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A simple synthesis of aplysinopsin analogues by dimethylamine substitution in *N*,*N*-(dimethylamino)methylidene derivatives of five-membered heterocycles

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Abstract—Some new aplysinopsin analogues were prepared by a simple coupling of *N*,*N*-(dimethylamino)methylidene substituted hydantoin, thiohydantoin, and thiazolone derivatives, with indole derivatives. Configuration around the exocyclic C=C double bond was determined on the basis of long-range heteronuclear coupling constants using 2D HMBC correlation technique. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Since their isolation from various marine organisms,[1–6] aplysinopsins (**1**) (Fig. 1) have attracted considerable interest, especially due to their cytotoxicity towards cancer cells[3] and their ability to affect neurotransmitters.[2] Synthetic routes towards aplysinopsins are generally based on two approaches: (a) condensation reaction between the 3-formylindole derivative and a suitable hydantoin derivative[4–7] and (b) condensation reaction between the 3-formylindole derivative and ethyl azidoacetate to give the corresponding 2-azido-3-(indol-3-yl)propenoate, followed by tandem Staudinger/aza-Wittig reaction and subsequent cyclisation.[8,9]

Recently, a series of alkyl 2-substituted 3-(dimethylamino)propenoates have been prepared as versatile reagents for the synthesis of various heterocyclic systems and fuctionalized heterocycles, such as heteroaryl substituted α-amino- and α-hydroxy acid derivatives.[10–12] In this connection, 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 and, (b) a one-step synthesis from 5-[(dimethylamino)methylidene]hydantoin derivatives and analogues.[13] In this manner, aplysinopsins, thioaplysinopsins, and analogues in which the hydantoin moiety is replaced 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 (Fig. 1).[13,14] As an extension of our work in this field, we now report the synthesis and structural characterisation of some novel aplysinopsin analogues.

2. Results and discussion

In this paper, we present further examples of formation of aplysinopsin analogues by the procedure including 5-(dimethylamino)methylidene derivatives of some five

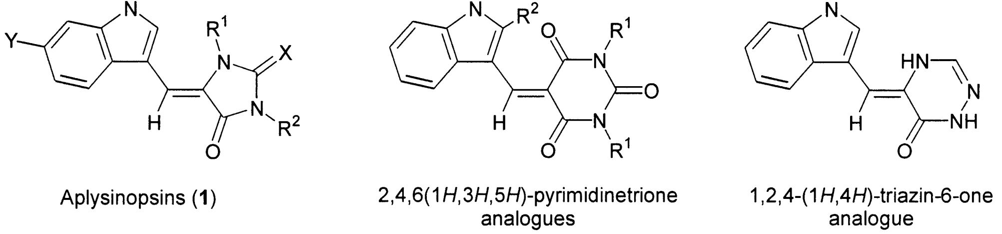

Figure 1. R[1], R[2]=H, Me; X=O, NH; Y=H, Br.

Keywords: aplysinopsins; enamines; hydantoins; indoles; NMR.

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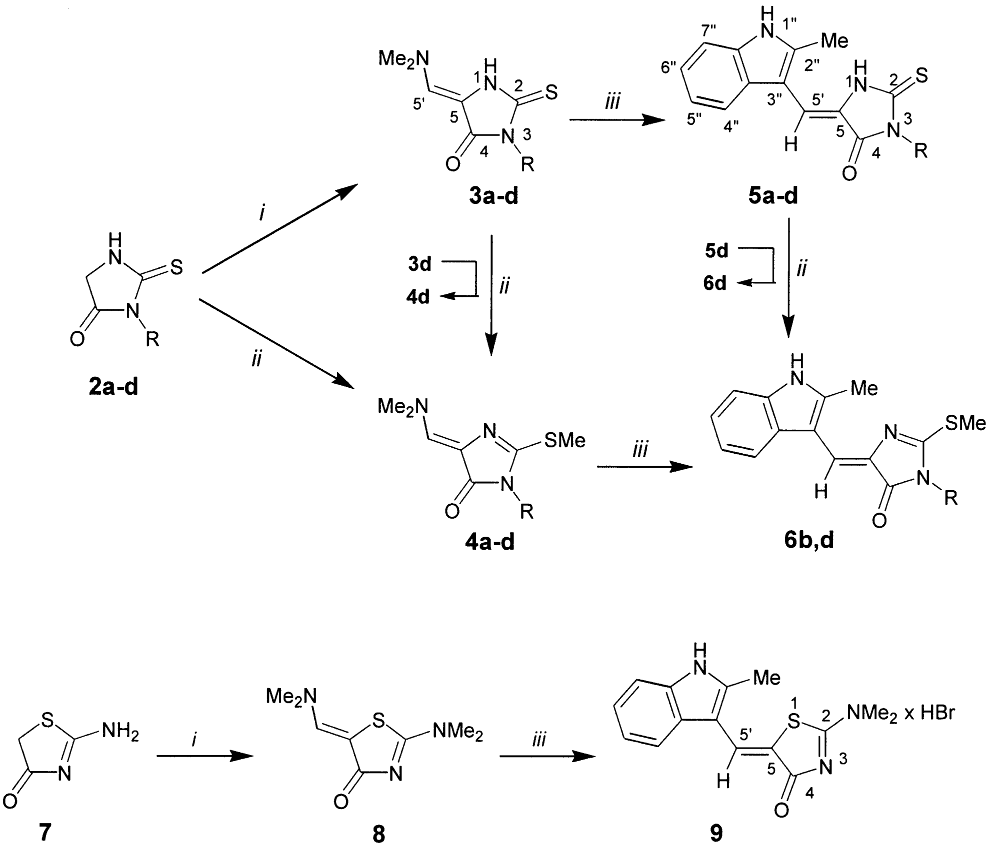
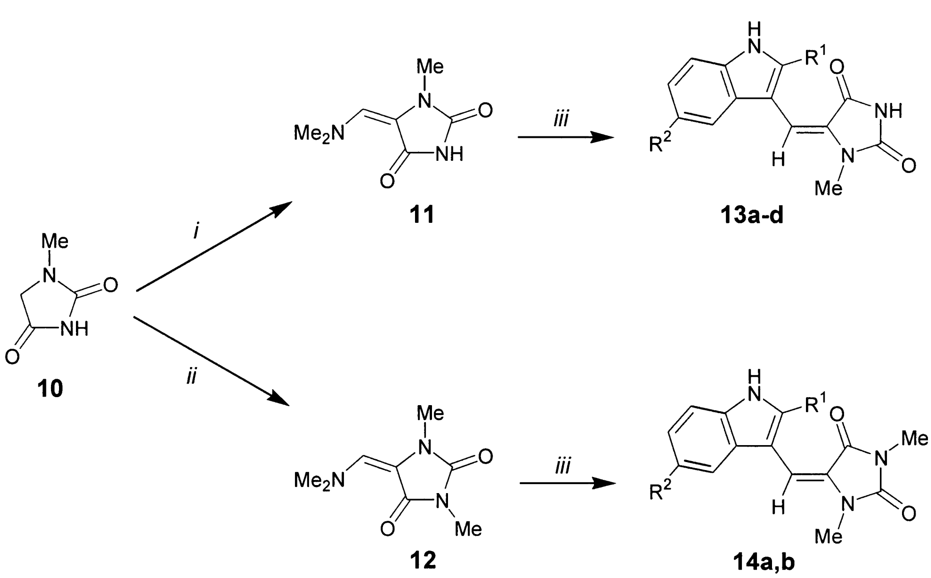
membered heterocycles, such as imidazolones, imidazolethiones, and thiazolones as the key intermediates. 3-Substituted thiohydantoins (2-thiooxoimidazolidin-4-ones) **2a–d** were converted with *tert*-butoxy-bis(dimethylamino)methane (Bredereck's reagent) into the corresponding 5-[(dimethylamino)methylidene]-2-thiooxo-4-imidazolidinones **3a–d** in 57–83% yield, while with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) also methylation at the exocyclic sulfur took place to give 5-[(dimethylamino)methylidene]-3-substituted-2-(methylsulfanyl)-3*H*-imidazol-4(5*H*)-ones **4a–d** in 7–65% yield. Compound **3d** was transformed with DMFDMA into **4d**, identical with the compound prepared from **2d**. 2-Amino-1,3-thiazol-4(5*H*)-one (**7**) gave by treatment with Bredereck's reagent in DMF 2-dimethylamino-5-[(dimethylamino)methylidene]-1,3-thiazol-4(5*H*)-one (**8**) in 65% yield. Treatment of 5-[(dimethylamino)methylidene]imidazole derivatives **3a–d**, **4b**,**d** with 2-methylindole in acetic acid in the presence of small amounts of hydrogen bromide at room temperature produced the corresponding 5-[(2-methyl-1*H*-indol-3-yl)methylidene]imidazole derivatives **5a–d**, **6b**,**d** as thioaplysinopsin analogues in 15–79% yield. Methylation of **5d** with DMFDMA took place at the sulfur atom to give **6d** in 51% yield. Upon reaction of **8** with 2-methylindole, 2-(dimethylamino)-5-[(*Z*)-1-(2-methyl-1*H*-indol-3-yl)methylidene]-1,3-thiazol-4(5*H*)-one (**9**) in the form of hydrobromide salt was isolated in 48% yield. (Scheme 1).

1-Methylimidazolidine-2,4-dione (1-methylhydantoin) (**10**) was transformed with *tert*-butoxy-bis(dimethylamino)methane into 5-[(dimethylamino)methylidene]-1-methylimidazolidine-2,4-dione (**11**) in 54% yield, while with DMFDMA also methylation occurred at the 3-position to give the corresponding 1,3-dimethyl derivative (**12**) in 98% yield. Compound **11** coupled with indole derivatives to give 5-[(1*H*-indol-3-yl)methylidene]-1-methylimidazolidine-2,4-diones **13a–d** in 38–81% yield. Similarly, treatment of compound **12** with indole and 2-methylindole furnished the corresponding 1,3-dimethyl derivatives **14a**,**b** in 65 and 61% yield, respectively. (Scheme 2).



Compound	R	Yield [%]				*Z*:*E*
		3	**4**	**5**	**6**	
2a–5a	Et	69	7	15		100:0
2b–6b	$CH_2CH{=}CH_2$	57	48	48	31	100:0
2c–5c	Ph	59	14	79		100:0
2d–6d	4-Me-C_6H_4	83	65	77	45	100:0

Scheme 1. (i) *tert*-BuOCH(NMe_2)$_2$, MeCN or DMF, reflux; (ii) DMFDMA, MeCN or DMF, reflux; (iii) 2-methylindole, AcOH, HBr, rt–50°.



Compound	R^1	R^2	Yield [%]	*Z*:*E*
11			54	0:100
12			98	0:100
13a	H	H	58	0:100
14a	H	H	65	0:100
13b	Me	H	81	62:38
14b	Me	H	61	28:72
13c	H	Br	38	0:100
13d	H	F	69	0:100

Scheme 2. (i) *tert*-BuOCH(NMe_2)$_2$, MeCN, reflux; (ii) DMFDMA, MeCN, reflux; (iii) indole derivative, AcOH, reflux.

3. Structure determination: (*Z*)- and/or (*E*)-orientation around the exocyclic double bond

Compounds **3–6**, **8**, **9**, **11–14** can exist in (*Z*)- and/or (*E*) isomeric forms with respect to the exocyclic C═C double bond. Since most of these compounds exist as single isomers, differentiation between (*Z*)- and (*E*)-form is not possible on the basis of chemical shifts or *J* values. However, the two isomeric forms can easily be differentiated on the basis of the magnitude of the long-range heteronuclear ^{13}C–^{1}H coupling constants, $^3J_{C-H}$, which have been used for determination of conformations and configurations in various systems.[15–17] Several methods for measuring $^3J_{C-H}$, such as TOCSY-based methods[18–20] and methods based on HMBC correlation techniques,[21–26] have been described in the literature. Recently, the orientation around the double bond in alkyl 2,3-(diamino)propenoates has been determined using the 2D HMBC method.[27] Generally, the magnitude of coupling constant $^3J_{C-H}$ for nuclei with *cis*-configuration around the C═C double bond is smaller (2–6 Hz) than that for *trans*-oriented nuclei (8–12 Hz).[25,27,28] Similar coupling constants have also been observed in some oxazolone derivatives with an analogous structural element.[29] For this reason, HMBC correlation technique was selected as the most suitable for the determination of the configurations around the exocyclic C═C double bonds in this study.

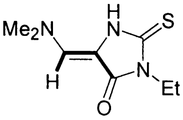
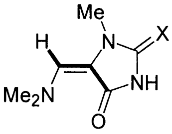
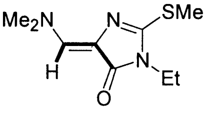
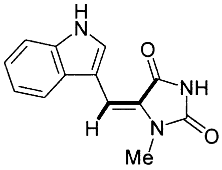
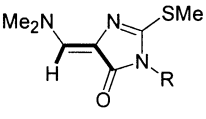
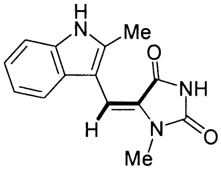
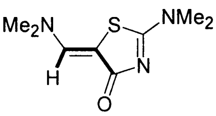
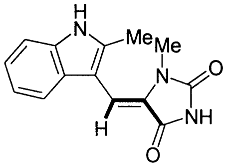
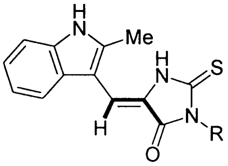
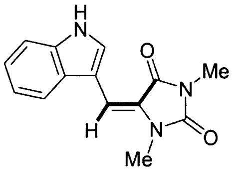
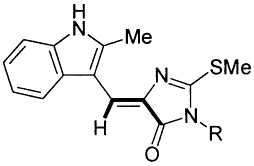
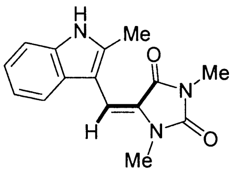
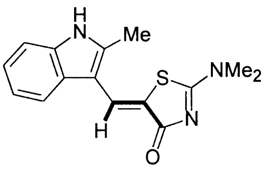
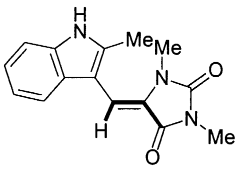
3.1. Structure of 5-[(dimethylamino)methylidene]azol-4-one derivatives 3, 4, 8, 11

The long-range coupling constants, $^3J_{C-H}$, between the methylidene protons (*H*–C(5′)) and the carbonyl carbon atoms (O═*C*(4)) in compounds **3a**, **4b**,**d**, **8**, **11** were measured from the antiphase splitting of cross peaks in the HMBC spectrum. In the case of compounds **3a**, **4b**,**d**, **8**, the magnitude of coupling constants, $^3J_{C-H}$=2.7–3.9 Hz, showed that these compounds exist in the (*Z*)-form, while for compound **11**, $^3J_{C-H}$=8.6 Hz, the (*E*)-configuration was established (Table 1).

3.2. Structure of aplysinopsin analogues 5, 6, 9, 13, 14

Orientation around the exocyclic double bond was determined analogously as for compounds **3**, **4**, **8**, **11** on the basis of the long-range heteronuclear coupling constants, $^3J_{C-H}$. Compounds **5d**, **6d**, **9**, **13a**, and **14a** were obtained in isomerically pure form. Thus, for compounds **5d**, **6d**, **9**, the (*Z*)-configuration, $^3J_{C-H}$=4.9–5.7 Hz, was established, while for compounds **13a** and **14a** the (*E*)-configuration,

Table 1. Configurations and $^{3}J_{C-H}$ coupling constants for compounds **3–6**, **8**, **9**, **11**, **13**, **14**

Compound	$^{3}J_{C-H}$ (Hz)	*Z* or *E*	Compound	$^{3}J_{C-H}$ (Hz)	*Z* or *E*
 **3a**	3.6	*Z*	 **11**	8.6	*E*
 **4b**	3.1	*Z*	 **13a**	10.9	*E*
 **4d** (R = 4-Me-C$_6$H$_4$)	2.7	*Z*	 **13b**	10.2	*E*
 **8**	3.9	*Z*	 **13b**	5.4	*Z*
 **5d** (R = 4-Me-C$_6$H$_4$)	5.1	*Z*	 **14a**	10.8	*E*
 **6d** (R = 4-Me-C$_6$H$_4$)	4.9	*Z*	 **14b**	11.0	*E*
 **9**	5.7	*Z*	 **14b**	5.5	*Z*

$^{3}J_{C-H}$=10.8–10.9 Hz, was determined (Table 1). The structure of **14a** was confirmed by X-ray analysis (Fig. 2, Table 1). On the other hand, compounds **13b** and **14b** were obtained as mixtures of isomers with $^{3}J_{C-H}$=5.4–5.5 Hz for the (*Z*)-isomers and with $^{3}J_{C-H}$=10.2–11.0 Hz for the (*E*)-isomers (Table 1). In the case of compound **14b**, both isomers were separated by medium pressure liquid chromatography (MPLC). Total assignment for H- and C-atoms in the (*E*)-isomer of compound **14b** has been done by means of HMBC, HMQC, and NOESY techniques. Furthermore, configuration of the (*E*)-isomer of **14b** was also confirmed by NOE-effect between the methylidene proton H–C(5′) and the Me–N(1) methyl group (Fig. 3).

4. Conclusion

Aplysinopsin analogues can be easily prepared by one-step synthesis from indole derivatives by dimethylamine substitution in substituted 5-[(dimethylamino)methylidene]azol-4-ones such as imidazolidine-2,4-diones, 2-thiooxoimidazolidin-4-ones, and 2-amino-5,6-dihydrothiazol-4-one, generally in good yields. The (*Z*)- and/or (*E*)-orientations around the methylidene (exocyclic) double bond were determined by 2D HMBC correlation technique, supported by NOE effect and X-ray analysis. Total assignment of ^{13}C signals for compound **14b** was achieved by means of HMQC, HMBC and NOESY. In conclusion, indole derivatives,

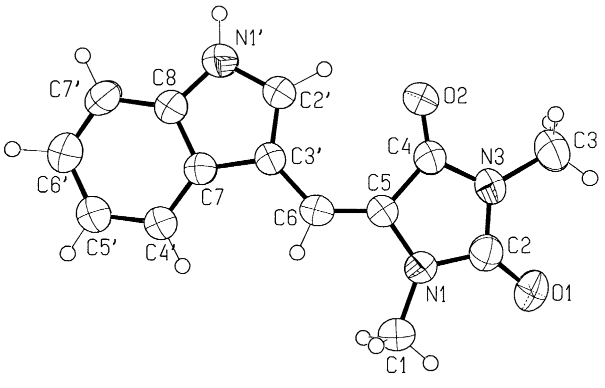
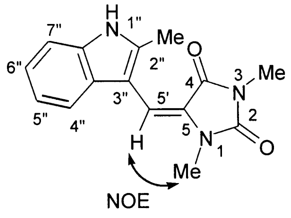


Figure 2. Ortep view of the asymmetric unit of compound **14a** with labelling of nonhydrogen atoms. (Ellipsoids are at 50% probability level.)



14b (*E*)-isomer

Figure 3. NOESY spectrum of the (*E*)-isomer of **14b** was taken in DMSO-d_6 at 302 K.

unsubstituted at position 2, reacted with 5-[(dimethylamino)methylidene]-1-methylimidazolidine-2,4-dione (**11**) and 5-[(dimethylamino)meth-ylidene]-1,3-dimethylimidazolidine-2,4-dione (**12**), affording only the (*E*)-aplysinopsin analogues **13a**,**c**,**d 14a**, while with 2-methylindole mixtures of (*Z*)- and (*E*)-isomers of **13b** and **14b** were formed. However, when 2-methylindole reacted with 5-[(*Z*)-(dimethylamino)methylidene]-2-thiooxoimidazolidin-4-one derivatives **3**, **4** and 5-[(*Z*)-(dimethylamino)-methylidene]-1,3-thiazol-4(5*H*)-one (**8**), the (*Z*)-aplysinopsin analogues **5a–d**, **6a–d**, and **9** were formed stereoselectively.

5. Experimental

5.1. General

Melting points were determined on a Kofler micro hot stage. The ^{1}H NMR, ^{13}C NMR, HMQC, HMBC, and NOESY spectra were obtained on a Bruker Avance DPX 300 at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C nucleus with DMSO-d_6 or $CDCl_3$ as solvents as stated and TMS as the internal standard. Mass spectra were recorded on an AutoSpecQ spectrometer and IR spectra on a Perkin–Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin–Elmer CHN Analyser 2400. TLC was performed on alu foils coated with silica gel 60, 0.2 mm (Merck). Column chromatography (CC) was performed on silica gel (Fluka, silica gel 60, 0.04–0.06 mm). Medium pressure liquid chromatography (MPLC) was performed with a Büchi isocratic system with detection[†] on silica gel (Merck, silica gel 40, 0.015–0.035 mm); column dimensions (dry filled): 15×460 mm; backpressure: 10–15 bar; detection: UV 254 nm.

3-Substituted-2-thiohydantoins **2a–d** were prepared according to the procedure described in the literature.[30]

5.2. General procedure for the preparation of 3-substituted 5-[(*Z*)-(dimethylamino)methylidene]- 2-thiooxoimidazolidin-4-ones (3a–d), 2-dimethylamino-5-[(*Z*)-(dimethylamino)methylidene]-1,3-thiazol-4(5*H*)-one (8), and 5-[(*E*)-(dimethylamino)methylidene]-1-methylimidazolidine-2,4-dione (11)

A mixture of compound **2a–d**, **7**, or **10** (3 mmol), acetonitrile (10 mL) or DMF (10 mL), and *tert*-butoxy-bis(dimethylamino)methane (783 mg, 4.5 mmol) was heated under reflux for 2–4 h. Volatile components were evaporated in vacuo, ethanol (10 mL) was added to the residue, and the precipitate was collected by filtration and washed with ethanol. Compounds **3a–d**, **8**, **11** were prepared in this manner.

5.2.1. 5-[(*Z*)-(Dimethylamino)methylidene]-3-ethyl-2-thiooxoimidazolidin-4-one (3a). Prepared from compound **2a** in acetonitrile, 4 h, 412 mg (69%) of a pale yellow solid; mp 201–203°C (EtOH). ^{1}H NMR (DMSO-d_6): δ 1.10 (3H, t, J=7.2 Hz, CH_3CH_2), 3.11 (6H, s, NMe_2), 3.74 (2H, q, J=7.2 Hz, CH_2CH_3), 6.76 (1H, s, H–C(5′)), 11.29 (1H, s, H–N(1)). ^{13}C NMR ($CDCl_3$): δ 13.5, 36.7, 43.3, 103.9, 132.0, 164.4, 171.3. (Found: C, 48.47; H, 6.75; N, 20.85. $C_8H_{13}N_3OS$ requires: C, 48.22; H, 6.58; N, 21.09.); ν_{max} (KBr) 3275, 2970, 1705, 1630, 1500, 1445 cm^{-1}; *m/z* (EI) 199 (M^+).

5.2.2. 5-[(*Z*)-(Dimethylamino)methylidene]-3-allyl-2-thiooxoimidazolidin-4-one (3b). Prepared from compound **2b** in acetonitrile, 2 h, 361 mg (57%) of a white solid; mp 188–190°C (EtOH). ^{1}H NMR (DMSO-d_6): δ 3.12 (6H, s, NMe_2), 4.32 (2H, ddd, J=1.5, 1.7, 5.3 Hz, $CH_2CH{=}CH_2$), 4.99 (1H, ddd, J=1.5, 1.7, 17.3 Hz, 1H of $CH{=}CH_2$), 5.07 (1H, ddd, J=1.5, 1.7, 10.2 Hz, 1H of $CH{=}CH_2$), 5.81 (1H, ddt, J=5.3, 10.2, 17.3 Hz, $CH{=}CH_2$), 6.84 (1H, s, H–C(5′)), 11.36 (1H, s, H–N(1)); ^{13}C NMR ($CDCl_3$): δ 43.4, 43.6, 103.5, 117.9, 131.7, 132.8, 164.4, 171.0. Anal. (Found: C, 51.41; H, 6.29; N, 20.12. $C_9H_{13}N_3OS$ requires: C, 51.16; H, 6.20; N, 19.89.); ν_{max} (KBr) 3215, 2990, 1705, 1640, 1495, 1480 cm^{-1}; *m/z* (EI) 211 (M^+).

5.2.3. 5-[(*Z*)-(Dimethylamino)methylidene]-3-phenyl-2-thiooxoimidazolidin-4-one (3c). Prepared from compound **2c** in acetonitrile, 4 h, 437 mg (59%) of a pinkish solid; mp 241–243°C (decomp.) (EtOH). ^{1}H NMR (DMSO-d_6): δ 3.17 (6H, s, NMe_2), 6.85 (1H, s, H–C(5′)), 7.26–7.49 (5H, m, Ph), 11.56 (1H, s, H–N(1)); ^{13}C NMR (DMSO-d_6): δ 42.5, 102.0, 127.9, 128.5, 128.7, 133.1, 134.4, 163.3, 169.7. (Found: C, 58.16; H, 5.32; N, 16.82. $C_{12}H_{13}N_3OS$ requires: C, 58.28; H, 5.30; N, 16.99.); ν_{max} (KBr) 3015, 2930, 1685, 1620, 1510, 1495 cm^{-1}; *m/z* (EI) 247 (M^+).

[†] Donation of Alexander von Humboldt Foundation, Germany.

5.2.4. 5-[(*Z*)-(Dimethylamino)methylidene]-3-(4-methylphenyl)-2-thiooxoimidazolidin-4-one (3d). Prepared from compound **2d** in acetonitrile, 3.5 h, 650 mg (83%) of a pinkish solid; mp 256°C (decomp.) (EtOH). ^{1}H NMR (DMSO-d$_6$): δ 2.35 (3H, s, *Me*–Ar), 3.16 (6H, s, NMe$_2$), 6.83 (1H, s, H–C(5′)), 7.13 (2H, dd, J=1.9, 7.9 Hz, 2H of Ar), 7.26 (2H, dd, J=1.9, 7.9 Hz, 2H of Ar), 11.52 (1H, s, H–N(1)). ^{13}C NMR (CDCl$_3$): δ 21.7, 43.4, 103.6, 128.5, 130.1, 131.6, 133.0, 139.1, 164.5, 171.5. (Found: C, 60.07; H, 5.93; N, 15.97. $C_{13}H_{15}N_3OS$ requires: C, 59.75; H, 5.79; N, 16.08.); ν_{max} (KBr) 3225, 2965, 1700, 1640, 1655, 1515, 1475, 1440 cm^{-1}; *m*/*z* (EI) 261 (M$^+$).

5.2.5. 2-Dimethylamino-5-[(*Z*)-(dimethylamino)methylidene]-1,3-thiazol-4(5*H*)-one (8). Prepared from compound **7** in DMF, 3 h, 388 mg (65%) of a white solid; mp 187–190°C (decomp.) (EtOH). ^{1}H NMR (DMSO-d$_6$): δ 3.06 (6H, s, NMe$_2$), 3.09 (6H, s, NMe$_2$), 7.40 (1H, s, H–C(5′)) ^{13}C NMR (DMSO-d$_6$): δ 42.2, 46.2, 94.5, 145.3, 174.3, 181.3. (Found: C, 48.31; H, 6.54; N, 21.20. $C_8H_{13}N_3OS$ requires: C, 48.22; H, 6.58; N, 21.09.); ν_{max} (KBr) 3005, 2915, 2815, 1665, 1595, 1560, 1435 cm^{-1}; *m*/*z* (EI) 199 (M$^+$).

5.2.6. 5-[(*E*)-(Dimethylamino)methylidene]-1-methylimidazolidine-2,4-dione (11). Prepared from compound **10** in acetonitrile, 4 h, 274 mg (54%) of a white solid; mp 200–202°C (EtOH). ^{1}H NMR (DMSO-d$_6$): δ 2.90 (3H, s, Me–N(1)), 3.15 (6H, s, NMe$_2$), 6.47 (1H, s, H–C(5′)), 10.31 (1H, s, NH). ^{13}C NMR (DMSO-d$_6$): δ 27.1, 44.8, 106.0, 135.7, 152.9, 161.4. (Found: C, 49.65; H, 6.81; N, 25.13. $C_7H_{11}N_3O_2$ requires: C, 49.70; H, 6.55; N, 24.84.); ν_{max} (KBr) 3145, 3015, 2800, 2720, 1690, 1610, 1485 cm^{-1}; *m*/*z* (EI) 169 (M$^+$).

5.3. General procedure for the preparation of 5-[(*Z*)-(dimethylamino)methylidene]-3-substituted-2-(methylsulfanyl)imidazolidin-4-ones (4a–d) and 5-[(*E*)-(dimethylamino)methylidene]-1,3-dimethyl-imidazolidine-2,4-dione (12)

A mixture of compound **2a–d** or **10** (3 mmol), acetonitrile (10 mL) or DMF (10 mL), and DMFDMA (94%, 608 mg, 4.8 mmol), was heated under reflux for 2–6 h. Volatile components were evaporated in vacuo, and the residue was triturated with an appropriate solvent (10 mL). The precipitate was collected by filtration and washed with the same solvent. Compounds **4a–d**, **12** were prepared in this manner.

5.3.1. 5-[(*Z*)-(Dimethylamino)methylidene]-3-ethyl-2-(methylsulfanyl)imidazolidin-4-one (4a). Prepared from compound **2a** in acetonitrile, 4 h, trituration with ethanol/isopropanol, 45 mg (7%) of a pale yellow solid; mp 85–88°C (ethanol/isopropanol, 1:1). ^{1}H NMR (DMSO-d$_6$): δ 1.09 (3H, t, J=7.2 Hz, C*H*$_3$CH$_2$), 2.52 (3H, s, SMe), 3.14 and 3.46 (6H, 2s, 1:1, NMe$_2$), 3.47 (2H, q, J=7.2 Hz, C*H*$_2$CH$_3$), 6.91 (1H, s, H–C(5′)); ^{13}C NMR (CDCl$_3$): δ 13.1, 14.8, 35.7, 40.1, 46.4, 116.3, 138.8, 148.2, 170.0. (Found: C, 50.43; H, 7.21; N, 19.59. $C_9H_{15}N_3OS$ requires: C, 50.68; H, 7.09; N, 19.70.); ν_{max} (KBr) 2970, 2930, 2815, 1685, 1640, 1610, 1510, 1440, 1415 cm^{-1}; *m*/*z* (EI) 213 (M$^+$).

5.3.2. 5-[(*Z*)-(Dimethylamino)methylidene]-3-allyl-2-(methylsulfanyl)imidazolidin-4-one (4b). Prepared from compound **2b** in DMF; 2.5 h, trituration with ethyl acetate, 324 mg (48%) of a pale yellow solid; mp 98–100°C (EtOAc). ^{1}H NMR (CDCl$_3$): δ 2.56 (3H, s, SMe), 3.15 and 3.55 (6H, 2s, 1:1, NMe$_2$), 4.32 (2H, ddd, J=1.5, 1.7, 5.3 Hz, C*H*$_2$CH═CH$_2$), 5.00 (1H, ddd, J=1.5, 1.7, 17.3 Hz, 1H of CH═C*H*$_2$), 5.08 (1H, ddd, J=1.5, 1.7, 10.2 Hz, 1H of CH═C*H*$_2$), 5.81 (1H, ddt, J=5.3, 10.2, 17.3 Hz, C*H*═CH$_2$), 6.94 (1H, s, H–C(5′)). ^{13}C NMR (DMSO-d$_6$): δ 13.2, 42.5, 46.4, 115.1, 117.1, 133.9, 139.6, 147.0, 168.8. (Found: C, 53.37; H, 6.79; N, 18.44. $C_{10}H_{15}N_3OS$ requires: C, 53.31; H, 6.71; N, 18.65.); ν_{max} (KBr) 2925, 2900, 2815, 1680, 1620, 1510, 1425, 1410 cm^{-1}; *m*/*z* (EI) 225 (M$^+$).

5.3.3. 5-[(*Z*)-(Dimethylamino)methylidene]-3-phenyl-2-(methylsulfanyl)imidazolidin-4-one (4c). Prepared from compound **2c** in DMF, 2 h, trituration with ethanol, 110 mg (14%) of a pinkish solid; mp 237–240°C (decomp.) (EtOH). ^{1}H NMR (CDCl$_3$): δ 2.53 (3H, s, SMe), 3.18 and 3.60 (6H, 2s, 1:1, NMe$_2$), 7.01 (1H, s, H–C(5′)), 7.26–7.40 (5H, m, Ph). ^{13}C NMR (DMSO-d$_6$): δ 31.3, 40.1, 44.7, 105.1, 127.9, 128.4, 128.9, 134.9, 140.7, 158.1, 167.0. (Found: C, 59.76; H, 5.83; N, 16.26. $C_{13}H_{15}N_3OS$ requires: C, 59.74; H, 5.79; N, 16.08.); ν_{max} (KBr) 3035, 3010, 2915, 2810, 1695, 1610, 1505, 1430, 1415, 1390 cm^{-1}; *m*/*z* (EI) 261 (M$^+$).

5.3.4. 5-[(*Z*)-(Dimethylamino)methylidene]-3-(4-methylphenyl)-2-(methylsulfanyl)imidazolidin-4-one (4d). Prepared from compound **2d** in acetonitrile, 4 h, trituration with ethyl acetate, 536 mg (65%) of a pinkish solid; mp 173–175°C (decomp.) (EtOAc). ^{1}H NMR (CDCl$_3$): δ 2.38 (3H, s, *Me*–Ar), 2.52 (3H, s, SMe), 3.17 and 3.99 (6H, 2s, 1:1, NMe$_2$), 7.00 (1H, s, H–C(5′)), 7.18 (2H, dd, J=1.9, 7.9 Hz, 2H of Ar), 7.21 (2H, dd, J=1.9, 7.9 Hz, 2H of Ar). ^{13}C NMR (DMSO-d$_6$): δ 12.4, 20.7, 41.3, 45.5, 114.4, 127.0, 129.5, 131.2, 137.6, 139.0, 145.8, 167.8. (Found: C, 61.33; H, 6.21; N, 15.54. $C_{14}H_{17}N_3OS$ requires: C, 61.07; H, 6.22; N, 15.26.); ν_{max} (KBr) 3020, 2970, 2920, 2795, 1685, 1620, 1510, 1410 cm^{-1}; *m*/*z* (EI) 275 (M$^+$).

Compound **4d** was also prepared by methylation of **3d** with DMFDMA: A mixture of **3d** (46 mg, 0.18 mmol), DMFDMA (94%, 36 mg, 0.3 mmol), and acetonitrile (3 mL) was heated under reflux for 4 h. Volatile components were evaporated in vacuo, and the residue was triturated with ethyl acetate (3 mL). The precipitate was collected by filtration and washed with EtOAc to give **4d**, 40 mg (81%).

5.3.5. 5-[(*E*)-(Dimethylamino)methylidene]-1,3-dimethylimidazolidine-2,4-dione (12). Prepared from **10** in acetonitrile, 6 h, trituration with chloroform/*n*-hexane 538 mg (98%) of a white solid; mp 49–51°C (chloroform/*n*-hexane). ^{1}H NMR (DMSO-d$_6$): δ 2.85 and 2.98 (6H, 2s, 1:1, Me–N(3) and Me–N(1)), 3.18 (6H, s, NMe$_2$), 6.59 (1H, s, H–C(5′)); ^{13}C NMR (DMSO-d$_6$): δ 24.9, 27.5, 44.8, 104.6, 136.3, 152.6, 160.0. ν_{max} (KBr) 3230, 1720, 1680, 1615, 1465 cm^{-1}; *m*/*z* (EI) 183 (M$^+$). HRMS: Calcd for $C_8H_{13}N_3O_2$: 183.100777, Found: 183.101500.

5.4. General procedure for the preparation of 5-[(Z)-(2-methyl-1*H*-indol-3-yl)methylidene]-3-substituted-2-thiooxoimidazolidin-4-ones (5a–d), 3-substituted 5-[(Z)-(2-methyl-1*H*-indol-3-yl)methylidene]-2-(methylsulfanyl)imidazolidin-4-ones (6b,d), and 2-(dimethylamino)-5-[(Z)-1-(2-methyl-1*H*-indol-3-yl)methylidene]-1,3-thiazol-4(5*H*)-one hydrobromide (9)

Hydrobromic acid (33% in acetic acid, 4.1 M, 5–6 drops, ~0.4 mmol) was added to a mixture of compound **3a**–**d**, **4b**,**d**, or **8** (0.5 mmol), 2-methylindole (66 mg, 0.5 mmol), and acetic acid (2 mL) and the mixture was stirred at rt–50° for 6–72 h. Volatile components were evaporated in vacuo, ethanol (3 mL) was added to the residue, and the precipitate was collected by filtration. Compounds **5a**–**d**, **6b**,**d**, **9** were prepared in this manner.

5.4.1. 5-[(Z)-(2-Methyl-1*H*-indol-3-yl)methylidene]-3-ethyl-2-thiooxoimidazolidin-4-one (5a). Prepared from compound **3a**, rt, 24 h, 21 mg (15%) of a yellow solid; mp 178–180°C (MeOH). ^{1}H NMR (DMSO-d_6): δ 1.18 (3H, t, J=6.8 Hz, C*H*$_3$CH$_2$), 2.46 (3H, s, Me–C(2″)), 3.84 (2H, q, J=6.8 Hz, C*H*$_2$CH$_3$), 6.87 (1H, s, H–C(5′)), 7.06–7.16 (2H, m, H–C(5″) and H–C(6″)), 7.35 (1H, dd, J=1.5, 6.0 Hz, H–C(7″)), 7.53 (1H, dd, J=1.9, 6.4 Hz, H–C(4″)), 11.66 and11.69 (2H, 2s, 1:1, H–N(1) and H–N(1″)). ^{13}C NMR (DMSO-d_6): δ 13.2, 13.5, 36.0, 106.9, 109.6, 111.7, 119.6, 120.6, 122.1, 124.6, 127.3, 136.4, 140.5, 163.8, 176.8. (Found: C, 63.34; H, 5.32; N, 14.50. C$_{15}$H$_{15}$N$_3$OS requires: C, 63.14; H, 5.30; N, 14.74.); ν_{max} (KBr) 3285, 1685, 1620, 1460, 1430 cm^{-1}; *m/z* (EI) 285 (M$^+$).

5.4.2. 5-[(Z)-(2-Methyl-1*H*-indol-3-yl)methylidene]-3-allyl-2-thiooxoimidazolidin-4-one (5b). Prepared from compound **3b**, rt, 24 h, 71 mg (48%) of a yellow solid; mp 128–130°C (EtOH); ^{1}H NMR (DMSO-d_6): δ 2.37 (3H, s, Me–C(2″)), 3.92–4.08 (3H, m, C*H*$_2$CH=CH$_2$ and 1H of CH=C*H*$_2$), 4.59 (1H, d, J=10.2 Hz, 1H of CH=C*H*$_2$), 4.95–5.20 (1H, m, C*H*=CH$_2$), 6.98 (1H, s, H–C(5′)), 6.95–7.07 (2H, m, H–C(5″) and H–C(6″)), 7.47 (1H, dd, J=8.3 Hz, H–C(7″)), 7.77 (1H, dd, J=7.9 Hz, H–C(4″)), 10.42 and 11.44 (2H, 2s, 1:1, H–N(1) and H–N(1″)). ^{13}C NMR (DMSO-d_6): δ 13.4, 43.3, 107.2, 110.2, 112.0, 117.8, 119.9, 121.0, 122.4, 124.7, 127.6, 132.7, 136.7, 140.9, 164.0, 177.1. (Found: C, 64.48; H, 5.13; N, 14.26. C$_{16}$H$_{15}$N$_3$OS requires: C, 64.63; H, 5.09; N, 14.14.); ν_{max} (KBr) 3260, 1705, 1620, 1580, 1530, 1465 cm^{-1}; *m/z* (EI) 297 (M$^+$).

5.4.3. 5-[(Z)-(2-Methyl-1*H*-indol-3-yl)methylidene]-3-phenyl-2-thiooxoimidazolidin-4-one (5c). Prepared from compound **3c**, rt, 48 h, 132 mg (79%) of a yellow solid; mp 281°C (decomp.) (EtOH). ^{1}H NMR (DMSO-d_6): δ 2.58 (3H, s, Me–C(2″)), 6.93 (1H, s, H–C(5′)), 7.09–7.18 (2H, m, H–C(5″) and H–C(6″)), 7.35–7.55 (6H, m, H–C(7″) and Ph), 7.62 (1H, dd, J=1.9, 6.4 Hz, H–C(4″)), 11.69 and 11.95 (2H, 2s, 1:1, H–N(1) and H–N(1″)). ^{13}C NMR (DMSO-d_6):δ 13.6, 107.3, 110.2, 112.0, 120.0, 121.0, 122.4, 125.0, 127.7, 129.4, 129.6, 129.7, 134.6, 136.7, 140.9, 164.2, 177.2. (Found: C, 68.82; H, 4.44; N, 12.23. C$_{19}$H$_{15}$N$_3$OS requires: C, 68.45; H, 4.54; N, 12.61.); ν_{max} (KBr) 3265, 1715, 1630, 1595, 1495, 1455 cm^{-1}; *m/z* (EI) 333 (M$^+$).

5.4.4. 5-[(Z)-(2-Methyl-1*H*-indol-3-yl)methylidene]-3-(4-methylphenyl)-2-thiooxoimidazolidin-4-one (5d). Prepared from compound **3d**, rt, 48 h, 132 mg (77%) of an orange solid; mp 208–211°C (EtOH). ^{1}H NMR (DMSO-d_6): δ 2.43 and 2.63 (6H, 2s, 1:1, *Me*–Ar and Me–C(2″)), 6.98 (1H, s, H–C(5′)), 7.15–7.24 (2H, m, H–C(5″) and H–C(6″)), 7.32 (2H, dd, J=1.9, 8.3 Hz, 2H of Ar), 7.38 (2H, dd, J=1.9, 8.3 Hz, 2H of Ar), 7.42 (1H, dd, J=1.9, 6.8, Hz, H–C(7″)), 7.65 (1H, dd, J=2.3, 6.8 Hz, H–C(4″)), 11.74 and 11.98 (2×1H, 2s, H–N(1) and H–N(1″)). ^{13}C NMR (DMSO-d_6): δ 13.6, 21.6, 107.3, 110.1, 112.0, 120.0, 121.0, 122.4, 125.0, 127.7, 129.4, 130.1, 132.0, 136.7, 139.0, 140.9, 164.2, 177.4. Found: C, 67.91; H, 5.30; N, 10.91. C$_{20}$H$_{17}$N$_3$OS·0.5 H$_2$O requires: C, 68.08; H, 5.44; N, 11.34.); ν_{max} (KBr) 3290, 1735, 1715, 1640, 1515, 1465, 1400 cm^{-1}; *m/z* (EI) 347 (M$^+$).

5.4.5. 5-[(Z)-(2-Methyl-1*H*-indol-3-yl)methylidene]-3-allyl-2-(methylsulfanyl)imidazolidin-4-one (6b). Prepared from compound **4b**, rt, 24 h, 48 mg (31%) of a yellow solid; mp 217–219°C (EtOH); ^{1}H NMR (CDCl$_3$): δ 2.66 and 2.77 (6H, 2s, 1:1, SMe and Me–C(2″)), 4.26 (2H, ddd, J=1.7, 5.3 Hz, C*H*$_2$CH=CH$_2$), 5.21 (1H, ddd, J=1.1, 1.7, 17.3 Hz, 1H of CH=C*H*$_2$), 5.25 (1H, ddd, J=1.1, 1.5, 6.8 Hz, 1H of CH=C*H*$_2$), 5.86 (1H, ddt, J=5.3, 6.8, 17.3 Hz, C*H*=CH$_2$), 7.16–7.30 (3H, m, H–C(5′), H–C(5″), and H–C(6″)), 8.32 (1H, d, J=8.3 Hz, H–C(7″)), 9.07 (1H, dd, J=7.9 Hz, H–C(4″)), N*H* is exchanged. ^{13}C NMR (DMSO-d_6): δ 13.0, 13.6, 43.1, 110.1, 111.9, 117.7, 120.0, 121.2, 123.1, 124.4, 127.1, 132.1, 133.3, 137.1, 145.4, 158.5, 169.4. Found: C, 65.31; H, 5.48; N, 13.28. C$_{17}$H$_{17}$N$_3$OS requires: C, 65.57; H, 5.51; N, 13.50.); ν_{max} (KBr) 3220, 2930, 1680, 1605, 1575, 1485, 1460 cm^{-1}; *m/z* (EI) 311 (M$^+$).

5.4.6. 5-[(Z)-(2-Methyl-1*H*-indol-3-yl)methylidene]-3-(4-methylphenyl)-2-(methylsulfanyl)imidazolidin-4-one (6d). Prepared from compound **4d**, rt, 48 h, 81 mg (45%) of a yellow solid; mp 269–272°C (decomp.) (EtOH). ^{1}H NMR (CDCl$_3$): δ 2.41, 2.67, and 2.73 (9H, 3s, 1:1:1, *Me*–Ar, Me–C(2″), and SMe), 7.19–7.31 (6H, m, H–C(5″), H–C(6″), and 4H of Ar), 7.35 (1H, s, H–C(5′)), 8.40 (1H, m, H–C(7″)), 9.11 (1H, m, H–C(4″)), N*H* is exchanged. ^{13}C NMR (DMSO-d_6): δ 13.0, 13.8, 21.6, 110.2, 111.9, 120.3, 121.3, 123.1, 124.4, 127.2, 128.2, 130.7, 131.4, 132.0, 137.1, 139.3, 145.5, 158.4, 169.2. (Found: C, 70.07; H, 5.25; N, 11.68. C$_{21}$H$_{19}$N$_3$OS requires: C, 69.78; H, 5.30; N, 11.63.); ν_{max} (KBr) 3190, 2920, 1680, 1605, 1575, 1515, 1460 cm^{-1}; *m/z* (EI) 361 (M$^+$).

Compound **6d** was also prepared by methylation of **5d** with DMFDMA: A mixture of **5d** (174 mg, 0.5 mmol), DMFDMA (94%, 95 mg, 0.8 mmol), and acetonitrile (2 mL) was stirred at rt for 72 h. Volatile components were evaporated in vacuo, ethyl acetate (3 mL) was added and the precipitate was collected by filtration to give **6d**, 92 mg (51%).

5.4.7. 2-(Dimethylamino)-5-[(Z)-1-(2-methyl-1*H*-indol-3-yl)methylidene]-4,5-dihydro-1,3-thiazol-4-one hydrobromide (9). Prepared from compound **8**, 50°, 6 h, 88 mg (48%) of an orange solid; mp 247–250°C (MeOH); ^{1}H NMR (DMSO-d_6): δ 3.20 (3H, s, SMe), 5.10 (6H, s, NMe$_2$), 7.12 (1H, dt, J=1.5, 6.8, 7.1 Hz, H–C(5″)), 7.15

(1H, dt, J=1.5, 6.8, 7.1 Hz, H–C(6″)), 7.38 (1H, ddd, J=0.8, 1.5, 6.8 Hz, H–C(7″)), 7.78 (1H, dd, J=1.5, 7.1 Hz, H–C(4″)), 7.82 (1H, s, H–C(5′)), 11.82 (1H, s, H–N(1″)). ^{13}C NMR (DMSO-d$_6$): δ 13.2, 40.2, 108.3, 112.6, 119.2, 120.1, 121.5, 123.0, 125.8, 128.4, 136.9, 143.8, 172.2, 175.8. (Found: C, 49.45; H, 4.69; N, 11.43. $C_{15}H_{15}N_3OS\cdot HBr$ requires: C, 49.31; H, 4.42; N, 11.51.); ν_{max} (KBr) 3120, 3085, 2955, 2765, 1720, 1655, 1595, 1520, 1460 cm^{-1}; m/z (EI) 285 (M$^+$−HBr).

5.5. General procedure for the preparation of 5-[(substituted 1*H*-indol-3-yl)methylidene]-1-methyl-2,4-diones (13a–d) and 5-[(*1H*-indol-3-yl)methylidene]-1,3-dimethylimidazolidine-2,4-dione (14a)

A mixture of compound **11** or **12** (0.5 mmol), indole derivative (indole, 2-methylindole, 5-bromoindole, or 5-fluoroindole) (0.5 mmol), and acetic acid (10 mL) was heated under reflux for 3–9 h. The volatile components were evaporated in vacuo, ethanol (3 mL) was added to the residue, and the precipitate was collected by filtration. Compounds **13a–d**, **14a** were prepared in this manner.

5.5.1. 5-[(*E*)-(1*H*-Indol-3-yl)methylidene]-1-methylimidazolidine-2,4-dione (13a). Prepared from compound **11** and indole, 3 h; 70 mg (58%) of a yellow solid; mp 310–313°C (EtOH). ^{1}H NMR (DMSO-d$_6$): δ 3.19 (3H, s, Me–N(1)), 6.68 (1H, s, H–C(5′)), 7.14 (1H, ddd, J=1.1, 7.2, 7.9, 8.3 Hz, H–C(5″)), 7.19 (1H, ddd, J=1.1, 7.2, 7.9, 8.3 Hz, H–C(6″)), 7.47 (1H, dd, J=1.1, 8.3 Hz, H–C(7″)), 7.93 (1H, dd, J=1.1, 7.2 Hz, H–C(4″)), 8.78 (1H, d, J=3.0 Hz, H–C(2″)), 11.17 and 11.59 (2H, 2s, 1:1, H–N(3) and H–N(1″)). ^{13}C NMR (DMSO-d$_6$): δ 26.6, 108.3, 109.4, 112.8, 119.0, 120.7, 122.9, 126.6, 128.6, 129.4, 136.5, 153.9, 164.2. (Found: C, 64.59; H, 4.32; N, 17.16. $C_{13}H_{11}N_3O_2$ requires: C, 64.71; H, 4.60; N, 17.43.); ν_{max} (KBr) 3355, 3155, 3050, 2735, 1740, 1700, 1625, 1515 cm^{-1}; m/z (EI) 241 (M$^+$).

5.5.2. 5-[(2-Methyl-1*H*-indol-3-yl)methylidene]-1-methylimidazolidine-2,4-dione (13b). Prepared from compound **11** and 2-methylindole, 9 h, 103 mg (81%) of a yellow solid; mp 250–259°C (EtOH), Z/E=62:38. (Found: C, 66.05; H, 5.03; N, 16.34. $C_{14}H_{13}N_3O_2$ requires: C, 65.86; H, 5.14; N, 16.47., ν_{max} (KBr) 3310, 3155, 3055, 2725, 1750, 1700, 1655, 1615, 1460 cm^{-1}; m/z (EI) 255 (M$^+$).

NMR data for the major (Z)-isomer. ^{1}H NMR (DMSO-d$_6$): δ 2.37 (3H, s, Me–C(2″)), 3.16 (3H, s, Me–N(1)), 6.67 (1H, s, H–C(5′)), 6.96–7.10 (2H, m, H–C(5″) and H–C(6″)), 7.27–7.38 (2 H, m, H–C(4″) and H–C(7″)), 11.14 and 11.40 (2H, 2s, 1:1, H–N(3) and H–N(1″)). ^{13}C NMR (DMSO-d$_6$): 13.1, 29.6, 105.5, 106.7, 111.9, 119.8, 120.5, 122.0, 129.0, 131.1, 136.2, 137.5, 157.1, 165.3.

NMR data for the minor (E)-isomer. ^{1}H NMR (DMSO-d$_6$): δ 2.29 (3H, s, Me–C(2″)), 2.74 (3H, s, Me–N(1)), 6.54 (1H, s, H–C(5′)), 6.96–7.10 (2H, m, H–C(5″) and H–C(6″)), 7.27–7.38 (2H, m, H–C(4″) and H–C(7″)), 11.14 and 11.28 (2H, 2s, 1:1, H–N(3) and H–N(1″)). ^{13}C NMR (DMSO-d$_6$): δ 14.1, 26.8, 105.3, 108.1, 111.9, 119.3, 120.0, 121.6, 128.4, 128.7, 136.0, 138.2, 154.2, 163.0.

5.5.3. 5-[(*E*)-(5-Bromo-1*H*-indol-3-yl)methylidene]-1-methylimidazolidine-2,4-dione (13c). Prepared from compound **11** and 5-bromoindole, 5 h, 61 mg (38%) of a yellow solid; mp 341–344°C (AcOH). ^{1}H NMR (DMSO-d$_6$): δ 3.19 (3H, s, Me–N(1)), 6.69 (1H, s, H–C(5′)), 7.28 (1H, dd, J=1.9, 8.6 Hz, H–C(6″)), 7.42 (1H, d, J=8.6 Hz, H–C(7″)), 7.24 (1H, d, J=1.9 Hz, H–C(4″)), 8.79 (1H, d, J=2.6 Hz, H–C(2″)), 11.19 and 11.74 (2×1H, 2s, H–N(3) and H–N(1″)). ^{13}C NMR (DMSO-d$_6$): δ 25.9, 106.9, 108.4, 112.7, 113.8, 120.9, 124.4, 126.2, 129.5, 129.6, 134.3, 153.0, 163.3. (Found: C, 48.70; H, 3.04; N, 13.01. $C_{13}H_{10}BrN_3O_2$ requires: C, 48.77; H, 3.15; N, 13.13.); ν_{max} (KBr) 3405, 3155, 3050, 2740, 1780, 1705, 1630, 1515, 1450 cm^{-1}; m/z (EI) 319 (^{79}Br), 321 (^{81}Br) (M$^+$).

5.5.4. 5-[(*E*)-(5-Fluoro-1*H*-indol-3-yl)methylidene]-1-methylimidazolidine-2,4-dione (13d). Prepared from compound **11** and 5-fluoroindole, 6 h, 89 mg (69%) of a yellow solid; mp 354–356°C (AcOH); ^{1}H NMR (DMSO-d$_6$): δ 3.18 (3H, s, Me–N(1)), 6.64 (1H, s, H–C(5′)), 7.09 (1H, ddd, J=2.4, 8.8, 9.4 Hz, H–C(6″)), 7.45 (1H, dd, J=4.7, 8.8 Hz, H–C(7″)), 7.81 (1H, dd, J=2.4, 10.6 Hz, H–C(4″)), 8.82 (1H, d, J=1.9 Hz, H–C(2″), 11.18 and 11.66 (2H, 2s, 1:1, H–N(3) and H–N(1″)). ^{13}C NMR (DMSO-d$_6$): δ 25.9, 103.3, 103.6, 107.2, 108.9, 109.0, 109.9, 110.2, 112.9, 113.0, 125.9, 128.3, 130.3, 132.2, 153.0, 156.2, 159.2, 163.4. (Found: C, 60.00; H, 3.80; N, 16.27. $C_{13}H_{10}FN_3O_2$ requires: C, 60.21; H, 3.89; N, 16.22.); ν_{max} (KBr) 3350, 3155, 3050, 2735, 1760, 1705, 1625, 1580, 1515, 1480, 1440, 1380 cm^{-1}; m/z (EI) 259 (M$^+$).

5.5.5. 5-[(*E*)-(1*H*-Indol-3-yl)methylidene]-1,3-dimethylimidazolidine-2,4-dione (14a). Prepared from compound **12** and indole, 2 h; 83 mg (65%) of a yellow solid; mp 270–272°C (AcOH). ^{1}H NMR (DMSO-d$_6$): δ 3.01 and 3.25 (6H, 2s, 1:1, Me–N(3) and Me–N(1)), 6.77 (1H, s, H–C(5′)), 7.14 (1H, dt, J=0.8, 7.2 Hz, H–C(6″)), 7.19 (1H, dt, J=1.1, 7.2 Hz, H–C(5″)), 7.46 (1H, dd, J=1.1, 7.2 Hz, H–C(7″)), 7.96 (1H, dd, J=0.8, 7.2 Hz, H–C(4″)), 8.84 (1H, d, J=2.6 Hz, H–C(2″)), 11.66 (1H, s, H–N(1″)). ^{13}C NMR (DMSO-d$_6$): δ 25.2, 27.0, 109.0, 109.4, 112.8, 119.0, 120.7, 122.9, 125.3, 128.6, 129.5, 136.5, 153.6, 162.8. (Found: C, 65.84; H, 5.10; N, 16.22. $C_{14}H_{13}N_3O_2$ requires: C, 65.86; H, 5.14; N, 16.47.); ν_{max} (KBr) 3300, 1740, 1690, 1620, 1515, 1495, 1460, 1430, 1405 cm^{-1}; m/z (EI) 255 (M$^+$).

5.5.6. 5-[(1*H*-2-Methylindol-3-yl)methylidene]-1,3-dimethylimidazolidine-2,4-dione (14b). A mixture of compound **12** (92 mg, 0.5 mmol), 2-methylindole (66 mg, 0.5 mmol), and in acetic acid (10 mL) was heated under reflux for 2.5 h. Volatile components were evaporated in vacuo and the residue was purified by CC (chloroform/ethyl acetate, 5:1). Fractions containing the product were combined and evaporated in vacuo to give crude **14b**, 82 mg (61%) of a yellow solid; mp 94–99°C, Z/E=28:72.[‡] (Found: C, 66.92; H, 5.51; N, 15.39. $C_{15}H_{15}N_3O_2$ requires: C, 66.89; H, 5.62; N, 15.61.); ν_{max} (KBr) 3255, 1760, 1700, 1650, 1540, 1460 cm^{-1}; m/z (EI) 269 (M$^+$). The isomers were separated by MPLC (chloroform/ethyl acetate (5:1),

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[‡] TLC: chloroform/ethyl acetate, 5:1, R_f [(E)-isomer]=0.18, R_f [(Z)-isomer]=0.27.

R_t [(*Z*)-isomer]=5.4 min, R_t [(*E*)-isomer]=8.4 min). Fractions containing single isomers were evaporated in vacuo to give the (*Z*)- and the (*E*)-isomer of **14b**.

Data for the (Z)-isomer. 32 mg (24%); mp 144–147°C.^{1}H NMR (DMSO-d_6): δ 2.38 (3H, s, Me–C(2″)), 2.78 (3H, s, Me–N(3)), 2.99 (3H, s, Me–N(1)), 6.79 (1H, d, *J*=0.8 Hz, H–C(5′)), 7.02 (1H, dt, *J*=1.5, 7.2 Hz, H–C(5″)), 7.08 (1H, dt, *J*=1.5, 7.2 Hz, H–C(6″)), 7.32 (1H, dd, *J*=1.5, 7.2 Hz, H–C(7″)), 7.38 (1H, dd, *J*=1.5, 7.2 Hz, H–C(4″)), 11.44 (1H, s, H–N(1″)). ^{13}C NMR (DMSO-d_6): δ 13.0, 25.5, 30.1, 105.4, 106.5, 111.9, 119.3, 120.6, 122.0, 128.9, 130.0, 136.3, 137.9, 157.1, 164.3.

Data for the (E)-isomer. 47 mg (35%); mp 176–178°C. ^{1}H NMR (DMSO-d_6): 2.30 (3H, s, Me–C(2″)), 2.94 (3H, s, Me–N(3)), 3.22 (3H, s, Me–N(1)), 6.64 (1H, d, *J*=0.8 Hz, H–C(5′)), 6.99 (1H, dt, *J*=1.1, 7.2 Hz, H–C(5″)), 7.06 (1H, dt, *J*=1.1, 7.2 Hz, H–C(6″)), 7.29 (1H, dd, *J*=1.1, 7.2 Hz, H–C(7″)), 7.37 (1H, dd, *J*=1.1, 7.2 Hz, H–C(4″)), 11.32 (1H, s, H–N(1″)). ^{13}C NMR (DMSO-d_6): δ 14.1 (*Me*–C(2″)), 25.2 (Me–N(3)), 27.2 (Me–N(1)), 106.8 (C(3″)), 109.0 (C(5′)), 111.5 (C(7″)), 119.9 (C(5″)), 120.1 (C(4″)), 121.7 (C(6″)), 127.5 (C(5)), 128.4 (C(3a)), 136.0 (C(7a)), 138.5 (C(2″)), 154.1 (C(2)), 161.7 (C(4)).

5.6. X-Ray structure analysis for compound 14a

Diffraction data were processed by DENZO[31] program. Structure was solved by direct methods using SIR97[32] program. The structure refinement and interpretation was done by Xtal3.4[33] program. ORTEP-II[34] picture of the asymmetric unit of compound **14a** is presented in Fig. 3. The crystallographic data have also been deposited with the Cambridge Crystallographic Data Center as supplementary material with the deposition number: 164527. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

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