The Reactivity of Related 6-Amino- and 5,6-Diaminouracils Derived from 2-Amino-5-(phenoxymethyl)-2-oxazoline: Efficient Access to Bicyclic Pyrimidine Derivatives

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Abstract: 8-(Dimethylamino)-3-(2-hydroxy-3-phenoxypropyl)-xanthine has been obtained from 6-amino-1-(2-hydroxy-3-phenoxypropyl)uracil by an azodicarboxylate Michael-type addition involving a reactive diene. 6-Amino-1-(2-hydroxy-3-phenoxypropyl)uracil was easily prepared from racemic 2-amino-5-(phenoxymethyl)-2-oxazoline. Moreover, these chemical investigations also led to the identification of a racemic 7-aminooxazolo[5,4-*d*]pyrimidin-5(6*H*)-one, obtained by the condensation reaction of the phosgeniminium chloride, Viehe's salt, with 5,6-diamino-1-(2-hydroxy-3-phenoxypropyl)uracil.

Key words: bicyclic compounds, ene reactions, uracils, fused-ring systems, Michael additions

In a previous paper, we reported the synthesis of new xanthines derived from racemic 2-amino-2-oxazoline **1** and evaluated as A1 and A2A adenosine receptor antagonists.[1] Preliminary structure–activity relationship (SAR) results were drawn on the basis of affinity data in relation to the nature and position of certain substituents on the xanthine moiety. For example, it was shown that the N-7 atom in the xanthine ring should be unsubstituted in order to establish a hydrogen bond with the A1 adenosine receptor required to increase the affinity and to modulate the selectivity. Conversely, large and functionalized substituents at N-3 in the xanthine moiety are well accepted by both A1 and A2A receptor subtypes.

In this paper, we report additional modulation around the xanthine moiety to fulfill the adenosine receptor antagonists pharmacophoric requirements. The introduction of an amino function in position 8 was selected for receptor-binding purpose, and we chose to promote the classical amino(phenoxy)propanol pharmacophore, associated with β-adrenergic receptor blockade, as the N-3 substituent on the xanthine ring. These considerations led us to design the racemic 8-(dimethylamino)-3-(2-hydroxy-3-phenoxypropyl)xanthine (**2**) as a lead compound (Figure 1).[2,3]

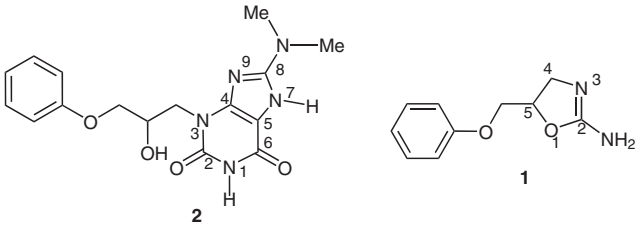

Figure 1 Structure of 8-(dimethylamino)-3-(2-hydroxy-3-phenoxypropyl)xanthine (**2**) and its precursor, 2-amino-2-oxazoline **1**

The first attempt to synthesize xanthine **2** was based on the reaction of 5,6-diaminouracil **3**[1] with *N,N*-dimethylformamide dimethyl acetal (DMFDMA) (Scheme 1). This only led to the formation of the 8-unsubstituted xanthine **4**,[1] probably through nucleophilic attack of the second amino function on the amidine carbon atom of the intermediate, followed by deamination.

Then, we reacted **3** with phosgeniminium chloride (Viehe's salt)[4] in dichloromethane at room temperature and at reflux. All experiments led to the stable racemic 7-aminooxazolo[5,4-*d*]pyrimidin-5(6*H*)-one **5** in 58% yield (Scheme 2) through two hypothetical mechanisms.

The first mechanism (Hypothesis A) involves the powerful electrophilic phosgeniminium chloride reacting with the amino group at the 5-position of **3** to form intermediate **I** after hydrogen chloride elimination (Figure 2). Then, the reactivity of the carbon–oxygen bond in the α-position, through its enolic form, allows the formation of the oxazolo[5,4-*d*]pyrimidin-5(6*H*)-one system. Alternatively (Hypothesis B), intermediate **I** could be rearranged to ammonium salt **II** after departure of a second hydrogen chloride molecule (Figure 2), followed by nucleophilic addition of the oxygen atom at C-4 of the uracil ring to the carbodiimide carbon atom. Hence, a 4,5-cyclization would occur via a positively charged oxygen atom, based on the near coplanarity of the nitrogen atoms.[5] Finally, the loss of a third hydrogen chloride molecule would lead to the oxazolo[5,4-*d*]pyrimidin-5(6*H*)-one **5**.[5]

Structural elucidation of **5** was achieved by ^{1}H and ^{13}C NMR spectroscopy on the basis of previous results for compounds from the oxazolo[5,4-*d*]pyrimidinone or -dione series.[5,6] As **5** could be isolated as a single monocrys-

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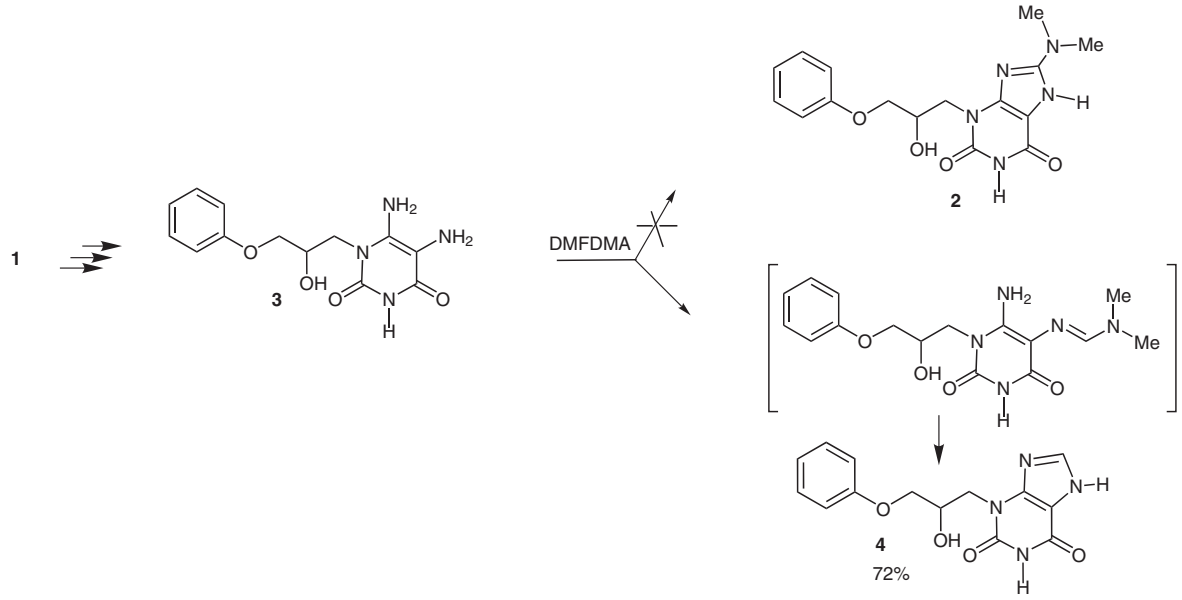
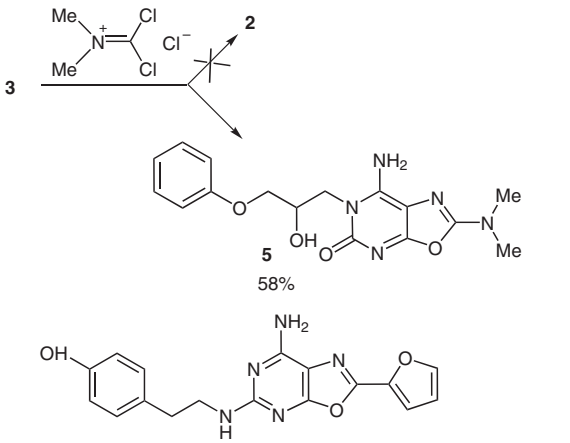


Scheme 1



Scheme 2

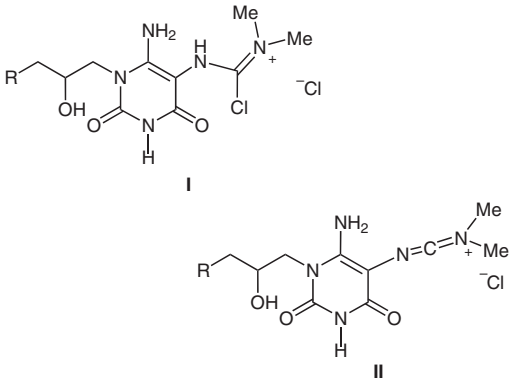


Figure 2 Structures of the hypothetical intermediates **I** and **II**

tal, we performed an X-ray crystallography study (Figure 3). The oxazolo[5,4-*d*]pyrimidin-5(6*H*)-one moiety is almost planar with the maximum deviation from planarity being found for N12 lying 0.013(2) Å from the plane defined by the bicyclic system. The N14–C15 and N22–C21 bonds were determined to be 1.31(7) and 1.29(8) Å, respectively, as typically observed for nitrogen–carbon double bonds,[7,8] while O20–C21, O20–C15, N22–C16, and N23–C21 were found to be identical in length to the comparable conjugated carbon–oxygen and carbon–nitrogen single bonds in the molecule, i.e. 1.37–1.38 and 1.34–1.39 Å, respectively. The dimethylamino nitrogen, N23, was determined to be sp^3 hybridized. All these X-ray data also confirmed the enamine tautomeric form of **5** in the solid state. Moreover, **5** was found to be a racemic (*R*/*S*) mixture as highlighted by the determined spatial group ($P2_1/c$).

Next, our attention turned to performing the synthesis of the target compound **2** via aminouracil **6**, which is easily prepared from the corresponding 2-amino-2-oxazoline **1**.[1] Access to the 8-(dimethylamino)xanthine moiety

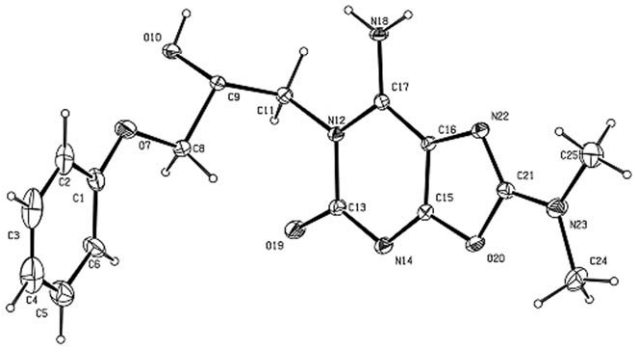
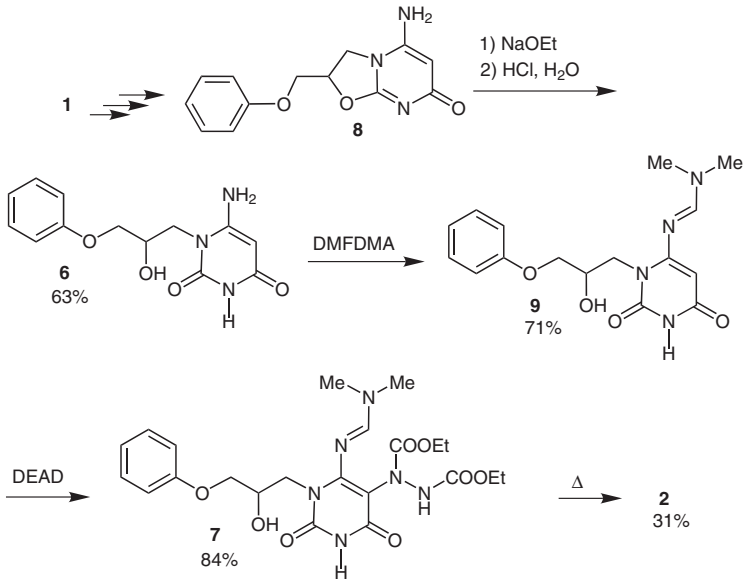


Figure 3 The ORTEP drawing of **5** with thermal ellipsoids at 30% level



Scheme 3

(Scheme 3) was based on the Walsh and Wamhoff procedure[9,10] consisting of a cyclization reaction of Michael adduct **7** leading to the 3-substituted 8-(dimethylamino)xanthine **2**.

6-Aminouracil **6** was directly formed by the hydrolysis of bicyclic compound **8**[1] in an alkaline medium that resulted in the opening of the oxazoline ring. Heating a toluene solution of **6** with DMFDMA[11] led to an efficient reactive heterocyclic diazadiene **9**. Compound **9** was then treated with diethyl azodicarboxylate (DEAD) in toluene (110 °C, 8 h) to give 5-hydrazinouracil **7**. As a Michael adduct model, **7** could be considered as a key intermediate in the formation of new 8-(dimethylamino)theophylline derivatives by thermal cyclization reactions.[9,10,12,13] Hence, the target 8-(dimethylamino)xanthine **2** was obtained by heating **7** in nitrobenzene at 190–200 °C (Scheme 3). The structure of **2** was assigned on the basis of elemental and spectral analyses. The ^{1}H NMR spectrum of **2** showed two singlets at 11.40 and 10.70 ppm, highly characteristic for NH protons in positions 7 and 1 of the xanthine moiety. Such a shielded signal observed at 11.40 ppm for the proton on the N-7 atom of the xanthine skeleton has been already described in the literature data (δ = ~11.30 ppm).[9,10]

In conclusion, this paper highlights the reactivity of 6-aminouracil **6** and 5,6-diaminouracil **3**, both derived from 2-amino-2-oxazoline **1**, leading to racemic 8-(dimethylamino)-3-(2-hydroxy-3-phenoxypropyl)xanthine (**2**) and oxazolo[5,4-*d*]pyrimidin-5(6*H*)-one **5**, respectively. From **3**, by using various dimethylformamide dialkyl acetals, it should now be possible to introduce new substituents in position 8 of the xanthine moiety, thereby increasing molecular diversity and allowing the synthesis of new polysubstituted xanthines. In addition, 7-amino-2-(2-furyl)-5-[(4-hydroxyphenyl)ethylamino]oxazolo[5,4-*d*]pyrimidine (Scheme 2) was recently identified as a potential A2A adenosine receptor antagonist for positron emission tomography (PET).[14] This prompted us to develop new substituted oxazolo[5,4-*d*]pyrimidin-5(6*H*)-ones such as **5**, easily designed from the 2-amino-2-oxazoline scaffold **1**, obtained through one heterocyclization using a Viehe's salt. Finally, pharmacological evaluation of compounds **2** and **5** as potential A1 and A2A adenosine receptor antagonists will be investigated.

Melting points were determined with an SM-LUX-POL Leitz hotstage microscope and are uncorrected. The IR spectra were recorded on a Bruker IFS-25 spectrophotometer; NMR spectra (^{1}H, ^{13}C, and ^{1}H COSY) were recorded at 300 MHz or 75 MHz with TMS as an internal standard using a Bruker AVANCE 300 spectrometer. Analytical TLC was carried out on 0.25-mm precoated silica gel plates (POLYGRAM SIL G/UV$_{254}$) with visualization by irradiation with a UV lamp. Silica gel 60 (70–230 mesh) was used for column chromatography. Analyses indicated by the symbols of the elements were within ±0.3% of the theoretical values.

3-(2-hydroxy-3-phenoxypropyl)xanthine (4)[1]

A stirring mixture of 5,6-diaminouracil **3** (0.7 g, 2.4 mmol), DMFDMA (0.33 g, 2.73 mmol), and AcOH (0.2 mL) in EtOH (14 mL) was refluxed for 4 h. The mixture was then evaporated under reduced pressure and the crude residue was triturated in Et_2O, filtered, and dried to give **4** as colorless crystals. Yield: 0.47 g (65%).

7-Amino-2-(dimethylamino)-6-(2-hydroxy-3-phenoxypropyl)oxazolo[5,4-*d*]pyrimidin-5(6*H*)-one (5)

A stirring mixture of 5,6-diaminouracil **3** (1.46 g, 5 mmol), Viehe's salt (1.95 g, 12 mmol), and anhyd CH_2Cl_2 (50 mL), protected from atmospheric moisture, was allowed to stand at r.t. for 5 h and then was refluxed until the evolution of HCl had ceased (5 h). After cooling at r.t., the solvent of the heterogeneous mixture was removed in vacuo and the residue was mixed with H_2O (30 mL) and then with $KHCO_3$, added slowly until the evolution of CO_2 had ceased. The resultant oxazolopyrimidinone **5** was isolated as colorless crystals by suction using a glass filter, washed with H_2O then EtOH, and dried. Yield: 1.00 g (58%); mp 330 °C.

IR (KBr): 3410, 3320, 3200, 1660, 1630 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.58 (s, 2 H, NH_2), 7.27 (t, J = 7.6 Hz, 2 H, H-3′, H-5′), 6.92 (t, J = 7.6 Hz, 1 H, H-4′), 6.89 (d, J = 7.6 Hz, 2 H, H-2′, H-6′), 5.48 (d, J = 4.1 Hz, 1 H, OH), 4.13–4.09 (m, 2 H, CH, CH_2), 4.00–3.94 (m, 3 H, CH_2), 3.00 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (75 MHz, DMSO-d_6): δ = 165.3, 158.5, 156.9, 154.4, 148.9, 129.5, 120.6, 114.5, 103.8, 70.3, 66.9, 46.4, 37.4.

Anal. Calcd for $C_{16}H_{19}N_5O_4$: C, 55.64; H, 5.54; N, 20.28. Found: C, 55.73; H, 5.46; N, 20.16.

The structure of compound **5** was established by X-ray crystallography (Figure 2). Colorless single crystals of **5** were obtained by slow evaporation from MeOH–$CHCl_3$ (20:80) soln. The unit cell dimensions were determined using the least-squares fit from 25 reflections (25° < c < 35°). Intensities were collected with an Enraf-Nonius CAD-4 diffractometer using the CuKα radiation and a graphite monochromator up to c = 45°. The data were collected to relatively low resolution, i.e. no reflections were observed for c >45° with λ_{Cu}. The data were corrected for Lorentz and polarization effects and for empirical absorption correction.[15] Structure **5** was determined by direct methods SHELX 86[16] and refined using SHELX 97[17] suite of programs. Crystallographic data for structure **8** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-612139.[18]

6-Amino-1-(2-hydroxy-3-phenoxypropyl)uracil (6)

To a solution of Na (1.29 g, 56 mmol) in anhyd EtOH (100 mL) was added **8** (3.62 g, 14 mmol). The resulting solution was refluxed for 8 h and the solvent was then removed in vacuo. The solid residue was dissolved in H_2O and the obtained solution was acidified to pH 5–6 with aq HCl. The precipitate was collected by filtration, washed with EtOH and then petroleum ether, and dried to give the product as pale yellow crystals. Yield: 2.44 g (63%); mp 182 °C.

IR (KBr): 3380, 3310, 3180, 1730, 1695 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.05 (br s, 1 H, NH), 7.28 (t, J = 7.6 Hz, 2 H, H-3′, H-5′), 6.92 (t, J = 7.6 Hz, 1 H, H-4′), 6.89 (d, J = 7.6 Hz, 2 H, H-2′, H-6′), 6.62 (s, 2 H, NH_2), 5.71 (br s, 1 H, OH), 4.60 (s, 1 H, H-5), 4.07–3.76 (m, 5 H, CH_2CHCH_2).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 162.5, 158.5, 156.8, 151.6, 129.5, 120.7, 114.5, 76.3, 70.1, 67.0, 44.8.

Anal. Calcd for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.15. Found: C, 56.54; H, 5.38; N, 15.22.

6-{[(Dimethylamino)methylene]amino}-1-(2-hydroxy-3-phenoxypropyl)uracil (9)

A stirring mixture of 6-aminouracil **6** (4.26 g, 15.4 mmol), DMFDMA (1.93 g, 16.2 mmol), and anhyd toluene (40 mL) was refluxed for 6 h. The mixture was cooled and filtered to remove small amounts of the starting amine. After evaporation of the toluene solution, the crude product was purified by column chromatography (CH_2Cl_2–MeOH, 4:1) to give yellow crystals. Yield: 3.63 g (71%); mp 134 °C.

IR (KBr): 3360, 3350, 1720, 1675 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.62 (br s, 1 H, NH), 7.93 (s, 1 H, N=CH), 7.23 (t, J = 7.5 Hz, 2 H, H-3′, H-5′), 6.89 (t, J = 7.5 Hz, 1 H, H-4′), 6.82 (d, J = 7.5 Hz, 2 H, H-2′, H-6′), 5.20 (br s, 1 H, OH), 4.97 (s, 1 H, H-5), 4.14–4.08 (m, 1 H, CH), 4.05–4.01 (m, 2 H, CH_2), 3.87–3.81 (m, 2 H, CH_2), 3.02 (s, 3 H, NCH_3), 2.93 (s, 3 H, NCH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 163.2, 158.5, 157.1, 156.4, 152.0, 129.4, 120.4, 114.3, 76.8, 70.2, 66.7, 47.3, 40.7, 34.4.

Anal. Calcd for $C_{16}H_{20}N_4O_4$: C, 57.82; H, 6.06; N, 16.86. Found: C, 57.69; H, 5.98; N, 16.92.

6{[(Dimethylamino)methylene]amino}-1-(2-hydroxy-3-phenoxypropyl)-5-[1,2-bis(ethoxycarbonyl)hydrazino]uracil (7)

A stirring mixture of uracil **9** (1.0 g, 3.03 mmol) and DEAD (0.53 g, 3.15 mmol) was refluxed in toluene (20 mL) for 8 h. The toluene was removed in vacuo to give a dark red oil. A small amount of EtOAc was added to the residue, the suspension was cooled, and the separated product was collected by filtration. The Michael adduct was washed with EtOAc and dried in vacuo to give the product as orange crystals. Yield: 1.29 g (84%); mp 70 °C.

IR (KBr): 3400, 3210, 1720, 1655 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.03 (br s, 1 H, NH-3), 8.99 (s, 1 H, N–NH), 7.76 (s, 1 H, N=CH), 7.25 (t, J = 7.7 Hz, 2 H, H-3′, H-5′), 6.90 (t, J = 7.7 Hz, 1 H, H-4′), 6.83 (d, J = 7.7 Hz, 2 H, H-2′, H-6′), 5.23 (br s, 1 H, OH), 4.20–3.84 (m, 9 H, CH_2CHCH_2, OCH_2), 3.02 (s, 3 H, NCH_3), 2.94 (s, 3 H, NCH_3), 1.19 (t, J = 7.4 Hz, 3 H, CH_3), 1.09 (t, J = 7.4 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 162.1, 160.4, 158.4, 157.0, 153.3, 151.7, 150.2, 129.5, 120.3, 114.3, 101.5, 69.5, 66.2, 63.3, 61.5, 44.1, 40.2, 34.3, 14.5.

Anal. Calcd for $C_{22}H_{30}N_6O_8$: C, 52.17; H, 5.97; N, 16.59. Found: C, 52.26; H, 5.83; N, 16.48.

8-(Dimethylamino)-3-(2-hydroxy-3-phenoxypropyl)xanthine (2)

Michael adduct **7** (1.30 g, 2.58 mmol) was heated in nitrobenzene (7 mL) between 190–200 °C for 1.5 h. The solution was then cooled to 10 °C. A small amount of Et_2O was added, and the resulting solid was filtered and washed with Et_2O. The crude product was then crystallized (EtOH) and obtained as beige crystals. Yield: 0.28 g (31%); mp 184 °C.

IR (KBr): 3425, 3170, 1700, 1630 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.40 (br s, 1 H, NH-7), 10.70 (br s, 1 H, NH-1), 7.24 (t, J = 7.4 Hz, 2 H, H-3′ and H-5′), 6.88–6.80 (m, 3 H, H-2′, H-4′, H-6′), 5.31 (br s, 1 H, OH), 4.39–4.31 (m, 1 H, CH), 4.02–3.91 (m, 4 H, CH_2), 2.93 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (75 MHz, DMSO-d_6): δ = 158.8, 156.1, 152.3, 151.8, 150.2, 129.8, 121.1, 114.8, 106.9, 70.7, 66.5, 46.3, 40.5, 40.2.

Anal. Calcd for $C_{16}H_{19}N_5O_4$: C, 55.64; H, 5.54; N, 20.28. Found: C, 55.56; H, 5.62; N, 20.35.

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