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Synthesis of thiazino[6,5-*b*]indole derivatives, analogues of the phytoalexin cyclobrassinin. A new method for preparation of 3-aminomethylindole

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Abstract—An efficient non-reductive synthesis of 3-aminomethylindole (**6**) was developed from gramine (**1**) via 3-phthalimidomethylindole (**2**). The reactions of amine **6** with substituted methyl dithiobenzoates gave 3-(arylthiocarbonylaminomethyl)indoles. The Hugerschoff ring-closure reactions of the thiobenzamide intermediates (**11a–f**) with phenyltrimethylammonium tribromide and subsequent basic treatment furnished 2-arylthiazino[6,5-*b*]indole derivatives (**14a–f**). By use of the latter bromine source, the phytoalexin cyclobrassinin (**8**) was prepared in a considerably higher yield than described previously. The structures of the novel products were elucidated by IR, ^{1}H and ^{13}C NMR spectroscopy, including 2D-HMQC, 2D-HMBC and DEPT measurements.

1. Introduction

The phytoalexins are a group of structurally diverse, low molecular weight, generally lipophilic antimicrobial substances formed in plants.[1] They are not present in healthy plant tissue and are synthesized in response to pathogen attack or physical or chemical stress, probably as a result of the de novo synthesis of enzymes. The accumulation of phytoalexins is one of an array of induced defence responses associated with plant disease resistance.[2]

Numerous phytoalexins are known in cruciferous plants that are important from economic and dietary aspects.[3] Brassinin has been identified as a constituent of cabbage. Some of the *cruciferae* species that have been examined accumulate a novel series of specific indole-sulfur compounds. The basic structures are characterized by an indole ring variably substituted at positions 2 and/or 3 with nitrogen- and sulfur-containing substituents.[4]

Among these compounds, brassinin (**7**) and cyclobrassinin (**8**) exhibit antitumour activity,[5] and brassinin also exerts an antiproliferative effect in human acute T-lymphoblastic leukaemia cells.[6] These compounds can serve as lead compounds for the generation of more efficient analogues.[7] As a continuation of our earlier work on the chemistry of sulfur- and nitrogen-containing condensed-skeleton heterocycles,[8–10] our present aim was the preparation and structural characterization of thiazino[6,5-*b*]indole derivatives, analogues of cyclobrassinin (**8**).

2. Results and discussion

For the synthesis of the above phytoalexins, the key intermediate is usually 3-aminomethylindole (**6**).[11] In the present work too this amine was the first choice as intermediate for the preparation of **7** and **8** and their aryl analogues.

Compound **6** was earlier obtained by the reduction of oxime **3** (Scheme 1),[5,12–15] although some of the reduction procedures (metallic sodium in ethanol,[12] lithium aluminium hydride,[13] and Devarda's alloy[14]) have been reported to be difficult to reproduce and gave low yields.[14–16]

Keywords: Phytoalexins; 3-Aminomethylindole; Thiazino[6,5-*b*]indole; Hugerschoff reaction.
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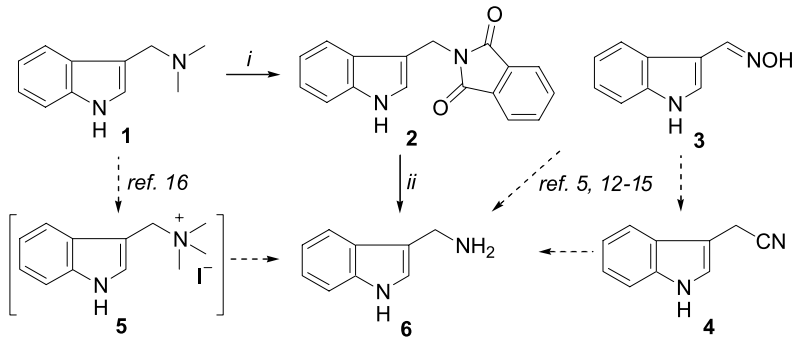


Scheme 1. (i) Phthalimide, neat, 2 h, vacuum; (ii) hydrazine hydrate, EtOH, Δ.

Good yields were obtained by nickel bromide-catalysed reduction with sodium borohydride and subsequent purification by column chromatography[15] and by catalytic hydrogenation with Raney nickel,[5] though amine **6** was not isolated in the latter case.

Another possible route to **6** is the catalytic reduction of the 3-cyano compound **4**.[17] A milligram-scale non-reductive procedure has been reported, starting with the quaternization of gramine (**1**) and subsequent treatment with concentrated ammonia solution. In this case, bis(indolylmethylamine) was formed as a by-product in 13% yield.[16] 3-Aminomethylindole was found to be rather unstable as the free base, and air and light accelerated its decomposition.

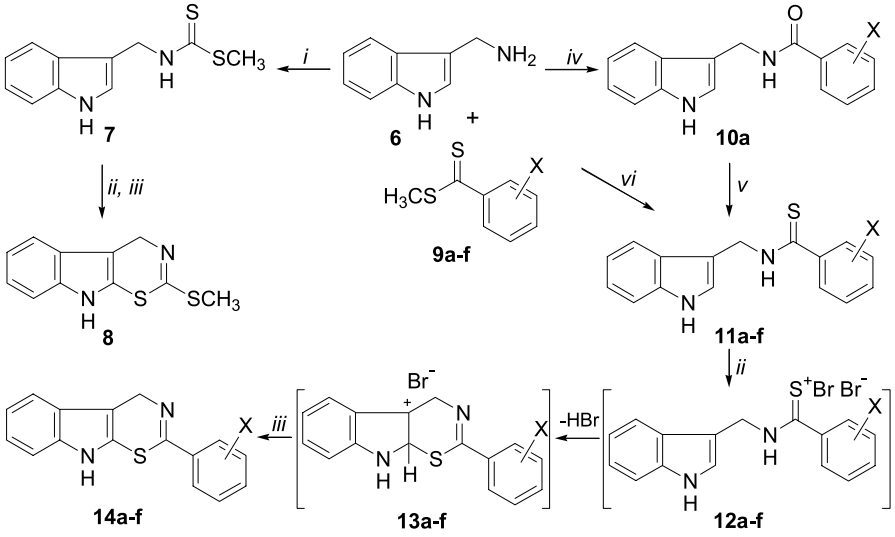
After unsuccessful attemps to reproduce the literature procedures,[13,14] we set out to develop a new method for the gram-scale preparation of **6**. Our attention turned to the phthalimido derivative **2**[18] and an effective, non-reductive method has been developed starting from gramine (**1**). To the best of our knowledge, the preparation of **6** from **2** has not been described previously.

The phthalimide derivative **2** was obtained by a literature procedure.[18] For the splitting-off of the phthalimido group, several reaction conditions were investigated. Finally, this step was performed with hydrazine hydrate under very strict reaction conditions (reflux, 10 min), resulting in **6** in good yield (Scheme 1).

Starting from amine **6**, brassinin (**7**) was prepared in 71% yield by a slight modification of a literature procedure,[19] using chloroform as solvent and triethylamine and catalytic 4-dimethylaminopyridine as base (Scheme 2).

As solid compounds, quaternary ammonium perhalogenides constitute convenient halogen sources. For the ring-closure reaction of brassinin, pyridinium tribromide (yield 35%),[19] *N*-bromosuccinimide (yield 34%)[5] and dioxane dibromide (yield 47%)[20] have been applied earlier. We used phenyltrimethylammonium tribromide. This has been stated to be a selective brominating reagent for arylalkyl ketones, ketones and ketals, which contain double bonds or activated aromatic nuclei, which would be attacked by bromine.[21] We found that a selective Hugerschoff ring-closure reaction with phenyltrimethylammonium tribromide gives cyclobrassinin (**8**) in higher yield (59%) than reported previously (Scheme 2).

The reactions of amine **6** in dichloromethane at rt with



X: H (**a**), 2-Cl (**b**), 4-Cl (**c**), 4-F (**d**), 4-Me (**e**), 2,4-diCl (**f**)

Scheme 2. (i) $CHCl_3$, Et_3N, DMAP, CS_2, MeI; (ii) CH_2Cl_2, $PhMe_3NBr_3$; (iii) Et_3N; (iv) toluene, 5% NaOH, PhCOCl; (v) Lawesson's reagent, THF, rt; (vi) CH_2Cl_2, Et_3N, DMAP.

substituted methyl dithiobenzoates (**9a–f**) furnished 3-(arylthiocarbonylaminomethyl)indoles (**11a–f**). Alternatively, **11a** was prepared by sulfurization from the corresponding benzamide **10a**, using Lawesson's reagent in tetrahydrofuran.

The Hugerschoff reactions of thiobenzamides **11a–f** were also performed with phenyl-trimethylammonium tribromide, affording moderate to good yields. The bromine-mediated cyclization process most probably involves electrophilic addition to the thiocarbonyl moiety, to furnish **12** as a transient intermediate, which is then attacked by the π-electron system of the aromatic ring to give **13**, followed by the rapid formation of **14a–f** in the presence of base (Scheme 2).[22]

3. Structure

The structures of the new compounds follow straightforwardly from the IR, ^{1}H and ^{13}C NMR data. Only a few additional remarks are necessary.

The ring closure of **11**-type thioamides to thiazines was proved by the characteristic changes in the spectra:

(1) Instead of the characteristic[23a] downfield line of the thiocarbonyls (194.3–197.5 ppm for compounds **7** and **11a–f**), the C=N bond of the thiazines gives a ^{13}C NMR line in the interval 150.0–152.0 ppm in the spectra of **8** and **14a–f**.
(2) In consequence of the $-I$ effect of the neighbouring thioimino moiety in the thiazines, the line of the methylene carbon is shifted downfield (48.8–49.3 ppm) as compared with that for the thioamides, where the electron-donating NH group is attached to the methylene carbon (42.0–43.1 ppm). The analogous change was also be observed in the ^{1}H NMR shifts, which are about 5.10 and 5.33 ppm for compounds in the series of types **11** and **14**.
(3) The β effect[23b] of the S substitution on C-9a leads to a significant upfield shift of the C-4a line in the ^{13}C NMR specra of thiazines (from ∼110.7 to ∼99.5 ppm).

The ^{1}H and ^{13}C NMR chemical shifts of the condensed benzene ring are not sensitive to ring closure because of the isolating function of the 9-NH group, which has an electron reservoir nature. Similarly, the aryl substituent does not have a significant influence on the spectral data of the other moieties of these molecules as a consequence of the equalizing role of the thioamide or thioimine groups. The spectroscopic characteristics, IR frequencies, ^{1}H and ^{13}C NMR chemical shifts, intensities, multiplicities and coupling constants are all in accord with those expected for the various aryl groups.

It is worthy of mention that the acidity of 9-NH is slightly stronger in the thiazines, due to the electron-withdrawing effect of the condensed hetero ring: the NH signal is downfield-shifted by ∼0.5 ppm relative to that for the thioamides, from ∼11.0 to ∼11.5 ppm.

4. Experimental

4.1. General

Melting points were determined on a Kofler apparatus and are uncorrected. Elemental analyses were performed with a Perkin-Elmer 2400 CHNS elemental analyser. Merck Kieselgel 60F_{254} plates were used for TLC; the eluent was dichloromethane–*n*-hexane 9/1. Gramine was prepared from indole, 35% formaldehyde solution and a 40% aqueous solution of dimethylamine.[24] Compounds **9a–f** were prepared from substituted benzyl halides and sulfur in the presence of triethylamine by the method of Thiel and Mayer.[25]

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, using TMS ($\delta_{TMS}=0$ ppm) as internal reference, with the deuterium signal of the solvent as the lock. Assignments were supported by DEPT, HMQC (except for **14d**,**e**) and HMBC (except for **14d–f**) mesaurements. DEPT spectra were run in a standard manner, using only the $\Theta=135°$ 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 INV4GS and INV4GSLPLRND, respectively.

4.2. 3-Aminomethylindole (6)

To a suspension of 3-phthalimidomethylindole[18,26] (**2**) (6.4 g, 23 mmol) in 27 mL of dry ethanol, 85% hydrazine hydrate (10.0 g, 170 mmol) was added and the mixture was intensively stirred on a preheated oil bath at 120 °C for 10 min (after ∼1.5 min, **8** has dissolved and after 4 min, a white precipitate has formed). The reaction mixture was then poured into a mixture of ice-water (120 g) and diethyl ether (100 mL). The mixture was shaken in an ice-bath, while 20% NaOH solution (40 mL) was added. The white precipitate partially dissolved and the aqueous phase was extracted with diethyl ether carefully in a separation funel. The extraction was repeated with diethyl ether (2× 100 mL). The combined organic phase was extracted in turn with 10% NaOH (50 mL) and with water (100 mL) and dried (Na_2SO_4), and the organic solvent was evaporated off (water bath <50 °C). The residue was coevaporated with toluene (2×20 mL; water bath <60 °C) and it was taken up in *n*-hexane and filtered. The crystalline residue was purified by recrystallization from diisopropyl ether and ethyl acetate. After standing at −18 °C, a white crystalline powder was obtained (2.2 g; yield 65%; mp 101–102 °C), lit.[14] mp 103–105 °C. Anal. Calcd for $C_9H_{10}N_2$ (146.19): C, 73.94; H, 6.89; N, 19.16. Found: C, 73.67; H, 7.02; N, 19.24.

4.2.1. 3-(*S*-Methyldithiocarbamoylaminomethyl)indole (7, brassinin). To a stirred solution of 3-aminomethylindole (**5**) (1.0 g, 6.9 mmol) in chloroform (20 mL), triethylamine (0.96 mL, 6.9 mmol) and 4-dimethylaminopyridine (0.06 g, 0.5 mmol) were added. Carbon disulfide (0.46 mL, 7.59 mmol) was next added dropwise under ice cooling and the mixture was stirred at the same temperature for 2 h. Methyl iodide (0.44 mL, 6.9 mmol) in chloroform (5 mL)

was then added dropwise to the solution and it was stirred for 5 h at rt. The organic phase was extracted in turn with 3% hydrochloric acid (10 mL) and with water (10 mL), dried (Na_2SO_4) and evaporated. Diisopropyl ether was added to the residue to give **1** as a crystalline powder. White crystals, mp 133–135 °C (lit.[19] mp 132–133 °C), yield 71% (from dichloromethane, *n*-hexane). Anal. Calcd for $C_{11}H_{12}N_2S_2$ (236.36): C, 55.90; H, 5.12; N, 11.85; S, 27.37. Found: C, 55.65; H, 5.24; N, 11.62; S, 27.40; ν_{max} (KBr disc) 3392, 3302, 1480, 1073, 745 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 10.99 (1H, s, N*H*CH), 10.21 (1H, s, N*H*CH_2), 7.62 (1H, dd, H-4), 7.38 (1H, dd, H-7), 7.34 (1H, s, H-2), 7.10 (1H, dt, H-6), 7.01 (1H, dt, H-5), 4.98 (2H, d, $J=5$ Hz, CH_2), 2.53 (3H, s, CH_3); δ_C (126 MHz, DMSO-d_6) 197.3 (NCSS), 137.0 (C-7a), 127.4 (C-3a), 125.8 (C-2), 122.1 (C-6), 119.6 (C-4 and C-5, overlapping lines), 112.4 (C-7), 111.0 (C-3), 43.1 (*C*H_2), 18.2 (*C*H_3).

4.2.2. 4,9-Dihydro-2-methylthio-1,3-thiazino[6,5-*b*]indole (8, cyclobrassinin). To an intensively stirred solution of brassinin **7** (0.20 g, 0.85 mmol) in dichloromethane (10 mL) at rt, phenyltrimethylammonium tribromide (0.32 g, 0.85 mmol) was added in one portion. After stirring for 45 s, triethylamine (0.24 mL, 1.7 mmol) was added in one portion. The mixture was evaporated (water bath <50 °C) and the residue was purified by column chromatography, using dichloromethane–*n*-hexane (1/1, followed by 2/1) as eluent, to give **8** after evaporation as a crystalline powder (0.12 g). White crystals, mp 135–136 °C (lit.[19] mp 136–137 °C), yield 59%. Anal. Calcd for $C_{11}H_{10}N_2S_2$ (234.34): C, 56.38; H, 4.30; N, 11.95; S, 27.37. Found: C, 56.21; H, 4.42; N, 12.02; S, 27.42; ν_{max} (KBr disc) 3370, 1602, 765 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 11.43 (1H, s, N*H*), 7.48 (1H, dd, H-5), 7.34 (1H, dd, H-8), 7.09 (1H, dt, H-7), 7.03 (1H, dt, H-6), 5.06 (2H, s, CH_2), ~2.50 (3H, s, CH_3 overlapped by the light isotope signal of the solvent); δ_C (126 MHz, DMSO-d_6) 151.7 (C-2), 137.4 (C-8a), 125.4 (C-4b), 122.3* (C-9a), 122.2* (C-7), 120.2 (C-6), 117.8 (C-5), 111.9 (C-8), 102.5 (C-4a), 48.9 (C-4), 15.5 (*C*H_3), *interchangeable assignments.

4.2.3. 3-(Benzoylaminomethyl)indole (10a). Amine **6** (0.72 g, 3.50 mmol) was dissolved in toluene (25 mL). To this solution, sodium hydroxide (0.62 g, 15.40 mmol) dissolved in water (10 mL) was added. After the addition of benzoyl chloride (0.42 g, 3.85 mmol), the reaction mixture was shaken intensively for 20 min. The crystals that separated out were filtered off and washed in turn with water and with toluene and dried. The white crystalline benzamide was recrystallized from diisopropyl ether. White powder, mp 157–159 °C, 0.82 g, yield 85%. Anal. Calcd for $C_{16}H_{14}N_2O$ (250.30): C, 76.78; H, 5.64; N, 11.19. Found: C, 76.92; H, 5.81; N, 11.29; ν_{max} (KBr disc) 3416, 3302, 1628, 738, 695 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 10.90 (1H, s, N*H*CH), 8.80 (1H, s, N*H*CH_2), 7.87 (2H, H2′,6′), 7.66 (1H, dd, H-4), 7.45 (1H, H-4′), 7.43 (2H, H-3′,5′), 7.36 (1H, dd, H-7), 7.29 (1H, d, H-2), 7.07 (1H, dt, H-6), 6.98 (1H, dt, H-5), 4.64 (2H, d, $J=5.6$ Hz, CH_2); δ_C (126 MHz, DMSO-d_6) 166.9 (CO), 137.2 (C-7a), 134.5 (C-1′), 131.9 (C-4′), 129.1 (C-3′,5′), 128.1 (C-2′,6′), 127.4 (C-3a), 124.8 (C-2), 122.0 (C-6), 119.7 (C-4), 119.4 (C-5), 113.5 (C-3), 112.3 (C-7), 35.5 (*C*H_2).

4.2.4. 3-(Thiobenzoylaminomethyl)indole (11a) from benzamide 10a. To a solution of 3-(benzoylaminomethyl)-indole (**10a**) (0.2 g, 0.8 mmol) in tetrahydrofuran (15 mL), Lawesson's reagent (0.32 g, 0.8 mmol) was added in one portion. The reaction mixture was stirred at rt for 24 h. After evaporation the residue was purified by column chromatography using dichloromethane–*n*-hexane as eluent to give **11a** as a pale-yellow crystalline powder (analytical data identical to those given above).

4.3. General procedure for 3-(arylthiocarbonylaminomethyl)indoles (11a–f) from 6 and methyl dithiobenzoates (9a–f)

Amine **6** (0.52 g, 2.53 mmol) was dissolved in dichloromethane (20 mL). To this solution, triethylamine (0.50 g, 11.12 mmol) and 4-dimethylaminopyridine (0.06 g, 0.5 mmol) were added. After the addition of the appropriate methyl dithiobenzoate (**9a–f**) (2.78 mmol), the reaction mixture was left at rt in a good hood for 2-3 days. After evaporation, the residue was dissolved in dichloromethane (30 mL). The organic phase was extracted in turn with 3% hydrochloric acid (10 mL), 3% sodium hydroxide (10 mL) and water (10 mL), dried (Na_2SO_4) and evaporated. Trituration of the residue with diisopropyl ether gave **11a–f** as crystalline powders.

4.3.1. 3-(Thiobenzoylaminomethyl)indole (11a). Pale-yellow crystals, mp 145–146 °C (from dichloromethane, *n*-hexane), yield 74%. Anal. Calcd for $C_{16}H_{14}N_2S$ (266.36): C, 72.15; H, 5.30; N, 10.52; S, 12.04. Found: C, 72.35; H, 5.51; N, 10.32; S, 12.30; ν_{max} (KBr disc) 3359, 3268, 1480, 1233, 775, s750, 690 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 11.02 (1H, s, N*H*CH), 10.59 (1H, s, N*H*CH_2), 7.72–7.73 (3H, m, H-4 and H2′,6′, overlapping signals), 7.38–7.45 (5H, m, H-2, H-7, H-3′,5′ and H-4′, overlapping signals), 7.12 (1H, dt, H-6), 7.03 (1H, dt, H-5), 5.14 (2H, d, $J=$ 4.2 Hz, CH_2); δ_C (126 MHz, DMSO-d_6) 197.5 (*C*S), 142.3 (C-1′), 137.1 (C-7a), 131.3 (C-4′), 128.7 (C-3′,5′), 128.2 (C-2′,6′), 127.6 (C-3a), 125.8 (C-2), 122.1 (C-6), 119.6 (C-4 and C-5, two overlapping lines), 112.4 (C-7), 111.1 (C-3), 43.1 (*C*H_2).

4.3.2. 3-(2-Chlorothiobenzoylaminomethyl)indole (11b). White crystals, mp 113–115 °C (from dichloromethane, *n*-hexane), yield 62%. Anal. Calcd for $C_{16}H_{13}ClN_2S$ (300.81): C, 63.89; H, 4.36; N, 9.31; S, 10.66. Found: C, 63.59; H, 4.32; N, 9.50; S, 10.82; ν_{max} (KBr disc) 3411, 3309, 1456, 1240, 756, 741 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 11.02 (1H, s, N*H*CH), 10.80 (1H, s, N*H*CH_2), ~7.4 (3H, m, H-2, H-7, H-6′, overlapping signals), ~7.32 (3H, m, H-3′,5′ and H-4′, overlapping signals), 7.69 (1H, dd, H-4), 7.12 (1H, dt, H-6), 7.04 (1H, dt, H-5), 5.05 (2H, d, $J=$ 5.0 Hz, CH_2); δ_C (126 MHz, DMSO-d_6) 195.5 (*C*S), 143.5 (C-1′), 137.1 (C-7a), 130.4* (C-4′), 130.1 (C-6′), 129.5* (C-3′), 129.1 (C-2′), 127.7* (C-5′), 127.5 (C-3a), 125.8 (C-2), 122.2 (C-6), 119.7 (C-4), 119.6 (C-5), 112.4 (C-7), 110.4 (C-3), 42.0 (*C*H_2). *interchangeable assignments.

4.3.3. 3-(4-Chlorothiobenzoylaminomethyl)indole (11c). Yellow crystals, mp 148–150 °C (from dichloromethane, *n*-hexane), yield 65%. Anal. Calcd for $C_{16}H_{13}ClN_2S$ (300.81): C, 63.89; H, 4.36; N, 9.31; S, 10.66. Found: C,

63.78; H, 4.50; N, 9.22; S, 10.82; ν_{max} (KBr disc) 3359, 3262, 1447, 1233, 839, 813, 751 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 11.03 (1H, s, N*H*CH), 10.66 (1H, s, N*H*CH_2), 7.74 (2H, H-2′,6′), 7.68 (1H, dd, H-4), 7.45 (2H, m, H-3′,5′), 7.42 (1H, s, H-2), 7.40 (1H, dd, H-7), 7.11 (1H, dt, H-6), 7.02 (1H, dt, H-5), 5.11 (2H, s, CH_2); δ_C (126 MHz, DMSO-d_6) 195.9 (*C*S), 140.8 (C-1′), 137.1 (C-7a), 136.1 (C-4′), 130.0 (C-2′,6′), 128.7 (C-3′,5′), 127.6 (C-3a), 125.8 (C-2), 122.1 (C-6), 119.7 (C-5), 119.6 (C-4), 112.4 (C-7), 110.8 (C-3), 42.8 (*C*H_2).

4.3.4. 3-(4-Fluorothiobenzoylaminomethyl)indole (11d). Yellow crystals, mp 125–127 °C (from dichloromethane, *n*-hexane), yield 57%. Anal. Calcd for $C_{16}H_{13}FN_2S$ (284.35): C, 67.58; H, 4.61; N, 9.85; S, 11.28. Found: C, 67.36; H, 4.82; N, 10.02; S, 11.10; ν_{max} (KBr disc) 3390, 3252, 1456, 840, 742 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 11.02 (1H, s, N*H*CH), 10.60 (1H, s, N*H*CH_2), 7.72 (2H, H-2′,6′), 7.68 (1H, dd, H-4), 7.41 (1H, s, H-2), 7.39 (1H, dd, H-7), 7.22 (2H, H-3′,5′), 7.10 (1H, dt, H-6), 7.01 (1H, dt, H-5), 5.10 (2H, d, $J=5.3$ Hz, CH_2); δ_C* (126 MHz, DMSO-d_6) 196.0 (*C*S), 164.3 (C-4′), 138.6 (C-1′), 137.1 (C-7a), 130.7 (C-2′,6′), 127.5 (C-3a), 125.8 (C-2), 122.1 (C-6), 119.63 (C-4), 119.58 (C-5), 115.5 (C-3′,5′), 112.4 (C-7), 110.9 (C-3), 42.8 (*C*H_2), *due to F,C-couplings, the signals of the aryl group are doublets, ^1J(F,C): 248.4 Hz, ^2J(F,C): 22.8 Hz, ^3J(F,C): 9.2 Hz, ^4J(F,C): 2.7 Hz.

4.3.5. 3-(4-Methylthiobenzoylaminomethyl)indole (11e). Yellow crystals, mp 133–135 °C (from dichloromethane, *n*-hexane), yield 55%. Anal. Calcd for $C_{17}H_{16}N_2S$ (280.39): C, 72.82; H, 5.75; N, 9.99; S, 11.44. Found: C, 72.96; H, 5.92; N, 10.18; S, 11.25; ν_{max} (KBr disc) 3302, 3250, 1456, 1278, 844, 737 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 11.00 (1H, s, N*H*CH), 10.47 (1H, s, N*H*CH_2), 7.70 (1H, dd, H-4), 7.66 (2H, H-2′,6′), 7.40 (1H, s, H-2), 7.39 (1H, dd, H-7), 7.19 (2H, m, H-3′,5′), 7.11 (1H, dt, H-6), 7.01 (1H, dt, H-5), 5.12 (2H, d, $J=5.3$ Hz, CH_2), 2.31 (3H, s, CH_3); δ_C (126 MHz, DMSO-d_6) 197.1 (*C*S), 141.3 (C-4′), 139.4 (C-1′), 137.1 (C-7a), 129.2 (C-3′,5′), 128.3 (C-2′,6′), 127.6 (C-3a), 125.7 (C-2), 122.1 (C-6), 119.66 (C-4), 119.59 (C-5), 112.4 (C-7), 111.2 (C-3), 42.6 (*C*H_2), 21.7 (*C*H_3).

4.3.6. 3-(2,4-Dichlorothiobenzoylaminomethyl)indole (11f). White crystals, mp 148–150 °C (from dichloromethane, *n*-hexane), yield 71%. Anal. Calcd for $C_{16}H_{12}Cl_2N_2S$ (335.25): C, 57.32; H, 3.61; N, 8.36; S, 9.56. Found: C, 57.18; H, 3.78; N, 8.28; S, 10.15; ν_{max} (KBr disc) 3302, 3248, 1456, 1281, 819, 801*, 758 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 11.04 (1H, s, N*H*CH), 10.84 (1H, s, N*H*CH_2), 7.69 (1H, dd, H-4), 7.59 (1H, s, H-3′), 7.30–7.40 (4H, m, H-2, H-7, H-5′, H-2′,6′, overlapping signals), 7.12 (1H, dt, H-6), 7.04 (1H, dt, H-5), 5.05 (2H, d, $J=4.5$ Hz, CH_2); δ_C (126 MHz, DMSO-d_6) 194.3 (*C*S), 142.3 (C-1′), 137.1 (C-7a), 134.1 (C-4′), 130.8 (C-6′), 130.3 (C-2′), 129.5 (C-3′), 128.0 (C-5′), 127.5 (C-3a), 125.9 (C-2), 122.2 (C-6), 119.6 (C-4 and C-5, two overlapping lines), 112.4 (C-7), 110.2 (C-3), 42.1 (*C*H_2).

4.4. General procedure for 4,9-dihydro-2-aryl-1,3-thiazino[6,5-*b*]indole (14a–f) from 3-(arylthiocarbonylaminomethyl)indoles (11a–f)

To an intensively stirred solution of thiocarboxamide **11a–f** (0.85 mmol) in dichloromethane (10 mL) at rt phenyltrimethylammonium tribromide (0.32 g, 0.85 mmol) was added in small portions during 1 min. After stirring for 5 min, triethylamine (0.24 mL, 1.7 mmol) was added in one portion. The mixture was evaporated (water bath <50 °C) and the residue was purified by column chromatography, using first dichloromethane–*n*-hexane (1/1, followed by 2/1) as eluent to give **14a–f** as a crystalline powder.

4.4.1. 4,9-Dihydro-2-phenyl-1,3-thiazino[6,5-*b*]indole (14a). Orange crystals, mp 132–135 °C (ethanol), yield 51%. 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, 72.62; H, 4.74; N, 10.81; S, 12.02; ν_{max} (KBr disc) 3390, 1620, 761, 737, 698 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 11.53 (1H, s, N*H*), 7.89 (2H, H-2′,6′), 7.55 (1H, H-4′), ~7.50 (3H, m, H-5 and H-3′,5′, overlapping signals), 7.37 (1H, dd, H-8), 7.11 (1H, dt, H-7), 7.05 (1H, dt, H-6), 5.32 (2H, s, CH_2); δ_C (126 MHz, DMSO-d_6) 152.0 (C-2), 138.2 (C-1′), 137.5 (C-8a), 132.1 (C-4′), 129.7 (C-3′,5′), 127.5 (C-2′,6′), 125.3 (C-4b), 123.0 (C-9a), 122.1 (C-7), 120.3 (C-6), 118.0 (C-5), 111.8 (C-8), 99.7 (C-4a), 49.0 (C-4).

4.4.2. 4,9-Dihydro-2-(2-chlorophenyl)-1,3-thiazino[6,5-*b*]indole (14b). Brown crystals, mp 143–145 °C (ethanol), yield 64%. 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, 64.15; H, 3.92; N, 9.45; S, 10.75; ν_{max} (KBr disc) 3500–2000, 1630, 759, 745 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 11.49 (1H, s, N*H*), 7.58 (1H, H-6′), ~7.50 (3H, m, H-5 and H-3′,5′, overlapping signals), 7.45 (1H, H-4′), 7.36 (1H, dd, H-8), 7.11 (1H, dt, H-7), 7.07 (1H, dt, H-6), 5.34 (2H, s, CH_2); δ_C (126 MHz, DMSO-d_6) 150.7 (C-2), 138.6 (C-2′), 137.4 (C-8a), 132.2 (C-5′), 131.4 (C-1′), 130.8 (C-6′), 130.4 (C-3′), 128.5 (C-4′), 125.3 (C-4b), 122.9 (C-9a), 122.2 (C-7), 120.3 (C-6), 118.0 (C-5), 111.8 (C-8), 99.2 (C-4a), 49.3 (C-4).

4.4.3. 4,9-Dihydro-2-(4-chlorophenyl)-1,3-thiazino[6,5-*b*]indole (14c). Light-brown crystals, mp 147–149 °C (ethanol), yield 61%. 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, 3.80; N, 9.56; S, 10.85; ν_{max} (KBr disc) 3500–2000, 1624, 834, 748 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 11.54 (1H, s, N*H*), 7.89 (2H, H-2′,6′), 7.56 (2H, H-3′,5′), 7.50 (1H, dd, H-5), 7.36 (1H, dd, H-8), 7.11 (1H, dt, H-7), 7.05 (1H, dt, H-6), 5.34 (2H, s, CH_2); δ_C (126 MHz, DMSO-d_6) 151.0 (C-2), 137.5 (C-8a), 136.9 (C-1′), 136.8 (C-4′), 129.8 (C-3′,5′), 129.2 (C-2′,6′), 125.2 (C-4b), 122.5 (C-9a), 122.2 (C-7), 120.3 (C-6), 118.0 (C-5), 111.8 (C-8), 99.7 (C-4a), 49.0 (C-4).

4.4.4. 4,9-Dihydro-2-(4-fluorophenyl)-1,3-thiazino[6,5-*b*]indole (14d). Brown crystals, mp 144–149 °C (ethanol), yield 54%. Anal. Calcd for $C_{16}H_{11}FN_2S$ (282.33): C, 68.06; H, 3.93; N, 9.92; S, 11.36. Found: C, 67.70; H, 4.11; N, 10.1; S, 11.46; ν_{max} (KBr disc) 3397, 1633, 1247, 842, 740 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 11.53 (1H, s, N*H*), 7.94 (2H, H-2′,6′), 7.50 (1H, dd, H-5), 7.36 (1H, dd, H-8), 7.34 (2H, H-3′,5′), 7.11 (1H, dt, H-7), 7.05 (1H, dt, H-6), 5.33 (2H, s, CH_2); δ_C* (126 MHz, DMSO-d_6) 164.7 (C-4′), 150.9 (C-2), 137.5 (C-8a), 134.7 (C-1′), 129.9 (C-2′,6′), 125.3 (C-4b), 122.7 (C-9a), 122.2 (C-7), 120.3 (C-6), 118.8

(C-5), 116.7 (C-3′,5′), 111.8 (C-8), 99.7 (C-4a), 48.9 (C-4), *due to F,C-couplings, the signals of the aryl group are doublets, ^{1}J(F,C): 249.3 Hz, ^{2}J(F,C): 22.0 Hz, ^{3}J(F,C): 9.2 Hz, ^{4}J(F,C): 2.7 Hz.

4.4.5. 4,9-Dihydro-2-(4-methylphenyl)-1,3-thiazino[6,5-*b*]indole (14e). Light-brown crystals, mp 148–150 °C (from dichloromethane, *n*-hexane), yield 71%. 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, 73.52; H, 5.12; N, 10.27; S, 11.61; ν_{max} (KBr disc) 3400, 1633, 842, 736 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 11.51 (1H, s, N*H*), 7.78 (2H, H-2′,6′), 7.49 (1H, dd, H-5), 7.36 (1H, dd, H-8), 7.29 (2H, H-3′,5′), 7.10 (1H, dt, H-7), 7.05 (1H, dt, H-6), 5.31 (2H, s, CH_2), 2.35 (3H, s, CH_3); δ_C (126 MHz, DMSO-d_6) 151.8 (C-2), 142.0 (C-4′), 137.4 (C-8a), 135.5 (C-1′), 130.2 (C-3′,5′), 127.4 (C-2′,6′), 125.3 (C-4b), 123.1 (C-9a), 122.1 (C-7), 120.2 (C-6), 117.9 (C-5), 111.7 (C-8), 99.8 (C-4a), 48.8 (C-4), 21.8 (*C*H_3).

4.4.6. 4,9-Dihydro-2-(2,4-chlorophenyl)-1,3-thiazino[6,5-*b*]indole (14f). Brown crystals, mp 157–160 °C (ethanol), yield 42%. Anal. Calcd for $C_{16}H_{10}Cl_2N_2S$ (333.24): C, 57.67; H, 3.02; N, 8.41; S, 9.56. Found: C, 57.82; H, 3.15; N, 8.53; S, 9.44; ν_{max} (KBr disc) 3366, 824, 753 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 11.50 (1H, s, N*H*), 7.75 (1H, H-3′), 7.57 (1H, H-6′), 7.53 (1H, H-5′), 7.50 (1H, dd, H-5), 7.36 (1H, dd, H-8), 7.11 (1H, dt, H-7), 7.06 (1H, dt, H-6), 5.34 (2H, s, CH_2); δ_C (126 MHz, DMSO-d_6) 150.0 (C-2), 137.40* (C-4′), 137.38* (C-8a), 136.0 (C-2′), 132.7 (C-1′), 131.8 (C-6′), 130.5 (C-3′), 128.7 (C-5′), 125.3 (C-4b), 122.5 (C-9a), 122.3 (C-7), 120.3 (C-6), 118.0 (C-5), 111.8 (C-8), 99.2 (C-4a), 49.3 (C-4), *interchangeable assignments.

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