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SYNTHESIS OF THIOAPLYSINOPSIN ANALOGS DERIVED FROM 5-DIMETHYLAMINOMETHYLIDENE-2-THIOXO-1,3-THIAZOL-4-ONES

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Dedicated to the memory of Dr. Ivar Ugi

Abstract – Some new thioaplysinopsin analogs **4a-d** were prepared from indole (**3a**) and or 2-methylindole (**3b**) and 5-dimethylaminomethylidene- (**2a-c)** or 5-ethoxymethylidene-2-thioxo-1,3-thiazol-4-ones (**2d**) derived rhodanine derivatives (**1a,b**). Cycloaddition of *N*-phenyl-4-chlorobenzonitrileimine to C=S bond in **4c** and in thioaplysinopsin derivatives **6a,b** afforded the corresponding spiro compounds 4,9-diphenyl-2-(4-chlorophenyl)-7-[1-(2-methylindol-3-yl)methylidene]-1,6-dithia-3,4,9-triazaspiro-[4.4]non-2-en-8-one (**5**) and 2-(4-chlorophenyl)-8-[(*Z*)-1-(2-methyl-1*H*-indol-3-yl)methylidene]-4,6-diaryl-1-thia-3, 4,6,9-tetraazaspiro[4.4]non-3-en-7-one (**7a,b**).

INTRODUCTION

A large number of indole derivatives substituted at 3 position exhibit various biological activities. The substituents at 3 position in the indole ring are formyl group, carboxymethyl group, a five or six membered heterocyclic ring, such as maleimidyl, imidazolyl, dihydroimidazolyl, oxazolyl, oxadiazinyl, pyrazinyl, pyrimidinyl, and others. Among these indole alkaloids are meridianins, isolated from south atlantic tunicate *Aplium meridianum*,[1] some of them have been described as potent kinase inhibitors,[2] while others display antitumor activity,[3] and dipodazines, a diketopiperazine condensation products derived from dehydrotryptophane and glycine, isolated from *Penicillium dipodomyis* and meat-associated

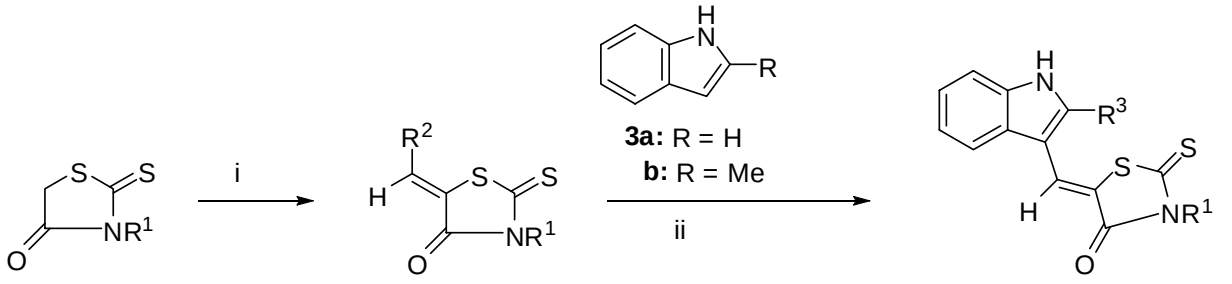
P. nalgiovese,[4] and others. Aplysinopsin and its derivatives were isolated from marine sponges *Aplysinopsis reticulata, Verongia spengellii, Dercitus sp.,* and *Tubastrea sp.*[5-8] Some of these compouds display biological activity,[8] such as specific cytotoxicity for cancer cells[5] and in affecting neuro-transimission.[9] These findings caused a great interest in their synthesis.[10-15]

In the course of our studies on the application of alkyl 3-dimethylaminopropenoates and related enaminones in the synthesis of heterocyclic systems and natural products and their analogs [16-18] we recently focused our attention also on preparation of chiral enaminones available from amino acids. [16,19-23]

In this connection, we already reported on the application of 5-[(dimethylamino)methylidene]imidazolidine-2,4-dione and its 3-methyl derivative as well as on the application of 5-[(dimethylamino)methylidene]-2-thioxoimidazolidin-4-one with an easy exchangeable dimethylamino group as an alternative way of preparing some aryl and heteroaryl aplysinopsin analogues.[24-28]

RESULTS AND DISCUSSION

As a continuation of research in this field we report on the stereoselective preparation of new thioaplysinopsin derivatives. Rhodanine (**1a**) and phenylrhodanine (**1b**) were converted with *N,N*-dimethylformamide dimethyl acetal (DMFDMA), *tert*-butoxybis(dimethylamino)methane (Bredereck's reagent), or triethyl orthoformate to the corresponding dimethylaminomethylidene (**2a-c**) and ethoxymethylidene (**2d**) derivatives. These compounds were then converted with indole (**3a**) and 2-methylindole (**3b**) to novel thioaplysinopsin analogs (**4a-d).** (Schemes 1).



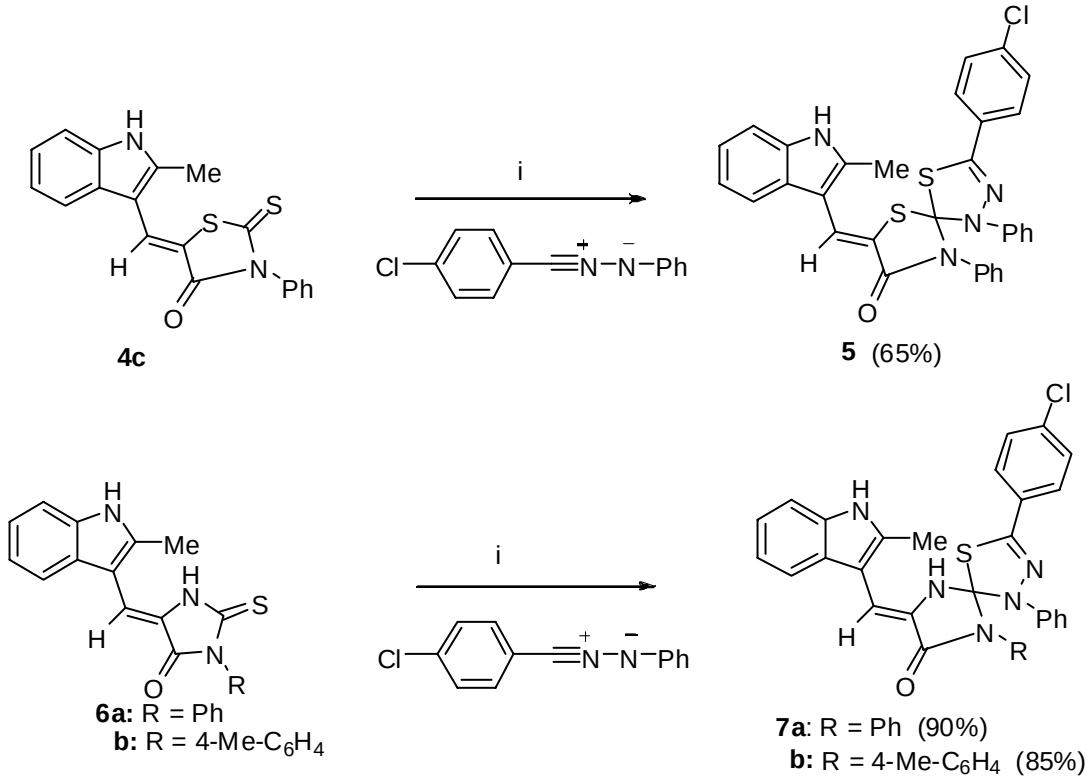
1a: R^1 = H
b: R^1 = Ph

2a: R^1 = H; R^2 = NMe_2 (62%)
b: R^1 = Me; R^2 = NMe_2 (91%)
c: R^1 = Ph; R^2 = NMe_2 (61%)
d: R^1 = H; R^2 = OEt (60%)

4a: R^1 = H; R^3 = Me (40%)
b: R^1 =Me; R^3 = Me (75%)
c: R^1 = Ph; R^3 = Me (50%)
d: R^1 = Me; R^3 = H (49%)

Scheme 1. *Reagents and reaction conditions*: i for **2a,c:** Bredereck´s reagent, DMF, reflux; for **2b**: *N,N*-dimethylformamide dimethyl acetal (DMFDMA), DMF, reflux; for **2d**: triethyl orthoformate, Ac_2O, reflux; ii AcOH, reflux.

Compound **4c** and two other thioaplysinopsin derivatives **6a,b**, prepared previously in our laboratory,[25] were treated with *N*-phenyl-4-chlorobenzonitrileimine, prepared *in situ* from *N*-phenyl-4-chlorobenzecarbohydrazonic chloride and Et_3N. 1,3-Dipolar cycloaddition took place across at exocyclic C=S double bond in the thiazole or imidazole ring to afford the corresponding spiro products **5** and **7a,b,** respectively. (Scheme 2).



Scheme 2. *Reagents and reaction conditions*: i *N*-phenyl- 4-chlorobenzenecarbohydrazonic chloride, Et_3N, THF, reflux.

STRUCTURE DETERMINATION

The structures of new compounds were determined on the basis of their MS spectra, elemental analyses for *C*, *H*, and *N*, ^{13}C NMR and ^{1}H NMR spectra. The (*Z*)-configuration around the exocyclic double bond in compounds **2b, 4b** and **5** was determined by NMR (HMBC technique) on the basis of the magnitude of longe-range heteronuclear coupling constant between the proton attached to the double bond and ^{13}C of the carbonyl group attached to the double bond $^{3}J_{C\text{-}H}$.[29-37] The magnitude of the coupling constant, $^{3}J_{C\text{-}H}$ = 4-6 Hz, indicates the *cis*-relationship between the methine proton and the carbonyl carbon atom and is also in agreement with the literature data.

EXPERIMENTAL

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 such solvent as DMSO-d_6 and $CDCl_3$ with TMS as the internal standard, MS spectra 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.

General Procedure for the Preparation of Starting Compounds 2a-d:

To the DMF or acetic acid anhydride solution of rhodanine (**1a**) or phenylrhodanine (**1b**), *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA), *tert*-butoxybis(dimethylamino)methane (Bredereck's reagent), or triethyl orthoformate was added. The mixture was heated under reflux for several hours, the volatile compounds were evaporated *in vacuo* and precipitate was collected by filtration. The solid residue was crystallised from an appropriate solvent.

5-Dimethylaminomethylidene-2-thioxo-1,3-thiazol-4-one (2a). This compound was prepared from rhodanine (**1a**; 0.40 g, 0.003 mol) and Bredereck's reagent (0.70 g, 0.004 mol) in DMF (8 mL), 3h, 62% yield (0.35g); mp 229-230 °C (from MeCN), ^{1}H NMR (DMSO-d_6) δ: 3.14 (6H, s, NMe_2), 7.54 (1H, s, CH), 12.82 (1H, s, NH). *Anal.* Calcd for $C_6H_8N_2OS_2$: C, 38.28; H, 4.28; N, 14.88. Found: C, 38.30; H, 4.23; N, 14.85.

5-Dimethylaminomethylidene-3-methyl-2-thioxo-1,3-thiazol-4-one (2b). This compound was prepared from rhodanine (**1a**; 0.27 g, 0.002 mol) and DMFDMA (0.60 g, 0.005 mol) in DMF (5 mL), 2h, 91% yield (0.37g); mp 172-173 °C (from DMF). ^{1}H NMR (DMSO-d_6) δ: 3.19 (6H, s, NMe_2), 3.31 (3H, s, NMe), 7.75 (1H, s, CH). *Anal.* Calcd for $C_7H_{10}N_2OS_2$: C, 41.56; H, 4.98; N, 13.85. Found: C, 41.62; H, 4.85; N, 13.89.

5-Dimethylaminomethylidene-3-phenyl-2-thioxo-1,3-thiazol-4-one (2c). This compound was prepared from phenylrhodanine (**1b**; 1.04 g, 0.005 mol) and Bredereck's reagent (1.4 g, 0.008 mol) in toluene (10 mL), 2h, 61% yield (0.81g); mp 193-194 °C, ^{1}H NMR (DMSO-d_6) δ: 3.22 (s, 6H, NMe_2), 7.21-7.25 (m, 2H, Ph), 7.44-7.55 (m, 3H, Ph), 7.73 (s, 1H, CH). ^{13}C NMR (DMSO-d_6) δ: 88.3, 129.6, 129.7, 130.0, 137.2, 147.6, 167.6, 191.4. *Anal.* Calcd for $C_{12}H_{12}N_2OS_2$: C, 54.52; H, 4.58; N, 10.60. Found: C, 54.39; H, 4.42; N, 10.62.

5-Ethoxymethylidene-2-thioxo-1,3-thiazol-4-one (2d). This compound was prepared from rhodanine (**1a**; 1.33 g, 0.010 mol) and triethyl ortoformate (1.70 g, 0.011 mol) in acetic andydride (20 mL), 3h, 60% yield (1.13 g); mp 144-145 °C (from a mixture of EtOH and *n*-heptane). ^{1}H NMR (DMSO-d_6) δ: 1.28 (3H, t, J_{CH2CH3} = 7.1 Hz, OCH_2CH_3), 4.33 (2H, q, J_{CH2CH3} = 7.1 Hz, OCH_2CH_3), 7.82 (1H, s, CH), 13.24 (1H, s,

NH). *Anal.* Calcd for $C_6H_7NO_2S_2$: C, 38.08; H, 3.73; N, 7.40. Found: C, 37.95; H, 3.49; N, 7.61.

General Procedure for the Preparation of Compounds 4a-d:

Compounds **2a-d** were dissolved in glacial acetic acid (8 mL). To the solution the corresponding indole derivative **3a** or **3b** was added and the mixture was heated under reflux for several hours. The volatile compounds were evaporated *in vacuo* and the precipitate was collected by filtration. The solid residue was crystallised from an appropriate solvent.

(*Z*)-5-[(2-Methylindol-3-yl)methylidene]-2-thioxo-1,3-thiazol-4-one (4a). This compound was prepared from compound **2a** (0.37 g, 0.002 mol) and 2-methylindole (**3b**; 0,28 g, 0.002 mol), 6h, 40% yield (0.22 g); mp 314 °C (from a mixture of MeCN and DMF (decomp)). ^{1}H NMR (DMSO-d_6) δ: 2.51 (3H, s, Me), 7.18-7.21 (2H, m, H_5, H_6), 7.39-7.41 (1H, m, H_4), 7.43-7.83 (1H, m, H_7), 8.84 (1H, s, *H*–C(5')), 12.16 (1H, s, NH), 13.47 (1H, s, NH). *Anal.* Calcd for $C_{13}H_{10}N_2OS_2$: C, 56.91; H, 3.67; N, 10.21. Found: C, 56.73; H, 3.52; N, 9.94.

(*Z*)-5-[(2-Methylindol-3-yl)methylidene]-3-methyl-2-thioxo-1,3-thiazol-4-one (4b). This compound was prepared from compound **2b** (0.40 g, 0.002 mol) and 2-methylindole (**3b**; 0.28 g, 0.002 mol), 8h, 75% yield (0.43 g), mp 290-291 °C (from AcOH). ^{1}H NMR (DMSO-d_6) δ: 2.58 (3H, s, 2-Me), 3.42 (3H, s, NMe), 7.22 (2H, dd, $J_{H4\text{-}H6} = J_{H7\text{-}H5} = 3.0$ Hz, $J_{H4\text{-}H5} = J_{H7\text{-}H6} = 6.0$ Hz, H_5, H_6), 7.43 (1H, dd, $J_{H4\text{-}H6} = 3.0$ Hz, $J_{H4\text{-}H5} = 6.0$ Hz, H_4), 7.85 (1H, dd, $J_{H7\text{-}H5} = 3.0$ Hz, $J_{H7\text{-}H6} = 6.0$ Hz, H_7), 8.00 (1H, s, *H*–C(5')), 12.24 (1H, s, NH). *Anal.* Calcd for $C_{14}H_{12}N_2OS_2 \cdot 1/2\ H_2O$: C, 56.55; H, 4.40; N, 9.42. Found: C, 56.57; H, 4.00; N, 9.16.

(*Z*)-5-[(2-Methylindol-3-yl)methylidene]-3-phenyl-2-thioxo-1,3-thiazol-4-one (4c). This compound was prepared from compound **2c** (0.132 g, 0.0005 mol) and 2-methylindole (**3b**; 0.06 g, 0.0005 mol), 1.5h, 50% yield (0.09 g); mp 314-315 °C (from acetone). IR 3300, 1670, 1550 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 2.59 (s, 3H, Me), 7.21-7.27 (m, 2H, Ph), 7.38-7.46 (m, 3H, Ph), 7.51-7.60 (m, 3H, 4-H, 5-H, 6-H), 7.88-7.93 (m, 1H, 7-H), 8.01 (s, 1H, CH), 12.25 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 13.3, 109.2, 112.9, 115.0, 120.3, 122.2, 123.6, 125.6, 129.6, 130.1, 136.7, 137.1, 146.3, 167.8, 193.4. *Anal.* Calcd for $C_{19}H_{14}N_2OS_2$: C, 65.12; H, 4.03; N, 7.99. Found: C, 65.10; H, 3.95; N, 7.72.

(*Z*)-5-[(Indol-3-yl)methylidene]-3-methyl-2-thioxo-1,3-thiazol-4-one (4d). This compound was prepared from compound **2d** (0.38 g, 0,002 mol) and indole (**3a**; 0.23 g, 0.002 mol), 4.5h, 49% yield (0.27 g); mp 286 °C (from AcOH). ^{1}H NMR (DMSO-d_6) δ: 3.36 (3H, s, NMe), 7.20-7.30 (2H, m, H_5, H_6),

7.51-7.54 (1H, m, H_4), 7.90-7.98 (2H, m, H_7, H_2), 8.10 (1H, s, *H*–C(5')), 12.35 (1H, s, NH). *Anal.* Calcd for $C_{13}H_{10}N_2OS_2$: C, 56.91; H, 3.67; N, 10.21. Found: C, 57.01; H, 3.74; N, 10.25.

General Procedure for the Preparation of Compounds 5, 7a,b.

To the THF solution of thioaplysinopsin derivative and *N*-phenyl-4-chlorobenzenecarbohydrazonic chloride, and Et_3N (2 mL) was added. The mixture was heated for 80 min. under reflux, the volatile compounds were evaporated *in vacuo* and the precipitate was collected by filtration. Solid residue was purified by column chromatography (silica gel 60 (Fluka) and toluene/Et_2O = 4/1).

4,9-Diphenyl-2-(4-chlorophenyl)-7-[(*Z*)-1-(2-methylindol-3-yl)methylidene]-1,6-dithia-3,4,9-triaza-spiro-[4.4]non-2-en-8-one (5). This compound was prepared from compound **4c** (0.07 g, 0.0002 mol) and *N*-phenyl-4-chlorobenzenecarbohydrazonic chloride (0.06 g, 0.0002 mol), 65% yield (0.07 g); mp 243-244 °C. MS 579 (M^+). IR 3280, 1740, 1600 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 2.46 (s, 3H, Me), 6.97-7.02 (m, 1H, Ar), 7.07-7.19 (m, 2H, Ar), 7.22-7.25 (m, 2H, Ar), 7.33-7.49 (m, 13H, Ar), 7.94 (s, 1H, 7′-H), 11.74 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 13.3, 103.9, 108.0, 118.7, 118.8, 120.6, 123.7, 124.4, 126.2, 128.3, 129.4, 130.0, 130.4, 135.5, 136.0, 136.6, 140.6, 141.7, 165.0. *Anal.* Calcd for $C_{32}H_{23}N_4OS_2Cl$: C, 66.37; H, 4.00; N, 9.67. Found: C, 66.59; H, 3.91; N, 9.52.

2-(4-Chlorophenyl)-8-[(*Z*)-1-(2-methyl-1*H*-indol-3-yl)methylidene]-4,6-diphenyl-1-thia-3,4,6,9-tetra-azaspiro[4.4]non-3-en-7-one (**7a**). This compound was prepared from 5-[(2-methylindol-3-yl) methylidene]-3-phenyl-2-thiooxoimidazolidin-4-one (**6a**; 0.333 g, 0.001 mol) and *N*-phenyl-4-chlorobenzenecarbohydrazonic chloride (0.265 g, 0.001 mol), 90% yield (0.46 g); mp 234-235 °C. MS 562 (M^+). IR 1654, 1610, 1600 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 2.54 (3H, s, CH_3), 6.93-7.10 (3H, m, *H*–C(4'), *H*–C(6'), *H*–C(5')), 6.93-7.10 (3H, m, *H*–C(4'), *H*–C(6'), *H*–C(5')), 6.99-7.12 (2H, m, *H*–C(6'), *H*–C(5')), 7.17 (1H, d, *J* = 7.9 Hz, *H*–C(7')), 7.37 (1H, d, *J* = 7.9 Hz, *H*–C(4')), 7.52 (1H, s, *H*–C(2')), 7.77 (1H, d, *J* = 7.9 Hz, *H*–C(7')), 7.63 – 7.27 (14H, m, 2Ph and 4-chlorophenyl), 7.99 (2H, d, *J* = 8.7 Hz, H_{ortho}), 8.16 (1H, s, NH), 8.82 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ: 13.2, 108.0, 111.7, 115.2, 119.8, 121.2, 121.7, 122.0, 124.4, 124.5, 126.1, 127.8, 128.1, 129.1, 129.5, 129.7, 130.1, 136.2, 136.6, 138.6, 139.5, 139.6, 140.2, 147.6, 157.6, 163.9. *Anal.* Calcd for $C_{32}H_{24}N_5OSCl$: C, 68.38; H, 4.30; N, 12.46. Found: C, 68.60; H, 4.06; N, 12.24.

2-(4-Chlorophenyl)-8-[(*Z*)-1-(2-methyl-1*H*-indol-3-yl)methylidene]-4-phenyl-6-(4-metylphenyl)-1-thia-3,4,6,9-tetraazaspiro[4.4]non-3-en-7-one (7b). This compound was prepared from 5-[(2-methyl indol-3-yl)methylidene]-3-(4-methylphenyl)-2-thiooxoimidazolidin-4-one (**6b**; 0.103 g, 0.0003 mol) and

N-phenyl- 4-chlorobenzenecarbohydrazonic chloride (0.080 g, 0.0003 mol), 85% yield (0.15 g); mp 250-251 °C. MS 576 (M^+). IR 1654, 1612 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 2.31 (3H, s, CH_3), 2.55 (3H, s, CH_3), 6.92-7.62 (15H, m, *H*–C(4'), *H*–C(6'), *H*–C(5'), *H*–C(5'), 5H Ph, 4H 4-chlorophenyl, 2H 4-methylphenyl), 7.99 (2H, d, J = 8.3 z, H_{ortho}), 8.10 (1H, s, NH), 8.75 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ: 13.2, 21.4, 67.9, 108.0, 111.7, 115.0, 119.7, 121.2, 121.6, 124.4, 126.1, 127.7, 128.2, 129.1, 129.5, 129.7, 129.9, 130.1, 133.4, 136.2, 136.5, 137.1, 138.7, 139.4, 140.2, 157.5, 163.7. *Anal.* Calcd for $C_{33}H_{26}N_5OSCl$: C, 68.80; H, 4.55; N, 12.16. Found: C, 68.87; H, 4.35; N, 11.83.

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