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DIASTEREOSELECTIVE SYNTHESIS OF CHROMENO[4,3-*D*] PYRIMIDINES

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Abstract. *The paper investigates the diastereoselective synthesis of chromeno[4,3-d]pyrimidines by isolation and cyclization of diastereomerically pure dihydropyrimidine addition intermediates to resorcinol. The authors discovered the reversibility of the addition reaction to be an important factor that could neutralize the dominant formation of one of the intermediate diastereomers.*

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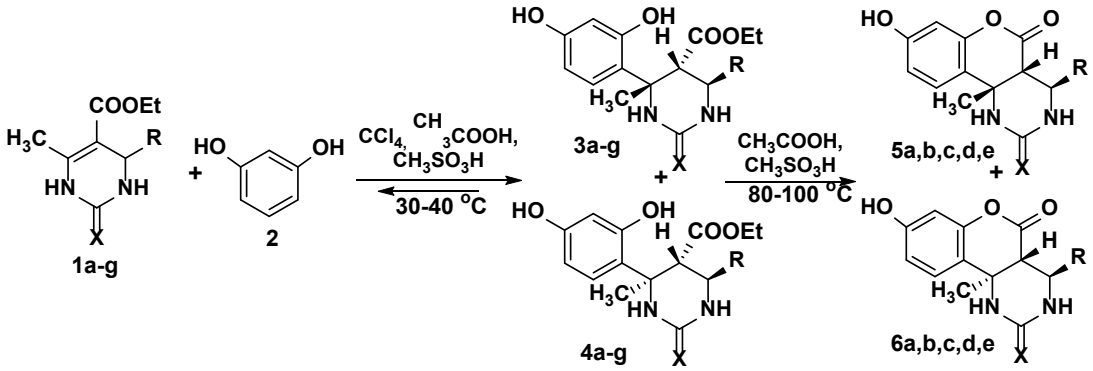
Introduction

Nowadays, the diastereoselectivity of pyrimidines and chromanes syntheses is a relevant issue [1, 2]. It is due to a great difference of the pharmacological activity of these structures having stereogenic centres and also with the presence of chirality in their natural analogues [3, 4]. For example, (*S*)-enantiomer of monastrol has 15 times stronger anticancer activity than (*R*)-monastrol [5, 6]. Most commonly, complex catalytic systems are used to produce dihydropyrimidines and chromanes with chiral atoms [7-9].

We have previously synthesized chromeno[4,3-*d*] pyrimidines based on urea and thiourea [10, 11] using available acid catalysts and solvents, and determined the diastereoselectivity of their formation [12]. However, based on the proposed reaction pathway, large differences in the diastereomeric composition of the substituted 2-thio- and 2-oxochromeno[4,3-*d*]pyrimidines remained unclear. Therefore, the isolation and determination of the structure of noncyclic intermediates and their further cyclization products was important to determine the stereoadjoint synthesis of chromeno[4,3-d]pyrimidines.

We developed a special technique allowed us to slow down the cyclization process. Therefore we reacted dihydropyrimidines **1a-g** and resorcinol **2** at 30-40 °C, which is lower than in analogous syntheses [10, 11]. Additionally, we added CCl_4 to catalytic system AcOH/$MeSO_3H$ (Fig.1). The reaction time increased significantly to 11-18 h, which allowed more intermediates to accumulate in the reaction mass. Extraction of the reaction mixture into water transferred all

the presented structures into solid form, including unreacted starting components, intermediates **3** and **4,** and, as a rule, two diastereomers of chromeno[4,3-*d*]pyrimidines **5** and **6**. It is worth noting that similar results were observed for thiourea- and urea-based chromenes but the accumulation of predominantly intermediates proved to be difficult due to the simultaneous occurrence of several processes during the reaction. Indeed, despite this, only one non-cyclic diastereomer **3** was dominant and compound **4** was fixed only in trace amounts, probably due to its better solubility in water. The purification by re-purification from weakly alkaline solution resulted in the isolation of the dominant diastereomer **3** with low yields up to 37%, and a diastereomeric purity of more than 90% according to NMR spectroscopy.



1, **3**, **4**, **5**, **6**: R = C_6H_5, X = S (**a**); R = 4-Me-C_6H_4, X = S (**b**); R = 4-MeO-C_6H_4, X = S (**c**); R = C_6H_5, X = O (**d**); R = 4-Me-C_6H_4, X = O (**e**); R = 4-MeO-C_6H_4, X = O (**f**); R = 3-NO_2-C_6H_4, X = O (**g**);

Fig. 1. Scheme of the cyclisation reaction of dihydropyrimidines **1a-g** and resorcinol **2**

We determined the structure of the **3a-g** compounds by NMR spectroscopy and mass spectrometry. The key signals in the ^{1}H NMR spectrum were the aliphatic protons of the pyrimidine cycle in the range of 3.8-4.1 ppm with small spin-spin coupling constants (SSCC) around 3.5-4.8 Hz and the signals of the ether group. Using the NOESY spectrum of compound **3d** we recorded a low intensity cross-peak of the 5-H proton at the carboxyl group with protons of the 4-Me group, along with the absence of 5-H cross-peaks with protons of the phenyl group. The NOESY spectrum also showed symmetrical 6-H cross-peaks with phenyl group protons and with the 1-NH group. This allowed us to define compound **3** as a (4*R**, 5*S**, 6*R**)-diastereomer, where protons of the 6-H, 4-Me group are in the equatorial position relative to the pyrimidine cycle plane.

The use of pure (4*R**,5*S**,6*R**)-diastereomers of **3a,b,c,d,e** for their cyclization into chromeno[4,3-*d*]pyrimidines allowed us to determine the diastereone-directed process, as structure **3** excludes epimerization at the defining C(4) position of the pyrimidine cycle. The best cyclization conditions were determined previously [10, 11]. The relative changes in the composition of the products were monitored by NMR spectroscopy. The signal of the proton H-4 of the main diastereomer **5**, which was not overlapped by other signals, was taken as the unit. In the case of cyclization of compound **3a** the diastereomeric composition of chromanes **5a**:**6a** changed insignificantly; before cyclization their ratio was 10:1 and after it was 10:0.7 (Fig. 2). The intermediate diastereomer **3a** was more than halved and the (4*R**,4a*S**,10b*R**)-product **5a** corresponding to the configuration of intermediate **3a** remained dominant. In the case of the urea-based structures, two chromeno[4,3-**d**]pyrimidines **5e** and ***6e*** diastereomers were formed from the dominant non-cyclic diastereomer **3e** in a ratio of

approximately 1:1 (Fig. 3). This result of the cyclization of **3e** is probably due to its reversible decomposition into its original components followed by the reattachment of resorcin **2** to the double bond of dihydropyrimidine **1**. This led to an equalization of the diastereomeric products **5** and **6**, even if the minor diastereomer **4** was initially formed in smaller amounts. Reversible decomposition of the **3e** structure was indicated by the accumulation of the initial pyrimidine **1e** in the cyclization products (the integral signal area increased by approximately 2-fold). Unlike the products on urea, the structures with thio-fragment exhibited an insignificant change in the initial dihydropyrimidine signal. For an alignment of the oxo-product ratio **5**:**6** to a 1:1 composition to occur, it should also be assumed that the minor diastereomer **4** cycles are faster than its competitor **3**.

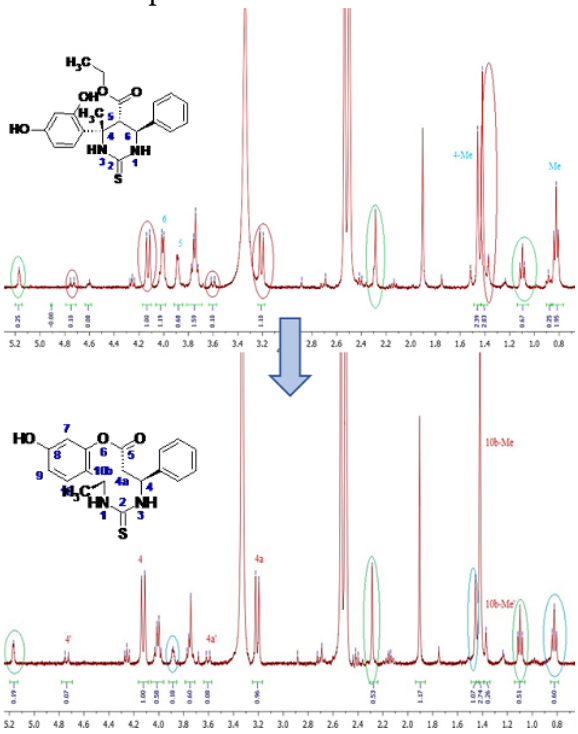


Fig. 2. ^{1}H NMR spectra when cyclizing **3a** to **5a**

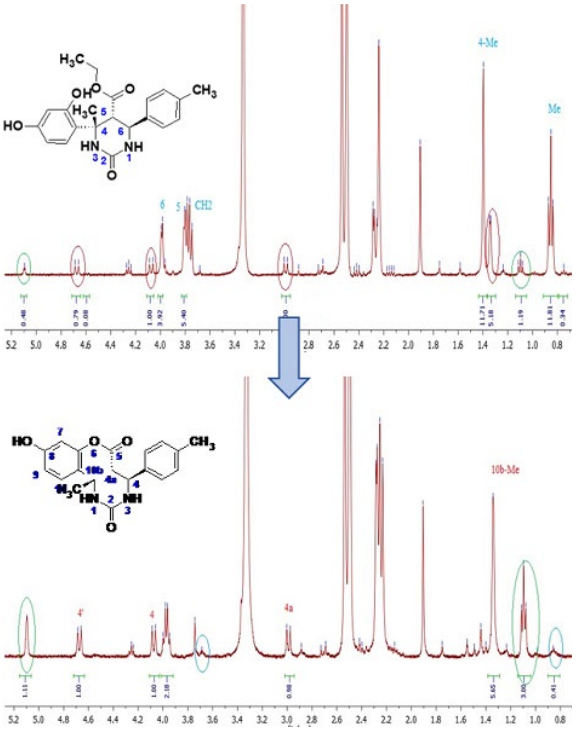


Fig. 3. ^{1}H NMR spectra when cyclizing **3e** to **5e** and **6e**

Through a series of cyclizations we have found the important factors for the diastereonation reaction of chromenopyrimidine formation. They are the ratio of diastereomeric esters formed during the initial attachment of resorcin to dihydropyrimidine-2-thiones via the double bond and the reversibility of this reaction. These parameters are key for determining the diastereomer ratios in the final products. Thus, the thiochromenopyrimidines the diastereomer ratio of the intermediate esters is dominant. The reversibility of the reaction in this case has no significant influence. In the example of dihydropyrimidin-2-ones the reversibility of the reaction has a greater influence on the alignment of the diastereomer ratio of the chromeno[4,3-*d*]pyrimidines. Therefore, even using one ester diastereomer for cyclization a mixture of chromeno[4,3-*d*]pyrimidine diastereomers in the ratio 1:1 is formed.

Experimental part

We recorded IR spectra in reflected light on a Spectrum Two PerkinElmer FT-IR spectrometer at 700-4000 cm^{-1}. Also we recorded the NMR spectra on a "Bruker DRX-400" instrument for DMSO-d_6 solutions at 30 °C. As reference for the chemical shifts we used the signals of

the residual solvent protons in ^{1}H NMR (δ_H = 2.50 ppm) and ^{13}C NMR (δ_C = 39.5 ppm). We used tetramethylsilane signal (IOC RAS, Moscow) as a marker. We recorded mass spectra on a FINNIGAN MAT.INCOS 50 mass spectrometer at an ionization voltage of 70 eV and a temperature of 100-220 °C in the ionization chamber (IOC RAS, Moscow). Elemental analysis we conducted in analytical laboratory INEOS RAS Moscow on analyzer "PerkinElmer 2400". To determine melting and boiling points we used apparatus BüchiM-560.

We heated pyrimidinone(thione) **1a-g** (1 mmol) with 1,3-benzoldiol **2** (2 mmol) in a mixture of CCl_4 (5 ml) and AsOH (0.5 ml) in presence of 50 μl $MeSO_3H$ ($7.7*10^{-4}$ M) at 30-40 °C for 11-18 hours. Then we cooled the reaction mixture and poured it into a three per cent aqueous $NaHCO_3$ solution (10 mL). We filtered off the precipitate and washed it with water. To purify the reaction mixture from the initial pyrimidine, we added 1 ml of a 6% NaOH solution to the obtained precipitate, separated the insoluble part by filtration. Then we added 1-2 ml of a 6% HCl solution to the filtrate until the alkali was completely neutralized. After it, we filtered the resulting precipitate, washed with water, and dried on air at room temperature.

Ethyl (4*R,5*S**,6*R**)-4-(2,4-dihydroxyphenyl)-4-methyl-6-phenyl-2-thiohexahydropyrimidine-5-carboxylate (3a)**. Yield 58 mg (15%), m.p. 182-184 °C. NMR spectrum ^{1}H (400 MHz, δ, ppm, *J*/Hz): 0.82 (mp, 3 H, $COOCH_2\underline{CH_3}$, *J* = 7.0), 1.46 (s, 3 H, $C(4)CH_3$), 3.76 (qu, 2 H, $COO\underline{CH_2}CH_3$, *J* = 7.0), 3.89 (d, 1 H, C(5)H, *J* = 4.2) 4.01 (d, 1 H, C(6)H, *J* = 4.2), 6.26 (dd, 1 H, C(5')H, *J* = 8.6, 1.8), 6.39 (d, 1 H, C(3')H, *J* = 1.8), 6.92 (d, 1 H, C(6')H, *J* = 8.6), 7.06 (d, 2 H, C(2",6")H, *J* = 8.1), 7.22-7.33 (m, 3 H, C(3",4",5")H), 8.22 (br.s, 1 H, NH), 8.49 (s, 1 H, NH), 9.32 (s, 1 H, OH), 9.71 (s, 1 H, OH). NMR spectrum ^{13}C (100 MHz, δ, ppm.): 13.72, 23.13, 48.72, 54.34, 57.99, 59.25, 104.10, 106.14, 121.57, 126.35, 126.46, 127.66 (2 C), 128.53 (2 C), 138.14, 157.75, 168.51, 175.90, 176, 75. Found (%): C, 61.91; H, 5.71; N, 7.22. $C_{20}H_{22}N_2O_4S$. Calculated (%): C, 62.16; H, 5.74; N, 7.25.

Ethyl (4*R,5*S**,6*R**)-4-(2,4-dihydroxyphenyl)-4-methyl-6-(4-methylphenyl)-2-thiohexahydropyrimidine-5-carboxylate (3b)**. Yield 109 mg (27%), m.p. 221-223 °C. NMR spectrum ^{1}H (400 MHz, δ, ppm, *J*/Hz): 0.86 (tr, 3 H, $COOCH_2\underline{CH_3}$, *J* = 7.1), 1.45 (s, 3 H, $C(4)CH_3$), 2.24 (c, 3 H, $C(4")CH_3$), 3.76 (qu, 2 H, $COO\underline{CH_2}CH_3$, *J* = 7.1), 3.89 (d, 1 H, C(5)H, *J* = 4.7), 3.97 (d, 1 H, C(6)H, *J* = 4.7), 6.22 (dd, 1 H, C(5')H, *J* = 8.6, 2.2), 6.41 (d, 1 H, C(3')H, *J* = 2.2), 6.88 (d, 1 H, C(6')H, *J* = 8.6), 6.93 (d, 2 H, C(2",6")H, *J* = 8.3), 7.08 (d, 2 H, C(3",5")H, *J* = 8.3), 8.14 (s, 1 H, NH), 8.41 (s, 1 H, NH), 10.30 (br. s, 2 H, OH). NMR spectrum ^{13}C (100 MHz, δ, ppm): 13.75, 20.60, 23.19, 48.77, 54.29, 58.02, 59.30, 104.10, 106.17, 121.63, 126.37 (2 C) 128.56 (2 C), 128.69, 135.09, 136.68, 148.25, 153.67, 158.42, 165.29. Found (%): C, 62.81; H, 6.01; N, 6.96. $C_{21}H_{24}N_2O_4S$. Calculated (%): C, 62.98; H, 6.04; N, 6.99.

Ethyl (4*R,5*S**,6*R**)-4-(2,4-dihydroxyphenyl)-4-methyl-6-(4-methylphenyl)-2-thiohexahydropyrimidine-5-carboxylate (3c)**. Yield 108 mg (26%), m.p. 180-182 °C. NMR spectrum ^{1}H (500 MHz, δ, ppm., *J*/Hz): 0.89 (mp, 3 H, $COOCH_2\underline{CH_3}$, *J* = 7.0), 1.46 (s, 3 H, $C(4)CH_3$), 3.71 (s, 3 H, $C(4")OCH_3$), 3.80 (qu, 2 H, $COO\underline{CH_2}CH_3$, *J* = 7.0), 3.84 (d, 1 H, C(5)H, *J* = 5.0), 3.96 (d, 1 H, C(6)H, *J* = 5.0), 6.26 (dd, 1 H, C(5')H, *J* = 8.5, 2.4), 6.39 (d, 1 H, C(3')H, *J* = 2.4), 6.84 (d, 2 H, C(2",6")H, *J* = 8.3), 6.93 (d, 1 H, C(6')H, *J* = 8.5), 7.08 (d, 2 H, C(3",5")H, *J* = 8.3), 8.13 (s, 1 H, NH), 8.41 (s, 1 H, NH), 9.33 (s, 1 H, OH), 9.72 (s, 1 H, OH). NMR spectrum ^{13}C (126 MHz, δ, ppm.): 13.71, 48.74, 53.73, 54.99, 59.20, 104.01, 106.05, 113.34, 121.53, 127.55,

128.57, 129.83, 153.58, 157.65, 158.59, 168.63, 176.48. Found (%): C, 50.27; H, 5.78; N, 6.69. $C_{21}H_{24}N_2O_5S$. Calculated (%): C, 60.56; H, 5.81; N, 6.73.

Ethyl (4*R,5*S**,6*R**)-4-(2,4-dihydroxyphenyl)-4-methyl-2-oxo-6-phenylhexahydropyrimidine-5-carboxylate (3d)**. Yield 136 mg (37%), m.p. 248-250 °C. IR spectrum, ν/cm^{-1}: 3442 (OH), 3298, 3214 (NH), 1726 (COOEt), 1650 (NH-C=O), 1596, 1518 (C=C), 1223, 1184 (C-O). NMR spectrum ^{1}H (400 MHz, δ, ppm., *J*/Hz): 0.82 (tr, 3 H, $COOCH_2\underline{CH_3}$, *J* = 7.1), 1.41 (s, 3 H, C(4)CH_3), 3.76 (qu, 2 H, $COO\underline{CH_2}CH_3$, *J* = 7.1), 3.85 (d, 1 H, C(5)H, *J* = 3.9), 4.04 (d, 1 H, C(6)H, *J* = 3.9), 6.26 (dd, 1 H, C(5')H, *J* = 8.6, 2.2), 6.38 (d, 1 H, C(3')H, *J* = 2.2), 6.60 (br. s., 1 H, NH), 6.79 (br. s., 1 H, NH), 7.06 (d, 1 H, C(6')H, *J* = 8.6), 7.09 (d, 2 H, C(2",6")H, *J* = 7.8), 7.21 (tr, 1 H, C(4")H, *J* = 7.8), 7.29 (tr, 2 H, C(3",5")H, *J* = 7.8), 9.26 (br. s., 1 H, OH), 9.62 (br. s., 1 H, OH). NMR spectrum ^{13}C (100 MHz, δ, ppm.): 13.81, 24.10, 49.96, 53.83, 56.84, 58.98, 104.00, 106.06, 122.69, 126.39 (2 C), 127.28, 127.97 (2 C), 128.51, 139.57, 153.87, 156.02, 157.56, 168.92. Found (%): 64.67; H, 5.97; N, 7.53. $C_{20}H_{22}N_2O_5$. Calculated (%): C, 64.85; H, 5.99; N, 7.56.

Ethyl (4*R,5*S**,6*R**)-4-(2,4-dihydroxyphenyl)-4-methyl-6-(4-methylphenyl)-2-oxohexahydropyrimidine-5-carboxylate (3e)**. Yield 62 mg (16%), m.p. 216-218 °C. IR spectrum, ν/cm^{-1}: 3500, 3401 (OH), 3206 (NH), 1724 (COOEt), 1644 (NH-C=O), 1600, 1511 (C=C), 1191, 1181 (C-O). NMR spectrum ^{1}H (400 MHz, δ, ppm., *J*/Hz): 0.86 (tr, 3 H, $COOCH_2\underline{CH_3}$, *J* = 7.0), 1.41 (s, 3 H, C(4)CH_3), 2.24 (s, 3 H, C(4")CH_3), 3.76 (qu, 2 H, $COO\underline{CH_2}CH_3$, *J* = 7.0), 3.82 (d, 1 H, C(5)H, *J* = 3.7), 4.00 (d, 1 H, C(6)H, *J* = 3.7), 6.26 (dd, 1 H, C(5')H, *J* = 7.8, 2.4), 6.37 (d, 1 H, C(3')H, *J* = 2.4), 6.48 (br. s., 1 H, NH), 6.73 (br. s., 1 H, NH), 6.97 (d, 2 H, C(2",6")H, *J* = 7.8), 7.02 - 7.11 (m, 3 H, C(6',3",5")H), 9.23 (br. s., 1 H, OH), 9.59 (s, 1 H, OH). NMR spectrum ^{13}C (100 MHz, δ, ppm.): 13.81, 20.57, 24.10, 49.97, 53.57, 56.85, 59.00, 103.98, 106.03, 106.17, 126.28 (2 C), 128.50 (2 C), 129.63, 136.36, 136.51, 153.83, 156.01, 157.53, 169.00. Found (%): C, 65.47; H, 6.26; N, 7.25. $C_{21}H_{24}N_2O_5$. Calculated (%): C, 65.61; H, 6.29; N, 7.29.

Ethyl (4*R,5*S**,6*R**)-4-(2,4-dihydroxyphenyl)-4-methyl-6-(4-methoxyphenyl)-2-oxohexahydropyrimidine-5-carboxylate (3f)**. Yield 70 mg (17%), m.p. 181-183 °C. NMR spectrum ^{1}H (400 MHz, δ, ppm., *J*/Hz): 0.87 (tr, 3 H, $COOCH_2\underline{CH_3}$, *J* = 7.1), 1.39 (s, 3 H, C(4)CH_3), 3.70 (s, 3 H, C(4")CH_3), 3.79 - 3.81 (m, 3 H, $COO\underline{CH_2}CH_3$, C(5)H), 3.97 (d, 1 H, C(6)H, *J* = 4.5), 6.25 (dd, 1 H, C(5')H, *J* = 8.5, 2.0), 6.36 (d, 1 H, C(3')H, *J* = 2.0), 6.43 (s, 1 H, NH), 6.68 (s, 1 H, NH), 6.83 (d, 2 H, C(2",6")H, *J* = 8.5), 6.97 (d, 2 H, C(3",5")H, *J* = 8.5), 7.04 (d, 2 H, C(6')H, *J* = 8.4), 9.25 (s, 1 H, OH), 9.60 (s, 1 H, OH). NMR spectrum ^{13}C (100 MHz, δ, ppm.): 13.86, 24.11, 50.07, 53.25, 55.06, 56.80, 58.99, 103.99, 106.01, 113.39 (2 C), 122.75, 127.50, 128.47 (2 C), 131.41, 153.83, 155.93, 157.51, 158.53, 169.06. Found (%): C, 62.73; H, 6.01; N, 6.97. $C_{21}H_{24}N_2O_6$. Calculated (%): C, 62.99; H, 6.04; N, 7.00.

Ethyl (4*R,5*S**,6*R**)-4-(2,4-dihydroxyphenyl)-4-methyl-6-(3-nitrophenyl)-2-oxohexahydropyrimidine-5-carboxylate (3g)**. Yield 35 mg (8%), m.p. 195-197 °C. IR spectrum, ν/cm^{-1}: 3378, 3316 (OH), 3245 (NH), 1710 (COOEt), 1649 (NH-C=O), 1605, (C=C), 1525, 1348 (NO_2), 1225, 1181 (C-O). NMR spectrum ^{1}H (400 MHz, δ, ppm, *J*/Hz): 0.79 (tr, 3 H, $COOCH_2\underline{CH_3}$, *J* = 7.0), 1.41 (s, 3 H, C(4)CH_3), 3.75 (qu, 2 H, $COO\underline{CH_2}CH_3$, *J* = 7.0), 3.92 (d, 1 H, C(5)H, *J* = 3.4), 4.18 (d, 1 H, C(6)H, *J* = 3.4), 6.26 (dd, 1 H, C(5')H, *J* = 8.4, 1.8), 6.39 (d, 1 H, C(3')H, *J* = 1.8), 6.86 (br. s., 1 H, NH), 8.90 (br/s., 1 H, NH), 7.05 (d, 1 H, C(6')H, *J* = 8.4), 7.52 (d, 1 H, C(6")H, *J* = 7.8), 7.59 (tr, 1 H, C(5")H, *J* = 7.8), 8.01 (s, 1 H, C(2")H), 8.11 (d, 1 H, C(4")H, *J* = 7.8), 9.21 (br. s., 1 H, OH), 9.73 (br. s., 1 H, OH). NMR spectrum ^{13}C (100 MHz, δ,

ppm.): 13.69, 24.15, 49.75, 53.20, 56.85, 59.31, 104.09, 106.15, 121.20, 122.20, 122.38, 128.35, 129.68, 133.52, 142.08, 147.46, 153.92, 155.78, 157.66, 168.69. Found (%): C, 57.61; H, 5.07; N, 10.08. $C_{20}H_{21}N_3O_7$. Calculated (%): C, 57.83; H, 5.10; N, 10.12.

Thus, we cyclized compounds **3** according to the corresponding procedures [10, 11].

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