A Simple Stereoselective Synthesis of Aplysinopsin Analogs

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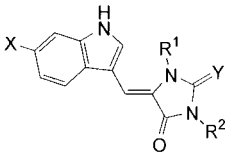
Simple and stereoselective syntheses of aplysinopsins and their analogs from either methyl 2-[(2,2-disubstituted ethenyl)amino]-3-(dimethylamino)prop-2-enoates **11** or 5-[(dimethylamino)methylidene]imidazolidine-2,4-diones **20** are described. The structures of products are established by ^{1}H- and ^{13}C-NMR, and NOESY spectroscopy, and X-ray crystal-structure analysis.

Introduction. – Recently, a series of alkyl 2-(acylamino)-3-(dimethylamino)prop-2-enoates and methyl 2-[(2,2-disubstituted ethenyl)amino]-3-(dimethylamino)prop-2-enoates, and related compounds have been prepared in our laboratory, which have been successfully employed for the preparation of various heterocyclic systems, including 2*H*-pyran-2-one and fused pyran-2-ones, fused pyridinones and pyrimidinones (for short reviews, see [1]; for recent reports, see [2]), polysubstituted pyrrole-2-carboxylates [3] and imidazole-4-carboxylates [4]. Here, we report on the application of these types of reagents for the synthesis of aplysinopsin-type compounds.

Aplysinopsin (**1**) has been isolated from the sponge *Aplysinopsis reticulata* of Australia's Great Barrier Reef [5] and *Verongia spengelii* [6]. Some other derivatives, such as 2′-demethylaplysinopsin (**2**), have been isolated from the marine sponge *Dercitus* sp. [7], 2′-demethyl-3′-methylaplysinopsin (**3**) and 3′-deimino-3′-oxoaplysinopsin (**4**) from the dendrophylliid coral *Tubastrea* sp. [8][9], and 3′-deimino-2′,4′-bis(demethyl)-3′-oxoaplysinopsin (**5**) from *Leptosammia pruvoti* [8], 6-bromoaplysinopsin derivatives **6**, **7**, and **8** from *Dendrophyllia* sp. [9], **9** from *Dercitus* [8], and **10** from *Leptosammia pruvoti* [8]. Some of these compounds display biological activities, such as specific cytotoxicity for cancer cells [6] and in affecting neurotransmission [10].



1 X=H, R^1=R^2= Me, Y=NH
2 X=H, R^1=H, R^2=Me, Y=NH
3 X=H, R^1=H, R^2= Me, Y=NMe
4 X=H, R^1=R^2= Me, Y=O
5 X=R^1=R^2=H, Y=O
6 X=Br, R^1=R^2= Me, Y=NH
7 X=Br, R^1=H, R^2=Me, Y=NH
8 X=Br, R^1=H, R^2=Me, Y=NMe
9 X=Br, R^1=R^2= Me, Y=O
10 X=Br, R^1=R^2=H, Y=O

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Synthetic approaches towards aplysinopsin-type structures involve base-catalyzed condensation of the 3-formylindole derivative with a five-membered ring containing an α-methylidene-carbonyl structural element, such as hydantoin, thiohydantoin, or creatinine derivatives [7–9][11]. However, poor yields, purification difficulties, and formation of mixtures of (*Z*)- and (*E*)-isomers are generally encountered in these procedures. These inconveniences have been circumvented by the introduction of a tandem *Staudinger*/aza-*Wittig* reaction, followed by electrocyclic ring closure [12]. In this context, the aplysinopsin skeleton has been prepared from iminophosphoranes, obtained from 3-formylindole in four steps, followed by the reaction with MeNCO to form the corresponding carbodiimide. This has been cyclized by treatment with nitrogen nucleophiles, such as ammonia, aliphatic amines, and hydrazines to give aplysinopsin derivatives [13]. In this context, a highly effective method for the synthesis of aza-carboline and aza-aplysinopsin mimic structures from heterocumulenes [14] and from alumina-supported heterocumulenes [15] have also been reported.

Results and Discussion. – Two methods for the preparation of aplysinopsin analogs with our recently described synthons were developed:

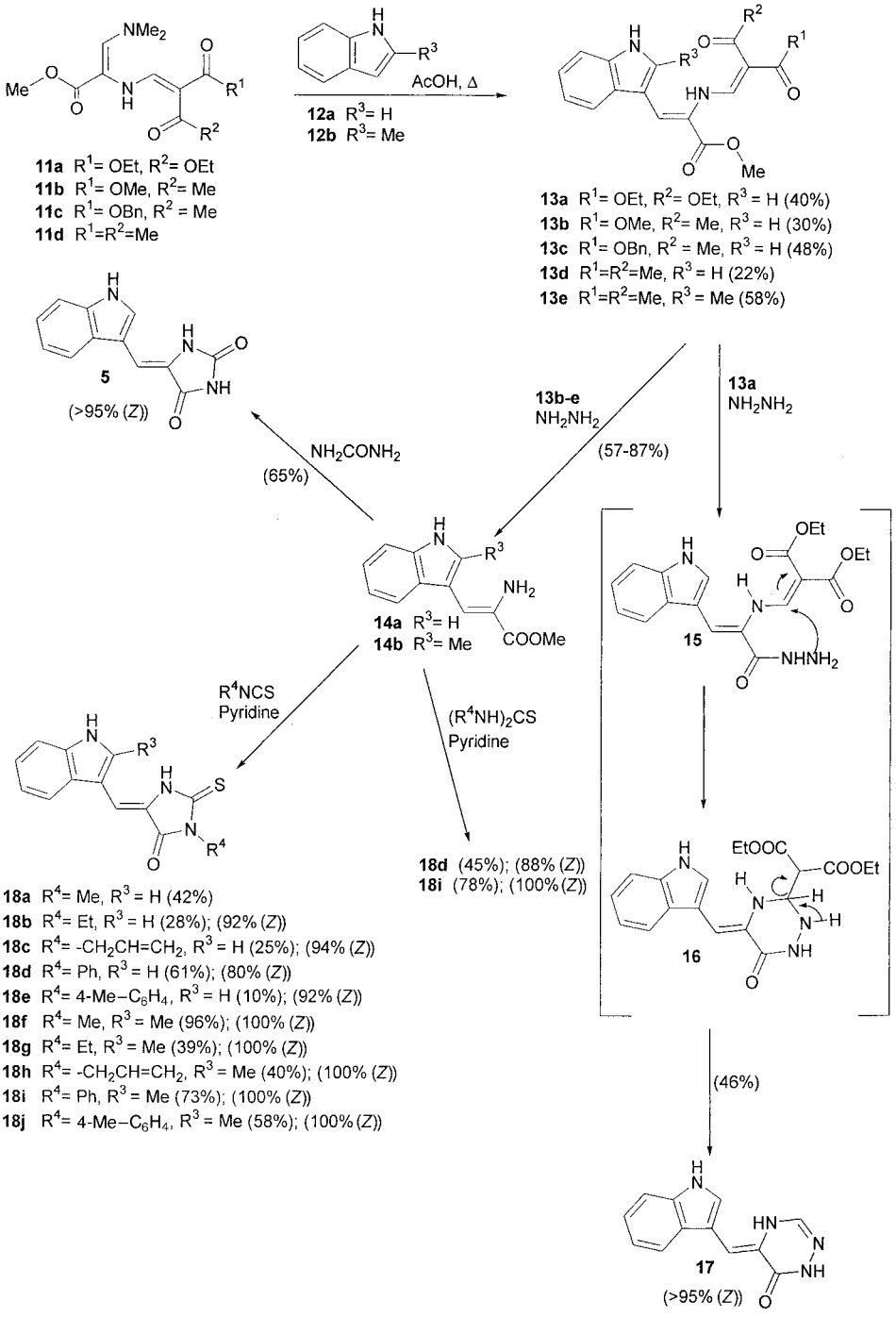
1) Reaction of methyl 2-[(2,2-disubstituted ethenyl)amino]-3-(dimethylamino)-prop-2-enoates **11a–d** with indole (**12a**) or 2-methyl-1*H*-indole (**12b**) led to substitution at C(3) of the indole skeleton to give 2-[(2,2-disubstituted ethenyl)amino]-3(1*H*-indol-3-yl)prop-2-enoates **13a–e**. The unsaturated side chain can be easily removed from the amino group by treatment with hydrazine to give methyl 2-amino-3-(1*H*-indol-3-yl)prop-2-enoates **14a**,**b** in 57–87% yield (*Scheme 1*).

Reaction of **13a** with hydrazine was an exception. In this case, the initially formed hydrazinocarbonyl derivative **15** cyclized to give compound **16**, which, after elimination of diethyl malonate, led to 1,4,5,6-tetrahydro-5-[(1*H*-indol-3-yl)methylidene]-6-oxo-1,2,4-triazine (**17**) in 46% yield (*Scheme 1*). By treatment of **14a** with urea, 3′-deimino-2′,4′-bis(demethyl)-3′-oxoaplysinopsin (**5**) was obtained in 65% yield. Compounds **14** were heated with isothiocyanates in pyridine for several hours to give thioaplysinopsin derivatives **18a–j** in 10–96% yield. Compounds **18d** and **18i** were also obtained from **14a** and **14b** by treatment with 1,3-diphenylthiourea in 45 and 78% yield, respectively (*Scheme 1*).

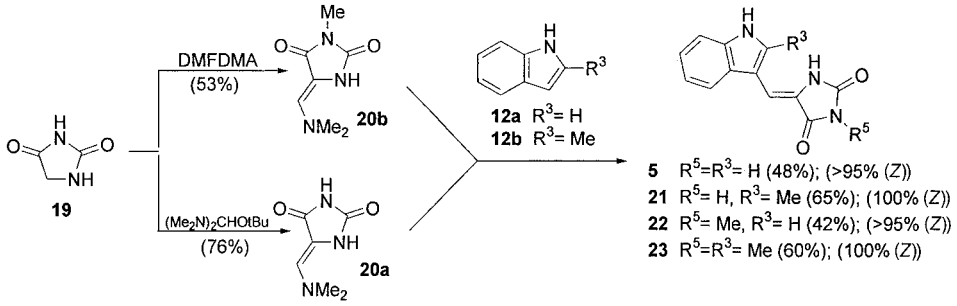
2) The second method is a two-step synthesis. In this case, hydantoin (**19**) is transformed with (*tert*-butoxy)bis(dimethylamino)methane (*Bredereck*'s reagent) into (*Z*)-5-[(dimethylamino)methylidene]imidazolidine-2,4-dione (**20a**) or with *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) into (*Z*)-5-[(dimethylamino)methylidene]-3-methylimidazolidine-2,4-dione (**20b**). The structure was confirmed with NOESY experiments. Compounds **20** react further with indole derivatives **12a** or **12b** to give aplysinopsin derivatives **5** and **21–23** in 42–65% yield (*Scheme 2*).

Structure. It has been demonstrated [8] that aplysinopsins with a Me group at N(2) exist as (*E*)-isomers due to steric repulsions between *H*–C(2′) and *Me*–N(2), whereas those unsubstituted at N(2) are (*Z*)-configured with gain of conjugation in the fully planar form. The differences between both forms are clearly visible from ^{1}H-NMR spectra, with the emphasis on the chemical shift of *H*–C(2′), which considerably depends on the configuration of the isomer; higher chemical shifts (8.7–9.2 ppm) for

Scheme 1


11a R1= OEt, R2= OEt
11b R1= OMe, R2= Me
11c R1= OBn, R2 = Me
11d R1=R2=Me
12a R3= H
12b R3= Me
AcOH, Δ
13a R1= OEt, R2= OEt, R3 = H (40%)
13b R1= OMe, R2= Me, R3 = H (30%)
13c R1= OBn, R2 = Me, R3 = H (48%)
13d R1=R2=Me, R3 = H (22%)
13e R1=R2=Me, R3 = Me (58%)
5
(>95% (Z))
NH2CONH2
(65%)
13b-e
NH2NH2
(57-87%)
13a
NH2NH2
14a R3= H
14b R3= Me
15
16
17
(46%)
(>95% (Z))
R4NCS
Pyridine
(R4NH)2CS
Pyridine
18a R4= Me, R3 = H (42%)
18b R4= Et, R3 = H (28%); (92% (Z))
18c R4= -CH2CH=CH2, R3 = H (25%); (94% (Z))
18d R4= Ph, R3 = H (61%); (80% (Z))
18e R4= 4-Me–C6H4, R3 = H (10%); (92% (Z))
18f R4= Me, R3 = Me (96%); (100% (Z))
18g R4= Et, R3 = Me (39%); (100% (Z))
18h R4= -CH2CH=CH2, R3 = Me (40%); (100% (Z))
18i R4= Ph, R3 = Me (73%); (100% (Z))
18j R4= 4-Me–C6H4, R3 = Me (58%); (100% (Z))
18d (45%); (88% (Z))
18i (78%); (100% (Z))

Scheme 2



the (*E*)-form, with *H*–C(2′) close to the C(4)=O group, and lower shifts (7.6–8.2 ppm) for the (*Z*)-form were observed.

NMR Data for compounds **5** and **22** ($\delta(H\text{–}C(2)) = 8.14$ and 8.15 ppm, resp.) indicate mainly the (*Z*)-form with traces of (*E*)-form. Based on the same conclusions, the configuration of triazinone derivative **17** was found to be (*Z*) ($\delta(H\text{–}C(2) = 7.79$ ppm).

In a similar manner, NMR spectra of thioaplysinopsins **18b**–**e** show signals for (*Z*)-*H*–C(2′) at 8.47–8.57 ppm, for (*E*)-*H*–C(2′) at 8.94–9.00 ppm, and for C*H*=C(5) in the 6.98–7.06 ppm range. They were isolated mostly in (*Z*)-form. An exception is compound **18a**, which exists as a 1:1 mixture of two isomers and cannot be unambiguously characterized on the basis of ^{1}H-NMR data.

On the other hand, thioaplysinopsins **18f**–**j** with a Me group attached at C(2′) of the indole skeleton show only one set of signals in ^{1}H-NMR. X-Ray analysis of **18f** shows the (*Z*)-configuration around the C=C bond with the imidazole ring twisted out of plane (torsion angle C(3′a)–C(3′)–(*C*H=C(5))–(*C*H$_3$–C(2′)) 31.9°) (*Fig.*). NOESY Experiments on compound **23** confirm (*Z*)-configuration and show interaction of *H*–N(2) with *H*–C(4′), as well as with protons of the Me group of the indole ring,

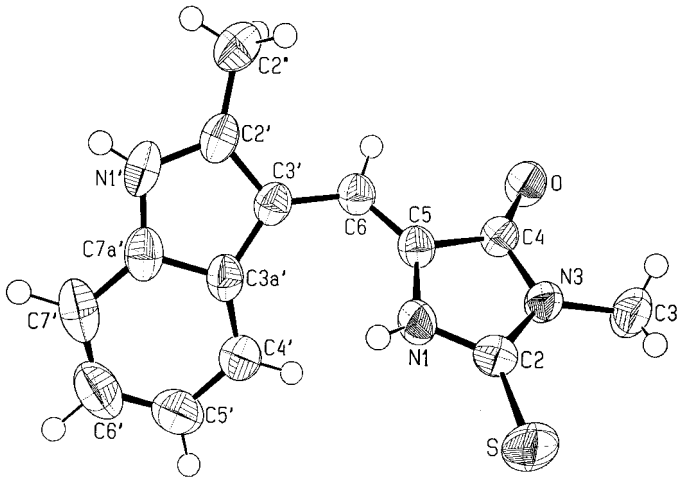


Figure. *ORTEP View of thioaplysinopsin* **18f**, *showing the labeling of non-H-atoms* (ellipsoids are rendered at 50% probability level)

indicating that the hydantoin moiety can freely rotate around the C(3′)–C(6) bond in DMSO solution.

Conclusion. – Two simple and efficient approaches towards the (*Z*)-aplysinopsin skeleton were developed. Both methods are stereoselective and can afford various types of (*Z*)-aplysinopsin analogs in moderate-to-good overall yields.

Experimental Part

General. M.p.: *Kofler* micro hot-stage. ^{1}H- and ^{13}C-NMR spectra: *Bruker Avance DPX 300* spectrometer, δ in ppm rel. to internal Me_4Si, recorded at 300 and 75 MHz, resp., *J* in Hz. MS: *AutoSpecQ* spectrometer. Elemental analyses for C, H, and N: *Perkin Elmer CHN Analyser 2400*.

Synthesis of the Starting Compounds. The following compounds were prepared according to the procedures described in the literature: *methyl 2-{[2,2-bis(ethoxycarbonyl)ethenyl]amino}-3-(dimethylamino)prop-2-enoate* (**11a**) [4], *methyl 2-{[2-acetyl-2-(methoxycarbonyl)ethenyl]amino}-3-(dimethylamino)prop-2-enoate* (**11b**) [2a], *methyl 2-{[2-acetyl-2-(benzyloxycarbonyl)ethenyl]amino}-3-(dimethylamino)prop-2-enoate* (**11c**) [2a], and *methyl 2-{[2,2-bis(acetyl)ethenyl]amino}-3-(dimethylamino)propenoate* (**11d**) [16].

*General Procedure for the Synthesis of Alkyl 2-[(2,2-Disubstituted ethenyl)amino}-3-(1*H*-indol-3-yl)prop-2-enoates.* A mixture of indole **12** (0.0225 mol) and starting prop-2-enoate **22** (0.0225 mol) in glacial AcOH (30–40 ml) was heated in an oil bath at 80–90° for several h. The solvent was evaporated *in vacuo*, and EtOH was added for the crystallization. Compounds were purified by crystallization from an appropriate solvent.

*Methyl 2-{[2,2-Bis(ethoxycarbonyl)ethenyl]amino}-3-(1*H*-indol-3-yl)prop-2-enoate* (**13a**). Prepared from **11a** and **12a**; 4 h; yield 40%. M.p. 170–172° (EtOH). ^{1}H-NMR ((D$_6$)DMSO): 1.14 (*t*, *J* = 7.1, *Me*CH$_2$OCO); 1.26 (*t*, *J* = 7.1, *Me*CH$_2$OCO); 3.82 (*s*, COOMe); 4.04 (*q*, *J* = 7.1, MeC*H*$_2$OCO); 4.20 (*q*, *J* = 7.1, MeC*H*$_2$OCO); 7.12 (*ddd*, *J* = 7.5, 7.9, 1.1, H–C(5), H–C(6)); 7.47 (*d*, *J* = 7.9, H–C(7)); 7.68 (*s*, –CH=); 7.75 (*d*, *J* = 7.5, H–C(4)); 7.88 (*s*, H–C(2)); 8.19 (*d*, *J* = 12.8, C*H*NH); 10.21 (*d*, *J* = 12.8, CHN*H*); 11.95 (*s*, NH(indole)). Anal. calc. for $C_{20}H_{22}N_2O_6$ (386.40): C 62.17, H 5.74, N 7.25; found: C 62.04, H 5.81, N 7.33.

*Methyl 2-{[2-Acetyl-2-(methoxycarbonyl)ethenyl]amino}-3-(1*H*-indol-3-yl)prop-2-enoate* (**13b**). Prepared from **11b** and **12a**; 5 h; yield 30%. M.p. 218–220° (DMF/i-PrOH). ^{1}H-NMR ((D$_6$)DMSO): 2.45 (*s*, Ac); 3.62 (*s*, COOMe); 3.83 (*s*, 3 H, COOMe); 7.13–7.25 (*ddd*, *J* = 7.5, 1.1, H–C(5), H–C(6)); 7.48 (*d*, *J* = 7.5, H–C(7)); 7.70 (*s*, –CH=); 7.75 (*d*, *J* = 7.5, H–C(4)); 7.97 (*s*, H–C(2)); 8.38 (*d*, *J* = 12.4, C*H*NH); 11.98 (*s*, NH(indole)); 12.22 (*d*, *J* = 12.4, CHN*H*). Anal. calc. for $C_{18}H_{18}N_2O_5$ (342.35): C 63.14, H 5.30, N 8.17; found: C 63.02, H 5.53, N 8.38.

*Methyl 2-{[2-Acetyl-2-(benzyloxycarbonyl)ethenyl]amino}-3-(1*H*-indol-3-yl)prop-2-enoate* (**13c**). Prepared from **11c** and **12a**; 8–10 h; yield 48%. M.p. 183–185° (EtOH). ^{1}H-NMR ((D$_6$)DMSO): 2.45 (*s*, Ac); 3.81 (*s*, COOMe); 5.13 (*s*, PhC*H*$_2$); 7.13–7.26 (*ddd*, *J* = 7.9, 1.1, H–C(5), H–C(6)); 7.48 (*d*, *J* = 7.9, H–C(7)); 7.69 (*s*, –CH=); 7.74 (*d*, *J* = 7.9, H–C(4)); 7.98 (*s*, H–C(2)); 8.46 (*d*, *J* = 11.7, C*H*NH); 11.08 (*s*, NH(indole)); 12.24 (*d*, *J* = 11.7, CHN*H*). Anal. calc. for $C_{24}H_{22}N_2O_5$ (418.45): C 68.89, H 5.30, N 6.70; found: C 68.60, H 5.52, N 6.73.

*Methyl 2-{[2,2-Bis(acetyl)ethenyl]amino}-3-(1*H*-indol-3-yl)prop-2-enoate* (**13d**). Prepared from **11d** and **12a**; 3 h; yield 22%. M.p. 201–203° (EtOH). ^{1}H-NMR ((D$_6$)DMSO): 2.10 (*s*, Ac); 2.42 (*s*, Ac); 3.85 (*s*, COOMe); 7.13–7.26 (*ddd*, *J* = 7.9, 1.1, H–C(5), H–C(6)); 7.49 (*d*, *J* = 7.9, H–C(7)); 7.69 (*s*, –CH=); 7.75 (*d*, *J* = 7.9, H–C(4)); 7.98 (*s*, H–C(2)); 8.40 (*d*, *J* = 10.6, C*H*NH); 11.97 (*s*, NH(indole)); 12.12 (*d*, *J* = 10.6, CHN*H*); MS 326 ($M^{+\bullet}$). Anal. calc. for $C_{18}H_{18}N_2O_4$ (326.35): C 66.26, H 5.52, N 8.59; found: C 65.74, H 5.74, N 8.44.

*Methyl 2-{[2,2-Bis(acetyl)ethenyl]amino}-3-(2-methyl-1*H*-indol-3-yl)prop-2-enoate* (**13e**). Prepared from **11d** and **12b**; 3 h; yield 58%. M.p. 254–255° (EtOH). ^{1}H-NMR ((D$_6$)DMSO): 1.56 (*s*, Me–C(2)); 2.33 (*s*, Ac); 2.45 (*s*, Ac); 3.85 (*s*, COOMe); 6.91–7.11 (*ddd*, *J* = 8.3, 1.1, H–C(5), H–C(6)); 7.25 (*d*, *J* = 8.3, H–C(7)); 7.33 (*d*, *J* = 8.3, H–C(4)); 7.84 (*s*, –CH=); 8.06 (*d*, *J* = 13.0, C*H*NH); 11.73 (*s*, NH(indole)); 12.00 (*d*, *J* = 13.0, CHN*H*). MS: 340 ($M^{+\bullet}$). Anal. calc. for $C_{19}H_{20}N_2O_4$ (340.38): C 67.04; H 5.92; N 8.23; found: C 66.99; H 5.84; N 8.58.

Reactions of **13** *with* $NH_2NH_2 \cdot H_2O$. *3-[(1,2,4,6-Tetrahydro-6-oxo-triazin-5-ylidene)methyl]-1*H*-indole* (**17**). To a suspension of **13a** (222 mg, 0.6 mmol) in EtOH (5 ml); 99% $N_2H_4 \cdot H_2O$ (6 mmol) was added, and the mixture was heated under reflux. MeCN was added to the boiling suspension until a clear soln. was obtained,

which was then heated under reflux for 2 h. After cooling, **17** was isolated as a precipitate in 46% yield (> 95% (*Z*)). M.p. 273–277°. ^{1}H-NMR ((D$_6$)DMSO): 6.51 (*s*, –CH=); 6.96–7.18 (*ddd*, *J* = 7.9, 7.5, 1.1, H–C(5), H–C(6), H–C(3′)); 7.61 (*d*, *J* = 7.5, H–C(4)); 7.79 (*d*, *J* = 2.3, H–C(2)); 9.02 (*s*, H–N(4′)); 10.65 (*s*, H–N(1′)); 11.46 (*d*, *J* = 2.3, NH(indole)). MS: 226 ($M^{+\bullet}$). Anal. calc. for $C_{12}H_{10}N_4O$ (226.24): C 63.22, H 4.66, N 24.94; found: C 63.61, H 4.46, N 24.75.

*Methyl 2-Amino-3-(1*H*-indol-3-yl)prop-2-enoate* (**14a**). To a suspension of **13b** (8.90 g, 26 mmol) in EtOH (10 ml); 4 × molar excess of 99% $N_2H_4 \cdot H_2O$ (105 mmol) was added, and the mixture was heated under reflux with dropwise addition of EtOH until a clear soln. was obtained, which was then heated under reflux for 20 min to 2 h. Volatile components were evaporated *in vacuo*. Then, EtOH (3–5 ml) was added to the oily residue, and conc. HCl (5–6 drops) was added to the soln. The hydrochloride was filtered off and suspended in H_2O (5 ml), the precipitate was collected by filtration and recrystallized from EtOH to give **14a** in 76% yield. Essentially the same procedure was applied to prepare **14a** from **13c** in 57 yield, and from **13d** in 87% yield. M.p. 173–175°. ^{1}H-NMR ((D$_6$)DMSO): 3.78 (*s*, COOMe); 4.59 (*s*, NH$_2$); 6.68 (*s*, –CH=); 7.04–7.17 (*ddd*, *J* = 7.5, 7.9, 1.1, H–C(5), H–C(6)); 7.39 (*d*, *J* = 7.5, H–C(7)); 7.64 (*d*, *J* = 7.9, H–C(4)); 7.77 (*d*, *J* = 2.3, H–C(2)); 11.41 (*d*, *J* = 2.3, NH(indole)). MS: 216 ($M^{+\bullet}$). Anal. calc. for $C_{12}H_{12}N_2O_2$ (216.24): C 66.65, H 5.59, N 12.96; found: C 66.36, H 5.78, N 12.97.

*Methyl 2-Amino-3-(2-methyl-1*H*-indol-3-yl)prop-2-enoate* (**14b**). To a suspension of **13e** (8.76 g, 26 mmol) in EtOH (10 ml); 4 × molar excess of 99% $N_2H_4 \cdot H_2O$ (105 mmol) was added, and the mixture was heated under reflux with dropwise addition of EtOH until clear soln. was obtained, which was then heated under reflux for 20 min. Volatile components were evaporated *in vacuo* to one-half of the initial volume. The precipitate was collected by filtration and recrystallized from EtOH to give **14b** in 39% yield. M.p. 138–140°. ^{1}H-NMR ((D$_6$)DMSO): 2.34 (*s*, Me–C(2)); 3.78 (*s*, COOMe); 4.20 (*s*, NH$_2$); 6.54 (*s*, –CH=); 6.95–7.07 (*ddd*, *J* = 7.9, 1.1, H–C(5), H–C(6)); 7.29 (*d*, *J* = 7.9, H–C(7)); 7.45 (*d*, *J* = 7.9, H–C(4)); 11.17 (*s*, NH(indole)). MS: 230 ($M^{+\bullet}$). Anal. calc. for $C_{13}H_{14}N_2O_2$ (230.27): C 67.81, H 6.13, N 12.16; found: C 67.96, H 6.18, N 12.45.

Synthesis of 5-[(Dimethylamino)methylidene]imidazolidine-2,4-diones **20**. *5-[(Z)-(Dimethylamino)methylidene]imidazolidine-2,4-dione* (**20a**). To a suspension of hydantoin (**19**; 1785 mg, 17.85 mmol) in MeCN (5 ml), (*tert*-butoxy)bis(dimethylamino)methane (4.2 ml, 21.42 mmol (1.2 × molar excess)) was added. The mixture was refluxed for 1.5 h, then cooled to form precipitate, which was collected by filtration to give **20a** in 76% yield. M.p. 273–276° (MeCN). ^{1}H-NMR ((D$_6$)DMSO): 2.96 (*s*, Me$_2$N); 6.41 (*s*, –CH=); 9.27 (*s*, NH); 10.22 (*s*, NH). ^{13}C-NMR ((D$_6$)DMSO): 42.5; 103.4; 129.1; 155.3; 166.3. Anal. calc. for $C_6H_9N_3O_2$ (155.16): C 46.45, H 5.83, N 27.08; found: C 46.11, H 5.72, N 26.99.

5-[(Z)-(Dimethylamino)methylidene]-3-methylimidazolidine-2,4-dione (**20b**). To a suspension of **19** (2331 mg, 23.31 mmol) in MeCN (5 ml), DMF-DMA (8.7 ml, 58.3 mmol (2.5 × molar excess)) was added. The mixture was refluxed for 5 h, then cooled to form a precipitate, which was collected by filtration to give **20b** in 53% yield. M.p. 228–232° (MeCN). ^{1}H-NMR ((D$_6$)DMSO): 2.85 (*s*, MeN); 2.98 (*s*, Me$_2$N); 6.56 (*s*, –CH=); 9.60 (*s*, NH). ^{13}C-NMR ((D$_6$)DMSO): 23.8; 41.8; 101.2; 129.0; 154.1; 164.1. MS: 169 ($M^{+\bullet}$). Anal. calc. for $C_7H_{11}N_3O_2$ (169.18): C 49.70, H 6.55, N 24.84; found: C 49.45, H 6.46, N 24.81.

Synthesis of Aplysinopsins. General Procedure. A mixture of indole derivative **12** (2 mmol) and **20** (2 mmol) in AcOH (4 ml) was heated under reflux for several h. Then, MeOH (1 ml) was added, and the mixture was left at r.t. to form a precipitate, which was collected by filtration, washed with MeOH, and recrystallized from an appropriate solvent.

3′-Deimino-2′,4′-bis(demethyl)-3′-oxoaplysinopsin (= *5-[(1*H*-Indol-3-yl)methylidene]imidazolidine-2,4-dione*; **5**). Prepared from **20a** and *indole* (**12a**); 6 h; 48% (> 95% (*Z*)). M.p. > 300° (DMF/MeCN) ([8]: > 300° (dec)). ^{1}H-NMR ((D$_6$)DMSO): 6.78 (*s*, –CH=); 7.11–7.23 (*ddd*, *J* = 7.9, 7.5, 1.1, H–C(5), H–C(6)); 7.44 (*d*, *J* = 7.9, H–C(7)); 7.77 (*d*, *J* = 7.5, H–C(4)); 8.14 (*d*,, *J* = 2.7, H–C(2)); 10.11 (*s*, NH); 11.03 (*s*, NH); 11.80 (*d*, *J* = 2.7, NH(indole)). ^{13}C-NMR ((D$_6$)DMSO): 102.8; 109.5; 112.7; 118.9; 121.0; 123.2; 123.8; 127.7; 127.8; 136.7; 156.1; 165.3. MS: 227 ($M^{+\bullet}$). This compound was also prepared in the following manner: a mixture of **14a** (225 mg, 1 mmol) and urea (60 mg, 1 mmol) was heated in DMF (5 ml) at reflux for 2 h. Volatile components were evaporated *in vacuo*, the EtOH (5 ml) was added for crystallization. The precipitate was collected by filtration and recrystallized from MeOH to give **5** in 65% yield (> 95% (*Z*)).

3′-Deimino-2′,4′-bis(demethyl)-2-methyl-3′-oxoaplysinopsin (= *5-[(2-Methyl-1*H*-indol-3-yl)methylidene]-imidazolidine-2,4-dione*; **21**). Prepared from **20a** and *2-methylindole* (**12b**); 5 h; 65% (100% (*Z*)). M.p. 295–305° (AcOH). ^{1}H-NMR ((D$_6$)DMSO): 2.41 (*s*, Me–C(2)); 6.64 (*s*, –CH=); 7.03–7.13 (*ddd*, *J* = 6.6, 6.8, 1.5, H–C(5), H–C(6)); 7.32 (*dd*, *J* = 6.6, 1.5, H–C(7)); 7.48 (*dd*, *J* = 6.8, 1.5, H–C(4)); 9.69 (*s*, NH); 11.00 (*s*, NH); 11.41 (*s*, NH(indole)). ^{13}C-NMR ((D$_6$)DMSO): 12.7; 104.0; 105.7; 111.0; 118.9; 119.7; 121.2; 126.4; 127.0; 135.7; 137.4; 155.3; 165.4. Anal. calc. for $C_{13}H_{11}N_3O_2$ (241.25): C 64.72, H 4.60, N 17.42; found: C 64.81, H 4.87, N 17.49.

3′-Deimino-2′-demethyl-3′-oxoaplysinopsin (*=5-[(1*H*-Indol-3-yl)methylidene]-3-methylimidazolidine-2,4-dione*; **22**). Prepared from **20b** and **12a**; 7 h; 42% (>95% (*Z*)). M.p. 305° (dec., AcOH). ^{1}H-NMR ((D$_6$)DMSO): 2.98 (*s*, MeN); 6.87 (*s*, –CH=); 7.11–7.22 (*ddd*, *J* = 7.5, 7.9, 1.5, H–C(5), H–C(6)); 7.43 (*dd*, *J* = 7.5, 1.5, H–C(7)); 7.78 (*d*, *J* = 7.9, H–C(4)); 8.15 (*d*, *J* = 2.6, H–C(2)); 10.31 (*s*, NH); 11.82 (*s*, *J* = 2.6, NH(indole)). ^{13}C-NMR ((D$_6$)DMSO): 25.0; 103.7; 109.2; 112.8; 118.9; 121.1; 123.2; 124.5; 127.6; 127.8; 136.7; 155.8; 164.9. Anal. calc. for $C_{13}H_{11}N_3O_2$ (241.25): C 64.72, H 4.60, N 17.42; found: C 64.41, H 4.65, N 17.52.

3′-Deimino-2′-demethyl-2-methyl-3′-oxoaplysinopsin (*=5-[(2-Methyl-1*H*-indol-3-yl)methylidene]-3-methylimidazolidine-2,4-dione*; **23**). Prepared from **20b** and **12b**; 5 h; 60% (100% (*Z*)). M.p. 242–244° (AcOH/MeOH). ^{1}H-NMR ((D$_6$)DMSO): 2.41 (*s*, Me–C(2)); 2.96 (*s*, MeN); 6.74 (*s*, –CH=); 7.01–7.12 (*ddd*, *J* = 6.8, 1.1, H–C(5), H–C(6)); 7.31 (*dd*, *J* = 6.8, 1.1, H–C(7)); 7.49 (*d*, *J* = 6.8, H–C(4)); 9.91 (*s*, NH); 11.44 (*s*, NH(indole)). ^{13}C-NMR ((D$_6$)DMSO): 12.6; 24.1; 104.9; 105.5; 110.9; 118.9; 119.6; 121.2; 125.2; 126.9; 135.7; 137.5; 154.9; 163.9. Anal. calc. for $C_{14}H_{13}N_3O_2$ (255.28): C 65.87, H 5.13, N 16.46; found: C 65.67, H 5.11, N 16.61.

Synthesis of Thioaplysinopsins. General Procedure. Compound **14** (107.6 mg, 0.5 mmol) was suspended in pyridine (2 ml, dried over KOH), and the appropriate isothiocyanate (0.75 mmol) was added. The mixture was heated under reflux for several h, then volatile components were evaporated *in vacuo*, and the oily residue was treated with an appropriate solvent to form a precipitate, which was collected by filtration and recrystallized.

3′-Deimino-2′-demethyl-3′-thioxoaplysinopsin (*=5-[(1*H*-Indol-3-yl)methylidene]-3-methyl-2-thioxoimidazolidin-4-one*; **18a**). Prepared from MeNCS and **14a**; 3 h; 42% (50% (*Z*)). M.p. 265–267° (EtOH). ^{1}H-NMR ((D$_6$)DMSO): 3.22 (*s*, MeN); 6.98 (*s*, –CH=); 7.15–7.26 (*ddd*, *J* = 7.9, 7.5, 1.1, H–C(5), H–C(6)); 7.48, 7.83 (*dd*, *J* = 7.9, 1.1, H–C(7)); 7.94, 7.97 (*dd*, *J* = 7.5, 1.1, H–C(4)); 8.85, 8.87 (*d*, *J* = 2.6, H–C(2)); 12.01 (*s*, NH); 12.10 (*s*, *J* = 2.6, NH(indole)). MS: 257 ($M^{+\cdot}$). Anal. calc. for $C_{13}H_{11}N_3OS$ (257.31): C 60.68, H 4.31, N 16.33; found: C 60.34, H 4.33, N 15.94.

3′-Deimino-2′,4′-bis(demethyl)-4′-ethyl-3′-thioxoaplysinopsin (*=5-[(1*H*-Indol-3-yl)methylidene]-3-ethyl-2-thioxoimidazolidin-4-one*; **18b**). Prepared from EtNCS and **14a**; 8.5 h; 28% (92% (*Z*)). M.p. 245–247° (EtOH). ^{1}H-NMR ((D$_6$)DMSO): 1.16 (*t*, *J* = 7.2, *Me*CH$_2$N); 3.83 (*q*, *J* = 7.2, MeC*H*$_2$N); 6.98 (*s*, 0.92 H, –CH=); 7.11 (*s*, 0.08 H, –CH=); 7.12–7.26 (*ddd*, *J* = 7.2, 1.0, H–C(5), H–C(6)); 7.47 (*dd*, *J* = 7.2, 1.0, H–C(7)); 7.81 (*dd*, *J* = 7.2, 1.0, H–C(4)); 8.47 (*d*, 0.92 H, *J* = 2.6, H–C(2)); 9.00 (*d*, 0.08 H, *J* = 2.6, H–C(2)); 11.99 (*s*, NH); 12.05 (*s*, 0.92 H, NH(indole)); 12.14 (*s*, 0.08 H, NH(indole)). MS: 271 ($M^{+\cdot}$). Anal. calc. for $C_{14}H_{13}N_3OS$ (271.34): C 61.97, H 4.82, N 15.49; found: C 62.44, H 4.80, N 15.02.

4′-Allyl-3′-deimino-2′,4′-bis(demethyl)-3′-thioxoaplysinopsin (*=3-Allyl-5-[(1*H*-indol-3-yl)methylidene]-2-thioxoimidazolidin-4-one*; **18c**). Prepared from allyl isothiocyanate and **14a**; 3 h; 25% (94% (*Z*)). M.p. 194–195° (prisms) and 232–234° (needles) (MeOH). ^{1}H-NMR ((D$_6$)DMSO): 4.43 (*d*, *J* = 5.3, CH$_2$=CHC*H*$_2$); 5.07–5.13 (*dd*, *J* = 17.1, C*H*$_2$=CH–CH$_2$)); 5.13–5.17 (*dd*, *J* = 10.3, 1 H, C*H*$_2$=CH–CH$_2$); 5.81–5.93 (*ddt*, *J* = 10.3, 17.1, CH$_2$=C*H*–CH$_2$); 6.98 (*s*, –CH=); 7.14–7.26 (*ddd*, *J* = 7.5, 7.2, 1.1, H–C(5), H–C(6)); 7.47 (*dd*, *J* = 7.2, H–C(7)); 7.84 (*dd*, *J* = 7.5, H–C(4)); 8.52 (*d*, *J* = 2.6, 0.94 H, H–C(2)); 8.99 (*d*, *J* = 2.6, 0.06 H, H–C(2)); 11.98 (*s*, NH); 12.07 (*s*, NH(indole)). MS: 283 ($M^{+\cdot}$). Anal. calc. for $C_{15}H_{13}N_3OS$ (283.35): C 63.58, H 4.62, N 14.83; found: C 63.43, H 4.56, N 14.79.

3′-Deimino-2′,4′-bis(demethyl)-4′-phenyl-3′-thioxoaplysinopsin (*=5-[(1*H*-Indol-3-yl)methylidene]-3-phenyl-2-thioxoimidazolidin-4-one*; **18d**). Prepared from PhNCS and **14a**; 10 h; 61% (80% (*Z*)). M.p. 284–285° (EtOH). ^{1}H-NMR ((D$_6$)DMSO): 7.04 (*s*, –CH=); 7.16–7.56 (*m*, *J* = 8.7, 7.2, 1.1, H–C(5), H–C(6), 5 arom. H; 7.73 (*dd*, *J* = 7.2, H–C(7)); 7.86 (*dd*, *J* = 8.7, H–C(4)); 8.57 (*d*, *J* = 2.6, 0.8 H, H–C(2)); 8.95 (*d*, *J* = 2.6, 0.2 H, H–C(2)); 11.99 (*s*, 0.2 H, NH); 12.10 (*s*, 0.8 H, NH); 12.24 (*s*, 0.8 H, NH(indole)); 12.41 (*s*, 0.2 H, NH(indole)). MS: 319 ($M^{+\cdot}$). Anal. calc. for $C_{18}H_{13}N_3OS$ (319.38): C 67.69, H 4.10, N 13.16; found: C 67.59, H 4.06, N 13.15. This compound was prepared also in the following manner: the mixture of **14a** (0.4 mmol) and *N*,*N*′-diphenylthiourea (0.4 mmol) in pyridine (1 ml) was heated under reflux for 2.5 h. Volatile components were evaporated *in vacuo*, and EtOH (1 ml) was added for the crystallization. The precipitate was collected by filtration to give **18d** in 45% yield (88% (*Z*)).

3′-Deimino-2′,4′-bis(demethyl)-4′-(4-methylphenyl)-3′-thioxoaplysinopsin (*=5-[(1*H*-Indol-3-yl)methylidene]-3-(4-methylphenyl)-2-thioxoimidazolidin-4-one*; **18e**). Prepared from 4-methylphenyl isothiocyanate and **14a**; 6.5 h; 10% (92% (*Z*)). M.p. 294–296° (EtOH). ^{1}H-NMR ((D$_6$)DMSO): 2.39 (*s*, 4-*Me*–C$_6$H$_4$); 7.02 (*s*, –CH=); 7.20–7.32 (*m*, *J* = 8.3, 1.1, H–C(5), H–C(6), 4 arom. H); 7.50 (*m*, *J* = 9.0, 1.1, H–C(7)); 7.71 (*dd*, *J* = 9.0, 1.1, H–C(4)); 8.57 (*d*, *J* = 2.6, 0.08 H, H–C(2)); 8.94 (*d*, *J* = 2.6, 0.92 H, H–C(2)); 11.96 (*s*, 0.92 H, NH); 12.09 (*s*, 0.08 H, NH); 12.20 (*s*, 0.08 H, NH(indole)); 12.37 (*s*, 0.92 H, NH(indole)). MS: 333 ($M^{+\cdot}$). Anal. calc. for $C_{19}H_{15}N_3OS$ (333.41): C 68.45, H 4.53, N 12.60; found: C 68.20, H 4.69, N 12.39.

3′-Deimino-2′-demethyl-2-methyl-3′-thioxoaplysinopsin (*=3-Methyl-5-[(2-methyl-1*H*-indol-3-yl)methylidene]-2-thioxoimidazolidin-4-one*; **18f**). Prepared from MeNCS and **14b**; 4 h; 96% (100% (*Z*)). M.p.

242–244° (EtOH). ^{1}H-NMR ((D$_6$)DMSO): 2.46 (*s*, Me–C(2)); 3.21 (*s*, MeN); 6.89 (*s*, –CH=); 7.06–7.16 (*ddd*, *J* = 6.9, 6.4, 1.1, H–C(5), H–C(6)); 7.34 (*dd*, *J* = 6.4, 1.1, H–C(7)); 7.54 (*d*, *J* = 6.9, H–C(4)); 11.65 (*s*, NH); 11.70 (*s*, NH(indole)). MS: 271 ($M^{+\bullet}$). Anal. calc. for $C_{14}H_{13}N_3OS$ (271.34): C 61.97, H 4.83, N 15.49; found: C 61.91, H 4.98, N 15.62.

3′-Deimino-2′,4′-bis(demethyl)-4′-ethyl-2-methyl-3′-thioxoaplysinopsin (= *3-Ethyl-5-[(2-Methyl-1*H*-indol-3-yl)methylidene]-2-thioxoimidazolidin-4-one*; **18g**). Prepared from EtNCS and **14b**; 3 h; 39% (100% (*Z*)). M.p. 184–185° (EtOH). ^{1}H-NMR ((D$_6$)DMSO): 1.21 (*t*, *J* = 6.8, *Me*EtN); 3.28 (*s*, Me–C(2)); 3.84 (*q*, *J* = 6.8, MeC*H*$_2$N); 6.87 (*s*, –CH=); 7.06–7.16 (*ddd*, *J* = 6.8, 6.4, 1.5, H–C(5), H–C(6)); 7.34 (*dd*, *J* = 6.4, 1.5, H–C(7)); 7.55 (*d*, *J* = 6.8, H–C(4)); 11.65 (br. *s*, NH, NH(indole)). MS: 285 ($M^{+\bullet}$). Anal. calc. for $C_{15}H_{15}N_3OS$ (285.36): C 63.09, H 5.29, N 14.78; found: C 63.38, H 5.32, N 14.56.

4′-Allyl-3′-deimino-2′,4′-bis(demethyl)-2-methyl-3′-thioxoaplysinopsin (= *3-Allyl-5-[(2-methyl-1*H*-indol-3-yl)methylidene]-2-thioxoimidazolidin-4-one*; **18h**). Prepared from allyl isothiocyanate and **14b**; 4 h; 40% (100% (*Z*)). M.p. 168–170° (purified by column chromatography with mixture of AcOEt/hexane 2:1). ^{1}H-NMR ((D$_6$)DMSO): 2.49 (*s*, Me–C(2)); 4.42 (*d*, *J* = 5.3, CH$_2$=CHC*H*$_2$); 5.09–5.18 (2*dd*, *J* = 10.3, 17.1, C*H*$_2$=CHCH$_2$); 5.81–5.94 (*m*, CH$_2$=C*H*–CH$_2$); 6.89 (*s*, –CH=); 7.07–7.16 (*m*, *J* = 7.2, 6.4, 1.5, H–C(5), H–C(6)); 7.34 (*dd*, *J* = 6.4, 1.5, H–C(7)); 7.55 (*dd*, *J* = 7.2, 1.5, H–C(4)); 11.67 (*s*, NH); 11.77 (*s*, NH(indole)). MS: 297 ($M^{+\bullet}$). Anal. calc. for $C_{16}H_{15}N_3OS$ (297.37): C 65.46, H 5.08, N 14.13; found: C 64.39, H 4.83, N 14.20.

3′-Deimino-2′,4′-bis(demethyl)-2-methyl-4′-phenyl-3′-thioxoaplysinopsin (= *5-[(2-Methyl-1*H*-indol-3-yl)-methylidene]-3-phenyl-2-thioxoimidazolidin-4-one*; **18i**). Prepared from PhNCS and **14b**; 4 h; 73% (100% (*Z*)). M.p. 272–274° (EtOH). ^{1}H-NMR ((D$_6$)DMSO): 3.30 (*s*, Me–C(2)); 6.93 (*s*, –CH=); 7.09–7.18 (*m*, *J* = 6.4, 1.1, H–C(5), H–C(6)); 7.33–7.55 (*m*, H–C(7), 5 arom. H); 7.62 (*dd*, *J* = 6.4, H–C(4)); 11.69 (*s*, NH); 11.95 (*s*, NH(indole)). MS: 333 ($M^{+\bullet}$). Anal. calc. for $C_{19}H_{15}N_3OS$ (333.41): C 68.45, H 4.53, N 12.60; found: C 68.78, H 4.53, N 12.85. This compound was prepared also in the following manner: the mixture of **14b** (0.4 mmol) and *N*,*N*′-diphenylthiourea (0.4 mmol) in pyridine (2 ml) was heated under reflux for 3.5 h. Volatile components were evaporated *in vacuo*, and EtOH (3 ml) was added for the crystallization. The precipitate was collected by filtration to give **18i** in 78% yield (100% (*Z*)).

3′-Deimino-2′,4′-bis(demethyl)-4′-(4-methylphenyl)-2-methyl-3′-thioxoaplysinopsin (= *5-[(2-Methyl-1*H*-indol-3-yl)methylidene]-3-(4-methylphenyl)-2-thioxoimidazolidin-4-one*; **18j**). This compound was prepared from 4-methylphenyl isothiocyanate and **14b**; 3.5 h; 58% (100%, (*Z*)). M.p. 192–194° (EtOH). ^{1}H-NMR ((D$_6$)DMSO): 2.38 (*s*, 4-Me–C$_6$H$_4$); 3.30 (*s*, Me–C(2)); 6.92 (*s*, –CH=); 7.09–7.17 (*ddd*, *J* = 6.8, 7.2, 1.5, H–C(5), H–C(6)); 7.25–7.38 (*m*, H–C(7), 4 arom. H); 7.60 (*d*, *J* = 6.8, H–C(4)); 11.68 (*s*, NH); 11.92 (*s*, NH(indole)). MS: 347 ($M^{+\bullet}$). Anal. calc. for $C_{20}H_{17}N_3OS \cdot 0.5H_2O$ (347.43): C 67.39, H 5.09, N 11.79; found: C 67.52, H 5.51, N 11.57.

Crystal-Structure Determination of **18f** (*Table*)[3]). The structure was solved by direct methods using the SIR92 program [17]. The positions of H-atoms were obtained from an intermediate difference *Fourier* map. Full-matrix least-squares refinement on F_o was employed with an empirical weighting scheme. H-Atom positions with their isotropic displacement parameters and non-H-atoms with their anisotropic displacement parameters were refined. In the final cycle were 3189 contributing reflections (including those unobserved reflections for which F_c was greater than F_o) and 211 parameters. The final R and R_w values were 0.040 and 0.043, resp. Average and maximum shift to e.s.d. ratios were 0.0008 and 0.02, resp. The Xtal3.4 [18] system of crystallographic programs was used for the correlation and reduction of data, structure refinement, and interpretation. ORTEPIII [19] was used to produce molecular graphics.

The authors would like to express their gratitude to the *Ministry of Science and Technology*, Slovenia, for financial support of this investigation.

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[3]) Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-144000. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

Table. *Crystallographic Data for* **18f**

Crystal data	
Chemical formula	$C_{14}H_{13}N_3OS$
Chemical formula weight [g mol^{-1}]	271.343
Cell setting	orthorhombic
Space group	*Pbca*
a [Å]	9.279(1)
b [Å]	12.997(1)
c [Å]	23.959(3)
V [Å^3]	2667.1(1)
Z	8
Calc. density [Mg m^{-3}]	1.351
Radiation type	MoK_α
Wavelength	0.71069
No. of refl. for cell parameters	75
θ Range(°)	8.0 – 14.6
μ [mm^{-1}]	2.266
Temp. [K]	293(1)
Crystal form	prism
Crystal size (mm)	$0.038 \times 0.49 \times 0.65$
Crystal color	pale yellow
Data collection	
Diffractometer	*Enraf Nonius CAD-4 diffractometer*
Data collection method	$\omega/2\theta$ scans
Absorbtion correction	none
No. of measured refl.	27973
No. of independent refl.	3629
No. of observed refl.	2034
Criterion of observed refl.	$I > 2.5\sigma(I)$
R_{int}	0.0176
θ_{max} [°]	28
Range of *h*, *k*, *l*	$-12 \rightarrow h \rightarrow 12$ $-15 \rightarrow k \rightarrow 15$ $-31 \rightarrow l \rightarrow 31$
No. of standard refl.	3
Frequency of standard refl.	every 20000 s of scanning time
Intensity decay [%]	2.77

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Received May 9, 2000