122.7, 122.3, 61.9 (NCH), 47.4 (CH_2), 47.0 (SCH), 36.9 (SCH_2).

4-phenyl-2-(*p*-tolyl)-1,3,4,6-tetrahydro-2H-benzo[c][1,5]thiazocine (4b)

Following the general procedure A, starting from substrate **3b** (64 mg, 0.14 mmol), product **4b** (22 mg, 0.06 mmol, 47%) has been obtained as a white amorphous solid. Recrystallization in $CDCl_3$ gave colorless crystals (M_p =141 °C). TLC (heptane/AcOEt 95/05, R_f =0.22).

Following the general procedure B, starting from substrate **3b** (65 mg, 0.14 mmol), products **4b** (28 mg, 0.08 mmol, 59%) and **4'b** (7 mg, 0.02 mmol, 15%) have been obtained as white amorphous solids.

1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.34 (m, 1H), 7.32–7.26 (m, 2H), 7.24–7.13 (m, 9H), 6.92–6.82 (m, 1H), 4.60 (d, J =13.2 Hz, 1H, SCH_2), 4.07 (dd, J =11.2, 2.1 Hz, 1H, NCH), 3.75 (d, J =13.2 Hz, 1H, SCH_2), 3.62 (dd, J =7.0, 2.1 Hz, 1H, SCH), 2.84 (ddd, J =15.3, 11.2, 7.0 Hz, 1H, CH_2), 2.56 (dt, J =15.3, 2.1 Hz, 1H, CH_2), 2.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.5, 143.8, 142.3, 137.2, 134.2, 130.2, 129.4 (2C), 128.5 (2C), 128.1, 127.6 (2C), 127.1, 126.4 (2C), 125.5, 125.3, 65.8 (NCH), 49.5 (CH_2), 46.8 (SCH), 32.8 (SCH_2), 21.1 (CH_3). HRMS (ESI-Q-TOF) m/z calcd for $C_{23}H_{24}NS$ $[M+H]^+$: 346.1624, found: 346.1634.

4'b: 1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.31 (m, 2H), 7.26–7.08 (m, 8H), 6.96 (td, J =7.5, 1.3 Hz, 1H), 6.78 (dd, J =7.8, 1.3 Hz, 1H), 5.13 (dd, J =7.5, 4.6 Hz, 1H, NCH), 4.38 (dd, J =8.8, 4.6 Hz, 1H, SCH), 4.28 (d, J =13.6 Hz, 1H, SCH_2), 4.17 (d, J =13.6 Hz, 1H, SCH_2), 3.37 (bs, 1H, NH), 2.54–2.48 (m, 2H, CH_2), 2.36 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.5, 143.0, 140.4, 137.3, 131.5, 129.4 (2C), 128.5 (2C), 128.2, 127.4 (2C), 127.0, 126.8 (2C), 122.3, 121.8, 61.4 (NCH), 47.6 (CH_2), 47.1 (SCH), 37.1 (SCH_2), 21.1 (CH_3). HRMS (ESI-Q-TOF) m/z calcd for $C_{23}H_{24}NS$ $[M+H]^+$: 346.1624, found: 346.1633

4-phenyl-2-(*m*-tolyl)-1,3,4,6-tetrahydro-2H-benzo[c][1,5]thiazocine (4c)

Following the general procedure A, starting from substrate **3c** (64 mg, 0.14 mmol), product **4c** (20 mg, 0.06 mmol, 43%) has been obtained as an colorless oil. TLC (heptane/AcOEt 95/05, R_f =0.22).

Following the general procedure B, starting from substrate **3c** (100 mg, 0.21 mmol), a mixture of products **4c** and **4'c** (49 mg, 0.14 mmol, 67%, ratio 1:0.25) have been obtained as a colorless oil.

1H NMR (400 MHz, $CDCl_3$) δ 7.43–7.39 (m, 1H), 7.31–7.19 (m, 11H), 7.17–7.12 (m, 1H), 6.93 (dd, J =7.4, 1.8 Hz, 1H), 4.67 (d, J =13.1 Hz, 1H, SCH_2), 4.10 (dd, J =11.2, 2.1 Hz, 1H, NCH), 3.79 (d, J =13.1 Hz, 1H, SCH_2), 3.65 (dd, J =7.0, 2.1 Hz, 1H, SCH), 3.37 (bs, 1H, NH), 2.90 (ddd, J =15.3, 11.2, 7.0 Hz, 1H, CH_2), 2.62 (dt, J =15.3, 2.1 Hz, 1H, CH_2), 2.41 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.5, 145.2, 143.8, 138.5, 134.2, 130.2, 128.7, 128.5 (2C), 128.3, 128.2, 127.6 (2C), 127.2, 127.1, 125.4, 125.3, 123.5, 66.2 (NCH), 49.6 (CH_2), 46.8 (SCH), 32.7 (SCH_2), 21.5 (CH_3). HRMS (ESI-Q-TOF) m/z calcd for $C_{23}H_{24}NS$ $[M+H]^+$: 346.1624, found: 346.1642.

2-(4-chlorophenyl)-4-phenyl-1,3,4,6-tetrahydro-2H-benzo[c][1,5]thiazocine (4e)

Following the general procedure A, starting from substrate **3e** (60 mg, 0.12 mmol), product **4e** (16 mg, 0.04 mmol, 35%) has been obtained as a yellow oil. Recrystallization in $CDCl_3$ gave colorless crystals (M_p =170 °C). TLC (heptane/AcOEt 95/05, R_f =0.16).

Following the general procedure B, starting from substrate **3e** (60 mg, 0.12 mmol), a mixture of products **4e** and **4'e** (30 mg, 0.08 mmol, 67%, ratio 1:0.25) have been obtained as a yellow oil. **1H NMR** (400 MHz, $CDCl_3$) δ 7.38–7.33 (m, 1H), 7.32 (s, 4H), 7.25–7.14 (m, 7H), 6.88–6.81 (m, 1H), 4.54 (d, J =13.2 Hz, 1H, SCH_2), 4.08 (dd, J =11.4, 2.2 Hz, 1H, NCH), 3.78 (d, J =13.2 Hz, 1H, SCH_2), 3.62 (dd, J =6.8, 2.2 Hz, 1H, SCH), 2.80 (ddd, J =15.2, 11.4, 6.8 Hz, 1H, CH_2), 2.53 (dt, J =15.3, 2.2 Hz, 1H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.9, 143.7, 143.5, 134.5, 133.2, 130.2, 128.9 (2C), 128.6 (2C), 128.2, 127.9 (2C), 127.6 (2C), 127.2, 125.7, 125.6, 65.3 (NCH), 49.2 (CH_2), 46.7 (SCH), 32.8 (SCH_2).

2-(4-fluorophenyl)-4-phenyl-1,3,4,6-tetrahydro-2H-benzo[c][1,5]thiazocine (4f)

Following the general procedure A, starting from substrate **3f** (50 mg, 0.11 mmol), product **4f** (12 mg, 0.03 mmol, 33%) has been obtained as a white amorphous solid. Recrystallization in CDCl₃ gave colorless crystals (Mp=142 °C). TLC (heptane/AcOEt 95/05, Rf=0.22).

Following the general procedure B, starting from substrate **3f** (24 mg, 0.05 mmol), a mixture of products **4f** and **4'f** (14 mg, 0.04 mmol, 80%, ratio 1:0.25) have been obtained as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.35 (ddd, J=8.9, 4.6, 2.0 Hz, 3H), 7.25–7.14 (m, 7H), 7.08–6.98 (m, 2H), 6.90–6.81 (m, 1H), 4.55 (d, J=13.2 Hz, 1H, SCH₂), 4.09 (dd, J=11.4, 2.2 Hz, 1H, NCH), 3.77 (d, J=13.2 Hz, 1H, SCH₂), 3.62 (dd, J=6.9, 2.2 Hz, 1H, SCH), 2.81 (ddd, J=15.3, 11.4, 6.9 Hz, 1H, CH₂), 2.54 (dt, J=15.3, 2.2 Hz, 1H, CH₂). ¹³C NMR (101 MHz, CDCl₃) δ 162.1 (d, J=245.8 Hz), 146.0, 143.8, 140.9 (d, J=3.3 Hz), 134.5, 130.2, 128.6 (2C), 128.1 (2C), 128.1, 127.6 (2C), 127.2, 125.7, 125.5, 115.5 (d, J=21.3 Hz, 2C), 65.3 (NCH), 49.4 (CH₂), 46.7 (SCH), 32.7 (SCH₂). ¹⁹F NMR (376 MHz, CDCl₃) δ –114.9.

4-phenyl-2-(4-(trifluoromethyl)phenyl)-1,3,4,6-tetrahydro-2H-benzo[c][1,5]thiazocine (4h)

Following the general procedure A, starting from substrate **3h** (100 mg, 0.19 mmol), product **4h** (14 mg, 0.03 mmol, 18%) has been obtained as a colorless oil. TLC (heptane/AcOEt 95/05, Rf=0.18).

Following the general procedure B, starting from substrate **3h** (88 mg, 0.17 mmol), a mixture of products **4h** and **4'h** (16 mg, 0.04 mmol, 24%, ratio 1:0.6) have been obtained as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.61 (d, J=8.3 Hz, 2H), 7.51 (d, J=8.3 Hz, 2H), 7.40–7.32 (m, 1H), 7.27–7.13 (m, 7H), 6.89–6.82 (m, 1H), 4.56 (d, J=13.1 Hz, 1H, SCH₂), 4.17 (dd, J=11.4, 2.2 Hz, 1H, NCH), 3.78 (d, J=13.1 Hz, 1H, SCH₂), 3.63 (dd, J=7.0, 2.2 Hz, 1H, SCH), 2.82 (ddd, J=15.3, 11.4, 7.0 Hz, 1H, CH₂), 2.56 (dt, J=15.3, 2.2 Hz, 1H, CH₂). ¹³C NMR (126 MHz, CDCl₃) δ 148.7, 145.9, 143.6, 134.4, 130.3, 129.8 (q, J=32.7 Hz), 128.6 (2C), 128.3, 127.5 (2C), 127.2, 126.9 (2C), 125.8 (q, J=3.6 Hz, 2C), 125.7, 125.6, 124.1 (q, J=272.0 Hz), 65.6 (NCH), 49.3 (CH₂), 46.6 (SCH), 32.7 (SCH₂). ¹⁹F NMR (376 MHz, CDCl₃) δ –62.5. HRMS (ESI-Q-TOF) *m/z* calcd for C₂₃H₂₁F₃NS [M+H]⁺: 400.1341, found: 400.1358.

4-phenyl-2-(3-(trifluoromethyl)phenyl)-1,3,4,6-tetrahydro-2H-benzo[c][1,5]thiazocine (4i)

Following the general procedure A, starting from substrate **3i** (63 mg, 0.12 mmol), product **4i** (16 mg, 0.04 mmol, 34%) has been obtained as a colorless oil. TLC (heptane/AcOEt 95/05, Rf=0.18).

Following the general procedure B, starting from substrate **3i** (60 mg, 0.11 mmol), a mixture of products **4i** and **4'i** (27 mg, 0.07 mmol, 59%, ratio 1:0.25) have been obtained as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.67–7.64 (m, 1H), 7.60–7.53 (m, 2H), 7.50–7.45 (m, 1H), 7.40–7.36 (m, 1H), 7.27–7.16 (m, 7H), 6.91–6.82 (m, 1H), 4.57 (d, J=13.2 Hz, 1H, SCH₂), 4.17 (dd, J=11.4, 2.2 Hz, 1H, NCH), 3.78 (d, J=13.2 Hz, 1H, SCH₂), 3.62 (dd, J=6.9, 2.2 Hz, 1H, SCH), 2.84 (ddd, J=15.3, 11.4, 6.9 Hz, 1H, H-5), 2.57 (dt, J=15.3, 2.2 Hz, 1H, CH₂). ¹³C NMR (101 MHz, CDCl₃) δ 145.8, 143.6, 134.5, 131.1 (q, J=32.2 Hz), 130.2, 130.0, 129.2, 128.6 (2C), 128.3, 127.6 (2C), 127.2, 125.8, 125.7, 124.4 (q, J=3.7 Hz), 124.0 (q, J=273 Hz), 123.4 (q, J=3.8 Hz), 65.7 (NCH), 49.4 (CH₂), 46.5 (SCH), 32.6 (SCH₂). ¹⁹F NMR (376 MHz, CDCl₃) δ –62.5. HRMS (ESI-Q-TOF) *m/z* calcd for C₂₃H₂₁F₃NS [M+H]⁺: 400.1341, found: 400.1356.

4-(4-chlorophenyl)-2-phenyl-1,3,4,6-tetrahydro-2H-benzo[c][1,5]thiazocine (4j)

Following the general procedure A, starting from substrate **3j** (74 mg, 0.15 mmol), product **4j** (14 mg, 0.04 mmol, 25%) has been obtained as a colorless oil. TLC (heptane/AcOEt 95/05, Rf=0.16).

Following the general procedure B, starting from substrate **3j** (60 mg, 0.12 mmol), a mixture of products **4j** and **4'j** (12 mg, 0.03 mmol, 27%, ratio 0.5:1) have been obtained as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.49–7.41 (m, 5H), 7.39–7.35 (m, 1H), 7.29–7.20 (m, 6H), 6.97–6.94 (m, 1H), 4.68 (d, J=13.2 Hz, 1H, SCH₂), 4.16 (dd, J=11.2, 2.2 Hz, 1H, NCH), 3.82 (d, J=13.2 Hz, 1H, SCH₂), 3.66 (dd, J=7.0, 2.1 Hz, 1H, SCH), 2.90 (ddd, J=15.3, 11.2, 7.0 Hz, 1H, CH₂), 2.58 (dt, J=15.3, 2.1 Hz, 1H, CH₂). ¹³C NMR (101 MHz, CDCl₃) δ 146.3, 145.0, 142.3, 134.2, 132.8, 130.2, 129.0 (2C), 128.9 (2C), 128.7 (2C), 128.3, 127.7, 126.5 (2C), 125.6, 125.5, 66.1 (NCH), 49.4 (CH₂), 46.0 (SCH), 32.7 (SCH₂). HRMS (ESI-Q-TOF) *m/z* calcd for C₂₂H₂₁ClNS [M+H]⁺: 366.1078, found: 366.1084.

2-isopropyl-4-phenyl-1,3,4,6-tetrahydro-2H-benzo[c][1,5]thiazocine (4k)

Following the general procedure A, starting from substrate **3k** (65 mg, 0.15 mmol), product **4k** (17 mg, 0.06 mmol, 40%) has been obtained as a colorless oil. TLC (heptane/AcOEt 90/10, Rf=0.38).

Following the general procedure B, starting from substrate **3k** (60 mg, 0.14 mmol), product **4k** (22 mg, 0.07 mmol, 52%) has been obtained as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.21–7.08 (m, 7H), 6.89 (td, J=7.5, 1.4 Hz, 1H), 6.82 (dd, J=8.2, 1.4 Hz, 1H), 4.22 (d, J=14.0 Hz, 1H, SCH₂), 3.75 (d, J=14.0 Hz, 1H, SCH₂), 3.50 (dd, J=8.0, 3.3 Hz, 1H, SCH), 2.90–2.86 (m, 1H, NCH), 2.37–2.25 (m, 2H, CH₂), 1.78–1.68 (m, 1H), 0.97 (d, J=7.2 Hz, 3H, CH₃), 0.96 (d, J=7.2 Hz, 3H, CH₃). ¹³C NMR (126 MHz, CDCl₃) δ 147.9, 143.7, 130.4, 129.3, 128.6 (2C), 128.4, 127.4 (2C), 127.1, 122.5, 122.4, 65.2 (NCH), 48.5 (CH₂), 46.2 (SCH), 34.8, 34.7, 19.6 (CH₃), 18.0 (CH₃). HRMS (ESI-Q-TOF) *m/z* calcd for C₁₉H₂₄NS [M+H]⁺: 298.1624, found: 298.1640.

2-benzyl-4-phenyl-1,3,4,6-tetrahydro-2H-benzo[c][1,5]thiazocine (4l)

Following the general procedure B, starting from substrate **3l** (55 mg, 0.12 mmol), product **4l** (10 mg, 0.03 mmol, 25%) has been obtained as a brown amorphous solid. TLC (heptane/AcOEt 90/10, Rf=0.33). ¹H NMR (400 MHz, CDCl₃) δ 7.40–7.34 (m, 2H), 7.31–7.19 (m, 9H), 7.10–7.05 (m, 2H), 6.52–6.48 (m, 1H), 4.45 (d, J=13.2 Hz, 1H, SCH₂), 3.68 (d, J=13.2 Hz, 1H, SCH₂), 3.55–3.47 (m, 1H, SCH), 3.30–3.22 (m, 1H, NCH), 2.89–2.73 (m, 2H), 2.54–2.48 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 146.7, 143.9, 138.7, 133.7, 130.1, 129.3 (2C), 128.8 (2C), 128.6 (2C), 128.0, 127.6 (2C), 127.1, 126.8, 124.8, 124.7, 62.6, 48.4, 46.9, 43.9, 32.8. HRMS (ESI-Q-TOF) *m/z* calcd for C₂₃H₂₄NS [M+H]⁺: 346.1624, found: 346.1627.

12-phenyl-2,3,4,4a,6,11,12,12a-octahydro-1H-dibenzo[b,f][1,5]thiazocine (4m)

Following the general procedure B, starting from substrate **3m** (13 mg, 0.03 mmol), product **4m** (3 mg, 0.01 mmol, 33%) has been obtained as a colorless oil. TLC (heptane/AcOEt 90/10, Rf=0.30). ¹H NMR (400 MHz, CDCl₃) δ 7.38–7.23 (m, 5H), 7.06–6.98 (m, 2H), 6.73 (td, J=7.4, 1.4 Hz, 1H), 6.64 (dd, J=7.9, 1.4 Hz, 1H), 4.42 (bs, 1H, NCH), 4.24 (d, J=16.7 Hz, 1H, SCH₂), 4.08 (d, J=16.7 Hz, 1H, SCH₂), 3.77 (bs, 1H, SCH), 3.34 (bs, 1H, CH₂), 2.25–2.18 (m, 1H), 2.10 (qd, J=13.2, 3.7 Hz, 1H), 1.94 (tt, J=13.7, 4.3 Hz, 1H), 1.85–1.76 (m, 1H), 1.67–1.61 (m, 1H), 1.59–1.51 (m, 1H), 1.46–1.36 (m, 1H), 0.92–0.81

(m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 146.0, 144.9, 131.6, 128.7 (2C), 128.1, 127.0, 126.2 (2C), 124.8, 120.6, 119.5, 61.4 (NCH), 54.2 (SCH), 46.5, 40.5, 34.7 (SCH₂), 26.0, 22.4, 21.0. HRMS (ESI-Q-TOF) *m/z* calcd for C₂₀H₂₄NS [M + H]⁺: 310.1624, found: 310.1636.

12-phenyl-2,3,4,4a,6,11,12,12a-octahydro-1H-1,4-methanodibenzo[b,f][1,5]thiazocine (4n)

Following the general procedure A, starting from substrate **3n** (50 mg, 0.11 mmol), product **4n** (23 mg, 0.07 mmol, 64%) has been obtained as a colorless oil.

Following the general procedure B, starting from substrate **3n** (60 mg, 0.13 mmol), product **4n** (42 mg, 0.13 mmol, 98%) has been obtained as a colorless oil. Recrystallization in CDCl₃ gave colorless crystals (Mp = 155 °C). TLC (heptane/AcOEt 95/05, Rf = 0.23). ¹H NMR (400 MHz, CDCl₃) δ 7.39 (dd, *J* = 8.2, 6.8 Hz, 2H), 7.34–7.25 (m, 3H), 7.13 (dd, *J* = 7.2, 1.9 Hz, 1H), 7.06–6.95 (m, 2H), 6.75–6.21 (m, 1H), 4.44–4.22 (bs, 1H, NCH), 3.94 (d, *J* = 14.0 Hz, 1H, SCH₂), 3.84 (d, *J* = 14.0 Hz, 1H, SCH₂), 3.58 (bs, 1H, SCH), 2.47–2.32 (m, 2H), 1.65–1.53 (m, 3H), 1.38–1.24 (m, 2H), 1.22–1.14 (m, 1H), 0.93–0.87 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 147.9, 145.1, 137.0, 129.4, 129.0 (2C), 127.7 (2C), 127.3, 127.1 (2C), 124.6, 123.8, 68.7 (NCH), 59.2 (SCH), 56.6 (CH₂), 45.0, 40.2, 35.7 (SCH₂), 34.9, 30.4, 28.3.

12-(p-tolyl)-2,3,4,4a,6,11,12,12a-octahydro-1H-1,4-methanodibenzo[b,f][1,5]thiazocine (4o)

Following the general procedure B, starting from substrate **3o** (100 mg, 0.22 mmol), product **4o** (50 mg, 0.15 mmol, 69%) has been obtained as a colorless oil. TLC (heptane/AcOEt 90/10, Rf = 0.36).

¹H NMR (400 MHz, CDCl₃) δ 7.19 (d, *J* = 7.8 Hz, 2H), 7.15 (d, *J* = 7.8 Hz, 2H), 7.11 (dd, *J* = 7.2, 1.8 Hz, 1H), 7.06–6.93 (m, 2H), 6.51 (d, *J* = 7.5 Hz, 1H), 4.28 (d, *J* = 11.1 Hz, 1H, NCH), 3.93 (d, *J* = 14.0 Hz, 1H, SCH₂), 3.82 (d, *J* = 14.0 Hz, 1H, SCH₂), 3.56 (bs, 1H, SCH), 2.44–2.30 (m, 5H), 1.64–1.51 (m, 3H), 1.37–1.23 (m, 2H), 1.22–1.12 (m, 1H), 0.91–0.84 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 147.9, 142.0, 136.8, 136.7, 129.6 (2C), 129.4, 127.7 (2C), 127.2, 124.5, 123.8, 68.5 (NCH), 58.9 (SCH), 56.6 (CH₂), 45.0, 40.3, 35.7 (SCH₂), 34.9, 30.4, 28.3, 21.2. HRMS (ESI-Q-TOF) *m/z* calcd for C₂₂H₂₆NS [M + H]⁺: 336.1780, found: 336.1805.

12-(4-(trifluoromethyl)phenyl)-2,3,4,4a,6,11,12,12a-octahydro-1H-1,4-methanodibenzo[b,f][1,5]thiazocine (4p)

Following the general procedure B, starting from substrate **3p** (53 mg, 0.10 mmol), product **4p** (21 mg, 0.05 mmol, 53%, no epimerization) has been obtained as a white amorphous solid. TLC (heptane/AcOEt 95/05, Rf = 0.28). ¹H NMR (500 MHz, CDCl₃) δ 7.58 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.05 (dd, *J* = 7.1, 1.8 Hz, 1H), 6.98–6.90 (m, 2H), 6.40 (d, *J* = 7.5 Hz, 1H), 4.26 (d, *J* = 11.2 Hz, 1H, NCH), 3.86 (d, *J* = 14.1 Hz, 1H, SCH₂), 3.73 (d, *J* = 14.1 Hz, 1H, SCH₂), 3.53 (bs, 1H, SCH), 2.37–2.27 (m, 2H), 1.60–1.42 (m, 3H), 1.31–1.15 (m, 2H), 1.15–1.06 (m, 1H), 0.88–0.84 (m, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 149.0, 147.5, 137.5, 129.4, 129.4 (q, *J* = 32.2 Hz), 127.9 (2C), 127.7, 125.9 (q, *J* = 3.8 Hz, 2C), 124.8, 124.3, 124.2 (q, *J* = 27.2 Hz), 68.3 (NCH), 59.4 (SCH), 56.8 (CH₂), 45.1, 39.9, 36.0 (SCH₂), 34.8, 30.3, 28.3. ¹⁹F NMR (376 MHz, CDCl₃) δ 62.4. HRMS (ESI-Q-TOF) *m/z* calcd for C₂₂H₂₃F₃NS [M + H]⁺: 390.1498, found: 390.1499.

12-(3-(trifluoromethyl)phenyl)-2,3,4,4a,6,11,12,12a-octahydro-1H-1,4-methanodibenzo[b,f][1,5]thiazocine (4q)

Following the general procedure B, starting from substrate **3q** (100 mg, 0.19 mmol), product **4q** (40 mg, 0.10 mmol, 53%) has been obtained as a white amorphous solid. TLC (heptane/AcOEt 90/10, Rf = 0.46). ¹H NMR (400 MHz, CDCl₃) δ 7.63–7.46 (m, 4H), 7.13 (dd, *J* = 7.2, 1.9 Hz, 1H), 7.09–6.96 (m, 2H), 6.48 (dd, *J* = 7.4, 1.6 Hz, 1H), 4.33 (d, *J* = 11.1 Hz, 1H, NCH), 3.93 (d, *J* = 14.3 Hz, 1H, SCH₂), 3.82 (d, *J* = 14.3 Hz, 1H, SCH₂), 3.59 (bs, 1H, SCH), 2.44–2.34 (m, 2H), 1.71–1.51 (m, 3H), 1.41–1.25 (m, 2H), 1.23–1.13 (m, 1H), 1.00–0.91 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 147.5, 146.1, 137.3, 131.2 (q, *J* = 32.3 Hz), 130.8, 129.3 (2C), 127.9, 124.8, 124.3 (2C), 124.2 (q, *J* = 27.2 Hz), 124.0 (q, *J* = 3.8 Hz), 68.2 (NCH), 56.9 (SCH), 45.1, 39.9, 36.1 (SCH₂), 34.9, 30.2, 28.3. ¹⁹F NMR (376 MHz, CDCl₃) δ 62.4. HRMS (ESI-Q-TOF) *m/z* calcd for C₂₂H₂₃F₃NS [M + H]⁺: 390.1498 found: 390.1506.

12-(4-bromophenyl)-2,3,4,4a,6,11,12,12a-octahydro-1H-1,4-methanodibenzo[b,f][1,5]thiazocine (4r)

Following the general procedure B, starting from substrate **3r** (80 mg, 0.15 mmol), product **4r** (31 mg, 0.08 mmol, 51%) has been obtained as a colorless oil. TLC (heptane/AcOEt 90/10, Rf = 0.35). ¹H NMR (400 MHz, CDCl₃) δ 7.52 (d, *J* = 8.6 Hz, 2H), 7.17 (d, *J* = 7.9 Hz, 2H), 7.12 (dd, *J* = 7.3, 1.8 Hz, 1H), 7.09–6.95 (m, 2H), 6.50 (dd, *J* = 7.4, 1.5 Hz, 1H), 4.24 (d, *J* = 11.1 Hz, 1H, NCH), 3.92 (d, *J* = 14.0 Hz, 1H, SCH₂), 3.80 (d, *J* = 14.0 Hz, 1H, SCH₂), 3.58 (bs, 1H, SCH), 2.43–2.28 (m, 2H), 1.70–1.47 (m, 3H), 1.42–1.25 (m, 2H), 1.21–1.12 (m, 1H), 0.99–0.89 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 147.7, 144.1, 137.1, 132.0 (2C), 129.4, 129.1, 127.8 (2C), 124.7, 124.1, 120.9, 68.1 (NCH), 59.3 (SCH), 56.8 (CH₂), 45.1, 40.0, 36.0 (SCH₂), 34.8, 30.3, 28.3. HRMS (ESI-Q-TOF) *m/z* calcd for C₂₁H₂₁BrNS [M + H]⁺: 398.0573, found: 398.0582.

Deposition Numbers 2042277 (for **4b**), 2056458 (for **4e**), 2042276 (for **4f**), and 2042275 (for **4n**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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Conflict of Interest

The authors declare no conflict of interest.

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