Stereoselective Synthesis of 5-[(*Z*)-Heteroarylmethylidene] Substituted Hydantoins and Thiohydantoins as Aplysinopsin Analogs*

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3-Substituted 5-[(*Z*)-heteroarylmethylidene]imidazolidine-2,4-dione and 5-[(*Z*)-heteroarylmethylidene]-2-thiooxoimidazolidin-4-one derivatives were prepared stereoselectively by coupling of 5-(dimethylamino)methylidene substituted hydantoin and thiohydantoin derivatives with carbocyclic and heterocyclic *C*-nucleophiles. Configuration around the exocyclic C=C double bond was determined by NMR, using NOESY and 2D HMBC techniques.

Introduction

Hydantoins (= imidazolidine-2,4-diones) belong to significant heterocycles, since many of hydantoin containing natural and synthetic products exhibit diverse biological activities, such as antitumor [1, 2], antiarrhytmic [3], anticonvulsant [4], herbicidal [5], and others [6–8]. Aplysinopsins, isolated from marine organisms [1, 8, 9] are examples of hydantoin containing natural products exhibiting cytotoxicity towards cancer cells [1] and the ability to affect neurotransmitters [8]. Synthetic routes towards aplysinopsins and their analogs are usually based on condensation of 3-formylindole derivative with either a suitable hydantoin derivative [10–13] or ethyl azidoacetate followed by tandem Staudinger/aza-Wittig reaction and cyclization [14, 15].

Alkyl 2-R-3-(dimethylamino)propenoates and their cyclic analogs are easily accessible and versatile reagents for the preparation of a variety of heterocyclic systems [16]. In this connection, we recently reported two simple and stereoselective syntheses of aplysinopsins which are based on: a) coupling of indole derivatives with alkyl 3-dimethylamino-2-(vinylamino)propenoates followed by deprotection and cyclization and b) coupling of indole derivatives with 5-[(dimethylamino)methylidene]hydantoin derivatives [17]. The second method (b) was extended towards the preparation of pyrimidinetrione [19], azolone [19], and spirohydantoin analogs [20] of aplysinopsins (Fig. 1).

In continuation of our work in this field, we report the stereoselective synthesis of 3-substituted 5-[(*Z*)-heteroarylmethylidene]imidazolidine-2,4-diones and 5-[(*Z*)-heteroarylmethylidene]-2-thiooxoimidazolidin-4-ones as novel aplysinopsin analogs, having the indole ring replaced by various carbocyclic and heterocyclic systems.

Results and Discussion

The 5-[(*Z*)-(dimethylamino)methylidene]imidazolidine derivatives **1a,b** [17] and **1c–f** [19] were selected as starting compounds. They were treated with carbocyclic (**2, 3**) and heterocyclic (**4–7**) *C*-nucleophiles in acetic acid under reflux to give the corresponding isomerically pure substitution products **9–13** in 36–84% yields. 5-[(*Z*)-(1,3-Dimethyl-2,4-dioxo-6-hydroxy-1,2,3,4-tetrahydropyrimidin-5-yl)methylidene]-imidazolidine-2,4-diones **13a,b** were obtained in the form of dimethylammonium salts. Formation of such dimethylammonium salts upon reaction of 3-(dimethylamino)-propenoates with active methylene compounds has already been observed previously [21, 22]. In some cases, the adducts have also been isolated [22]. This indicates, that the substitution of the di-

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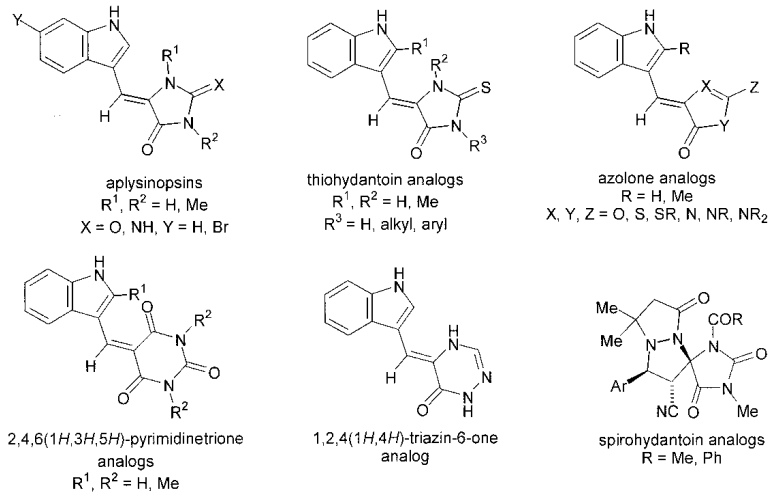
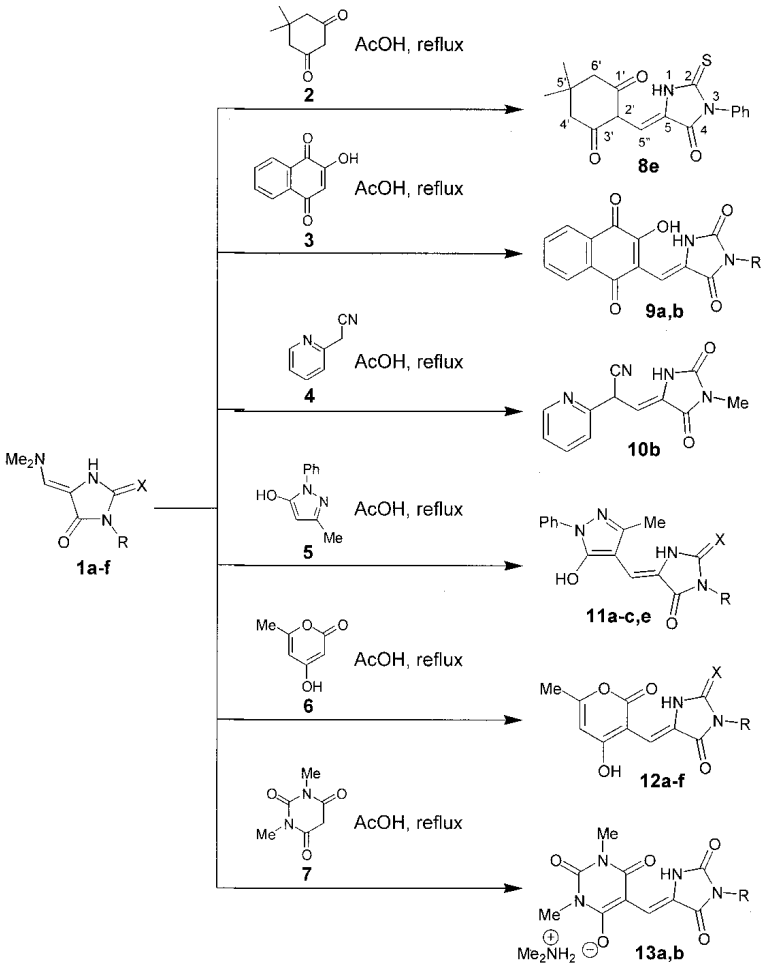


Fig. 1. Aplisynopsins and their analogs.



Compound	R	X
1a, **9a**, **11a–13a**	H	O
1b, **9b–13b**	Me	O
1c, **11c**, **12c**	Et	S
1d, **12d**	$CH_2CH{=}CH_2$	S
1e, **8e**, **11e**, **12e**	Ph	S
1f, **12f**	4-Me–C_6H_4	S

Scheme 1.

methylamino group most probably proceeds *via* the addition-elimination mechanism (Scheme 1).

Structure Determination

Structures of novel compounds were confirmed by spectroscopic methods and by analyses for C, H, and N. The (*Z*)-configuration around the exocyclic C=C double bond in compounds **11a,c** and **13a** was determined by NMR (HMBC technique) on the basis of the magnitude of long-range heteronuclear coupling constant, $^3J_{C-H}$. The magnitude of the coupling constant, $^3J_{C-H}$ = 5.3–5.9 Hz, indicates the *cis*-relationship between the methine proton at the 5″-position and the carbonyl carbon atom at the 4-position and is also in agreement with the literature data [19, 21, 23]. The (*Z*)-configuration, around the exocyclic double bond C=C in compounds **11a**, **13a,b** was additionaly confirmed by NOESY spectroscopy. Absence of NOE between the protons at the positions 1 (NH) and 5″ (CH) indicates the *trans*-relationship between these two protons. On the other hand, NOE was observed between the following protons: a) ·5″-H···H_3C–C(3′)] and [N(1)–H···H_{ortho} of Ph] in the case of compound **11a** and b) [N(1)–H···H_3C–N(1′/3′)] in the case of compounds **13a,b** (Fig. 2).

Conclusion

Various 5-(hetero)arylmethylidene substituted hydantoin and 2-thiohydantoin derivatives were obtained stereoselectively in one step and in fair yields by treatment of the corresponding 5-(dimethylamino)methylidene substituted hydantoins with various carbocyclic and heterocyclic *C*-nucleophiles. Upon reaction with 1,3-dimethylbarbituric acid, the substitution products were obtained in the form of dimethylammonium salts; this result offered an additional proof for the previously proposed addition-elimination mechanism of substitution of the dimethylamino group in 3-(dimethylamino)propenoates and related compounds. Configuration around the C=C double bond was determined by NMR (HMBC and NOESY techniques). These transformations showed the diversity of this synthetic approach towards aplysinopsins, since not only the hydantoin part, but also the indole part of the aplysinopsin scaffold can be varied without affecting the yield or stereochemical outcome of the coupling reaction.

Experimental Section

Melting points were determined on a Kofler micro hot stage. The ^{1}H NMR, ^{13}C NMR, HMBC, and NOESY spectra were obtained on a Bruker

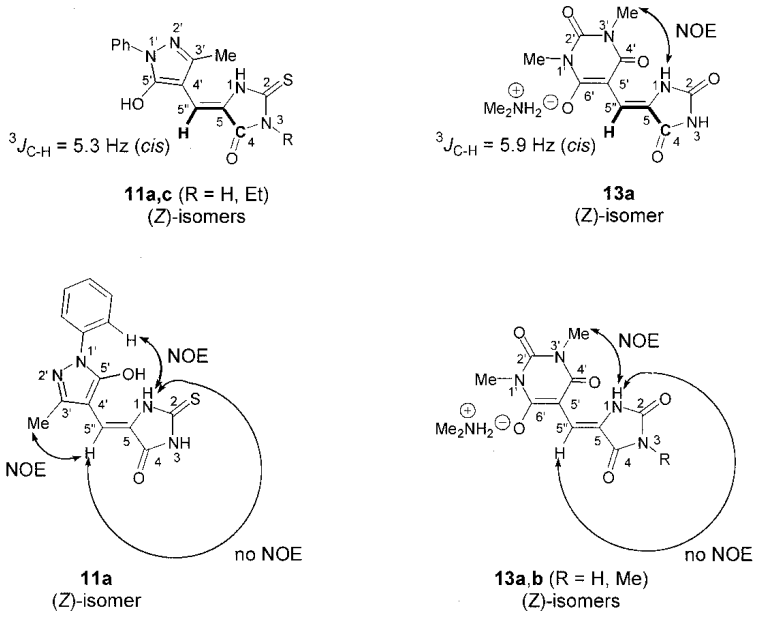


Fig. 2. Determination of configuration around the C=C double bond in compounds **11a,c** and **13a,b**.

Avance DPX 300 at 300 MHz for ^{1}H and at 75.5 MHz for ^{13}C nucleus with DMSO-d_6 as solvent 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.

All starting materials were commercially available (in most cases from Fluka) and purified following standard techniques. The following compounds were prepared according to the literature procedures: 5-[(*Z*)-(dimethylamino)methylidene]-imidazolidine-2,4-dione (**1a**), 5-[(*Z*)-(dimethylamino)methylidene]-3-methylimidazolidine-2,4-dione (**1b**) [17], 3-ethyl-5-[(*Z*)-(dimethylamino)-methylidene]-2-thiooxoimidazolidin-4-one (**1c**), 3-allyl-5-[(*Z*)-(dimethylamino)methylidene]-2-thiooxoimidazolidin-4-one (**1d**), 5-[(*Z*)-(dimethylamino)methylidene]-3-phenyl-2-thiooxoimidazolidin-4-one (**1e**), and 5-[(*Z*)-(dimethylamino)methylidene]-3-(4-methylphenyl)-2-thiooxoimidazolidin-4-one (**1f**) [19].

Synthesis of 3-substituted 5-[(Z)-heteroarylmethylidene]imidazolidine-2,4-diones and 5-[(Z)-heteroarylmethylidene]-2-thiooxoimidazolidin-4-ones (**8–12**)

General procedure

A mixture of compound **1a-f** (1 mmol), *C*-nucleophile **2–6** (1 mmol), and acetic acid (5 ml) was heated under reflux for 0.25–14 h. The reaction mixture was cooled, the precipitate was collected by filtration, and crystallized from an appropriate solvent to give **8–12**.

The following compounds were prepared in this manner:

5-[(Z)-(5,5-Dimethyl-1,3-dioxocyclohex-2-yl)-methylidene]-3-phenyl-2-thiooxoimidazolidin-4-one (**8e**)

Prepared from compound **1e** and 5,5-dimethylcyclohexane-1,3-dione (**2**), reflux for 14 h, 123 mg (36%). – M.p. 238–241 °C (MeOH). – IR (KBr): ν = 1696, 1660 (C=O) cm^{-1}. – ^{1}H NMR (DMSO-d_6): δ = 1.03 (s, 6H, 2 Me), 2.41 (s, 4H, 2 CH_2), 6.69 (s, 1H, 5″-H, 7.32–7.52 (m, 5H, Ph), 11.85 (s, 1H, NH). – MS (EI): *m/z* = 342 (M^+). – $C_{18}H_{18}N_2O_3S$ (342.41): calcd. C 63.14; H 5.30; N8.18; found C 62.98; H 5.23; N 8.41.

5-[(Z)-(2-Hydroxy-1,4-naphthoquinon-3-yl)-methylidene]imidazolidine-2,4-dione (9a)

Prepared from compound **1a** and 2-hydroxy-1,4-naphthoquinone (**3**), reflux for 15 min, 159 mg (56%). – M.p. 328–331 °C (EtOH/DMF). – IR (KBr): ν = 1732, 1633 (C=O) cm^{-1}. – ^{1}H NMR (DMSO-d_6): δ = 6.40 (s, 1H, 5″-H), 7.78–7.89 (m, 2H, 2H of Ar), 8.00–8.06 (m, 2H, 2H of Ar), 9.73 (s, 1H, NH), 11.14 (s, 1H, NH). – MS (EI): *m/z* = 284 (M^+). – $C_{14}H_8N_2O_5$ (284.22): calcd. C 59.16, H 2.84, N 9.86; found C 59.42, H 2.73, N 9.47.

5-[(Z)-(2-Hydroxy-1,4-naphthoquinon-3-yl)-methylidene]-3-methylimidazolidine-2,4-dione (**9b**)

Prepared from compound **1b** and 2-hydroxy-1,4-naphthoquinone (**3**), reflux for 15 min, 250 mg (84%). – M.p. 316–318 °C (EtOH). – IR (KBr): ν = 1766, 1708, 1658, 1635 (C=O) cm^{-1}. – ^{1}H NMR (DMSO-d_6): δ = 2.94 (s, 3H, Me), 6.57 (s, 1H, 5″-H), 7.77–7.89 (m, 2H, 2H of Ar), 7.96–8.06 (m, 2H, 2H of Ar), 10.11 (s, 1H, NH). – MS (EI) *m/z* = 298 (M^+). – $C_{15}H_{10}N_2O_5$ (298.25): calcd. C 60.41, H 3.38, N 9.39; found C 60.81, H 3.26, N 8.99.

5-[(Z)-2-Cyano-2-(pyridin-2-yl)-1-ethylidene]-imidazolidine-2,4-dione (**10b**)

Prepared from compound **1b** and 2-pyridineacetonitrile (**4**), reflux for 1.5 h, 105 mg (43%). – M.p. 337–340 °C (AcOH). – IR (KBr): ν = 2188 (C≡N), 1742, 1689 (C=O) cm^{-1}. – ^{1}H NMR (DMSO-d_6): δ = 2.91 (s, 3H, Me), 6.55–6.65 (m, 2H, =C*H*C*H*–CN), 7.12 (br d, 1H, *J* = 8.6 Hz, 3′-H), 7.49 (br t, 1H, *J* = 6.8 Hz, 4′-H), 7.62 (br d, 1H, *J* = 6.0 Hz, 5′-H), 8.88 (br s, 1H, 6′-H), 11.50 (s, 1H, NH). – MS (EI) *m/z* = 242 (M^+). – $C_{12}H_{10}N_4O_2$ (242.23): calcd. C 59.50, H 4.16, N 23.13; found C 59.49, H 3.99, N 22.95.

5-[(Z)-(5-Hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)methylidene]imidazolidine-2,4-dione (**11a**)

Prepared from compound **1a** and 5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazole (**5**), reflux for 1 h, 121 mg (43%). – M.p. 310–313 °C (AcOH). – IR (KBr): ν = 1723, 1660 (C=O) cm^{-1}. – ^{1}H NMR (DMSO-d_6): δ = 2.31 (s, 3H, Me), 6.06 (s, 1H, 5″-H), 7.31 (tt, 1H, *J* = 1.5, 7.1 Hz, 1H of Ph), 7.46–7.53 (m, 2H, 2H of Ph), 7.65–7.71 (m, 2H, 2H of Ph), 10.87 (s, 1H, NH), 11.06 (s, 1H, NH). – MS (EI) *m/z* = 284 (M^+). – $C_{14}H_{12}N_4O_3$ (284.27): calcd. C 59.15, H 4.25, N 19.71; found C 58.83, H 4.17, N 19.30.

5-[(Z)-(5-Hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)methylidene]-3-methylimidazolidine-2,4-dione (**11b**)

Prepared from compound **1b** and 5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazole (**5**), reflux for 1 h, 149 mg (50%). – M.p. 287–290 °C (AcOH). – IR (KBr): ν = 1731, 1679 (C=O) cm^{-1}. – ^1H NMR (DMSO-d_6): δ = 2.33 (s, 3H, 3′-Me), 2.92 (s, 3H, 3-Me), 6.17 (s, 1H, 5″-H), 7.32 (tt, 1H, *J* = 1.1, 7.2 Hz, 1H of Ph), 7.45–7.55 (m, 2H, 2H of Ph), 7.64–7.72 (m, 2H, 2H of Ph), 11.35 (s, 1H, NH). – ^{13}C NMR (DMSO-d_6): δ = 10.5, 24.1, 100.4, 100.7, 120.7, 124.0, 126.3, 129.1, 135.3, 147.8, 152.3, 160.4, 163.2. – MS (EI) *m/z* = 298 (M^+). – $C_{15}H_{14}N_4O_3$ (298.30): calcd. C 60.40, H 4.73, N 18.78; found C 60.65, H 4.73, N 18.78.

3-Ethyl-5-[(Z)-(5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)methylidene]-2-thiooxoimidazolidin-4-one (**11c**)

Prepared from compound **1c** and 5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazole (**5**), reflux for 11 h, 255 mg (78%). – M.p. 287–290 °C (MeOH/H_2O). – IR (KBr): ν = 1738, 1704, 1658 (C=O) cm^{-1}. – ^1H NMR (DMSO-d_6): δ = 1.16 (t, 3H, *J* = 6.8 Hz, CH_3CH$_2$), 2.35 (s, 3H, NMe), 3.79 (q, 2H, *J* = 6.8 Hz, CH$_2$CH$_3$), 6.35 (s, 1H, 5″-H), 7.31 (t, 1H, *J* = 7.5 Hz, 1H of Ph), 7.50 (dd, 2H, *J* = 7.5, 8.3 Hz, 2H of Ph), 7.74 (d, 2H, *J* = 8.3 Hz, 2H of Ph), 13.23 (s, 1H, NH). – ^{13}C NMR (DMSO-d_6): δ = 11.5, 13.9, 36.2, 101.6, 106.2, 121.9, 123.9, 127.4, 130.0, 136.0, 149.4, 161.4, 163.3, 172.8. – $C_{16}H_{16}N_4O_2S$ (328.39): calcd. C 58.52, H 4.91, N 17.06; found C 58.58, H 4.88, N 16.82. – MS (EI) *m/z* = 328 (M^+).

5-[(Z)-(5-Hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)methylidene]-3-phenyl-2-thiooxoimidazoidin-4-one (**11e**)

Prepared from compound **1e** and 5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazole (**5**), reflux for 10 h, 188 mg (50%). – M.p. 305 °C (decomp.)(MeOH/H_2O). – IR (KBr): ν = 1694, 1651 (C=O) cm^{-1}. – ^1H NMR (DMSO-d_6): δ = 2.37 (s, 3H, Me–N(3′)), 6.42 (s, 1H, 5″-H), 7.30–7.77 (m, 10H, 2Ph), 13.51 (s, 1H, H–N(1)). – MS (EI) *m/z* = 376 (M^+). – $C_{20}H_{16}N_4O_2S$ (376.43): calcd. C 63.81, H 4.28, N 14.88; found C 63.86, H 4.19, N 14.72.

5-[(Z)-(4-Hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)methylidene]imidazolidine-2,4-dione (**12a**)

Prepared from compound **1a** and 4-hydroxy-6-methyl-2*H*-pyran-2-one (**6**), reflux for 1 h, 121 mg (51%). – M.p. 337–340 °C (AcOH). – IR (KBr): ν = 1727, 1685, 1652 (C=O) cm^{-1}. – ^1H NMR (DMSO-d_6): δ = 2.24 (s, 3H, Me), 6.16 (s, 1H, 5′-H), 6.40 (s, 1H, 5″-H), 9.35 (s, 1H, NH), 11.02 (s, 1H, NH). – MS (EI) *m/z* = 236 (M^+); MS (FAB) *m/z* = 237 (MH^+). $C_{10}H_8N_2O_5$ (236.18): calcd. C 50.85, H 3.41, N 11.86; found C 50.74, H 3.49, N 11.76.

5-[(Z)-(4-Hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)methylidene]-3-methylimidazolidine-2,4-dione (**12b**)

Prepared from compound **1a** and 4-hydroxy-6-methyl-2*H*-pyran-2-one (**6**), reflux for 1 h, 178 mg (71%). – M.p. 287–290 °C (*n*-PrOH). – IR (KBr): ν = 1770, 1702, 1642 (C=O) cm^{-1}. – ^1H NMR (DMSO-d_6): δ = 2.24 (s, 3H, 6′-Me), 2.92 (s, 3H, 3-Me), 6.15 (s, 1H, 5′-H), 6.40 (s, 1H, 5″-H), 9.62 (s, 1H, NH). – ^{13}C NMR (DMSO-d_6): δ = 19.5, 24.2, 96.7, 100.2, 100.4, 125.1, 153.0, 163.0, 163.67, 163.71, 169.1. – MS (EI) *m/z* = 250 (M^+). – $C_{11}H_{10}N_2O_5$ (250.21): calcd. C 52.80, H 4.03, N 11.20; found C 53.01, H 4.11, N 11.13.

3-Ethyl-5-[(Z)-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)methylidene]-2-thiooxoimidazolidin-4-one (**12c**)

Prepared from compound **1c** and 4-hydroxy-6-methyl-2*H*-pyran-2-one (**6**), reflux for 3 h, 213 mg (76%). – M.p. 284–288 °C (MeOH/H_2O). – IR (KBr): ν = 1779, 1694 (C=O) cm^{-1}. – ^1H NMR (DMSO-d_6): δ = 1.14 (t, 3H, *J* = 7.2 Hz, CH_3CH$_2$), 2.22 (s, 3H, Me), 3.78 (q, 2H, *J* = 7.2 Hz, CH$_2$CH$_3$), 6.09 (s, 1H, 5′-H), 6.61 (s, 1H, 5″-H), 11.61 (s, 1H, NH). – MS (EI) *m/z* = 280 (M^+). – $C_{12}H_{12}N_2O_4S$ (280.30): calcd. C 51.42, H 4.32, N 9.99; found C 51.42, H 4.29, N 10.06.

3-Allyl-5-[(Z)-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)methylidene]-2-thiooxoimidazolidin-4-one (**12d**)

Prepared from compound **1d** and 4-hydroxy-6-methyl-2*H*-pyran-2-one (**6**), reflux for 3.5 h, 164 mg (56%). – M.p. 220–227 °C (MeOH/H_2O). – IR (KBr): ν = 1767, 1698 (C=O) cm^{-1}. – ^1H NMR (DMSO-d_6): δ = 2.24 (s, 3H, Me), 4.37 (d, 2H, *J* = 5.3 Hz, CH_2CH=CH$_2$), 5.06 (dd, 1H, *J* = 1.5, 17.3 Hz, 1H of CH=CH_2), 5.13 (dd, 1H, *J* = 1.5, 10.5 Hz, 1H of CH=CH_2), 5.83 (ddt, 1H, *J* = 5.3, 10.5, 17.3 Hz, CH=CH$_2$), 6.12 (s, 1H, 5′-H), 6.62 (s, 1H, 5″-H), 11.62 (s, 1H, NH). – MS (EI) *m/z* = 292 (M^+). – $C_{13}H_{12}N_2O_4S$ (292.31):

calcd. C 53.42, H 4.14, N 9.58; found C 53.77, H 4.03, N 9.45.

5-[(Z)-(4-Hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)methylidene]-3-phenyl-2-thiooxoimidazolidin-4-one (**12e**)

Prepared from compound **1e** and 4-hydroxy-6-methyl-2*H*-pyran-2-one (**6**), reflux for 5 h, 269 mg (82%). – M.p. 298 °C (decomp.) (MeOH/H_2O). – IR (KBr): ν = 1740, 1687, 1644 (C=O) cm^{-1}. – ^1H NMR (DMSO-d_6): δ = 2.20 (s, 3H, Me), 6.09 (s, 1H, 5′-H), 6.69 (s, 1H, 5″-H), 7.33–7.53 (m, 5H, Ph), 11.97 (s, 1H, NH). – MS (EI) *m/z* = 328 (M^+). – $C_{16}H_{12}N_2O_4S$ (328.34): calcd. C 58.53, H 3.68, N 8.53; found C 58.54, H 3.67, N 8.68.

5-[(Z)-(4-Hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)methylidene]-3-(4-methylphenyl)-2-thiooxo-imidazolidin-4-one (**12f**)

Prepared from compound **1f** and 4-hydroxy-6-methyl-2*H*-pyran-2-one (**6**), reflux for 8 h, 222 mg (65%). – M.p. 290 °C (decomp.) (MeOH/H_2O). – IR (KBr): ν = 1743, 1637 (C=O) cm^{-1}. – ^1H NMR (DMSO-d_6): δ = 2.21 (s, 3H, 6′-Me), 2.36 (s, 3H, Me-C_6H_4), 6.03 (s, 1H, 5′-H), 6.70 (s, 1H, 5″-H), 7.20 (d, 2H, *J* = 8.3 Hz, 2H of C_6H_4), 7.29 (d, 2H, *J* = 8.3 Hz, 2H of C_6H_4), 12.09 (s, 1H, NH). – MS (EI) *m/z* = 342 (M^+). – $C_{17}H_{14}N_2O_4S$ (342.07): calcd. C 59.64, H 4.12, N 8.18; found C 59.29, H 4.12, N 8.25.

Synthesis of 1-substituted 5-[(Z)-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-methylidene]imidazolidine-2,4-diones (**13a,b**)

General procedure

A mixture of compound **1a,b** (1 mmol), 1,3-dimethylbarbituric acid (**7**) (0.156 g, 1 mmol), and acetic acid (5 ml) was heated under reflux for 45 min. Volatile components were evaporated *in vacuo*, ethanol (3 ml) was added to the residue, the precipitate was collected by filtration, and crystallized from methanol to give **13a,b**.

The following compounds were prepared in this manner:

5-[(Z)-(1,3-Dimethyl-2,4-dioxo-6-hydroxy-1,2,3,4-tetrahydropyrimidin-5-yl)methylidene]imidazolidine-2,4-dione dimethylammonium salt (**13a**)

Prepared from compound **1a** and 1,3-dimethylbarbituric acid (**7**), reflux for 45 min, 162 mg (52%). – M.p. 242–244 °C (MeOH). – IR (KBr): ν = 1732, 1685, 1640 (C=O) cm^{-1} – ^1H NMR (DMSO-d_6): δ = 2.55 (s, 6H, NMe_2), 3.12 (s, 6H, 1′-Me and 3′-Me), 6.74 (s, 1H, 5″-H), 8.13 (s, 1H, NH), 10.26 (s, 1H, NH), 10.33 (s, 1H, OH). – MS (EI) *m/z* = 266 (M^+–Me_2NH). – $C_{12}H_{17}N_5O_5$ (311.29): calcd. C 46.30, H 5.50, N 22.50; found C 46.23, H 5.28, N 22.42.

5-[(Z)-(1,3-Dimethyl-2,4-dioxo-6-hydroxy-1,2,3,4-tetrahydropyrimidin-5-yl)methylidene]-3-methyl imidazolidine-2,4-dione dimethylammonium salt (**13b**)

Prepared from compound **1b** and 1,3-dimethylbarbituric acid (**7**), reflux for 45 min, 215 mg (66%). – M.p. 230–232 °C (*n*-PrOH). – IR (KBr): ν = 1729, 1676, 1634 (C=O) cm^{-1}. – ^1H NMR (DMSO-d_6): δ = 2.55 (s, 6H, NMe_2), 2.87 (s, 3H, 3-Me), 3.12 (s, 6H, 1′-Me and 3′-Me), 6.86 (s, 1H, 5″-H), 8.13 (s, 1H, NH), 10.53 (s, 1H, OH). – MS (EI) *m/z* = 280 (M^+–Me_2NH). – $C_{13}H_{19}N_5O_5$ (325.32): calcd. C 48.00, H 5.89, N 21.53; found C 47.78, H 5.76, N 21.11. HRMS ($C_{11}H_{12}N_4O_5$) calcd. 280.081950; found: 280.080770.

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