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ORIGINAL PAPER

Synthesis and Characterization of Aplysinopsin Analogs

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Abstract Three aplysinopsin analogs were synthesized by reacting 5-bromo-5-fluoro- and 6-bromoindole-3-carboxaldehyde with either creatinine or 2-imino-1,3-dimethylimidazolidin-4-one or 2-imino-1-methyl-3-ethylimidazolidin-4-one Single crystal structures on 5-bromo-4′-de-*N*-methylaplysinopsin DMF solvate [from creatinine, space group $P2_1/n$, lattice parameters a = 13.117(3) Å, b = 8.6663(15) Å, c = 14.743(3) Å, β = 99.538(10)° at 173 K], 5-fluoroaplysinopsin DMF solvate [from 2-imino-1,3-dimethyl-imidazolidin-4-one, space group $P2_1/c$, lattice parameters a = 11.114(3) Å, b = 19.118(2) Å, c = 8.503(2) Å, β = 112.290(7)°], and 6-bromoindole-3-carboxaldehyde (space group $P2_1/n$, lattice parameters a = 7.657(2) Å, b = 7.933(2) Å, c = 13.521(3) Å, β = 99.046(13)°) have been determined. Characterizations include spectrometric identifications employing IR, UV, HRMS, and ^{1}H and ^{13}C NMR. 5-Bromo-4′-de-*N*-methylaplysinopsin and 5-fluoroaplysinopsin exist in the *E* configuration.

Keywords Crystal structures · Aplysinopsin analogs · Indole alkaloids

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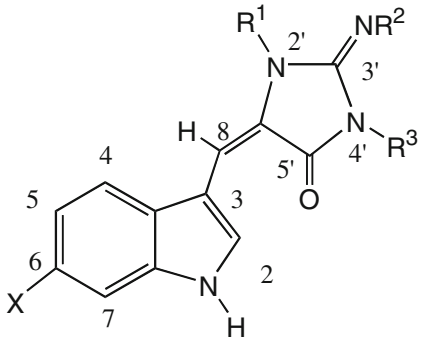
Introduction

Aplysinopsin (**1**) was first isolated in 1977 from the marine sponges *Thorecta aplysinopsis* and *Verongia spengelii* [1, 2]. Subsequently, Djura and Falukner [3] isolated aplysinopsin (**1**), isoaplysinopsin (**2**), and two aplysinopsin derivatives, 2′-de-*N*-methylaplysinopsin (**3**), and 6-bromo-2′-de-*N*-methylaplysinopsin (**4**) from the Belize sponge *Dercitus*. Several other aplysinopsins (**5**–**8**) have been isolated from marine sponges, including two additional 6-bromoaplysinopsins (**5** and **6**) [4–6], 1′, 8-dihydroaplysinopsins [7, 8] and aplysinopsins with a carbonyl group in the 3′ position [9–12].

Various aplysinopsins have been reported to have anti-tumor [2] or anti-filarial activity [13], and to bind to 5-HT_{2A} and 5-HT_{2C} serotonin receptors [4]. A structure-affinity study [4] of a series of naturally occurring aplysinopsins indicated that a bromine atom in the six position of the indole ring (**4**) increases selective binding for the 5-HT_{2C} subtype. Here we report the synthesis of three halogen containing aplysinopsin analogs (**5**, **11**, and **15**). The method used for the synthesis of these aplysinopsin analogs is an adaptation of a procedure reported by Djura and Faulkner [3]. The single crystal structures were determined for two of the aplysinopsins (**11** and **15**), as

well as for 6-bromoindole-3-carboxaldehyde, which was used for the synthesis of 6-bromoaplysinopsin (**5**).



1: X = R^2 = H; R^1 = R^3 = CH_3
2: X = R^3 = H; R^1 = R^2 = CH_3
3: X = R^1 = R^2 = H; R^3 = CH_3
4: X = Br; R^1 = R^2 = H; R^3 = CH_3
5: X = Br; R^1 = R^3 = CH_3; R^2 = H
6: X = Br; R^1 = CH_3; R^2 = R^3 = H
7: X = H; R^1 = R^2 = R^3 = CH_3
8: X = H; R^1 = R^3 = CH_3; R^2 = CH_2CH_3

Experimental

General Methods

^{1}H NMR spectra were acquired in d_6-DMSO at 300 MHz, and the ^{13}C NMR spectra at 75.5 MHz using a Varian Mercury 300 spectrometer. Ultraviolet–visible spectra were obtained with a Thermo Electron Vision spectrometer using DMF as a solvent. Infrared spectral data were recorded on a Nicolet Magna 560 FTIR over the frequency range of 4000–600 cm^{-1} using a Nujol mull technique. The high resolution mass spectra were run at the University of Minnesota on either a Finnigan MAT 95 or Bruker BioTOF mass spectrometer (Table 1).

Preparation of 5-Bromo-2′-de-*N*-methylaplysinopsin (**11**)

5-Bromoindole-3-carboxaldehyde (5.00 g) and creatinine (2.52 g) were placed in a 100 mL three-neck round-bottomed flask fitted with a nitrogen gas inlet, and a probe from a JKEM 210 for monitoring the temperature. The flask was then heated carefully with a Bunsen burner and the temperature was kept at approximately 153 °C for 10 min. Considerable frothing of the mixture took place during the course of the reaction. The reaction mixture was allowed to cool to room temperature and then extracted with ether (2 × 50 mL). Evaporation of the ether gave a solid that was recrystallized from DMF-water to give light orange needles (2.30 g, 32%), m.p. 309–310 °C (decomposition begins at 280 °C). HRMS: $M^{\bullet+}$ + H, 318.9959. Requires: $M^{\bullet+}$ + H, 318.9951.

*IR, UV, ^{1}H and ^{13}C NMR Spectra of **11***

Selected infrared absorptions (cm^{-1}): 3318, 3163, 1696, 1661, 1624 cm^{-1}.

^{1}H NMR: δ 11.63 (s, 1H, NH), 9.13 [d, J = 2.7 Hz, 1H, C(2)H], 8.19 [d, J = 1.8 Hz, 1H, C(4)H], 7.96 (s, DMF), 7.73 (s, 2H, NH_2), 7.40 [d, J = 9.0 Hz, 1H, C(7)H], 7.26 [dd, J = 8.4 Hz and J = 2.1 Hz, 1H, C(6)H], 6.55 [s, 1H, C(8)H], 3.30 (s, 3H, CH_3).

^{13}C NMR: δ 175.49, 165.13, 162.34 (DMF), 134.33, 131.27, 129.89, 129.67, 124.10, 120.73, 113.77, 112.40, 108.98, 104.25, 35.80, 30.79 (DMF), 27.95 (DMF).

Ultraviolet–visible spectrum: λ_{max} at 473 nm (log ε = 2.95), 450 nm (log ε = 2.91), and 365 nm (log ε = 4.68).

Preparation of 5-Fluoroindole-3-carboxaldehyde (**12**)

Phosphorus(V) oxychloride (4.25 g) was added dropwise to DMF (6 mL) cooled in an ice bath. The mixture was kept at 0 °C for 30 min. A solution of 5-fluoroindole (3 g) in DMF (22 mL) was added dropwise, keeping the reaction temperature below 10 °C. After 3 h at 20 °C, the syrupy solid was poured into ice-water (180 g), neutralized with 1 N NaOH, and left standing overnight. The crude product was collected by filtration and recrystallized from ethanol to give the 5-fluoroindole-3-carboxaldehyde (2.15 g, 72%); m.p. 170–171 °C (reported m.p. 170–171 °C) [14].

*IR, ^{1}H NMR Spectra of **12***

Selected infrared absorptions (cm^{-1}): 2724, 1641, 1614, 1581 cm^{-1}.

^{1}H NMR: δ 12.29 (s, 1H, NH), 9.93 (s, 1H, CH=O), 8.37 (s, 1H, C(2)H), 7.77 (dd, J = 3 Hz and J = 10 Hz, 1H, C(4)H), 7.54 (dd, J = 5 Hz, and J = 9 Hz, 1H, C(7)H), 7.13 (tt, J = 9 Hz and J = 3 Hz, 1H, C(6)H).

Preparation of 5-Fluoroaplysinopsin (**15**)

5-Fluoroindole-3-carboxaldehyde (1.00 g) and 2-imino-1,3-dimethyl-imidazolidin-4-one (**14**) (0.935 g) were placed in a 100 mL three-neck round-bottomed flask fitted with a nitrogen gas inlet, and a probe from a JKEM 210 for monitoring the temperature. The flask was then heated carefully with a Bunsen burner and the temperature was

Table 1 Crystal data and structure refinement

	11	**15**	**13**
Empirical formula	$C_{13}H_{11}BrN_4O \cdot C_3H_7NO$	$C_{14}H_{13}FN_4O \cdot C_3H_7NO$	C_9H_6BrNO
CCDC deposition no.	CCDC 666374	CCDC 666375	CCDC 666376
fw	392.26	345.38	224.06
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_1/c$	$P2_1/n$
Cell dimensions			
a (Å)	13.117(3)	11.114(3)	7.657(2)
b (Å)	8.6663(15)	19.118(2)	7.933(2)
c (Å)	14.743(3)	8.503(2)	13.521(3)
β (°)	99.538(10)	112.290(7)	99.046(13)
V (Å^3)	1652.8(6)	1671.7(6)	811.1(3)
T (K)	173	90	90
Z	4	4	4
Crystal size	0.03 × 0.05 × 0.32	0.22 × 0.25 × 0.30	0.10 × 0.12 × 0.20
ρ_{calc} (g cm^{-3})	1.576	1.372	1.835
μ (mm^{-1})	2.507	0.101	5.010
Transm. coeff.	0.501–0.929	–	0.434–0.634
$2\theta_{max}$ (°)	55.8	62.2	65.2
Data collected	14,846	21,615	15,724
Independent/observed (I > 2σ(I))	3928/3035	4652/3295	2902/2429
R_{int}	0.032	0.034	0.019
R	0.035	0.043	0.027
wR2 [I > 2σ(I)]	0.070	0.100	0.059
Data/param	3928/229	4652/237	2902/112
Resid. dens. (eÅ^{-3})	0.31, −0.30	0.38, −0.23	0.62, −0.44

kept at approximately 153 °C for 10 min. Considerable frothing of the mixture took place during the course of the reaction. The reaction mixture was allowed to cool to room temperature and then extracted with methanol (4 × 50 mL). Evaporation of the methanol gave a solid that was recrystallized from DMF-water to give orange crystals (0.850 g, 85%), m.p. begins to decompose at 245 °C, m.p. 295–300 °C. HRMS: $M^{\bullet+}$ + H, 273.1149. Requires: $M^{\bullet+}$ + H, 273.1146.

*IR, UV, ^{1}H NMR Spectra of **15***

Selected infrared absorptions (Nujol mull, cm^{-1}): 3357, 3311, 3132, 1722, 1651, 1632 cm^{-1}.

^{1}H NMR: δ 11.57 (s, 1H, NH), 8.76 [d, J = 2.7 Hz, 1H, C(2)H], 7.75 [dd, J = 2 Hz and J = 10 Hz, 1H, C(4)H], 7.42 [dd, J = 9 Hz and J = 5 Hz, 1H, C(7)H], 6.99 [tt, J = 9 Hz and J = 2 Hz, 1H, C(6)H], 6.64 (s, br, 1H, C=NH), 6.40 [s, 1H, C(8)H], 3.26 [s, 3H, N(2′)CH$_3$], 3.07 [s, 3H, N(4′)CH$_3$].

Ultraviolet–visible spectrum: λ_{max} at 376 nm (log ε = 4.52).

Preparation of 2-Amino-3-ethyl-1-methylimidazolidin-4-one (**15**)

Creatinine (**10**, 10 g) and iodoethane (22.1 g) were dissolved in 100 mL of 95% ethanol and refluxed for 7 days. The solvent was removed by rotary evaporation. The crude product was dissolved in anhydrous methanol and passed through a basic ion exchange column (Bio-Rad AG 3-X4 washed with 200 mL of anhydrous methanol prior to use), after 300 mL of eluent had been collected, the methanol was removed by rotary evaporation, the product was extracted with benzene (2 × 30 mL) and the benzene was removed by rotary evaporation. The crude product was recrystallized three times from acetonitrile to give a light yellow solid (4.5 g, 36%), m.p. 201–203 °C. Anal. Calcd. For $C_6H_{12}N_3OI$: C, 26.78, H, 4.49, N, 15.61; Found: C, 27.38, H, 4.47, 16.23.

*IR, ^{1}H NMR Spectra of **15***

Selected infrared absorptions (Nujol mull, cm^{-1}): 3145, 3066, 1671, 1658, 1628 cm^{-1}.

^{1}H NMR: 4.24 (s, 2H, CH_2), 3.61 (q, $J = 7$ Hz, 2H, $\underline{CH_2}$ CH_3), 3.08 (s, 3H, NCH_3), 2.93 (s, 1H, NH) and 1.11 (t, $J = 7$ Hz, 3H, CH_2 $\underline{CH_3}$).

Preparation of 5-Bromo-3′-de-*N*-methyl-3′-ethylaplysinopsin (**19**)

5-Bromoindole-3-carboxaldehyde (0.37 g) and 2-amino-3-ethyl-1-methylimidazolidin-4-one (0.23 g) gave **19** (0.26 g, 70% yield), m.p. begins to decompose at 295 °C, m.p. 305–307 °C. HRMS: $M^{\bullet+}$ + H, 347.0508. Requires $M^{\bullet+}$ + H, 347.0502.

*IR, ^{1}H NMR Spectra of **19***

Selected infrared absorptions (cm^{-1}): 3318, 3194, 3148, 1716, 1666, 1612 cm^{-1}.

^{1}H NMR: 12.99 (d, $J = 3$ Hz, 1H, NH), 9.40 (s, 1H, C=NH), 8.99 (d, $J = 3$ Hz, 1H, C(2)H), 8.39 (d, $J = 2$ Hz, 1H, C(4)H), 7.49 (d, $J = 2$ Hz, 1H, C(7)H), 7.36 (dd, $J = 9$ and 2 Hz, 1H, C(6)H), 7.34 (s, 1H, C(8)H), 3.79 (m, $J = 7$ Hz, 2H, CH_2), 3.51 (s, 3H, N-CH_3) and 1.19 (t, $J = 7$ Hz, 3H, CH_3).

Preparation of 6-Bromoindole-3-carboxaldehyde (**13**)

Phosphorus(V) oxychloride (1.96 g) was added dropwise to DMF (3 mL) cooled in an ice bath. The mixture was kept at 0 °C for 30 min. A solution of 6-bromoindole (2.00 g) in DMF (22 mL) was added dropwise, keeping the reaction temperature below 10 °C. After 3 h at 20 °C, the syrupy solid was poured into ice-water (180 g), neutralized with 1N NaOH, and left standing overnight. The crude product was collected by filtration and recrystallized from ethanol or DMF to give the 6-bromoindole-3-carboxaldehyde (**13**) (1.42 g, 71%); m.p. 200–201 °C. The ^{1}H NMR spectrum of **13** is identical to ^{1}H NMR reported by Rasmussen et al. [15].

Preparation of 6-Bromoaplysinopsin (**5**)

6-Bromoindole-3-carboxaldehyde (1.00 g) and 2-imino-1,3-dimethyl-imidazolidin-4-one (14) (0.567 g) were heated at approximately 153 °C for 10 min. Considerable frothing of the mixture took place during the course of the reaction. The reaction mixture was extracted with methanol (4 × 50 mL). Evaporation of the methanol gave a solid that was recrystallized from DMF-water to give orange needles (0.550 g, 56%), m.p. begins to decompose at 269 °C, m.p. 281–282 °C). HRMS: $M^{\bullet+}$ + H, 333.0346. Requires: $M^{\bullet+}$ + H, 333.0345.

*IR, UV, ^{1}H NMR Spectra of **5***

Selected infrared absorptions (Nujol mull, cm^{-1}): 3333, 3122 (w), 3065 (w), 1724, 1646, 1632 cm^{-1}.

^{1}H NMR: δ 11.58 (s, 1H, NH), 8.69 [s, 1H, C(2)H], 7.87 [d, $J = 9$ Hz, 1H, C(4)H], 7.61 [d, $J = 1.5$ Hz, 1H, C(7)H], 7.23 [dd, $J = 9$ Hz and $J = 1.5$ Hz, 1H, C(5)H], 6.75 and 6.54 (two s, br, 0.6H and 0.4H, C=NH), 6.39 [s, 1H, C(8)H], 3.25 [s, 3H, N(2′)CH_3], 3.06 [s, 3H, N(4′)CH_3].

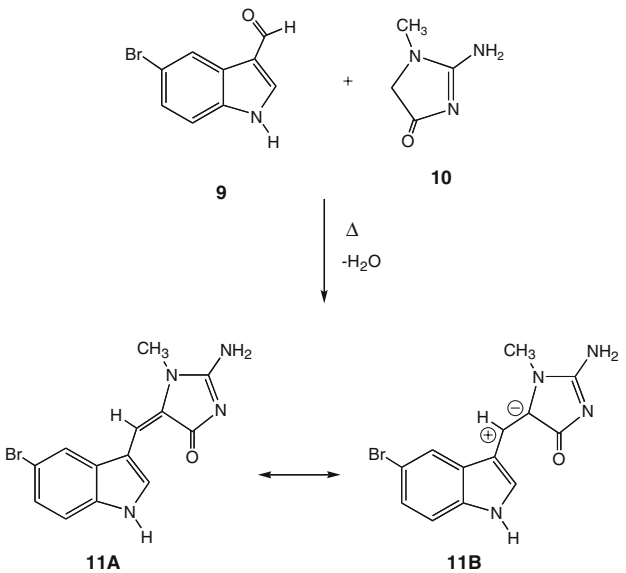
Ultraviolet–visible spectrum: 381 nm (log $\varepsilon = 4.50$).

X-ray Data Collection and Structure Determination

Diffraction data for **11**, **13**, and **15** were collected at low temperature on a Nonius Kappa CCD diffractometer fitted with an Oxford Cryostream cooler and graphite-monochromated Mo Kα (0.71073 Å) radiation. Data for **11** were collected at 173 K, and for **13** and **15** at 90 K. Data reduction included absorption corrections for the Br-containing compounds by the multi-scan method, with HKL SCALEPACK [16]. Structures were solved by direct methods and difference Fourier techniques and refined by full-matrix least squares techniques using SHELXL97 [17]. All nonhydrogen atoms were refined anisotropically. All hydrogen atoms were visible in difference maps, but were placed in idealized positions with $U_{iso} = 1.2U_{eq}$ for the bonded atom (1.5 for methyl groups). A torsional parameter was refined for each methyl group, and coordinates of N–H hydrogen atoms were refined.

Results and Discussion

The synthesis of 5-bromo-4′-de-*N*-methylaplysinopsin (**11**) was carried out by an aldol condensation of 5-bromoindole-3-carboxaldehyde (**9**) with creatinine(**10**).



This synthesis is particularly attractive since creatinine is commercially available and indole-3-carboxaldehydes are either commercially available or can be readily prepared from substituted indoles [18]. Crystals of 5-bromo-4′-de-*N*-methylaplysinopsin (**11**) suitable for a single crystal X-ray structure determination were obtained by crystallization from DMF. The X-ray structure shows that a molecule of DMF is incorporated into the crystalline lattice (Fig. 1).

The structure of **11** shows that the molecule is nearly planar, with its 19 nonhydrogen atoms having an average deviation of only 0.028 Å. The C–Br distance is 1.914(2) Å. The near-planarity of the molecule allows an intramolecular close contact between the H atom on indole C2 and O1′. This interaction has C···O distance 2.927(2) Å and a 136° angle about H, and can be considered a C–H···O hydrogen bond [19]. All N–H groups are also involved in intermolecular N–H···O and N–H···N hydrogen bonds, having N···X distances in the range 2.785(2)–3.000(3) Å, the longest involving the NH_2 group as donor and DMF oxygen as acceptor. The shortest Br…Br distance is 4.472(1) Å, approximately 0.8 Å longer than twice the van der Waals radius of Br, indicating a lack of significant Br–Br contacts.

Compound **11** has been synthesized previously by the reaction of 5-bromoindole-3-carboxaldehyde with creatinine in an acetic acid mixture containing sodium acetate [5]. The compound was isolated as its acetate salt from the reaction mixture and was not further purified.

There are several structural characteristics that were resolved by our X-ray structure determination. First of all the carbon–carbon double bond linking the indole ring to the imidazole ring was determined to be in the *E* configuration. Although the configurations of some aplysinopsins have been determined from heteronuclear coupling constants between the hydrogen on C8 and the C5′ carbonyl carbon atom [4, 10, 20], the X-ray structures provide unambiguous assignment of the configuration about this bond in the aplysinopsin analogs reported herein.

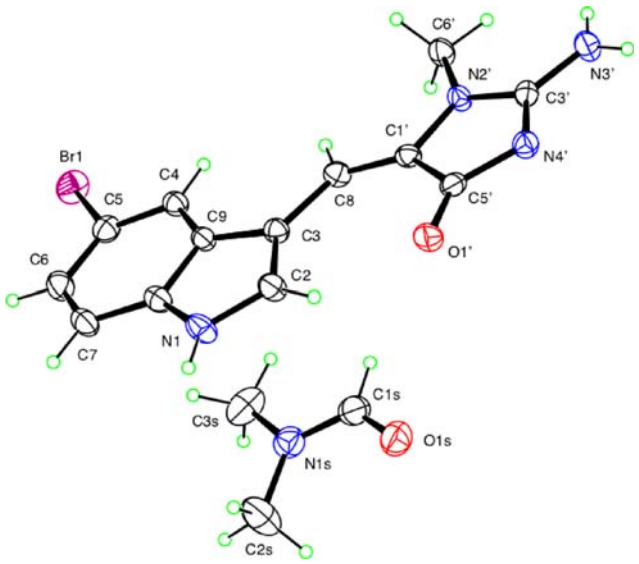
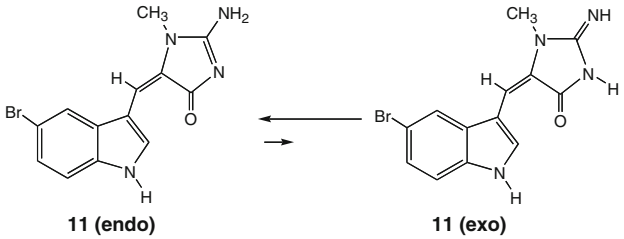


Fig. 1 ORTEP drawing of **11**, with 50% ellipsoids, showing the numbering scheme

Secondly, the imidazolone ring can exist in two different tautomeric forms, one where the imine double bond is endocyclic (**11-endo**) and the other



where the imine double bond is exocyclic (**11-exo**). The crystal structure shows that the imidazolone ring exists in the endocyclic tautomeric form in the solid state. The ^{1}H NMR of **11** shows an absorption at 7.73 ppm integrating for two hydrogen atoms. This absorption must be due to the NH_2 group, which demonstrates that the **11-endo** tautomeric form also exits in d_6-DMSO solution. While the naturally occurring aplysinopsins **1**, **5**, **7**, and **8** have methyl groups on the imidazolone nitrogen atoms and therefore must exist in the exocylic imine form, the aplysinopsins **2**–**4** and **6** are capable of existing in either form. In the literature, aplysinopsins **2**–**4** and **6** have been reported in either the endocyclic or the exocyclic tautomer, usually without explanation. The aplysinopsins **3**, **4**, **6**, and **11** were drawn [5] as the endocyclic tautomer based on work carried out on imidazolidin-4-ones, which have been shown to exist in the endocyclic tautomer [21]. The ^{1}H NMR evidence to support these assignments in aplysinopsins has not been discussed.

Another structural feature of aplysinopsin **11** concerns the polarization of the carbon–carbon double bond linking the indole ring with the imidazolone ring. Polarization of this bond so that the negative charge is in the imidazolone ring makes the ring aromatic with six π electrons and creates a conjugated indole carbocation (see resonance structure **11B**). The X-ray structure shows that the carbon–carbon double bond (C8–C1′) linking these two rings is only slightly longer [1.347 (3) Å] than a typical conjugated double bond (1.33 Å) and the C3–C8 single bond is slightly shorter [1.446 (3) Å] than the typical single bond adjacent to a conjugated double bond (1.54 Å). This

suggests that that resonance structure **11B** only makes a minor contribution to the resonance hybrid. This also implies that the degree of overlap of the p-orbitals in the C8–C1′ double bond should be high and the barrier for thermal *Z/E* isomerization should be high enough for both the *Z* and *E* isomers of aplysinopsins and aplysinopsin analogs to be isolated.

It is not clear from the literature on aplysinopsins whether the two geometric isomers of these compounds can be separated and isolated. There are reports of mixtures of the *Z* and *E* isomers of aplysinopsins, including some samples that contain as much as 50% of each isomer [9]. In one instance an aplysinopsin that was predominately in the *Z* configuration [*Z/E* > 95/5] was photoisomerized at 350 nm to give a mixture enriched in the *E* isomer [10]. When this mixture was kept at room temperature in the dark for a few days the *E* isomer isomerized back to the *Z* isomer. It has been suggested that synthetic analogs and naturally occurring aplysinopsins without an alkyl group on N(2′) exist predominately in the *Z* configuration while aplysinopsins with an alkyl group on N(2′) are mainly in the *E* configuration [10]. In a review article by Wells [11], it was reported that X-ray structures for the *Z* and *E* isomers of methylaplysinopsin (**7**) have been carried out. The reference in this review is to unpublished work that to our knowledge has never appeared in print.

Two other aplysinopsin analogs (**18** and **19**) and one naturally occurring aplysinopsin (**5**) were prepared in this work by the reaction of 5-fluoroindole-3-carboxaldehyde (**12**) or 5-bromoindole-3-carboxaldehyde with the hydroiodide salt of 2-imino-1,3-dimethyl-imidazolidin-4-one (**14**) and the reaction of 5-bromoindole-3-carboxaldehyde (**12**) with the hydroiodide salt of 2-imino-1-methyl-3-ethyl-imidazolidin-4-one (**15**). The imidazolidin-4-ones **14** and **15** were prepared by alkylation of creatinine (**10**) [21]. Crystals of **15** were obtained by crystallization from DMF. Again a molecule of DMF was incorporated into the crystalline lattice. The structure of **15** is illustrated in Fig. 2, which does not include the DMF solvent molecule. The molecule is slightly less planar than **11**, with its 20 nonhydrogen atoms having a mean deviation of 0.055 Å from coplanarity, with methyl groups C6′ and C7′ deviating the most, 0.156(1) and 0.161(1) Å, respectively. The C–F distance is 1.3719(15) Å. The C2–H···O1′ interaction is very similar to that in **11**, with a C···O distance of 2.889(1) Å and a 135° angle about H. Both N–H groups are involved in intermolecular hydrogen bonds, but are somewhat longer than those in **11**. Nitrogen atom N1 donates to N3′ with a N···N distance of 2.9137(15) Å, and N3′ donates to the solvent oxygen, with a N···O distance of 3.1230(15) Å.

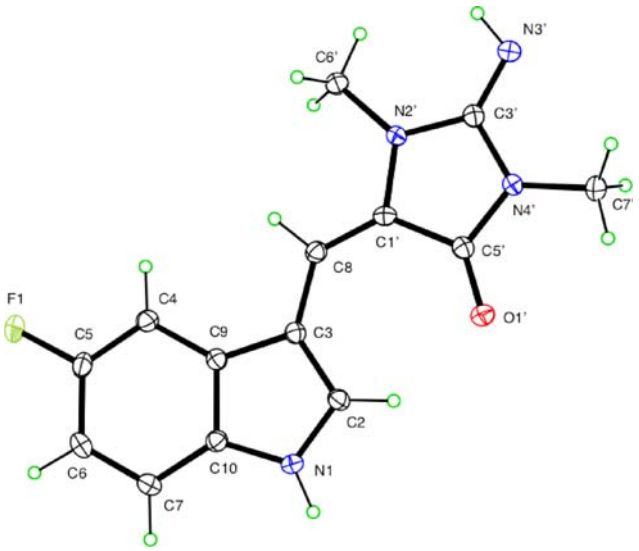
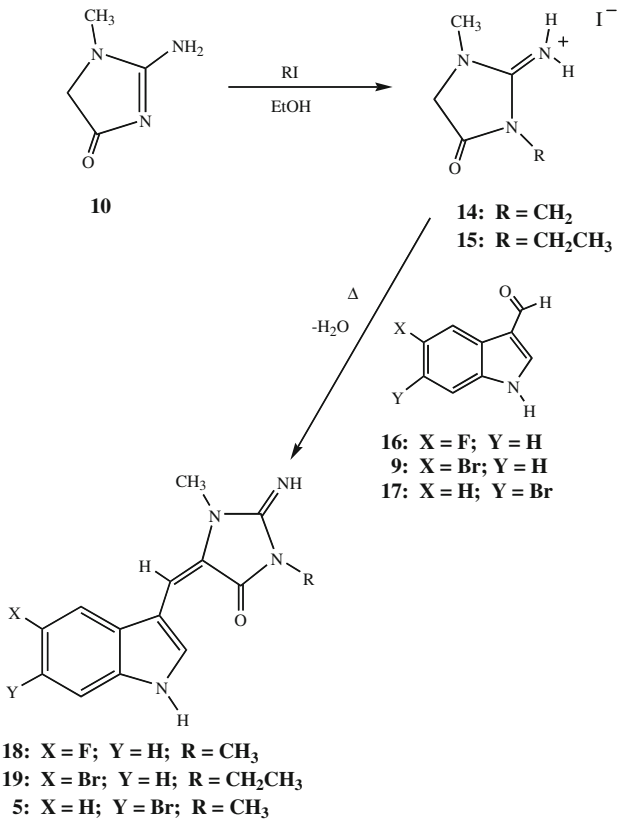
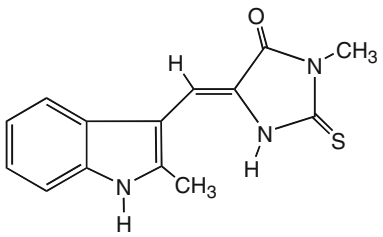


Fig. 2 ORTEP drawing of **15**, with 50% ellipsoids



The naturally occurring 5-Bromoaplysinopsin has been (**5**) synthesized previously by Fattorusso et al. [6] and their ^{1}H NMR is identical to the one that we obtained. This compound has been reported [6] to be identical to a naturally occurring aplysinopsin [6].

The only X-ray structure of an aplysinopsin or aplysinopsin analog that has been published was carried out on a thioaplysinopsin (**20**) [22]. The X-ray



20

structure of **20** shows that this aplysinopsin analog is in the *Z* configuration.

During the course of our work on the synthesis of aplysinopsin analogs we obtained a crystal structure on 6-bromoindole-3-carboxaldehyde (**13**), which is the indole precursors used to prepare **5**. This compound has been found in marine sponges [12, 15, 23, 24]. The structure of **13** is shown in Fig. 3. The C–Br distance is 1.9015(16) Å. The C, N, and Br atoms are coplanar to within an average deviation of 0.017 Å, with the O atom lying 0.156(1) Å out of that plane, a result of a small torsional twist about the C3–C8 bond, 4.9(3)°. The N–H group forms a nearly linear intermolecular hydrogen bond with the O atom, at a N···O distance of 2.821(1) Å. There are no significant intermolecular Br…Br contacts, the shortest such distance being 4.682(1) Å. The structure of indole-3-carboxaldehyde, which lacks the bromine atom, has been reported [25, 26]. There are also structures on two indole-3-carboxaldehydes with substituents on the benzene ring [27, 28].

In summary, three new aplysinopsins analogs (**11**, **18**, and **19**) have been synthesized. The X-ray structures of **11** and **18** have established that these compounds exist in the *Z* configuration about the C8-1′ double bond. The X-ray structure of **11** establishes that the carbon–nitrogen double bond in the imidazolone ring is in the endocylic tautomeric form in the solid state. The ^{1}H NMR of **15** shows that this double bond in the endocyclic position in DMSO solution.

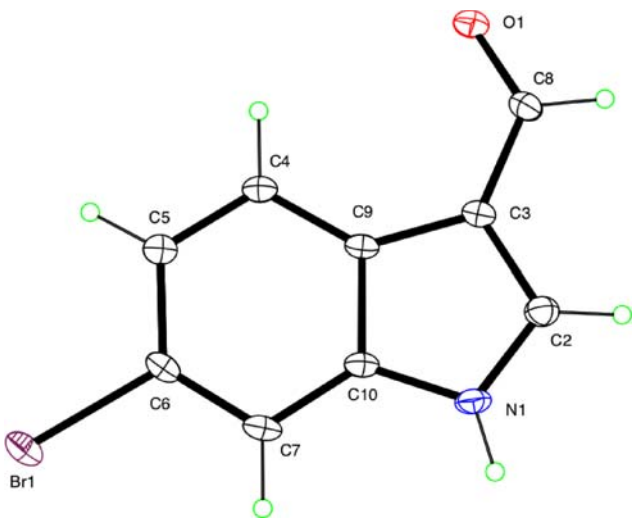


Fig. 3 ORTEP drawing of **13**, with 50% ellipsoids

Supplementary Material

CCDC 666374-666376 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44-1223-336033.

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