Tetrahedron 64 (2008) 8646–8651

Contents lists available at ScienceDirect

Tetrahedron

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

Synthesis of 4-thiaharmalan analogue 4-aryl-1,3-thiazino[5,6-*b*]indole derivatives by prevention of rearrangements to position two of the indole moiety

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ARTICLE INFO

Article history:
Received 15 April 2008
Received in revised form 18 June 2008
Accepted 3 July 2008
Available online 8 July 2008

Keywords:
Amidomethylation
4-Thiaharmalan
Thiazino[5,6-*b*]indole
Bischler–Napieralski reaction

ABSTRACT

An efficient and selective non-acidic protocol has been developed for the synthesis of derivatives of a new ring system: 4-aryl-1,3-thiazino[5,6-*b*]indole, a 4-thiaharmalan analogue. The convenient amidomethylation of indole-3-thiol (**5**) afforded 3-benzoylaminomethylthio-1*H*-indole (**7a**), with *ortho*-amidomethylated 2-benzoylamino-methyl-3-benzoylaminomethylthio-1*H*-indole (**8**) as side product. Following the Bischler–Napieralski reaction of **7a** the rearranged 2-benzoylaminomethylthio-1*H*-indole **11** could be isolated. In order to prevent such rearrangements the target thiazinoindoles were prepared via 3-thiobenzoylaminomethylthioindole (**13**) via a modified Bischler–Napieralski reaction.

1. Introduction

Synthetic interest in compounds containing an indole core has been fuelled by the wide range of indole derivatives, which occur in nature and by the biological activity of many natural and synthetic indole derivatives. The family of indole compounds includes a huge number of pharmaceuticals, alkaloids and potentially therapeutic agents. Accordingly, there is a continuous demand for novel synthetic procedures for indole alkaloid analogues and indoles condensed with different heterocycles.[1] Although there are natural phytoalexins with 1,3-thiazinoindoles condensed at bond *b* of the indole skeleton, few synthetic indole compounds of this type are known.[2] Phytoalexins are antimicrobial substances formed in plants in response to pathogen attack or physical or chemical stress, probably as a result of the de novo synthesis of enzymes.[3] Since Takasugi et al. isolated the first cruciferous phytoalexins, among them cyclobrassinin (**1**) (2-methylthio-thiazino[6,5-*b*]indole, Fig. 1) from Chinese cabbage,[4] increasing attention has been paid to 1,3-thiazino[6,5-*b*]indole derivatives. Approximately 30 phytoalexins are known so far in cruciferous plants, of which six of them are thiazinoindoles.[5] Cyclobrassinin, the most valuable of these compounds, exerts an antiproliferative effect against human cancer cell lines.[6] A series of 2-alkyl- or arylimino-1,3-thiazino[5,4-*b*]indol-4-one derivatives (**2**, Fig. 1) are also pharmacologically interesting; they inhibit human leukocyte elastase and α-chymotrypsin.[7]

We recently prepared 2-methylthio-1,3-thiazino[5,6-*b*]indole (isocyclobrassinin) and its 2-benzylthio analogue (**3**, Fig. 1), which exerted good in vitro antiproliferative effects on cervical adenocarcinoma (HeLa), breast adenocarcinoma (MCF7) and squamous skin carcinoma (A431) cell lines. For the investigation of structure–activity relationships, further 2-aryl-1,3-thiazino[5,6-*b*]indole analogues were synthesized. The highest cytotoxic effect was displayed by 2-phenylimino-1,3-thiazino[5,6-*b*]indole, which demonstrated inhibitory activity on the above three cell lines comparable to that of cisplatin.[8]

Subsequent to our recent investigations on 1,3-thiazinoindole derivatives[2,8,9] and the chemistry of sulfur- and nitrogen-containing condensed-skeleton heterocycles,[10–13] we set out to devise an efficient route for the synthesis of new 4-aryl-1,3-thiazino[5,6-*b*]indoles. The formation of positional isomers of possible 1,3-thiazinoindoles is a great challenge,[2] because counterparts of this isomer are analogues of the β-carboline indole alkaloid harmalan (**4**, Fig. 1).

2. Results and discussion

The planned route for the synthesis of the target molecule, 4-aryl-1,3-thiazino[5,6-*b*]indole, was via the Bischler–Napieralski

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doi:10.1016/j.tet.2008.07.014

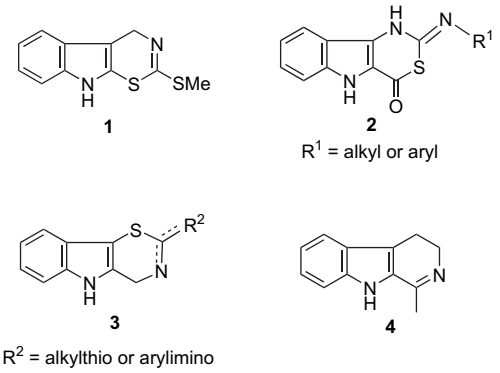
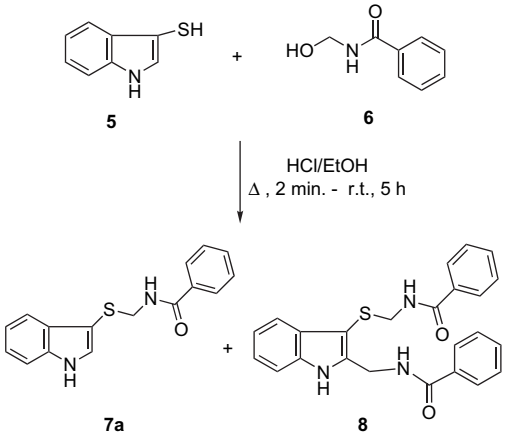


Figure 1. 1,3-Thiazinoindole derivatives.

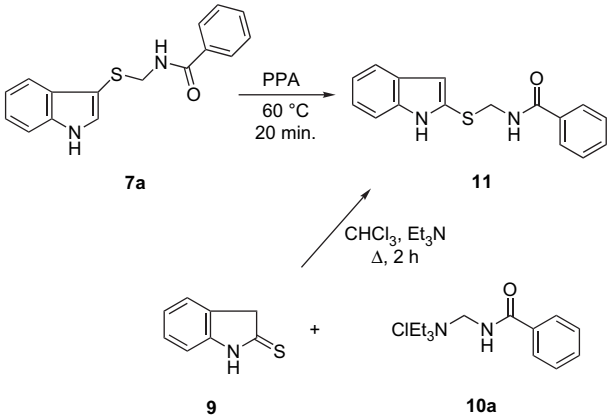
reaction of 3-benzamidomethylthioindole **7a** (Scheme 1). However, different methodologies are available to introduce a sulfur moiety at position 3 of the indole ring.[14–16] In our case, indole-3-thiol (**5**) proved to be the ideal starting material.[17] For the construction of the benzamidomethylthioether core, different agents have been utilized in the literature. *N*-Benzotriazol-1-ylmethylamides react readily with a variety of thiols.[18] In some cases, the amidoalkylation of thiols is possible with triethylaminomethylacylamides.[19] The most widely used and readily available amidomethylating derivatives are hydroxymethylacylamides, which have been applied successfully for the formation of thioethers.[20] In the present case, the reaction of indole-3-thiol with *N*-hydroxymethylbenzamide under mild acidic conditions gave two products, which could be separated by fractionated crystallization. As the major product, 3-benzoylaminomethylthioindole **7a** was obtained from chloroform in good yield. On dilution of the evaporation residue with ethanol, the 2-benzoylaminomethyl derivative **8** was isolated as minor product. The latter compound was most probably formed by a Tscherniak–Einhorn reaction; under the mildly acidic conditions, the ortho-amidomethylation of the indole moiety took place. For the reaction of **7a** under classical Bischler–Napieralski conditions, several solvents were examined. In the presence of phosphorus oxychloride, the reaction mixture gave different non-separable products: decomposition occurred. Several modified Bischler–Napieralski reactions were also tried. Hell et al. recently developed an environmentally friendly, mild and efficient Ersorb 4, small-pore-size zeolite-catalysed variation of the Bischler–Napieralski reaction to obtain dihydroisoquinoline derivatives.[21] Unfortunately, in our case under similar conditions, no reaction occurred.

Similarly, no reaction was observed with the triphenylphosphine–carbon tetrachloride system.[22] Harsher conditions, such as phosphorus pentachloride in dichloromethane also gave a mixture



Scheme 1.

of decomposed non-separable products.[23] In polyphosphoric acid (PPA) at 100 °C, an interesting product, 2-benzamidomethylthioindole (**11**), was isolated in low yield from the reaction mixture. After optimization of the reaction conditions, treatment with polyphosphoric acid at 60 °C for 20 min led to **11** in good yield (Scheme 2). This type of reaction was examined in a few cases previously for 3-substituted indole thioethers by Ottenheijm et al.[24,25] An extensive series of elegant experiments were performed by Hamel et al. for the sulfenylation of indole derivatives, including reactions relating to the mechanism of isomerization of 3-indolyl sulfides to 2-indolyl sulfides.[26,27] They found evidence for a complex intermolecular process in polyphosphoric acid. Although **7a** is not a simple thioether, the mechanism is most probably the same in our case. For verification of the structure of 2-benzamidomethylthioether (**11**), this compound was also prepared from indole-2-thione (**9**) and benzamidomethyltriethylammonium chloride[19] (**10a**) (Scheme 2). To the best of our knowledge, this is the first example of the selective amidomethylation of the sulfur of a thioamide functional group.

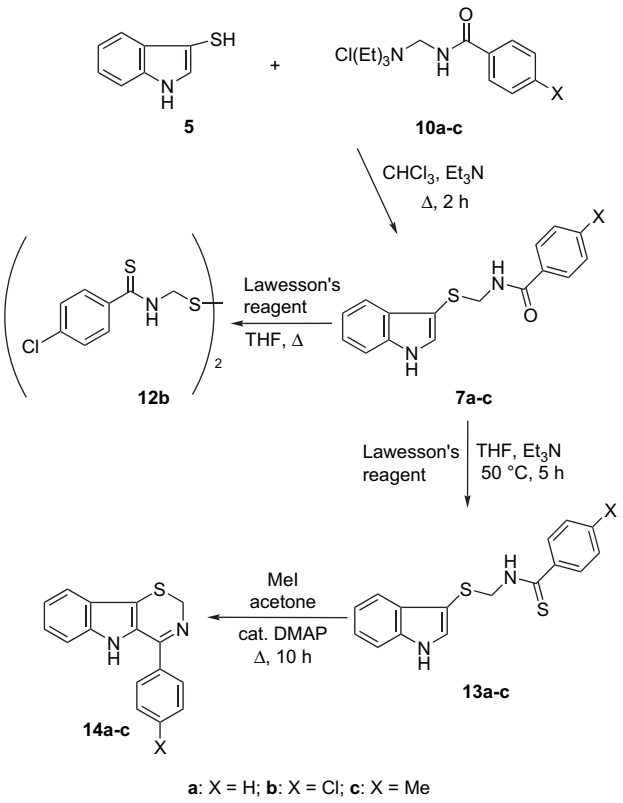


Scheme 2.

Finally, the selective benzamidomethylation of indole-3-thiol (**5**) was performed under basic conditions with substituted benzoylaminomethyltriethylammonium chlorides (**10a–c**) obtained from chloromethylbenzamides. In chloroform at reflux in the presence of triethylamine, **7a–c** were obtained in excellent yields.

For the preparation of 1-methyl-3,4-dihydro-β-carboline derivatives, mild, non-acidic conditions were applied by Ishida et al.[28] This modified Bischler–Napieralski reaction involves the treatment of a thioamide moiety with an alkyl halide. In order to avoid acidic conditions in the Bischler–Napieralski reaction, thiobenzamidomethyl derivatives **13a–c** were prepared by the reaction of the corresponding amides **7a–c** and Lawesson's reagent. During this reaction under reflux conditions in tetrahydrofuran, the partial decomposition of **7a–c** takes place, especially in the case of *p*-chloro-substituted **7b**, *N*-mercaptomethyl-*p*-chlorothiobenzamide disulfide **12b** could be isolated from the reaction mixture as decomposition product, which exist in dimethylsulfoxide solution as a 1:2 mixture of two possible rotamers. After the addition of triethylamine to the sulfur-exchange reaction mixture, at lower temperature the decomposition was not observed, and thioamides **13a–c** could be prepared in relatively good yields. Treatment of thiobenzamidomethyl derivatives **13a–c** with methyl iodide in acetone at reflux gave thiazinoindole derivatives **14a–c** via a thioiminium salt intermediate (Scheme 3).

In summary, a novel method has been developed for the synthesis of derivatives of a new ring system, 4-aryl-1,3-thiazino[5,6-*b*]indole, a 4-thiaharmalan analogue with potential pharmacological activity.



Scheme 3.

The reaction of indole-3-thiol and *N*-hydroxymethylbenzamide furnished 3-benzamidomethylthioindole (**7a**) and *ortho*-amidomethylated 2-benzoylaminomethyl-3-benzoylaminomethylthioindole (**8**). The Bischler–Napieralski reaction of **7a** was performed under different conditions. Interestingly, under acidic conditions, the 3-benzoylaminomethylthio group rearranged to position 2, affording 2-benzoylaminomethylthioindole (**11**) in good yield. Further investigations on the possible mechanism of this reaction are currently in progress. The target thiazinoindole compounds **14a–c** were prepared via 3-thiobenzoylaminomethylthioindole (**13a–c**) in a modified, non-acidic Bischler–Napieralski reaction.

3. Structure

The structures of the new compounds in this paper follow straightforwardly from the IR and NMR spectral data (Tables 1 and 2 in Supplementary data). Only a few remarks are necessary.

An interesting difference was observed in the ^{1}H NMR spectra of **7a–c** and **13a–c**. The H-2 signal of the thioamides **13a–c** is a singlet, while it is a doublet for **7a–c**, the amide analogues.

In view of the same solvent (DMSO-d_6) and the identical structure of the indole moiety in **7** and **13**, it is conceivable that this splitting isn't the consequence of spin–spin coupling with the NH in position 1. Furthermore, the NH signal is a singlet for **7a–c** and the splitting of the H-2 signal (2.5 Hz) is smaller than would be expected for a vicinal coupling.

The strong polarization of the amide group or the shift of the amide–iminohydrin tautomeric equilibrium towards the latter form may lead to the existence of two geometric isomers of the iminohydrin and consequently to two different environments for H-2. On the other hand, a similar duplication for e.g., the methylene signal was not observable.

This presumption seems to be supported by the IR spectra. For **13a–c**, two broadened, but well identifiable νNH bands are detected, whereas for **7a–c** only one. The mobile NH (or OH) hydrogen of the polarized amide or iminohydrin group is capable of forming strong H-bonds, which leads to an extremely diffuse, unidentifiable νNH (νOH) band. The amide-I band has a strikingly low frequency for **7a–c** ($\sim$1610 cm^{-1}), while for **10b,c** the values are in the expected region (1672 and 1664 cm^{-1}). This supports the strong polarization of the amide group in **7a–c**.

To clear this problem we carried out ^{15}N,^{1}H-HMQC and 2D-COSY measurements with **7a** and **13a**, respectively. The analogous N,H-correlations for **7a** proved that an NH→OH change (tautomerization) did not happen and the COSY spectrum of **13a** confirmed the NH(1), H-2 interaction. The absence of the split of NH signal in **13**-type compounds is due to exchange processes of the H's in this group resulting in broadening of the NH signal and thus the merging of the two split lines.

The condensed thiazine ring-containing compounds **14a–c** give singlet methylene signals in the ^{1}H NMR spectra, while the open-chain analogues with CH_2NH group give doublet CH_2 (and singlet NH) signals, split by 6.5±0.5 Hz, due to the vicinal coupling of the hydrogens in this moiety. Naturally, numerous other changes also provide evidence of the presumed condensed three-ring system. For example, instead of the ^{13}C NMR line of the thioamide carbon (at 197.3±0.8 ppm for **13**-type compounds), **14a–c** have the C=N carbon signal at 159.6±0.5 ppm. The H-2 singlet of **13a–c** (7.56±0.02 ppm) is absent in the ^{1}H NMR spectra of **14a–c**.

4. Experimental

4.1. General

Melting points were determined on a Kofler micromelting 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 (0.063–0.200) for column chromatography. Indol-2-one was purchased from Fluka. Indole-3-thiol,[17] benzoylaminomethyltriethylammonium chloride,[19] hydroxymethylbenzamides[29] and *N*-chloromethylbenzamides[30] were prepared by literature methods.

ESI mass spectra were obtained with a Finnigan MAT 95S double focussing sector-field instrument. Acetonitrile solutions of compounds were infused into the ESI at a constant flow of 100 μL/min (water–acetonitrile 50:50 containing 0.1% acetic acid) through a plastic capillary. The ions were produced by using N_2 as sheath gas at 2 psi, with a spray voltage of 2.5 kV and a capillary temperature of 210 °C. Poly(propylene glycol) solution was used for the calibration. IR spectra were recorded in KBr pellets with a Bruker IFS 55 FT-spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 solution in 5 mm tubes at rt, on a Bruker DRX 500 spectrometer at 500 (^{1}H) or 125 (^{13}C) MHz, with TMS (δ_{TMS}=0 ppm) as internal reference, and the deuterium signal of the solvent as the lock. Assignments were supported by DEPT (except for **7c** and **14a**), HMQC (**7a**, **8**, **11** and **14a**), HMBC (**8**, **11** and **14a**), for **7a** also by 2D-COSY measurements. DEPT spectra were run in a standard manner, using only the Θ=135° pulse to separate CH/CH$_3$ and CH$_2$ lines phased 'up' and 'down', respectively. 2D-HMQC and 2D-HMBC spectra were obtained by using the standard Bruker pulse programs.

4.2. Preparation of 3-benzoylaminomethylthio-1*H*-indole (7a) and 2-benzoylamino-methyl-3-benzoylaminomethylthio-1*H*-indole (8) from 1*H*-indole-3-thiol (5) and *N*-hydroxymethylbenzamide (6)

Indole-3-thiol (1.49 g, 10 mmol) and *N*-hydroxymethylbenzamide (1.51 g, 10 mmol) were dissolved in ethanol (5 mL) and to the solution was added a saturated solution of

hydrogen chloride in ethanol (2 mL). The mixture was heated to its boiling point, allowed to cool and left to stand for 5 h at ambient temperature. The reaction mixture was then poured onto ice (100 g), extracted exhaustively with ethyl acetate (4×80 mL), and the extract was dried and evaporated. The residue was taken up in chloroform (5 mL), from which compound **7a** separated as a white crystalline powder (0.78 g). The mother liquor from the separation of **7a** was evaporated to dryness and the residue was taken up in ethanol (2 mL). The ethanol solution slowly deposited **8** as a white crystalline powder (0.11 g).

*4.2.1. 3-Benzoylaminomethylthio-1H-indole (**7a**)*

A white crystalline powder, mp 121–123 °C (from chloroform), yield 28%. ν_{max} (KBr disc) 3276 and 3200–2500 (νNH), 1620 (νC=O), 740 ($\gamma C_{Ar}H$, indole and monosubstituted benzene ring), 690 ($\gamma C_{Ar}C_{Ar}$, monosubstituted benzene ring). ^{1}H NMR (DMSO-d_6) δ: 11.40 (1H, br, indole-NH), 9.04 (1H, br, CONH), 7.79 (2H, d, H-2′,6′)*, 7.63 (1H, d, H-4), 7.52 (1H, t, H-4′)*, 7.49 (1H, d, J=2.5 Hz, H-2), 7.44 (2H, m, H-3′,5′)*, 7.41 (1H, d, H-7), 7.14 (1H, t, H-6), 7.05 (1H, t, H-5), 4.45 (2H, d, J=6.2 Hz, SCH_2N); *part of an AA′BB′C spectrum; ^{13}C NMR (DMSO-d_6) δ: 166.7 (C=O), 137.3 (C-7a), 135.0 (C-1′), 132.2 (C-4′), 131.8 (C-2), 130.2 (C-3a), 129.1 (C-3′,5′), 128.1 (C-2′,6′), 122.6 (C-6), 120.4 (C-5), 119.4 (C-4), 112.8 (C-7), 103.1 (C-3), 46.9 (CH_2). MS (ESI): $[M+H]^+$=283. Anal. Calcd for $C_{16}H_{14}N_2OS$ (282.36): C, 68.06; H, 5.00; N, 9.92; S, 11.36. Found: C, 67.83; H, 5.21; N, 9.81; S, 11.47.

*4.2.2. 2-Benzoylaminomethyl-3-benzoylaminomethylthio-1H-indole (**8**)*

A white crystalline powder, mp 235–238 °C (from ethanol, *N*,*N*-dimethylformamide), yield 3%. ν_{max} (KBr disc) 3286 (νNH), 1641 and 1610 (νC=O), 732 ($\gamma C_{Ar}H$, indole and monosubstituted benzene ring), 694 ($\gamma C_{Ar}C_{Ar}$, monosubstituted benzene ring). ^{1}H NMR (DMSO-d_6) δ: 11.30 (1H, br, indole-NH), 9.09 (1H, br s, CONH), 7.89–7.39 (12H, overlapping m's, H-4, H-7, H-2′-6′, H-2″-6″), 7.11 (1H, t, H-6), 7.04 (1H, t, H-5), 4.75 (2H, d, J=5.3 Hz, CCH_2N), 4.48 (2H, d, J=6.2 Hz, SCH_2N); ^{13}C NMR (DMSO-d_6) δ: 167.2 (C=O, in Pos. 2), 166.9 (C=O), 142.4 (C-2), 136.6 (C-7a), 134.9 (C-1″), 134.8 (C-1′), 132.2* (C-4′ and C-4″), 129.1* (C-3′,5′ and C-3″,5″), 128.3 (C-2″,6″), 128.1 (C-2′,6′), 122.6 (C-6), 120.5 (C-5), 119.2 (C-4), 112.6 (C-7), 101.2 (C-3), 46.9 (SCH_2N), 36.0 (CH_2 in Pos. 2); *overlapping lines. $[M+H]^+$=416. Anal. Calcd for $C_{24}H_{21}N_3O_2S$ (415.51): C, 69.37; H, 5.09; N, 10.11; S, 7.72. Found: C, 69.19; H, 5.22; N, 9.97; S, 7.85.

4.3. General procedure for substituted benzoylaminomethyltriethylammonium chlorides (10b,c)

To a vigorously stirred solution of triethylamine (15.3 mL, 110 mmol) in dry acetone (150 mL), freshly synthesized substituted *N*-chloromethylbenzamide[30] (100 mmol) dissolved in dry acetone (80 mL) was added in one portion. A white precipitate formed immediately. After the addition of a further portion of acetone (100 mL), the mixture was stirred at rt for 1 h. The white precipitate was filtered off, washed with acetone (2×25 mL) and recrystallized from chloroform–acetone.

*4.3.1. 4-Chlorobenzoylaminomethyltriethylammonium chloride (**10b**)*

A white crystalline powder, mp 151–154 °C (dec), yield 73%. ν_{max} (KBr disc) 3490 and 3407 (νNH), 1672 (νC=O), 787 ($\gamma C_{Ar}H$). ^{1}H NMR (DMSO-d_6) δ: 10.10 (1H, br, NH), 8.14 (2H, d, J=8.5 Hz, H-2′,6′)*, 7.58 (2H, m, H-3′,5′)*, 4.74 (2H, s, NCH_2N), 3.24 (6H, q, J=7.1 Hz, CH_2CH_3), 1.27 (9H, t, J=7.1 Hz, CH_2CH_3); *part of an AA′BB′ spectrum; ^{13}C NMR (DMSO-d_6) δ: 168.5 (C=O), 138.2 (C-4′), 132.1 (C-1′), 131.3 (C-2′,6′), 129.3 (C-3′,5′), 60.9 (NCH_2N), 51.2 (CH_2CH_3), 8.4 (CH_2CH_3). $[M+H]^+$=269. Anal. Calcd for $C_{14}H_{22}Cl_2N_2O$ (305.24): C, 55.09; H, 7.26; N, 9.18. Found: C, 55.38; H, 6.99; N, 9.42.

*4.3.2. 4-Methylbenzoylaminomethyltriethylammonium chloride (**10c**)*

A white crystalline powder, mp 180–183 °C (dec), yield 64%. ν_{max} (KBr disc) 3499 and 3486 (νNH), 1664 (νC=O), 836 ($\gamma C_{Ar}H$). ^{1}H NMR (DMSO-d_6) δ: 9.85 (1H, br, NH), 7.98 (2H, J=8.0 Hz, H-2′,6′)*, 7.31 (2H, m, H-3′,5′)*, 4.73 (2H, s, NCH_2N), 3.24 (6H, q, J=7.1 Hz, CH_2CH_3), 2.37 (3H, s, CH_3), 1.27 (9H, t, J=7.1 Hz, CH_2CH_3); *part of an AA′BB′ spectrum; ^{13}C NMR (DMSO-d_6) δ: 169.3 (C=O), 138.2 (C-4′), 130.5 (C-1′), 129.8** (C-3′,5′), 129.3** (C-2′,6′), 61.0 (NCH_2N), 51.2 (CH_2CH_3), 21.9 (CH_3), 8.4 (CH_2CH_3); **reversed assignments are also possible. $[M+H]^+$=249. Anal. Calcd for $C_{15}H_{25}ClN_2O$ (284.82): C, 63.25; H, 8.85; N, 9.84. Found: C, 63.44; H, 8.69; N, 9.88.

4.4. Preparation of 2-benzoylaminomethylthio-1H-indole (11)

*4.4.1. Preparation of 2-benzoylaminomethylthio-1H-indole (**11**) from 3-benzoylaminomethylthio-1H-indole (**7a**)*

3-Benzoylaminomethylthio-1*H*-indole (**7a**) (0.5 g, 1.77 mmol) was thoroughly mixed with polyphosphoric acid and heated at 60 °C for 20 min. Water (10 mL) was added to the reaction mixture and then was neutralized by the addition of a solution of 10% sodium carbonate. The aqueous phase was extracted with chloroform (2×10 mL), and the organic phase was dried (sodium sulfate), filtered and evaporated to dryness. The residue was triturated with diethyl ether–*n*-hexane to give a light-grey crystalline powder, which was recrystallized from diisopropyl ether.

A light-grey crystalline powder, mp 146–148 °C, yield 68%. ν_{max} (KBr disc) 3297 (νNH), 1629 (νC=O), 751 ($\gamma C_{Ar}H$, indole ring), 704 ($\gamma C_{Ar}H$, monosubstituted benzene ring), 668 ($\gamma C_{Ar}C_{Ar}$, monosubstituted benzene ring). ^{1}H NMR (DMSO-d_6) δ: 11.40 (1H, br, indole-NH), 9.33 (1H, br, CONH), 7.87 (2H, d, J=7.5 Hz, H-2′,6′)*, 7.54 (1H, t, H-4′)*, 7.48 (1H, d, H-4), 7.47 (2H, m, H-3′,5′)*, 7.36 (1H, d, H-7), 7.11 (1H, t, H-6), 7.00 (1H, t, H-5), 6.62 (1H, s, H-3), 4.78 (2H, d, J=6.0 Hz, SCH_2N); *part of an AA′BB′C spectrum; ^{13}C NMR (DMSO-d_6) δ: 167.2 (C=O), 138.4 (C-7a), 134.7 (C-1′), 132.4 (C-4′), 129.2 (C-3′,5′), 129.0 (C-2), 128.9 (C-3a), 128.3 (C-2′,6′), 122.5 (C-6), 120.4 (C-4), 120.1 (C-5), 111.9 (C-7), 108.1 (C-3), 46.8 (CH_2). MS (ESI): $[M+H]^+$=283. Anal. Calcd for $C_{16}H_{14}N_2OS$ (282.36): C, 68.06; H, 5.00; N, 9.92; S, 11.36. Found: C, 68.18; H, 5.11; N, 9.94; S, 11.52.

*4.4.2. Preparation of 2-benzoylaminomethylthio-1H-indole (**11**) from 1,3-dihydro-2H-indole-2-thione (**9**) and benzoylaminomethyltriethylammonium chloride (**7a**)*

A mixture of 1,3-dihydro-2*H*-indole-2-thione **9** (1,0 g, 6.7 mmol), benzoylaminomethyltriethylammonium chloride (**10a**) (2.0 g, 7.4 mmol) and triethylamine (0.8 mL, 5.7 mmol) in chloroform (20 mL) was heated at reflux for 2 h. The organic phase was then extracted with water (2×40 mL), dried (sodium sulfate) and evaporated, and the residue was purified by column chromatography (*n*-hexane–ethyl acetate 3:2) to provide **11**. Yield: 91% (analytical data identical to those given above).

4.5. General procedure for the preparation of substituted 3-benzoylaminomethylthio-1*H*-indoles (7a–c) from 1*H*-indole-3-thiol (5) and substituted benzoylaminomethyltriethylammonium chlorides (10a–c)

A mixture of 1*H*-indole-3-thiol **5** (2.0 g, 13.4 mmol), the corresponding substituted benzoylaminomethyltriethylammonium chloride (**10a–c**) (14.7 mmol) and triethylamine (0.8 mL, 5.7 mmol) in chloroform (30 mL) was heated at reflux for 2 h. The organic phase was then extracted with water (2×40 mL). The white precipitate formed in the second extraction was filtered off, and washed with water (2×10 mL) and chloroform (5 mL). The white crystalline powder was dissolved in chloroform (50 mL)+methanol

(1 mL). The organic layer was extracted with water (20 mL), dried (sodium sulfate) and evaporated to provide **7a–c**.

*4.5.1. 3-Benzoylaminomethylthio-1H-indole (**7a**)*

Yield: 89% (analytical data identical to those given above).

*4.5.2. 3-(4-Chlorobenzoylaminomethylthio)-1H-indole (**7b**)*

A white crystalline powder, mp 120–123 °C (from chloroform), yield 94%. ν_{max} (KBr disc) 3269 (νNH), 1610 (νC=O), 852 ($\gamma C_{Ar}H$, *para*-disubstituted benzene ring), 741 ($\gamma C_{Ar}H$, indole ring). ^{1}H NMR (DMSO-d_6) δ: 11.40 (1H, br, indole-NH), 9.16 (1H, br, CONH), 7.81 (2H, d, J=8.5 Hz, H-2′,6′)*, 7.63 (1H, d, H-4), 7.51 (1H, d, J=2.5 Hz, H-2), 7.51 (2H, m, H-3′,5′)*, 7.42 (1H, d, H-7), 7.14 (1H, t, H-6), 7.06 (1H, t, H-5), 4.46 (2H, d, J=6.0 Hz, SCH_2N); *part of an AA′BB′ spectrum; ^{13}C NMR (DMSO-d_6) δ: 165.7 (C=O), 137.3 (C-4′)**, 137.1 (C-7a)**, 133.7 (C-1′), 132.0 (C-2), 130.2 (C-3a), 130.1 (C-2′,6′), 129.2 (C-3′,5′), 122.6 (C-6), 120.5 (C-5), 119.4 (C-4), 112.9 (C-7), 102.9 (C-3), 46.9 (CH_2); **reversed assignments are also possible. $[M+H]^+$=317. Anal. Calcd for $C_{16}H_{13}N_2OSCl$ (316.81): C, 60.66; H, 4.14; N, 8.84; S, 10.12. Found: C, 60.78; H, 4.04; N, 8.62; S, 10.24.

*4.5.3. 3-(4-Methylbenzoylaminomethylthio)-1H-indole (**7c**)*

A white crystalline powder, mp 154–156 °C (from chloroform), yield 92%. ν_{max} (KBr disc) 3260 (νNH), 1610 (νC=O), 842 ($\gamma C_{Ar}H$, *para*-disubstituted benzene ring), 737 ($\gamma C_{Ar}H$, indole ring). ^{1}H NMR (DMSO-d_6) δ: 11.40 (1H, br, indole-NH), 8.99 (1H, br, CONH), 7.71 (2H, d, J=8.0 Hz, H-2′,6′)*, 7.63 (1H, d, H-4), 7.48 (1H, d, J=2.5 Hz, H-2), 7.42 (1H, d, H-7), 7.24 (2H, m, H-3′,5′)*, 7.14 (1H, t, H-6), 7.06 (1H, t, H-5), 4.46 (2H, d, J=6.2 Hz, SCH_2N), 2.35 (3H, s, CH_3); *part of an AA′BB′ spectrum; ^{13}C NMR (DMSO-d_6) δ: 166.6 (C=O), 142.1 (C-4′), 137.3 (C-7a), 132.2 (C-1′), 131.8 (C-2), 130.2 (C-3a), 129.7 (C-3′,5′), 128.2 (C-2′,6′), 122.6 (C-6), 120.4 (C-5), 119.4 (C-4), 112.8 (C-7), 103.2 (C-3), 46.9 (CH_2), 21.8 (CH_3). $[M+H]^+$=297. Anal. Calcd for $C_{17}H_{16}N_2OS$ (296.39): C, 68.89; H, 5.44; N, 9.45; S, 10.82. Found: C, 68.95; H, 5.31; N, 9.27; S, 10.97.

4.6. General procedure for preparation of 3-thiobenzoylaminomethylthio-1*H*-indoles (13a–c)

To a solution of substituted 3-benzoylaminomethylthio-1*H*-indole (**7a–c**) (4.0 mmol) in tetrahydrofuran (40 mL), triethylamine (0.36 mmol, 0.05 mL) and Lawesson's reagent (0.96 g, 2.4 mmol) were added in one portion. The reaction mixture was heated under reflux for 5 h. After the addition of more triethylamine (1.0 mL) and evaporation, the residue was purified by column chromatography, using *n*-hexane–ethyl acetate 4:1 containing 0.25% triethylamine as eluent, to give **13a–c** as a crystalline powder after trituration with *n*-hexane and a few drops of diisopropyl ether.

*4.6.1. 3-Thiobenzoylaminomethylthio-1H-indole (**13a**)*

A yellow crystalline powder, mp 114–116 °C, yield 67%. ν_{max} (KBr disc) 3556 and 3406 (νNH), 770 ($\gamma C_{Ar}H$, monosubstituted benzene ring), 755 ($\gamma C_{Ar}H$, indole ring), 686 ($\gamma C_{Ar}C_{Ar}$, monosubstituted benzene ring). ^{1}H NMR (DMSO-d_6) δ: 11.50 (1H, br, indole-NH), 10.70 (1H, br s, CSNH), 7.70 (2H, d, J=7.5 Hz, H-2′,6′)*, 7.64 (1H, d, H-4), 7.57 (1H, s, H-2), 7.48 (1H, t, H-4′)*, 7.44 (1H, d, H-7), 7.40 (2H, m, H-3′,5′)*, 7.17 (1H, t, H-6), 7.09 (1H, t, H-5), 4.85 (2H, d, J=6.0 Hz, SCH_2N); *part of an AA′BB′C spectrum; ^{13}C NMR (DMSO-d_6) δ: 198.1 (C=S), 141.7 (C-1′), 137.3 (C-7a), 132.2 (C-4′), 131.7 (C-2), 130.2 (C-3a), 128.8 (C-3′,5′), 128.1 (C-2′,6′), 122.7 (C-6), 120.6 (C-5), 119.4 (C-4), 112.9 (C-7), 103.0 (C-3), 52.8 (CH_2). $[M+H]^+$=299. Anal. Calcd for $C_{16}H_{14}N_2S_2$ (298.42): C, 64.39; H, 4.73; N, 9.39; S, 19.27. Found: C, 64.65; H, 4.63; N, 9.45; S, 19.39.

*4.6.2. 3-(4-Chlorothiobenzoylaminomethylthio)-1H-indole (**13b**)*

A yellow crystalline powder, mp 95–97 °C, yield 79%. ν_{max} (KBr disc) 3363 and 3328 (νNH), 831 ($\gamma C_{Ar}H$, *para*-disubstituted benzene ring), 756 ($\gamma C_{Ar}H$, indole ring). ^{1}H NMR (DMSO-d_6) δ: 11.50 (1H, br, indole-NH), 10.80 (1H, br, CONH), 7.73 (2H, d, J=8.3 Hz, H-2′,6′)*, 7.64 (1H, d, H-4), 7.58 (1H, s, H-2), 7.47 (3H, m, H-7, H-3′,5′)*, 7.18 (1H, t, H-6), 7.10 (1H, t, H-5), 4.88 (2H, d, J=5.5 Hz, SCH_2N); *part of an AA′BB′ spectrum; ^{13}C NMR (DMSO-d_6) δ: 196.5 (C=S), 140.2 (C-1′), 137.3 (C-7a), 136.6 (C-4′), 132.3 (C-2), 130.3 (C-3a), 129.9 (C-2′,6′), 128.8 (C-3′,5′), 122.7 (C-6), 120.6 (C-5), 119.4 (C-4), 113.0 (C-7), 102.9 (C-3), 52.9 (CH_2). $[M+H]^+$=333. Anal. Calcd for $C_{16}H_{13}N_2S_2Cl$ (332.87): C, 57.73; H, 3.94; N, 8.42; S, 19.27. Found: C, 57.56; H, 4.11; N, 8.34; S, 19.52.

*4.6.3. 3-(4-Methylthiobenzoylaminomethylthio)-1H-indole (**13c**)*

A yellow crystalline powder, mp 133–135 °C, yield 77%. ν_{max} (KBr disc) 3382 and 3349 (νNH), 755 ($\gamma C_{Ar}H$, indole ring). ^{1}H NMR (DMSO-d_6) δ: 11.40 (1H, br, indole-NH), 10.60 (1H, br, CONH), 7.64 (2H, d, J=8.0 Hz, H-2′,6′)*, 7.63 (1H, d, H-4), 7.55 (1H, s, H-2), 7.44 (1H, d, H-7), 7.20 (2H, m, H-3′,5′)*, 7.17 (1H, t, H-6), 7.09 (1H, t, H-5), 4.86 (2H, d, J=4.9 Hz, SCH_2N), 2.33 (3H, s, CH_3); *part of an AA′BB′ spectrum; ^{13}C NMR (DMSO-d_6) δ: 197.7 (C=S), 141.8 (C-4′), 138.8 (C-1′), 137.3 (C-7a), 132.2 (C-2), 130.2 (C-3a), 129.3 (C-3′,5′), 128.2 (C-2′,6′), 122.7 (C-6), 120.6 (C-5), 119.4 (C-4), 112.9 (C-7), 103.1 (C-3), 52.9 (CH_2), 21.7 (CH_3). $[M+H]^+$=313. Anal. Calcd for $C_{17}H_{16}N_2S_2$ (312.45): C, 65.35; H, 5.16; N, 8.97; S, 20.53. Found: C, 65.31; H, 5.23; N, 8.87; S, 20.71.

4.7. General procedure for the preparation of 2,5-dihydro-4-aryl-1,3-thiazino[5,6-*b*]indole (14a–c)

A solution of **13a–c** (3.4 mmol), methyl iodide (1.0 mL, 16.1 mmol) and a catalytic amount of 4-dimethylaminopyridine (DMAP) in acetone (15 mL) was heated at reflux for 10 h under an argon atmosphere with protection from light. The acetone solution was then concentrated under reduced pressure. To the residue, ethanol and diethyl ether were added to furnish the iodide salt of **14a–c** as a red crystalline powder. After filtration, the crystals were washed with cold acetone (2×2 mL) and recrystallized from ethanol–diethyl ether. The crystals were dissolved in water (10 mL) and a small amount of methanol (until complete dissolution), chloroform was added and the mixture was neutralized by the portionwise addition of 10% potassium hydroxide solution. The organic layer was separated, washed with water, dried (sodium sulfate) and evaporated. After trituration with *n*-hexane, **14a–c** were obtained as yellow crystalline powders.

*4.7.1. 2,5-Dihydro-4-phenyl-1,3-thiazino[5,6-b]indole (**14a**)*

A yellow crystalline powder, mp 181–183 °C (dec), yield 54%. ν_{max} (KBr disc) 3200–2500 (νNH), 748 ($\gamma C_{Ar}H$, monosubstituted benzene ring), 718 ($\gamma C_{Ar}H$, indole ring), 697 ($\gamma C_{Ar}C_{Ar}$, monosubstituted benzene ring). ^{1}H NMR (DMSO-d_6) δ: 11.50 (1H, br, indole-NH), 7.70 (2H, d, H-2′,6′)*, 7.55 (3H, m, H-4, H-3′,5′)*, 7.53 (1H, t, H-4′)*, 7.46 (1H, d, H-7), 7.30 (1H, t, H-6), 7.14 (1H, t, H-5), 4.87 (2H, s, CH_2); *part of an AA′BB′C spectrum; ^{13}C NMR (DMSO-d_6) δ: 160.1 (C=N), 138.0 (C-1′), 137.7 (C-7a), 131.1 (C-4′), 129.6 (C-2′,6′), 129.4 (C-3′,5′), 127.6 (C-3), 126.1 (C-6), 124.9 (C-3a), 121.0 (C-5), 120.8 (C-4), 114.4 (C-2), 114.0 (C-7), 50.3 (CH_2). $[M+H]^+$=265. Anal. Calcd for $C_{16}H_{12}N_2S$ (264.35): C, 72.70; H, 4.58; N, 10.60; S, 12.13. Found: C, 72.75; H, 4.51; N, 10.54; S, 12.15.

*4.7.2. 2,5-Dihydro-4-(4-chlorophenyl)-1,3-thiazino[5,6-b]-indole (**14b**)*

A yellow crystalline powder, mp 199–202 °C (dec), yield 48%. ν_{max} (KBr disc) 3200–2500 (νNH), 832 ($\gamma C_{Ar}H$, *para*-disubstituted benzene ring), 734 ($\gamma C_{Ar}H$, indole ring). ^{1}H NMR (DMSO-d_6) δ: 11.50

(1H, br, indole-NH), 7.71 (2H, *J*=8.5 Hz, H-2′,6′)*, 7.59 (2H, m, H-3′,5′)*, 7.56 (1H, d, H-4), 7.45 (1H, d, H-7), 7.31 (1H, t, H-6), 7.13 (1H, t, H-5), 4.87 (2H, s, CH_2); *part of an AA′BB′ spectrum; ^{13}C NMR (DMSO-d_6) δ: 159.1 (C=N), 137.7 (C-7a), 136.7 (C-1′)**, 135.9 (C-4′)**, 131.5 (C-2′,6′), 129.4 (C-3′,5′), 127.3 (C-3), 126.3 (C-6), 124.9 (C-3a), 121.1 (C-5), 120.8 (C-4), 114.7 (C-2), 114.0 (C-7), 50.3 (CH_2); **reversed assignments are also possible. $[M+H]^+$=299. Anal. Calcd for $C_{16}H_{11}ClN_2S$ (298.79): C, 64.32; H, 3.71; N, 9.38; S, 10.73. Found: C, 64.38; H, 3.87; N, 9.32; S, 10.85.

*4.7.3. 2,5-Dihydro-4-(4-methylphenyl)-1,3-thiazino[5,6-b]-indole (**14c**)*

A yellow crystalline powder, mp 188–191 °C (dec), yield 57%. ν_{max} (KBr disc) 3200–2500 (νNH), 827 ($\gamma C_{Ar}H$, *para*-disubstituted benzene ring), 737 ($\gamma C_{Ar}H$, indole ring). ^{1}H NMR (DMSO-d_6) δ: 11.50 (1H, br, indole-NH), 7.60 (2H, d, *J*=8.0 Hz, H-2′,6′)*, 7.56 (1H, d, H-4), 7.46 (1H, d, H-7), 7.30 (1H, t, H-6), 7.24 (2H, m, H-3′,5′)*, 7.13 (1H, t, H-5), 4.87 (2H, s, CH_2), 2.40 (3H, s, CH_3); *part of an AA′BB′ spectrum; ^{13}C NMR (DMSO-d_6) δ: 159.9 (C=N), 140.8 (C-4′), 137.6 (C-7a), 135.2 (C-1′), 129.9 (C-3′,5′)**, 129.6 (C-2′,6′)**, 127.6 (C-3), 126.0 (C-6), 124.9 (C-3a), 121.0 (C-5), 120.7 (C-4), 114.2 (C-2), 114.0 (C-7), 50.3 (CH_2), 21.8 (CH_3); **reversed assignments are also possible. $[M+H]^+$=279. Anal. Calcd for $C_{17}H_{14}N_2S$ (278.37): C, 73.35; H, 5.07; N, 10.06; S, 11.52. Found: C, 73.42; H, 5.14; N, 10.12; S, 11.67.

Acknowledgements

The authors express their thanks to the Hungarian Scientific Research Foundation (OTKA) for financial support. They are indebted to Prof. Z. Hell for the kind gift of Ersorb 4 (E4) and Ersorb 4a (E4a) zeolite samples, to Dr. M. Juhász for the helpful discussions and the MS spectra measurements, and to Ms. E. Juhász Dinya for excellent technical assistance.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.07.014.

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