One-Step Ring-Closure Procedure for 4,5-Dihydro-1,3-thiazino[5,4-*b*]indole Derivatives with Lawesson's Reagent. The Fifth Dihydro-1,3-thiazino[*b*]indole Isomer

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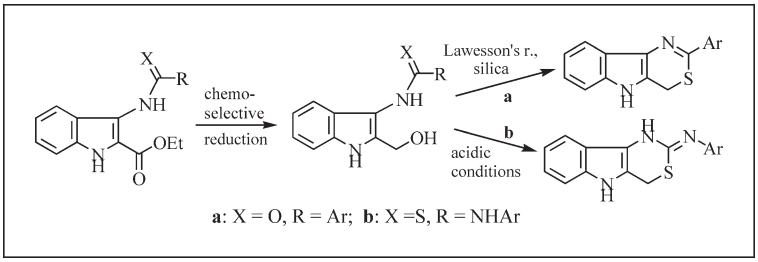

We report a convenient approach for the synthesis of a new ring system: 4,5-dihydro-1,3-thiazino[5,4-*b*]indoles. The procedure involves the use of Lawesson's reagent in the presence of silica to achieve the one-step ring-closure reactions of 2-benzoylamino-3-hydroxymethylindole intermediates to furnish 4,5-dihydro-2-aryl-1,3-thiazino[5,4-*b*]indoles. 2-Phenylimino-1,3-thiazino[5,4-*b*]indoles were obtained via the corresponding 3-phenylthiourea-2-carboxylic acid ester derivatives by chemoselective reduction of the ester group, followed by ring closure under acidic conditions. The structures of the novel products were elucidated by IR, ^{1}H-NMR, and ^{13}C-NMR spectroscopy, including 2D-HMQC, 2D-HMBC, and DEPT measurements.

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INTRODUCTION

In contrast with their valuable pharmacological activities, few derivatives are known of the six possible 1,3-thiazinoindoles condensed at bond *b* of the indole skeleton (Fig. 1). Probably the best-known compounds of this family are 1,3-thiazino[6,5-*b*]indole phytoalexins [1]. The phytoalexins, not present in healthy plant tissues, are synthesized in plants in response to by attack pathogens or physical or chemical stress, probably as a result of the *de novo* synthesis of enzymes [2]. Takasugi *et al.* isolated the first thiazinoindole phytoalexin, cyclobrassinin (2-methylthio-thiazino[6,5-*b*]indole), from Chinese cabbage [3], and ~30 phytoalexins are now known in cruciferous plants, 6 of them possessing a thiazinoindole skeleton [1]. Besides its antimicrobial activity, cyclobrassinin exerts an antiproliferative effect against human cancer cell lines [4]. As concerns the remaining thiazino[6,5-*b*]indoles, only a few derivatives of cyclobrassinone [5] and 2-phenyl analogues of cyclobrassinin [6] have been synthesized and investigated.

We recently prepared two regioisomeric 1,3-thiazinoindoles (**2,** Fig. 1); 2-methylthio-1,3-thiazino[5,6-*b*]indole (isocyclobrassinin) and its 2-benzylthio analogue, both of which exerted good *in vitro* antiproliferative effects on cervix adenocarcinoma (HeLa), breast adenocarcinoma (MCF7), and squamous skin carcinoma (A431) cell lines [7]. For structure-activity relationships, further analogues were synthesized [8]. The highest cytotoxic effect was displayed by 2-phenylimino-1,3-thiazino[5,6-*b*]indole, which demonstrated inhibition activity comparable to that of cisplatin on the above three cell lines. This sulfur analogue of β-carboline proved to be a novel type of antitumor compound [7].

Procedures were also devised for a further two new thiazinoindole ring systems: 4-thiaharmalan analogues (2,5-dihydro-1,3-thiazino[5,6-*b*]indoles, **3** Fig. 1) [9] and γ-carboline analogue 2,9-dihydro-4-aryl-1,3-thiazino[6,5-*b*]indoles (**4**, Fig. 1) were obtained [10].

Among the remaining positional isomers (types **5** and **6**, Fig. 1), 1,5-dihydro-1,3-thiazino[5,4-*b*]indole-2,4-dithione was prepared from 3-aminoindole with carbon disulfide [11]. A series of 2-alkyl- or arylimino-1,3-thiazino[5,4-*b*]indol-4-one derivatives have been synthesized by ring closure of the appropriate indolylthiourea derivatives in polyphosphoric acid [12]. Members of this class

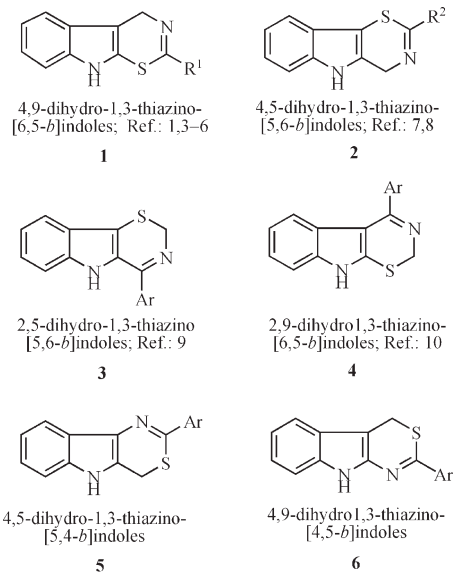


Figure 1. R^1 = MeS, Ar; R^2 = MeS, BnS, Ar, PhN.

of compounds inhibit human leukocyte elastase and α-chymotrysin. To the best of our knowledge, a procedure for the synthesis of 4,5-dihydro-1,3-thiazino[5,4-*b*]indoles (**5**, Fig. 1) has not yet been published previously.

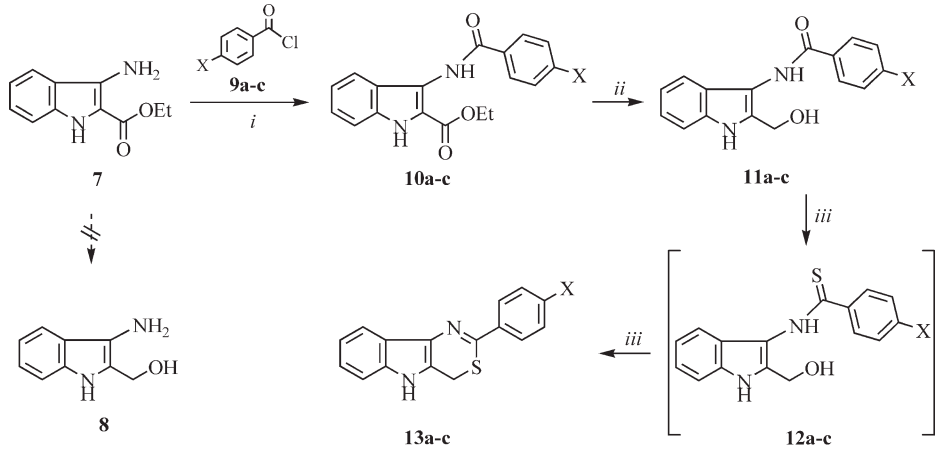
As a continuation of our work on *S*,*N* heterocycles [13–15], including thiazinoindoles [6–10], we now describe an efficient route for the synthesis of the fifth 1,3-thiazinoindole isomer: 4,5-dihydro-1,3-thiazino[5,4-*b*]indoles (**13a**−**c,** Scheme 1) and 2-phenylimino derivatives **17a**−**c** (Scheme 2). These compounds are bioisosteres of 4,5-dihydro-1,3-thiazino[5,6-*b*]indoles (**2**, Fig. 1) [7] possessing *in vitro* antiproliferative effects.

RESULTS AND DISCUSSION

For the preparation of different 1,3-thiazines, 1,3-aminoalcohols are generally used by using two-component reactions [16]. In our hands, the reduction of ethyl 3-aminoindole-2-carboxylate (**7**) to obtain aminoalcohol **8** under different reduction conditions failed. One step procedures for 1,3-*S*,*N* heterocycles generally utilize thioamides containing a hydroxy group [17] or amides containing a hydroxy group [18]. In the latter case 1,3-thiazines are formed in low yields, and side products can also be isolated. To attempt one-component ring-closure reactions, we prepared substituted ethyl 3-benzoylaminoindole-2-carboxylate derivatives **10a**−**c** from ethyl 3-aminoindole-2-carboxylate **7** and the corresponding benzoyl chlorides **9a**−**c** under Schotten-Baumann conditions. The chemoselective reduction of benzamido esters **10a**−**c** with lithium aluminum hydride in THF provided substituted *N*-benzoyl aminoalcohols **11a**−**c** under mild reaction conditions. The one-step cyclization reaction of **11a**−**c** with Lawesson's reagent in toluene proceeded smoothly and various side-products were observed on TLC. Interestingly, when silica gel was added to the reaction mixture (Lawesson's reagent in toluene at 90°C), the target thiazines were achieved within a relatively short reaction time and in good yield. Thus, 2-aryl-1,3-thiazino[5,4-*b*]indole derivatives **13a**−**c** were obtained, most probably via intermediates **12a**−**c**.

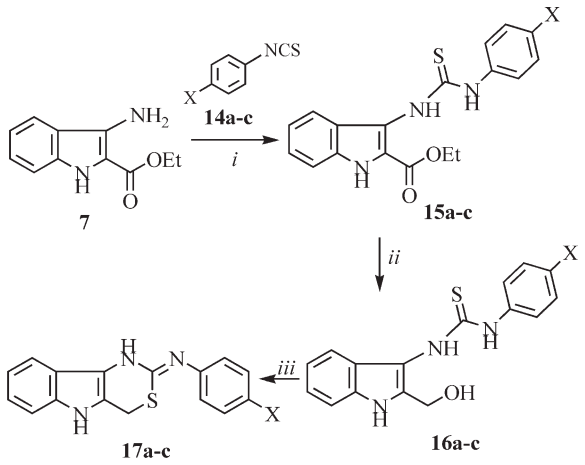
To prepare 2-phenylimino-substituted thiazinoindoles, **7** was reacted with phenyl isothiocyanates at 110°C to provide thioureas **15a**−**c**. Chemoselective reduction of

Scheme 1. Reagents and conditions: (i) Toluene, chloroform, 6% NaOH, 20 min; (ii) $LiAlH_4$,THF, 0°C, 1 h; (iii) Lawesson's reagent, silica gel, toluene, 90°C, 1 h.



a: X = H; **b**: X = Cl; **c**: X = Me

Scheme 2. Reagents and conditions: (i) Neat, 110°C, 30 min; (ii) $LiAlH_4$,THF, 0°C, 1 h; (iii) 5% HCl/EtOH, reflux, 20 min.



a: X = H; **b**: X = Cl; **c**: X = OMe

the ester functionality with lithium aluminum hydride in THF gave 2-hydroxymethylindole derivatives **16a**−**c**. 2-Phenylimino-1,3-thiazino[5,4-*b*]indoles **17a**−**c** were obtained from **16a**−**c** in HCl/EtOH, followed by column chromatographic purification.

The spectral data (IR, ^{1}H- and ^{13}C-NMR) on the new compounds are reported in Tables 1 and 2. The presumed structures follow unambiguously from these data. Only the following additional remarks are necessary:

The lower amide-I frequencies of **11a–c** (1627 ± 1 cm^{-1}) are noteworthy relative to those of **10a–c** (1655 ± 6 cm^{-1}). The values observed for the compounds of type **11** do not lie in the expected interval characteristic of secondary amides [19]. This can be explained by the strong polarization of the amide group resulting in a lower bond order and consequently lower amide-I frequency in such derivatives. This effect is hindered in **10a–c** by the electron-withdrawing influence of the 2-carbethoxy group. This phenomenon confirms strong conjugation between the ester and arylamide groups via the 2,3-double bond of the indole skeleton of **10a–c**. In accord with this, the ^{13}C-NMR chemical shifts of C-3 are higher for **10a–c** (120–124 ppm) than for **11a–c** (110 ppm), indicating lower electron density for the former carbons. A similar delocalization is not present in thioureas **16a–c** as the other NH substituent attached to the thiocarbonyl group acts as an electron reservoir. The high ^{1}H-NMR chemical shift of the *ortho* aryl hydrogens (7.92 ± 0.03 ppm) is a consequence of the tautomeric preference with a C=N bond for **17a–c**; this can be explained by the substitution of the electron-attracting C=N bond (instead of NH) on C_{Ar}-1 and by the upfield shift of the indole C-2 line in the ^{13}C-NMR spectra (113.4 ± 0.1 ppm) as compared with those for **13a–c** (116.2 ± 0.2 ppm).

In summary, we report a convenient approach for the synthesis of a new ring system: 4,5-dihydro-1,3-thiazino[5,6-*b*]indoles. Indole 3-benzamido- and 3-phenylthiourea-2-carboxylic acid esters (**10a**−**c, 15a**−**c**) were chemoselectively reduced to the corresponding 2-hydroxymethylindole derivatives (**11a**−**c, 16a**−**c**). Treatment of intermediates **11a**−**c** with Lawesson's reagent in the presence of silica gel provided thiazinoindoles **13a**−**c** in good yields in a one-step protocol. The target 2-phenyliminothiazinoindoles (**17a**−**c**) were obtained from **16a**−**c** by acidic treatment.

EXPERIMENTAL

Melting points were determined on a Kofler micro melting apparatus and are uncorrected. Elemental analyses were performed with a PerkinElmer 2400 CHNS elemental analyser. Merck Kieselgel 60F_{254} plates were used for TLC, and Merck Silica gel 60 (0.063–0.100) for column chromatography. Ethyl 3-aminoindole-2-carboxylate (**7**) was prepared by a literature method [20].

The ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes at room temperature, on a Bruker DRX 500 spectrometer at 500.13 (^{1}H) and 125.76 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. The standard Bruker micro-program to generate NOE was used. DEPT spectra were run in a standard manner, using only the $\theta = 135^o$ pulse to separate CH/CH_3 and CH_2 lines phased "up" and "down," respectively. The 2D-HSC spectra were obtained by using the standard Bruker pulse program.

General procedure for substituted ethyl 3-benzoylaminoindole-2-carboxylates (10a−**c).** Amino acid ester **7** (0.72 g, 3.5 mmol) was dissolved in a mixture of toluene (25 mL) and chloroform (50 mL). To this solution, sodium hydroxide (0.62 g, 15.4 mmol) dissolved in water (10 mL) was added. After the addition of benzoyl chloride (0.42 g, 3.9 mmol), the reaction mixture was shaken intensively for 20 min. The crystals that separated out were filtered off, washed in turn with water and with toluene, and dried. The white crystalline benzamides were recrystallized.

Ethyl 3-benzoylaminoindole-2-carboxylate (10a). White crystalline needles, mp: 166–168°C (from EtOH), Lit [21] mp: 171–171.5°C yield 1.00 g (92%). Anal. Calcd. for $C_{18}H_{16}N_2O_3$ (308.33): C, 70.12; H, 5.23; N, 9.09. Found: C, 70.38; H, 5.39; N, 8.89.

Ethyl 3-(4-chlorobenzoyl)aminoindole-2-carboxylate (10b). White crystalline powder, mp: 245–246°C (from EtOH, $CHCl_3$), yield 1.02 g (85%). Anal. Calcd. for $C_{18}H_{15}ClN_2O_3$ (342.78): C, 63.07; H, 4.41; N, 8.17. Found: C, 63.28; H, 4.55; N, 8.09.

Ethyl 3-(4-methylbenzoyl)aminoindole-2-carboxylate (10c). White crystalline needles, mp: 204–206°C (from EtOH), yield 0.94 g (83%). Anal. Calcd. for $C_{19}H_{18}N_2O_3$ (322.36): C, 70.79; H, 5.63; N, 8.69. Found: C, 70.65; H, 5.83; N, 8.84.

General procedure for chemoselective reduction of substituted ethyl 3-benzoylaminoindole-2-carboxylates (10a−**c).** To intensively stirred and cooled (ice-water) THF (5 mL), lithium aluminum hydride (0.24 g, 6.3 mmol) was added in small portions. To this cooled suspension a solution of **10a**−**c** (2.5

Table 1

Characteristic IR frequencies[a] and ^{1}H NMR data[b] for compounds **10a–c, 11a–c, 13a–c, 15a–c, 16a–c**, and **17a–c**.[c]

Compound	νNH + νOH band[d]	νC=O band[e]	$\gamma C_{Ar}H$ band[f]	CH_3 t(3H)[g]	XCH_2[h] *s, d* or *qa*	H-4 ~*d*[f]	H-5 ~*t*[f]	H-6 ~*t*[f]	H-7 ~*d*[f]	H-2′,6′ ~*d* (2H)[i]	H-3′,5′ ~*t* (2H)[j]	H-4′ ~*t* (1H)[k]	NH amide	NH indole
10a	3322	1681	737	1.27	4.32	7.76	7.10	7.14	7.32	8.09	7.57	7.60	10.14	11.80
10b	3313	1678	741	1.25	4.30	7.67	7.08	7.30	7.46	8.07	7.64	–	10.2	11.8
10c	3322	1676	740	1.26	4.31	7.72	7.08	7.30	7.46	7.96	7.36	–	10.03	11.76
11a	~3250	1627	723	–	4.62	7.42	7.00	7.10	7.38	8.08	7.55	7.59	9.90	11.06
11b	3355, 3265	1628	746	–	4.56	7.38	6.97	7.07	7.35	8.07	7.61	–	9.94	11.05
11c	3352, 3266	1626	743	–	4.56	7.38	6.97	7.07	7.35	7.96	7.34	–	9.78	11.02
13a	3250–2800	1582	758	–	4.52	7.73	7.12	7.16	7.39	8.04	7.51[l]	7.50[l]	–	11.35
13b	3383	1534	750	–	4.51	7.71	7.11	7.16	7.39	8.03	7.56	–	–	11.38
13c	~3245	1532	742	–	4.49	7.70	7.10	7.14	7.37	7.92	7.31	–	–	11.30
15a	3311	1653	736	1.33	4.33	7.57	7.08	7.27	7.44	7.52	7.32	7.12	9.38	11.78
15b	3311	1651	735	1.32	4.32	7.55[l]	7.08	7.28	7.45	7.55[l]	7.36	–	9.53, 9.72	11.81
15c	3306	1658	738	1.34	4.32	7.57	7.08	7.27	7.43	7.35	6.89	–	9.22, 9.50	11.75
16a	3350–2800	1661	735	–	4.58	7.36[l]	7.00	7.09	7.36[l]	7.47[m]	7.29[m]	7.10	8.8, 9.3[n]	9.3[n]
16b	3166	1524	744	–	4.58	~7.35	7.00	7.09	~7.36	~7.35	~7.35	–	8.88, 9.52	11.2
16c	3299, 3180	1535	738	–	4.58	7.37	7.01	7.09	7.36	~7.3[l]	6.87	–	~7.3,[l] ~8.7	11.18
17a	3200–2800	1605	741	–	4.38	7.57	7.02	7.07	~7.3[l]	7.91	~7.3[l]	6.94	9.10	10.85
17b	3390	1600	747	–	4.39	7.57	7.02	7.07	7.30	7.95	7.35	–	9.25	10.88
17c	3406	1592	737	–	4.35	7.54	7.00	7.05	7.28	7.82	6.90	–	~8.93	10.79

[a] In KBr discs (cm^{-1}). Further bands, Amide-I: 1661 (**10a),** 1649 (**10b**), 1651 (**10c**); νC—O: 1253 (**10a**), 1248 (**10b,c**), 1023 (**11a**), 1007 (**11b**), 1015 (**11c**), 1271 (**15a** and **16a**), 1263 (**15b**), 1243 (**15c** and **16b,c**); $\gamma C_{Ar}H$ and $\gamma C_{Ar}C_{Ar}$ bands (*mono-* or *para*-disubst. benzene ring): 710 (**10a**), 843 (**10b**), 834 (**10c**), 688 (**11a**), 845 (**11b**), 836 (**11c**), 737, 686 (**11a**), 828 (**13b**, **15c**, **16c** and **17b**), 819 (**13c** and **15b**), 693 (**16a**), 832 (**16b** and **17c**) 690 (**17a**).

[b] In DMSO-d_6 solution at 500.1 MHz. Chemical shifts in ppm ($\delta_{TMS} = 0$ ppm), coupling constants in Hz. Further signals: $ArCH_3$, *s* (3H): 2.40 (**10c** and **11c**), 2.37 (**13c**); OCH_3, *s* (3H): 3.74 (**15c**, **16c** and **17c**); OH, *t*, *J*: 5.3 (1H): 5.20 (**11a**), 5.16 (**11b**,**c** and **16c**), 5.18 (**16a,b**).

[c] Assignments were supported by HMQC (except for **10c**, **11c**, **13c**, **15c** and **17a**), HMBC (except for **10a,c**, **11a,c**, **13c**, **15c** and **17a**)

[d] Broad or very broad overlapping bands of NH and OH groups, separated maximum at 3395 (**17a**).

[e] Ester (**10a–c** and **15a–c**), amide I (**11a–c**), νC=N (**13a–c** and **17a–c**), thiourea (**16a–c**). Split, with the second maximum at 1511 (**16a**), 1583 (**17a**), 1579 (**17c**).

[f] Indole ring.

[g] Ethyl group, *J*: 7.1, 7.3 (**15a,b**).

[h] X=O, *qa* (**10a–c** and **15a–c**), X=O, *d* (*J*: 5.2, (**11a,c**), 5.5 (**11b** and **15b)** 4.9 (**16a,c**), X=S, *s* (**13a–c** and **17a–c**).

[i,j,k] A/B/C part of an AA′BB′C (for **a**-type compd.) or AA′BB′ spectrum (**b** and **c**-type compd.).

[l,n] Overlapping signals.

[m] Broad signal due to hindered rotation of the thiourea moiety.

mmol) in THF (10 mL) was added dropwise over a period of 30 min. The reaction mixture was stirred at the same temperature for 30 min. Ethyl acetate (40 mL) was then added dropwise during 5 min, followed by the dropwise addition of water (30 mL) during 10 min. After stirring for 10 min, the phases were separated, the organic phase was dried (sodium sulfate) and evaporated (water bath <50°C) and the residue was purified by column chromatography, with ethyl acetate:*n*-hexane (2:1) as eluent to give **11a–c** as a crystalline powder.

3-Benzoylamino-2-hydroxymethylindole (11a). Pale-brown crystalline needles, mp: 222–224°C, yield 0.47 g (71%). Anal. Calcd. for $C_{16}H_{14}N_2O_2$ (266.29): C, 72.16; H, 5.30; N, 10.52. Found: C, 72.28; H, 5.41; N, 10.39.

3-(4-Chlorobenzoyl)amino-2-hydroxymethylindole (11b). Pale-brown crystalline powder, mp: 219–221°C, yield 0.56 g (74%). Anal. Calcd. for $C_{16}H_{13}ClN_2O_2$ (300.74): C, 63.90; H, 4.36; N, 9.31. Found: C, 64.15; H, 4.39; N, 9.09.

3-(4-Methylbenzoyl)amino-2-hydroxymethylindole (11c). Pale-brown crystalline powder, mp: 208–212°C, yield 0.46 g (65%). Anal. Calcd. for $C_{17}H_{16}N_2O_2$ (280.32): C, 72.84; H, 5.75; N, 9.99. Found: C, 72.71; H, 5.57; N, 9.72.

General procedure for 4,5-dihydro-2-aryl-1,3-thiazino[5,4-b]indoles (13a−c) from 3-benzoylamino-2-hydroxymethylindole (11a−c). To a suspension of 3-benzoylamino-2-hydroxymethylindoles (**11a**−**c**) (1.6 mmol) in toluene (20 mL), Lawesson's reagent (0.7 g, 1.7 mmol) was added in one portion, followed by the addition of silica gel powder (0.5 g). The reaction mixture was stirred at 95°C for 3 h. After evaporation, the residue was purified by column chromatography, with *n*-hexane:ethyl acetate 4:1 as eluent, to give **13a**−**c** as a crystalline powder.

4,5-Dihydro-2-phenyl-1,3-thiazino[5,4-b]indole (13a). Brownish-green crystalline powder, mp: 180–186°C, yield 0.26 g (61%). 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, 72.92; H, 4.44; N, 10.51; S, 12.31.

4,5-Dihydro-2-(4-chlorophenyl)-1,3-thiazino[5,4-b]indole (13b). Brownish-green crystalline powder, mp: 185–189°C, yield 0.25 g (53%). 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, 64.54; H, 3.65; N, 9.22; S, 10.97.

4,5-Dihydro-2-(4-methylphenyl)-1,3-thiazino[5,4-b]indole (13c). Brownish-green crystalline powder, mp: 164–168°C,

Table 2

^{13}C NMR chemical shifts[a] for compounds **10a–c**, **11a–c**, **13a–c**, **15a–c**, **16a–c**, and **17a–c**.[b]

Compound	CH_3 (Et)	C=O ester	C=O amide[c]	C-2	C-3	C-3a	C-4 Indole	C-5 Ring	C-6	C-7	C-7a	OCH_2 or SCH_2[d]	C-1′	C-2′,6′ Aryl	C-3′,5′ Group	C-4′
10a	15.1	162.3	165.9	119.7[e]	123.7	121.4[e]	122.9	120.5	126.1	113.5	136.2	61.3	135.3	128.4	129.4	132.5
10b	15.1	162.1	165.0	120.2[e]	120.7[e]	123.9	122.5	120.6	126.1	113.5	136.1	61.3	134.0	130.4	129.5	137.3
10c	15.1	162.3	165.7	119.5[e]	123.6	121.5[e]	123.0	120.4	126.1	113.4	136.2	61.3	132.4	129.9	128.5	142.5
11a	–	–	166.7	134.2	110.4	125.3	119.1	119.4	121.9	112.2	134.8	55.8	135.5	128.6	129.2	132.2
11b	–	–	165.6	134.16[e]	110.1	125.2	119.1	119.4	121.8	112.2	134.8	55.7	134.2[e]	130.5	129.3	137.0
11c	–	–	166.6	134.1	110.5	125.3	119.1	119.3	121.8	112.2	134.1	55.8	132.6	128.6	129.7	142.1
13a	–	–	149.3	124.4	116.2	125.1	117.7	120.9	122.8	112.7	135.5	24.0	138.7	127.5	129.5	131.1
13b	–	–	147.9	124.5	116.3	125.1	117.7	121.0	122.9	112.7	135.6	24.0	137.4	129.1	129.5	135.7
13c	–	–	149.3	124.4	116.0	125.1	117.7	120.8	122.8	112.6	135.5	24.0	136.0	130.0	127.5	141.0
15a	15.2	161.7	181.6	121.8	121.0	124.7	121.6	120.7	125.8	113.6	136.0	61.3	140.6	124.8	129.1	125.3
15b	15.2	161.6	181.7	120.6[e]	122.0	124.7	121.4	120.8	125.9	113.6	136.0	61.3	139.7	126.5	128.9	129.1
15c	15.2	161.7	181.8	121.69[e]	121.1[e]	124.7	121.75	120.7	125.8	113.5	136.0	61.2	133.4	127.1	114.4	157.4
16a	–	–	181.9	135.6			118.5	119.9	122.2	112.5	135.0	55.4	140.7	125.3[f]	129.0	125.3[f]
16b	–	–	181.9	135.6[e]		125.0	118.4	119.9	122.1	112.5	135.0[f]	55.4	139.8	127.5	128.8	129.1
16c	–	–	182.3	135.1	127.4	125.2	118.5	119.9	122.1	112.5	135.7	55.4	133.5	127.4	114.2	157.4
17a	–	–	144.2[e]	124.3[g]	113.4	124.5[g]	117.6	119.5[h]	122.0[k]	112.3	135.2	25.0	142.4[e]	122.13[k]	129.4	119.7[h]
17b	–	–	144.1	124.1	113.5	124.4	117.6	119.7	122.1	112.3	135.2	25.0	141.3	120.9	129.3	125.5
17c	–	–	144.3	124.5[e]	113.3	124.6[e]	117.6	119.6	122.0	112.2	135.1	25.0	135.8	121.0	114.6	154.8

[a] In ppm (δ_{TMS} = 0 ppm) at 125.7 MHz. Solvent: DMSO-d_6. Further signals, $ArCH_3$: 21.9 (**10c** and **11c**), 21.8 (**13c**); OCH_3: 56.1 (**15c** and **16c**), 56.0 (**17c**). Due to slow motion (hindered rotation) of the thiourea moiety, it was not possible to identify the C-3 (**16a,b**) and C-3a lines(**16a**).
[b] Assignments were supported by DEPT (except for **16b** and **15a**), HMQC (except for **10c**, **11c**, **13c, 15c** and **17a**) and HMBC (except for **10a,c**, **11a,c, 13c**, **15c** and **17a**) measurements.
[c] C=S (**15a–c** and **16a–c**), C=N (**13a–c** and **17a–c**).
[d] For **13a–c** and **17a–c**.
[e g,h,k] Reversed assignments are also possible.
[f] Overlapping lines.

yield 0.33 g (75%). 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, 4.92; N, 9.83; S, 11.77.

General procedure for thiourea derivatives (15a-c) from ethyl 3-aminoindole-2-carboxylate (7) and substituted phenylisothiocyanates (14a-c). Amino acid ester **7** (1.2 g, 4.8 mmol) was mixed thoroughly with the corresponding substituted phenyl isothiocyanate **(14a−c)** (5 mmol) in a round bottle, and the mixture was heated at 110°C for 30 min. To the crystalline thiourea derivatives, ethyl acetate was then added. The crystals were filtered off, washed with ethyl acetate, and recrystallized.

Phenyl thiourea ester derivative (15a). White crystalline powder, mp: 194–196°C (from EtOH, $CHCl_3$), Lit [3] mp: 184–185°C, yield 1.50 g (92%). Anal. Calcd. for $C_{18}H_{17}N_3O_2S$ (339.41): C, 63.70; H, 5.05; N, 12.38; S, 9.45. Found: C, 63.49; H, 5.12; N, 12.51; S, 9.67.

4-Chlorophenyl thiourea ester derivative (15b). White crystalline powder, mp: 187–188°C (from EtOH, $CHCl_3$), Lit [22] mp: 179–180°C, yield 1.68 g (94%). Anal. Calcd. for $C_{18}H_{16}ClN_3O_2S$ (373.86): C, 57.83; H, 4.31; N, 11.24; S, 8.58. Found: C, 58.04; H, 4.53; N, 11.26; S, 8.42.

4-Methoxyphenyl thiourea ester derivative (15c). White crystalline flakes, mp: 181–182°C (from EtOH), yield 1.15 g (65%). Anal. Calcd. for $C_{19}H_{19}N_3O_3S$ (369.43): C, 61.77; H, 5.18; N, 11.37; S, 8.68. Found: C, 61.52; H, 5.07; N, 11.49; S, 8.72.

General procedure for chemoselective reduction of thiourea derivatives (15a−c). To an intensively stirred and cooled (ice water) THF (5 mL) lithium aluminum hydride was added (0.24 g, 6.3 mmol) was added in small portions. To this cooled suspension a solution of **15a−c** (3.2 mmol) in THF (10 mL) was added dropwise over a period of 30 min. The reaction mixture was stirred at the same temperature for 30 min. Ethyl acetate (40 mL) was then added dropwise (5 min), followed by the dropwise addition of water (1 mL). After stirring for 10 min. the reaction mixture was filtered, and the filtrate dried (sodium sulphate) evaporated (water bath <50°C), and the residue was purified by column chromatography, using ethylacetate:*n*-hexane (2:1) as eluent to give **16a-c** as a crystalline powder.

Phenyl thiourea alcohol derivative (16a). Pale-brown crystalline powder, mp: 195–197°C, yield 0.51 g (54%). Anal. Calcd. for $C_{16}H_{15}N_3OS$ (297.38): C, 64.62; H, 5.08; N, 14.13; S, 10.78. Found: C, 64.82; H, 5.21; N, 13.91; S, 10.89.

4-Chlorophenyl thiourea alcohol derivative (16b). Pale-brown crystalline powder, mp: 177–178°C, yield 0.58 g (55%). Anal. Calcd. for $C_{16}H_{14}ClN_3OS$ (331.82): C, 57.91; H, 4.25; N, 12.66; S, 9.66. Found: C, 58.21; H, 4.07; N, 12.42; S, 58.48.

4-Methoxyphenyl thiourea alcohol derivative (16c). Pale-brown crystalline powder, mp: 190–192°C, yield 0.65 g (62 %). Anal. Calcd. for $C_{17}H_{17}N_3O_2S$ (327.40): C, 62.36; H, 5.23; N, 12.83; S, 9.79. Found: C, 62.55; H, 5.49; N, 12.61; S, 9.51.

General procedure for preparation of 2-arylimino-1,3-thiazino[5,4-b]indoles 17a–c from thiourea alcohol derivatives (16a–c). The appropriate thiourea alcohol derivative **16a–c** (0.9 mmol) was suspended in absol. EtOH (10 mL). 20% HCl/EtOH (2.5 mL) was added to the mixture, and it was refluxed for 20 min. After evaporation the residue was

dissolved in an extraction funnel in $CHCl_3$ (20 mL) and MeOH (1 mL), water was added (10 mL) and the mixture was neutralized with 10% $NaHCO_3$ solution. The organic layer was separated, extracted with water (10 mL), dried and evaporated. The residue was purified by column chromatography, with ethyl acetate:*n*-hexane (3:2) as eluent, to give **17a–c** as a crystalline powder.

2-Phenylimino-1,3-thiazino[5,4-b]indole (17a). Pale-brown crystalline powder, mp: 179–183°C, yield 0.11 g (42%). Anal. Calcd. for $C_{16}H_{13}N_3S$ (279.36): C, 68.79; H, 4.69; N, 15.04; S, 11.48. Found: C, 68.71; H, 4.88; N, 14.87; S, 11.73.

2-(4-Chlorophenylimino)-1,3-thiazino[5,4-b]indole (17b). Pale-brown crystalline powder, mp: 184–190°C, yield 0.11 g (40%). Anal. Calcd. for $C_{16}H_{12}ClN_3S$ (313.81): C, 61.24; H, 3.85; N, 13.39; S, 10.22. Found: C, 61.10; H, 4.02; N, 13.61; S, 10.51.

2-(4-Methoxyphenylimino)-1,3-thiazino[5,4-b]indole (17c). Pale-brown crystalline powder, mp: 174–177°C, yield 0.14 g (49 %). Anal. Calcd. for $C_{17}H_{15}N_3OS$ (309.39): C, 66.00; H, 4.89; N, 13.58; S, 10.36. Found: C, 65.82; H, 6.17; N, 13.71; S, 10.56.

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