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An expeditious synthesis for γ-carboline analogue 4-aryl-1,3-thiazino[6,5-*b*]indole derivatives via the trifluoromethanesulfonic acid-promoted isomerization of 3-amidomethylthioindole intermediates to 2-indolyl sulfides

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ABSTRACT

A highly efficient trifluoromethanesulfonic acid-mediated rearrangement of the benzoylaminomethylthio group of 3-benzoylaminomethylthioindoles (**7a**–**e**) to position 2 of the indole ring was developed. Thus, 2-benzoylaminomethylthioindoles (**9a**–**e**) were obtained in good yields and were involved as key intermediates in the synthesis of the new γ-carboline analogue ring system: 2,9-dihydro-4-aryl-1,3-thiazino[6,5-*b*]indole derivatives (**11a**–**e**). The target thiazinoindoles (**11a**–**e**) were prepared via 2-thiobenzoylaminomethylindoles (**10a**–**e**) in modified Bischler–Napieralski reactions.

1. Introduction

The indole substructure is a basic core unit for a huge number of biologically active natural and synthetic molecules.[1] This plays a key role in the current interest in novel syntheses and transformations of indole compounds.[2] Special attention is focused on the functionalization of the C-3 and C-2 positions of the indole ring as reactive sites of the heterocyclic system. Sulfur-containing substituents at position C-3 or C-2 of indole moieties are common in many pharmacologically important compounds. In particular, numerous thioindoles demonstrate antiproliferative,[3] cyclooxygenase inhibitory,[4] factor Xa inhibitory,[5] HIV reverse transcriptase inhibitory,[6] or antibacterial[7] activities. A number of tricyclic or polycyclic natural products or compounds having specific biological activity also contain the indole-2- or 3-thiol fragment. Probably the best known among them is the cyclic fungal toxin phalloidin, produced by *Amanita phalloides*.[8] Benzothienoindole derivatives have been found to be selective estrogen receptor modulators.[9] Interesting tetracyclic counterparts were recently prepared by intramolecular electrophilic sulfenylation from sulfinyl indoleanilides.[10] A huge number of tricyclic derivatives can be found in S-containing cruciferous phytoalexins.[11] The phytoalexins are not present in healthy plant tissue, but are synthesized in response to pathogen attack or physical or chemical stress, probably as a result of the de novo synthesis of enzymes.[12] They also exhibit various useful pharmacological effects (e.g., antimicrobial or antiproliferative activity). For example, 1,3-thiazino[6,5-*b*]indole or isothiazolo[5,4-*b*]indole derivatives such as cyclobrassinin, brassilexin, and sinalexin have been isolated from Chinese cabbage.[11] In the course of our studies on S- and N-containing condensed-skeleton heterocycles,[13–16] we have developed novel methodologies for the synthesis of different ring positional isomers of 1,3-thiazinoindole derivatives condensed at the *b*-bond of indole.[3b,17–19] These synthesized derivatives include phytoalexins and analogous substances (4,9-dihydro-1,3-thiazino[6,5-*b*]indoles, **1**, Fig. 1),[17] compounds with interesting in vitro antiproliferative effects (4,5-dihydro-1,3-thiazino[5,6-*b*]indoles, **2**, Fig. 1),[3b,18] and 4-thiaharmalan analogues (2,5-dihydro-1,3-thiazino[5,6-*b*]indoles, **3**, Fig. 1).[19]

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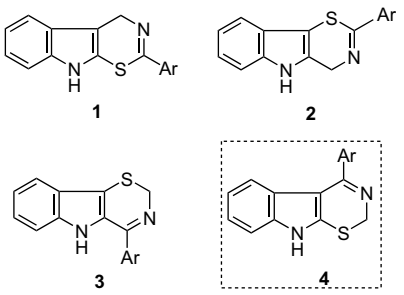


Figure 1. Different aryl-substituted ring positional isomers of 1,3-thiazinoindole derivatives condensed at the *b*-bond of indole.

We now describe an efficient route for the synthesis of the fourth 1,3-thiazinoindole isomer: 2,9-dihydro-4-aryl-1,3-thiazino[6,5-*b*]indoles, **4** (Fig. 1). These compounds have a new ring system and are thia analogues of pharmacologically important γ-carbolines.[20] The procedure utilizes the super acid-mediated C-3→C-2 migration of the amidomethylthio group on the indole ring of 3-benzoylaminomethylthioindole intermediates.

2. Results and discussion

The synthesis of the substituted 3-benzoylaminomethylthioindole derivatives (**7a**–**e**) started from indole-3-thiol (**5**) by selective benzamidomethylation under basic conditions with substituted benzoylaminomethyltriethylammonium chlorides (**6a**–**e**), prepared from chloromethylbenzamides. In refluxing $CHCl_3$ in the presence of Et_3N, **7a**–**e** were obtained in excellent yields. In order to improve the 3C→2C migration of the 3-amidomethylthio groups different reagents (trifluoroacetic acid and polyphosphoric acid) and conditions were examined. To our surprise, in the initial experiments, trifluoromethanesulfonic acid (TfOH) without any solvent was found to be a powerful agent that promoted the above migration. After optimization of the reaction conditions, isomerizations were performed in TfOH at 45 °C for 30 min 2-benzamidomethyl thioether derivatives (**9a**–**e**) were obtained in relatively good yields (69–84%). To the best of our knowledge, this is the first example of the TfOH catalyzed isomerization of 3-indolyl sulfides to 2-indolyl sulfides. It is noteworthy that successful extension of this reaction would allow the convenient preparation of other substituted indole derivatives with sulfur at position 2.

Alternatively, **9a**–**e** were prepared from indole-2-thione (**8**) and different benzoylaminomethyltriethylammonium chlorides (**6a**–**e**) under reflux in $CHCl_3$ in the presence of Et_3N (Scheme 1).

Unfortunately, the reaction of **9a** under classical Bischler–Napieralski conditions led to decomposition of the benzamidomethyl moiety, and in some cases indole-2-thione was observed in the reaction mixture. In order to perform a modified Bischler–Napieralski reaction under non-acidic conditions, thiobenzamidomethyl derivatives **10a**–**e** were prepared by reaction of the corresponding amides **9a**–**e** and Lawesson's reagent (Scheme 2). The S-exchange reactions were carried out in refluxing THF after the addition of a small amount of Et_3N to the mixture; in this way, thioamides **10a**–**e** could be prepared in relatively good yields. Treatment of thiobenzamidomethyl derivatives **10a**–**e** with methyl iodide in refluxing acetone provided the cyclized thiazinoindole derivatives **11a**–**e** after methyl mercaptan elimination (Scheme 2).

In summary, we report a convenient approach for the synthesis of a new γ-carboline analogue ring system: 4-aryl-1,3-thiazino[6,5-*b*]indoles. For the intermediate **9a**–**e**, a convenient TfOH-catalyzed rearrangement was achieved with good yields: under mild conditions, the 3-benzoylaminomethylthio group rearranged to position 2 of the indole ring. The target thiazinoindoles (**11a**–**e**) were prepared via **10a**–**e** under Bischler–Napieralski conditions.

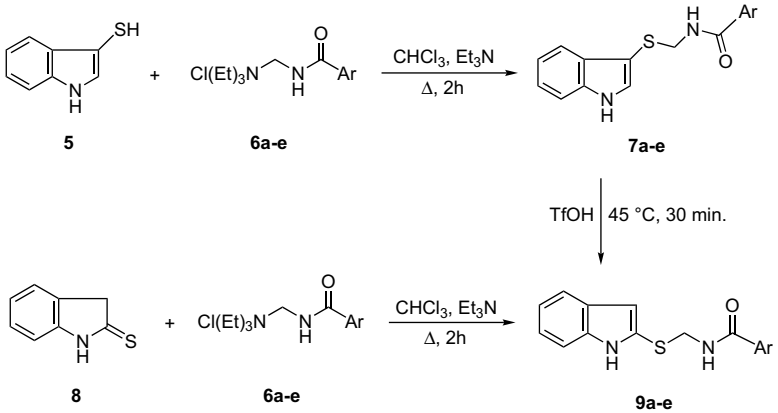
3. Structure

The presumed structures of the new compounds were confirmed unambiguously via the IR and NMR spectra (Tables 1–3). Only a few additional remarks are necessary.

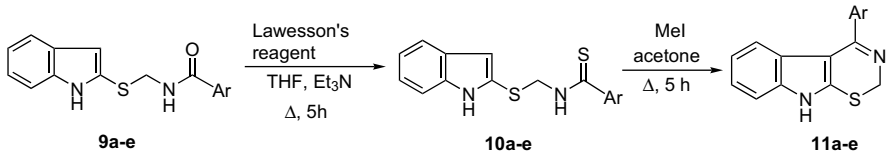
The *–I* effect of the *ortho*-chloro substituent[21] in **6d** is revealed in a νC=O frequency higher by 39 cm^{-1} in comparison with **6e**. A similar effect was not observed for the pairs **7d**,**e** and **9d**,**e**. A nonplanar conformation due to the bulky indole moiety may be responsible for this fact. Such an arrangement in the latter compounds is preferred, assuming a cyclic dimer association of the amide group.

It is noteworthy that the Me hydrogens are more shielded in **11e** (by ca. 0.4 ppm) than in **7e**, **9e**, and **10e**. This difference can be explained in terms of the anisotropic shielding[22a] of the delocalized electrons in the skeleton, due to the perpendicular arrangement of the *ortho*-tolyl substituent to that in the preferred conformation formed as a consequence of the steric hindrance between the skeleton and the Me group. A similar, but more pronounced effect (>0.5 ppm) can be observed for H-4 of the indole part in **11d** and **11e** (anisotropy of the ring current in the Ar group on H-4 lying above the benzene ring).

The signal C=S in the ^{13}C NMR spectra of compounds of type **10** appears in the expected interval (197–201 ppm),[22b] in contrast with the carbonyl signal (166–172 ppm) of compounds of types **6**,



Scheme 1. **a**: Ar=Ph; **b**: Ar=*p*-Cl-C_6H_4; **c**: Ar=*p*-Me-C_6H_4; **d**: Ar=*o*-Cl-C_6H_4; **e**: Ar=*o*-Me-C_6H_4.



Scheme 2. **a**: Ar=Ph; **b**: Ar=*p*-Cl-C_6H_4; **c**: Ar=*p*-Me-C_6H_4; **d**: Ar=*o*-Cl-C_6H_4; **e**: Ar=*o*-Me-C_6H_4.

Table 1
Characteristic IR frequencies[a] of compounds **6d**,**e**, **7d**,**e**, **9b**–**e**, **10a**–**e**, and **11a**–**e**

Compound	νNH band	Amide-I band	$\gamma C_{Ar}H$ band	
			Ar	Indole
6d	3500–3400	1709	741	—
6e	3500–3400	1670	736	—
7d	3313	1646	746[b]	746[b]
7e	3200	1643	739[b]	739[b]
9b	3275	1631	842	748
9c	3320	1619	840	742
9d	3297	1629	73[b]	737[b]
9e	3275, 3245	1623	732[b]	732[b]
10a	~3300	—	744[b]	744[b]
10b	3354, 3165	—	829	736
10c	3328	—	817	738
10d	3350–2900	—	734[c]	749[c]
10e	3350–2900	—	730[c]	747[c]
11a	3500–1800	—	721	740
11b	3500–1800	—	842	751
11c	3500–1800	—	827	744
11d	3500–1800	—	737[b]	737[b]
11e	3500–1800	—	747[b]	747[b]

[a] In KBr discs (cm^{-1}). Further bands, $\gamma C_A C_{Ar}$ (Ar group): 690 (**10a**), 696 (**11a**), 827 (**11c**).
[b] Coalesced bands.
[c] Reversed assignments are also possible.

7, and **9**. The attached thioamide group causes a downfield shift by ca. 0.5 ppm on the NCH_2S signal relative to that for amide compounds. The more extensive conjugation in compounds of type **11** is manifested in a downfield shift of the indole-NH signal (ca. 12.2 ppm, as compared with 11.5 ppm for all the other compounds).

We demonstrated earlier that a vicinal spin–spin coupling of H-2 with the indole-NH leads to a splitting by 2.5 Hz in related compounds.[19] The analogue split is also observable for **7d**,**e**, while the similar allylic-type ^4J interaction (between H-3 and the indole-NH) causes only a smaller split (by 1.2–1.6 Hz) for **9b**,**d** and **10a**,**d**,**e**. The NH signal (for **9c**,**e** and **10b**,**c**) and also the H-3 signal are singlets in the routine spectra.

The condensed thiazine ring-containing compounds **11a**–**e** give singlet methylene ^1H NMR signals, while the open-chain analogues with a CH_2NH group give doublet CH_2 and triplet NH signals, split by 6.5±0.5 Hz, due to the vicinal coupling of the hydrogens in this moiety.

Of course, a few other changes also provide evidence of the presumed condensed three-ring system. For example, instead of the ^{13}C NMR line of the thioamide carbon, **11a**–**e** (see above) have the C=N carbon signal at 140.5±1.0 ppm. The H-3 singlet of **10a**–**e** (6.65±0.05 ppm) is absent from the ^1H NMR spectra of **11a**–**e**.

Table 2
^1H NMR data[a] on compounds **6d**,**e**, **7d**,**e**, **9b**–**e**, **10a**–**e**, and **11a**–**e**[b]

Compound	CH_3 (3H)	NCH_2S d[c] or s	H-2/3[d] d[e] or s	H-4[d] ~d	H-5[d] ~t	H-6[d] ~t	H-7[d] ~d	H-2′,6′ d (2H)[f]	H-3′,5′ d/t (2H)[g]	H-4′ t (1H)	NH amide	NH indole
5[j]	—	—	7.46	7.59	7.11	7.16	7.42	—	—	—	—	11.5
6d	1.31	4.80	—	—	—	—	—	7.70	7.51	7.58	9.98	—
6e	1.32	4.78	—	—	—	—	—	7.66	7.34[h]	7.47	9.75	—
7d	—	4.54	7.65	7.78	7.19	7.24	7.51	7.53	7.40	7.48	9.11	11.5
7e	2.25	4.44	7.51	7.66	7.05	7.13	7.40	7.20[h]	7.19[h]	7.27	8.80	11.4
9b	—	4.78	6.64	7.52	7.04	7.15	7.39	7.91	7.60	—	9.43	11.5
9c	2.40	4.80	6.64	7.52	7.04	7.15	7.39	7.81	7.32	—	9.28	11.5
9d	—	4.78	6.70	7.55	7.05	7.16	7.40	7.53	7.44	7.49	9.30	11.5
9e	2.35	4.78	6.67	7.53	7.05	7.15	7.40	7.35[i]	7.26[h]	7.37[i]	9.11	11.5
10a	—	5.12	6.68	7.54	7.05	7.16	7.39	7.81	7.47	7.56	11.0	11.5
10b	—	5.05	6.61	~7.45[h]	6.97	7.08	7.32	7.76	~7.46[h]	—	11.0	11.4
10c	2.39	5.15	6.69	7.55	7.06	7.17	7.41	7.77	7.28	—	10.9	11.5
10d	—	5.12	6.70	7.53	7.04	7.15	~7.4[h]	7.50	~7.4[h]	~7.4[h]	11.2	11.5
10e	2.30	5.12	6.66	7.52	7.04	7.14	7.38	7.25	7.21	7.30	11.0	11.5
11a	—	4.93	—	6.61	6.89	7.07	7.37	7.4–7.6	—	~12.3	—	Br
11b	—	4.94	—	6.68	6.95	7.100	7.40	7.53[h]	7.53[h]	—	—	~12.4
11c	2.35	4.86	—	6.64	6.86	7.03	7.32	7.37	7.23	—	—	~12.2
11d	—	4.99	—	6.11	6.76	6.98	7.28	7.50	7.48	7.42	—	~12.2
11e	1.96	4.96	—	6.05	6.71	6.96	~7.27[i]	7.15	~7.27[i]	7.36	—	~12.1

[a] In DMSO-d_6 solution at 500 MHz. Chemical shifts in parts per million (δ_{TMS}=0 ppm), coupling constants in hertz. Further signals: CH_3 and CH_2 (Et, **6d**,**e**): 1.31, t, *J*: 7.3 and 3.30 qa, H-3′ (**d** and **e**-type compds): 7.62 (**6d**), 7.34[h] (**6e**, **7d**, **11d**), 7.15[h] (**7e**), 7.43 (**9d**), 7.27 (**9e**,[h] **11e**[i]), ~7.4[h] (**10d**), 7.23 (**10e**).
[b] Assignments were supported by HMQC (except for **9b**) and HMBC (except for **9b**), for compds **7e** and **11d** also by 2D-COSY measurements.
[c] *J*: 6.2±0.2, 7.1 (NCH_2N, **6d**,**e**), s for **11a**–**e**.
[d] Indole skeleton.
[e] *J*: 2.5 (**7d**,**e**), 1.6 (**9b**, **10a**), 1.2 (**9d**, **10d**,**e**), s (**9c**,**e**, **10b**,**c**).
[f] The A part of an AA′BB′C (**a**-type compd) or AA′BB′ spectrum (**b** and **c**-type compds), *J*: 8.4 (**b**-type compd), 7.9 (**c**-type compd), H-6′ (**d** and **e**-type compds).
[g] H-5′ (**d** and **e**-type compds).
[h] Overlapping signals.
[i] Overlapping signals.
[j] In $CDCl_3$ solution, SH: 4.00.

Table 3
^{13}C NMR chemical shifts[a] of compounds **6d**,**e**, **7d**,**e**, **9b**–**e**, **10a**–**e**, and **11a**–**e**[b]

Compound	CH_3 (Ar)	C=O or C=X[c]	C-2	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	SCH_2N or NCH_2N[d]	C-1′	C-2′[e]	C-3′[e]	C-4′
			Indole ring									Aryl group			
5[i]	—	—	129.8	96.4	130.3	122.6	120.2	119.4	112.7	137.1	—	—	—	—	—
6d	—	169.2	—	—	—	—	—	—	—	—	60.0	135.9	130.7	130.6	132.6
6e	—	171.8	—	—	—	—	—	—	—	—	60.5	135.4	136.9	131.6	131.3
7d	—	166.8	132.2	102.8	130.2	119.5	120.5	122.6	112.9	137.3[f]	46.3	130.9	137.3[f]	129.8	131.7
7e	20.2	169.5	131.9	103.0	130.3[f]	119.4	120.4	122.6	112.9	137.3[g]	46.3	137.4[g]	136.4	126.2	130.3[f]
9b	—	166.1	129.0	108.2	128.7	120.4	120.1	122.5	111.9	138.4	46.9	133.4	130.2	129.3	137.3
9c	21.8	167.0	129.0[f]	107.9	129.0[f]	120.4	120.0	122.4	111.8	138.4	46.9	131.9	128.3	129.7	142.4
9d	—	167.1	128.4	108.3	129.0	120.4	120.1	122.5	111.8	138.4	45.8	130.9	137.0	127.9	131.9
9e	20.2	169.8	128.7	108.1	129.0	120.4	120.0	122.5	111.8	138.5	45.9	137.1	136.4	128.0	131.3
10a	—	198.7	128.9[f,g]	108.5	128.9[f,g]	120.5	120.1	122.7	111.9	138.5	52.5	141.4	128.2	128.8[g]	131.9
10b	—	197.1	128.7[f]	108.6	128.7[f]	120.6	120.2	122.7	111.9	138.5	52.7	140.0	130.0	129.0	136.9
10c	21.8	198.3	129.0[f]	108.4	129.0[f]	120.5	120.1	122.6	111.9	138.5	52.6	138.6	128.3	129.4	142.1
10d	—	197.2	128.4	108.4	128.9	120.5	120.1	122.6	111.9	138.4	50.8	142.9	129.2	129.7	130.9
10e	19.7	201.2	128.6	108.1	128.9	120.4	120.1	122.6	111.8	138.5	50.7	144.3	133.5	131.0	129.3
11a	—	141.3	165.2	108.4	125.4	119.4	121.5	122.6	112.4	~137	~51.2	139.6	129.0	129.6	130.8
11b	—	141.3	164.0	108.0	125.2	119.3	121.7	122.7	112.4	136.8	51.4	135.0	131.4	129.1	138.4
11c	21.9	140.5[f]	~165	108.7	126.0	119.4	121.5	122.7	~113	135.9	~50.7	136.5[g]	129.6[h]	129.6[h]	140.5[f]
11d	—	141.6	163.3	109.0	125.7	117.9	121.8	122.7	112.6	137.5	50.8	132.3	139.3	130.9	128.3
11e	19.6	139.5	164.4	109.6	126.2	118.1	121.7	122.8	113.1	136.0[f]	50.2	136.0[f]	136.0[f]	131.0	129.7

[a] In parts per million (δ_{TMS}=0 ppm) at 125.7 MHz. Solvent: DMSO-d_6. Further signals, C-5′ and C-6′ (for **d** and **e**-type compounds): 128.1 and 130.2 (**6d**), 126.4 and 128.9 (**6e**), 127.8 and 130.5 (**7d**), 131.3 and 127.9 (**7e**), 129.8 and 130.6 (**9d**), 126.3 and 130.4 (**9e**), 127.8 and 130.3 (**10d**), 127.5 and 126.3 (**10e**), 131.3 and 130.4 (**11d**), 126.7 and 128.9 (**11e**); CH_3(Et): 8.2, 8.3 (**6d**,**e**); CH_2(Et): 51.1 (**6d**,**e**).
[b] Assignments were supported by DEPT (except for **11c**–**e**), HMQC (except for **9b**) and also by HMBC (except for **9b**) measurements.
[c] X=S (**10a**–**e**), X=N (**11a**–**e**).
[d] For **6d**,**e**.
[e] C-2′6′ and C-3′,5′ lines for **a**–**c**-type compounds.
[f] Overlapping lines.
[g] Overlapping lines.
[h] Reversed assignments are also possible.
[i] Solvent: $CDCl_3$.

4. Experimental

4.1. General

Melting points were determined on a Kofler micro melting apparatus and are uncorrected. Elemental analyses were performed with a Perkin–Elmer 2400 CHNS elemental analyser in the Institute of Pharmaceutical Chemistry. Merck Kieselgel 60F_{254} plates were used for TLC, and Merck Silica gel 60 (0.063–0.100) for column chromatography. TfOH was purchased from AlfaAesar. Indol-2-one was purchased from Fluka. Indole and thiourea were purchased from Reanal. Substituted benzoylaminomethyltriethylammonium chlorides (**6a**–**c**),[19,23] *N*-hydroxymethylbenzamides,[24] *N*-chloromethylbenzamides,[25] and 3-benzoylaminomethylthio-1*H*-indoles (**7a**–**c**)[19] were prepared by the literature methods.

ESI mass spectra were obtained with a Finnigan MAT 95S double-focusing sector-field instrument. MeCN solutions of compounds were infused into the ESI through a plastic capillary at a constant flow of 100 μL/min (H_2O/MeCN 50:50 containing 0.1% AcOH). The ions were produced by using N_2 as sheath gas at 2 psi, with a spray voltage of 2.5 kV and a capillary temperature of 210 °C. Poly(propylene glycol) solution was used for the calibration. IR spectra were recorded in KBr pellets with a Bruker IFS 55 FT-spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 solution in 5-mm tubes at rt, on a Bruker DRX 500 spectrometer at 500 (^{1}H) or 125 (^{13}C) MHz, with TMS (δ_{TMS}=0 ppm) as internal reference, and the deuterium signal of the solvent as the lock. Assignments were supported by DEPT, HMQC, and HMBC measurements. DEPT spectra were run in a standard manner, using only the Θ=135° pulse to separate CH/CH_3 and CH_2 lines phased 'up' and 'down', respectively. 2D-HMQC and 2D-HMBC spectra were obtained by using the standard Bruker pulse programs.

4.2. Preparation of 1*H*-indole-3-thiol (5)

For the preparation of compound **5**, the method of Harris[26] was used, which is as follows.

To a vigorously stirred solution of indole (7.0 g, 60 mmol) and thiourea (4.7 g, 60 mmol) in 240 mL of methanol and water (2:1) was added a potassium iodide iodine (10.0 g, 60 mmol; 15.2 g, 60 mmol) solution in 120 mL of methanol and water (2:1) dropwise. The mixture was stirred (30 min) until the solution turned yellow. The solution was then evaporated to remove methanol and extracted with ethyl acetate. The remaining aqueous solution on further concentration in vacuum (50 mL), after cooling with ice-water yielded light brown crystals, which were filtered off and recrystallized from water to give 16.2 g of *S*-(3-indolyl)isothiouronium iodide. The isothiouronium salt (16.0 g, 50 mmol) was rapidly added to a 10% sodium hydroxide solution (120 mL), purged with nitrogen (0.5 h). With continued nitrogen purging, the mixture was heated to reflux for another 15 min, cooled down and the solution was filtered through a thin pad of Celite to a mixture of concentrated HCl (50 mL) and ice (60 g). The yellow precipitate formed was filtered off, washed with H_2O (3×20 mL) and dissolved in 10% sodium hydroxide solution (100 mL) rapidly, and the solution was filtered through a thin pad of Celite again to a mixture of concentrated HCl (40 mL) and ice (20 g). The precipitate formed was filtered off, washed with H_2O (4×20 mL), dried in vacuum exsiccator to provide **5** (6.6 g). Compound **5** was used without further purification.

Small sample was purified further on a short column of silica (CH_2Cl_2/*n*-hexane 3:2 purged with nitrogen) for analytical investigations.

Pale cream plates, mp: 101–103 °C (lit.[26] mp: 100–101 °C). $[M+H]^+$=149. Anal. Calcd for C_8H_7NS (149.21): C, 64.39; H, 4.73; N, 9.39; S, 21.49. Found: C, 64.67; H, 4.51; N, 9.21; S, 21.72; R_f (CH_2Cl_2/*n*-hexane 3:2) 0.63.

4.3. General procedure for substituted benzoylaminomethyltriethylammonium chlorides (6d,e)

The appropriate freshly synthesized substituted *N*-chloromethylbenzamide[25](0.1 mol) dissolved in dry acetone (80 mL) was added in one portion to a vigorously stirred solution of Et_3N (15.3 mL, 0.11 mol) in dry acetone (150 mL). After a white precipitate had formed, a further portion of acetone (100 mL) was added and the mixture was stirred at room temperature for 1 h. The white crystalline product was filtered off, and washed with acetone (2×25 mL). Compounds **6d**,**e** were used without further purification. Small samples were recrystallized from $CHCl_3$–acetone for analytical investigations.

*4.3.1. 2-Chlorobenzoylaminomethyltriethylammonium chloride (**6d**)*

A white crystalline powder, mp: 122–125 °C (decomp.), yield 82%. $[M+H]^+$=269. Anal. Calcd for $C_{14}H_{22}Cl_2N_2O$ (305.24): C, 55.09; H, 7.26; N, 9.18. Found: C, 54.87; H, 7.37; N, 9.08.

*4.3.2. 2-Methylbenzoylaminomethyltriethylammonium chloride (**6e**)*

A white crystalline powder, mp: 102–105 °C (decomp.), yield 58%. $[M+H]^+$=249. Anal. Calcd for $C_{15}H_{25}ClN_2O$ (284.82): C, 63.25; H, 8.85; N, 9.84. Found: C, 63.11; H, 9.02; N, 9.91.

4.4. General procedure for the preparation of substituted 3-benzoylaminomethylthio-1*H*-indoles (7d,e) from 1*H*-indole-3-thiol (5) and substituted benzoylaminomethyltriethylammonium chlorides (6d,e)

A mixture of 1*H*-indole-3-thiol **5** (3 g, 20.1 mmol), the corresponding substituted benzoylaminomethyltriethylammonium chloride (**6d**,**e**) (22.1 mmol) and Et_3N (1.2 mL, 8.6 mmol) in $CHCl_3$ (50 mL) was refluxed for 2 h. The organic phase was then extracted with H_2O (2×50 mL). The white precipitate formed in the second extraction was filtered off, and washed with H_2O (2×15 mL) and $CHCl_3$ (5 mL). The white crystalline powder was dissolved in $CHCl_3$ (60 mL)+MeOH (2 mL). The organic layer was extracted with H_2O (30 mL), dried (Na_2SO_4), and evaporated to provide **7d**,**e**.

*4.4.1. 3-(2-Chlorobenzoylaminomethylthio)-1H-indole (**7d**)*

A white crystalline powder, mp: 129–130 °C (from chloroform), yield 93%. $[M+H]^+$=317. Anal. Calcd for $C_{16}H_{13}ClN_2OS$ (316.81): C, 60.66; H, 4.14; N, 8.84; S, 10.12. Found: C, 60.50; H, 4.17; N, 8.98; S, 9.96.

*4.4.2. 3-(2-Methylbenzoylaminomethylthio)-1H-indole (**7e**)*

A white crystalline powder, mp: 146–149 °C (from chloroform), yield 90%. $[M+H]^+$=297. Anal. Calcd for $C_{17}H_{16}N_2OS$ (296.39): C, 68.89; H, 5.44; N, 9.45; S, 10.82. Found: C, 68.97; H, 5.50; N, 9.65; S, 10.99.

4.5. Preparation of substituted 2-benzoylaminomethylthio-1*H*-indoles (9a–e) from substituted 3-benzoylaminomethylthio-1*H*-indoles (7a–e)

To intensively stirred TfOH (1 mL), the well-powdered appropriate 3-benzoylaminomethylthio-(1*H*)-indole (**7a**–**e**) (0.5 g) was added portionwise over a period of 10–15 min at room temperature. If dissolution was not complete, the undissolved compound was dissolved by adjusting the mixture with a glass rod. The reaction mixture was then heated and stirred at 45 °C for 30 min, followed by the addition of EtOAc (20 mL). The organic layer was extracted with H_2O (20 mL), 5% $NaHCO_3$ solution (20 mL), and brine (10 mL). The organic phase was dried (Na_2SO_4), filtered, and evaporated to dryness, and the residue was purified by column chromatography (*n*-hexane/EtOAc 4:1) to provide **9a**–**e**.

*4.5.1. 2-Benzoylaminomethylthio-1H-indole (**9a**)*

A white crystalline powder, mp: 147–148 °C (mp:[19] 146–148 °C), yield 76%; R_f (*n*-hexane/EtOAc 4:1) 0.12. Analytical data are identical with the previously published results.[19]

*4.5.2. 2-(4-Chlorobenzoylaminomethylthio)-1H-indole (**9b**)*

A white crystalline powder, mp: 116–117 °C, yield 84%. $[M+H]^+$=317. Anal. Calcd for $C_{16}H_{13}ClN_2OS$ (316.81): C, 60.66; H, 4.14; N, 8.84; S, 10.12. Found: C, 60.82; H, 4.32; N, 8.92; S, 10.23; R_f (*n*-hexane/EtOAc 4:1) 0.12.

*4.5.3. 2-(4-Methylbenzoylaminomethylthio)-1H-indole (**9c**)*

A white crystalline powder, mp: 117–118 °C, yield 79%. $[M+H]^+$=297. Anal. Calcd for $C_{17}H_{16}N_2OS$ (296.39): C, 68.89; H, 5.44; N, 9.45; S, 10.82. Found: C, 68.82; H, 5.61; N, 9.49; S, 10.68; R_f (*n*-hexane/EtOAc 4:1) 0.12.

*4.5.4. 2-(2-Chlorobenzoylaminomethylthio)-1H-indole (**9d**)*

A white crystalline powder, mp: 59–62 °C, yield 81%. $[M+H]^+$=317. Anal. Calcd for $C_{16}H_{13}ClN_2OS$ (316.81): C, 60.66; H, 4.14; N, 8.84; S, 10.12. Found: C, 60.83; H, 4.05; N, 8.69; S, 9.92; R_f (*n*-hexane/EtOAc 4:1) 0.07.

*4.5.5. 2-(2-Methylbenzoylaminomethylthio)-1H-indole (**9e**)*

A white crystalline powder, mp: 97–99 °C, yield 69%. $[M+H]^+$=297. Anal. Calcd for $C_{17}H_{16}N_2OS$ (296.39): C, 68.89; H, 5.44; N, 9.45; S, 10.82. Found: C, 69.02; H, 5.59; N, 9.62; S, 10.77; R_f (*n*-hexane/EtOAc 4:1) 0.12.

4.6. Preparation of substituted 2-benzoylaminomethylthio-1*H*-indoles (9b–e) from 1,3-dihydro-2*H*-indole-2-thione (8) and substituted benzoylaminomethyltriethylammonium chlorides (6b–e)

A mixture of 1,3-dihydro-2*H*-indole-2-thione **8** (1 g, 6.7 mmol), the corresponding substituted benzoylaminomethyltriethylammonium chlorides (**6b**–**e**) (7.4 mmol) and Et_3N (0.8 mL, 5.7 mmol) in $CHCl_3$ (20 mL) was refluxed for 2 h. The organic phase was then extracted with H_2O (2×40 mL), dried (Na_2SO_4) and evaporated, and the residue was purified by column chromatography ($CHCl_3$/ethyl acetate 9:1) to provide **9b**–**e**.

The analytical data on **9b**–**e** were identical to those given above; **9b**: yield 91%, R_f ($CHCl_3$/ethyl acetate 9:1) 0.21; **9c**: yield 78%, R_f ($CHCl_3$/ethyl acetate 9:1) 0.23; **9d**: yield 64%, R_f ($CHCl_3$/ethyl acetate 9:1) 0.25; **9e**: yield 86%, R_f ($CHCl_3$/ethyl acetate 9:1) 0.25.

4.7. General procedure for the preparation of 2-thiobenzoylaminomethylthio-1*H*-indoles (10a–e)

To a solution of substituted 2-benzoylaminomethylthio-1*H*-indoles (**9a**–**e**) (4.0 mmol) in THF (60 mL), Lawesson's reagent (0.96 g, 2.4 mmol) and Et_3N (0.05 mL) were added in one portion. The reaction mixture was then heated under reflux for 5 h. After the addition of Et_3N (1 mL) and evaporation, the residue was purified by column chromatography, using *n*-hexane/EtOAc 4:1 containing 0.25% Et_3N as eluent, to give **10a**–**e**.

*4.7.1. 2-Thiobenzoylaminomethylthio-1H-indole (**10a**)*

A yellow oil, yield 56%. $[M+H]^+$=299. Anal. Calcd for $C_{16}H_{14}N_2S_2$ (298.43): C, 64.39; H, 4.73; N, 9.39; S, 21.49. Found: C, 64.61; H, 4.65; N, 9.41; S, 21.65; R_f (*n*-hexane/EtOAc 4:1) 0.27.

*4.7.2. 2-(4-Chlorothiobenzoylaminomethylthio)-1H-indole (**10b**)*

A yellow crystalline powder, mp: 101–103 °C, yield 81%. $[M+H]^+$=333. Anal. Calcd for $C_{16}H_{13}ClN_2S_2$ (332.87): C, 57.73; H, 3.94; N, 8.42; S, 19.27. Found: C, 57.91; H, 3.84; N, 8.40; S, 19.45; R_f (*n*-hexane/EtOAc 4:1) 0.29.

*4.7.3. 2-(4-Methylthiobenzoylaminomethylthio)-1H-indole (**10c**)*

A light-green crystalline powder, mp: 108–111 °C, yield 68%. $[M+H]^+$=313. Anal. Calcd for $C_{17}H_{16}N_2S_2$ (312.45): C, 65.35; H, 5.16; N, 8.97; S, 20.53. Found: C, 65.41; H, 5.23; N, 8.81; S, 20.74; R_f (*n*-hexane/EtOAc 4:1) 0.23.

*4.7.4. 2-(2-Chlorothiobenzoylaminomethylthio)-1H-indole (**10d**)*

A yellow oil, yield 72%. $[M+H]^+$=333. Anal. Calcd for $C_{16}H_{13}ClN_2S_2$ (332.87): C, 57.73; H, 3.94; N, 8.42; S, 19.27. Found: C, 57.62; H, 3.78; N, 8.40; S, 19.35; R_f (*n*-hexane/EtOAc 4:1) 0.15.

*4.7.5. 2-(2-Methylthiobenzoylaminomethylthio)-1H-indole (**10e**)*

A light-green oil, yield 54%. $[M+H]^+$=313. Anal. Calcd for $C_{17}H_{16}N_2S_2$ (312.45): C, 65.35; H, 5.16; N, 8.97; S, 20.53. Found: C, 65.31; H, 4.92; N, 9.14; S, 20.70; R_f (*n*-hexane/EtOAc 4:1) 0.26.

4.8. General procedure for the preparation of 2,9-dihydro-4-aryl-1,3-thiazino[6,5-*b*]indole (11a–e)

A solution of **10a–e** (0.5 g) and methyl iodide (0.5 mL) in acetone (15 mL) and a catalytic amount of 4-dimethylaminopyridine was heated to reflux for 5 h under an argon atmosphere with protection from light (Al foil). The acetone solution was then concentrated under reduced pressure. To the residue, EtOH (0.1 mL) and Et_2O (10 mL) were added to furnish the iodide salt of **11a–e** as a yellow crystalline powder. After filtration, the crystals were washed with cold acetone (2×2 mL), and recrystallized from EtOH/Et_2O. The crystals were dissolved in H_2O (20 mL) and a small amount of MeOH (until complete dissolution), $CHCl_3$ (15 mL) was added and the mixture was neutralized by the portionwise addition of 10% KOH solution. The organic layer was separated, washed with H_2O (10 mL), dried (Na_2SO_4) and evaporated. After trituration with *n*-hexane, **11a–e** were obtained as yellow crystalline powders.

*4.8.1. 2,9-Dihydro-4-phenyl-1,3-thiazino[6,5-b]indole (**11a**)*

A yellow crystalline powder, mp: 209–211 °C (iodide salt mp: 260–263 °C), yield 58%. $[M+H]^+$=265. Anal. Calcd for $C_{16}H_{12}N_2S$ (264.35): C, 72.70; H, 4.58; N, 10.60; S, 12.13. Found: C, 72.91; H, 4.63; N, 10.74; S, 12.01.

*4.8.2. 2,9-Dihydro-4-(4-chlorophenyl)-1,3-thiazino[6,5-b]-indole (**11b**)*

A yellow crystalline powder, mp: 245–247 °C (iodide salt mp: 256–258 °C), yield 62%. $[M+H]^+$=299. Anal. Calcd for $C_{16}H_{11}ClN_2S$ (298.79): C, 64.32; H, 3.71; N, 9.38; S, 10.73. Found: C, 64.11; H, 3.75; N, 9.47; S, 10.86.

*4.8.3. 2,9-Dihydro-4-(4-methylphenyl)-1,3-thiazino[6,5-b]-indole (**11c**)*

A yellow crystalline powder, mp: 227–229 °C (iodide salt mp: 254–257 °C), yield 65%. $[M+H]^+$=279. Anal. Calcd for $C_{17}H_{14}N_2S$ (278.37): C, 73.35; H, 5.07; N, 10.06; S, 11.52. Found: C, 73.18; H, 5.26; N, 9.92; S, 11.65.

*4.8.4. 2,9-Dihydro-4-(2-chlorophenyl)-1,3-thiazino[6,5-b]-indole (**11d**)*

A yellow crystalline powder, mp: 146–148 °C (iodide salt mp: 257–259 °C), yield 57%. $[M+H]^+$=299. Anal. Calcd for $C_{16}H_{11}ClN_2S$ (298.79): C, 64.32; H, 3.71; N, 9.38; S, 10.73. Found: C, 64.27; H, 3.87; N, 9.46; S, 10.81.

*4.8.5. 2,9-Dihydro-4-(2-methylphenyl)-1,3-thiazino[6,5-b]-indole (**11e**)*

A yellow crystalline powder, mp: 177–179 °C (iodide salt mp: 263–266 °C), yield 35%. $[M+H]^+$=279. Anal. Calcd for $C_{17}H_{14}N_2S$ (278.37): C, 73.35; H, 5.07; N, 10.06; S, 11.52. Found: C, 73.48; H, 5.27; N, 10.14; S, 11.64.

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