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A new approach to the synthesis of rare thiazino[6,5-*b*]indol-4-one derivatives. First total synthesis of the indole phytoalexin cyclobrassinon

Peter Kutschy,[a,*] Mojmír Suchý,[a] Aldo Andreani,[b] Milan Dzurilla,[a] Vladimír Kováčik,[c] Juraj Alföldi,[c] Maddalena Rossi[b] and Mária Gramatová[a]

[a]*Faculty of Science, Institute of Chemical Sciences, P.J. Šafárik University, Moyzesova 11, 041 67 Košice, Slovak Republic*
[b]*Department of Pharmaceutical Sciences, University of Bologna, Via Belmeloro 6, I-40126 Bologna, Italy*
[c]*Institute of Chemistry, Slovak Academy of Sciences, Dúbravská cesta 9, 842 38 Bratislava, Slovak Republic*

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Abstract—The first synthesis of the indole phytoalexin cyclobrassinon and some of its analogues, possessing a thiazino[6,5-*b*]indol-4-one tricyclic ring system was performed starting from 1-substitued 2-chloroindole-3-carboxaldehydes. The route employed the intramolecular Et_3N-mediated or photochemical nucleophilic substitution of a chlorine atom in the 2-position of the indole ring with a sulfur atom as a key step. Examination of biological activity against the selected tumor cell lines, bacteria and fungi revealed no expressive activity of synthesized compounds.

1. Introduction

1,3-Thiazinoindoles represent an interesting group of heterocyclic compounds, because of their unusual chemical structure and interesting biological properties. There are four possible types (A–D) of ring fusion of the indole at the bond *b* and the 1,3-thiazine ring or its hydrogenated forms (Fig. 1).

The compounds of type A, possessing a 1,3-thiazino[5,4-*b*]indole ring system, were prepared for the first time by treatment of 3-aminoindole with carbon disulfide in ethanol.[1] When *N*′-alkyl or *N*′-aryl-*N*-3[(2-ethoxycarbonyl-indolyl)]thioureas were heated with polyphosphoric acid, 1,3-thiazino[5,4-*b*]indol-4-one derivatives with interesting serine protease inhibitory activity were obtained.[2] Compounds of type B, 1,3-thiazino[6,5-*b*]indoles, **4**–**10** are the indole phytoalexins (Fig. 2).

Phytoalexins are low molecular weight secondary metabolites, produced by plants after their exposure to physical, biological or chemical stress.[3] A specific group of these natural products represent the indole phytoalexins, produced by economically important plants of the family *Cruciferae*, cultivated worldwide.[4] With respect to the well known anticarcinogenic properties of brassica vegetables[5] it

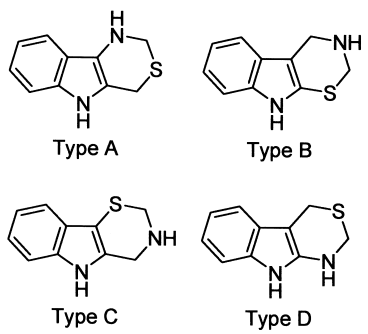

Figure 1.

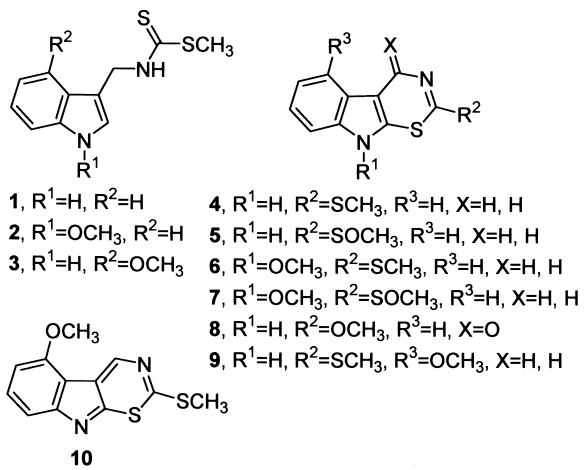

Figure 2.

Keywords: indoles; phytoalexins; natural products; substitution; photochemical; antitumor activity; antimicrobial activity.

* Corresponding author. Tel.: +421-55-62-22610x192; fax: +421-55-62-22124; e-mail: kutschy@kosice.upjs.sk

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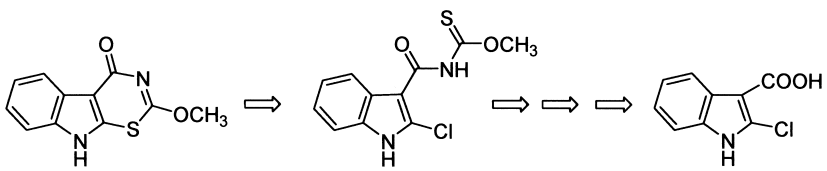


Scheme 1.

is important to study the biological activity of the indole phytoalexins. Isolation from plants is difficult and time consuming and therefore the amounts required for screening should be provided by synthesis. Approximately 30 indole phytoalexins have been isolated to date[4b] and biological screening has disclosed antifungal,[6] canceroprotective[7] and antitumor[8] activity of several compounds. The synthesis and biological properties of cyclobrassinon (**8**), isolated in 1994 from kohlrabi,[9] have not been described to date. Cyclobrassinin (**4**) was prepared by cyclization of brassinin (**1**) with pyridinium tribromide[10] or *N*-bromosuccinimide (NBS).[7b] Sinalbin B (**6**) has been synthesized analogously, by cyclization of 1-methoxybrassinin (**2**) with *N*-bromosuccinimide.[11] The subsequent oxidation of **6** with 3-chloroperoxybenzoic acid afforded sinalbin A (**7**).[11] Treatment of 4-methoxybrassinin (**3**) with NBS, followed by dehydrobromination, employing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded an unstable 4-methoxycyclobrassinin (**9**), which after heating with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in benzene gave a dehydrogenated product, dehydro-4-methoxycyclobrassinin (**10**).[12] 1,3-Thiazino[6,5-*b*]indole skeleton was also prepared by heating of 2-chloroindole-3-carboxaldehyde with thiourea in ethanol.[13] Derivatives of the types C and D have not been described to date.

2. Results and discussion

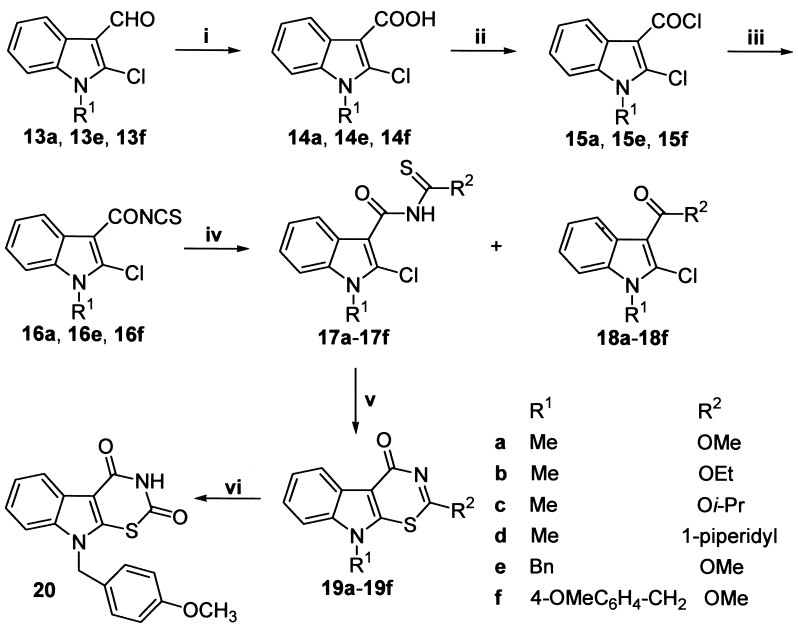
Within our continuing research in the field of the synthesis of cruciferous phytoalexins and congeneric indoles,[14] we have recently focused our attention on investigation of the first synthesis of the hitherto synthetically not available phytoalexin cyclobrassinon (**8**) and its analogues as interesting synthetic target.[15] Our aim also included the first examination of antitumor, antibacterial and antifungal activity of a new group of thiazino[6,5-*b*]indol-4-one derivatives. Retrosynthesis of cyclobrassinon (Scheme 1) led us via thiocarbamate **11** to 2-chloroindole-3-carboxylic acid (**12**), as a suitable starting compound.

The preparation of acid **12** was described by oxidation of 2-chloroindole-3-carboxaldehyde (**21**) with $KMnO_4$ in aqueous acetone in the presence of phosphate buffer[16a] or $NaClO_2$ in aqueous dioxane in the presence of 2-methyl-2-butene.[16b] However, oxidation of **21** in our hands did not afford acid **12** in a reasonable yield. It was decided to solve the problem by introduction of protecting groups on the indole nitrogen. For this purpose, electron-withdrawing acyl groups are not suitable, since oxidation of the corresponding aldehydes affords only low yields of the required acids.[16a] Therefore benzyl and 4-methoxybenzyl groups were selected and a methyl derivative was also investigated with the aim to synthesize 9-methylcyclobrassinon (**19a**) as a close analog of natural product **8**. Starting aldehydes **13a**,[16a] **13e**[16c] and **13f**,[16d] afforded by oxidation with $KMnO_4$ the corresponding acids **14a**,[16a] **14e**[16c] and **14f** in good yields (Scheme 2). Acid chlorides **15a**, **15e** and **15f** were prepared by heating of acids with PCl_3 in dry benzene. It was important to keep the bath temperature between 85–90°C since at a lower temperature the reaction did not proceed whereas over 90°C decomposition had occurred. Treatment of the crude products of highly instable acid chlorides with KSCN in acetone afforded surprisingly stable isothiocyanates **16a**, **16e** and **16f**, showing in their IR spectra a characteristic absorption bands of N═C═S group at 1960 cm^{-1}. The isothiocyanates could be isolated by flash chromatography as crystalline compounds, however with significant loss, caused by decomposition on silica gel. Therefore in the next reaction, crude isothiocyanates were used. Reaction of **16a**, **16e** and **16f** with methanol, ethanol, 2-propanol and piperidine afforded the key intermediates, thiocarbamoyl compounds **17a–17f** accompanied with side products, carboxylic acid esters **18a–18c**, **18e** and **18f** and amide **18d** (Scheme 2). The formation of **18a–18f** can be explained via the extrusion of the thiocyanate anion under the reaction conditions, facilitated by the electron-donating group, with the formation of a reactive ketene, which immediately reacts with the nucleophilic reagent. Analogous reactivity has been previously observed in the reactions of indol-3-ylcarbonyl isothiocyanate with nucleophilic reagents.[17] The formation of **18a–18f** by direct alcoholysis or aminolysis of **16a**, **16e** and **16f** is less probable, since the reaction of nucleophiles with 1-Boc-2-chloroindole-3-ylcarbonylisothiocyanate (**23**) did not afford analogous side products. Another possible way, alcoholysis or aminolysis of **17a–17f** can be excluded, since the prolonged heating of **17a–17f** in the presence of corresponding alcohols or piperidine did not result in the formation of corresponding esters or amide. Thiocarbamoyl compounds **17a–17f** were separated from the reaction mixtures by simple crystallization from acetone/cyclohexane.

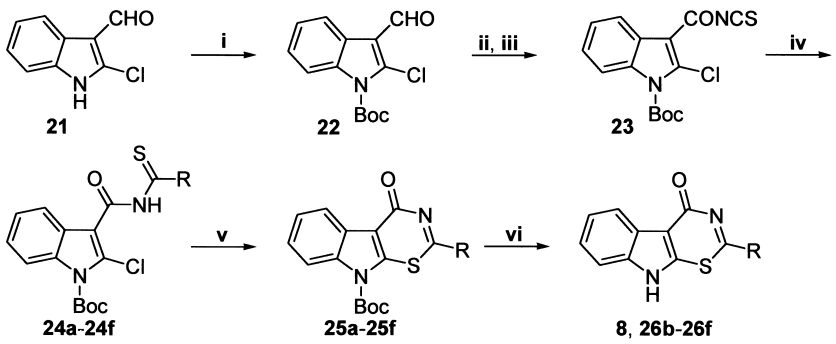
After the preparation of key intermediates **17a–17f**, the possibility of their cyclization by intramolecular nucleophilic replacement of a chlorine atom in the 2-position of an indole ring with sulfur, was studied. There are several examples of 2 and 4-chloronicotionoyl thioureas with activated carbon–chlorine bonds, where similar substitution was achieved by heating with LiH in DMF.[18] Many attempts to cyclize thiocarbamoyl compounds **17a–17f** under the action of various bases (for example Et_3N, NaH, MeONa) and temperatures up to 150°C resulted in decomposition and no cyclization took place. Another possibility for substitution of the chlorine is the weakening of the carbon–halogen bond by photochemical excitation. Despite several examples of nucleophilic substitutions of chlorine with

sulfur in the 2-position of the indole,[13,19] the photochemical approach has not been applied for this purpose.[20] UV spectra of compounds **17a–17f** exhibit long wave absorption maxima at 308 nm, except for **17d** (287 nm). Therefore, their photolysis was realized by irradiation of a high-pressure mercury discharge lamp through a Pyrex filter (λ>300 nm) under a nitrogen atmosphere. It was found that the desired intramolecular photosubstitution of chlorine by sulfur advantageously proceeds in methanolic solutions of **17a–17f** (Scheme 2). Due to the decomposition of the final products caused by liberated HCl, the addition of Et_3N to the reaction mixture was necessary. Since the thiazinoindoles **19a–19f** formed appeared to be photolabile, the reaction time was optimised and the reaction was stopped, before all the starting material was consumed. Analogues of cyclobrassinon were isolated by column chromatography in 16–55% yield. The IR spectra of thiazinoindoles **19a–19f** lack the characteristic NH stretching frequency, present in the starting thiocarbamoyl compounds in the region of 3400 cm^{-1}, while their characteristic C=O absorption bands appeared at lower frequency by about 40 cm^{-1} as a result of conjugation with the endocyclic C=N bond. In contrast to ^{13}C NMR spectra of thiocarbamoyl compounds **17a–17f** exhibiting signals of the thiocarbonyl group at 178–190 ppm, the photocyclization products **19a–19f** show the signals of C=N bond at 156–164 ppm. In the mass spectra of thiazinoindoles **19a–19f** their structure was unambiguously confirmed by the presence of the expected molecular ions and the base-peaks corresponding to retro Diels–Alder splitting. In the next step we examined the possibility of the removal of protecting Bn and 4-$MeOC_6H_4CH_2$ groups from the indole nitrogen of thiazinoindoles **19e** and **19f**. The benzyl protecting group can be removed from protected indoles by employing sodium in liquid ammonia,[21a] $AlCl_3$ in dry benzene,[21b] and by methyl lithium or lithiumdiisopropylamide (LDA) in dry tetrahydrofuran.[21c] The 4-methoxybenzyl protecting group can be removed by DDQ in refluxing toluene and by trifluoroacetic acid (TFA) in refluxing dichloromethane.[22a] Cerium–ammonium nitrate (CAN) has been also applied for this purpose.[22b] Except for the use of TFA, where dione **20** (Scheme 2) was formed by acidolysis of the 2-methoxy group, the above methods produced intractable mixtures of decomposition products.

Although a new photocyclization methodology for the preparation of 1,3-thiazino[6,5-*b*]indol-4-one derivatives substituted on the indole nitrogen with an electron-donating substituent has been developed, it appeared not suitable for the synthesis of cyclobrassinon (**8**). Since we did not succeed with removal of the electron-donating protecting groups, we turned our attention to the mere easily removed electron-withdrawing groups. It is well known, that the *tert*-butoxycarbonyl (Boc) group has a wide scope of application for the protection of nitrogen[23] and therefore we selected 1-Boc-2-chloroindole-3-carboxaldehyde (**22**) as a suitable starting compound. As expected, its oxidation to 1-Boc-2-chloroindole-3-carboxylic acid failed, as described for the other 1-acyl-2-chloro-3-carboxaldehydes.[16a] The problem was solved by application of radical bromination methodology (NBS, AIBN, tetrachloromethane, reflux), previously used for the direct conversion of some aliphatic and aromatic aldehydes to acid bromides.[24] Whereas unprotected aldehyde **21** completely decomposed under these conditions, the radical bromination of 1-Boc-2-chloroindole-3-carboxaldehyde (**22**) gave the corresponding unstable acid bromide, which after treatment with KSCN afforded stable 1-Boc-2-chloroindole-3-ylcarbonylisothiocyanate **23** (Scheme 3), showing in its IR spectrum the characteristic absorption band of the N=C=S group at



Scheme 2. *Reagents and conditions*: (**i**) $KMnO_4$, **14a**,[16a] **14e**,[16c] **14f**: acetone/water, rt, 58%; (ii) PCl_3, benzene, 85–90°C, **a**: 35 min, **e**: 30 min, **f**: 1 h; (iii) KSCN, acetone, rt, **a**: 20 min, 30%, **e**: 1 h, 40%, **f**: 1 h, 29%, the yields of isolated isothiocyanates are based on carboxylic acids **14**; (iv) MeOH, 60°C, 1 h, 26% (**17a**), 18% (**18a**); EtOH, 60°C, 1 h, 23% (**17b**), 8% (**18b**); *i*-PrOH, 60°C, 2 h, 21% (**17c**), 19% (**18c**); piperidine, acetone, rt, 20 min, 21% (**17d**), 20% (**18d**); MeOH, 60°C, 1 h, 42% (**17e**), 2% (**18e**); MeOH, 60°C, 1 h, 40% (**17f**), 10% (**18f**), for **17** and **18** yields are based on carboxylic acids **14**, using the crude isothiocyanates **16**; (v) $h\nu$, Pyrex filter, N_2, Et_3N, methanol, rt, **a**: 35 min, 33%, **b**: 75 min, 38%, **c**: 35 min, 55%, **d**: 6 h, 16%, **e**: 35 min, 47%, **f**: 35 min, 40%; (vi) TFA, dichloromethane, reflux, 48 h, 29%.



Scheme 3. *Reagents and conditions*: (i) Boc_2O, DMAP, THF, 5°C, 1 h, 68%; (ii) NBS, AIBN, tetrachloromethane, reflux, 10 min; (iii) KSCN, acetone, rt, 15 min, 41% (based on aldehyde **22**); (iv) **a**: MeOH, acetone, rt, 2 h, **b**: EtOH, acetone, rt, 2.5 h, **c**: *i*-PrOH, acetone, reflux, 5 min, **d**: $MeNH_2$, acetone, 0°C, 10 min, 44%, **e**: 4-toluidine, acetone, 0°C, 15 min **f**: piperidine, acetone, 0°C, 5 min; (v) **a**: Et_3N, acetone, rt, 1 h, 61%, **b**: Et_3N, acetone, rt, 1.5 h, 64%, **c**: Et_3N, acetone, reflux, 1 h, 47%, **d**: Et_3N, acetone, reflux, 3 h, 70%, **e**: Et_3N, acetone, reflux, 75 min, 66%, **f**: Et_3N, acetone, rt, 2 h, 67% (for **25a**–**25c**, **25e** and **25f** yields are based on isothiocyanate **23**); (vi) **a**: 165–170°C, 40 min, 70%, **b**: 165–170°C, 30 min, 80%, **c**: 160–165°C, 30 min, 66%, **d**: 180–185°C, 20 min, 72%, **e**: 155–160°C, 25 min, 81%, **f**: 155–160°C, 25 min, 77%.

1967 cm^{-1}. Nucleophilic addition of methanol to isothiocyanate **23** afforded the corresponding monothiocarbamate **24a**. Cyclization of **24a** to 9-Boc-cyclobrassinon (**25a**) proceeded smoothly in 61% yield (from isothiocyanate **23**) by nucleophilic substitution of the chlorine in the presence of triethylamine, significantly facilitated by the activating effect of the Boc group. It was found that monothiocarbamate **24a** cannot be isolated in a pure state, since after its formation and during isolation it undergoes spontaneous partial cyclization to thiazinoindole **25a**. This behaviour can be explained by an unusually high reactivity of the chlorine atom in the 2-position activated by the electron-withdrawing effect of the carbonyl groups in the 1 and 3-positions. The best yield of **25a** as a sole reaction product was obtained when **24a** was generated in situ and cyclization completed by addition of triethylamine. The last step in the synthesis of cyclobrassinon (**8**) was the removal of the protecting group from **25a**. The Boc group can be removed thermally,[25a,b] under acidic[25c] or basic[25d] conditions. We found that deprotection of **25a** to **8** can be effectively achieved in 70% yield by heating without solvent to 165–170°C, whereas treatment with acidic or basic reagents led to decomposition. The spectral data of synthetic cyclobrassinon are in agreement with the data of the natural product.[9]

After the successful synthesis of cyclobrassinon (**8**) we studied the scope and limitations of our elaborated synthetic sequence. Thus, isothiocyanate **23** was reacted with ethanol, 2-propanol, methylamine, piperidine and 4-toluidine (Scheme 3). Thiocarbamates **24b** and **24c** and thiourea derivatives **24d**–**24f** cyclized smoothly to protected thiazinoindoles in 47–70% yield (based on isothiocyanate **23**). Except for **24d**, thiocarbamoyl compounds **24b**, **24c**, **24e** and **24f** appeared to be equally reactive as **24a** and during attempted isolation partially cyclized to the corresponding thiazinoindoles. Analogously to **25a**, the deprotection of thiazinoindoles **25b**–**25f** was advantageously performed thermally in 70–80% yield. The structure of thiazino[6,5-*b*]indol-4-one derivatives **25a**–**25f** and **26b**–**26f** was confirmed by spectral data, fully corresponding with the data for compounds **19a**–**19f**.

The in vitro antimicrobial activity of the synthesized compounds was tested against representative strains of bacteria, yeasts and molds. The activity of most compounds was very low or absent against bacteria (MIC≥100 $\mu g\ mL^{-1}$) and fungi (MIC≥200 $\mu g\ mL^{-1}$). Compouds **16a**, **22** and **23**, exhibited a good antifungal activity against *Cryptococcus neoformans* (MIC=75, 25 and 10 $\mu g\ mL^{-1}$, respectively). Compounds **17a** and **24d** exhibited activity against *Staphylococcus aureus* (MIC=50 $\mu g\ mL^{-1}$).

As a primary in vitro screening for growth inhibition and cytotoxicity, selected compounds were submitted to NCI (National Cancer Institute, Bethesda, Md) and evaluated for their cytotoxic potency on three human cell lines, such as NCI-H460 lung cancer, MCF7 breast cancer and SF-268 glioma. A compound is considered active when it reduces the growth of any of the cell lines to 32% or less and it is passed on for evaluation in the full panel of sixty cell lines. Compounds **22**, **25e**, **25f**, **26e** and **26f** were active in this test. The panel of 60 human tumor cell lines is organised into subpanels representing leukemia, melanoma and cancers of lung, colon, kidney, ovary, breast, prostate and central nervous system. The test compounds were dissolved in DMSO and evaluated using five concentrations at ten-fold dilutions, the highest being 10^{-4} M and the others 10^{-5}–10^{-8} M L^{-1}. They did not show a level of activity sufficient to enter the subsequent in vivo step.

3. Conclusion

The first total synthesis of indole phytoalexin cyclobrassinon (six steps, overall yield 12%) and some of its analogues was achieved starting from 1-substituted 2-chloroindole-3-carboxaldehydes. The photochemical or Et_3N-mediated nucleophilic cyclization of indolyl thiocarbamates and thioureas was employed as a key step. Specific antifungal activity of compounds **16a**, **22** and **23** against *C. neoformans* is very promising: in fact life-threatening infections caused by this encapsulated fungal pathogen have been increasing steadly over the past 10

years because of the onset of AIDS and the expanded use of immunosuppressive drugs. Compounds **17a** and **24d** exhibited activity against *S. aureus*. It is noteworthy to consider that this Gram-positive bacterium is one of the major pathogens that causes hospital infections. It is characterized by an extreme flexibility in adapting to antibiotic pressure, acquiring resistance to practically all antibiotics so far introduced in clinical practice. Therefore there is large interest in every new molecule that can be used in intensive antibacterial therapy. The results from the antitumor tests will be taken into account for the design of new potential antitumor agents.

4. Experimental

4.1. General

Melting points were determined on a Koffler hot-stage apparatus and are uncorrected. Infrared spectra were recorded on an IR-75 (Zeiss, Jena) spectrometer in the region 400–4000 cm^{-1}. ^1H and ^{13}C NMR spectra were measured on Varian Gemini 2000 (300 MHz for ^1H, 75 MHz for ^{13}C). Chemical shifts (δ) are reported in ppm downfield from TMS, the coupling constants (J) are given in Hz. The mass spectra were recorded on a SSQ-700 spectrometer (Finigan) at an ionization energy 70 eV. The ultraviolet spectra were recorded on a Specord M42 spectrometer in methanol. Microanalyses were performed with a Perkin–Elmer, Model 2400 analyser. The reaction course was monitored by TLC on Silufol plates (Kavalier®, Czech Republic). The preparative column chromatography (flash chromatography) was performed over the Kieselgel Merck Typ 9385, 230–400 mesh. The in vitro antibacterial activity of synthesized compounds was investigated against representative Gram positive and Gram negative bacteria, such as *Escherichia coli* ATCC 11105, *Proteus mirabilis* M81, *Streptococcus faecalis* SF 8043 and *S. aureus* 6538/P. Minimal inhibitory concentrations (MIC $\mu g\ mL^{-1}$) were determined by the 2-fold agar dilution method,[26] culturing all bacteria on Mueller-Hinton agar (Difco, Detroit, MI, USA). The in vitro antimycotic activity was tested against *Candida albicans* L16, *Candida lypolitica* L6, *C. neoformans* L35 and *Aspergillus niger* NRLL330 on Sabauroad dextrose agar (Merck) by the 2-fold agar dilution method. All experiments were performed in triplicate, using inocula of 10^6 cfu (colony forming units)/mL of bacteria and yeasts and 10^5 conidia mL^{-1} of molds. Fungal and bacteria plates were incubated at 30°C for 48 h and 37°C for 24 h, respectively. All compounds were dissolved in DMSO: the final concentration of DMSO in tested media never exceeded 1%. This concentration produced no visible inhibition of growth in the controls. The cytotoxic activity was evaluated according to the NCI protocols.[27]

4.1.1. 1-(4-Methoxybenzyl)-2-chloroindole-3-carboxylic acid (14f). The acid **14f** was prepared following the procedure for 1-phenyl-2-chloroindole-3-carboxylic acid.[28] Yield 58%, white solid, mp 215–219°C (decomp., ethanol); (Found: C, 64.4; H, 4.7; N, 4.2. $C_{17}H_{14}NO_3Cl$ requires C, 64.66; H, 4.47; N, 4.44%); ν_{max} ($CHCl_3$) 1664 (C═O), 2200–3300 cm^{-1} (OH); δ_H (300 MHz, DMSO-d_6) 3.69 (3H, s, CH_3), 5.52 (2H, s, CH_2), 6.87 (2H, d, J=8.6 Hz, H_{arom}), 7.11 (2H, d, J=8.6 Hz, H_{arom}), 7.17–7.41 (2H, m, H_{arom}), 7.62 (1H, d, J=7.0 Hz, H_{arom}), 8.05 (1H, d, J=7.0 Hz, H_{arom}).

4.1.2. 1-Substitued 2-chloroindole-3-ylcarbonylchlorides 15a, 15e and 15f. To a stirred suspension of carboxylic acid (**14a**, 1.048 g, 5 mmol; **14e**, 1.143 g, 4 mmol; **14f**, 1.263 g, 4 mmol) in dry benzene (**14a**, 45 mL; **14e** and **14f**, 36 mL) was added PCl_3 (**14a**, 0.587 g, 0.44 mL, 5 mmol; **14e** and **14f**, 0.549 g, 0.35 mL, 4 mmol) and the reaction mixture was stirred at 85–90°C (bath) until all carboxylic acid has dissolved (**14a**, 15 min; **14e**, 10 min; **14f**, 40 min) and heating was continued for 20 min. The reaction mixture was then cooled to room temperature, decanted from the phosphorous acid, deposited on the flask walls, the flask washed with dry benzene (10 mL) and the collected benzene solution evaporated to dryness (bath temperature up to 40°C). The chlorides **15a**, **15e** and **15f** were obtained as unstable orange oils, immediately used for the next reaction.

4.1.3. 1-Substitued 2-chloroindole-3-ylcarbonyl isothiocyanates 16a, 16e and 16f. The freshly prepared acyl chlorides **15a**, **15e** and **15f** were dissolved in dry acetone (**16a**, 20 mL; **16e** and **16f**, 10 mL) and added in one portion to the solution of KSCN (**16a**, 0.49 g, 5 mmol; **16e** and **16f**, 0.389 g, 4 mmol) in dry acetone (30 mL). The reaction mixture was stirred at room temperature for 20 min (**16a**) or 1 h (**16e** and **16f**). After the evaporation of acetone the crude isothiocyanates are pure enough for the next reaction, however they can be isolated in a pure crystalline form as follows: to the acetone solution of isothiocyanate, prepared from 2.5 mmol of corresponding acid was added a small amount of silica gel and after the evaporation of acetone the preadsorbed isothiocyanate was chromatographed on 50 g of SiO_2, cyclohexane/acetone (3:1, **16a**), dichloromethane/-hexane (3:1, **16e** and **16f**). *1-Methyl-2-chloroindole-3-ylcarbonyl isothiocyanate (**16a**)*. Yield 30%, colourless needles, mp 135–137°C (acetone/cyclohexane); (Found: C, 52.5; H, 3.0; N, 11.0. $C_{11}H_7ClN_2OS$ requires C, 52.70; H, 2.81; N, 11.17%); ν_{max} ($CHCl_3$) 1670 (C═O), 1970 cm^{-1} (N═C═S); δ_H (300 MHz, $CDCl_3$) 3.80 (3H, s, CH_3), 7.27–7.52 (3H, m, H_{arom}), 8.12–8.37 (1H, m, H_{arom}). *1-Benzyl-2-chloroindole-3-ylcarbonyl isothiocyanate (**16e**)*. Yield 40%, colourless needles, mp 106–108°C (dichloromethane/hexane); (Found: C, 62.7; H, 3.5; N, 8.3. $C_{17}H_{11}ClN_2OS$ requires C, 62.48; H, 3.39; N, 8.57%); ν_{max}($CHCl_3$) 1667 (C═O), 1960 cm^{-1} (N═C═S); δ_H (300 MHz, $CDCl_3$) 5.47 (2H, s, CH_2), 6.95–7.08 (8H, m, H_{arom}), 8.05–8.42 (1H, m, H_{arom}). *1-(4-Methoxybenzyl)-2-chloroindole-3-ylcarbonyl isothiocyanate (**16f**)*. Yield 29%, colourless needles, mp 91–92°C (dichloromethane/hexane); (Found: C, 60.4; H, 3.9; N, 7.8. $C_{18}H_{13}ClN_2O_2S$ requires C, 60.59; H, 3.67; N, 7.85%); ν_{max} ($CHCl_3$) 1660 (C═O), 1960 cm^{-1} (N═C═S); δ_H (300 MHz, $CDCl_3$) 3.77 (3H, s, CH_3), 5.42 (2H, s, CH_2), 6.84 (2H, d, J=8.7 Hz, H_{arom}), 7.08 (2H, d, J=8.7 Hz, H_{arom}), 7.30–7.35 (3H, m, H_{arom}), 8.24–8.27 (1H, m, H_{arom}); δ_C (75 MHz, $CDCl_3$) 42.7 (CH_3), 50.8 (CH_2), 101.4 (C), 106.0 (CH), 109.9 (CH), 116.8 (CH), 119.2 (CH), 119.9 (CH), 121.4 (C), 122.2 (C), 123.5 (CH), 130.1 (C), 130.9 (C), 141.2 (C), 150.0 (C═O), 155.0 (N═C═S); EIMS: m/z (%): 356 (M^+, 5), 298 (6), 177 (6), 121 (100), 114 (7), 77 (7).

4.1.4. Reaction of isothiocyanates 16a, 16e and 16f with methanol. To the crude isothiocyanate **16a**, **16e** and **16f**, freshly prepared from 5 mmol of corresponding carboxylic acid was added dry methanol (50 mL) and the mixture was stirred for 1 h at 60°C (bath). After the evaporation of methanol, the residue was dissolved in ethyl acetate (100 mL) and washed with 4% solution of sodium hydrogencarbonate (**16a**, 2×50 mL) or 5% solution of pottasium carbonate (**16e** and **16f**; 1×80 mL, 1×60 mL, 1×40 mL) and then with water (60 mL). The organic layer was dried (Na_2SO_4), solvent evaporated and the residue crystallized from acetone/cyclohexane (**17a**, rt, 30 min; **17e** and **17f**, 3°C, 12 h). The precipitated thiocarbamates were filtered off, washed with cyclohexane and dried. The mother liquor was evaporated and residue chromatographed on 30 g SiO_2, cyclohexane/acetone (3:1, **17a**), 20 g SiO_2, cyclohexane/acetone (3:1, **17e**) or 100 g SiO_2, cyclohexane/acetone (5:1, **17f**), affording a small amount of thiocarbamates **17a**, **17e** and **17f** (4–10%) and methyl carboxylates **18a**, **18e** and **18f**. *O-Methyl N-(1-methyl-2-chloroindole-3-ylcarbonyl)thiocarbamate (**17a**)*. Yield 26%, colourless needles, mp 127–129°C (acetone/cyclohexane); (Found: C, 51.1; H, 4.2; N, 9.8. $C_{12}H_{11}ClN_2O_2S$ requires C, 50.98; H, 3.92; N, 9.91%); ν_{max} ($CHCl_3$) 1690 (C═O), 3413 cm^{-1} (NH); δ_H (300 MHz, $CDCl_3$) 3.82 (3H, s, CH_3), 4.24 (3H, s, CH_3), 7.30–7.34 (3H, m, H_{arom}), 8.25–8.26 (1H, m, H_{arom}), 9.60 (1H, s, NH); δ_C (75 MHz, $CDCl_3$) 30.5 (CH_3), 59.4 (CH_3), 105.6 (C), 109.6 (CH), 121.4 (CH), 123.2 (CH), 124.0 (CH), 126.0 (C), 128.3 (C), 135.6 (C), 157.7 (C═O), 190.4 (C═S); UV, λ_{max} (ε_{max}): 308 (1850); 267 (1980); 217 (3520). *1-Methyl-2-chloroindole-3-methylcarboxylate (**18a**)*. Yield 18%, colourless needles, mp 111–113°C (methanol); (Found: C, 59.3; H, 4.6; N, 6.1. $C_{11}H_{10}ClNO_2$ requires C, 59.01; H, 4.51; N, 6.26%); ν_{max} ($CHCl_3$) 1687 cm^{-1} (C═O); δ_H (300 MHz, $CDCl_3$) 3.78 (3H, s, CH_3), 3.95 (3H, s, CH_3), 7.12–7.43 (3H, m, H_{arom}), 7.97–8.27 (1H, m, H_{arom}). *O-Methyl N-(1-benzyl-2-chloroindole-3-ylcarbonyl)thiocarbamate (**17e**)*. Yield 42%, colourless needles, mp 127–129°C (acetone/cyclohexane); (Found: C, 60.5; H, 4.0; N, 7.6. $C_{18}H_{15}ClN_2O_2S$ requires C, 60.25; H, 4.21; N, 7.81%); ν_{max} ($CHCl_3$) 1687 (C═O), 3400 cm^{-1} (NH); δ_H (300 MHz, $CDCl_3$) 4.23 (3H, s, CH_3), 5.45 (2H, s, CH_2), 7.08–7.10 (2H, m, H_{arom}), 7.28–7.33 (6H, m, H_{arom}), 8.27–8.31 (1H, m, H_{arom}), 9.61 (1H, s, NH); δ_C (75 MHz, $CDCl_3$) 47.6 (CH_2), 59.4 (CH_3), 106.2 (C), 110.3 (CH), 121.5 (CH), 121.7 (C), 123.4 (CH), 124.0 (C), 124.3 (CH), 126.2 (C), 126.5 (CH), 128.0 (C), 128.2 (CH), 129.1 (CH), 135.1 (CH), 135.5 (C), 157.8 (C═O), 190.3 (C═S); EIMS: *m/z* (%): 358 (M^+, 5), 323 (22), 268 (80), 177 (11), 114 (12), 91 (100), 65 (12); UV, λ_{max} (ε_{max}): 308 (2100); 268 (2400); 209 (5700). *1-Benzyl-2-chloroindole-3-methylcarboxylate (**18e**)*. Yield 2%, white solid, mp 88–90°C (hexane); (Found: C, 68.4; H, 4.9; N, 4.6. $C_{17}H_{14}ClNO_2$ requires C, 68.12; H, 4.71; N, 4.67%); ν_{max} ($CHCl_3$) 1687 cm^{-1} (C═O); δ_H (300 MHz, $CDCl_3$) 4.00 (3H, s, CH_3), 5.48 (2H, s, CH_2), 6.90–7.75 (8H, m, H_{arom}), 8.02–8.35 (1H, m, H_{arom}). *O-Methyl N-[1-(4-methoxybenzyl)-2-chloroindole-3-ylcarbonyl]thiocarbamate (**17f**)*. Yield 40%, colourless needles, mp 120–122°C (acetone/cyclohexane); (Found: C, 58.8; H, 4.3; N, 7.6. $C_{18}H_{17}ClN_2O_3S$ requires C, 58.68; H, 4.41; N, 7.20%); ν_{max} ($CHCl_3$) 1687 (C═O), 3400 cm^{-1} (NH); δ_H (300 MHz, $CDCl_3$) 3.76 (3H, s, CH_3), 4.23 (3H, s, CH_3), 5.38 (2H, s, CH_2), 6.83 (2H, d, J=8.6 Hz, H_{arom}), 7.05 (2H, d, J=8.6 Hz, H_{arom}), 7.26–7.32 (3H, m, H_{arom}), 8.26–8.29 (1H, m, H_{arom}), 9.61 (1H, s, NH); δ_C (75 MHz, $CDCl_3$) 47.1 (CH_2), 55.3 (CH_3), 59.4 (CH_3), 106.1 (C), 110.3 (CH), 114.5 (CH), 121.5 (CH), 123.3 (CH), 124.3 (CH), 126.2 (C), 127.1 (C), 128.0 (CH), 135.4 (CH), 157.8 (C═O), 159.5 (C), 190.3 (C═S); UV, λ_{max} (ε_{max}): 308 (1440); 270 (1570); 209 (5400). *1-(4-Metoxybenzyl)-2-chloroindole-3-methylcarboxylate (**18f**)*. Yield 10%, white solid, mp 88–91°C (hexane); (Found: C, 65.3; H, 5.0; N, 4.5. $C_{18}H_{16}ClNO_3$ requires C, 65.56; H, 4.89; N, 4.25%); ν_{max} ($CHCl_3$) 1687 cm^{-1} (C═O); δ_H (300 MHz, $CDCl_3$) 3.77 (3H, s, CH_3), 3.98 (3H, s, CH_3), 5.42 (2H, s, CH_2), 6.80 (2H, d, J=8.4 Hz, H_{arom}), 7.08 (2H, d, J=8.4 Hz, H_{arom}), 7.18–7.40 (3H, m, H_{arom}), 8.02–8.35 (1H, m, H_{arom}).

4.1.5. Reaction of isothiocyanate 16a with ethanol. To the isothiocyanate **16a**, freshly prepared from 7.5 mmol of carboxylic acid **16a** was added dry ethanol (70 mL) and the mixture was stirred for 1 h at 60°C (bath). After evaporation of ethanol, the residue was dissolved in ethyl acetate (130 mL) and washed with 4% solution of sodium hydrogencarbonate (2×70 mL) and water (60 mL). The organic layer was dried (Na_2SO_4), solvent evaporated and the residue crystallized from acetone/cyclohexane to afford **17b**. The mother liquor was evaporated and the residue crystallized from methanol to afford methyl carboxylate **18b**. *O-Ethyl N-(1-methyl-2-chloroindole-3-ylcarbonyl)thiocarbamate (**17b**)*. Yield 23%, colourless needles, mp 131–133°C (acetone/cyclohexane); (Found: C, 52.8; H, 4.3; N, 9.6. $C_{13}H_{13}ClN_2O_2S$ requires C, 52.61; H, 4.42; N, 9.44%); ν_{max} ($CHCl_3$) 1686 (C═O), 3410 cm^{-1} (NH); δ_H (300 MHz, $CDCl_3$) 1.48 (3H, t, J=7.0 Hz, CH_3), 3.78 (3H, s, CH_3), 4.71 (2H, q, J=7.0 Hz, CH_2), 7.13–7.50 (3H, m, H_{arom}), 8.05–8.30 (1H, m, H_{arom}), 9.60 (1H, s, NH); UV, λ_{max} (ε_{max}): 308 (933); 274 (1122); 215 (2754). *1-Methyl-2-chloroindole-3-ethylcarboxylate (**18b**)*. Yield 8%, white solid, mp 79–80°C (methanol); (Found: C, 60.5; H, 5.2; N, 6.0. $C_{12}H_{12}ClNO_2$ requires C, 60.64; H, 5.09; N, 5.89%); ν_{max} ($CHCl_3$) 1683 cm^{-1} (C═O); δ_H (300 MHz, $CDCl_3$) 1.45 (3H, t, J=7.0 Hz, CH_3), 3.76 (3H, s, CH_3), 4.43 (2H, q, J=7.0 Hz, CH_2), 7.07–7.30 (3H, m, H_{arom}), 7.95–8.27 (1H, m, H_{arom}).

4.1.6. Reaction of isothiocyanate 16a with 2-propanol. To the isothiocyanate **16a**, freshly prepared from 5 mmol of carboxylic acid **16a** was added dry 2-propanol (50 mL) and the mixture was stirred for 2 h at 60°C (bath). After the evaporation of 2-propanol, the residue was dissolved in ethyl acetate (100 mL) and washed with 4% solution of sodium hydrogencarbonate (2×50 mL) and water (60 mL). The organic layer was dried (Na_2SO_4), solvent evaporated and the residue chromatographed on 70 g SiO_2, cyclohexane/acetone (3:1), affording thiocarbamate **17c** and 2-propyl carboxylate **18c**. *O-2-Propyl N-(1-methyl-2-chloroindole-3-ylcarbonyl)thiocarbamate (**17c**)*. Yield 21%, colourless needles, mp 112–114°C (acetone/cyclohexane); (Found: C, 53.9; H, 4.7; N, 9.2. $C_{14}H_{15}ClN_2O_2S$ requires C, 54.10; H, 4.86; N, 9.01%); ν_{max} ($CHCl_3$) 1687 (C═O), 3417 cm^{-1} (NH); δ_H (300 MHz, $CDCl_3$) 1.46 (6H, d, J=6.0 Hz, 2×CH_3), 3.80 (3H, s, CH_3), 5.70 (1H, septet, J=6.0 Hz, CH), 7.16–7.50 (3H, m, H_{arom}), 8.10–8.40 (1H, m, H_{arom}), 9.54 (1H, s, NH); UV, λ_{max} (ε_{max}): 308 (2188);

272 (2455); 213 (5248). *1-Methyl-2-chloroindole-3-(2-propyl)carboxylate (**18c**)*. Yield 19%, white solid, mp 57–59°C (hexane); (Found: C, 62.2; H, 5.5; N, 5.7. $C_{13}H_{14}ClNO_2$ requires C, 62.03; H, 5.61; N, 5.56%); ν_{max} ($CHCl_3$) 1683 cm^{-1} (C=O); δ_H (300 MHz, $CDCl_3$) 1.43 (6H, d, J=6.0 Hz, 2×CH_3), 3.77 (3H, s, CH_3), 5.35 (1H, septet, J=6.0 Hz, CH), 7.15–7.45 (3H, m, H_{arom}), 8.00–8.35 (1H, m, H_{arom}).

4.1.7. Reaction of isothiocyanate 16a with piperidine. To an acetone solution of isothiocyanate **16a**, filtered with charcoal, freshly prepared from 5 mmol of carboxylic acid **16a**, piperidine (0.639 g, 0.74 mL, 7.5 mmol) was added with stirring. The reaction mixture was stirred for 20 min at room temperature. Acetone was evaporated, the residue dissolved in ethyl acetate (100 mL), washed with 4% solution of sodium hydrogencarbonate (2×50 mL) and water (60 mL). The water layer was extracted with ethylacetate (30 mL), combined extracts dried (Na_2SO_4), solvent evaporated and the residue crystallized from acetone/cyclohexane (0°C, 30 min) to afford thiourea **17d**. The mother liquor was evaporated and the residue chromatographed on 80 g SiO_2, benzene/acetone (7:1), affording a small amount of thiourea **17d** and the carboxylic acid amide **18d**. *1-[N-(1-Methyl-2-chloroindole-3-ylcarbonyl)thiocarbamoyl]piperidine (**17d**)*. Yield 21%, colourless needles, mp 147–149°C (acetone/cyclohexane); (Found: C, 57.1; H, 5.3; N, 12.4. $C_{16}H_{18}ClN_3OS$ requires C, 57.22; H, 5.40; N, 12.51%); ν_{max} ($CHCl_3$) 1670 (C=O), 3400 cm^{-1} (NH); δ_H (300 MHz, $CDCl_3$) 1.60–1.92 (6H, m, 3×CH_2), 3.65–3.92 (2H, m, CH_2), 3.81 (3H, s, CH_3), 4.07–4.32 (2H, m, CH_2), 7.15–7.50 (3H, m, H_{arom}), 8.05–8.28 (1H, m, H_{arom}), 8.56 (1H, s, NH); δ_C (75 MHz, $CDCl_3$) 24.0 (CH_2), 25.7 (CH_2), 30.4 (CH_3), 49.9 (CH_2), 105.6 (C), 109.7 (CH), 120.9 (CH), 122.9 (CH), 123.8 (CH), 125.7 (C), 129.0 (C), 135.6 (C), 159.0 (C=O), 178.4 (C=S); UV, λ_{max} (ε_{max}): 289 (2188); 241 (2089); 214 (3631). *1-Methyl-2-chloroindole-3-ylcarbonylpiperidine (**18d**)*. Yield 20%, white solid, mp 117–119°C (dichloromethane/hexane); (Found: C, 65.3; H, 6.0; N, 10.4. $C_{15}H_{17}ClN_2O$ requires C, 65.09; H, 6.19; N, 10.12%); ν_{max} ($CHCl_3$) 1609 cm^{-1} (C=O); δ_H (300 MHz, $CDCl_3$) 1.65 (6H, m, 3×CH_2), 3.59 4H, (m, 2×CH_2), 3.72 (3H, s, CH_3), 7.00–7.40 (3H, m, H_{arom}), 7.43–7.75 (1H, m, H_{arom}).

4.1.8. Photochemical cyclization of thiocarbamoyl compounds 17a–17f. To a stirred solution of thiocarbamoyl compounds **17a–17f** (1 mmol) in methanol (200 mL) was added triethylamine (0.202 g, 0.28 mL, 2 mmol) and the mixture was irradiated (high pressure mercury lamp, Tesla RVK-125) through a pyrex filter in a water-cooled immersed apparature equipped with a quarz-jacketed discharge lamp, cooled with water for 35 min (**17a**, **17c** and **17e**), 75 min (**17b**), 1 h (**17f**) or 6 h[29] (**17d**). Nitrogen gas was bubbled through a solution 15 min before irradiation and during the reaction. After evaporation of methanol the residue was dissolved in chloroform (5 mL) and chromatographed on 50 g SiO_2 (**19a–19c**, **19e** and **19f**, benzene/acetone (7:1); **19d**, cyclohexane/acetone (2:1)). The eluate was evaporated and thiazinoindoles **19a–19f** were crystallized from an appropriate solvent. *2-Methoxy-9-methyl-1,3-thiazino[6,5-b]indol-4-one (**19a**)*. Yield 33%, colourless needles, mp 202–205°C (acetone/cyclohexane); (Found: C, 58.4; H, 3.9; N, 11.5. $C_{12}H_{10}N_2O_2S$ requires C, 58.52; H, 4.09; N, 11.37%); ν_{max} ($CHCl_3$) 1580 and 1650 cm^{-1} (C=N–C=O); δ_H (300 MHz, $CDCl_3$) 3.69 (3H, s, CH_3), 4.17 (3H, s, CH_3), 7.13–7.50 (3H, m, H_{arom}), 8.25–8.55 (1H, m, H_{arom}); δ_C (75 MHz, $CDCl_3$) 30.7 (CH_3), 57.7 (CH_3), 102.7 (C), 108.6 (CH), 121.8 (CH), 122.5 (CH), 124.1 (CH), 125.1 (C), 138.3 (C), 139.5 (C), 164.5 and 166.4 (C=N–C=O); EIMS: *m/z* (%): 246 (M^+, 61), 189 (100), 160 (15), 117 (25), 89 (10). *2-Ethoxy-9-methyl-1,3-thiazino[6,5-b]indol-4-one (**19b**)*. Yield 38%, colourless needles, mp 198–201°C (acetone/cyclohexane); (Found: C, 60.1; H, 4.5; N, 10.6. $C_{13}H_{12}N_2O_2S$ requires C, 59.98; H, 4.65; N, 10.76%); ν_{max} ($CHCl_3$) 1570 and 1640 cm^{-1} (C=N–C=O); δ_H (300 MHz, $CDCl_3$) 1.45 (3H, t, J=7.0 Hz, CH_3), 3.65 (3H, s, CH_3), 4.68 (2H, q, J=7.0 Hz, CH_2), 7.13–7.55 (3H, m, H_{arom}), 8.25–8.63 (1H, m, H_{arom}); EIMS: *m/z* (%): 260 (M^+, 61), 189 (100), 160 (20), 117 (44), 89 (15). *2-(2-Propoxy)-9-methyl-1,3-thiazino[6,5-b]indol-4-one (**19c**)*. Yield 55%, colourless needles, mp 193–196°C (acetone/cyclohexane); (Found: C, 61.0; H, 5.3; N, 10.5. $C_{14}H_{14}N_2O_2S$ requires C, 61.29; H, 5.14; N, 10.21%); ν_{max} ($CHCl_3$) 1570 and 1640 cm^{-1} (C=N–C=O); δ_H (300 MHz, $CDCl_3$) 1.42 (6H, d, J=6.1 Hz, 2×CH_3), 3.69 (3H, s, CH_3), 5.75 (1H, septet, J=6.1 Hz, CH), 7.16–7.58 (3H, m, H_{arom}), 8.28–8.62 (1H, m, H_{arom}); EIMS: *m/z* (%): 274 (M^+, 100), 233 (20), 189 (66), 160 (26), 128 (10), 117 (61), 89 (15), 43 (21). *2-(1-Piperidyl)-9-methyl-1,3-thiazino[6,5-b]indol-4-one (**19d**)*. Yield 16%, colourless needles, mp 227–229°C (acetone/cyclohexane); (Found: C, 64.4; H, 5.4; N, 13.2. $C_{16}H_{17}N_3OS$ requires C, 64.19; H, 5.72; N, 14.04%); ν_{max} ($CHCl_3$) 1540 and 1607 cm^{-1} (C=N–C=O); δ_H (300 MHz, $CDCl_3$) 1.60–1.85 (6H, m, 3×CH_2), 3.65 (3H, s, CH_3), 3.72–3.90 (4H, m, 2×CH_2), 7.13–7.48 (3H, m, H_{arom}), 8.30–8.63 (1H, m, H_{arom}); δ_C (75 MHz, $CDCl_3$) 24.5 (CH_2), 25.7 (CH_2), 30.3 (CH_3), 47.9 (CH_2), 101.6 (C), 108.3 (CH), 121.9 (CH), 122.0 (CH), 123.2 (CH), 125.3 (C), 137.8 (C), 138.0 (C), 156.3 and 167.7 (C=N–C=O); EIMS: *m/z* (%): 299 (M^+, 28), 189 (100), 160 (15), 117 (32), 89 (10). *2-Methoxy-9-benzyl-1,3-thiazino[6,5-b]indol-4-one (**19e**)*. Yield 37%, colourless needles, mp 187–189°C (dichloromethane/hexane); (Found: C, 67.3; H, 4.6; N, 8.9. $C_{18}H_{14}N_2O_2S$ requires C, 67.06; H, 4.38; N, 8.69%); ν_{max} ($CHCl_3$) 1567 and 1640 cm^{-1} (C=N–C=O); δ_H (300 MHz, $CDCl_3$) 4.17 3H, (s, CH_3), 5.35 (2H, s, CH_2), 7.12–7.14 (2H, m, H_{arom}), 7.31–7.38 (6H, m, H_{arom}), 8.49–8.52 (1H, m, H_{arom}); δ_C (75 MHz, $CDCl_3$) 48.4 (CH_2), 57.8 (CH_3), 103.2 (C), 109.2 (CH), 122.1 (CH), 122.8 (CH), 124.4 (CH), 125.4 (C), 126.8 (CH), 128.6 (CH), 129.2 (CH), 134.4 (C), 138.2 (C), 139.2 (C), 164.8 and 166.6 (C=N–C=O); EIMS: *m/z* (%): 322 (M^+, 36), 265 (100), 236 (61), 204 (5), 91 (5). *2-Methoxy-9-(4-methoxybenzyl)-1,3-thiazino[6,5-b]indol-4-one (**19f**)*. Yield 48%, colourless needles, mp 134–137°C (dichloromethane/hexane); (Found: C, 64.5; H, 4.7; N, 7.7. $C_{19}H_{16}N_2O_3S$ requires C, 64.76; H, 4.58; N, 7.96%); ν_{max} ($CHCl_3$) 1572 and 1642 cm^{-1} (C=N–C=O); δ_H (300 MHz, $CDCl_3$) 3.76 (3H, s, CH_3), 4.15 (3H, s, CH_3), 5.26 (2H, s, CH_2), 6.83 (2H, d, J=9.0 Hz, H_{arom}), 7.06 (2H, d, J=9.0 Hz, H_{arom}), 7.33–7.37 (3H, m, H_{arom}), 8.47–8.50 (1H, m, H_{arom}); δ_C (75 MHz, $CDCl_3$) 48.2 (CH_2), 55.5 (CH_3), 57.9 (CH_3), 103.6 (C), 109.4 (CH), 114.8 (C), 122.2 (CH), 122.9 (CH), 124.5 (C), 125.6 (CH), 126.4 (CH), 128.6 (C), 138.3 (C),

139.4 (C), 160.0 and 165.0 (C═N–C═O); EIMS: *m/z* (%): 352 (M^+, 44), 295 (8), 266 (5), 236 (6), 148 (7), 121 (100), 91 (5), 77 (7).

4.1.9. Reaction of thiazinoindole 19f with trifluoroacetic acid. To a solution of thiazinoindole **19f** (0.135 g, 0.38 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (4.44 g, 3 mL, 38.3 mmol) and the reaction mixture was refluxed for 48 h. The solvent was evaporated and the residue chromatographed on 50 g SiO_2, chloroform/acetonitrile (11:1). *9-(4-Methoxybenzyl)-1,3-thiazino[6,5-b]indol-2,4-dione (**20**)*. Yield 0.04 g (30%), white solid, mp 228–232°C (methanol); (Found: C, 64.1; H, 4.3; N, 9.5. $C_{18}H_{14}N_2O_3S$ requires C, 63.89; H, 4.17; N, 8.29%); ν_{max} ($CHCl_3$) 1670 (C═O), 3350 cm^{-1} (NH); δ_H (300 MHz, $CDCl_3$) 3.78 (3H, s, CH_3), 5.25 (2H, s, CH_2), 6.86 (2H, d, J=9.0 Hz, H_{arom}), 7.12 (2H, d, J=9.0 Hz, H_{arom}), 7.33–7.41 (3H, m, H_{arom}), 8.27–8.30 (1H, m, H_{arom}), 8.38 (1H, s, NH); δ_C (75 MHz, $CDCl_3$) 48.7 (CH_2), 55.6 (CH_3), 100.3 (C), 110.0 (CH), 114.9 (CH), 121.5 (CH), 123.6 (CH), 124.6 (CH), 125.7 (C), 126.2 (C), 128.7 (CH), 138.8 (C), 139.2 (C), 159.7 (C), 160.2 and 161.6 (C═O); EIMS: *m/z* (%): 338 (M^+, 18), 266 (5), 236 (5), 146 (5), 121 (100), 91 (5), 77 (7).

4.1.10. 1-(*tert*-Butoxycarbonyl)-2-chloroindole-3-carboxaldehyde (22). To a solution of aldehyde **21** (4.32 g, 24 mmol) in dry tetrahydrofuran (100 mL), was added in one portion a solution of di-*tert*-butyl dicarbonate (6.288 g, 28.8 mmol) in dry tetrahydrofuran (20 mL) and the mixture was cooled to 5°C. Then DMAP (0.058 g, 0.5 mmol) was added and the mixture was stirred for 1 h at 5°C. The solvent was evaporated, the residue dissolved in ethyl acetate (150 mL) and consecutivelly washed with a 70 mL portions of 5% solution of potassium hydroxide, 1 M solution of HCl and brine. The organic layer was dried (Na_2SO_4) and solvent evaporated. Yield 4.38 g (65%), white solid, mp 88–90°C (ethanol/water); (Found: C, 60.3; H, 5.0; N, 4.8. $C_{14}H_{14}ClNO_3$ requires C, 60.11; H, 5.04; N, 5.01%); ν_{max} ($CHCl_3$) 1673 and 1760 cm^{-1} (C═O); δ_H (300 MHz, $CDCl_3$) 1.75 (9H, s, 3×CH_3), 7.37–7.41 (2H, m, H_{arom}), 8.05–8.08 (1H, m, H_{arom}), 8.29–8.32 (1H, m, H_{arom}), 10.29 (1H, s, CHO); δ_C (75 MHz, $CDCl_3$) 28.1 (CH_3), 86.9 (C), 114.9 (CH), 117.5 (C), 121.1 (CH), 124.6 (C), 125.0 (CH), 125.9 (CH), 135.3 (C), 140.0 (C), 148.0 and 185.8 (C═O); EIMS: *m/z* (%): 279 (M^+, 22), 206 (11), 181 (14), 179 (45), 150 (28), 114 (12), 57 (100), 41 (28).

4.1.11. 1-(*tert*-Butoxycarbonyl)-2-chloroindole-3-ylcarbonyl isothiocyanate (23). To a solution of **22** (0.55 g, 2 mmol) in dry tetrachloromethane (3 mL) was added a catalytic amount of AIBN and NBS (0.464 g, 2.6 mmol). The mixture was stirred at reflux for 10 min, cooled to 3°C, separated precipitate filtered off and the filtrate treated with a solution of KSCN (0.196 g, 2 mmol) in dry acetone (10 mL). After stirring for 15 min at room temperature and filtration with charcoal, the filtrate was evaporated and the residue flash chromatographed on 10 g SiO_2, benzene, to afford **23**. Yield 0.28 g (41%), colourless needles mp 131–132°C (dichloromethane/hexane); (Found: C, 53.6; H, 4.0; N, 8.5. $C_{15}H_{13}ClN_2O_3S$ requires C, 53.49; H, 3.89; N, 8.32%); ν_{max} ($CHCl_3$) 1673 and 1755 (C═O), 1967 cm^{-1} (N═C═S); δ_H (300 MHz, $CDCl_3$) 1.74 (9H, s, 3×CH_3), 7.39–7.42 (2H, m, H_{arom}), 8.00–8.03 (1H, m, H_{arom}), 8.22–8.25 (1H, m, H_{arom}); δ_C (75 MHz, $CDCl_3$) 28.1 (CH_3), 87.3 (C), 111.4 (C), 114.5 (CH), 121.1 (CH), 124.9 (CH), 125.6 (C), 125.9 (CH), 133.2 (C), 135.0 (C), 146.6 and 147.8 (C═O), 155.4 (N═C═S); EIMS: *m/z* (%): 336 (M^+, 22), 278 (10), 236 (10), 178 (21), 114 (10), 57 (100), 41 (14).

4.1.12. Conversion of isothiocayanate 23 to thiazino[6,5-b]indol-4-one derivatives via thiocarbamates 24a–24c. To a solution of isothiocyanate **23** (1 mmol) in dry acetone (**24a** and **24b**, 13 mL; **24c**, 10 mL) was added methanol (13 mL), ethanol (13 mL) or 2-propanol (10 mL) and mixture was stirred at room temperature for 2 h (**24a**), 2.5 h (**24b**) or refluxed for 5 min (**24c**). Then triethylamine (0.203 g, 0.28 mL, 2 mmol) was added and mixture was stirred at room temperature for 1 h (**25a**), 1.5 h (**25b**) with the formation of white precipitate or refluxed for 1 h (**25c**). To a formed suspension of **25a**, **25b** was added water (40 mL) and mixtures were set aside for 1 h at 3°C. The precipitated thiazinoindoles were filtered with suction, dried and crystallized. In the case of **25c**, the solvent was evaporated and the residue chromatographed on 40 g SiO_2, benzene. *2-Methoxy-9-tert-butoxycarbonyl-1,3-thiazino[6,5-b]indol-4-one (**25a**)*. Yield 61%, colourless needles, mp 212–214°C (dichloromethane/hexane); (Found: C, 58.1; H, 4.9; N, 8.5. $C_{16}H_{16}N_2O_4S$ requires C, 57.82; H, 4.85; N, 8.43%); ν_{max} ($CHCl_3$) 1580 and 1653 (C═N–C═O), 1727 cm^{-1} (C═O); δ_H (300 MHz, $CDCl_3$) 1.78 (9H, s, 3×CH_3), 4.19 (3H, s, CH_3), 7.41–7.44 (2H, m, H_{arom}), 8.07–8.10 (1H, m, H_{arom}), 8.53–8.56 (1H, m, H_{arom}); δ_C (75 MHz, $CDCl_3$) 28.2 (CH_3), 57.5 (CH_3), 87.9 (C), 108.5 (C), 114.6 (CH), 122.1 (CH), 124.8 (CH), 125.9 (CH), 126.9 (C), 136.0 (C), 139.0 (C), 149.8 (C═O), 167.4 and 169.7 (C═N–C═O); EIMS: *m/z* (%): 332 (M^+, 22), 276 (81), 232 (10), 175 (41), 146 (18), 57 (100), 41 (22). *2-Ethoxy-9-tert-butoxycarbonyl-1,3-thiazino[6,5-b]indol-4-one (**25b**)*. Yield 64%, colourless needles, mp 214–216°C (dichloromethane/hexane); (Found: C, 59.1; H, 5.3; N, 8.4. $C_{17}H_{18}N_2O_4S$ requires C, 58.94; H, 5.24; N, 8.09%); ν_{max} ($CHCl_3$) 1570 and 1647 (C═N–C═O), 1723 cm^{-1} (C═O); δ_H (300 MHz, $CDCl_3$) 1.46 (3H, t, J=7.0 Hz, CH_3), 1.77 (9H, s, 3×CH_3), 4.68 (2H, q, J=7.0 Hz, CH_2), 7.40–7.43 (2H, m, H_{arom}), 8.07–8.10 (1H, m, H_{arom}), 8.52–8.55 (1H, m, H_{arom}); δ_C (75 MHz, $CDCl_3$) 14.2 (CH_3), 28.2 (CH_3), 67.0 (CH_2), 87.8 (C), 108.4 (C), 114.6 (CH), 122.1 (CH), 124.8 (CH), 125.8 (CH), 126.9 (C), 136.0 (C), 139.1 (C), 149.8 (C═O), 167.6 and 169.1 (C═N–C═O); EIMS: *m/z* (%): 346 (M^+, 26), 290 (100), 246 (13), 172 (78), 141 (24), 51 (44). *2-(2-Propoxy)-9-tert-butoxycarbonyl-1,3-thiazino[6,5-b]indol-4-one (**25c**)*. Yield 47%, colourless needles, mp 206–208°C (dichloromethane/hexane); (Found: C, 60.1; H, 5.7; N, 8.0. $C_{18}H_{20}N_2O_4S$ requires C, 59.98; H, 5.59; N, 7.77%); ν_{max} ($CHCl_3$) 1567 and 1647 (C═N–C═O), 1727 cm^{-1} (C═O); δ_H (300 MHz, $CDCl_3$) 1.45 (6H, d, J=6.1 Hz, 2×CH_3), 1.78 (9H, s, 3×CH_3), 5.75 (1H, septet, J=6.1 Hz, CH), 7.41–7.44 (2H, m, H_{arom}), 8.09–8.11 (1H, m, H_{arom}), 8.53–8.56 (1H, m, H_{arom}); δ_C (75 MHz, $CDCl_3$) 21.7 (CH_3), 28.2 (CH_3), 75.1 (CH), 87.7 (C), 108.3 (C), 114.6 (CH), 122.1 (CH), 124.8 (CH), 125.7 (CH), 127.0 (C), 136.0 (C), 139.3 (C), 149.7 (C═O), 167.7 and 168.7 (C═N–C═O); EIMS: *m/z* (%): 360 (M^+, 9), 304 (27), 262 (7), 260 (5), 218 (9), 175 (69), 146 (29), 120 (13), 102 (6), 57 (100), 41 (62).

4.1.13. *N'*-Methyl *N*-(1-tert-butoxycarbonyl-2-chloroindole-3-ylcarbonyl)thiourea (24d). To a stirred solution of isothiocyanate **23** (0.36 g, 1.07 mmol) in acetone (25 mL) cooled to 0°C was added 30% water solution of methylamine (0.144 g, 0.16 mL, 2.67 mmol), the mixture was stirred for 10 min at 0°C, then poured into 150 mL of water and set aside for 24 h at 3°C. The separated precipitate was filtered with suction, dried and crystallized. Yield 0.172 g (44%), white solid, mp 250–252°C (acetone/water); (Found: C, 52.6; H, 5.0; N, 11.5. $C_{16}H_{18}ClN_3O_3S$ requires C, 52.24; H, 4.93; N, 11.42%); ν_{max} ($CHCl_3$) 1658 and 1753 (C═O), 3260 and 3403 cm^{-1} (NH); δ_H (300 MHz, $CDCl_3$) 1.73 (9H, s, 3×CH_3), 3.28 (3H, d, *J*=4.8 Hz, CH_3), 7.29–7.43 (2H, m, H_{arom}), 8.04–8.13 (2H, m, H_{arom}), 9.53 (1H, s, NH), 10.68 (1H, s, NH); δ_C (75 MHz, $CDCl_3$) 28.1 (CH_3), 32.3 (CH_3), 87.1 (C), 111.4 (C), 114.8 (CH), 120.8 (CH), 124.7 (CH), 125.7 (C), 126.0 (CH), 126.3 (C), 135.0 (C), 147.9 and 162.3 (C═O), 180.8 (C═S); EIMS: *m/z* (%): 367 (M^+, 1), 332 (6), 276 (18), 232 (5), 177 (5), 114 (6), 77 (6), 57 (99), 41 (100).

4.1.14. Synthesis of thiazino[6,5-b]indol-4-one derivatives 25d–25f. To a solution of isothiocyanate **23** (1 mmol) in acetone (25 mL) cooled to 0°C was added 4-toluidine (**24e**, 0.107 g, 1 mmol) or piperidine (**24f**, 0.086 g, 0.1 mL, 1 mmol) and the mixture was stirred at 0°C for 15 min (**24e**) or 5 min (**24f**). Then triethylamine (0.203 g, 0.28 mL, 2 mmol) was added and stirring was continued for 75 min at reflux (**24e**) or for 2 h at room temperature (**24f**). In the case of thiourea **24d**, to a solution of **24d** (1 mmol) in acetone (25 mL) was added triethylamine (0.203 g, 0.28 mL, 2 mmol) and refluxed with stirring for 3 h with the formation of white precipitate. Thiazinoindoles **25d–25f** were isolated as follows: To the mixture containing precipitated **25d** was added water and mixture was set aside for 30 min at 3°C. The precipitate was filtered with suction, dried and crystallized. The solution containing thiazinoindole **25e** was concentrated to a half of its original volume, water (20 mL) was added and mixture set aside for 1 h at 3°C, formed precipitate filtered with suction, dried and crystallized. The mixture containing thiazinoindole **25f** was evaporated and the residue chromatographed on 30 g SiO_2, benzene/acetone (7:1). *2-Methylamino-9-tert-butoxycarbonyl-1,3-thiazino[6,5-b]indol-4-one (**25d**)*. Yield 70%, white solid, mp 290–292°C (methanol/water); (Found: C, 58.1; H, 5.3; N, 12.5. $C_{16}H_{17}N_3O_3S$ requires C, 57.99; H, 5.17; N, 12.68%); ν_{max} (KBr) 1607 and 1627 (C═N–C═O), 1703 cm^{-1} (C═O); δ_H (300 MHz, DMSO-d_6) 1.79 (9H, s, 3×CH_3), 3.03 (3H, s, CH_3), 7.20–7.58 (2H, m, H_{arom}), 8.39–8.18 (1H, m, H_{arom}), 8.18–8.50 (1H, m, H_{arom}), 8.92 (1H, s, NH); δ_C (75 MHz, DMSO-d_6) 27.8 (CH_3), 29.5 (CH_3), 87.4 (C), 106.3 (C), 114.8 (CH), 121.0 (CH), 124.4 (CH), 125.1 (CH), 127.1 (C), 135.1 (C), 137.5 (C), 149.4 (C═O), 161.1 and 167.2 (C═N–C═O); EIMS: *m/z* (%): 331 (M^+, 15), 275 (49), 231 (41), 172 (100), 141 (25), 113 (17), 50 (90), 41 (91). *2-(4-Tolylamino)-9-tert-butoxycarbonyl-1,3-thiazino[6,5-b]indol-4-one (**25e**)*. Yield 66%, white solid, mp 280–282°C (acetone/water); (Found: C, 65.1; H, 5.3; N, 10.5. $C_{22}H_{21}N_3O_3S$ requires C, 64.85; H, 5.19; N, 10.31%); ν_{max}($CHCl_3$) 1560 and 1620 (C═N–C═O), 1727 (C═O), 3433 cm^{-1} (NH); δ_H (300 MHz, $CDCl_3$) 1.66 (9H, s, 3×CH_3), 2.43 (3H, s, CH_3), 6.61 (1H, s, NH), 7.06 (2H, d, *J*=8.1 Hz, H_{arom}), 7.25 (2H, d, *J*=8.1 Hz, H_{arom}), 7.38–7.40 (2H, m, H_{arom}), 8.04–8.07 (1H, m, H_{arom}), 8.34–8.37 (1H, m, H_{arom}); δ_C (75 MHz, $CDCl_3$) 21.1 (CH_3), 28.0 (CH_3), 88.1 (C), 107.1 (C), 114.8 (CH), 121.4 (CH), 122.6 (CH), 125.1 (CH), 125.6 (CH), 126.5 (C), 130.6 (CH), 135.8 (C), 136.1 (C), 137.4 (C), 139.7 (C), 149.3 (C═O), 153.1 and 160.6 (C═N–C═O); EIMS: *m/z* (%): 407 (M^+, 4), 351 (5), 175 (6), 57 (10), 56 (38), 41 (100). *2-(1-Piperidyl)-9-tert-butoxycarbonyl-1,3-thiazino[6,5-b]indol-4-one (**25f**)*. Yield 68%, white solid, mp 310–312°C (dichloromethane/hexane); (Found: C, 62.6; H, 6.2; N, 11.0. $C_{20}H_{23}N_3O_3S$ requires C, 62.32; H, 6.01; N, 10.90%); ν_{max} ($CHCl_3$) 1555 and 1627 (C═N–C═O), 1720 cm^{-1} (C═O); δ_H (300 MHz, $CDCl_3$) 1.35–1.86 (6H, m, 3×CH_2), 1.76 (9H, s, 3×CH_3), 3.77–3.98 (4H, m, 2×CH_2), 7.34–7.41 2H, (m, H_{arom}), 8.0–8.03 (1H, m, H_{arom}), 8.55–8.58 (1H, m, H_{arom}); δ_C (75 MHz, $CDCl_3$) 24.5 (CH_2), 25.8 (CH_2), 28.2 (CH_3), 47.8 (CH_2), 87.1 (C), 107.4 (C), 114.5 (CH), 122.5 (CH), 124.6 (CH), 125.2 (CH), 127.4 (C), 135.5 (C), 137.3 (C), 150.3 (C═O), 160.6 and 168.0 (C═N–C═O); EIMS: *m/z* (%): 385 (M^+, 4), 341 (17), 285 (100), 172 (47), 141 (14), 50 (41), 41 (46).

4.1.15. Removal of the protecting Boc group. The protected thiazinoindoles **25a–25f** (0.5 mmol) were heated without solvent as follows: (**25a**, 170°C, 40 min); (**25b**, 170°C, 30 min); (**25c**, 160°C, 30 min); (**25d**, 185°C, 20 min); (**25e**, 160°C, 25 min); (**25f**, 155°C, 25 min) and after cooling to room temperature crystallized from an appropriate solvent, except for thiazinoindole **26c**, which was preadsorbed on silica gel and chromatographed on 15 g SiO_2, benzene/acetone (7:1). *2-Methoxy-1,3-thiazino[6,5-b]indol-4-one; Cyclobrassinon (**8**)*. Yield 70%, white solid, mp 221–223°C (methanol); (Found: C, 57.1; H, 3.6; N, 12.2. $C_{11}H_8N_2O_2S$ requires C, 56.88; H, 3.47; N, 12.06%); ν_{max} (KBr) 1567 and 1627 cm^{-1} (C═N–C═O); δ_H (300 MHz, DMSO-d_6) 4.18 (3H, s, OCH_3), 7.37–7.42 (2H, m, H-6, H-7), 7.66 (1H, d, *J*=7.5 Hz, H-5), 8.27 (1Hd, *J*=7.5 Hz, H-8), 12.69 (1H, s, NH); δ_C (75 MHz, DMSO-d_6) 57.6 (CH_3), 102.2 (C), 111.9 (CH), 120.4 (CH), 122.0 (CH), 124.0 (CH), 124.3 (C), 136.9 (C), 137.5 (C), 165.5 and 165.7 (C═N–C═O); EIMS: *m/z* (%): 232 (M^+, 45), 175 (100), 146 (23), 120 (33). *2-Ethoxy-1,3-thiazino[6,5-b]indol-4-one (**26b**)*. Yield 81%, white solid, mp 223–225°C (ethanol/water); (Found: C, 58.7; H, 4.3; N, 11.5. $C_{12}H_{10}N_2O_2S$ requires C, 58.52; H, 4.09; N, 11.37%); ν_{max} (KBr) 1567 and 1630 cm^{-1} (C═N–C═O); δ_H (300 MHz, DMSO-d_6) 1.48 (3H, t, *J*=7.0 Hz, CH_3), 4.67 (2H, q, *J*=7.0 Hz, CH_2), 7.37–7.43 (2H, m, H_{arom}), 7.65 (1H, d, *J*=7.7 Hz, H_{arom}), 8.27 (1H, d, *J*=7.7 Hz, H_{arom}), 12.68 (1H, s, NH); δ_C (75 MHz, DMSO-d_6) 14.1 (CH_3), 67.0 (CH_2), 102.2 (C), 111.9 (CH), 120.4 (CH), 122.0 (CH), 124.0 (CH), 124.3 (C), 136.8 (C), 137.6 (C), 164.8 and 165.8 (C═N–C═O); EIMS: *m/z* (%): 246 (M^+, 46), 172 (100), 141 (17), 113 (19). *2-(2-Propoxy)-1,3-thiazino[6,5-b]indol-4-one (**26c**)*. Yield 66%, white solid, mp 208–210°C (acetone/cyclohexane); (Found: C, 60.1; H, 4.7; N, 10.6. $C_{13}H_{12}N_2O_2S$ requires C, 59.98; H, 4.65; N, 10.76%); ν_{max}(KBr) 1554 and 1614 cm^{-1} (C═N–C═O); δ_H (300 MHz, DMSO-d_6) 1.49 (6H, d, *J*=6.2 Hz, 2×CH_3), 5.62 (1H, septet, *J*=6.2 Hz, CH), 7.36–7.42 (2H, m, H_{arom}), 7.65 (1H, d, *J*=7.5 Hz, H_{arom}), 8.26 (1H, d, *J*=7.5 Hz, H_{arom}), 12.68 (1H, s, NH); δ_C (75 MHz, DMSO-d_6) 21.5 (CH_3), 75.1 (CH), 102.1 (C), 111.9 (CH), 120.4 (CH), 122.0

(CH), 124.0 (CH), 124.3 (C), 136.8 (C), 137.7 (C), 164.3 and 165.9 (C=N–C=O); EIMS: *m/z* (%): 260 (M^+, 23), 175 (100), 146 (38), 120 (44), 103 (11), 43 (28). *2-Methylamino-1,3-thiazino[6,5-b]indol-4-one* (***26d***). Yield 72%, white solid, mp 290–292°C (methanol); (Found: C, 57.2; H, 4.0; N, 18.4. $C_{11}H_9N_3OS$ requires C, 57.13; H, 3.92; N, 18.17%); ν_{max} (KBr) 1540 and 1607 cm^{-1} (C=N–C=O); δ_H (300 MHz, DMSO-d_6) 3.03 (3H, s, CH_3), 7.26–7.35 (2H, m, H_{arom}), 7.56 (1H, d, J=7.0 Hz, H_{arom}), 8.23 (1H, d, J=7.0 Hz, H_{arom}), 8.74 (1H, s, NH), 12.36 (1H, s, NH); δ_C (75 MHz, DMSO-d_6) 29.6 (CH_3), 101.3 (C), 111.4 (CH), 120.3 (CH), 121.4 (CH), 123.0 (CH), 124.8 (C), 136.1 (C), 136.4 (C), 157.7 and 167.0 (C=N–C=O); EIMS: *m/z* (%): 231 (M^+, 58), 172 (100), 141 (22), 113 (27). *2-(4-Tolylamino)-1,3-thiazino[6,5-b]indol-4-one* (***26e***). Yield 81%, white solid, mp 282–284°C (acetone/cyclohexane); (Found: C, 66.7; H, 4.4; N, 13.5. $C_{17}H_{13}N_3OS$ requires C, 66.43; H, 4.26; N, 13.67%); ν_{max} (KBr) 1547 and 1607 cm^{-1} (C=N–C=O); δ_H (300 MHz, DMSO-d_6) 2.32 (3H, s, CH_3), 7.22 (1H, s, NH), 7.21–7.28 (6H, m, H_{arom}), 7. 47 (1H, d, J=8.3 Hz, H_{arom}), 8.07 (1H, d, J=8.3 Hz, H_{arom}), 12.27 (1H, s, NH); δ_C (75 MHz, DMSO-d_6) 20.7 (CH_3), 101.3 (C), 111.7 (CH), 120.0 (CH), 121.3 (CH), 121.9 (CH), 123.3 (CH), 124.9 (C), 130.0 (CH), 133.7 (C), 147.2 and 160.8 (C=N–C=O); EIMS: *m/z* (%): 307 (M^+, 96), 176 (100), 146 (52), 120 (93), 103 (18), 91 (30), 77 (22). *2-(1-Piperidyl)-1,3-thiazino[6,5-b]indol-4-one* (***26f***). Yield 77%, white solid, mp 320–322°C (methanol/water); (Found: C, 63.4; H, 5.4; N, 15.0. $C_{15}H_{15}N_3OS$ requires C, 63.13; H, 5.30; N, 14.73%); ν_{max} (KBr) 1547 and 1600 cm^{-1} (C=N–C=O); δ_H (300 MHz, DMSO-d_6) 1.68–1.77 (6H, m, 3×CH_2), 3.79–3.91 (4H, m, 2×CH_2), 7.26–7.27 (2H, m, H_{arom}), 7.58 (1H, d, J=7.5 Hz, H_{arom}), 8.24 (1H, d, J=7.5 Hz, H_{arom}), 12.54 (1H, s, NH); δ_C (75 MHz, DMSO-d_6) 24.1 (CH_2), 25.4 (CH_2), 47.5 (CH_2), 101.1 (C), 111.5 (CH), 120.5 (CH), 121.5 (CH), 123.3 (CH), 124.4 (C), 136.2 (C), 136.3 (C), 157.0 and 166.5 (C=N–C=O); EIMS: *m/z* (%): 285 (M^+, 56), 172 (100), 141 (22), 113 (27).

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