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Dimethylamine substitution in *N*,*N*-dimethyl enamines. Synthesis of aplysinopsin analogues and 3-aminotetrahydrocoumarin derivatives

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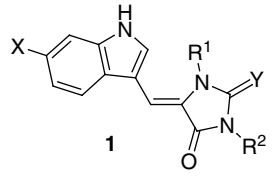
Abstract—Some new six-membered aplysinopsin analogues were prepared from 5-dimethylaminomethylidene-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetriones and indole derivatives. Also 2-[[(2,4,6-trioxohexahydropyrimidin-5-ylidene)methyl]amino]-3-dimethylaminopropenoates were synthesized and employed in the synthesis of fused 2*H*-pyran-2-ones.

Aplysinopsins (**1**) (Fig. 1), isolated from various marine organisms (sponges, corals, etc.),[1–6] have aroused considerable interest due to their cytotoxicity towards cancer cells[3] and their ability to affect neurotransmitters.[2]

Recently, a series of alkyl 2-[(2,2-disubstituted ethenyl) amino]-3-dimethylaminopropenoates have been prepared as versatile reagents for the synthesis of various heterocyclic systems, such as 2*H*-pyran-2-ones and fused derivatives, fused pyridinones and pyrimidinones,[7,8] polysubstituted pyrrole-2-carboxylates[9] and imidazole-4-carboxylates.[10] As an extension of this work, we have recently described[11] a simple and stereoselective syntheses which afford aplysinopsins, thioaplysinopsins and derivatives in which the hydantoin moiety is replaced with 1,4,5,6-tetrahydro-1,2,4(1*H*,4*H*)-triazin-6-one, with good overall yields. The methodology, which describes a series of simple syntheses of heterocycles from a group of simple reagents, can perhaps be further developed into automated or semiautomated parallel synthesis. In a continuation of our study, we now present the synthesis of aplysinopsin analogues in which the hydantoin moiety is replaced with barbituric acid, and the preparation of 3-[(2,4,6-trioxohexahydropyrimidin-5-ylidene)methyl]amino-substituted 2*H*-1-benzopyran-2-one derivatives.



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X=H, Br; Y=O, NH, NMe; R^1,R^2=H, Me.

Figure 1.

Barbituric acid (**2a**) and its 1,3-dimethyl derivative (**2b**) were stirred in an appropriate solvent in the presence of dimethylformamide dimethyl acetal (DMFDMA) to form 5-dimethylaminomethylidene-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetriones **3a** and **b** in quantitative yield. The latter were heated with an indole derivative (viz. indole, 5-bromoindole, 7-ethylindole and 2-methylindole) in glacial acetic acid to give 5-[(1*H*-indol-3-yl)methylidene]-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetriones **4** in 11–85% yield (Scheme 1).

Compounds **4a**–**f** show a characteristic signal for the indole H-2 in the 9.45–9.54 ppm region, suggesting a weak hydrogen bond to the pyrimidinone oxo group, and a signal for the bridge methylidene group at 8.6–8.8 ppm. Compound **4g**, with methyl group at the indole position 2, has a signal for the bridge methylidene group at 8.48 ppm. Furthermore, compounds **4a**–**f** show the signal for the indole H-4 proton at 7.68–8.03 ppm, while in **4g** it appears at 7.39 ppm. Based on these data and NMR and X-ray studies published earlier,[5,11] we conclude that compound **4g** exists in a non planar form, due to steric repulsion between the indole methyl group and pyrimidinone oxo group, while compounds **4a**–**f** are probably planar, with a hydrogen bond between the indole H-2 and a pyrimidinone oxygen atom (Scheme 1).

Compound **3b** reacts with 2-methylindole in a different manner from **3a**. Instead of the expected 1,3-dimethyl-5-[(2-methyl-1*H*-indol-3-yl)methylidene]-2,4,6(1*H*,3*H*,5*H*)-

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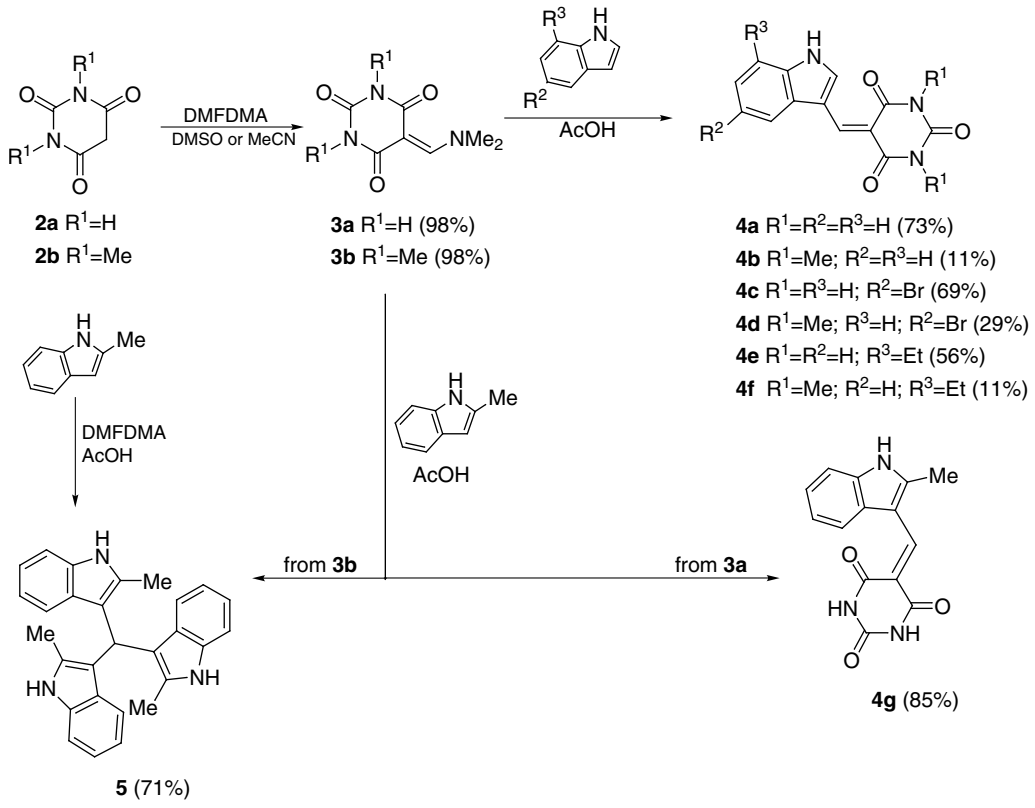
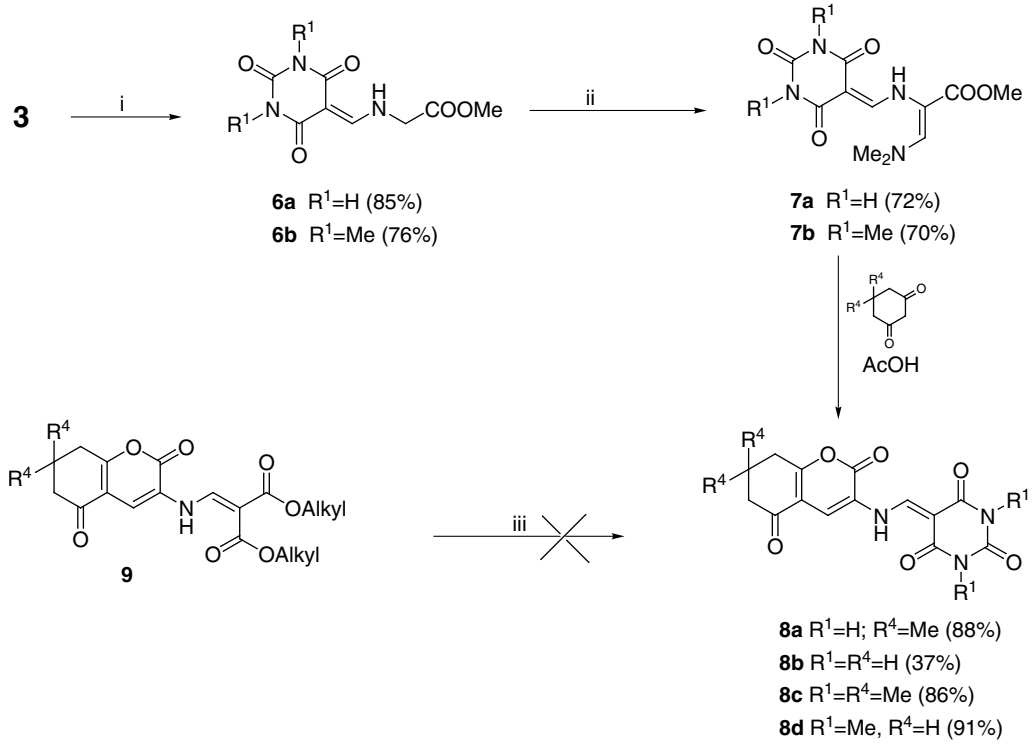


Scheme 1.

pyrimidinetrione, tris(2-methyl-1*H*-indol-3-yl)methane (**5**) was isolated in 71% yield. This is a known compound[12] and was identical with a sample prepared by an unambiguous synthesis.

In the second part of this research, compounds **3a** and **b** were transformed into 2-[[(2,4,6-trioxohexahydropyrimidin-5-ylidene)methyl]amino]-3-dimethylaminopropenoates **7** in two steps, by reaction with methyl glycinate hydrochloride



Scheme 2. (i) $MeOOCCH_2NH_2 \cdot HCl$, AcOH; (ii) DMFDMA, MeCN; (iii) NH_2CONH_2.

in the initial and introduction of dimethylaminomethylene group with DMFDMA in the second step (Scheme 2), in overall yields of 53% (**7a**) and 62% (**7b**).

It has been shown that all alkyl 2-[(2,2-disubstituted ethenyl) amino]-3-dimethylaminopropenoates synthesized to date, exist in the *Z* form.[7c,8,13] The chemical shift of the H-3 proton in DMSO-d_6 in these compounds is always found in the narrow interval of 7.27–7.33 ppm. Compounds **7a** and **b** exhibit the H-3 at δ=7.32 and 7.33 ppm, respectively, so we can assume that they exist in the *Z* form as well.

Propenoates **7**, together with 1,3-cyclohexanedione and 5,5-dimethylcyclohexane-1,3-dione, gave 3-[[(2,4,6-trioxohexahydropyrimidin-5-ylidene)methyl]amino]-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-ones **8** in good yields (Scheme 2). Note that these compounds cannot be prepared from the corresponding 3-[[2,2-bis(alkoxycarbonyl)ethenyl]amino]-2*H*-1-benzopyranone derivatives **9** and urea derivatives, since the ethenyl group is very sensitive to nucleophiles and its elimination takes place preferentially.[14]

In conclusion, we have demonstrated that our previously described approach towards aplysinopsins[11] can be easily generalized to provide diverse aplysinopsin mimic structures. Apart from that, 3-[[(2,4,6-trioxohexahydropyrimidin-5-ylidene)methyl]amino]-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-ones **8** were prepared from barbituric acid and its *N*,*N*-dimethyl derivative in good overall yields.

1. Experimental

1.1. General

Melting points were determined on a Kofler hot-plate melting point apparatus. NMR spectra were recorded on Varian VXR 300 at 300 MHz for ^{1}H and 75 MHz for ^{13}C nucleus, using DMSO-d_6 as a solvent. Microanalyses were performed on a Perkin–Elmer 2400C instrument, mass spectra recorded on Autospec Q spectrometer and IR spectra on BIO-RAD FTS 60 spectrometer. NMR data are summarized in Tables 1 and 2.

1.1.1. 5-Dimethylaminomethylidene-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (3a). To a suspension of barbituric acid (**2a**, 8.5 mmol, 1084 mg) in DMSO (5 mL), DMFDMA (12.7 mmol, 2 mL) was added and the mixture was stirred at rt for 3–6 h. After that, 5 mL of 2-propanol was added to the mixture and solid residue was filtered off and recrystallized from DMF to give the title compound **3a** (1526 mg, 98%) as yellow crystals; mp>260°C; *m/z* (EI) 183 (M^+). (Found: C, 45.61; H, 4.78; N, 22.56. $C_7H_9N_3O_3$ requires C, 45.90; H, 4.95; N, 22.94.); ν_{max} (KBr) 3430, 3000, 2810, 1700, 1630 cm^{-1}.

1.1.2. 1,3-Dimethyl-5-dimethylaminomethylidene-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (3b). To a suspension of 1,3-dimethylbarbituric acid (**2b**, 52.1 mmol, 8.14 g) in acetonitrile (5 mL), DMFDMA (67.8 mmol, 11 mL) was added and the mixture was stirred at rt for 5–6 h. After that, 2-propanol (10 mL) was added, solid residue was filtered off and recrystallized from 2-propanol to give the title compound **3b** (10.77 g, 98%) as yellow crystals; mp 108–111°C. (Found: C, 49.01; H, 6.37; N, 19.09. $C_9H_{13}N_3O_3{\cdot}0.5H_2O$ requires C, 49.09; H, 6.41; N, 19.08.); ν_{max} (KBr) 3430, 2960, 1710, 1630 cm^{-1}.

1.2. General procedure for the synthesis of 5-[(1*H*-indol-3-yl)methylidene]-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetriones 4

Indole derivative (1 mmol) and compound **3** (1 mmol) in glacial acetic acid (4 mL) were heated at 90–100°C for several hours. After that, volatile components were evaporated in vacuo and 2-propanol was added for the crystallization or alternatively, 2-propanol was added directly into the cooled reaction mixture to form precipitate, which was collected by filtration and purified with recrystallization from an appropriate solvent. Compounds **4a–g** were prepared according to this procedure.

1.2.1. 5-[(1*H*-Indol-3-yl)methylidene]-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (4a). Prepared from indole and **3a**, 4 h, 187 mg (73%) of a yellow solid; mp>260°C (DMF). (Found: C, 61.45; H, 3.42; N, 16.41. $C_{13}H_9N_3O_3$ requires C, 61.18; H, 3.55; N, 16.46.); ν_{max} (KBr) 3350, 3280, 3160, 2810, 1730, 1690, 1660, 1550, 1220 cm^{-1}.

1.2.2. 1,3-Dimethyl-5-[(1*H*-indol-3-yl)methylidene]-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (4b). Prepared from indole and **3b**, 5 h, 31 mg (11%) of a yellow solid; mp>260°C (AcOH/2-propanol). (Found: C, 63.86; H, 4.29; N, 14.75. $C_{15}H_{13}N_3O_3$ requires C, 63.60; H, 4.63; N, 14.83.); ν_{max} (KBr) 3420, 3270, 1720, 1660, 1630, 1550, 1220 cm^{-1}.

1.2.3. 5-[(5-Bromo-1*H*-indol-3-yl)methylidene]-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (4c). Prepared from 5-bromoindole and **3a**, 3.5 h, 231 mg (69%) of a yellow solid; mp>260°C (2-propanol). (Found: C, 45.32; H, 2.61; N, 12.01. $C_{13}H_8N_3O_3{\cdot}0.5H_2O$ requires C, 45.50; H, 2.64; N, 12.25.); ν_{max} (KBr) 3440, 3160, 2840, 1740, 1690, 1650, 1530, 1190 cm^{-1}.

1.2.4. 1,3-Dimethyl-5-[(5-bromo-1*H*-indol-3-yl)methylidene]-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (4d). Prepared from 5-bromoindole and **3b**, 5 h, 105 mg (29%) of a yellow solid; mp>260°C (AcOH). (Found: C, 49.98; H, 3.09; N, 11.51. $C_{15}H_{12}BrN_3O_3$ requires C, 49.74; H, 3.34; N, 11.60.); ν_{max} (KBr) 3440, 3310, 1720, 1650, 1550, 1190 cm^{-1}.

1.2.5. 5-[(7-Ethyl-1*H*-indol-3-yl)methylidene]-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (4e). Prepared from 7-ethylindole and **3a**, 1 h, 159 mg (56%) of a yellow solid; mp>260°C (DMF). (Found: C, 61.24; H, 5.13; N, 14.70. $C_{15}H_{13}N_3O{\cdot}0.5H_2O$ requires: C, 61.64; H, 4.83; N, 14.38.); ν_{max} (KBr) 3440, 3250, 2840, 1750, 1640, 1540, 1200 cm^{-1}.

1.2.6. 1,3-Dimethyl-5-[(7-ethyl-1*H*-indol-3-yl) methylidene]-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (4f). Prepared from 7-ethylindole and **3b**, 40 min, 34 mg (11%) of a yellow solid; mp>260°C (AcOH). (Found: C, 65.78; H, 5.59; N, 13.32. $C_{17}H_{17}N_3O_3$ requires C, 65.58; H, 5.50; N, 13.50.); ν_{max} (KBr) 3360, 1720, 1660, 1630, 1560, 1200 cm^{-1}.

Table 1. ^{1}H and ^{13}C NMR data for compounds **3–5**

Compound	^{1}H NMR	^{13}C NMR
3a	3.25 and 3.39 (3H, s, NMe_2), 8.02 (1H, s, –CH═), 10.08 and 10.36 (1H, s, NH)	44.3, 48.3, 89.0, 100.4, 151.2, 156.2, 161.0
3b	3.06 (3H, s, NMe), 3.10 (6H, s, NMe_2), 3.22 (3H, s, NMe), 8.11 (1H, s, –CH═)	26.5, 27.4, 44.4, 48.2, 89.0, 95.4, 152.0, 161.9, 185.3
4a	7.28–7.34 (2H, m, H-5, H-6), 7.58 (1H, dd, *J*=6.0, 2.5 Hz, H-7), 7.86 (1H, dd, *J*=6.3, 2.9 Hz, H-4), 8.72 (1H, s, –CH═), 9.49 (1H, d, *J*=2.9 Hz, H-2), 10.90 and 10.98 (1H, s, NH), 12.62 (1H, brs, NH–indole)	108.5, 111.2, 112.9, 117.4, 122.4, 123.4, 129.0, 136.2, 139.5, 143.6, 150.1, 163.0, 164.3
4b	3.26 and 3.27 (1H, s, NMe), 7.32–7.35 (2H, m, H-5, H-6), 7.58–7.62 (1H, m, H-7), 7.87–7.90 (1H, m, H-4), 8.81 (1H, s, –CH═), 9.54 (1H, d, *J*=2.8 Hz, H-2), 12.82 (1H, s, NH–indole)	27.7, 28.3, 108.1, 111.6, 113.1, 117.5, 122.7, 123.7, 129.3, 136.4, 139.9, 144.5, 151.2, 161.5, 163.0
4c	7.45 (1H, dd, *J*=1.7, 8.7 Hz, H-6), 7.57 (1H, d, *J*=8.7 Hz, H-7), 8.03 (1H, d, *J*=1.7 Hz, H-4), 8.61 (1H, s, –CH═), 9.48 (1H, s, H-2), 11.10 and 11.18 (1H, s, NH), 12.82 (1H, s, NH–indole)	109.6, 110.7, 115.1, 115.3, 120.4, 126.2, 131.0, 135.2, 140.3, 143.3, 150.3, 163.2, 164.3
4d	3.21 and 3.22 (3H, s, NMe), 7.42 (1H, dd, *J*=1.6, 8.5 Hz, H-6), 7.54 (1H, d, *J*=8.5 Hz, H-7), 7.97 (1H, d, *J*=1.6 Hz, H-4), 8.66 (1H, s, –CH═), 9.45 (1H, s, H-2), 12.74 (1H, s, NH–indole)	27.5, 28.1, 108.9, 110.7, 114.8, 115.2, 120.0, 126.0, 130.9, 135.0, 140.1, 143.9, 150.9, 161.2, 162.6
4e	1.29 (3H, t, *J*=7.6 Hz, Et), 2.93 (2H, q, *J*=7.6 Hz, Et), 7.16 (1H, d, *J*=7.3 Hz, H-6), 7.27 (1H, dd, *J*=7.3, 7.7 Hz, H-5), 7.71 (1H, d, *J*=7.7 Hz, H-4), 8.72 (1H, s, –CH═), 9.50 (1H, d, *J*=3.3 Hz, H-2), 11.05 and 11.13 (1H, s, NH), 12.78 (1H, s, NH–indole)	14.6, 23.4, 108.6, 111.8, 115.3, 122.6, 123.0, 128.9, 129.2, 135.1, 139.4, 143.8, 150.4, 163.3, 164.6
4f	1.27 (3H, t, *J*=7.5 Hz, Et), 2.91 (2H, q, *J*=7.5 Hz, Et), 3.22 and 3.24 (3H, s, NMe), 7.15 (1H, d, *J*=7.2 Hz, H-6), 7.26 (1H, dd, *J*=7.2, 7.9 Hz, H-5), 7.68 (1H, d, *J*=7.9 Hz, H-4), 8.77 (1H, s, –CH═), 9.47 (1H, s, H-2), 12.82 (1H, s, NH–indole)	14.6, 23.4, 27.8, 28.4, 108.2, 112.0, 115.2, 122.7, 123.1, 128.9, 129.3, 135.1, 139.4, 144.7, 151.2, 161.6, 163.1
4g	2.54 (3H, s, 2-Me), 7.11–7.24 (3H, m, H-5, H-6, H-7), 7.39 (1H, d, *J*=7.8 Hz, H-4), 8.48 (1H, s, –CH═), 10.86 and 11.02 (1H, s, NH), 12.53 (1H, s, NH–indole)	13.5, 108.9, 111.6, 112.0, 121.3, 122.6, 123.1, 126.7, 136.4, 146.0, 150.6, 151.3, 161.6, 164.4
5	1.92 (9H, s, 2-Me), 6.09 (1H, s, CH), 6.62 (3H, dd, *J*=7.1, 8.1 Hz, H-6), 6.79 (3H, d, *J*=7.1 Hz, H-7), 6.86 (3H, dd, *J*=8.1, 8.1 Hz, H-5), 7.19 (3H, d, *J*=8.1 Hz, H-4), 10.61 (3H, s, NH–indole)	11.7, 30.5 (3), 110.1 (3), 112.2 (3), 117.8 (3), 118.2 (3), 119.3 (3), 128.8 (3), 131.6 (3), 134.8 (3)

1.2.7. 5-[(2-Methyl-1*H*-indol-3-yl)methylidene]-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (4g). Prepared from 2-methylindole and **3a**, 5.5 h, 229 mg (85%) of a yellow solid; mp>260°C (DMF). (Found: C, 62.06; H, 3.93; N, 15.46. $C_{14}H_{11}N_3O_3$ requires C, 62.45; H, 4.12; N, 15.61.); ν_{max} (KBr) 3430, 3120, 3030, 2840, 1720, 1690, 1630, 1550, 1530, 1240 cm^{-1}.

1.3. Tris(2-methyl-1*H*-indol-3-yl)methane (5)

2-Methylindole (1 mmol) and compound **3b** (1 mmol) in glacial acetic acid (4 mL) were heated at 90–100°C for 2 h. After that, 4 mL of 2-propanol was added, precipitate was collected by filtration and dissolved in boiling DMF. After cooling, 2-propanol was added and precipitate

Table 2. ^{1}H and ^{13}C NMR data for compounds **6–8**

Compound	^{1}H NMR	^{13}C NMR
6a	3.68 (3H, s, COOMe), 4.37 (2H, d, *J*=6.1 Hz, CH_2), 8.13 (1H, d, *J*=14.4 Hz, –CH═), 10.11 (1H, td, *J*=6.1 Hz, 14.4, NH), 10.60 and 10.79 (1H, s, NH)	49.9, 52.2, 90.4, 150.9, 160.0, 163.9, 165.9, 169.6
6b	3.13 and 3.14 (s, 3H, NMe), 3.68 (3H, s, COOMe), 4.41 (2H, d, *J*=6.1, CH_2), 8.23 (1H, d, *J*=14.6, –CH═), 10.27 (1H, td, *J*=6.1, 14.6, NH)	26.8, 27.4, 50.0, 52.2, 90.4, 151.6, 160.6, 162.2, 163.7, 169.5
7a	2.99 (6H, s, NMe_2), 3.62 (3H, s, COOMe), 7.32 (1H, s, H-3), 7.84 (1H, d, *J*=14.3 Hz, *CH*NH), 10.36 and 10.67 (1H, s, NH), 10.75 (1H, d, *J*=14.3 Hz, CH*NH*)	42.6 (2), 51.2, 90.5, 98.1, 145.0, 151.0, 160.1, 163.8, 166.1
7b	2.98 (6H, s, NMe_2), 3.14 and 3.15 (3H, s, NMe), 3.59 (3H, s, COOMe), 7.33 (1H, s, H-3), 7.92 (1H, d, *J*=14.1 Hz, *CH*NH), 10.83 (1H, d, *J*=14.1 Hz, CH*NH*)	26.3, 26.8, 42.1 (2), 50.5, 90.3, 98.0, 144.4, 151.1, 160.0, 163.6, 165.3
8a	1.09 (6H, s, 2×7-Me), 2.45 and 2.82 (2H, s, CH_2), 7.86 (1H, s, H4), 8.60 (1H, d, *J*=13.7 Hz, *CH*NH), 10.65 and 10.83 (1H, s, NH), 11.68 (1H, d, *J*=13.7 Hz, CH*NH*)	27.2 (2), 32.0, 40.0, 49.5, 94.3, 112.8, 118.3, 123.5, 149.9, 150.5, 157.1, 162.5, 165.8, 167.8, 193.0
8b	2.10 (2H, m, CH_2), 2.53 and 2.89 (2H, t, *J*=5.9 Hz, CH_2), 7.86 (1H, s, H-4), 8.60 (1H, d, *J*=13.7 Hz, *CH*NH), 10.65 and 10.83 (1H, s, NH), 11.68 (1H, d, *J*=13.7 Hz, CH*NH*)	19.4, 26.6, 35.6, 94.3, 113.7, 118.5, 123.5, 149.9, 150.4, 156.8, 162.5, 165.8, 169.4, 193.2
8c	1.09 (6H, s, 2×7-Me), 2.45 and 2.82 (2H, s, CH_2), 3.18 and 3.20 (3H, s, NMe), 7.91 (1H, s, H-4), 8.70 (1H, d, *J*=13.9 Hz, *CH*NH), 11.78 (1H, d, *J*=13.9 Hz, NH)	26.6, 27.2, 27.3 (2), 32.0, 40.1, 49.6, 94.3, 112.8, 118.7, 123.5, 150.9, 151.2, 157.2, 161.1, 163.9, 168.0, 193.1
8d	2.10 (2H, m, CH_2), 2.53 (2H, t, *J*=6.0 Hz, CH_2), 2.90 (2H, m, CH_2), 3.17 and 3.18 (3H, s, NMe), 8.00 (1H, s, H-4), 8.74 (1H, d, *J*=13.8 Hz, *CH*NH), 11.86 (1H, d, *J*=13.8 Hz, NH)	19.8, 27.0 (2), 27.7, 36.1, 94.5, 114.0, 119.0, 123.7, 151.3, 151.6, 157.4, 161.5, 164.3, 170.1, 194.0

collected by filtration to give the title compound **5** (96 mg, 71%) as a pink solid; mp>260°C (Lit.[12] 319°C). (Found: C, 83.56; H, 6.06; N, 10.32. $C_{28}H_{25}N_3$ requires C, 83.34; H, 6.24; N, 10.41.); *m/z* (EI) 403 ($1M^+$), 402 (2), 273 (100%).

Alternative procedure: 2-methylindole (12 mmol) was dissolved in glacial acetic acid (10 mL) and DMFDMA (4.8 mmol) was added to the solution which was then heated at 80°C for 60 min. Precipitate was collected from the hot suspension and washed with 2-propanol to give the title compound **5** (1065 mg, 66%) as a pink solid.

1.4. General procedure for glycinates 6

Compound **3** (10 mmol) and methyl glycinate hydrochloride (10 mmol) in acetic acid (12 mL) were heated at 90–100°C for 3 h. After that, volatile components were evaporated in vacuo and 2-propanol was added for the crystallization. The precipitate was collected by filtration and recrystallized from an appropriate solvent. Compounds **6a** and **b** were prepared according to this procedure.

1.4.1. Methyl *N*-[(2,4,6-trioxohexahydropyrimidin-5-ylidene)methyl]glycinate (6a). Prepared from **3a**, 1930 mg (85%) of white crystals; mp >260°C (DMF). (Found: C, 42.12; H, 4.00; N, 18.25. $C_8H_9N_3O_5$ requires C, 42.30; H, 3.99; N, 18.50.); ν_{max} (KBr) 3240, 1760, 1680, 1650, 1590, 1470 cm^{-1}.

1.4.2. Methyl *N*-[(1,3-dimethyl-2,4,6-trioxohexahydropyrimidin-5-ylidene)methyl]glycinate (6b). Prepared from **3b**, 1938 mg (76%) of white crystals; mp 164–166°C (acetonitrile/2-propanol 1:1). (Found: C, 47.05; H, 5.05; N, 16.41. $C_{10}H_{13}N_3O_5$ requires C, 47.06; H, 5.13; N, 16.46.); ν_{max} (KBr) 3250, 2970, 2940, 1750, 1660, 1630, 1480 cm^{-1}.

1.4.3. (*Z*)-Methyl 2-[[(2,4,6-trioxohexahydropyrimidin-5-ylidene)methyl]amino]-3-dimethylaminopropenoate (7a). To a suspension of **6a** (485 mg, 2.14 mmol) in acetonitrile (4 mL), DMFDMA (0.5 mL, 3.33 mmol) was added and the mixture was heated at 80–90°C for 3 h. After that, solution was concentrated in vacuo and 2-propanol was added and precipitate collected by filtration and recrystallized from DMF to give the title compound **7a** (435 mg, 72%) as a pale orange solid; mp>260°C. (Found: C, 44.26; H, 4.92; N, 18.52. $C_{11}H_{14}N_4O_5 \cdot H_2O$ requires C, 44.00; H, 5.37; N, 18.66.); ν_{max} (KBr) 3440, 3180, 3000, 2820, 1710, 1650, 1590 cm^{-1}.

1.4.4. (*Z*)-Methyl 2-[[(1,3-dimethyl-2,4,6-trioxohexahydropyrimidin-5-ylidene)methyl]amino]-3-dimethylaminopropenoate (7b). To a suspension of **6b** (1045 mg, 4.10 mmol) in acetonitrile (10 mL), DMFDMA (0.8 mL, 5.33 mmol) was added and the mixture was heated at 80–90°C for 10 min. Precipitate was collected by filtration and recrystallized from the mixture of DMF and acetonitrile (4:1) to give the title compound **7b** (890 mg, 70%) as white crystals; mp>260°C. (Found: C, 50.29; H, 5.73; N, 17.92. $C_{13}H_{18}N_4O_5$ requires C, 50.32; H, 5.85; N, 18.06.); ν_{max} (KBr) 3450, 2960, 1700, 1630 cm^{-1}.

1.5. General procedure for 2*H*-1-benzopyran-2-ones 8

To the suspension of **7** (1 mmol) in glacial acetic acid (4–5 mL), appropriate cyclohexanedione (1 mmol) was added and the mixture was heated at 90–100°C for several hours. After that, volatile components were evaporated in vacuo and 2-propanol was added for the crystallization. Precipitate was collected by filtration and recrystallized from an appropriate solvent. Compounds **8a–d** were prepared in this manner.

1.5.1. 7,7-Dimethyl-5-oxo-3-[[(2,4,6-trioxohexahydropyrimidin-5-ylidene)methyl]amino]-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-one (8a). Prepared from **7a** and 5,5-dimethylcyclohexan-1,3-dione, 2.5 h, 304 mg (88%) of a slightly yellow solid; mp>260°C (DMF). (Found: C, 55.33; H, 4.36; N, 12.07. $C_{16}H_{15}N_3O_6$ requires C, 55.65; H, 4.38; N, 12.17.); ν_{max} (KBr) 3440, 3250, 3040, 1735, 1680, 1600 cm^{-1}.

1.5.2. 5-Oxo-3-[[(2,4,6-trioxohexahydropyrimidin-5-ylidene)methyl]amino]-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-one (8b). Prepared from **7a** and 1,3-cyclohexanedione, 2 h, 117 mg (37%) of a slightly yellow solid; mp>260°C (DMF). (Found: C, 51.62; H, 3.65; N, 12.82. $C_{14}H_{11}N_3O_6 \cdot 0.5H_2O$ requires C, 51.54; H, 3.71; N, 12.88.); ν_{max} (KBr) 3500, 3240, 3060, 1735, 1680, 1600 cm^{-1}.

1.5.3. 7,7-Dimethyl-5-oxo-3-[[(1,3-dimethyl-2,4,6-trioxohexahydropyrimidin-5-ylidene)methyl]amino]-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-one (8c). Prepared from **7b** and 5,5-dimethylcyclohexan-1,3-dione, 4 h, 321 mg (86%) of green–yellow crystals; mp 243–246°C (MeCN). (Found: C, 57.82; H, 4.99; N, 11.34. $C_{18}H_{19}N_3O_6$ requires C, 57.90; H, 5.13; N, 11.25.); ν_{max} (KBr) 3470, 3060, 2970, 1735, 1670, 1630, 1590 cm^{-1}.

1.5.4. 5-Oxo-3-[[(1,3-dimethyl-2,4,6-trioxohexahydropyrimidin-5-ylidene)methyl]amino]-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-one (8d). Prepared from **7b** and 1,3-cyclohexanedione, 2.5 h, 314 mg (91%) of a yellow solid; mp 218–222 (dec.) (MeCN). (Found: C, 53.82; H, 4.29; N, 11.47. $C_{16}H_{15}N_3O_6 \cdot 0.5H_2O$ requires C, 54.24; H, 4.55; N, 11.86.); ν_{max} (KBr) 3430, 3060, 2960, 1735, 1670, 1630, 1590 cm^{-1}.

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