Synthesis and Transformations of Ethyl 3-Formyl-1*H*-indole-2-carboxylate. Preparation of Aplysinopsin and β-Carboline Thiohydantoin Analogues*

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Z. Naturforsch. **61b,** 413 – 419 (2006); received January 6, 2006

Various aplysinopsin and β-carboline thiohydantoin analogues were prepared starting from ethyl 3-formyl-1*H*-indole-2-carboxylate by condensation with the active methylene group of 2-thiohydantoin, rhodanine, or thiobarbituric acid derivatives.

Key words: Aplysinopsin Analogues, β-Carbolines, Thiohydantoins

Introduction

Recently, a series of alkyl 2-substituted 3-(dimethylamino)prop-2-enoates and related enaminones have been prepared as versatile reagents for the preparation of various dehydroalanine derivatives, heterocyclic systems, and natural product analogues. In extension, chiral cyclic enamino lactams and lactones, derived from α-amino acids and (+)-camphor have been used in the synthesis of functionalised heterocycles, such as heteroarylalanines, heteroarylalaninols, heteroarylpropanediols, 3-heteroaryl-(+)-camphors, and heterocyclic compounds with an α-amino acid or a dipeptide structural element incorporated into the ring system [1, 2]. Recently, alkyl 2-substituted 3-(dimethylamino)prop-2-enoates and related enaminones have been employed in combinatorial synthesis of heterocycles and *N*-acyldehydroalanine esters [3] and in the synthesis of natural product analogues, such as aplysinopsins [4], meridianins [5], and dipodazines [6].

3-(Dimethylamino)prop-2-enoates and their chiral analogues are usually prepared by treatment of a suitably functionalised methylene compound with formamide acetal, *e.g.* with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) or with *tert*-butoxybis(dimethylamino)methane (Bredereck's reagent) [1].

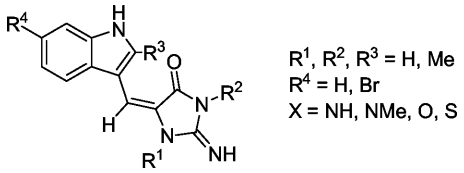


Fig. 1. Naturally occurring aplysinopsins.

Aplysinopsins (Fig. 1) were first isolated from the sponge genus *Thorecta* of the Australian Great Barrier Reef [7, 8] and others [9 – 12]. Their significant biological activities caused an increased interest in aplysinopsin-type alkaloids. Some of them are active as a specific cytotoxin of cancer cells and affect neurotransmission [8]. Several synthetic approaches towards aplysinopsin-type structures have been reported. However, poor yields, purification difficulties and formation of *Z* and *E* isomers are generally encountered in these procedures [11 – 14]. These inconveniences have been circumvented by the Staudinger aza/Wittig reaction followed by electrocyclic ring closure [15 – 19]. Recently, two novel and stereoselective synthetic approaches towards aplysinopsins have been developed: a) a three-step synthesis from alkyl 3-dimethylamino-2-[(2,2-disubstituted 1-vinyl)amino]propenoates [4a] and, b) a one-step synthesis from 5-[(dimethylamino)methylidene]hydantoin derivatives and analogues [4b, e]. In this manner, aplysinopsins, thioaplysinopsins, and analogues, in which the hydantoin moiety is re-

* Presented in part at the 7th Conference on Iminium Salts (ImSaT-7), Bartholomä/Ostalbkreis, September 6 – 8, 2005.

placed with 1,4,5,6-tetrahydro-1,2,4-(1*H*,4*H*)-triazin-6-one and 2,4,6-(1*H*,3*H*,5*H*)-pyrimidinetrione, have been prepared [4f].

Ethyl β-carboline-3-carboxylate derived from indole derivatives was shown to bind with high affinity to the so-called benzodiazepine receptors in the central nervous system [20]. The above considerations might become an important basis for the design of ethyl β-carboline-3-carboxylate-like compounds in the quest of new biologically active molecules [21 – 24].

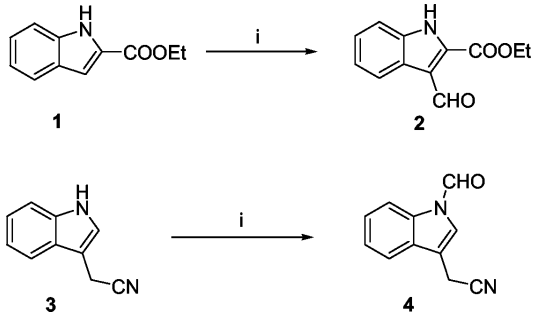
However, the aplysinopsins and derivatives of analogous systems could not be prepared from indole derivatives bearing electron withdrawing groups, such as an ethoxycarbonyl group attached at 2-position of the indole nucleus, by our enaminone methodology reported previously [1a, c, f].

Therefore, we developed a new method, as an extension of our work in this field. We now report an alternative synthesis in relation to our enaminone methodology *via* condensation of ethyl 3-formyl-1*H*-indole-2-carboxylate with a suitable nucleophile, such as 2-hydantoin, rhodanine, or barbituric acid derivative. Aplysinopsin and thioaplysinopsin analogues, and β-carboline derivatives were thus prepared starting from 3-formyl-1*H*- (**12**) and ethyl 3-formyl-1-*H*-2-carboxylate (**2**).

Results and Discussion

Ethyl 3-formyl-1*H*-indol-2-carboxylate (**2**) was prepared by formylation of ethyl indole-2-carboxylate (**1**) by $POCl_3$ in dimethyl formamide (Scheme 1) [25, 26]. Formylation of indole-2-acetonitrile (**3**) under the same reaction conditions produced 4-formyl-1*H*-indol-2-acetonitrile **3** (Fig. 2).

β-Carboline thiohydantoin derivatives (Scheme 2) were prepared by condensation of the activated methylene group of the 2-thiohydantoin derivative **5** and the formyl group of ethyl 3-formyl-1*H*-indol-2-carboxylate (**2**). Thioaplysinopsin derivatives **6a**–**f** were formed as intermediates. Simultaneously, cyclocondensation between the hydantoin thioamide NH group and the ester group of the indole nucleus occurred in acetic acid/NaOAc under reflux, forming the final products **7a**–**f**. The orange-coloured solids, that eventually precipitated from the reaction mixture, were highly insoluble. The precipitates were purified by washing with water, absolute ethanol and diethyl ether.



Scheme 1. Reagents and conditions: (i) NaOAc/AcOH, reflux.

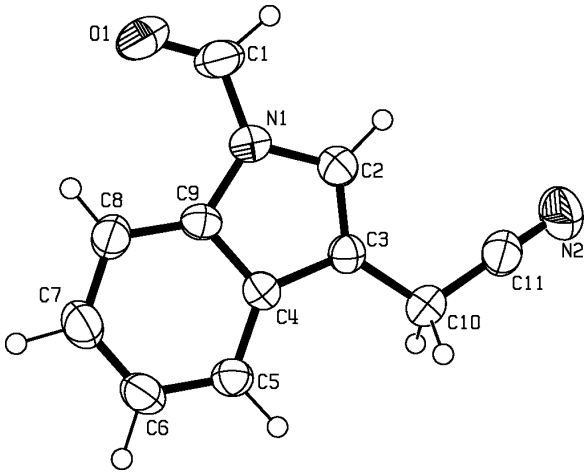


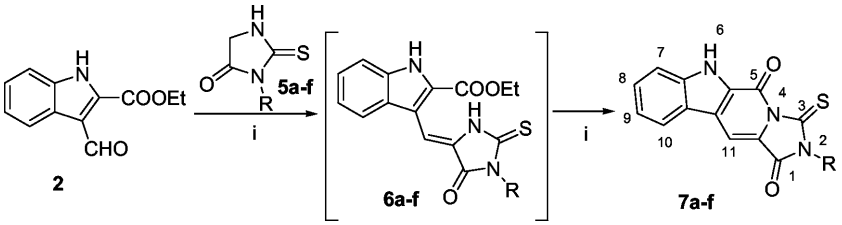
Fig. 2. ORTEP view of the asymmetric unit of compound **4** with labeling of non-hydrogen atoms. Ellipsoids are drawn at 50% probability level.

Aplysinopsin-like products **9** and **11** were isolated when the condensation reaction was carried out with substituted rhodanines **8** or thiobarbituric acid (**10**) (Scheme 3).

Ethyl 3-formyl-1*H*-indole-2-carboxylate (**2**) and indole-3-carboxaldehyde (**12**) were also used in the formation of azomethine imines. 5,5-Dimethylamino-3-pyrazolidinone reacted with both of them in anhydrous ethanol in the presence of catalytic amounts of trifluoroacetic acid. The (*Z*)-configuration at the C=N double bond was confirmed by the NOESY spectrum of compound **15**, which showed interactions among the methylidene proton and the two methyl groups (Scheme 4).

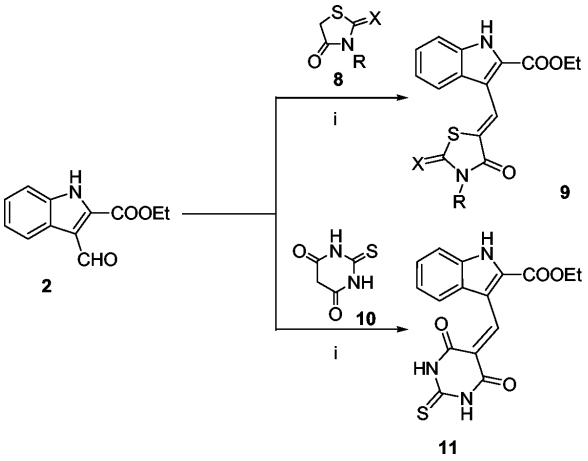
Structure Determination

Structures of novel compounds were confirmed by IR, ^{1}H, and ^{13}C NMR methods, and by elemental analyses for C, H, and N. The (*Z*)-configuration of



Compound	R	Reaction time (h)	Yield [%]
5a, 6a, 7a	H	5	74
5b, 6b, 7b	Et	5	49
5c, 6c, 7c	CH_2Ph	7	65
5d, 6d, 7d	Ph	4	52
5e, 6e, 7e	4-Me-C_6H_4	8	20
5f, 6f, 7f	3,4-Cl-C_6H_4	6	36

Scheme 2. Reagents and conditions: (i) NaOAc/AcOH, reflux.



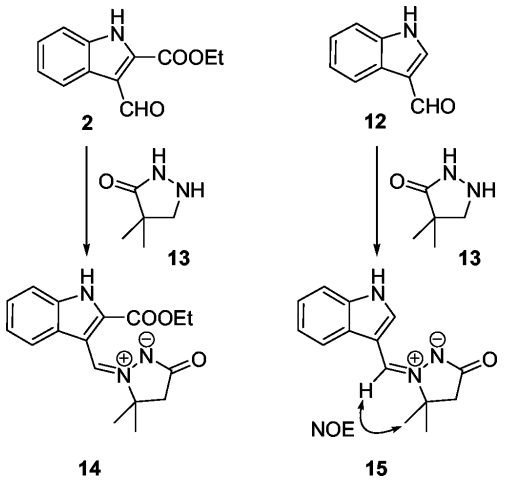
Compound	R	X	Reaction time (h)	Yield [%]
9**a**	H	S	8	60
9**b**	Ph	S	5	85
9**c**	H	NH	8.5	67
11			1	69

Scheme 3. Reagents and conditions: (i) NaOAc/AcOH, reflux.

compound **15** was confirmed by a NOESY NMR experiment, and the structure of compound **4** was established by X-ray crystal structure analysis. In favor of the (*Z*)-configuration of intermediates **6a**–**f** speaks also the cyclization into the corresponding β-carboline derivatives **7a**–**f**, which takes place under relatively mild reaction conditions.

Conclusion

Various aplysinopsin analogues with an ester group attached at 2-position of the indole and β-carboline ring system were prepared in fair yields by condensation of ethyl 3-formyl-1*H*-indole-2-carboxylate with heterocyclic active methylene compounds **5**, **8**, and **10**.



Scheme 4. Reagents and conditions: (i) EtOH, TFA, r.t.

This method represents an extension to our enaminone methodology reported previously, according to which only at 2-position unsubstituted or alkyl- or aryl- substituted derivatives can be used.

Experimental Section

Melting points were taken on a Kofler micro hot stage. The ^{1}H NMR spectra were obtained on a Bruker Avance DPX 300 (300 MHz) spectrometer in [D_6]-DMSO or $CDCl_3$ as solvent with TMS as the internal standard. MS spectra were recorded on an AutoSpecQ spectrometer, IR spectra on a Perkin-Elmer 1310 infrared spectrophotometer and elemental analyses for *C*, *H* and *N* on a Perkin-Elmer CHN Analyser 2400.

Procedure for the preparation of ethyl 3-formyl-1H-indole-2-carboxylate and (1-formyl-1H-indol-3-yl)acetonitrile (**2**, **4**)

Compounds **1a,c** (0.050 mol) were dissolved in 20 ml of *N*,*N*-dimethylformamide (DMF) and dropwise added to

a mixture of $POCl_3$ (5 ml, 0.55 mol) and DMF (16 g, 0.22 mol), and the mixture was stirred at room temperature for 1 h. The reaction mixture was then poured on crushed ice and aqueous NaOH solution (50 ml, 4.8 M) was slowly added. The reaction mixture had to remain acidic until approximately three quarters of the prepared NaOH solution was added. The last quarter was added instantaneously. The solution was brought to boiling and then cooled to room temperature. A white precipitate was collected by filtration and washed with water to give **2** or **4**.

Ethyl 3-formyl-1H-indole-2-carboxylate (**2**)

This compound was prepared from compound **1a** (9.45 g, 0.050 mol), 1 h, 91% yield (9.87 g). – M. p. 185 – 186 °C (from ethanol). – IR (KBr): $\nu = 1723, 1635, 1576, 1533$ cm^{-1}. – ^{1}H NMR ([D$_6$]-DMSO): $\delta = 1.41$ (t, 3H, $J = 7.1$ Hz, CH_3), 4.47 (q, 2H, $J = 7.1$ Hz, CH_2), 7.30 (ddd, 1H, $J = 1.1$, 6.8, 7.9 Hz, 5'-H), 7.40 (ddd, 1H, $J = 1.1$, 6.8, 8.3 Hz, 6'-H), 7.58 (dd, 1H, $J = 1.1$, 8.3 Hz, 7'-H), 8.26 (dd, 1H, $J = 1.1$, 7.9 Hz, 4'-H), 10.62 (s, 1H, CHO), 12.80 (s, 1H, NH). – ^{13}C NMR ([D$_6$]-DMSO): $\delta = 114.0$, 119.3, 123.2, 124.3, 125.6, 126.7, 133.5, 136.6, 161.0, 188.4. – MS (EI): $m/z = 217$ (M$^+$); HRMS: calcd. 217.0739; found 217.0744. – $C_{12}H_{11}NO_3$ (217.22): calcd. C 66.35, H 5.10, N 6.45; found C 66.07, H 5.32, N 6.52.

(1-Formyl-1H-indol-3-yl)acetonitrile (**4**)

This compound was prepared from compound **1c** (7.8 g, 0.050 mol), 2 h, 33% yield (3.03 g). – M. p. 125 – 126 °C (from ethanol). – IR (KBr): $\nu = 3106, 2255, 1699, 1612$ cm^{-1}. – ^{1}H NMR ([D$_6$]-DMSO): $\delta = 4.16$ (s, 2H, CH_2), 7.39 (ddd, 1H, $J = 1.5$, 6.8, 7.2 Hz, 5'-H), 7.43 (ddd, 1H, $J = 1.5$, 6.8, 7.2 Hz, 6'-H), 7.70 (dd, 1H, $J = 1.5$, 6.8 Hz, 7'-H), 7.85 (s, 1H, 2'-H), 8.25 (dd, 1H, $J = 1.5$, 6.8 Hz, 4'-H), 9.33 (s, 1H, CHO). – MS (EI): $m/z = 184$ (M$^+$), 185 (MH$^+$); HRMS: calcd. 184.0637; found 184.0642. – $C_{11}H_8N_2O$ (184.20): calcd. C 71.73, H 4.38, N 15.21; found C 71.51, H 4.69, N 15.13.

General procedure for the preparation of aplysinopsin and β-carboline thiohydantoin analogues (**7a** – **f**, **9a** – **c**, **11**)

Compound **2** (1 mmol) and the nucleophile **5a** – **f**, **8**, **10** were dissolved in a mixture of of acetic acid (10 ml) and sodium acetate (0.2 g), and the mixture was heated under reflux for 1 – 8.5 h. The solution was concentrated *in vacuo*, the precipitate was collected by filtration, and washed with water, ethanol and diethyl ether to give **7a** – **f**, **9a** – **c**, and **11**.

1,5-Dioxo-2,3,5,6-tetrahydro-1H-imidazo[1',5':1,6]pyrido[3,4-b]indole-3(2H)-thione (**7a**)

This compound was prepared from compound **2** (0.22 g, 0.001 mol) and 2-thiohydantoin (**5a**) (0.12 g, 0.001 mol), 5 h, 74% yield (0.20 g). – M. p. 343 – 345 °C. – IR (KBr): $\nu = 1720, 1664, 1614, 1510, 1490$ cm^{-1}. – ^{1}H NMR ([D$_6$]-DMSO): $\delta = 7.32$ (ddd, 1H, $J = 0.8$, 7.2, 7.9 Hz, 5'-H), 7.51 (ddd, 1H, $J = 1.1$, 7.2, 8.3 Hz, 6'-H), 7.61 (dd, 1H, $J = 0.8$, 8.3 Hz, 7'-H), 8.03 (s, 1H, 3-H), 8.24 (dd, 1H, $J = 1.1$, 7.9 Hz, 4'-H), 12.95 (s, 1H, NH), 13.13 (s, 1H, NH). – ^{13}C NMR ([D$_6$]-DMSO): $\delta = 105.4$, 114.1, 121.4, 122.6, 122.7, 123.8, 126.1, 128.3, 132.0, 140.6, 152.6, 162.6, 176.2. – MS (EI): $m/z = 269$ (M$^+$). – $C_{20}H_{13}N_3O_2S$ (359.41): calcd. C 66.84, H 3.65, N 11.69; found C 67.07, H 3.71, N 11.48.

2-Ethyl-1,5-dioxo-2,3,5,6-tetrahydro-1H-imidazo-[1',5':1,6]pyrido[3,4-b]indole-3(2H)-thione (**7b**)

This compound was prepared from compound **2** (0.22 g, 0.001 mol) and 3-ethyl-2-thiohydantoin (**5b**) (0.14 g, 0.001 mol), 5 h, 49% yield (0.15 g). – M. p. 275 – 277 °C. – IR (KBr): $\nu = 1731, 1665, 1619, 1573, 1512, 1490$ cm^{-1}. – ^{1}H NMR ([D$_6$]-DMSO): $\delta = 1.22$ (t, 3H, $J = 6.8$ Hz, CH_3), 3.95 (q, 2H, $J = 6.8$ Hz, CH_2), 7.33 (ddd, 1H, $J = 1.1$, 7.7, 8.3 Hz, 5'-H), 7.51 (ddd, 1H, $J = 1.1$, 7.7, 8.3 Hz, 6'-H), 7.62 (dd, 1H, $J = 1.1$, 8.3 Hz, 7'-H), 8.16 (s, 1H, 3-H), 8.25 (dd, 1H, $J = 1.1$, 8.3 Hz, 4-H), 12.99 (s, 1H, NH). – MS (EI): $m/z = 297$ (M$^+$). – $C_{15}H_{11}N_3O_2S$ (297.34): calcd. C 60.59, H 3.73, N 14.13; found C 60.92, H 3.86, N 14.44.

2-Benzyl-1,5-dioxo-2,3,5,6-tetrahydro-1H-imidazo-[1',5':1,6]pyrido[3,4-b]indole-3(2H)-thione (**7c**)

This compound was prepared from compound **2** (0.22 g, 0.001 mol) and 3-benzyl-2-thiohydantoin (**5c**) (0.21 g, 0.001 mol), 7 h, 65% yield (0.23 g). – M. p. > 350 °C. – IR (KBr): $\nu = 3232, 1738, 1673, 1618, 1514, 1504$ cm^{-1}. – ^{1}H NMR ([D$_6$]-DMSO): $\delta = 5.14$ (s, 2H, CH_2), 7.27 – 7.40 (m, 6H, Ph, 5'-H), 7.52 (ddd, 1H, $J = 1.1$, 7.2, 8.3 Hz, 6'-H), 7.62 (dd, 1H, $J = 1.1$, 8.3 Hz, 7'-H), 8.22 (s, 1H, 3-H), 8.27 (dd, 1H, $J = 0.8$, 8.38 Hz, 4'-H), 13.04 (s, 1H, NH). – MS (EI): $m/z = 359$ (M$^+$); HRMS calcd. 359.0728, found 359.0738. – $C_{20}H_{13}N_3O_2S$ (359.41): calcd. C 66.84, H 3.65, N 11.69; found C 67.07, H 3.71, N 11.48.

2-Phenyl-1,5-dioxo-2,3,5,6-tetrahydro-1H-imidazo–[1',5':1,6]pyrido[3,4-b]indole-3(2H)-thione (**7d**)

This compound was prepared from compound **2** (0.22 g, 0.001 mol) and 3-phenyl-2-thiohydantoin (**5d**) (0.19 g, 0.001 mol), 4 h, 52% yield (0.18 g). – M. p. > 350 °C. – IR (KBr): $\nu = 1738, 1673, 1617, 1502$ cm^{-1}. – ^{1}H NMR ([D$_6$]-DMSO): $\delta = 7.35$ (ddd, 1H, $J = 1.1$, 6.8, 7.2 Hz, 5'-H), 7.44 – 7.61 (m, 6H, Ph, 6'-H), 7.64 (dd, 1H, $J = 1.1$, 8.3 Hz, 7'-H), 8.26 (s, 1H, 3-H), 8.30 (dd, 1H, $J = 1.1$, 6.8 Hz, 4'-H), 13.06 (s, 1H, NH). – MS (EI): $m/z = 345$ (M$^+$). – $C_{19}H_{11}N_3O_2S$ (345.38): calcd. C 66.08, H 3.21, N 12.17; found C 66.34, H 3.32, N 12.42.

2-(4-Methylphenyl)-1,5-dioxo-2,3,5,6-tetrahydro-1H-imidazo[1',5':1,6]pyrido-[3,4-b]indole-3(2H)-thione (**7e**)

This compound was prepared from compound **2** (0.22 g, 0.001 mol) and 3-(4-methylphenyl)-2-thiohydantoin (**5e**) (0.21 g, 0.001 mol), 8 h, 20% yield (0.07 g). – M. p. > 350 °C. – IR (KBr): ν = 1720, 1709, 1670, 1629, 1575, 1518 cm^{-1}. – MS (EI): m/z = 359 (M$^+$); HRMS: calcd 359.0728, found 359.0740. – $C_{20}H_{13}N_3O_2S$ (359.41): calcd. C 66.84, H 3.65, N 11.69; found C 66.75, H 3.66, N 11.55.

2-(3,4-Dichlorophenyl)-1,5-dioxo-2,3,5,6-tetrahydro-1H-imidazo[1',5':1,6]-pyrido[3,4-b]indole-3(2H)-thione (**7f**)

This compound was prepared from compound **2** (0.22 g, 0.001 mol) and 3-(3,4-dichlorophenyl)-2-thiohydantoin (**5f**) (0.14 g, 0.001 mol), 6 h, 36% yield (0.15 g). – M. p. > 350 °C. – IR (KBr): ν = 1736, 1673, 1614, 1575, 1502, 1474 cm^{-1}. – MS (EI): m/z = 413 (M$^+$); HRMS calcd. 412.9792, found 412.9806. – $C_{19}H_9N_3O_2SCl_2\times1/3H_2O$ (414.27): calcd. C 54.30, H 2.32, N 10.00; found C 54.47, H 2.59, N 9.78.

Ethyl 3-[(Z)-(4-oxo-2-thioxothiazolidin-5-yliden)methyl]-1H-indole-2-carboxylate (**9a**)

This compound was prepared from compound **2** (0.22 g, 0.001 mol) and rhodanine (**8a**) (0.13 g, 0.001 mol), 8 h, 60% yield (0.20 g). – M. p. 293 – 295 °C (EtOH). – IR (KBr): ν = 3312, 1682, 1599, 1572 cm^{-1}. – ^{1}H NMR ([D$_6$]-DMSO): δ = 1.38 (t, 3H, J = 7.1 Hz, CH$_3$), 4.43 (q, 2H, J = 7.1 Hz, CH$_2$), 7.29 (ddd, 1H, J = 1.1, 7.2, 8.3 Hz, 5'-H), 7.41 (ddd, 1H, J = 1.1, 7.2, 8.3 Hz, 6'-H), 7.58 (dd, 1H, J = 1.1, 8.3 Hz, 7'-H), 7.81 (dd, 1H, J = 1.1, 8.3 Hz, 4'-H), 8.35 (s, 1H, 2-H), 12.69 (s, 1H, NH), 13.69 (s, 1H, NH). – ^{13}C NMR ([D6]-DMSO): δ = 15.0, 62.2, 114.4, 115.4, 122.3, 122.5, 124.6, 126.4, 126.6, 128.0, 128.4, 137.4, 161.3, 169.9, 196.0. – MS (EI): m/z = 332 (M$^+$)M; HRMS calcd. 332.0289; found 332.0298.

Ethyl 3-[(Z)-(4-oxo-3-phenyl-2-thioxothiazolidin-5-yliden)-methyl]-1H-indole-2-carboxylate (**9b**)

This compound was prepared from compound **2** (0.22 g, 0.001 mol) and phenylrhodanine (**8b**) (0.21 g, 0.001 mol), 5 h, 60% yield (0.35 g). – M. p. 251 – 253 °C. – IR (KBr): ν = 3306, 2988, 1712, 1682, 1591, 1573, 1495 cm^{-1}. – ^{1}H NMR ([D$_6$]-DMSO): δ = 1.38 (t, 3H, J = 7.1 Hz, CH$_3$), 4.41 (q, 2H, J = 7.1 Hz, CH$_2$), 7.34 (ddd, 1H, J = 1.1, 6.8, 8.3 Hz, 5'-H), 7.42 – 7.58 (m, 2H, Ph, 6'-H), 7.62 (dd, 1H, J = 1.1, 8.3 Hz, 7'-H), 7.92 (dd, 1H, J = 1.1, 8.3 Hz, 4'-H), 8.53 (s, 1H, 2-H), 12.76 (s, 1H, NH). – ^{13}C NMR ([D6]-DMSO): δ = 15.0, 62.2, 114.6, 115.4, 122.4, 122.7, 123.9, 124.6, 126.7, 128.7, 129.1, 129.6, 130.2, 130.3, 136.3, 137.5, 161.3, 167.5, 194.3. – MS (EI): m/z = 408 (M$^+$), 409 (MH$^+$); HRMS calcd. 376.0882; found 376.0890.

Ethyl 3-[(Z)-(4-imino-2-oxothiazolidin-5-ylidene)methyl]-1H-indole-2-carboxylate (**9c**)

This compound was prepared from compound **2** (0.22 g, 0.001 mol) and 4-imino-2-oxo-1,3-thiazolidine (**8c**) (0.12 g, 0.001 mol), 8.5 h, 67% yield (0.21 g). – M. p. 215 – 219 °C. – IR (KBr): ν = 3306, 3135, 1691, 1641, 1603 cm^{-1}. – ^{1}H NMR ([D$_6$]-DMSO): δ = 1.35 (t, 3H, J = 7.1 Hz, CH$_3$), 4.38 (q, 2H, J = 7.1 Hz, CH$_2$), 7.20 (ddd,1H, J = 1.1, 7.2, 8.3 Hz, 5'-H), 7.37 (ddd,1H, J = 1.1, 7.2, 8.3 Hz, 6'-H), 7.55 (dd, 1H, J = 1.1, 8.3 Hz, 7'-H), 7.77 (dd, 1H, J = 1.1, 8.3 Hz, 4'-H), 8.21 (s, 1H, 2-H), 8.92 (s, 1H, NH), 9.24 (s, 1H, NH), 12.37 (s, 1H, NH). – ^{13}C NMR ([D6]-DMSO): δ = 15.0, 61.8, 114.2, 117.0, 121.6, 122.6, 124.8, 124.9, 126.3, 126.8, 137.2, 137.4, 161.6, 176.2, 180.9. – MS (EI): m/z = 315 (M$^+$). – $C_{15}H_{13}N_3O_3S$ (315.35): calcd. C 57.13, H 4.16, N 13.33; found C 57.19, H 4.18, N 13.09.

Ethyl 3-[(4,6-dioxo-2-thioxotetrahydropyrimidin-5(2H)yl-idene)methyl]-1H-indole-2-carboxylate (**11**)

This compound was prepared from compound **2** (0.22 g, 0.001 mol) and 2-thiobarbituric acid (**10**) (0.14 g, 0.001 mol), 1 h, 69% yield (0.24 g). – M. p. 285 °C (EtOH, decomp.). – IR (KBr): ν = 3300, 1684, 1562, 1534, 1503 cm^{-1}. – ^{1}H NMR ([D$_6$]-DMSO): δ = 1.35 (t, 3H, J = 6.8 Hz, CH$_3$), 4.38 (q, 2H, J = 6.8 Hz, CH$_2$), 7.19 (ddd, 1H, J = 1.1, 7.2, 8.3 Hz, 5'-H), 7.35 (ddd, 1H, J = 1.1, 7.2, 7.9 Hz, 6'-H), 7.42 (dd, 1H, J = 1.1, 7.9 Hz, 7'-H), 7.55 (dd, 1H, J = 1.1, 8.3 Hz, 4'-H), 8.88 (s, 1H, 2-H), 12.24 (s, 1H, NH), 12.33 (s, 1H, NH), 12.87 (s, 1H, NH). – ^{13}C NMR ([D6]-DMSO): δ = 14.9, 62.3, 114.1, 116.3, 117.8, 122.7, 124.4, 126.1, 126.7, 131.5, 137.0, 148.6, 160.1, 161.4, 162.6, 179.4. – MS (EI): m/z = 343 (M$^+$). – $C_{16}H_{13}N_3O_4S$ (343.36): calcd. C 55.97, H 3.82, N 12.24; found C 55.72, H 4.05, N 12.39.

General procedure for the preparation of azomethine imines (**14**, **15**)

Compounds (**2**, **12**) (1 mmol) and 5,5-dimethylpyrazolidin-3-one (**13**) (0.11 g, 1 mmol) were dissolved in ethanol (10 ml), a catalytic amount of trifluoroacetic acid was added (5 drops) and the mixture was either left to react at r. t. or heated under reflux for 2 h. The volatile components were evaporated *in vacuo*, water (5 ml) was added, the precipitate was collected by filtration and washed with ethanol and diethyl ether.

5,5-Dimethyl-1-[2-(ethoxycarbonyl)-1H-indol-3-yl]-3-pyrazolidinone-(1Z)-azomethine imine (**14**)

This compound was prepared from compound **2** (0.22 g, 0.001 mol), reflux 2 h, 52% yield (0.16 g). – M. p. 115 –

118 °C. – IR (KBr): ν = 2984, 1713, 1650, 1594, 1506, 1459, 1411 cm^{-1} – ^{1}H NMR ([D$_6$]-DMSO): δ = 1.40 (t, 3H, J = 7.1 Hz, CH$_3$), 1.70 (s, 6H, CH$_3$), 2.71 (s, 2H, CH$_2$), 4.43 (q, 2H, J = 7.1 Hz, CH$_2$), 7.20 (ddd, 1H, J = 0.8, 7.1, 8.3 Hz, 5'-H), 7.37 (ddd, 1H, J = 1.1, 7.1, 8.3 Hz, 6'-H), 7.54 (1 dd, H, J = 0.8, 8.3 Hz, 7'-H), 8.33 (s, 1H, 2-H), 8.51 (dd, 1H, J = 1.1, 8.3 Hz, 4'-H), 12.78 (s, 1H, NH). – ^{13}C NMR ([D6]-DMSO): δ = 15.0, 29.0, 45.4, 62.6, 73.3, 111.5, 113.8, 122.3, 125.2, 126.5, 127.0, 130.3, 131.3, 137.5, 161.4, 180.5. – MS (EI): m/z = 313 (M$^+$); HRMS calcd. 313.1426, found 313.1420. – $C_{17}H_{19}N_3O_3$ (313.36): calcd. C 67.92, H 4.18, N 15.84; found C 68.03, H 4.23, N 15.79.

5,5-Dimethyl-1-[1H-indol-3-yl]-3-pyrazolidinone-(1Z)-azomethine imine (**15**)

This compound was prepared from 3-formylindole (**12**) (0.15 g, 0.001 mol), r.t. 24 h, 82% yield (0.20 g). – M.p. 173–175 °C, 290–295 °C. – IR (KBr): ν = 1637, 1581, 1497, 1451, 1410, 1369 cm^{-1} – ^{1}H NMR ([D$_6$]-DMSO): δ = 1.66 (s, 6H, CH$_3$), 2.56 (s, 2H, CH$_2$), 7.22 (ddd, 1H, J = 1.5, 6.8, 7.2 Hz, 5'-H), 7.25 (ddd, 1H, J = 1.5, 6.8, 7.2 Hz, 6'-H), 7.51 (dd, 1H, J = 1.5, 6.8 Hz, 7'-H), 8.01 (s, 1H, 2-H), 8.15 (dd, 1H, J = 1.5, 6.8 Hz, 4'-H), 8.71 (d, 1H, J = 3.0 Hz, 2'-H), 12.11 (s, 1H, NH). – MS (EI): m/z = 241 (M$^+$), 242 (MH$^+$); HRMS calcd. 241.1215, found 241.1222. – $C_{14}H_{15}N_3O$ (241.29): calcd. C 69.69, H 6.27, N 17.41; found C 69.37, H 6.38, N 17.20.

X-ray crystal structure analysis

Diffraction data for compound **4** were collected on a Nonius Kappa CCD diffractometer with graphite monochromated Mo-K$_\alpha$ radiation. The data were processed using the DENZO [27] program. The structure was solved by direct methods using SIR97 [28]. The positions of hydrogen atoms were obtained from the difference Fourier maps. We employed full-matrix least-squares refinements on F values with anisotropic displacement factors for all non-hydrogen atoms and with isotropic displacement factors for hydrogen atoms using Xtal3.4 [29]. In the final cycle of the refinement we used 1722 reflections (included were those "less than" reflections for which F_c was larger than F_o) and 159 parameters. The resulting crystal data and details concerning data collection and refinement are quoted in Table 1. An ORTEP [30] drawing of the content of the asymmetric unit showing the atom-labeling scheme is presented in Fig. 2. The crystallographic data for compound **4** have been deposited with the Cambridge Crystallographic Data Center with the deposition number: CCDC 294093. These data can be obtained, free of charge *via* http://www.ccdc.cam.ac.uk/conts/retrieving.html.

Acknowledgements

The financial support from the Slovenian Research Agency through grants P0-0502-0103, P1-0179, and J1-6689-0103-04 is gratefully acknowledged. We acknowledge with thanks the financial support from the pharmaceutical companies Krka d.d. (Novo mesto, Slovenia) and Lek d.d., a new Sandoz Company (Ljubljana, Slovenia). The crystallographic data were collected on the Nonius Kappa CCD diffractometer in the Laboratory of Inorganic Chemistry, Faculty of Chemistry and Chemical Technology, University of Ljubljana, Slovenia. We acknowledge with thanks the financial contribution of the Ministry of Education, Science and Sport, Republic of Slovenia through grants X-2000 and PS-511-103.

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