Tetrahedron 68 (2012) 9685–9693

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Pyridinium salts—versatile reagents for the regioselective synthesis of functionalized thiazocino[2,3-*b*]indoles by tandem dinucleophilic reactions of thiooxindoles

Mostafa Kiamehr [a,b], Firouz Matloubi Moghaddam [b,*], Pavel V. Gormay [a], Volodymyr Semeniuchenko [c], Alexander Villinger [a], Peter Langer [a,d], Viktor O. Iaroshenko [a,c,*]

[a] Institut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, 18059 Rostock, Germany
[b] Laboratory of Organic Synthesis and Natural Products, Department of Chemistry, Sharif University of Technology, PO Box 11155-9516, Tehran, Iran
[c] National Taras Shevchenko University, 62 Volodymyrska st., 01033 Kyiv-33, Ukraine
[d] Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Str. 29a, 18059 Rostock, Germany

ARTICLE INFO

Article history:
Received 7 June 2012
Received in revised form 5 September 2012
Accepted 11 September 2012
Available online 18 September 2012

Keywords:
Condensation
Heterocycles
Nucleophilic addition
Pyridines
Regioselectivity

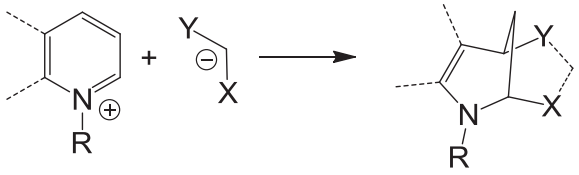
ABSTRACT

The reaction of thiooxindoles with various 2- and 3-substituted pyridinium salts afforded a variety of functionalized thiazocinoindoles. The products have been prepared in good to excellent yields by regioselective dinucleophilic C/S-cyclocondensation of thiooxindoles with pyridinium salts.

1. Introduction

Pyridinium salts are well known for their reactions with nucleophilic species with or without ring opening. They represent important building blocks[1,2] for the synthesis of various pharmacologically relevant tetrahydropyridine derivatives.[3,4] These substructures occur in various natural products and synthetic pharmaceuticals.[5,6] At the same time, heterocyclic systems containing an annulated pyridinium core, such as quinolinium and isoquinolinium salts, are of considerable importance as building blocks for the synthesis of various alkaloid frameworks.[7]

In recent years, our laboratory studied various cyclization reactions of dinucleophiles with pyridinium salts, e.g., the cyclization of 1,3-bis(silyl enol ethers), masked 1,3-dicarbonyl dianions, with quinolinium,[8] isoquinolinium,[9] quinazolinium,[10] and quinoxalinium[11] salts. Moghaddam and co-workers studied cyclization reactions of quinolinium[12] and isoquinolinium[13] salts with various other 1,3-dinucleophiles. In these reactions the pyridinium salt reacts as a 1,3-dielectrophile, which opens up possibilities of various [3+3] cycloadditions (Scheme 1). Reactions of this type offer routes to the bridged nitrogen-containing scaffolds, such as pyrroles and indoles, which are of pharmacological significance.



Scheme 1.

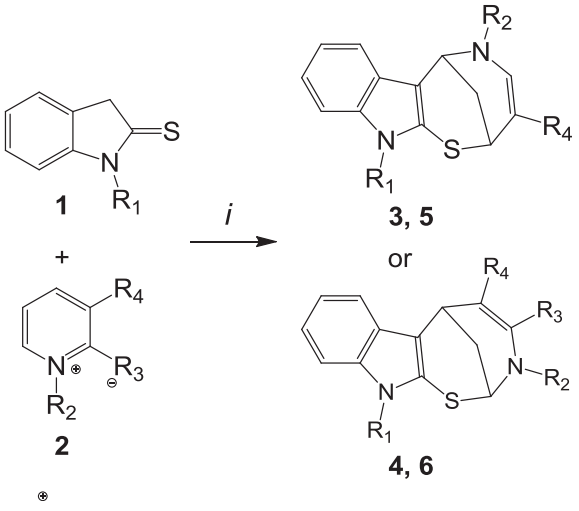
Herein, we report for the first time the formation of a bridged thiazocinoindole framework by reaction of thiooxindoles with substituted pyridinium salts (Scheme 2).

2. Results and discussion

At the beginning, we have investigated the optimal conditions for reactions of 3-acyl-pyridinium iodide and bromide with thiooxindoles. The optimization was carried out using the unsubstituted thiooxindole **1a** (R_1=H) and 3-(ethoxycarbonyl)-1-methylpyridin-1-ium iodide **2h** (R_2=Me, R_3=H, R_4=COOEt, X=I).

* Corresponding authors. Tel.: +49 381 4986410; fax: +49 381 49864112; e-mail addresses: viktor.iaroshenko@uni-rostock.de, iva108@googlemail.com (V.O. Iaroshenko).

0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2012.09.059



Scheme 2. Reagents and conditions: (i) conditions see Table 1.

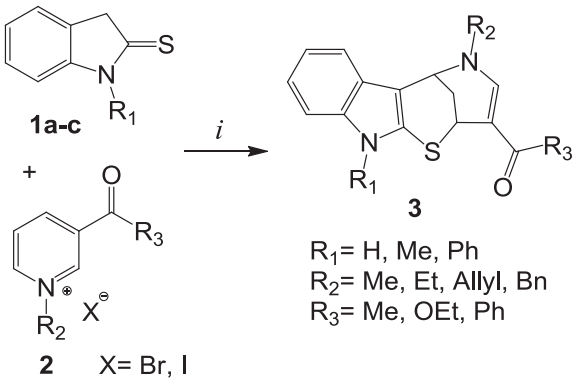
In all cases, we observed the formation of only one product of condensation, i.e., thiazocino[2,3-*b*]indole **3g** (Table 1, Scheme 3).

The effect of solvent, base nature and temperature on the reaction was studied to optimize the reaction conditions. Our investigation revealed that the base plays an important role. There is no reaction without base, and the yield is low in case of employment of a weak base, such as sodium bicarbonate. Organic bases like tertiary amines or pyridine are also unfavourable. The best yield was observed for potassium carbonate using acetonitrile as the solvent (reaction at room temperature) (Table 1).

Table 1
Optimization of the synthesis of **3g**[a]

Entry	Base	Solvent	Temp (°C)	Time (h)	Yield
1	No base	CH_3CN	20–80	16	0
2	$NaHCO_3$	CH_3CN	20	24	5
3	$NaHCO_3$	CH_3CN	80	8	18
4	K_2CO_3	CH_3CN	20	12	54
5	K_2CO_3	CH_3CN	20	24	84
6	K_2CO_3	CH_3CN	20	48	82
7	Na_2CO_3	CH_3CN	20	24	58
8	K_2CO_3	CH_3CN	80	8	25
9	Cs_2CO_3	CH_3CN	20	24	34
10	NEt_3	CH_3CN	20	24	16
11	Pyridine	CH_3CN	20	24	0
12	NaH	DMF	−5 to 20	24	0
13	AcOK	AcOH	20	24	0
14	K_2CO_3	CH_2Cl_2	20	24	8
15	K_2CO_3	Acetone	20	24	45
16	K_2CO_3	H_2O	20	24	0
17	No base	CH_3CN	20–80	16	0

[a] Yields of isolated products. Reaction of **1a** (R_1=H) with **2h** (R_2=Me, R_3=H, R_4=COOEt, X=I), Scheme 3.



Scheme 3. Tandem dinucleophilic reaction of thiooxindoles with 3-carbonylpyridinium salts. Reagents and conditions: (i) CH_3CN, K_2CO_3, 20 °C, 24 h.

To generalize this methodology, we investigated the scope and limitation of the reaction with a series of 3-acyl-pyridinium iodides and bromides and different thiooxindoles under the optimized reaction conditions (Scheme 3).

The reactions of thiooxindoles **1** and 3-carbonyl pyridinium salts **2** proceeded cleanly under mild conditions to give the corresponding polycyclic 2,5,6,11-tetrahydro-2,6-methano[1,5]thiazocino-[2,3-*b*]indoles **3a**–**r** in 56–99% yield (Table 2). All reactions proceeded with high regioselectivity. It can be noticed that reaction with *N*-substituted thiooxindoles offers higher yields of the desired products. The reason may be their inability to undergo a competing N-deprotonation.

Table 2
Synthesis of compounds **3**

Product	R_1	R_2	R_3	X	Yield[a] (%)
3a	H	Me	Me	I	69
3b	H	Allyl	Me	Br	56
3c	H	Bn	Me	Br	64
3d	H	Me	Ph	I	78
3e	H	Allyl	Ph	Br	80
3f	H	Bn	Ph	Br	56
3g	H	Me	OEt	I	84
3h	Me	Me	Me	I	98
3i	Me	Bn	Me	Br	84
3j	Me	Me	Ph	I	70
3k	Me	Et	Ph	Br	85
3l	Me	Bn	Ph	Br	76
3m	Me	Me	OEt	I	94
3n	Ph	Me	Me	I	97
3o	Ph	Et	Me	Br	94
3p	Ph	Allyl	Me	Br	99
3q	Ph	Allyl	Ph	Br	85
3r	Ph	Me	OEt	I	98

[a] Yields of isolated products.

It is worth to mention that no reaction is observed in the case of pyridinium salts, which do not contain any electron-withdrawing groups. In case of a 3-nitro-substituted pyridinium salt, no formation of thiazocinoindoles was detected; we speculate that a ring opening process occurred instead, however the reason was not specially investigated.

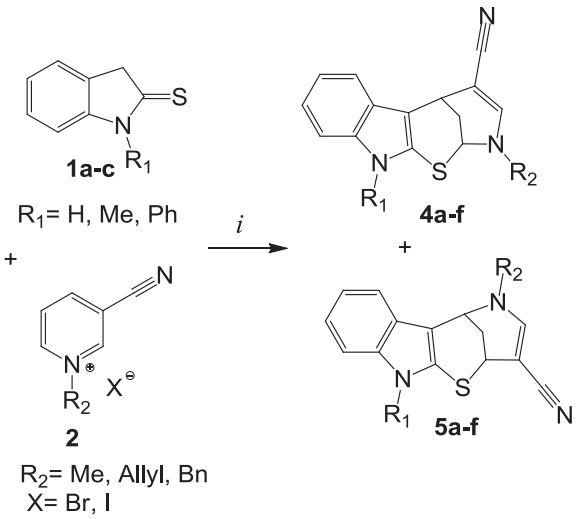
The reaction of 3-cyano-substituted pyridinium salts with thiooxindole resulted in the formation of mixtures of the regioisomeric thiazocinoindoles **4** and **5** (Scheme 4, Table 3). The structures of the products **4** and **5** were elucidated by ^{1}H NMR and ^{13}C NMR spectroscopy. The structures of compounds **4e** and **5e** were independently confirmed by X-ray crystal structure analysis (Figs. 3 and 4).[14]

The structures of products **3** were established by spectroscopic methods. The structures of **3g** and **3j** were independently confirmed by X-ray[14] crystallography (Figs. 1 and 2).

To demonstrate the scope of this reaction, the reaction of thiooxindoles **1** with different 2-, 3-, and 4-substituted pyridinium salts was investigated. The latter were prepared by simple alkylation of appropriate pyridines and could be used without additional purification.

The reaction of thiooxindoles **1** with 2-cyano-substituted pyridiniumsaltsaffordedtheisomericthiazocinoindoles**6a**–**e**(Scheme5) ingoodtoexcellentyieldsastheonlyproducts(Table4).

To explain the mechanism of the formation of products **3**–**6**, we proposed a mechanism as shown in Scheme 6. Pyridinium salts **2** can be attacked by nucleophiles at positions 2, 4 and 6. Due to the steric effect of the substituent located at carbon C-2, carbons C-4 and C-6 in the pyridinium salts they become more susceptible to attack by nucleophiles. According to our assumptions, a base-mediated dinucleophilic addition of the thiooxindole **1** and



Scheme 4. Tandem dinucleophilic reaction of thiooxindoles with 3-cyanopyridinium salts. Reagents and conditions: (i) CH_3CN, K_2CO_3, 20 °C, 24 h.

Table 3
Synthesis of compounds **4** and **5**

Products	R_1	R_2	X	Ratio **4**/**5**	Overall yield[a] (%)
4a/**5a**	H	Me	I	60:40	87
4b/**5b**	H	Bn	Br	86:14	87
4c/**5c**	Me	Allyl	Br	100:0	64
4d/**5d**	Me	Bn	Br	80:20	67
4e/**5e**	Ph	Me	I	65:35	85
4f/**5f**	Ph	Allyl	Br	73:27	88

[a] Yields of isolated products.

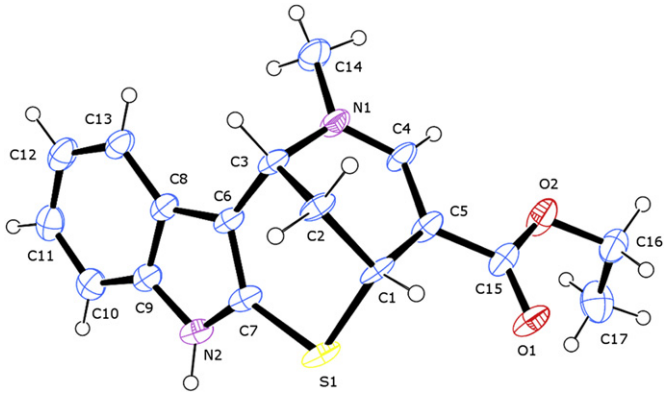


Fig. 1. ORTEP plot of structure **3g**.

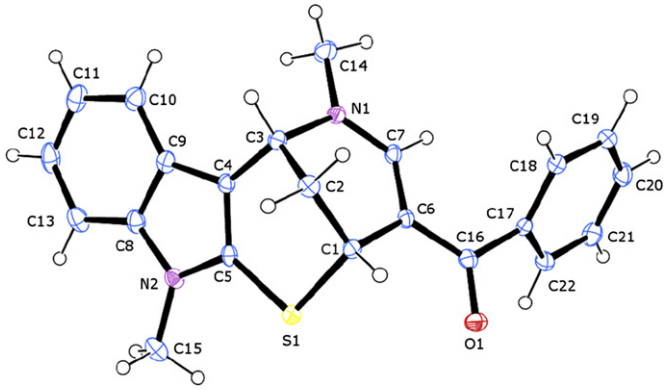


Fig. 2. ORTEP plot of structure **3j**.

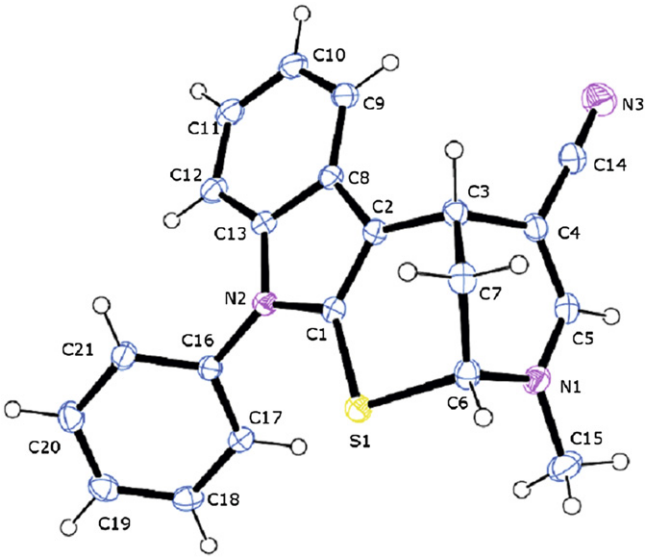


Fig. 3. ORTEP plot of structure **4e**.

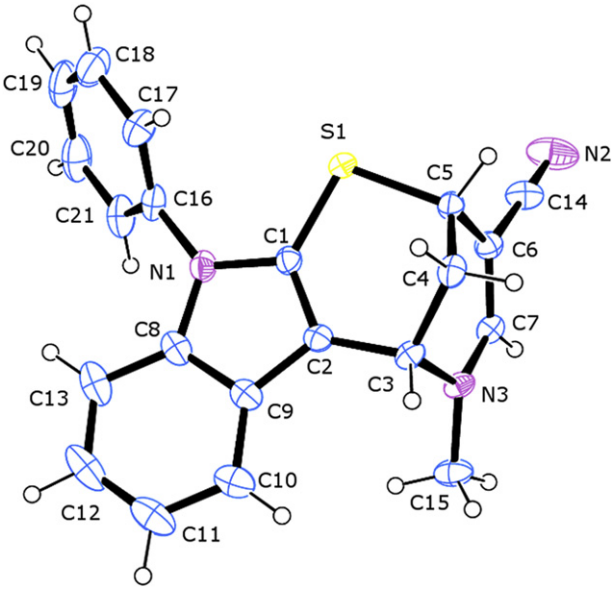
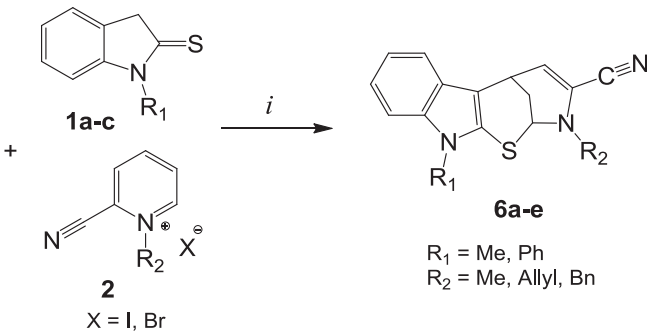


Fig. 4. ORTEP plot of structure **5e**.



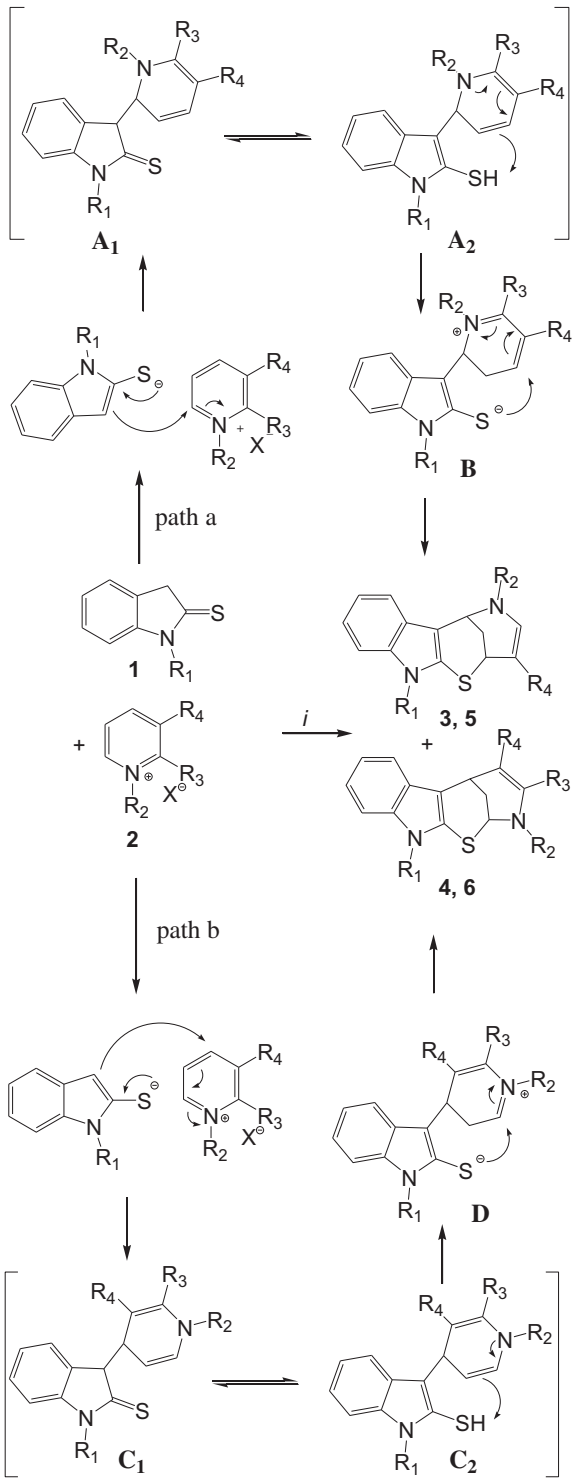
Scheme 5. Tandem dinucleophilic reaction of thiooxindoles with 2-cyanopyridinium salts. Reagents and conditions: (i) CH_3CN, K_2CO_3, 20 °C, 24 h.

pyridinium salts **2** to produce compounds **3** and **5** can proceed via intermediates **A** and **B** (path a). Initially, the thioxindole is deprotonated by base to yield a carbanion. Subsequently, its nucleophilic addition onto carbon C-6 of the pyridinium salt leads to the

Table 4
Synthesis of compounds **6**

Product	R_1	R_2	X	Yield[a] (%)
6a	Me	Me	I	65
6b	Me	Bn	Br	80
6c	Ph	Me	I	88
6d	Ph	Allyl	Br	92
6e	Ph	Bn	Br	78

[a] Yields of isolated products.



Scheme 6. A plausible mechanism for the formation of compounds **3**–**6**.

formation of intermediate **A**, which can exist in the thioamide-form $\mathbf{A_1}$ as well as in the thioenol-form $\mathbf{A_2}$. Intermolecular proton migration delivers the zwitterionic structure **B**; this is followed by a second nucleophile attack to give compounds **3** and **5**. The formation of the other isomer can be explained by attack of the thiooxindole anion to position C-4 of the pyridinium salt (path b). The subsequent protonation converts **C** to the next key intermediate **D**, which is then transformed to products **4** and **6**.

In the case of the presence of a moderate electron-withdrawing group (e.g., acetyl) located at position-3 in pyridinium salts, the difference between the reactivities of carbons C-6 and C-4 seems to be sufficient resulting in a good selectivity. In contrast, the selectivity is low for pyridinium salts containing a strong electron-withdrawing group, such as the cyano-group. For 2-substituted pyridinium salts it seems that the steric effects of the substituent located at the nitrogen atom plays an important role to direct the attack of the nucleophile to the sterically less hindered position 4.

3. Conclusions

In conclusion, we have reported a novel dinucleophilic cyclocondensation for the synthesis of various bridged thiazocinoindoles starting from thiooxindoles and pyridinium salts. The latter must carry an EWG as substituent, otherwise the reaction cannot proceed; the base (K_2CO_3) was found also to be crucial component. The reaction regioselectivity depends on substituent: 3-acyl group in pyridinium salt leads no only one regioisomer (attack of 4-C of pyridine ring, product **3**) while 3-CN group results in bad discrimination of 2-C and 4-C thus leading to the regioisomeric mixture of products **4** and **5**. 2-CN group directs the nucleophile to 4-C due to steric effect thus leading regiospecifically to products **6**.

4. Experimental part

4.1. General methods

Commercially available materials were purchased from *Sigma–Aldrich* and *ACROS* and were used without any additional purification. Analytical thin layer chromatography was performed on 0.20 mm 60 Å silica gel plates. Column chromatography was performed using 60 Å silica gel (60–200 mesh). Infrared spectra were recorded in an ATR apparatus. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, isobutane) or electrospray ionization (ESI). Melting points are uncorrected. ^{1}H and C NMR and DEPT spectra in $CDCl_3$ and DMSO-d_6 at room temperature; δ in parts per million relative to Me_4Si as internal standard, J in Hz.

4.2. General procedure for the synthesis of compounds 2

Alkyl bromide or iodide (0.2 mol) was added dropwise to the acetone solution (150–200 mL) of corresponding pyridine derivative (0.1 mol). The mixture was stirred under argon for 2–3 days (progress of alkylation was controlled by TLC). After completion the formed precipitate was filtered, washed with acetone and dried in vacuum at room temperature (heating caused decomposition). The obtained pyridinium salt was used without further purification or characterization.

4.3. General procedure for the synthesis of compounds 3–6

In the 25 mL Schlenk flask, under argon flow, 0.75 mmol of indolin-2-thiones **1**, 0.75 mmol of appropriate pyridinium salts **2** and 0.75 mmol (104 mg) of K_2CO_3 were loaded. The flask was covered with septum stopper and 7 mL of absolute CH_3CN was added by syringe; reaction mixture stirred at room temperature for

24 h. Then the solvent was removed under reduced pressure and the crude material was subjected to column chromatography.

*4.3.1. 1-(5-Methyl-2,5,6,11-tetrahydro-2,6-methano[1,5]thiazocino [2,3-b]indol-3-yl)ethanone (**3a**).* Pale white solid, mp 234–236 °C, yield: 69% (147 mg). ^{1}H NMR (300 MHz, DMSO-d_6) δ=2.05 (s, 3H, COMe), 2.17–2.35 (m, 2H, CH_2), 3.31 (s, 3H, NMe), 4.49 (s, 1H, CH), 4.82 (s, 1H, CH), 7.00–7.04 (m, 2H, H_{Ar}), 7.21–7.24 (m, 1H, H_{Ar}), 7.60–7.63 (m, 1H, H_{Ar}), 7.65 (s, 1H, CH), 11.22 (s, 1H, NH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ=23.6 (CH_3), 28.1 (CH_2), 30.8 (CH), 41.9 (CH), 47.2 (NCH_3), 109.6 (C), 110.0 (CH), 111.2 (C), 115.8, 119.1, 119.9 (CH), 127.6, 129.8, 135.9 (C), 149.2 (CH), 189.6 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$=3167 (w), 1614 (w), 1557 (s), 1488 (w), 1436 (m), 1384 (m), 1331 (s), 1195 (m), 1165 (s), 1093 (m), 1008 (m), 742 (s), 664 (s), 569 (s). MS (GC, 70 eV): *m*/*z* (%)=284 (M^+, 100), 283 (26), 251 (21), 241 (23), 161 (76), 136 (21). HRMS (ESI): calcd for $C_{16}H_{17}N_2OS$ (M+H) 285.10561, found 285.10614.

*4.3.2. 1-(5-Allyl-2,5,6,11-tetrahydro-2,6-methano[1,5]thiazocino[2,3-b]indol-3-yl)ethanone (**3b**).* Pale yellow solid, mp 189–191 °C, yield: 56% (130 mg). ^{1}H NMR (300 MHz, DMSO-d_6) δ=2.04 (s, 3H, COMe), 2.17–2.31 (m, 2H, CHCH_2CH), 4.18–4.20 (m, 2H, NCH_2CHCH_2), 4.49 (m, 1H, CH), 4.83 (s, 1H, CH), 5.31–5.46 (m, 2H, NCH_2CHCH_2), 5.94–6.07 (m, 1H, NCH_2CHCH_2), 6.97–7.06 (m, 2H, H_{Ar}), 7.20–7.23 (m, 1H, H_{Ar}), 7.51–7.54 (m, 1H, H_{Ar}), 7.66 (s, 1H, CH), 11.20 (s, 1H, NH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ=23.4 (CH_3), 28.2 (CH_2), 30.7 (CH), 45.8 (CH), 57.0 (NCH_2), 109.1 (C), 110.1 (CH), 112.0 (C), 114.8 (CH), 118.4 (CH_2), 119.0, 119.7 (CH), 127.0, 130.0 (C), 132.8 (CH), 136.0 (C), 147.2 (CH), 190.8 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$=3272 (w), 1644 (w), 1611 (w), 1568 (s), 1557 (s), 1428 (m), 1393 (m), 1338 (s), 1192 (m), 1010 (m), 923 (m), 735 (s), 651 (m), 536 (m). MS (GC, 70 eV): *m*/*z* (%)=310 (M^+, 100), 277 (20), 269 (85), 267 (17), 162 (23), 161 (35). HRMS (ESI): calcd for $C_{18}H_{18}N_2OS$ (M^+) 310.11344, found 310.113214.

*4.3.3. 1-(5-Benzyl-2,5,6,11-tetrahydro-2,6-methano[1,5]thiazocino [2,3-b]indol-3-yl)ethanone (**3c**).* White solid, mp 225–227 °C, yield: 64% (173 mg). ^{1}H NMR (300 MHz, DMSO-d_6) δ=2.11 (s, 3H, COMe), 2.19 (m, 2H, CHCH_2CH), 4.52 (s, 1H, CH), 4.73–4.88 (m, 3H, NCH_2, CH), 7.01–7.10 (m, 2H, H_{Ar}), 7.24–7.27 (m, 1H, H_{Ar}), 7.40–7.57 (m, 6H, H_{Ar}), 7.91 (s, 1H, CH), 11.27 (s, 1H, NH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ=23.8 (CH_3), 28.5 (CH_2), 30.9 (CH), 45.1 (CH), 57.6 (NCH_2), 109.5 (C), 110.1 (CH), 111.7 (C), 115.6, 119.3, 120.0 (CH), 127.1 (C), 127.4, 127.7, 128.9 (CH), 129.9, 136.0, 137.2 (C), 148.9 (CH), 190.1 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$=3306 (w), 1614 (w), 1580 (s), 1575 (s), 1428 (m), 1343 (s), 1192 (m), 1024 (m), 730 (s), 695 (m), 643 (m). MS (GC, 70 eV): *m*/*z* (%)=360 (M^+, 80), 327 (15), 270 (17), 269 (100), 161 (17), 149 (16), 91 (53), 69 (26), 57 (17), 44 (41), 43 (39), 40 (23). HRMS (ESI): calcd for $C_{22}H_{20}N_2OS$ (M^+) 360.12909, found 360.128886.

*4.3.4. (5-Methyl-2,5,6,11-tetrahydro-2,6-methano[1,5]thiazocino [2,3-b]indol-3-yl)(phenyl)methanone (**3d**).* Yellow solid, mp 217–219 °C, yield: 78% (202 mg). ^{1}H NMR (300 MHz, DMSO-d_6) δ=2.24–2.45 (m, 2H, CH_2), 3.24 (s, 3H, NMe), 4.70 (m, 1H, CH), 4.90 (s, 1H, CH), 6.99–7.05 (m, 2H, H_{Ar}), 7.17 (s, 1H, CH), 7.23–7.25 (m, 1H, H_{Ar}), 7.33–7.44 (m, 5H, H_{Ar}), 7.60–7.63 (m, 1H, H_{Ar}), 11.29 (s, 1H, NH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ=28.0 (CH_2), 31.1 (CH), 42.3 (CH), 47.7 (NCH_3), 109.5 (C), 110.1 (CH), 110.5 (C), 115.8, 119.2, 120.0 (CH), 127.5 (C), 127.8, 128.0, 129.3 (CH), 129.7, 136.0, 140.4 (C), 151.7 (CH), 189.1 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$=3258 (w), 1610 (w), 1578 (w), 1544 (s), 1538 (s), 1440 (m), 1384 (m), 1328 (m), 1201 (m), 1124 (m), 1027 (m), 936 (m), 737 (s), 704 (m), 639 (m). MS (GC, 70 eV): *m*/*z* (%)=346 (M^+, 100), 345 (20), 313 (15), 241 (14), 198 (18), 186 (15), 161 (27), 105 (41), 77 (18). HRMS (ESI): calcd for $C_{21}H_{18}N_2OS$ (M^+) 346.11344, found 346.113238.

*4.3.5. (5-Allyl-2,5,6,11-tetrahydro-2,6-methano[1,5]thiazocino[2,3-b]indol-3-yl)(phenyl)methanone (**3e**).* Pale brown solid, mp 207–209 °C, yield: 80% (223 mg). ^{1}H NMR (300 MHz, DMSO-d_6) δ=2.17–2.42 (m, 2H, CHCH_2CH), 4.07–4.24 (m, 2H, NCH_2CHCH_2), 4.73 (s, 1H, CH), 4.93 (s, 1H, CH), 5.23–5.36 (m, 2H, NCH_2CHCH_2), 5.84–5.96 (m, 1H, NCH_2CHCH_2), 7.00–7.07 (m, 2H, H_{Ar}), 7.23–7.26 (m, 2H, H_{Ar}, CH), 7.32–7.44 (m, 5H, H_{Ar}), 7.56–7.58 (m, 1H, H_{Ar}), 11.29 (s, 1H, NH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ=28.4 (CH_2), 31.3 (CH), 46.2 (CH), 56.7 (NCH_2), 109.6 (C), 110.2 (CH), 110.9 (C), 115.8 (CH), 118.2 (CH_2), 119.2, 120.0 (CH), 127.2 (C), 127.9, 128.0, 129.5 (CH), 129.8 (C), 133.9 (CH), 136.0, 140.3 (C), 150.7 (CH), 189.4 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$=3140 (w), 1643 (w), 1600 (w), 1578 (m), 1556 (s), 1549 (s), 1435 (m), 1394 (m), 1345 (m), 1216 (m), 1202 (m), 1024 (m), 926 (m), 740 (s), 7001 (s), 643 (m). MS (GC, 70 eV): *m*/*z* (%)=372 (M^+, 100), 331 (82), 224 (15), 161 (11), 105 (70), 77 (29). HRMS (ESI): calcd for $C_{23}H_{20}N_2OS$ (M^+) 372.12909, found 372.128832.

*4.3.6. (5-Benzyl-2,5,6,11-tetrahydro-2,6-methano[1,5]thiazocino [2,3-b]indol-3-yl)(phenyl)methanone (**3f**).* Pale yellow solid, mp 211–213 °C, yield: 56% (177 mg). ^{1}H NMR (300 MHz, DMSO-d_6) δ=2.23–2.35 (m, 2H, CHCH_2CH), 4.72–4.74 (m, 3H, NCH_2, CH), 4.84 (s, 1H, CH), 7.00–7.25 (m, 2H, H_{Ar}), 7.27–7.46 (m, 12H, H_{Ar}, CH), 7.53–7.56 (m, 1H, H_{Ar}), 11.31 (s, 1H, NH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ=28.4 (CH_2), 31.3 (CH), 46.2 (CH), 57.8 (NCH_2), 109.4 (C), 110.2 (CH), 110.9 (C), 115.7, 119.3, 120.1 (CH), 127.3 (C), 127.6, 127.7, 127.8, 127.9, 128.8, 129.5 (CH), 129.9, 136.1, 136.7, 140.2 (C), 151.1 (CH), 189.5 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$=3241 (w), 1602 (w), 1577 (w), 1538 (s), 1438 (m), 1386 (m), 1350 (m), 1340 (s), 1234 (m), 1197 (s), 1109 (m), 1020 (m), 887 (m), 739 (s), 698 (s), 662 (m). MS (GC, 70 eV): *m*/*z* (%)=422 (M^+, 44), 331 (61), 183 (23), 149 (23), 105 (84), 91 (100), 77 (40). HRMS (ESI): calcd for $C_{27}H_{23}N_2OS$ (M+H) 423.15256, found 423.15244.

*4.3.7. Ethyl 5-methyl-2,5,6,11-tetrahydro-2,6-methano[1,5]thiazocino[2,3-b]indole-3-carboxylate (**3g**).* Pale yellow solid, mp 200–202 °C, yield: 84% (198 mg). ^{1}H NMR (300 MHz, DMSO-d_6) δ=1.18 (t, 3H, J=7.2 Hz, OCH_2CH_3), 2.23–2.39 (m, 2H, CHCH_2CH), 3.14 (s, 3H, NMe), 4.04–4.16 (m, 2H, OCH_2CH_3), 4.43–4.44 (m, 1H, CH), 4.55 (s, 1H, CH), 6.96–7.03 (m, 2H, H_{Ar}), 7.13–7.18 (m, 1H, H_{Ar}), 7.32 (s, 1H, CH), 7.40–7.43 (m, 1H, H_{Ar}), 8.14 (s, 1H, NH). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ=14.7 (CH_3), 28.9 (CH_2), 33.5 (CH), 42.6 (CH), 48.1 (NCH_3), 59.3 (OCH_2), 99.2 (C), 110.3 (CH), 110.5 (C), 115.7, 120.0, 120.8 (CH), 128.0, 130.4, 136.2 (C), 147.2 (CH), 167.1 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$=3271 (m), 2929 (w), 1651 (s), 1598 (s), 1451 (m), 1318 (m), 1284 (m), 1162 (s), 1070 (s), 1027 (s), 928 (m), 771 (m), 735 (s), 671 (m), 642 (m). MS (GC, 70 eV): *m*/*z* (%)=314 (M^+, 100), 313 (21), 285 (29), 267 (17), 241 (32), 235 (23), 207 (27), 186 (25), 166 (23), 161 (74). HRMS (ESI): calcd for $C_{17}H_{19}N_2O_2S$ (M+H) 315.11618, found 315.11681.

*4.3.8. 1-(5,11-Dimethyl-2,5,6,11-tetrahydro-2,6-methano[1,5]thiazocino[2,3-b]indol-3-yl)ethanone (**3h**).* Pale yellow solid, mp 174–176 °C, yield: 98% (219 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ=2.14 (s, 3H, COMe), 2.28–2.43 (m, 2H, CH_2), 3.30 (s, 3H, NMe), 3.57 (s, 3H, NMe), 4.68–4.70 (m, 2H, 2xCH), 7.08–7.22 (m, 3H, H_{Ar}), 7.28 (s, 1H, CH), 7.50–7.53 (m, 1H, H_{Ar}). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=23.8 (CH_3), 28.3 (CH_2), 30.5 (NCH_3), 31.3 (CH), 42.9 (CH), 48.6 (NCH_3), 108.5 (CH), 108.6, 112.7 (C), 115.6, 119.8, 120.3 (CH), 127.5, 133.6, 137.1 (C), 148.9 (CH), 191.4 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$=1613 (w), 1564 (s), 1460 (m), 1329 (s), 1170 (m), 1047 (m), 947 (m), 749 (s), 627 (m), 566 (m). MS (GC, 70 eV): *m*/*z* (%)=298 (M^+, 98), 297 (18), 265 (22), 255 (22), 224 (13), 200 (17), 175 (100), 136 (27). HRMS (ESI): calcd for $C_{17}H_{18}N_2OS$ (M^+) 298.11344, found 298.113405.

*4.3.9. 1-(5-Benzyl-11-methyl-2,5,6,11-tetrahydro-2,6-methano [1,5]thiazocino[2,3-b]indol-3-yl)ethanone (**3i**).* Yellow solid, mp 97–99 °C, yield: 84% (236 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ=2.15 (s, 3H, COMe), 2.31–2.34 (m, 2H, CHCH_2CH), 3.58 (s, 3H, NMe), 4.52 (d, 1H, J=15.0 Hz, NCH_2), 4.74 (m, 2H, 2xCH), 4.85 (d, 1H,

J=15.0 Hz, NCH_2), 7.12–7.23 (m, 3H, H_{Ar}), 7.38–7.50 (m, 7H, H_{Ar}, CH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=23.9 (CH_3), 28.6 (CH_2), 30.4 (NCH_3), 31.4 (CH), 46.1 (CH), 59.0 (NCH_2), 108.5 (CH), 108.6, 113.0 (C), 115.5, 119.8, 120.3 (CH), 127.4 (C), 127.4, 128.3, 129.1 (CH), 133.7, 136.3, 137.1 (C), 148.6 (CH), 191.7 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$=1573 (s), 1464 (m), 1333 (s), 1188 (s), 1151 (m), 1046 (m), 1013 (m), 735 (s), 705 (m), 670 (m). MS (GC, 70 eV): m/z (%)=374 (M^+, 57), 284 (16), 283 (100), 175 (25), 91 (37), 43 (16). HRMS (ESI): calcd for $C_{23}H_{22}N_2OS$ (M^+) 374.14474, found 374.144680.

*4.3.10. (5,11-Dimethyl-2,5,6,11-tetrahydro-2,6-methano[1,5]thiazocino[2,3-b]indol-3-yl)(phenyl)methanone (**3j**).* Pale yellow solid, mp 200–202 °C, yield: 70% (190 mg). ^1H NMR (300 MHz, $CDCl_3$) δ=2.36–2.53 (m, 2H, CH_2), 3.23 (s, 3H, NMe), 3.61 (s, 3H, NMe), 4.73–4.74 (m, 1H, CH), 4.90–4.92 (m, 1H, CH), 7.06 (s, 1H, CH), 7.11–7.16 (m, 2H, H_{Ar}), 7.21–7.25 (m, 1H, H_{Ar}), 7.31–7.42 (m, 6H, H_{Ar}). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=28.2 (CH_2), 30.5 (NCH_3), 31.4 (CH), 42.9 (CH), 48.9 (NCH_3), 108.4 (C), 108.5 (CH), 112.0 (C), 115.5, 119.8, 120.3 (CH), 127.5 (C), 127.9, 128.3, 129.5 (CH), 133.8, 137.1, 140.4 (C), 152.3 (CH), 191.2 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$=1608 (w), 1599 (w), 1576 (m), 1548 (s), 1463 (m), 1411 (m), 1379 (m), 1328 (s), 1206 (m), 1121 (m), 1037 (m), 946 (m), 739 (s), 702 (m), 662 (m), 572 (m). MS (GC, 70 eV): m/z (%)=360 (M^+, 98), 327 (16), 255 (16), 198 (26), 175 (100), 105 (41), 77 (26). HRMS (ESI): calcd for $C_{22}H_{20}N_2OS$ (M^+) 360.12909, found 360.128978.

*4.3.11. (5-Athyl-11-methyl-2,5,6,11-tetrahydro-2,6-methano[1,5]thiazocino[2,3-b]indol-3-yl)(phenyl)methanone (**3k**).* Yellow solid, mp 167–169 °C, yield: 85% (238 mg). ^1H NMR (300 MHz, $CDCl_3$) δ=1.30 (t, 3H, J=7.1 Hz, NCH_2CH_3), 2.41 (t, 2H, J=3.2 Hz, $CHCH_2CH$), 3.23–3.35 (m, 1H, NCH_2CH_3), 3.61 (s, 3H, NMe), 3.65–3.76 (m, 1H, NCH_2CH_3), 4.88 (m, 1H, CH), 4.93–4.95 (m, 1H, CH), 7.11–7.16 (m, 3H, H_{Ar}, CH), 7.22–7.25 (m, 1H, H_{Ar}), 7.31–7.43 (m, 6H, H_{Ar}). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=14.4 (CH_3), 28.8 (CH_2), 30.5 (NCH_3), 31.8 (CH), 46.8 (CH), 49.8 (NCH_2), 108.5 (CH), 108.7, 111.8 (C), 115.4, 119.8, 120.3 (CH), 127.2 (C), 127.9, 128.3, 129.5 (CH), 133.9, 137.1, 140.5 (C), 150.9 (CH), 191.2 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$=1598 (w), 1575 (w), 1546 (s), 1463 (m), 1440 (m), 1381 (m), 1329 (m), 1201 (m), 1123 (s), 1036 (m), 752 (m), 735 (s), 701 (m), 660 (m). MS (GC, 70 eV): m/z (%)=374 (M^+, 100), 341 (23), 322 (51), 321 (22), 269 (15), 212 (35), 175 (79), 163 (24), 105 (38), 77 (23). HRMS (ESI): calcd for $C_{23}H_{22}N_2OS$ (M^+) 374.14474, found 374.144616.

*4.3.12. (5-Benzyl-11-methyl-2,5,6,11-tetrahydro-2,6-methano[1,5]thiazocino[2,3-b]indol-3-yl)(phenyl)methanone (**3l**).* Light brown solid, mp 180–182 °C, yield: 76% (249 mg). ^1H NMR (300 MHz, $CDCl_3$) δ=2.24–2.37 (m, 2H, $CHCH_2CH$), 3.53 (s, 3H, NMe), 4.30 (d, 1H, J=15.5 Hz, NCH_2), 4.68–4.74 (m, 2H, NCH_2, CH), 4.87 (m, 1H, CH), 7.02–7.35 (m, 15H, H_{Ar}, CH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=28.6 (CH_2), 30.5 (NCH_3), 31.7 (CH), 46.4 (CH), 59.1 (NCH_2), 108.5 (C), 108.5 (CH), 112.3 (C), 115.4, 119.8, 120.3, 127.3 (CH), 127.4 (C), 127.9, 128.3, 128.4, 129.2, 129.7 (CH), 133.9, 136.0, 137.1, 140.3 (C), 152.1 (CH), 191.4 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$=1609 (w), 1580 (m), 1563 (s), 1556 (s), 1464 (m), 1435 (m), 1352 (m), 1334 (s), 1195 (m), 1106 (m), 1025 (m), 733 (s), 695 (s), 654 (m). MS (GC, 70 eV): m/z (%)=436 (M^+, 64), 346 (20), 345 (100), 322 (65), 321 (28), 290 (16), 275 (19), 274 (17), 183 (18), 175 (17), 163 (28), 105 (49), 91 (35), 77 (27). HRMS (ESI): calcd for $C_{28}H_{24}N_2OS$ (M^+) 436.16039, found 436.160388.

*4.3.13. Ethyl 5,11-dimethyl-2,5,6,11-tetrahydro-2,6-methano[1,5]thiazocino[2,3-b]indole-3-carboxylate (**3m**).* Yellow solid, mp 86–88 °C, yield: 94% (231 mg). ^1H NMR (300 MHz, $CDCl_3$) δ=1.29 (t, 3H, J=7.1 Hz, OCH_2CH_3), 2.30–2.49 (m, 2H, $CHCH_2CH$), 3.23 (s, 3H, NMe), 3.58 (s, 3H, NMe), 4.15–4.26 (m, 2H, OCH_2CH_3), 4.58–4.60 (m, 1H, CH), 4.65 (s, 1H, CH), 7.08–7.21(m, 3H, H_{Ar}), 7.41 (s, 1H, CH), 7.49–7.54 (m, 1H, H_{Ar}). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=14.7 (CH_3), 28.7 (CH_2), 30.5 (NCH_3), 33.4 (CH), 42.4 (CH), 48.2 (NCH_3), 59.2 (OCH_2), 99.2 (C), 108.3 (CH), 108.9 (C), 115.7, 119.7, 120.2 (CH), 127.6, 133.2, 137.1 (C), 147.1 (CH), 166.9 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$=2916 (w), 1672 (m), 1667 (m), 1599 (s), 1463 (m), 1315 (m), 1281 (m), 1241 (m), 1155 (s), 1068 (s), 1049 (s), 1011 (m), 770 (m), 736 (s), 704 (m), 651 (m). MS (GC, 70 eV): m/z (%)=328 (M^+, 100), 299 (28), 281 (24), 255 (35), 254 (22), 249 (16), 224 (16), 221 (27), 200 (46), 187 (20), 175 (80), 166 (27). HRMS (ESI): calcd for $C_{18}H_{20}N_2O_2S$ (M^+) 328.12400, found 328.123997.

*4.3.14. 1-(5-Methyl-11-phenyl-2,5,6,11-tetrahydro-2,6-methano[1,5]thiazocino[2,3-b]indol-3-yl)ethanone (**3n**).* Grey solid, mp 127–129 °C, yield: 97% (262 mg). ^1H NMR (300 MHz, $CDCl_3$) δ=2.07 (s, 3H, COMe), 2.27–2.40 (m, 2H, CH_2), 3.32 (s, 3H, NMe), 4.57–4.59 (m, 1H, CH), 4.70–4.71 (m, 1H, CH), 6.99–7.21 (m, 4H, H_{Ar}), 7.31 (s, 1H, CH), 7.32–7.54 (m, 5H, H_{Ar}). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=23.8 (CH_3), 28.2 (CH_2), 31.1 (CH), 43.1 (CH), 48.6 (NCH_3), 109.7 (CH), 110.2, 112.8 (C), 115.6 (CH), 117.8 (C), 1120.5, 120.9, 127.1, 128.0, 129.4 (CH), 134.0, 136.9, 137.5 (C), 148.6 (CH), 191.4 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$=1574 (s), 1568 (s), 1558 (s), 1497 (m), 1446 (m), 1327 (s), 1320 (s), 1166 (s), 1088 (m), 1024 (m), 739 (s), 695 (s), 670 (m), 595 (m). MS (GC, 70 eV): m/z (%)=360 (M^+, 100), 359 (18), 327 (32), 317 (23), 262 (19), 238 (18), 237 (91), 236 (87), 136 (32). HRMS (ESI): calcd for $C_{22}H_{20}N_2OS$ (M^+) 360.12909, found 360.128093.

*4.3.15. 1-(5-Ethyl-11-phenyl-2,5,6,11-tetrahydro-2,6-methano[1,5]thiazocino[2,3-b]indol-3-yl)ethanone (**3o**).* Pale grey solid, mp 188–190 °C, yield: 94% (264 mg). ^1H NMR (300 MHz, $CDCl_3$) δ=1.43 (t, 3H, J=7.5 Hz, CH_2CH_3), 2.13 (s, 3H, COMe), 2.29–2.42 (m, 2H, $CHCH_2CH$), 3.40–3.52 (m, 1H, CH_2CH_3), 3.76–3.88 (m, 1H, CH_2CH_3), 4.64–4.65 (m, 1H, CH), 4.89 (s, 1H, CH), 7.03–7.18 (m, 3H, H_{Ar}), 7.36–7.54 (m, 7H, H_{Ar}, CH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=14.6 (CH_3), 23.9 (CH_3), 28.7 (CH_2), 31.6 (CH), 46.5 (CH), 49.9 (NCH_2), 109.8 (CH), 110.6, 112.6 (C), 115.5, 120.5, 120.9, 127.1 (CH), 127.8 (C), 128.0, 129.4 (CH), 134.1, 136.9, 137.5 (C), 147.2 (CH), 191.4 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$=1594 (w), 1565 (s), 1498 (m), 1448 (m), 1336 (s), 1318 (m), 1160 (s), 1013 (m), 746 (s), 696 (s), 671 (m), 615 (m). MS (GC, 70 eV): m/z (%)=374 (M^+, 100), 345 (25), 341 (36), 331 (23), 262 (18), 237 (87), 236 (72), 150 (33). HRMS (ESI): calcd for $C_{23}H_{22}N_2OS$ (M^+) 374.14474, found 374.144467.

*4.3.16. 1-(5-Allyl-11-phenyl-2,5,6,11-tetrahydro-2,6-methano[1,5]thiazocino[2,3-b]indol-3-yl)ethanone (**3p**).* Grey solid, mp 122–124 °C, yield: 99% (287 mg). ^1H NMR (300 MHz, $CDCl_3$) δ=2.13 (s, 3H, COMe), 2.36–2.39 (m, 2H, $CHCH_2CH$), 3.98–4.05 (m, 1H, NCH_2CHCH_2), 4.35 (dd, 1H, J=15, 6 Hz, NCH_2CHCH_2), 4.64–4.66 (m, 1H, CH), 4.87–4.88 (m, 1H, CH), 5.40–5.50 (m, 2H, NCH_2CHCH_2), 5.91–6.00 (m, 1H, NCH_2CHCH_2), 7.04–7.18 (m, 3H, H_{Ar}), 7.36–7.55 (m, 7H, H_{Ar}, CH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=23.9 (CH_3), 28.5 (CH_2), 31.3 (CH), 46.5 (CH), 57.7 (NCH_2), 109.7 (CH), 110.4, 113.1 (C), 115.6 (CH), 119.1 (CH_2), 120.5, 120.9, 127.1 (CH), 127.7 (C), 128.0, 129.3, 129.4, 133.2 (CH), 134.1, 136.9, 137.5 (C), 147.7 (CH), 191.6 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$=1574 (s), 1568 (s), 1557 (s), 1497 (s), 1446 (m), 1338 (m), 1191 (m), 1150 (m), 1015 (m), 912 (m), 738 (s), 695 (s), 670 (m). MS (GC, 70 eV): m/z (%)=386 (M^+, 75), 353 (19), 346 (24), 345 (100), 237 (25), 236 (29), 162 (20). HRMS (ESI): calcd for $C_{24}H_{22}N_2OS$ (M^+) 386.14474, found 386.144703.

*4.3.17. (5-Allyl-11-phenyl-2,5,6,11-tetrahydro-2,6-methano[1,5]thiazocino[2,3-b]indol-3-yl)(phenyl)methanone (**3q**).* Yellow solid, mp 93–95 °C, yield: 85% (286 mg). ^1H NMR (300 MHz, $CDCl_3$) δ=2.45–2.47 (m, 2H, $CHCH_2CH$), 3.85–3.92 (m, 1H, NCH_2CHCH_2),

4.28–4.35 (dd, 1H, *J*=15.6, 7.0 Hz, NC*H*$_2$CHCH$_2$), 4.88–4.93 (m, 2H, 2×CH), 5.36–5.45 (m, 2H, NCH$_2$CHC*H*$_2$), 5.89–5.91 (m, 1H, NCH$_2$*C*HCH$_2$), 7.07–7.22 (m, 4H, H$_{Ar}$, CH), 7.31–7.57 (m, 11H, H$_{Ar}$). ^{13}C NMR (62.9 MHz, CDCl$_3$): δ=28.4 (CH$_2$), 31.5 (CH), 46.7 (CH), 57.8 (NCH$_2$), 109.8 (CH), 110.3, 112.5 (C), 115.6 (CH), 119.1 (CH$_2$), 120.6, 121.0, 127.1 (CH), 127.8 (C), 127.9, 128.1, 128.3, 129.5, 129.7, 133.0 (CH), 134.2, 136.9, 137.6, 140.4 (C), 151.4 (CH), 191.4 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$=1595 (w), 1580 (s), 1562 (s), 1556 (s), 1498 (m), 1447 (m), 1340 (m), 1219 (m), 1201 (s), 1020 (m), 735 (s), 697 (s), 648 (m). MS (GC, 70 eV): *m*/*z* (%)=448 (M$^+$, 73), 415 (19), 408 (25), 407 (100), 262 (12), 237 (19), 236 (20), 225 (46), 224 (70), 183 (18), 105 (53), 77 (29). HRMS (ESI): calcd for C$_{29}$H$_{24}$N$_2$OS (M$^+$) 448.16039, found 448.160276.

*4.3.18. Ethyl 5,11-dimethyl-2,5,6,11-tetrahydro-2,6-methano[1,5]thiazocino[2,3-b]indole-3-carboxylate (**3r**).* Pale white solid, mp 178–180 °C, yield: 98% (287 mg). ^{1}H NMR (300 MHz, CDCl$_3$) δ=1.25 (t, 3H, *J*=7.1 Hz, OCH$_2$*CH*$_3$), 2.35–2.50 (m, 2H, CHC*H*$_2$CH), 3.30 (s, 3H, NMe), 4.16 (q, 2H, *J*=7.1 Hz, OC*H*$_2$CH$_3$), 4.52–4.53 (m, 1H, CH), 4.72 (m, 1H, CH), 7.04–7.17 (m, 3H, H$_{Ar}$), 7.38–7.59 (m, 7H, H$_{Ar}$, CH). ^{13}C NMR (62.9 MHz, CDCl$_3$): δ=14.6 (CH$_3$), 28.6 (CH$_2$), 33.2 (CH), 42.6 (CH), 48.3 (NCH$_3$), 59.2 (OCH$_2$), 99.5 (C), 109.6 (CH), 110.7 (C), 115.8, 120.5, 120.9, 127.2, 128.0 (CH), 128.1 (C), 129.4 (CH), 133.7, 137.1, 137.6 (C), 147.0 (CH), 166.9 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$=1664 (s), 1604 (s), 1497 (m), 1449 (m), 1379 (m), 1315 (m), 1284 (m), 1163 (s), 1124 (m), 1073 (s), 1022 (m), 754 (m), 743 (s), 698 (s), 659 (m). MS (GC, 70 eV): *m*/*z* (%)=390 (M$^+$, 100), 361 (21), 343 (17), 317 (23), 316 (17), 302 (13), 283 (23), 262 (38), 249 (16), 237 (37), 236 (48), 166 (31). HRMS (ESI): calcd for C$_{23}$H$_{22}$N$_2$O$_2$S (M$^+$) 390.13965, found 390.139663.

*4.3.19. 3-Methyl-2,3,6,11-tetrahydro-2,6-methano[1,3]thiazocino[8,7-b]indole-5-carbonitrile (**4a**).* Light brown solid, mp 202–204 °C, yield: 52% (105 mg). ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ=2.17–2.44 (m, 2H, CHC*H*$_2$CH), 3.02 (s, 3H, NMe), 3.91–3.93 (m, 1H, CH), 5.35 (m, 1H, SCHN), 7.00–7.05 (m, 2H, H$_{Ar}$), 7.16 (s, 1H, CH), 7.22–7.27 (m, 1H, H$_{Ar}$), 7.49–7.52 (m, 1H, H$_{Ar}$), 11.19 (s, 1H, NH). ^{13}C NMR (62.9 MHz, DMSO-*d*$_6$): δ=24.1 (CH), 28.2 (CH$_2$), 40.0 (NCH$_3$), 58.0 (CH), 80.2 (C), 110.1 (CH), 114.6 (C), 116.1, 118.9, 120.1 (CH), 122.1, 123.9, 126.3, 136.1 (C), 146.0 (CH). IR (ATR, cm^{-1}): $\tilde{\nu}$=3239 (m), 2911 (w), 2184 (s), 1731 (w), 1614 (s), 1451 (m), 1396 (m), 1338 (m), 1317 (m), 1229 (m), 1117 (m), 1085 (m), 1029 (m), 756 (m), 734 (s), 680 (m), 596 (m). MS (GC, 70 eV): *m*/*z* (%)=267 (M$^+$, 99), 266 (100), 234 (44), 211 (13), 186 (21), 161 (13), 119 (37), 117 (14). HRMS (ESI): calcd for C$_{15}$H$_{14}$N$_3$S (M+H) 268.09029, found 268.09068.

*4.3.20. 5-Methyl-2,5,6,11-tetrahydro-2,6-methano[1,5]thiazocino[2,3-b]indole-3-carbonitrile (**5a**).* Pale green solid, mp 198–200 °C, yield: 35% (70 mg). ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ=2.20–2.44 (m, 2H, CHC*H*$_2$CH), 3.18 (s, 3H, NMe), 4.35–4.36 (m, 1H, CH), 4.81 (m, 1H, CH), 7.00–7.06 (m, 2H, H$_{Ar}$), 7.21 (s, 1H, CH), 7.23–7.26 (m, 1H, H$_{Ar}$), 7.58–7.61 (m, 1H, H$_{Ar}$), 11.33 (s, 1H, NH). ^{13}C NMR (75.5 MHz, DMSO-*d*$_6$): δ=28.6 (CH$_2$), 34.8 (CH), 41.5 (NCH$_3$), 46.5 (CH), 77.5, 109.6 (C), 110.2, 116.2, 119.3, 120.3 (CH), 122.1, 127.5, 128.2, 136.1 (C), 148.9 (CH). IR (ATR, cm^{-1}): $\tilde{\nu}$=3272 (m), 2931 (w), 2185 (s), 1731 (w), 1609 (s), 1446 (s), 1427 (m), 1337 (m), 1310 (m), 1233 (m), 1118 (m), 1023 (m), 935 (m), 741 (s), 675 (m), 529 (m). MS (GC, 70 eV): *m*/*z* (%)=267 (M$^+$, 100), 266 (28), 252 (13), 234 (14), 186 (58), 161 (55), 117 (17). HRMS (ESI): calcd for C$_{15}$H$_{14}$N$_3$S (M+H) 268.09029, found 268.0899.

*4.3.21. 3-Benzyl-2,3,6,11-tetrahydro-2,6-methano[1,3]thiazocino[8,7-b]indole-5-carbonitrile (major) (**4b**).* Pale yellow solid, mp 181–183 °C, overall yield: 87% (224 mg) (**4b**/**5b**; 86:14). ^{1}H NMR (300 MHz, CDCl$_3$) δ=2.18–2.32 (m, 2H, CHC*H*$_2$CH), 3.91 (s, 1H, CH), 4.18–4.33 (m, 2H, NCH$_2$), 4.83 (s, 1H, SCHN), 6.75 (s, 1H, CH), 6.98–7.32 (m, 8H, H$_{Ar}$), 7.60 (d, *J*=7.8 Hz, 1H, H$_{Ar}$), 7.85 (s, 1H, NH). ^{13}C NMR (62.9 MHz, CDCl$_3$): δ=25.4 (CH), 28.8 (CH$_2$), 56.4 (CH), 57.1 (NCH$_2$), 82.9 (C), 110.1 (CH), 115.4 (C), 117.0, 120.4, 121.4 (CH), 121.7, 122.9, 126.7 (C), 128.0, 128.5, 129.2 (CH), 135.1, 136.4 (C), 145.1 (CH). IR (ATR, cm^{-1}): $\tilde{\nu}$=3271 (w), 2183 (s), 1613 (s), 1449 (m), 1415 (m), 1189 (m), 1108 (m), 1023 (m), 739 (s), 697 (m), 606 (m). MS (GC, 70 eV): *m*/*z* (%)=343 (M$^+$, 46), 342 (27), 252 (24), 161 (10), 149 (20), 104 (14), 91 (100). HRMS (ESI): calcd for C$_{21}$H$_{18}$N$_3$S (M+H) 344.12159, found 344.12111.

*4.3.22. 5-Benzyl-2,5,6,11-tetrahydro-2,6-methano[1,5]thiazocino[2,3-b]indole-3-carbonitrile (minor) (**5b**).* ^{1}H NMR (300 MHz, CDCl$_3$) δ=2.18–2.32 (m, 2H, CHC*H*$_2$CH), 4.09 (s, 1H, CH), 4.18–4.33 (m, 2H, NCH$_2$), 4.58 (s, 1H, SCHN), 6.82 (s, 1H, CH), 6.98–7.32 (m, 9H, H$_{Ar}$), 8.07 (s, 1H, NH).

*4.3.23. 3-Allyl-11-methyl-2,3,6,11-tetrahydro-2,6-methano[1,3]thiazocino[8,7-b]indole-5-carbonitrile (**4c**).* Pale yellow solid, mp 169–171 °C, yield: 64% (148 mg). ^{1}H NMR (300 MHz, CDCl$_3$) δ=2.31–2.47 (m, 2H, CHC*H*$_2$CH), 3.59 (s, 3H, NMe), 3.77–3.92 (m, 2H, NC*H*$_2$CHCH$_2$), 4.01–4.04 (m, 1H, CH), 5.13–5.15 (m, 1H, SCHN), 5.28–5.36 (m, 2H, NCH$_2$CHC*H*$_2$), 5.79–5.85 (m, 1H, NCH$_2$*C*HCH$_2$), 6.75 (s, 1H, CH), 7.12–7.21 (m, 3H, H$_{Ar}$), 7.67–7.70 (m, 1H, H$_{Ar}$). ^{13}C NMR (62.9 MHz, CDCl$_3$): δ=25.5 (CH), 28.7 (CH$_2$), 30.5 (NCH$_3$), 55.8 (NCH$_2$), 56.5 (CH), 83.2 (C), 108.1 (CH), 113.8 (C), 117.0 (CH), 119.8 (CH$_2$), 119.9, 120.8 (CH), 121.6, 125.8, 126.2 (C), 132.2 (CH), 137.2 (C), 144.6 (CH). IR (ATR, cm^{-1}): $\tilde{\nu}$=2910 (w), 2184 (s), 1644 (w), 1613 (s), 1462 (m), 1416 (m), 1326 (m), 1195 (m), 1027 (m), 914 (m), 728 (s), 646 (m), 600 (m). MS (GC, 70 eV): *m*/*z* (%)=307 (M$^+$, 100), 306 (74), 274 (16), 266 (44), 265 (26), 233 (29), 232 (23), 225 (19), 200 (42), 175 (15), 163 (24), 145 (34), 41 (25). HRMS (ESI): calcd for C$_{18}$H$_{18}$N$_3$S (M+H) 308.12159, found 308.12197.

*4.3.24. 3-Benzyl-11-methyl-2,3,6,11-tetrahydro-2,6-methano[1,3]thiazocino[8,7-b]indole-5-carbonitrile (major) (**4d**).* Grey solid, mp 176–178 °C, overall ield: 67% (201 mg) (**4d**/**5d**; 80:20). ^{1}H NMR (300 MHz, CDCl$_3$) δ=2.19–2.38 (m, 2H, CHC*H*$_2$CH), 3.53 (s, 3H, NMe), 3.95–3.97 (m, 1H, CH), 4.24–4.39 (m, 2H, NCH$_2$), 4.90 (m, 1H, SCHN), 6.78 (s, 1H, CH), 7.04–7.39 (m, 8H, H$_{Ar}$), 7.60–7.63 (m, 1H, H$_{Ar}$). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ=25.6 (CH), 28.7 (CH$_2$), 30.5 (NCH$_3$), 56.1 (CH), 57.1 (NCH$_2$), 83.4 (C), 108.2 (CH), 113.8 (C), 117.1, 120.0, 120.9 (CH), 121.6, 126.2, 127.7 (C), 128.1, 128.6, 129.2 (CH), 135.2, 137.3 (C), 145.1 (CH). IR (ATR, cm^{-1}): $\tilde{\nu}$=2928 (w), 2188 (s), 1617 (s), 1463 (m), 1416 (m), 1327 (m), 1194 (m), 1113 (m), 1037 (m), 734 (s), 723 (m), 697 (m), 601 (m). MS (GC, 70 eV): *m*/*z* (%)=357 (M$^+$, 97), 356 (47), 266 (52), 233 (15), 200 (26), 175 (14), 91 (100). HRMS (ESI): calcd for C$_{22}$H$_{20}$N$_3$S (M+H), 358.13724 found 358.13652.

*4.3.25. 5-Benzyl-11-methyl-2,5,6,11-tetrahydro-2,6-methano[1,5]thiazocino[2,3-b]indole-3-carbonitrile (minor) (**5d**).* ^{1}H NMR (300 MHz, CDCl$_3$) δ=2.19–2.38 (m, 2H, CHC*H*$_2$CH), 3.55 (s, 3H, NMe), 4.17 (m, 1H, CH), 4.24–4.67 (m, 2H, NCH$_2$), 4.67 (m, 1H, SCHN), 6.86 (s, 1H, CH), 7.04–7.39 (m, 9H, H$_{Ar}$). ^{13}C NMR (75.5 MHz, CDCl$_3$): 29.1 (CH$_2$), 30.6 (NCH$_3$), 35.7 (CH), 45.8 (CH), 58.6 (NCH$_2$), 80.3 (C), 108.6 (CH), 113.2 (C), 115.9, 120.0, 120.8 (CH), 121.6, 126.2, 127.7 (C), 128.4, 128.6, 129.2 (CH), 136.0, 137.3 (C), 148.2 (CH).

*4.3.26. 5-Methyl-11-phenyl-2,5,6,11-tetrahydro-2,6-methano[1,5]thiazocino[2,3-b]indole-3-carbonitrile (**4e**).* Pale white solid, mp 186–188 °C, yield: 55% (142 mg). ^{1}H NMR (300 MHz, CDCl$_3$) δ=2.26–2.44 (m, 2H, CHC*H*$_2$CH), 2.86 (s, 3H, NMe), 3.96–3.98 (m, 1H, CC*H*C), 4.81–4.83 (m, 1H, SCHN), 6.63 (s, 1H, CH), 6.97–7.12 (m, 3H, H$_{Ar}$), 7.32–7.46 (m, 5H, H$_{Ar}$), 7.64–7.65 (m, 1H, H$_{Ar}$). ^{13}C NMR (62.9 MHz, CDCl$_3$): δ=25.2 (CH), 28.4 (CH$_2$), 41.0 (NCH$_3$), 58.9 (CH),

82.1 (C), 109.4 (CH), 115.7 (C), 117.1, 120.8, 121.6 (CH), 121.7, 125.9, 126.7 (C), 126.9, 127.9, 129.4 (CH), 137.3, 137.6 (C), 145.5 (CH). IR (ATR, cm^{-1}): $\tilde{\nu}$=2901 (w), 2174 (s), 1615 (s), 1595 (m), 1499 (m), 1445 (m), 1368 (m), 1323 (m), 1227 (m), 1094 (m), 1027 (m), 940 (m), 752 (s), 738 (s), 699 (m), 658 (m), 598 (m). MS (GC, 70 eV): *m*/*z* (%)=343 (M^+, 100), 342 (88), 310 (26), 308 (13), 262 (47), 236 (16), 119 (26). HRMS (ESI): calcd for $C_{21}H_{17}N_3S$ (M^+), 343.11377 found 343.112945.

*4.3.27. 5-Methyl-11-phenyl-2,5,6,11-tetrahydro-2,6-methano[1,5] thiazocino[2,3-b]indole-3-carbonitrile (**5e**).* Pale white solid, mp 191–192 °C, yield: 30% (77 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ=2.29–2.48 (m, 2H, CHCH_2CH), 3.18 (s, 3H, NMe), 4.05–4.06 (m, 1H, CH), 4.65–4.67 (m, 1H, CH), 6.75 (s, 1H, CH), 6.98–7.11 (m, 3H, H_{Ar}), 7.34–7.49 (m, 6H, H_{Ar}). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=28.6 (CH_2), 35.3 (CH), 42.6 (NCH_3), 47.9 (CH), 79.5 (C), 109.8 (CH), 110.2 (C), 115.9, 120.7, 121.3 (CH), 121.8 (C), 127.2 (CH), 127.8 (C), 128.3, 129.5 (CH), 132.2, 136.8, 137.7 (C), 148.5 (CH). IR (ATR, cm^{-1}): $\tilde{\nu}$=2927 (m), 2183 (s), 1612 (s), 1596 (m), 1498 (m), 1447 (m), 1313 (s), 1228 (m), 1123 (m), 1020 (m), 941 (m), 760 (m), 737 (s), 699 (s), 662 (m), 590 (m). MS (GC, 70 eV): *m*/*z* (%)=343 (M^+, 100), 342 (32), 328 (14), 310 (11), 263 (23), 262 (99), 249 (13), 237 (21), 236 (47), 119 (8). HRMS (ESI): calcd for $C_{21}H_{17}N_3S$ (M^+), 343.11377 found 343.113502.

*4.3.28. 3-Allyl-11-phenyl-2,3,6,11-tetrahydro-2,6-methano[1,3]thiazocino[8,7-b]indole-5-carbonitrile (major) (**4f**).* Pale yellow solid, mp 167–168 °C, overall yield: 88% (244 mg) (**4f**/**5f**; 73:27). ^{1}H NMR (300 MHz, $CDCl_3$) δ=2.38–2.51 (m, 2H, CHCH_2CH), 3.69–3.78 (m, 2H, NCH_2CHCH_2), 4.08–4.10 (m, 1H, CH), 5.06 (m, 1H, SCHN), 5.22–5.32 (m, 2H, NCH$_2$CHCH_2), 5.72–5.80 (m, 1H, NCH$_2$C*H*CH$_2$), 6.79 (s, 1H, CH), 7.07–7.21 (m, 3H, H_{Ar}), 7.41–7.53 (m, 5H, H_{Ar}), 7.76 (d, *J*=7.8 Hz, H_{Ar}). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=25.6 (CH), 28.6 (CH_2), 55.8 (NCH_2), 56.4 (CH), 82.7 (C), 109.4 (CH), 115.6 (C), 117.1 (CH), 119.9 (CH_2), 120.8, 121.6 (CH), 121.7, 126.0, 126.7 (C), 126.9, 127.9, 129.4, 132.1 (CH), 137.3, 137.6 (C), 144.8 (CH).

*4.3.29. 5-Allyl-11-phenyl-2,5,6,11-tetrahydro-2,6-methano[1,5]thiazocino[2,3-b]indole-3-carbonitrile (minor) (**5f**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ=2.38–2.51 (m, 2H, CHCH_2CH), 3.81–3.95 (m, 1H, NCH_2CHCH_2), 4.14–4.16 (m, 1H, CH), 4.20–4.25 (m, 1H, NCH_2CHCH_2), 4.85 (m, 1H, SCHN), 5.35–5.45 (m, 2H, NCH$_2$CHCH_2), 5.80–5.89 (m, 1H, NCH$_2$C*H*CH$_2$), 6.91 (s, 1H, CH), 7.07–7.21 (m, 3H, H_{Ar}), 7.41–7.53 (m, 6H, H_{Ar}). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=29.0 (CH_2), 35.5 (CH), 46.2 (CH), 57.4 (NCH_2), 79.9 (C), 109.9 (CH), 110.4 (C), 115.9 (CH), 119.5 (CH_2), 120.7, 121.4 (CH), 121.8 (C), 127.2 (CH), 127.5 (C), 128.3, 129.5 (CH), 132.2 (C), 133.0 (CH), 136.8, 137.7 (C), 147.5 (CH). IR (ATR, cm^{-1}): $\tilde{\nu}$=2922 (w), 2180 (s), 1644 (w), 1614 (s), 1592 (m), 1495 (s), 1446 (s), 1413 (m), 1341 (m), 1317 (m), 1222 (m), 1195 (m), 1024 (m), 907 (m), 757 (m), 744 (s), 697 (s), 621 (m). MS (GC, 70 eV): *m*/*z* (%)=369 (M^+, 100), 368 (48), 336 (11), 328 (42), 327 (12), 295 (12), 262 (36), 236 (13). HRMS (ESI): calcd for $C_{23}H_{20}N_3S$ (M+H) 370.13724, found 370.13758.

*4.3.30. 3,11-Dimethyl-2,3,6,11-tetrahydro-2,6-methano[1,3]thiazocino[8,7-b]indole-4-carbonitrile (**6a**).* Grey solid, mp 88–90 °C, yield: 65% (136 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ=2.02–2.49 (m, 2H, CHCH_2CH), 2.92 (s, 3H, NCH_3), 3.55 (s, 3H, NCH_3), 3.79–3.84 (m, 1H, CH), 5.06–5.09 (m, 1H, SC*H*N), 5.71 (dd, 1H, *J*=6.6, 1.8 Hz, C*H*CCN), 7.01–7.14 (m, 3H, H_{Ar}), 7.34–7.38 (m, 1H, H_{Ar}). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=24.4 (CH), 28.5 (CH_2), 30.6 (NCH_3), 39.1 (NCH_3), 62.0 (CH), 108.5 (CH), 112.9, 115.4 (C), 115.9, 117.5 (CH), 118.9 (C), 119.6, 120.5 (CH), 125.5, 128.5, 137.3. IR (ATR, cm^{-1}): $\tilde{\nu}$=2917 (w), 2221 (m), 1608 (m), 1518 (w), 1463 (s), 1387 (m), 1327 (s), 1232 (m), 1141 (m), 1069 (m), 1061 (m), 966 (m), 906 (m), 728 (s), 624 (m), 572 (m), 551 (m). MS (GC, 70 eV): *m*/*z* (%)=281 (M^+, 100), 280 (64), 254 (43), 248 (36), 233 (17), 225 (19), 200 (34), 175 (20), 163 (35), 130 (20), 124 (23), 119 (47), 104 (19), 77 (18), 43 (16). HRMS (ESI): calcd for $C_{16}H_{15}N_3S$ (M^+) 281.09812, found 281.097720.

*4.3.31. 3-Benzyl-11-methyl-2,3,6,11-tetrahydro-2,6-methano[1,3] thiazocino[8,7-b]indole-4-carbonitrile (**6b**).* Grey solid, mp 90–92 °C, yield: 80% (215 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ=2.00–2.38 (m, 2H, CHCH_2CH), 3.56 (s, 3H, NMe), 3.81–3.89 (m, 1H, CH), 4.18 (d, 1H, *J*=14.8 Hz, NCH_2), 4.74 (d, 1H, *J*=14.8 Hz, NCH_2), 4.92–4.95 (m, 1H, SC*H*N), 5.78 (dd, 1H, *J*=6.6, 1.6 Hz, C*H*CCN), 7.00–7.15 (m, 3H, H_{Ar}), 7.27–7.39 (m, 6H, H_{Ar}). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=24.6 (CH), 28.4 (CH_2), 30.6 (NCH_3), 54.5 (NCH_2), 57.8 (CH), 108.5 (CH), 112.6, 115.6 (C), 115.9, 117.7 (CH), 119.2 (C), 119.6, 120.6 (CH), 125.6 (C), 128.2 (CH), 128.3 (C), 128.6, 129.0 (CH), 135.9, 137.3 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$=2916 (w), 2221 (m), 1606 (s), 1494 (w), 1463 (m), 1455 (m), 1363 (m), 1326 (s), 1145 (m), 1097 (s), 964 (m), 777 (m), 735 (s), 721 (s), 695 (s), 551 (m). MS (GC, 70 eV): *m*/*z* (%)=357 (M^+, 57), 356 (12), 330 (26), 266 (51), 233 (32), 163 (41), 130 (17), 104 (25), 91 (100), 77 (14), 65 (12). HRMS (ESI): calcd for $C_{22}H_{20}N_3S$ (M+H) 358.13724, found 358.1366.

*4.3.32. 3-Methyl-11-phenyl-2,3,6,11-tetrahydro-2,6-methano[1,3] thiazocino[8,7-b]indole-4-carbonitrile (**6c**).* Grey solid, mp 166–168 °C, yield: 88% (226 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ=2.09–2.50 (m, 2H, CHCH_2CH), 2.86 (s, 3H, NCH_3), 3.85–3.89 (m, 1H, CH), 4.97–5.00 (m, 1H, SC*H*N), 5.76 (dd, 1H, *J*=6.5, 1.7 Hz, C*H*CCN), 6.97–7.11 (m, 3H, H_{Ar}), 7.34–7.46 (m, 6H, H_{Ar}). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=24.4 (CH), 28.4 (CH_2), 39.0 (NCH_3), 61.9 (CH), 109.7 (CH), 114.8, 115.4 (C), 116.0, 117.1 (CH), 119.3 (C), 120.4, 121.2 (CH), 126.1 (C), 126.9, 127.9 (CH), 128.7 (C), 129.4 (CH), 137.4, 137.7 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$=2926 (w), 2223 (m), 1608 (m), 1595 (m), 1501 (s), 1446 (s), 1363 (m), 1277 (m), 1216 (m), 1242 (m), 1088 (m), 1057 (m), 968 (m), 750 (m), 740 (s), 699 (s), 680 (m), 570 (m). MS (GC, 70 eV): *m*/*z* (%)=343 (M^+, 100), 342 (56), 316 (27), 310 (29), 308 (10), 287 (10), 262 (19), 236 (22), 119 (20). HRMS (ESI): calcd for $C_{21}H_{17}N_3S$ (M^+) 343.11377, found 343.113021.

*4.3.33. 3-Allyl-11-phenyl-2,3,6,11-tetrahydro-2,6-methano[1,3]thiazocino[8,7-b]indole-4-carbonitrile (**6d**).* Light brown solid, mp 78–80 °C, yield: 92% (255 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ=2.15–2.45 (m, 2H, CHCH_2CH), 3.63 (dd, 1H, *J*=15.5, 7.9 Hz, NCH_2CHCH_2), 3.88–3.91 (m, 1H, CH), 4.02–4.09 (m, 1H, NCH_2CHCH_2), 5.12–5.14 (m, 1H, SC*H*N), 5.18–5.25 (m, 2H, NCH$_2$CHCH_2), 5.71–5.75 (m, 1H, NCH$_2$C*H*CH$_2$), 5.79 (dd, 1H, *J*=6.8, 1.6 Hz, C*H*CCN), 6.97–7.11 (m, 3H, H_{Ar}), 7.33–7.47 (m, 6H, H_{Ar}). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=24.6 (CH), 28.4 (CH_2), 53.4 (NCH_2), 58.1 (CH), 109.7 (CH), 114.6, 115.4 (C), 116.0, 117.1 (CH), 119.0 (C), 119.6 (CH_2), 120.4, 121.2 (CH), 126.2 (C), 126.9, 127.9 (CH), 128.6 (C), 129.4, 132.8 (CH), 137.3, 137.7 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$=2916 (w), 2222 (m), 1605 (m), 1595 (m), 1497 (s), 1446 (s), 1366 (m), 1278 (m), 1153 (m), 1100 (m), 966 (m), 737 (s), 696 (s), 682 (m), 571 (m). MS (GC, 70 eV): *m*/*z* (%)=369 (M^+, 100), 368 (30), 342 (29), 336 (12), 329 (15), 328 (78), 327 (23), 295 (33), 294 (10), 262 (14), 249 (12), 236 (19), 225 (16), 224 (14), 145 (9), 41 (10). HRMS (ESI): calcd for $C_{23}H_{19}N_3S$ (M^+) 369.12942, found 369.129104.

*4.3.34. 3-Benzyl-11-phenyl-2,3,6,11-tetrahydro-2,6-methano[1,3] thiazocino[8,7-b]indole-4-carbonitrile (**6e**).* Pale yellow solid, mp 172–174 °C, yield: 78% (245 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ=2.06–2.39 (m, 2H, CHCH_2CH), 3.87–3.92 (m, 1H, CH), 4.12 (d, 1H, *J*=14.9 Hz, NCH_2), 4.69 (d, 1H, *J*=14.9 Hz, NCH_2), 4.84–4.87 (m, 1H, SCHN), 5.83 (dd, 1H, *J*=6.6, 1.6 Hz, CHCCN), 6.97–7.48 (m, 14H, H_{Ar}). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=24.7 (CH), 28.4 (CH_2), 54.4 (NCH_2), 57.7 (CH), 109.8 (CH), 114.5, 115.6 (C), 116.0, 117.3 (CH), 119.5 (C), 120.5, 121.3 (CH), 126.2 (C), 127.0, 128.0, 128.1 (CH), 128.4 (C), 128.6,

129.0, 129.5 (CH), 136.0, 137.4, 137.8 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$=2925 (w), 2221 (m), 1738 (w), 1610 (m), 1595 (m), 1498 (s), 1448 (s), 1388 (m), 1372 (m), 1317 (m), 1136 (s), 1104 (m), 968 (m), 781 (m), 752 (m), 742 (s), 736 (s), 694 (s), 573 (s). MS (GC, 70 eV): *m*/*z* (%)=419 (M^+, 56), 392 (21), 328 (65), 295 (35), 236 (15), 225 (73), 224 (67), 223 (36), 193 (15), 104 (42), 91 (100), 77 (34), 65 (18), 51 (18), 44 (15). HRMS (ESI): calcd for $C_{27}H_{21}N_3S$ (M^+) 419.14507, found 419.144996.

Supplementary data

These data include NMR spectra of compounds **3**–**6**. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.09.059.

References and notes

1. (a) Bennasar, M. L.; Jimfnez, J. M.; Sufi, B. A.; Bosch, J. *Tetrahedron Lett.* **1996**, *37*, 7653–7656; (b) Bennasar, M. L.; Lavilla, R.; Alvarez, M.; Bosch, J. *Heterocycles* **1988**, *27*, 789–824; (c) Spitzner, D.; Zaubitzer, T.; Shi, Y. J.; Wenkert, E. *J. Org. Chem.* **1988**, *53*, 2274–2278; (d) Bieraugel, H.; Brands, K. M. J.; Pandit, U. K. *Heterocycles* **1988**, *27*, 1589–1593.
2. (a) Comins, D. L.; Joseph, S. P. In *Advances in Nitrogen Heterocycles*; Moody, C. J., Ed.; JAI: London, 1996; Vol. 2, pp 251–294; (b) Comins, D. L.; LaMunyon, D. H.; Chen, X. *J. Org. Chem.* **1997**, *62*, 8182–8187; (c) Comins, D. L.; Libby, A. H.; Al-awar, R. S.; Foti, C. J. *J. Org. Chem.* **1999**, *64*, 2184–2185; (d) Kuethe, J. T.; Comins, D. L. *Org. Lett.* **2000**, *2*, 855–857; (e) Pays, C.; Mangeney, P. *Tetrahedron Lett.* **2001**, *42*, 589–592; (f) Bennasar, M. L.; Zulaica, E.; Ramirez, A.; Bosch, J. *J. Org. Chem.* **1996**, *61*, 1239–1251; (g) Bennasar, M. L.; Vidal, B.; Bosch, J. *J. Org. Chem.* **1996**, *61*, 1916–1917; (h) Amann, R.; Spitzner, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1320–1321.
3. Lyle, R. E. In *Pyridine and its Derivatives: Supplement*; Abramovich, R. A., Ed.; Wiley: New York, NY, 1974; Vol. 1, p 137.
4. (a) Goldman, S.; Stoltefuss, J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1559–1578; (b) Sunkel, C. E.; Fau de Casa-Juana, M.; Santos, L.; Gomes, M. M.; Villarroya, M.; Gonzalez-Morales, M. A.; Priego, J. G.; Ortega, M. P. *J. Med. Chem.* **1990**, *33*, 3205–3210; (c) Jaing, J. L.; Li, A. H.; Jang, S. Y.; Chang, L.; Melman, N.; Moro, S.; Ji, X.; Lobkovsky, E.; Clardy, J.; Jacobson, K. A. *J. Med. Chem.* **1999**, *42*, 3055–3060.
5. Mateeva, N. N.; Winfield, L. L.; Redda, K. K. *Curr. Med. Chem.* **2005**, *12*, 551–571.
6. (a) Ito, S.; Satoh, A.; Nagatomi, Y.; Hirata, Y.; Suzuki, G.; Kimura, T.; Satow, A.; Maehara, S.; Hikichi, H.; Hata, M.; Kawamoto, H.; Ohta, H. *Bioorg. Med. Chem.* **2008**, *16*, 9817–9829; (b) Jones, P.; Griffin, A. M.; Gawell, L.; Lavoie, R.; Delorme, D.; Roberts, E.; Brown, W.; Walpole, C.; Xiao, W. H.; Boulet, J.; Labarre, M.; Coupal, M.; Butterworth, J.; St-Onge, S.; Hodzic, L.; Salois, D. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5994–5998; (c) Liras, S.; McHardy, S. F.; Allen, M. P.; Segelstein, B. E.; Heck, S. D.; Bryce, D. K.; Schmidt, A. W.; Vanase-Frawley, M.; Callegari, E.; McLean, S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 503–507; (d) Chowdhury, M. A.; Abdellatif, K. R. A.; Dong, Y.; Knaus, E. E. *Bioorg. Med. Chem.* **2008**, *16*, 8882–8888; (e) Misra, M.; Pandey, S. K.; Pandey, V. P.; Pandey, J.; Tripathi, R.; Tripathi, R. P. *Bioorg. Med. Chem.* **2009**, *17*, 625–633; (f) Krishna, P. R.; Reddy, P. S. *J. Comb. Chem.* **2008**, *10*, 426–435; (g) Scott, J. D.; Li, S. W.; Wang, H. W.; Xia, Y.; Jayne, C. L.; Miller, M. W.; Duffy, R. A.; Boykow, G. C.; Kowalski, T. J.; Spar, B. D.; Stamford, A. W.; Chackalamannil, S.; Lachowicz, J. E.; Greenlee, W. J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1278–1283.
7. (a) Bosch, J.; Bennasar, M. L. *Synlett* **1995**, 587–596; (b) Bennasar, M. L.; Alvarez, M.; Lavilla, R.; Zulaica, E.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 1156–1168; (c) Bennasar, M. L.; Zulaica, E.; Jimenez, J. M.; Bosch, J. *J. Org. Chem.* **1993**, *58*, 7756–7767; (d) Alvarez, M.; Salas, M.; de Veciana, A.; Lavilla, R.; Bosch, J. *Tetrahedron Lett.* **1990**, *31*, 5089–5092; (e) Amat, M.; Linares, A.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 6299–6312; (f) Bennasar, M. L.; Zulaica, E.; Ramırez, A.; Bosch, J. *Tetrahedron* **1999**, *55*, 3117–3128; (g) Bennasar, M. L.; Vidal, B.; Bosch, J. *Chem. Commun.* **1996**, 2755–2756; (h) Bennasar, M.-L.; Vidal, B.; Bosch, J. *J. Org. Chem.* **1997**, *62*, 3597–3609; (i) Le Men, J.; Taylor, W. *Experientia* **1965**, *21*, 508–510; (j) Bennasar, M. L.; Jiménez, J. M.; Sufi, B. A.; Bosch, J. *Tetrahedron Lett.* **1996**, *37*, 9105–9109; (k) Bennasar, M. L.; Vidal, B.; Sufi, B. A.; Bosch, J. *Chem. Commun.* **1998**, 2639–2641.
8. (a) Albrecht, U.; Preuss, A.; Schmidt, A.; Fischer, C.; Langer, P. *Heterocycles* **2010**, *80*, 289–302; (b) Schmidt, A.; Michalik, D.; Rotzoll, S.; Ullah, E.; Fischer, C.; Reinke, H.; Gorls, H.; Langer, P. *Org. Biomol. Chem.* **2008**, *6*, 2804–2814.
9. (a) Schmidt, A.; Gütlein, J. P.; Preuss, A.; Albrecht, U.; Reinke, H.; Langer, P. *Synlett* **2010**, 2489–2491; (b) Ullah, E.; Rotzoll, S.; Schmidt, A.; Michalik, D.; Langer, P. *Tetrahedron Lett.* **2005**, *46*, 8997–8999; (c) Yawer, M. A.; Hussain, I.; Gütlein, J. P.; Schmidt, A.; Jiao, H.; Reinke, H.; Spannenberg, A.; Fischer, C.; Langer, P. *Eur. J. Org. Chem.* **2008**, 4193–4199.
10. (a) Karapetyan, V.; Mkrtchyan, S.; Schmidt, A.; Gutlein, J. P.; Villinger, A.; Reinke, H.; Jiao, H.; Fischer, C.; Langer, P. *Org. Biomol. Chem.* **2008**, *6*, 2961–2968; (b) Schmidt, A.; Gütlein, J. P.; Mkrtchyan, S.; Görls, H.; Langer, P. *Synlett* **2007**, 1305–1307.
11. Schmidt, A.; Gutlein, J. P.; Langer, P. *Tetrahedron Lett.* **2007**, *48*, 2067–2069.
12. (a) Moghaddam, F. M.; Mirjafary, Z.; Saeidian, H.; Taheri, S.; Khodabakhshi, M. R. *Tetrahedron Lett.* **2010**, *51*, 2704–2707; (b) Moghaddam, F. M.; Mirjafary, Z.; Saeidian, H.; Taheri, S.; Doulabi, M.; Kiamehr, M. *Tetrahedron* **2010**, *66*, 134–138; (c) Moghaddam, F. M.; Mirjafary, Z.; Saeidian, H.; Taheri, S.; Soltanzadeh, B. *Tetrahedron* **2010**, *66*, 3678–3681; (d) Moghaddam, F. M.; Taheria, S.; Mirjafarya, Z.; Saeidianb, H.; Kiamehra, M.; Tafazzolia, M. *Helv. Chim. Acta* **2011**, *94*, 142–147; (e) Moghaddam, F. M.; Saeidian, H.; Kiamehr, M.; Mirjafary, Z.; Taheri, S. *Arkivoc* **2010**, *xi*, 91–97.
13. Moghaddam, F. M.; Taheri, S.; Mirjafary, Z.; Saeidian, H. *Synlett* **2010**, 123–127.
14. X-ray Crystallographic data (excluding structure factors) for the structures **3g**, **3j**, **4e** and **5e** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. 856704–856707 and can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk, or via www.ccdc.cam.ac.uk/data_request/cif.