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An efficient route for the synthesis of 2-arylthiazino[5,6-*b*]indole derivatives

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Abstract—Substituted 2-thiobenzamidomethylindole derivatives (**14a–e**) were prepared by the reaction of 2-aminomethylindole (**9**) with substituted benzoyl chlorides, followed by sulfurization using Lawesson's reagent. Alternatively, these thioamides were obtained from the amine in one step in an efficient manner by using substituted benzaldehydes in the presence of sulfur, or at room temperature with the aid of substituted methyl dithiobenzoates. The Hugerschoff reactions of thiobenzamides (**14a–e**) with phenyltrimethylammonium tribromide provided the rare title 2-arylthiazino[5,6-*b*]indoles (**15a–e**) in good yields. A convenient one-pot approach for the synthesis of 2-phenyl-1,3-thiazino[5,6-*b*]indole (**15a**) from 2-aminomethylindole (**9**) is also described.

1. Introduction

Indole derivatives condensed with different heterocycles are physiologically active compounds found in abundance in materials such as pharmaceuticals, alkaloids and potential therapeutic agents.[1] Accordingly, there is a continuous demand for novel synthetic procedures in this area. Unlike other heterocycles condensed with indole (e.g., pyrido-, or imidazo-), few derivatives are known from among the four possible 1,3-thiazinoindoles condensed at bond *b* of the indole skeleton (Fig. 1). In the past two decades, increasing attention has been paid to 1,3-thiazino[6,5-*b*]indole derivatives (type **1**, Fig. 1)[2] since Takasugi and co-workers isolated the first cruciferous phytoalexins, among them cyclobrassinin (2-methylthiothiazino[6,5-*b*]indole), from Chinese cabbage.[3] The phytoalexins are a group of structurally diverse, low molecular weight, generally lipophilic antimicrobial substances formed in plants.[4] 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. Approximately 30 phytoalexins are known so far in cruciferous plants, 6 of them possessing a thiazinoindole skeleton.[2] Cyclobrassinin, the most valuable of these compounds, exerts an antiproliferative effect against human cancer cell lines.[5] Although cyclobrassinin is a natural lead molecule, the different analogues of this phytoalexin have been much less studied. Only a few derivatives of cyclobrassinone[6] and 2-phenyl derivatives of cyclobrassinin[7] have been prepared and investigated. The remaining three 1,3-thiazinoindole isomers condensed at bond *b* of the indole moiety are a relatively unexplored class of compounds; only a few examples of these heterocyclic systems are known. The first derivative, 1,5-dihydro-1,3-thiazino[5,4-*b*]indole-2,4-dithione, was prepared from 3-aminoindole with carbon disulfide.[8] 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.[9] Members of this class of compounds inhibit human leukocyte elastase and α-chymotrysin. Of the type **2** thiazinoindoles, 4,5-dihydro-5-methoxy-2-methylthio-1,3-thiazino[5,6-*b*]indole and its

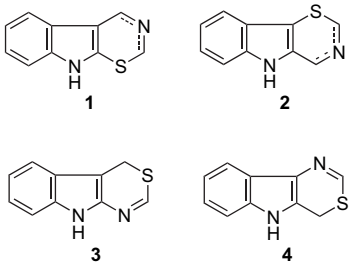

Figure 1. The four possible isomers of 1,3-thiazinoindoles condensed at bond *b* of indole.

Keywords: 2-Aminomethylindole; Thioamide; Thiazino[5,6-*b*]indole; Hugerschoff reaction.
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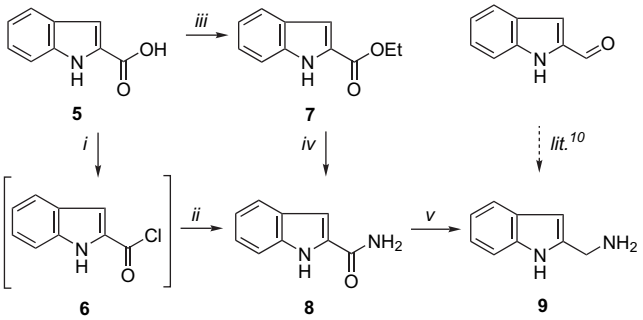
4-one derivatives were prepared during the synthesis of erucalexin, a phytoalexin produced by wild crucifer dog mustard.[10] We recently prepared 2-methylthio-1,3-thiazino[5,6-*b*]indole (isocyclobrassinin) and its 2-benzylthio analogue, which exerted good in vitro antiproliferative effects on cervix adenocarcinoma (HeLa), breast adenocarcinoma (MCF7) and squamous skin carcinoma (A431) cell lines.[11] For structure–activity relationships, further analogues were synthesized. 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 antitumour compound.[11]

As a continuation of our work on the chemistry of sulfur- and nitrogen-containing condensed-skeleton heterocycles,[12–16] including 1,3-thiazino[6,5-*b*]indole derivatives (cyclobrassinin and analogues)[7] and their regioisomers (1,3-thiazino[5,6-*b*]indoles),[11] our present aim was to devise an efficient route for the synthesis of rare 2-aryl-1,3-thiazino[5,6-*b*]indole derivatives with potential antiproliferative effects.

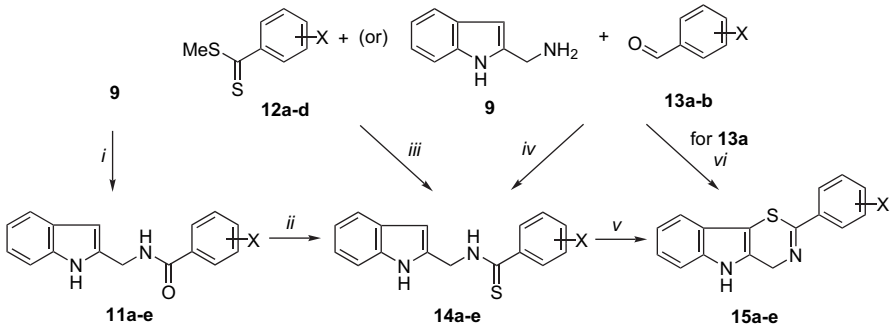
2. Results and discussion

We earlier prepared a number of 1,3-thiazino[6,5-*b*]indole derivatives as analogues of the phytoalexin cyclobrassinin.[7] In that synthesis, 3-aminomethylindole was used as the key intermediate and a new non-reductive strategy was developed for the amine. In the present study, the synthesis of the 1,3-thiazino[5,6-*b*]indole core was planned to be accomplished via 2-aminomethylindole (**9**). Compound **9** was earlier obtained by reduction of the oxime,[10] prepared from indole-2-carboxaldehyde (Scheme 1). Another possible synthetic route is the reduction of indole-2-carboxamide, which can be prepared from commercial indole-2-carboxylic acid. In our hands, the different literature approaches[17–19] for this latter method did not provide the amide precursor in the expected yields. In these procedures, the first step is the preparation of indole-2-carboxylic acid chloride with thionyl chloride, followed by the formation of amide with aqueous ammonia or with ammonia in tetrahydrofuran or dichloromethane. Further literature data revealed that a higher temperature and a longer time should most probably be used for the preparation of intermediate acid chloride **6**.[20] The reaction conditions given by Spadoni et al.[21] for the preparation of 7-methoxyindole-2-carboxamide were further optimized and indole-2-carboxamide (**8**) was obtained in good yield. Thus, treatment of indole-2-carboxylic acid (**5**) with thionyl chloride in tetrahydrofuran at 50 °C for 4 h, followed by amidation with ammonia in dichloromethane, provided **8**. Alternatively, esterification of indole-2-carboxylic acid (**5**) gave ethyl indole-2-carboxylate (**7**). The amidation of **7** in 25% methanolic ammonia at room temperature furnished indole-2-carboxamide (**8**), also in good yield (Scheme 1). Although this reaction takes a long time, the unreacted ester can easily be separated from the product and reused in the amidation reaction. The reduction of indole-2-carboxamide (**8**) to 2-aminomethylindole (**9**) was performed with lithium aluminium hydride in refluxing tetrahydrofuran.



Scheme 1. (i) $SOCl_2$, THF, 50 °C, 4 h; (ii) THF, NH_3/CH_2Cl_2, −10 °C, 0 °C to rt, 10 h, yield for (i) and (ii): 84%; (iii) $SOCl_2$, EtOH, −10 °C, 0 °C, 30 min, rt, 1 h, Δ, 3 h, 83%; (iv) THF, NH_3/MeOH, rt, 5 weeks, 88% and (v) $LiAlH_4$, THF, Δ, 7 h, 71%.

The reactions of amine **9** with substituted benzoyl chlorides provided benzamides **11a–e** (Scheme 2). The thioamides **14a–e** were prepared by sulfurization from the corresponding benzamides **11a–e**, using Lawesson's reagent in tetrahydrofuran. The reactions of amine **9** with substituted methyl dithiobenzoates (**12a–d**) in dichloromethane at room temperature yielded 3-(arylthiocarbonylaminomethyl)indoles (**14a–d**).



a: X = H; **b**: X = pCl; **c**: X = pF; **d**: X = pMe; **e**: X = oF

Scheme 2. (i) ArCOCl, toluene, 6% NaOH, 20 min, **11a**: 86%, **11b**: 91%, **11c**: 83%, **11d**: 95%, **11e**: 57%; (ii) Lawesson's reagent, THF, Δ, 2 h, **14a**: 89%, **14b**: 81%, **14c**: 75%, **14d**: 91%, **14e**: 57%; (iii) CH_2Cl_2, Et_3N, 6 days, **14a**: 67%, **14b**: 74%, **14c**: 58%, **14d**: 56%; (iv) S, DMF, Δ, 3 h, **14a**: 82%, **14b**: 42%; (v) CH_2Cl_2, $PhMe_3NBr_3$, 1 min, Et_3N, 5 min, **15a**: 82%, **15b**: 77%, **15c**: 54%, **15d**: 71% (for **15e**: CH_2Cl_2, I_2, 30 s, Et_3N, 5 min, 44%); (vi) S, DMF, Δ, 3 h, $PhMe_3NBr_3$, 5 s, Et_3N, **15a**: 38%.

Alternatively, thioamides **14a** and **b** were obtained in a simple way[22] via the reaction of amine **9** and benzaldehydes **13a** and **b** in the presence of sulfur.

For the construction of the 1,3-thiazino[5,6-*b*]indole moiety, we planned to apply the oxidative ring closure of thiocarboxamides (**14a**–**e**) in the Hugerschoff reaction. Instead of molecular bromine, different bromine sources (benzyltrimethylammonium tribromide,[23] pyridinium tribromide,[24] *N*-bromosuccinimide[5] and dioxane dibromide,[25] etc.) have been applied earlier in the Hugerschoff reaction. As concerns the mechanism of the reaction, different theories have been proposed.[23,25] As solid compounds, quaternary ammonium perhalides constitute convenient halogen sources. It is simpler to control the stoichiometry of the addition with an organic ammonium tribromide, which minimizes aromatic bromination caused by excess reagent. Phenyltrimethylammonium tribromide has been reported to be a selective brominating reagent for aralkyl ketones, ketones and ketals, which contain double bonds or activated aromatic nuclei, which would be attacked by bromine.[26] We recently utilized this bromine source successfully in the Hugerschoff reaction for the preparation of cyclobrassinin and its 2-aryl analogues.[7] In the present work, the selective Hugerschoff reactions of thiobenzamides **14a**–**d** were also performed with phenyltrimethylammonium tribromide, affording 2-aryl-1,3-thiazino[5,6-*b*]indoles **15a**–**d** in good yields. It is interesting that the preparation of 2-(2-fluorophenyl)-1,3-thiazino[5,6-*b*]indole (**15e**) by oxidative ring closure could be performed only with iodine in dichloromethane, with a moderate yield. In this case (**14e**), the reaction of phenyltrimethylammonium tribromide gave different unseparable products, and decomposition of the thioamide occurred. Finally, we were able to prepare 2-phenyl-1,3-thiazino[5,6-*b*]indole **15a** directly from amine **9** in a simple one-pot reaction. This is a convenient approach, which could be used for the synthesis of different 2-substituted 1,3-thiazino[5,6-*b*]-indole derivatives from 2-aminomethylindoles.

The ring closure of thioamides **14a**–**e** to give thiazines **15a**–**e** was proved by the changes in the spectra. Instead of the characteristic[7,27] downfield line of the thiocarbonyls (192.8–197.7 ppm for compounds **14a**–**e**), the C=N bond of the thiazines gives a ^{13}C NMR line in the interval 151.1–154.7 ppm in the spectra of **15a**–**e**. As a consequence of the −I effect of the neighbouring thioimino moiety in the thiazines, the line of the methylene carbon is shifted downfield (47.6–48.0 ppm) as compared with that for the thioamides, where the electron-donating NH group is attached to the methylene carbon (43.3–43.8 ppm). The analogous change was also observed in the ^{1}H NMR shifts, which are ~5.10 and ~5.30 ppm for compounds in the series of types **14** and **15**.

3. Conclusion

In summary, we have developed an efficient synthetic method for the preparation of functionalized 1,3-thiazino [5,6-*b*]indole derivatives from 2-(thiobenzoylaminomethyl)-indoles via a selective Hugerschoff ring-closure reaction, using phenyltrimethylammonium tribromide as bromine source. A convenient one-pot approach for the synthesis of 2-phenyl-1,3-thiazino[5,6-*b*]indole from 2-aminomethylindole is also described. Some of the synthesized compounds (**14b** and **d** and **15b** and **d**) were screened for their in vitro antiproliferative effects. The ring-closed derivatives (**15b** and **d**) exhibited noteworthy cytostatic effects on human carcinoma cell lines (HeLa, MCF7 and A431). Further studies aimed at introducing novel functionalities into the thiazinoindole skeleton and determination of the in vitro antiproliferative activities of the remaining compounds are currently in progress.

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, and Merck Silica gel 60 (0.063–0.100) for column chromatography. Compounds **12a**–**d** were prepared from substituted benzyl halides and sulfur in the presence of triethylamine by the method of Thiel and Mayer.[28]

IR spectra were recorded in KBr pellets with a BIO-RAD Digilab Division FTS-65A/896 FT-spectrometer. NMR spectra were acquired with a Bruker Spectrospin spectrometer operating at 400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C. Spectra were recorded at 25 °C in DMSO-d_6 as solvent in 5-mm NMR tubes. Proton and carbon spectra were referenced internally by using TMS as an internal reference, with the deuterium signal of the solvent as the lock. All spectra were measured by using the standard pulse programs installed by Bruker. Due to F,C-couplings, the signals of the aryl group in compounds **11c**,**e**, **14c**,**e** and **15c**,**e** are doublets.

4.1.1. Ethyl indole-2-carboxylate (7). Thionyl chloride (5.40 mL, 74.03 mmol) was added dropwise with stirring to dry ethanol (50 mL) at −10 °C, indole-2-carboxylic acid (**5**) (10.0 g, 62.1 mmol) was then added in one portion and the mixture was stirred for 30 min at 0 °C. After stirring for a further 1 h at room temperature, the mixture was heated to reflux for 3 h and evaporated. The residue was taken up in diethyl ether, filtered and washed with another portion of diethyl ether. The white crystalline powder was dissolved in dichloromethane, extracted with 5% sodium hydrogencarbonate solution and dried over sodium sulfate. After evaporation, the white crystalline powder obtained was used for the next step. A small sample was purified further by recrystallization. A white crystalline powder, mp: 124–125 °C (from ethyl acetate, ethanol), lit.[29] mp: 120–121 °C; yield 83%. ν_{max} (KBr disc) 3430, 3313, 3081, 3059, 2986, 2927, 2907, 2870, 2853, 1695, 1620, 1576, 1529, 1476, 1447, 1435, 1397, 1383, 1370, 1341, 1310, 1252, 1231, 1205, 1147, 1119, 1023, 974.5, 933.2, 873.2, 822.6, 774.4, 747.9, 671.7, 610, 581.2, 547.7, 435.5. ^{1}H NMR δ (DMSO-d_6): 11.84 (1H, br s, NH), 7.65 (1H, d, J=8.0 Hz, H-4), 7.46 (1H, d, J=7.8 Hz, H-7), 7.26 (1H, t, J=7.8 Hz, H-6), 7.14 (1H, s, H-3), 7.07 (1H, t, J=8.0 Hz, H-5), 4.34 (2H, q, J=7.1 Hz, CH_2), 1.34 (3H, t, J=7.1 Hz, CH_3); ^{13}C NMR δ (DMSO-d_6): 161.3, 137.3, 127.3, 126.7, 124.5, 122.0, 120.1, 112.5, 107.6, 60.3, 14.2.

4.1.2. Indole-2-carboxamide (8). *Method A*: Ethyl indole-2-carboxylate **7** (8.0 g, 2.93 mmol) was dissolved in tetrahydrofuran (50 mL) and 25% ammonia in dry methanol (200 mL) was added to the solution. The solution was kept at room temperature for 5 weeks. The solvent was then evaporated off and the resulting white crystalline powder was washed with ethanol and recrystallized. The ethanolic washings were evaporated and subjected to the amidation reaction again. A white crystalline powder, mp: 234–235 °C (from ethanol), lit.[30] mp: 232–234 °C, yield 88%. ν_{max} (KBr disc) 3465, 3318, 3263, 3213, 3183, 3109, 3081, 3055, 3030, 2980, 2922, 2851, 2810, 2735, 2650, 1667, 1652, 1618, 1593, 1524, 1436, 1417, 1384, 1344, 1330, 1289, 1228, 1153, 1129, 1095, 1008, 965.6, 947.9, 814.7, 781.8, 755, 747.5, 685.7, 670.6, 613.6, 591.3, 573, 541.1, 484.7, 441.2. ^{1}H NMR δ (DMSO-d_6): 11.52 (1H, br s, NH), 7.96 (1H, br s, $CONH_2$), 7.60 (1H, d, J=8.0 Hz, H-4), 7.44 (1H, d, J=7.8 Hz, H-7), 7.36 (1H, br s, $CONH_2$), 7.17 (1H, t, J=7.8 Hz, H-6), 7.13 (1H, s, H-3), 7.03 (1H, t, J=8.0 Hz, H-5); ^{13}C NMR δ (DMSO-d_6): 162.9, 136.6, 131.8, 127.2, 123.3, 121.5, 119.6, 112.3, 103.2.

Method B: For the preparation of compound **8**, the method of Spadoni et al.[21] (synthesis of 7-methoxyindole-2-carboxamide) was used, with slight modifications as follows. To a stirred and ice-cooled solution of indole-2-carboxylic acid (3.22 g, 20 mmol) in tetrahydrofuran (60 mL), thionyl chloride (2.60 mL, 35.64 mmol) in tetrahydrofuran (5 mL) was added dropwise during 15 min under nitrogen. The mixture was stirred at 50 °C for 4 h, and then at room temperature for 2 h. The mixture was evaporated (water bath <35 °C) and the residue was washed with *n*-hexane and decanted (2×10 mL). The acid chloride obtained was dissolved in tetrahydrofuran (40 mL) and used without further purification in the next step.

Dichloromethane (40 mL) was cooled to −10 °C and ammonia gas was bubbled through the solvent for 30 min. The cooling bath was then removed and the ammonia solution was added immediately in one portion to the stirred and ice-cooled solution of the above acid chloride. The reaction mixture was stirred further at room temperature for 10 h. The white precipitate formed was filtered off, washed with water (20 mL) twice followed by diethyl ether (20 mL) and dried, furnishing 2.6 g of **8**. The organic filtrate was evaporated and the residue was taken up in water, filtered, washed with diethyl ether and dried (0.2 g of **8**). The combined indole-2-carboxamide fractions were used without further purification in the next step. A small portion was purified by column chromatography, using ethyl acetate/*n*-hexane 3:2 as an eluent (analytical data identical to those given above).

4.1.3. 2-Aminomethylindole (9). To an ice-cooled, stirred suspension of lithium aluminium hydride (3.20 g, 84.30 mmol) in tetrahydrofuran (130 mL), amide **8** (5.80 g, 36.22 mmol) was added in small portions during 10 min. After the addition, the mixture was heated at reflux for 7 h. The reaction mixture was then cooled with ice-water and a mixture of water (6 mL) and tetrahydrofuran (10 mL) was added dropwise. The mixture was stirred for a further 1 h under ice cooling, and for 2 h at room temperature, then filtered, washed with tetrahydrofuran (40 mL) and ethyl acetate (2×40 mL), dried (sodium sulfate), filtered and evaporated. Trituration of the oily residue with diisopropyl ether gave **9** as a crystalline powder. White crystals, mp: 73–75 °C (from diisopropyl ether), lit.[17] mp: 70–72 °C, yield 71%. ν_{max} (KBr disc) 3406, 3390, 3299, 3109, 3084, 3051, 2925, 2855, 2685, 2629, 1667, 1652, 1618, 1593, 1524, 1436, 1417, 1384, 1344, 1330, 1289, 1228, 1153, 1129, 1095, 1008, 965.5, 947.9, 814.7, 781.8, 755, 747.5, 658.7, 670.6, 613.6, 591.3, 573, 541.1, 484.7, 441.2. ^{1}H NMR δ (DMSO-d_6): 10.95 (1H, br s, NH), 7.41 (1H, d, J=8.1 Hz, H-4), 7.29 (1H, d, J=7.9 Hz, H-7), 6.99 (1H, t, J=7.9 Hz, H-6), 6.91 (1H, t, J=8.1 Hz, H-5), 6.21 (1H, s, H-3), 3.82 (2H, s, CH_2); ^{13}C NMR δ (DMSO-d_6): 141.4, 136.2, 128.1, 120.3, 119.5, 118.6, 110.9, 98.1, 56.9.

4.1.4. General procedure for substituted 2-(benzoylaminomethyl)indoles (11a–e). Amine **9** (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 the substituted benzoyl chloride (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 crystalline benzamides were purified by recrystallization.

4.1.4.1. 2-(Benzoylaminomethyl)indole (11a). Light-brown crystals, mp: 171–173 °C (from toluene), lit.[31] mp: 164 °C, yield 86%. ν_{max} (KBr disc) 3293, 3051, 1639, 1577, 1524, 1488, 1456, 1414, 1340, 1292, 1079, 1251, 1195, 1079, 797.7, 740, 706.6. ^{1}H NMR δ (DMSO-d_6): 10.91 (1H, br s, NH), 9.04–8.91 (1H, t, J=6.4 Hz, CONH), 7.98–7.87 (2H, m, H-2′, H-6′), 7.58–7.39 (4H, m, H-3′, H-5′, H-4′, H-4), 7.35 (1H, d, J=7.8 Hz, H-7), 7.03 (1H, t, J=7.8 Hz, H-6), 6.95 (1H, t, J=8.2 Hz, H-5), 6.29 (1H, s, H-3), 4.63 (2H, d, J=6.4 Hz, CH_2); ^{13}C NMR δ (DMSO-d_6): 166.3, 137.2, 136.1, 134.3, 131.2, 128.2 (2C), 127.9, 127.3 (2C), 120.5, 119.4, 118.7, 111.1, 99.0, 36.7. Anal. Calcd for $C_{16}H_{14}N_2O$ (250.30): C, 76.78; H, 5.64; N, 11.19. Found: C, 76.59; H, 5.47; N, 11.44.

4.1.4.2. 2-(4-Chlorobenzoylaminomethyl)indole (11b). Light-brown crystals, mp: 190–191 °C (from toluene), yield 91%. ν_{max} (KBr disc) 3423, 3301, 3080, 3057, 3032, 2923, 2853, 1641, 1615, 1558, 1527, 1484, 1457, 1417, 1396, 1360, 1339, 1303, 1289, 1277, 1240, 1218, 1154, 1146, 1110, 1095, 1036, 979.8, 934.5, 893, 848, 826.4, 799.2, 159, 743.4, 724.9, 687.7, 665.8, 626.9, 603.7, 572.9, 527.2, 464.8, 439.9. ^{1}H NMR δ (DMSO-d_6): 10.92 (1H, br s, NH), 9.07 (1H, t, J=5.9 Hz, CONH), 7.95 (2H, d, J=8.5 Hz, H-2′, H-6′), 7.56 (2H, d, J=8.5 Hz, H-3′, H-5′), 7.45 (1H, d, J=8.0 Hz, H-4), 7.35 (1H, d, J=7.8 Hz, H-7), 7.03 (1H, t, J=7.8 Hz, H-6), 6.95 (1H, t, J=8.0 Hz, H-5), 6.30 (1H, s, H-3), 4.64 (2H, d, J=5.9 Hz, CH_2); ^{13}C NMR δ (DMSO-d_6): 165.3, 137.0, 136.1, 133.0, 129.3, 129.2 (2C), 128.3 (2C), 127.9, 120.6, 119.5, 118.8, 111.1, 99.1, 36.8. Anal. Calcd for $C_{16}H_{13}ClN_2O$ (284.74): C, 67.49; H, 4.60; N, 9.84. Found: C, 67.23; H, 4.49; N, 10.02.

4.1.4.3. 2-(4-Fluorobenzoylaminomethyl)indole (11c). Light-brown crystals, mp: 172–173 °C (from toluene), yield 83%. ν_{max} (KBr disc) 3428, 3301, 3084, 3046, 2924, 2853, 1643, 1615, 1602, 1590, 1531, 1499, 1457, 1414, 1405, 1362, 1339, 1310, 1289, 1241, 1219, 1160, 1121, 1113,

1095, 1010, 979.8, 970.2, 935.5, 895, 850.8, 801.6, 765.5, 743.4, 726.1, 689.6, 668.5, 608, 522.7, 486.1, 422.5, 415.6. ^{1}H NMR δ (DMSO-d_6): 10.91 (1H, br s, NH), 9.01 (1H, t, J=6.1 Hz, CONH), 8.07–7.95 (2H, m, H-2′, H-6′), 7.45 (1H, d, J=8.0 Hz, H-4), 7.39–7.25 (3H, m, H-3′, H-5′, H-7), 7.03 (1H, t, J=7.8 Hz, H-6), 6.95 (1H, t, J=8.0 Hz, H-5), 6.29 (1H, s, H-3), 4.63 (2H, d, J=6.1 Hz, CH_2); ^{13}C NMR δ (DMSO-d_6): 165.3, 165.1, 137.1, 136.1, 130.7, 130.0 (2C), 127.9, 120.5, 119.4, 118.8, 115.2 (2C), 111.1, 99.0, 36.8, due to F,C-couplings, the signals of the aryl group are doublets, ^1J(F,C): 249.5 Hz, ^2J(F,C): 22.1 Hz, ^3J(F,C): 9.2 Hz, ^4J(F,C): 2.7 Hz. Anal. Calcd for $C_{16}H_{13}FN_2O$ (268.29): C, 71.63; H, 4.88; N, 10.44. Found: C, 71.67; H, 4.71; N, 10.62.

4.1.4.4. 2-(4-Methylbenzoylaminomethyl)indole (11d). Light-brown crystals, mp: 190–192 °C (from toluene), yield 95%. ν_{max} (KBr disc) 3430, 3290, 3200, 3080, 3052, 3025, 2940, 2921, 2853, 1640, 1614, 1571, 1529, 1499, 1457, 1414, 1362, 1340, 1312, 1291, 1238, 1217, 1187, 1154, 1144, 1118, 1094, 1041, 1008, 979.7, 929.4, 893, 849.2, 831.6, 801.2, 773.5, 751.9, 738.6, 693.1, 670.6, 609.3, 511.2, 450, 440.6. ^{1}H NMR δ (DMSO-d_6): 10.88 (1H, br s, NH), 8.89 (1H, t, J=6.0 Hz, CONH), 7.83 (2H, d, J=7.5 Hz, H-2′, H-6′), 7.44 (1H, d, J=7.8 Hz, H-4), 7.34 (1H, d, J=7.5 Hz, H-7), 7.28 (2H, J=7.5 Hz, H-3′, H-5′), 7.02 (1H, t, J=7.5 Hz, H-6), 6.94 (1H, t, J=7.8 Hz, H-5), 6.28 (1H, s, H-3), 4.61 (2H, d, J=6.0 Hz, CH_2), 2.35 (3H, s, CH_3); ^{13}C NMR δ (DMSO-d_6): 166.2, 141.1, 137.3, 136.1, 131.5, 128.7 (2C), 127.9, 127.3 (2C), 120.5, 119.4, 118.7, 111.1, 98.9, 36.7, 20.9. Anal. Calcd for $C_{17}H_{16}N_2O$ (264.32): C, 77.25; H, 6.10; N, 10.60. Found: C, 77.11; H, 5.91; N, 10.82.

4.1.4.5. 2-(2-Fluorobenzoylaminomethyl)indole (11e). White crystals, mp: 138–141 °C (from toluene), yield 57%. ν_{max} (KBr disc) 3453, 3311, 3085, 2927, 1643, 1615, 1531, 1481, 1455, 1433, 1416, 1360, 1338, 1302, 1262, 1210, 1161, 1148, 1097, 1042, 1010, 979.3, 952.8, 925, 840.3, 787.1, 750.4, 739.2, 726.2, 687.6, 662, 650.6, 618.9, 606.9, 553.6, 538.1, 528.8, 502.9, 464.2, 438.3, 415.3. ^{1}H NMR δ (DMSO-d_6): 10.94 (1H, br s, NH), 8.79 (1H, t, J=4.7 Hz, CONH), 7.79–7.21 (6H, m, H-3′, H-4′, H-5′, H-6′, H-4, H-7), 7.04 (1H, t, J=7.8 Hz, H-6), 6.96 (1H, t, J=8.1 Hz, H-5), 6.32 (1H, s, H-3), 4.63 (2H, d, J=4.7 Hz, CH_2); ^{13}C NMR δ (DMSO-d_6): 163.7, 158.0, 136.8, 136.1, 132.5, 130.2, 127.9, 124.4, 123.9, 120.6, 119.5, 118.8, 116.2, 111.1, 99.0, 36.7, due to F,C-couplings, the signals of the aryl group are doublets, ^1J(F,C): 249.1 Hz, ^2J(F,C): 22.1 Hz, ^3J(F,C): 13.7 Hz, ^4J(F,C): 8.7 Hz, ^5J(F,C): 8.3 Hz, ^6J(F,C): 3.1 Hz. Anal. Calcd for $C_{16}H_{13}FN_2O$ (268.29): C, 71.63; H, 4.88; N, 10.44. Found: C, 71.45; H, 4.59; N, 10.47.

4.1.5. General procedure for substituted 2-(thiobenzoylaminomethyl)indole (14a–e) from benzamides 11a–e. To a solution of substituted 2-(benzoylaminomethyl)indole (**11a–e**) (4.0 mmol) in tetrahydrofuran (40 mL), Lawesson′s reagent (0.96 g, 2.4 mmol) was added in one portion. The reaction mixture was heated at reflux for 2 h. After evaporation, the residue was taken up in ethyl acetate (40 mL) and extracted with saturated sodium hyrogencarbonate solution (20 mL), water (20 mL), dried (sodium sulfate), evaporated and purified by column chromatography, using *n*-hexane/ethyl acetate 4:1 as an eluent, to give **14a–e** as a crystalline powder after trituration with *n*-hexane and a few drops of diisopropyl ether.

4.1.5.1. 2-(Thiobenzoylaminomethyl)indole (14a). Yellow crystals, mp: 155–157 °C, yield 89%. ν_{max} (KBr disc) 3454, 3384, 3252, 3047, 1642, 1615, 1594, 1530, 1488, 1456, 1421, 1389, 1352, 1339, 1308, 1281, 1271, 1197, 1138, 1094, 1077, 1032, 999.7, 960.8, 924.6, 889.2, 849.7, 795.4, 771.3, 752.6, 737.7, 717.9, 690, 639.5, 567.1, 460.8, 431.4. ^{1}H NMR δ (DMSO-d_6): 11.03 (1H, br s, NH), 10.68 (1H, t, J=6.2 Hz, CSNH), 7.87–7.40 (6H, m, H-2′, H-6′, H-3′, H-5′, H-4′, H-4), 7.36 (1H, d, J=8.1 Hz, H-7), 7.05 (1H, t, J=8.1 Hz, H-6), 6.96 (1H, t, J=8.2 Hz, H-5), 6.38 (1H, s, H-3), 5.10 (2H, d, J=6.2 Hz, CH_2); ^{13}C NMR δ (DMSO-d_6): 197.7, 141.0, 136.1, 134.6, 130.7, 127.9 (2C), 127.8, 127.4 (2C), 120.8, 119.6, 118.8, 111.1, 99.9, 43.6. Anal. Calcd for $C_{16}H_{14}N_2S$ (266.37): C, 72.15; H, 5.30; N, 10.52; S, 12.04. Found: C, 71.95; H, 5.41; N, 10.27; S, 12.28.

4.1.5.2. 2-(4-Chlorothiobenzoylaminomethyl)indole (14b). Yellow crystals, mp: 156–158 °C, yield 81%. ν_{max} (KBr disc) 3467, 3377, 3249, 3080, 3052, 2961, 2920, 1638, 1616, 1591, 1534, 1487, 1455, 1427, 1403, 1354, 1340, 1307, 1277, 1213, 1198, 1150, 1136, 1112, 1089, 1013, 960.5, 928.1, 834.7, 792.2, 752.2, 739.2, 722.1, 645.3, 631.5, 574.8, 567.1, 494.6, 433.5, 408.9. ^{1}H NMR δ (DMSO-d_6): 11.06 (1H, br s, NH), 10.77 (1H, t, J=5.0 Hz, CSNH), 7.85 (2H, d, J=8.2 Hz, H-2′, H-6′), 7.51 (2H, d, J=8.2 Hz, H-3′, H-5′), 7.48 (1H, d, J=7.9 Hz, H-4), 7.37 (1H, d, J=8.1 Hz, H-7), 7.06 (1H, t, J=8.1 Hz, H-6), 6.97 (1H, t, J=7.9 Hz, H-5), 6.39 (1H, s, H-3), 5.09 (2H, d, J=4.9 Hz, CH_2); ^{13}C NMR δ (DMSO-d_6): 196.1, 139.6, 136.1, 135.5, 134.4, 129.3 (2C), 127.9 (2C), 127.8, 120.8, 119.6, 118.9, 111.1, 100.0, 43.7. 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, 63.76; H, 4.11; N, 9.54; S, 10.93.

4.1.5.3. 2-(4-Fluorothiobenzoylaminomethyl)indole (14c). Yellow crystals, mp: 170–173 °C, yield 75%. ν_{max} (KBr disc) 3378, 3245, 3053, 1599, 1538, 1504, 1456, 1427, 1410, 1353, 1340, 1307, 1289, 1271, 1247, 1212, 1197, 1166, 1137, 1107, 1088, 1013, 961.1, 928.6, 841.5, 815.9, 791.9, 751.9, 735.4, 658.8, 631.2, 574.6, 494.6, 468.5, 433.3. ^{1}H NMR δ (DMSO-d_6): 11.02 (1H, br s, NH), 10.68 (1H, t, J=5.0 Hz, CSNH), 7.94–7.84 (2H, m, H-2′, H-6′), 7.46 (1H, d, J=7.8 Hz, H-4), 7.34 (1H, d, J=8.0 Hz, H-7), 7.30–7.19 (2H, m, H-3′, H-5′), 7.04 (1H, t, J=8.0 Hz, H-6), 6.95 (1H, t, J=7.8 Hz, H-5), 6.37 (1H, s, H-3), 5.07 (2H, d, J=4.9 Hz, CH_2); ^{13}C NMR δ (DMSO-d_6): 196.2, 164.8, 137.4, 136.1, 134.5, 129.9 (2C), 127.8, 120.8, 119.6, 118.9, 114.8 (2C), 111.1, 100.0, 43.7, due to F,C-couplings, the signals of the aryl group are doublets, ^1J(F,C): 248.9 Hz, ^2J(F,C): 21.8 Hz, ^3J(F,C): 9.3 Hz, ^4J(F,C): 2.7 Hz. 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, 67.32; H, 4.42; N, 10.03; S, 11.51.

4.1.5.4. 2-(4-Methylthiobenzoylaminomethyl)indole (14d). Yellow crystals, mp: 154–156 °C, yield 91%. ν_{max} (KBr disc) 3402, 3327, 2923, 1522, 1504, 1456, 1417, 1382, 1341, 1325, 1279, 1221, 1189, 1067, 926.7, 826.3, 809, 739.6, 723.8, 665, 639.8, 606.4, 413.3. ^{1}H NMR δ (DMSO-d_6): 11.02 (1H, br s, NH), 10.58 (1H, t, J=4.9 Hz, CSNH), 7.78 (2H, d, J=7.9 Hz, H-2′, H-6′), 7.48 (1H, d,

J=7.2 Hz, H-4), 7.37 (1H, d, J=8.1 Hz, H-7), 7.24 (2H, d, J=7.9 Hz, H-3′, H-5′), 7.06 (1H, t, J=8.1 Hz, H-6), 6.97 (1H, t, J=7.2 Hz, H-5), 6.38 (1H, s, H-3), 5.11 (2H, d, J=4.9 Hz, CH_2), 2.35 (3H, s, CH_3); ^{13}C NMR δ (DMSO-d_6): 197.4, 140.8, 138.1, 136.1, 134.8, 128.4 (2C), 127.8, 127.5 (2C), 120.7, 119.6, 118.8, 111.1, 99.9, 43.5, 20.8. 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, 72.66; H, 5.71; N, 10.21; S, 11.31.

4.1.5.5. 2-(2-Fluorothiobenzoylaminomethyl)indole (14e). Yellow crystals, mp: 142–144 °C, yield 57%. ν_{max} (KBr disc) 3346, 3311, 1611, 1580, 1533, 1520, 1485, 1451, 1419, 1387, 1359, 1340, 1323, 1291, 1260, 1231, 1209, 1155, 1112, 1078, 1066, 1032, 1012, 968.1, 936.5, 814.6, 797.5, 761.2, 736.1, 665, 639.8, 635–440. ^{1}H NMR δ (DMSO-d_6): 11.01 (1H, br s, NH), 10.85 (1H, t, J=5.2 Hz, CSNH), 7.54–7.07 (6H, m, H-3′, H-4′, H-5′, H-6′, H-4, H-7), 6.97 (1H, t, J=7.9 Hz, H-6), 6.88 (1H, t, J=7.3 Hz, H-5), 6.32 (1H, s, H-3), 4.98 (2H, d, J=5.2 Hz, CH_2); ^{13}C NMR δ (DMSO-d_6): 192.8, 157.9, 136.1, 134.1, 131.3, 131.0, 130.8, 127.9, 124.2, 121.0, 119.7, 119.0, 115.9, 111.2, 100.1, 43.3, due to F,C-couplings, the signals of the aryl group are doublets, ^1J(F,C): 248.8 Hz, ^2J(F,C): 21.8 Hz, ^3J(F,C): 14.5 Hz, ^4J(F,C): 8.3 Hz, ^5J(F,C): 7.7 Hz, ^6J(F,C): 3.0 Hz. 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, 67.34; H, 4.57; N, 9.67; S, 11.12.

4.1.6. General procedure for 2-(arylthiocarbonylaminomethyl)indoles (14a–d) from 2-(aminomethyl)indole (9) and methyl dithiobenzoates (12a–d). Amine **9** (0.52 g, 2.53 mmol) was dissolved in dichloromethane (20 mL). To this solution, triethylamine (0.50 g, 2.53 mmol) and 4-dimethylaminopyridine (0.06 g, 0.5 mmol) were added. Following the addition of the appropriate methyl dithiobenzoates (**12a–d**) (2.78 mmol), the reaction mixture was left to stand at room temperature in a good hood for 6 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 (sodium sulfate) and evaporated. Trituration of the residue with *n*-hexane and with a few drops of diisopropyl ether gave a yellow crystalline powder, which was purified further by column chromatography (*n*-hexane/ethyl acetate 4:1), providing **14a** (67%), **14b** (74%), **14c** (58%) or **14d** (56%) (analytical data identical to those given above).

4.1.7. General procedure for 2-(arylthiocarbonylaminomethyl)indoles (14a,b) from 2-aminomethylindole (9) and benzaldehydes (13a,b). To a solution of amine (**9**) (0.42 g, 2.9 mmol) in *N*,*N*-dimethylformamide (3 mL) at room temperature benzaldehyde **13a** or **b** (3.0 mmol) was added. Sulfur (0.10 g, 3.1 mmol) was added to the resulting solution and the mixture was stirred at 90 °C for 3 h. Water (30 mL) was next added to the reaction mixture and it was extracted with diethyl ether (3×20 mL). The combined organic layers were washed with 3% hydrochloric acid, followed by water, dried (sodium sulfate) and evaporated. The residue was purified by column chromatography, using *n*-hexane/ethyl acetate 4:1 as an eluent to give **14a** (82%) and **b** (42%) as crystalline powders (analytical data identical to those given above).

4.1.8. General procedure for 4,5-dihydro-2-aryl-1,3-thiazino[5,6-*b*]indole (15a–d) from 2-(arylthiocarbonylaminomethyl)indoles (14a–d). To an intensively stirred solution of thiocarboxamides **14a–d** (1.66 mmol) in dichloromethane (20 mL), phenyltrimethylammonium tribromide (0.62 g, 1.66 mmol) was added in one portion at room temperature. After stirring for 1 min, triethylamine (0.69 mL, 4.98 mmol) was added in one portion. The mixture was evaporated (water bath <50 °C) and the residue was purified by column chromatography, using first *n*-hexane/ethyl acetate 4:1, followed by 3:2 as an eluent, to give **15a–d** as crystalline powders.

4.1.8.1. 4,5-Dihydro-2-phenyl-1,3-thiazino[5,6-*b*]indole (15a). Light-grey crystals, mp: 163–165 °C (decomp.), yield 82%. ν_{max} (KBr disc) 3409, 3378, 2923, 1603, 1452, 1423, 1312, 1163, 1116, 1078, 908.2, 764.5, 745.2, 688, 671.8, 611, 578.6, 503.1. ^{1}H NMR δ (DMSO-d_6): 11.44 (1H, br s, NH), 7.92 (2H, d, J=6.8 Hz, H-2′, H-6′), 7.60–7.33 (5H, m, H-3′, H-5′, H-4′, H-9, H-6), 7.16 (1H, t, J=7.9 Hz, H-7), 7.07 (1H, t, J=8.4 Hz, H-8), 5.29 (2H, s, CH_2); ^{13}C NMR δ (DMSO-d_6): 154.7, 137.5, 136.0, 131.0, 128.6 (2C), 126.6 (2C), 124.6, 124.0, 121.8, 119.5, 116.8, 111.8, 95.3, 47.7. 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, 72.48; H, 4.76; N, 10.51; S, 12.15.

4.1.8.2. 4,5-Dihydro-2-(4-chlorophenyl)-1,3-thiazino[5,6-*b*]indole (15b). Light-grey crystals, mp: 182–185 °C (decomp.), yield 77%. ν_{max} (KBr disc) 3373, 1601, 1486, 1452, 1397, 1311, 1093, 1080, 1012, 907.2, 835, 745.7, 740–450. ^{1}H NMR δ (DMSO-d_6): 11.50 (1H, br s, NH), 7.94 (2H, d, J=8.2 Hz, H-2′, H-6′), 7.58 (2H, d, J=8.2 Hz, H-3′, H-5′), 7.48–7.35 (2H, m, H-9, H-6), 7.16 (1H, t, J=7.8 Hz, H-7), 7.07 (1H, t, J=7.8 Hz, H-8), 5.31 (2H, s, CH_2); ^{13}C NMR δ (DMSO-d_6): 153.7, 136.2, 136.1, 135.8, 128.8 (2C), 128.4 (2C), 124.6, 124.0, 121.9, 119.6, 116.9, 111.9, 95.0, 47.8. 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, 64.17; H, 3.84; N, 9.57; S, 10.91.

4.1.8.3. 4,5-Dihydro-2-(4-fluorophenyl)-1,3-thiazino[5,6-*b*]indole (15c). Light-grey crystals, mp: 144–149 °C (decomp.), yield 54%. ν_{max} (KBr disc) 3377, 2905, 2402, 2388, 2252, 1609, 1503, 1452, 1370, 1311, 1235, 1158, 1115, 1078, 908.9, 841, 744.9, 600.8, 500.4. ^{1}H NMR δ (DMSO-d_6): 11.45 (1H, br s, NH), 8.03–7.83 (2H, m, H-2′, H-6′), 7.48–7.19 (4H, m, H-3′, H-5′, H-9, H-6), 7.16 (1H, t, J=8.1 Hz, H-7), 7.07 (1H, t, J=8.0 Hz, H-8), 5.29 (2H, s, CH_2); ^{13}C NMR δ (DMSO-d_6): 165.0, 153.7, 136.1, 134.0, 129.1 (2C), 124.6, 124.1, 121.9, 119.5, 116.8, 115.7 (2C), 111.9, 95.3, 47.7, due to F,C-couplings, the signals of the aryl group are doublets, ^1J(F,C): 249.7 Hz, ^2J(F,C): 21.8 Hz, ^3J(F,C): 9.2 Hz, ^4J(F,C): 2.7 Hz. 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, 67.73; H, 3.75; N, 9.94; S, 11.52.

4.1.8.4. 4,5-Dihydro-2-(4-methylphenyl)-1,3-thiazino[5,6-*b*]indole (15d). Light-grey crystals, mp: 143–146 °C (decomp.), yield 71%. ν_{max} (KBr disc) 3377, 3054, 2823, 1607, 1453, 1313, 1228, 1181, 1081, 910, 818.4, 740.8, 740–440. ^{1}H NMR δ (DMSO-d_6): 11.44 (1H, br s, NH), 7.83 (2H, d, J=8.0 Hz, H-2′, H-6′), 7.49–7.35 (2H, m,

H-9, H-6), 7.31 (2H, d, J=8.0 Hz, H-3′, H-5′), 7.15 (1H, t, J=7.0 Hz, H-7), 7.07 (1H, t, J=7.3 Hz, H-8), 5.27 (2H, s, CH_2), 2.37 (3H, s, CH_3); ^{13}C NMR δ (DMSO-d_6): 154.5, 140.9, 136.0, 134.8, 129.2 (2C), 126.6 (2C), 124.7, 124.2, 121.8, 119.4, 116.8, 111.8, 95.5, 47.6, 20.8. 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, 73.21; H, 5.14; N, 10.9.98; S, 11.69.

4.1.8.5. 4,5-Dihydro-2-(2-fluorophenyl)-1,3-thiazino[5,6-*b*]indole (15e). To an intensively stirred solution of iodine (0.21 g, 0.84 mmol) in dichloromethane (10 mL), thiocarboxamide **13e** (0.84 mmol) was added in one portion at room temperature. After stirring for 30 s, triethylamine (0.48 mL, 3.4 mmol) was added in one portion. The mixture was evaporated (water bath <50 °C) and the residue was triturated with ethanol, filtered and recrystallized from ethyl acetate and ethanol to give **15e** as a crystalline powder. Light-grey crystals, mp: 186–189 °C (decomp.), yield 44%. ν_{max} (KBr disc) 3377, 3054, 2869, 2819, 1605, 1486, 1451, 1318, 1231, 1079, 986.2, 917.9, 807.7, 769.7, 739.2, 735–440. ^{1}H NMR δ (DMSO-d_6): 11.48 (1H, br s, NH), 7.70–7.26 (6H, m, H-3′, H-4′, H-5′, H-6′, H-9, H-6), 7.15 (1H, t, J=8.2 Hz, H-7), 7.05 (1H, t, J=7.9 Hz, H-8), 5.29 (2H, s, CH_2); ^{13}C NMR δ (DMSO-d_6): 160.1, 151.1, 136.0, 132.1, 129.5, 126.8, 124.6, 124.4, 123.5, 121.9, 119.5, 116.9, 116.4, 111.9, 95.6, 48.0, due to F,C-couplings, the signals of the aryl group are doublets, ^1J(F,C): 250.6 Hz, ^2J(F,C): 21.6 Hz, ^3J(F,C): 13.1 Hz, ^4J(F,C): 8.1 Hz, ^5J(F,C): 3.3 Hz. 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, 67.72; H, 3.79; N, 10.18; S, 11.47.

4.1.9. One-pot synthesis of 4,5-dihydro-2-phenyl-1,3-thiazino[5,6-*b*]indole (15a) from 2-aminomethylindole (9). To a solution of amine (**9**) (0.14 g, 0.96 mmol) in *N*,*N*-dimethylformamide (1 mL) at room temperature, benzaldehyde (**13a**) (0.1 mL, 1.0 mmol) was added. To the resulting solution, sulfur (35 mg, 1.0 mmol) was added and the mixture was stirred at 90 °C for 3 h. The reaction mixture was allowed to cool down to room temperature, and phenyltrimethylammonium tribromide (0.34 g, 0.90 mmol) was added in one portion. After 5 s, triethylamine (1 mL, 7.18 mmol) was added and the mixture was diluted with dichloromethane (20 mL). The organic phase was extracted with water (2×10 mL), dried (sodium sulfate) and evaporated. The residue was purified by column chromatography, using first *n*-hexane/ethyl acetate 4:1, and then 3:2 as an eluent, to give **15a** (38%) as a crystalline powder (analytical data identical to those given above).

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References and notes

1. Sundberg, R. J. *Indoles*; Academic: London, 1996.
2. Pedras, M. S. C.; Jha, M.; Ahiahonu, P. W. K. *Curr. Org. Chem.* **2003**, *7*, 1635–1647.
3. Takasugi, M.; Katsui, N.; Shirata, A. *J. Chem. Soc., Chem. Commun.* **1986**, 1077–1079.
4. Dixon, R. A.; Lamb, C. J. *Ann. Rev. Plant Physiol. Plant Mol. Biol.* **1990**, *41*, 339–367.
5. Metha, R. G.; Liu, J.; Constantinou, A.; Thomas, C. F.; Hawthorne, M.; You, M.; Gerhäuser, C.; Pezutto, J. M.; Moon, R. C.; Moriarty, M. R. *Carcinogenesis* **1995**, *16*, 399–404.
6. Kutschy, P.; Suchý, M.; Adreani, A.; Dzurilla, M.; Kováčik, V.; Alföldi, J.; Rossi, M.; Gramatová, M. *Tetrahedron* **2002**, *58*, 9029–9039.
7. Csomós, P.; Fodor, L.; Sohár, P.; Bernáth, G. *Tetrahedron* **2005**, *61*, 9257–9262.
8. Velezheva, V. S.; Yarosl, A. V.; Kozik, T. A.; Suvorov, U. N. *Khim. Geterofsikl. Soedin.* **1978**, 1497–1503; *Chem. Abstr.* **1979**, *90*, 87375f.
9. Romeo, G.; Russo, F.; Guccione, S.; Chabin, R.; Kuo, D.; Knight, W. B. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2399–2404.
10. Pedras, M. S. C.; Suchy, M.; Ahiahonu, P. W. K. *Org. Biomol. Chem.* **2006**, *4*, 691–701.
11. Csomós, P.; Zupkó, I.; Réthy, B.; Fodor, L.; Falkay, G.; Bernáth, G. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6273–6276.
12. Fodor, L.; Szabó, J.; Szűcs, E.; Bernáth, G.; Sohár, P.; Tamás, J. *Tetrahedron* **1984**, *40*, 4089–4095.
13. Fodor, L.; MacLean, D. B. *Can. J. Chem.* **1987**, *65*, 18–26.
14. Szabó, J.; Fodor, L.; Bani-Akoto, E.; Talpas, G. S.; Bernáth, G.; Sohár, P. *Tetrahedron* **1992**, *48*, 4957–4962.
15. Fodor, L.; Bernáth, G.; Sinkkonen, J.; Pihlaja, K. *J. Heterocycl. Chem.* **2002**, *39*, 927–931.
16. Csomós, P.; Fodor, L.; Sinkonen, J.; Pihlaja, K.; Bernáth, G. *Tetrahedron Lett.* **2006**, *47*, 5665–5667.
17. Wright, W. B., Jr.; Brabander, H. J. *J. Med. Chem.* **1968**, *11*, 1164–1167.
18. Nógrádi, T. *Monatsh. Chem.* **1958**, *88*, 1087–1094.
19. Pletnev, A. A.; Tian, Q.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9276–9287.
20. Borza, I.; Kolok, S.; Ignácz-Szendrei, G.; Greiner, I.; Tárkányi, G.; Galgóczy, K.; Horváth, C.; Farkas, S.; Domány, G. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5439–5441.
21. Spadoni, G.; Balsamini, C.; Diamantini, G.; Tontini, A.; Giorgio Tarzia, G.; Marco Mor, M.; Rivara, S.; Plazzi, P. V.; Nonno, R.; Lucini, V.; Pannacci, M.; Franco Fraschini, F.; Stankov, B. M. *J. Med. Chem.* **2001**, *44*, 2900–2912.
22. Shibahara, F.; Kitagawa, A.; Yamaguchi, E.; Murai, T. *Org. Lett.* **2006**, *8*, 5621–5624.
23. Jordan, A. D.; Luo, C.; Reitz, A. B. *J. Org. Chem.* **2003**, *68*, 8693–8696.
24. Takasugi, M.; Monde, K.; Katsui, M.; Shirata, A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 285–289.
25. Kutschy, P.; Suchý, M.; Monde, K.; Harada, N.; Maruškova, R.; Čurillova, Z.; Dzurilla, M.; Miklošova, M.; Mezencev, R.; Mojžiš, J. *Tetrahedron Lett.* **2002**, *43*, 9489–9492.
26. Noland, W. E. *Organic Synthesis*; Wiley: New York, NY, 1988; Coll. Vol. 6, pp 175–177.
27. Sohár, P. *Nuclear Magnetic Resonance Spectroscopy*; CRC: Boca Raton, FL, 1983; Vol. 2, p 185.
28. Thiel, W.; Mayer, R. *J. Prakt. Chem./Chem.-Ztg.* **1989**, *331*, 243–262.
29. Fagan, G. P.; Chapleo, C. B.; Lane, A. C.; Myers, M.; Roach, A. G. *J. Med. Chem.* **1988**, *31*, 944–948.
30. Acheson, R. M.; Prince, R. J.; Proctor, G. *J. Chem. Soc.* **1979**, *P1*, 595–598.
31. Rosemund, P.; Sauer, D.; Trommer, W. *Chem. Ber.* **1970**, *103*, 496–509.