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A SYNTHESIS OF SOME NOVEL 2-PHENYL- AND 5-BROMO-SUBSTITUTED APLYSINOPSIN ANALOGUES

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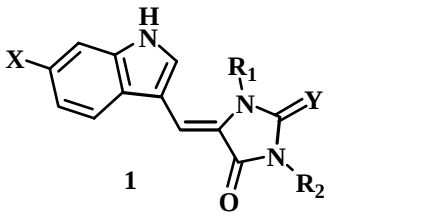
Dedicated to Prof. A. I. Meyers, Colorado State University, on the occasion of his 70th birthday.

Abstract – 5-(2-Phenyl-1*H*-indol-3-ylmethylene)-2-thioxoimidazolidin-4-one (**2**) and its oxo derivatives as well as some novel 5-bromoaplysinopsin analogues were synthesized employing dimethylamine substitution in *N,N*-dimethyl-methylideneimidazolidinones (**6**).

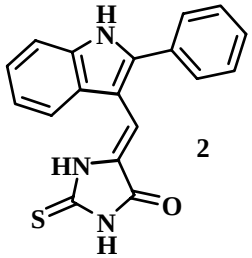
A large number of imidazolinylindoles have been isolated from sponges and soft corals in the past.[1] Among them, aplysinopsins (**1**, Figure 1) aroused considerable interest due to their diverse biological activities.[2]

Figure 1



1

X=H, Br; Y=O, NH, NMe; R_1,R_2=H, Me.



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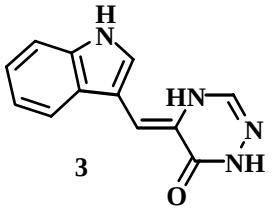
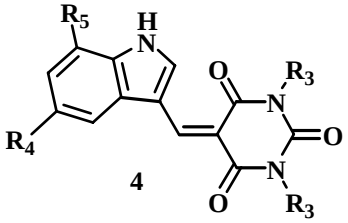


3



4

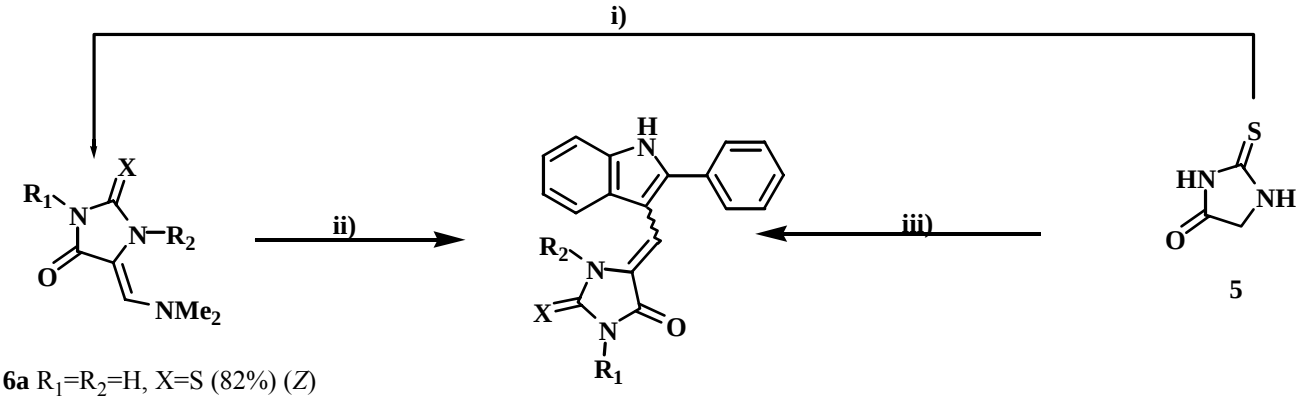
R_3=H, Me; R_4=H, Br; R_5=H, Et.

Recently, indolylmethylidenethiohydantoins (thioaplysinopsins) have been tested as aldose reductase inhibitors[3] and have been found to exhibit weak anti-HIV activity[4] and 5-(2-phenyl-1*H*-indol-3-ylmethylene)-2-thioxoimidazolidin-4-one (**2**, Figure 1) inhibitory activity against several cancer cell lines.[5]

As a continuation of our studies on dimethylamine substitution in *N,N*-dimethylenamines,[6] we have described recently a novel and stereoselective synthesis of aplysinopsins, thioaplysinopsins and their analogues in which hydantoin moiety is replaced with 4,5-dihydro-1,2,4-triazin-6(1*H*)-one (**3**) or barbituric acid (**4**) (Figure 1).[7]

Compound (**2**) has been originally synthesized from 2-phenylindole,[3] by conversion into 3-formyl derivative under Reimer-Tiemann reaction conditions,[8] followed by reaction with 2-thiohydantoin. The yield of this synthesis is not disclosed in the literature.[3] On the basis of our previous experience we decided to devise a simpler synthesis of 2-phenyl substituted aplysinopsin derivatives.

Scheme 1



6a R_1=R_2=H, X=S (82%) (*Z*)
6b R_1=R_2=H, X=O (*Z*)
6c R_1=Me, R_2=H, X=O (*Z*)
6d R_1=R_2=Me, X=O (*Z*)
6e R_1=H, R_2=Me, X=O (89%) (*Z*)

2 R_1=R_2=H, X=S (55%) (*Z*) **A** from **6a**
2 R_1=R_2=H, X=S (52%) (*Z*) **B** from **5**
7a R_1=R_2=H, X=O (68%) (*Z*) **A** from **6b**
7b R_1=Me, R_2=H, X=O (46%) (*Z*) **A** from **6c**
7c R_1=R_2=Me, X=O (10%) (*E*) **A** from **6d**
7d R_1=H, R_2=Me, X=O (14%) (*E*) **A** from **6e**

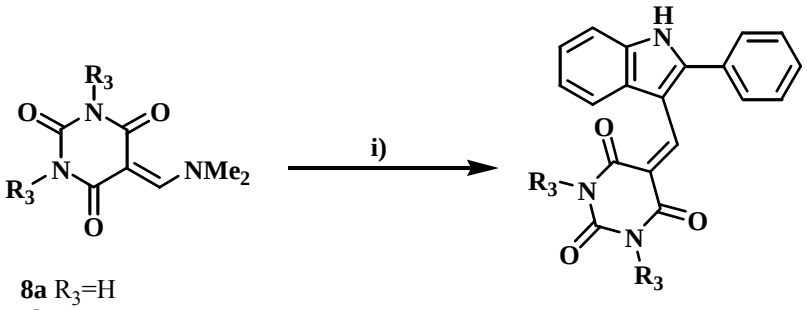
i) $(Me_2N)_2CH(OBu\text{-}t)$, MeCN; ii) ***Method A:*** *2-phenylindole, HCl, i-PrOH; iii)*
Method B: *2-phenylindole, $CH(OEt)_3$, AcOH*

We employed first our *aplysinopsin making* methodology in the synthesis of **2**, but failed when heated compound (**6a**)**,** prepared by standard protocols from 2-thiohydantoin (**5**), and 2-phenylindole in glacial acetic acid. Searching for milder conditions, we substituted acetic acid with aliphatic alcohols and hydrochloric acid, and found that 2-propanol/HCl works best to our advantage. In this manner, **2**, its oxo derivatives (**7**) (Scheme 1), and pyrimidinetrione analogues (**9**) (Scheme 2) were prepared in 10-76% yields.

Heating the mixture of 2-phenylindole, 2-thiohydantoin and triethyl orthoformate in acetic acid gave **2** in a single step in 52% yield (Scheme 1, method B).

The configuration around the exocyclic double bond was determined on the basis of long-range heteronuclear coupling constants using 2D HMBC correlation technique. Generally, the magnitude of coupling constants $^3J_{C\text{-}H}$ for the nuclei with (*Z*) configuration around the C=C double bond is smaller (2-6 Hz) than that for the (*E*) oriented nuclei (8-12 Hz).[7c,9]

Scheme 2



8a R_3=H
8b R_3=Me

9a R_3=H (76%)
9b R_3=Me (46%)

i) 2-Phenylindole, HCl, i-PrOH

The coupling constants ($^3J_{C\text{-}H}$) were then measured for compounds (**2**), (**7a-d**). In the case of compounds (**2**) and (**7a**), $^3J_{C\text{-}H}$ are 5.1 and 5.3 Hz, respectively, indicating that compounds (**2**) and (**7a,b**) exist as *Z*-isomers, while the magnitude of $^3J_{C\text{-}H}$= 10.5 Hz for compound (**7d**) indicates that compounds (**7c,d**) exist as *E*- isomers. Methyl group at N(1) (R^2 = Me) in compounds (**7c,d**) obviously adds to the strain of the molecule, which affects consistently poor yields of these two compounds.

After standing at room temperature for several months, isomerization occurred in compound (**7c**). Thus, after five months, the solid sample of compound (**7c**) (100 % (*E*) isomer), appeared to contain 35 % of (*Z*) isomer.

With indole and 5-bromoindole as starting compounds and 5-dimethylaminomethylidenehydantoins (**6**) in 2-propanol saturated with HCl, some novel 5-bromo aplysinopsins (good yield) and some known aplysinopsins[2,7] (improved yield) were formed (Scheme 3).

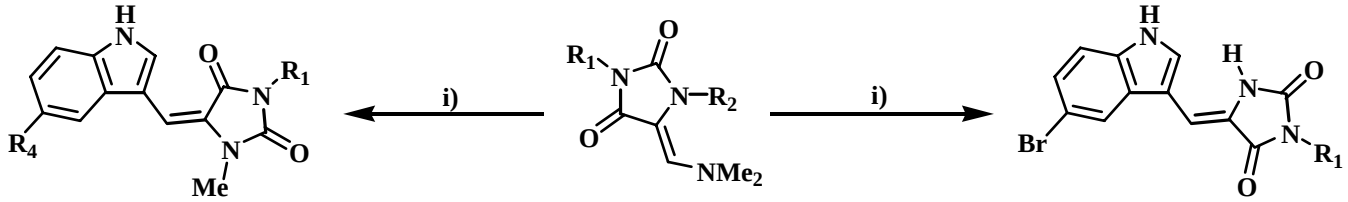
Thus, the method described above is currently the most effective way for the preparation of naturally occurring 3'-deimino-3'-oxoaplysinopsin (**10a**).

As it has been demonstrated before,[2a,7a] aplysinopsins with methyl group at N(1) exist as (*E*) isomers due to steric repulsions between H-C(2') and Me-N(1), whereas, aplysinopsins without substituent at N(1) exist as (*Z*) isomers in the fully conjugation form. These data are consistent with those for **2** and its analogues mentioned above. The structures were unambiguously established with ^{1}H NMR as follows: H-

C(2') in (*E*)-aplysinopsins is found in the range δ 8.7-9.2, due to proximity of C(4)=O group (anisotropy), while H-C(2') for (*Z*)-aplysinopsins is found always in the range δ 7.6-8.2.

According to our expectations, compounds (**10**) exist as (*E*) isomers ($\delta_{H\text{-}C(2')}$ 8.78 (**10a**), 8.84 (**10b**) and 8.85 (**10c**)) and compounds (**11**) occur as (*Z*) isomers ($\delta_{H\text{-}C(2')}$ 8.14 (**11a**) and 8.15 (**11b**)) (Table 2).

Scheme 3



10a R_1=Me, R_4=H (78%) (*E*)
10b R_1=Me, R_4=Br (35%) (*E*)
10c R_1=H, R_4=Br (44%) (*E*)

6b R_1=R_2=H, (*Z*)
6c R_1=Me, R_2=H, (*Z*)
6d R_1=R_2=Me, (*Z*)
6e R_1=H, R_2=Me, (*Z*)

11a R_1=H, (45%) (92% *Z*)
11b R_1=Me, (40%) (>95% *Z*)

i) Indole or 5-bromoindole, HCl, i-PrOH

In conclusion, we demonstrated that our approach towards aplysinopsin[7] can be easily generalized to provide diverse aplysinopsin mimic structures, such as biologically active 5-(2-phenyl-1*H*-indol-3-ylmethylene)-2-thioxoimidazolidin-4-one (**2**), naturally occurring compounds and their synthetically modified derivatives. This methodology consisting of simple reagents and simple reactions would be further developed into automatic or semiautomatic parallel synthesis.

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. ^{1}H- and ^{13}C-NMR Spectra were obtained on a Varian VXR 300 spectrometer at 300 MHz. HMBC Spectra were measured on Bruker Avance DPX 300 at 300 MHz. MS Spectra were obtained on Autospec Q spectrometer, and elemental analyses were performed for C, H, and N on Perkin Elmer CHN Analyser 2400.

Synthesis of the Starting Compounds. The following compounds were prepared according to the procedures described in the literature: 5-[(*Z*)-dimethylaminomethylidene]imidazolidine-2,4-dione (**6b**),[7a] 5-[(*Z*)-dimethylaminomethylidene]-3-methylimidazolidine-2,4-dione (**6c**),[7a] 5-[(*Z*)-dimethylaminomethylidene]-1,3-dimethylimidazolidine-2,4-dione (**6d**),[7c] 5-dimethylaminomethylidene-2,4,6-(1*H*,3*H*,5*H*)-pyrimidinetrione (**8a**),[7b] and 1,3-dimethyl-5-dimethylaminomethylidene-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**8b**).[7b]

5-[(*Z*)-Dimethylaminomethylidene]-2-thioxoimidazolidin-4-one (6a). To 2-thiohydantoin (**5**, 13.22 mmol, 1535 mg) in acetonitrile (25 mL) *tert*-butoxybis(dimethylamino)methane (3.60 mL, 17.19 mmol) was added and the mixture was stirred for 2 h at 60-65°C. After cooling to rt, compound (**6a**) was isolated as crystals, washed with 2-propanol and recrystallized from DMF to give **6a** in 82% yield; mp 281-284°C. ^{1}H NMR (DMSO-d_6) δ: 3.07 (6H, *s*, NMe_2), 6.60 (1H, *s*, -C*H*=), 11.11 (1H, *s*, N*H*), 11.47 (1H, *s*, N*H*). ^{13}C NMR (DMSO-d_6) δ: 42.4(2), 103.8, 131.8, 165.3, 169.8. *Anal*. Calcd for $C_6H_9N_3OS$: C, 42.08; H, 5.30; N, 24.54. Found: C, 42.26; H, 5.45; N, 24.43.

5-[(*Z*)-Dimethylaminomethylidene]-1-methylimidazolidine-2,4-dione (6e). This compound was prepared according to the published procedure,[7c] but optimized as follows: 1-methylhydantoin (733 mg, 6.43 mmol) in acetonitrile (5 mL) and *tert*-butoxybis(dimethylamino)methane (1.75 mL, 8.37 mmol) were heated at reflux for 3.5 h. After cooling, precipitate was collected by filtration and recrystallized from 2-propanol to give compound (**6e**) in 89% yield, in all respects identical to previously published.[7c]

General Procedure for the Synthesis of 2, 7, and 9: Coupling of 5-Dimethylaminoethylidene-imidazolidinones (6) and 5-dimethylaminomethylidenepyrimidinetriones (8) with 2-Phenylindole. Method A:

A mixture of 2-phenylindole (0.193 g, 1 mmol) and starting compound (**6**) (1 mmol) was suspended in 2-propanol (5 mL), 37% HCl (0.8 mL) was added, and the suspension was refluxed for several hours. Products were isolated as crystals and recrystallized from appropriate solvents.

5-[(*Z*)-(2-Phenyl-1*H*-indol-3-yl)methylidene]-2-thioxoimidazolidin-4-one (2). This compound was prepared from **6a**; 4 h; yield 55%; mp 285-286°C (PrOH). *Anal.* Calcd for $C_{18}H_{13}N_3OS$: C, 67.69; H, 4.10; N, 13.16. Found: C, 67.35; H, 4.15; N, 12.93.

5-[(*Z*)-(2-Phenyl-1*H*-indol-3-yl]methylidene]imidazolidine-2,4-dione (7a). This compound was prepared from **6b**; 4 h; yield 68%; mp 269-271°C (*i*-PrOH). *Anal.* Calcd for $C_{18}H_{13}N_3O_2$ + ½ *i*-PrOH: C, 70.26; H, 5.14; N, 12.60. Found: C, 70.40; H, 5.02; N, 12.45.

3-Methyl-5-[(*Z*)-(2-phenyl-1*H*-indol-3-yl)methylidene]imidazolidine-2,4-dione (7b). This compound was prepared from **6c**; 4 h; yield 46%; mp 248-251°C (DMF/MeCN). *Anal.* Calcd for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.47; H, 4.90; N, 13.38.

1,3-Dimethyl-5-[(*E*)-(2-phenyl-1*H*-indol-3-yl)methylidene]imidazolidine-2,4-dione (7c). This compound was prepared from **6d**; 3 h; yield 10%; mp 265-272°C (MeOH). *Anal.* Calcd for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.50; H, 5.26; N, 12.44.

Isomerization of compound (**7c**) (pure (*E*) isomer) was observed in solid state. Namely, after leaving the crystalline sample for five months at room temperature it contained 35 % of (*Z*) isomer, as determined by ^{1}H NMR.

Table 1. ^{1}H and ^{13}C NMR Spectral Data for Compounds (**2**), (**7**) and (**9**) in DMSO-d_6

Compound	**^{1}H-NMR** (δ, *J* in Hz)	**^{13}C-NMR**
2	6.63 (1H, *s*, -C*H*=), 7.14-7.26 (2H, *m,* Ind), 7.44-7.49 (2H, *m*, Ph), 7.53-7.58 (3H, *m*, Ph), 7.64-7.67 (2H, *m*, Ind), 11.80 (1H, *s*, N*H*), 12.05 (1H, *s*, N*H*-ind), 12.16 (1H, *s*, N*H*)	106.2, 107.6, 111.9, 120.3, 122.8, 126.7, 127.7, 128.6(2), 128.9(2), 129.9, 131.3, 136.5, 139.9, 165.4, 177.1
7a	6.59 (1H, *s*, -C*H*=), 7.13 (1H, *dt*, *J*=7.0, 1.1, Ind), 7.21 (1H, *dt*, *J*=7.0, 1.1, Ind), 7.41-7.46 (2H, *m*, Ph), 7.52-7.58 (3H, *m*, Ph), 7.66 (2H, *dd*, *J*=7.0, 1.1, Ind), 9.80 (1H, *s*, N*H*), 11.05 (1H, *s*, N*H*), 11.89 (1H, *s*, N*H*-ind)	103.9, 105.8, 111.6, 120.0, 120.5, 122.4, 126.6, 128.2(2), 128.3(2), 128.9(2), 131.7, 136.4, 138.2, 155.0, 165.3
7b	2.95 (3H, *s*, N*Me*), 6.69 (1H, *s*, -C*H*=), 7.13 (1H, *dt*, *J*=7.0, 1.1, Ind), 7.21 (1H, *dt*, *J*=7.0, 1.1, Ind), 7.41-7.47 (2H, *m*, Ph), 7.52-7.60 (3H, *m*, Ph), 7.66 (2H, *dd*, *J*=7.0, 1.1, Ind), 10.06 (1H, *s*, N*H*), 11.92 (1H, *s*, N*H*-ind)	24.2, 105.0, 105.8, 111.7, 120.0, 120.5, 122.4, 126.6, 126.8, 128.3(3), 128.9(2),131.6, 136.4, 138.5, 154.7, 164.0
7c	2.92 (3H, *s*, N*Me*), 3.17 (3H, *s*, N*Me*), 6.47 (1H, *s*, -C*H*=), 7.01 (1H, *dd*, *J*=7.2, 7.8, Ind), 7.14 (1H, *dd*, *J*=7.2, 7.8, Ind), 7.27 (1H, *d*, *J*=7.8, Ph), 7.40 (2H, *m*, Ph), 7.52 (2H, *m*, Ph), 7.72 (2H, *d*, *J*=7.2, Ind), 11.77 (1H, *s*, N*H*-ind)	24.3, 26.4, 106.4, 108.2, 111.3, 119.2, 121.6, 121.9, 126.8, 127.7, 128.2(2), 128.8(2), 128.9, 132.0, 136.2, 137.7, 153.5, 160.8
7d	3.12 (3H, *s*, N*Me*), 6.39 (1H, *s*, -C*H*=), 7.01 (1H, *ddd*, *J*=7.0, 7.5, 1.1, Ind), 7.14 (1H, *ddd*, *J*=7.0, 7.6, 1.2, Ind), 7.27 (1H, *d*, *J*=8.0, Ph), 7.37-7.42 (2H, *m*, Ph), 7.49-7.54 (2H, *m*, Ph), 7.70-7.73 (2H, *m*, Ind), 11.05 (1H, *s*, N*H*), 11.73 (1H, *s*, N*H*-ind)	25.9, 106.3, 107.1, 111.3, 119.1, 121.3, 121.8, 126.9, 127.9, 128.0(2), 128.8(2), 129.7, 132.1, 136.1, 137.4, 153.5, 161.9
9a	7.15-7.31 (3H, *m*, Ar), 7.53 (1H, *d*, *J*=8.1, Ar), 7.54-7.66 (5H, *m*, Ar), 8.21 (1H, *s*, -C*H*=), 10.98 (1H, *s*, N*H*), 11.10 (1H, *s*, N*H*), 12.81 (1H, *s*, N*H*-ind)	111.3, 112.0, 112.2, 121.2, 123.4, 124.5, 126.1, 129.1, 130.1, 130.2(2), 130.3(2), 137.2, 147.7, 149.3, 150.6, 161.6, 164.4
9b	3.22 (3H, *s*, N*Me*), 3.23 (3H, *s*, N*Me*), 7.19-7.32 (3H, *m*, Ar), 7.53 (1H, *d*, *J*=8.0, Ar), 7.58-7.63 (5H, *m*, Ar), 8.30 (1H, *s*, -C*H*=), 12.84 (1H, *s*, N*H*-ind)	27.9, 28.2, 111.5, 111.6, 112.2, 121.3, 123.3, 124.6, 126.1, 129.0(2), 130.0, 130.2, 130.3(2), 137.2, 148.8, 149.6, 151.5, 159.9, 162.9

1-Methyl-5-[(*E*)-(2-phenyl-1*H*-indol-3-yl)methylidene]imidazolidine-2,4-dione (7d). This compound was prepared from **6e**; 4 h; yield 14%; mp 267-271°C (MeOH). *Anal.* Calcd for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.56; H, 4.76; N, 12.96.

5-[(2-Phenyl-1*H*-indol-3-yl)methylidene]-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (9a). This compound was prepared from **8a**; 1.5 h; yield 76%; mp 304-305°C (DMF). MS 332 ($(M+H)^+$, 100%). *Anal*. Calcd for $C_{19}H_{13}N_3O_3$: C, 68.88; H, 3.95; N, 12.68. Found: C, 68.78; H, 3.88; N, 12.55.

1,3-Dimethyl-5-[(2-phenyl-1*H*-indol-3-yl)methylidene]-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (9b). This compound was prepared from **8b**; 1.5 h; yield 46%; mp 309-311°C (DMF/*i*-PrOH). MS 360 ($(M+H)^+$, 100%). *Anal.* Calcd for $C_{21}H_{17}N_3O_3$: C, 70.18; H, 4.77; N, 11.69. Found: C, 69.79; H, 4.69; N, 11.59.

Alternative Procedure for the Synthesis of 2. Method B. A mixture of 2-thiohydantoin (**5**, 1100 mg, 9.48 mmol), 2-phenylindole (1833 mg, 9.48 mmol), triethyl orthoformate (2.75 mL, 16.12 mmol) in acetic acid (25 mL) was heated at 90°C for 5.5 h. Volatile components were evaporated *in vacuo* to give an oily residue, which was triturated with propanol to give **2** as crystals in 52% yield.

General Procedure for the Synthesis of 10 and 11: Coupling of the 5-Dimethylamino-methylideneimidazilidinones (6) with Indole and 5-Bromoindole.

A mixture of indole or 5-bromoindole (2.5 mmol) and compound (**6**) (2.5 mmol) was suspended in 2-propanol (6 mL), 37% HCl (1 mL) was added and suspension was refluxed for several hours. Products were isolated as crystals and recrystallized from appropriate solvents.

(*E*)-3'-Deimino-3'-oxoaplysinopsin ((*E*)-5-[(1*H*-Indol-3-yl)methylidene]-1,3-dimethylimidazolidine-2,4-dione; 10a). This compound was prepared from indole and **6d**; 2 h; yield 78% (100% *E*); mp 271-274°C (*i*-PrOH) (lit.,[2b] 281-282°C).

(*E*)-5-Bromo-3'-deimino-3'-oxoaplysinopsin ((*E*)-5-[(5-Bromo-1*H*-indol-3-yl)methylidene]-1,3-dimethylimidazolidine-2,4-dione; 10b). This compound was prepared from 5-bromoindole and **6d**; 4 h; yield 35% (100% *E*); mp 288-291°C (*i*-PrOH). *Anal.* Calcd for $C_{14}H_{12}N_3O_2Br$: C, 50.32; H, 3.62; N, 12.57. Found: C, 50.25; H, 3.55; N, 12.44.

(*E*)-5-Bromo-4'-demethyl-3'-deimino-3'-oxoaplysinopsin ((*E*)-5-[(5-Bromo-1*H*-indol-3-yl)methyl-

idene]-1-methylimidazolidine-2,4-dione; 10c). This compound was prepared from 5-bromoindole and **6e**; 4 h; yield 44% (100% *E*); mp 301-304°C (*i*-PrOH) (lit.,[7c] 341-344°C).

(*Z*)-5-Bromo-2',4'-demethyl-3'-deimino-3'-oxoaplysinopsin ((*Z*)-5-[(5-Bromo-1*H*-indol-3-yl)methyl-idene]imidazolidine-2,4-dione; 11a). This compound was prepared from 5-bromoindole and **6b**; 4 h; yield 45% (92% *Z*); mp >300°C (MeOH). *Anal.* Calcd for $C_{12}H_8N_3O_2Br$: C, 47.08; H, 2.63; N, 13.73; Found: C, 46.62; H, 2.64; N 13.44.

Table 2. ^{1}H and ^{13}C NMR Spectral Data for Compounds (**10**) and (**11**) in DMSO-d_6

Compound	^{1}H NMR (δ, *J* in Hz)	^{13}C NMR
10a	2.99 (3H, *s*, N*Me*), 3.23 (3H, *s*, N*Me*), 6.76 (1H, *s*, -C*H*=), 7.13 (1H, *dt*, *J*=1.3, 7.0, *H*-C(5')), 7.18 (1H, *dt*, *J*=1.4, 7.0, *H*-C(6')), 7.45 (1H, *dd*, *J*=1.4, 7.0, *H*-C(7')), 7.94 (1H, *dd*, *J*=1.3, 7.0, *H*-C(4')), 8.84 (1H, d, *J*=2.6, *H*-C(2')), 11.67 (1H, *br s*, N*H*-ind)	24.0, 25.9, 107.8, 108.3, 111.7, 117.8, 119.6, 121.8, 124.3, 127.5, 128.4, 135.5, 152.6, 161.7
10b	2.99 (3H, *s*, N*Me*), 3.24 (3H, *s*, N*Me*), 6.78 (1H, *s*, -C*H*=), 7.28 (1H, *dd*, *J*=2.0, 8.7, *H*-C(6')), 7.41 (1H, *d*, *J*=8.7, *H*-C(7')), 8.25 (1H, *d*, *J*=2.0, *H*-C(4')), 8.85 (1H, d, *J*=1.7, *H*-C(2')), 11.82 (1H, *br s*, N*H*-ind)	24.3, 26.3, 107.6, 108.4, 112.8, 113.8, 120.8, 124.5, 124.9, 129.6, 129.8, 134.4, 152.7, 161.9
10c	3.17 (3H, *s*, N*Me*), 6.68 (1H, *s*, -C*H*=), 7.26 (1H, *dd*, *J*=1.8, 8.6, *H*-C(6')), 7.40 (1H, *d*, *J*=8.6, *H*-C(7')), 8.23 (1H, *d*, *J*=1.8, *H*-C(4')), 8.78 (1H, d, *J*=2.7, *H*-C(2')), 11.20 (1H, *br s*, N*H*), 11.74 (1H, *br s*, N*H*-ind)	26.0, 107.0, 108.5, 112.8, 113.9, 120.9, 124.6, 126.3, 129.6, 129.8, 134.4, 153.1, 163.4
11a	6.72 (1H, *s*, -C*H*=), 7.28 (1H, *dd*, *J*=1.7, 8.7, *H*-C(6')), 7.38 (1H, *d*, *J*=8.7, *H*-C(7')), 7.98 (1H, *d*, *J*=1.7, *H*-C(4')), 8.14 (1H, d, *J*=2.6, *H*-C(2')), 10.13 (1H, *br s*, N*H*), 11.06 (1H, *br s*, N*H*), 11.97 (1H, *br s*, N*H*-ind)	101.3, 106.3, 108.3, 112.9, 113.9, 120.8, 124.2, 124.9, 128.0, 134.6, 155.4, 165.4
11b	2.96 (3H, *s*, N*Me*), 6.84 (1H, *s*, -C*H*=), 7.28 (1H, *dd*, *J*=1.8, 8.6, *H*-C(6')), 7.38 (1H, *d*, *J*=8.6, *H*-C(7')), 8.02 (1H, *d*, *J*=1.8, *H*-C(4')), 8.15 (1H, d, *J*=2.9, *H*-C(2')), 10.34 (1H, *br s*, N*H*), 12.00 (1H, *br s*, N*H*-ind)	24.2, 103.4, 108.3, 113.0, 114.0, 120.8, 122.9, 124.8, 125.1, 128.8, 134.6, 155.0, 164.1

(*Z*)-5-Bromo-2'-demethyl-3'-deimino-3'-oxoaplysinopsin ((*Z*)-5-[(5-Bromo-1*H*-indol-3-yl)methyl-idene]-3-methylimidazolidine-2,4-dione; 11b). This compound was prepared from 5-bromoindole and **6c**; 4.5 h; yield 40% (>95% *Z*); mp >300°C (MeOH). *Anal.* Calcd for $C_{13}H_{10}N_3O_2Br$: C, 48.77; H, 3.15; N, 13.13. Found: C, 48.35; H, 3.21; N, 12.88.

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