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DIASTEREOMERIC COMPOSITION OF THE REACTION OF THE FORMATION OF HEXAHYDRO-5*H*-CHROMENO[4,3-*D*]PYRIMIDIN-5-ONES

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2-thio-1,2,3,4,4a,10b-hexahydro-5H-chromeno[4,3-d]pyrimidine-ones, acid-catalyzed condensation, monitoring

Abstract. *The paper dwells on the formation and accumulation patterns of diastereomeric 2-thio-1,2,3,4,4a,10b-hexahydro-5H-chromeno[4,3-d]pyrimidin-5-ones resulting from the acid-catalyzed condensation of dihydropyrimidin-2-thions with resorcinols.*

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Introduction

Chemists are interested in nitrogen-containing heterocyclic systems of various structures [1-3]. Pyrimidine-2-ones(thions) are the important heterocyclic system, through the modification of which new biologically active substances are developed [4-6]. Chromanes are also the important classes of oxygen-containing heterocyclic systems and play a major role in the metabolism of various plants, microorganisms, animals and humans [7-9].

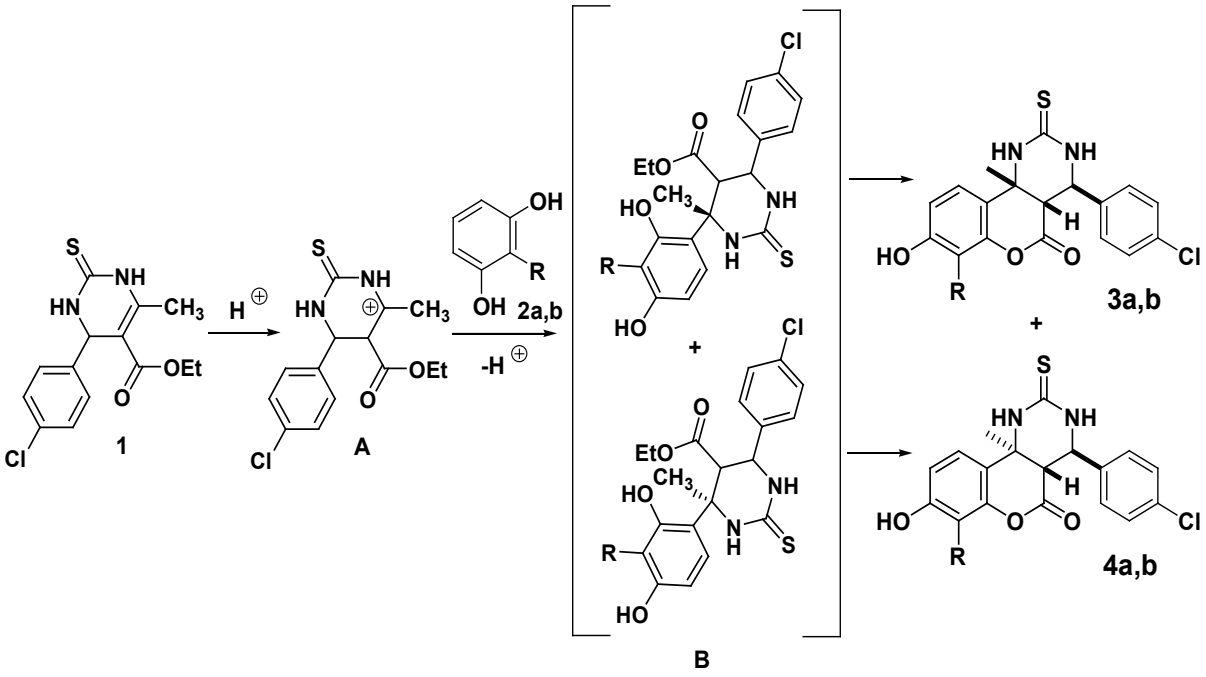
The obtaining of dihydro-1*H*-chromeno[4,3-*d*] pyrimidine derivatives is in the focus because heterocycles based on the combination of dihydropyrimidine and chromane moieties exhibit diverse biological activities such as antifungal, antibacterial and anticancer as well as being anticoagulant, vasodilator and antianaphylactic agents [10-13].

Earlier for synthesis of substituted 2-thio-1,2,3,4,4a,10b-hexahydro-5*H*-chromeno[4,3-*d*]pyrimidine-5-ones we developed condensation of dihydropyrimidine-2-thions with 1,3-benzolders [14] As a resut of this reaction we obtained two diastereomers which have not been examined in previous publications.

The aim of the work is the optimization of the (4*R**, 4a*S**, 10b*R**)/(4*R**, 4a*S**, 10b*S**) of diastereomers replaced by 2-thio-1,2,3,4,4a,10b-hexahydro-5*H*-chromene[4,3-*d*]pyrimidine-5-

ones synthesis method based on monitoring of the reaction proceeding by NMR ^{1}H spectroscopy.

The difficulty in determining the best reaction conditions, as shown earlier, lies in the fact that the formation of the target diastereomers is accompanied by a degradation process [14]. Therefore, the reaction is not always carried out until the complete exhaustion of the starting components, which results with a satisfactory yield of the target products. There is often a significant change in the diastereomeric composition of the products. Thus, it was experimentally proved that when the reaction is carried out for 6-8 hours, the (4*R**, 4a*S**, 10b*R**)-diastereomer dominates, while when the reaction is continued for more than 10-12 hours, on the contrary, the (4*R**, 4a*S**, 10b*S**)-diastereomer dominates.



R = **a** – H; **b** – CH_3

Fig.1

The formation of two diastereomers is determined by a possible reaction mechanism (Fig. 1) by protonation at the double bond occuring to form the most stable pyrimidine **A** ion. Electrophilic addition of **A** to resorcinol produces two intermediate isomers **B**, in which the methyl substituent takes an axial or equatorial position. Intramolecular esterification occurs under reaction conditions, leading to the corresponding chromane cycles. The formation of two diastereomers upon addition of dihydropyrimidines to resorcinol was shown previously [14].

To understand the dynamics of diastereomer formation and accumulation, the reaction was monitored using dihydropyrimidine **1** condensation with resorcinol **2a,b** as a model synthesis one (see Fig. 1). The choice of chlorinated derivative was made in accordance with those compounds were almost always separated as one (4*R**, 4a *S**, 10b *R*)-diastereomer. But the diastereomer (4*R**, 4a*S**, 10b*S**)- was only detected in trace amounts.

After dissolution of the starting compounds, samples of the reaction mixture were taken after 0.5-1 hours and treated with water only, without further cleaning of the resulting sludge. The analysis of the reaction products using ^{1}H NMR spectroscopy showed the prevalence of the signals of the starting pyrimidination **1** and the corresponding diastereomers **3a** and **4a** (Fig. 2, 3).

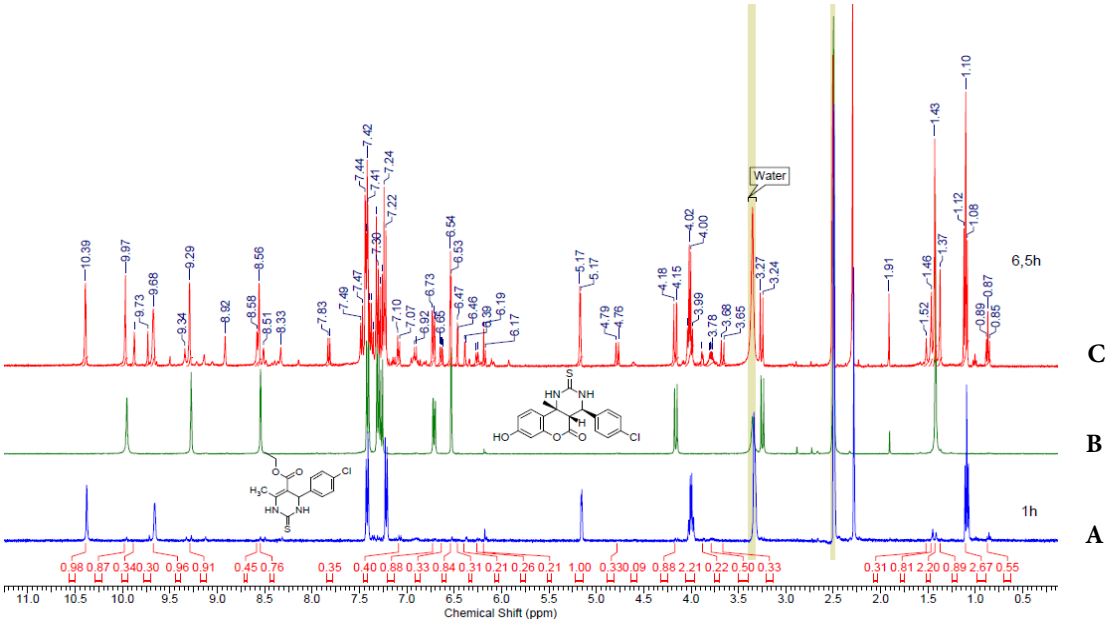


Fig. 2. Comparison of the ^{1}H NMR spectra of the preparation of 3,4a: **A** - almost pure initial ethyl 4-(4-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-thiopyrimidine-5-carboxylate **1** (after 1 hour); **B**, pure (4*R**,4a*S**,10b*R**)-8-hydroxy-10b-methyl-2-thio-4-(4-chlorophenyl)-1,2,3,4,4a,10b-hexahydro-5*H*-chromeno[4,3-*d*]pyrimidin-5-one **3a**; **C**, reaction mixture after 6.5 hours

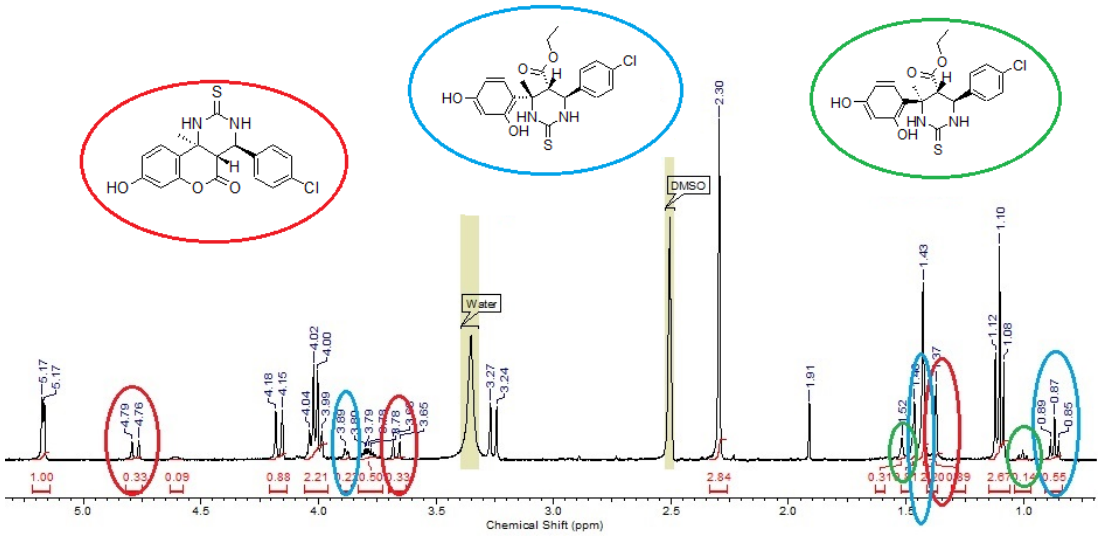


Fig. 3. Fragment of the spectrum of the reaction mixture after 6.5 h when 3,4a was obtained: **red** colored signals (4*R**,4a*S**,10b*S**)-8-hydroxy-10b-methyl-2-thio-4-(4-chlorophenyl)-1,2,3,4,4a,10b-hexahydro-5*H*-chromeno[4,3-*d*]pyrimidin-5-one **3a**; **blue** - ethyl (4*R**,5*S**,6*R**)-6-(4-chlorophenyl)-hexahydro-4-(2,4-dihydroxyphenyl)-4-methyl-2-thiopyrimidine-5-carboxylate; **green** - ethyl (4*S**,5*S**,6*R**)-6-(4-chlorophenyl)-hexahydro-4-(2,4-dihydroxyphenyl)-4-methyl-2-thiopyopyrimidine-5-carboxylate.

There is probably a general relationship of **3a**/**4a** (4*R**, 4a*S**, 10b*R**)/(4*R**, 4a*S**, 10b*S**) diastereomer formation with the resorcinol fragment in the ratio 3:1. In addition, a detailed analysis of the reaction mixture after 6.5 h reveals the presence of intermediates fixed at about 15 and 5% respectively, making it impossible to determine their spectral characteristics accurately. Nevertheless, by the chemical shifts of the 4-methyl groups as well as the ester group could be suggested the determination of the ratio of the target products by the dominant formation of the intermediate ethyl (4*R**, 5*S**, 6*R**)-6-(4-chlorophenyl)-hexahydro-4-(2,4-

dihydroxyphenyl)-4-methyl-2-thiopyrimidine-5-carboxylate as compared to the (4*S**, 5*S**, 6*R**)-diastereomer, at the same ratio of 3:1. The accumulation of (4*R**, 4a*S**, 10b*S**)-chromanes in large quantities is due to the intermediate separation of the dominant isomer, which is less soluble in acetic acid and an artificial ratio shift of the (4*R**, 4a*S**, 10b*S**)-diastereomer. Also there may be a different resistance of the diastereomers to degradation under reaction conditions, which will also affect the diastereomer ratio, especially during prolonged heating.

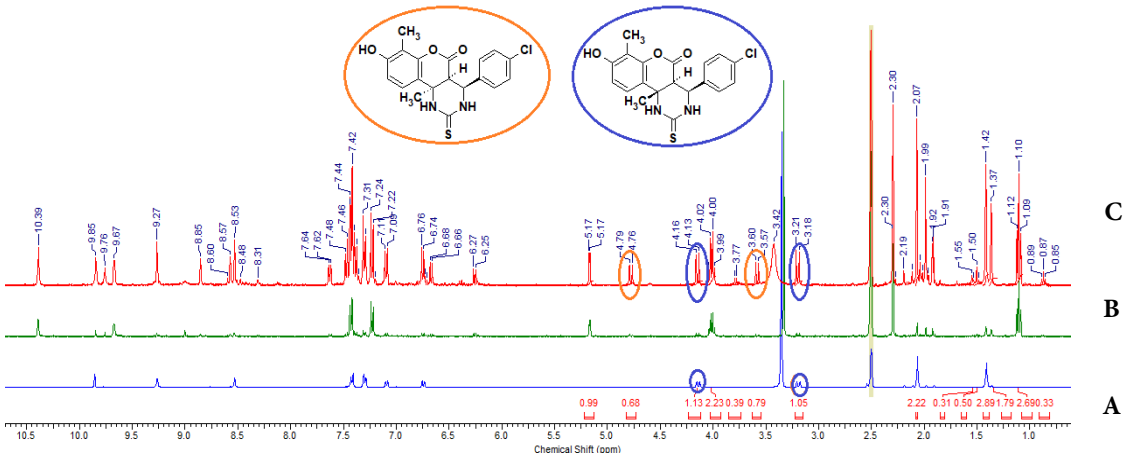


Fig. 4. Comparison of ^{1}H NMR spectra of 3,4b: **A** – pure (4*R**,4a*S**,10b*R**)-8-hydroxy-7, 10b-dimethyl-2-thio-4-(4-chlorophenyl)-1,2,3,4,4a,10b-hexahydro-5*H*-chromeno[4,3-*d*]pyrimidin-5-one **3b**; **B** - practically pure starting ethyl 4-(4-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-thiopyrimidine-5-carboxylate **1** (after 1 hour); **C** - reaction mixture after 8 hours

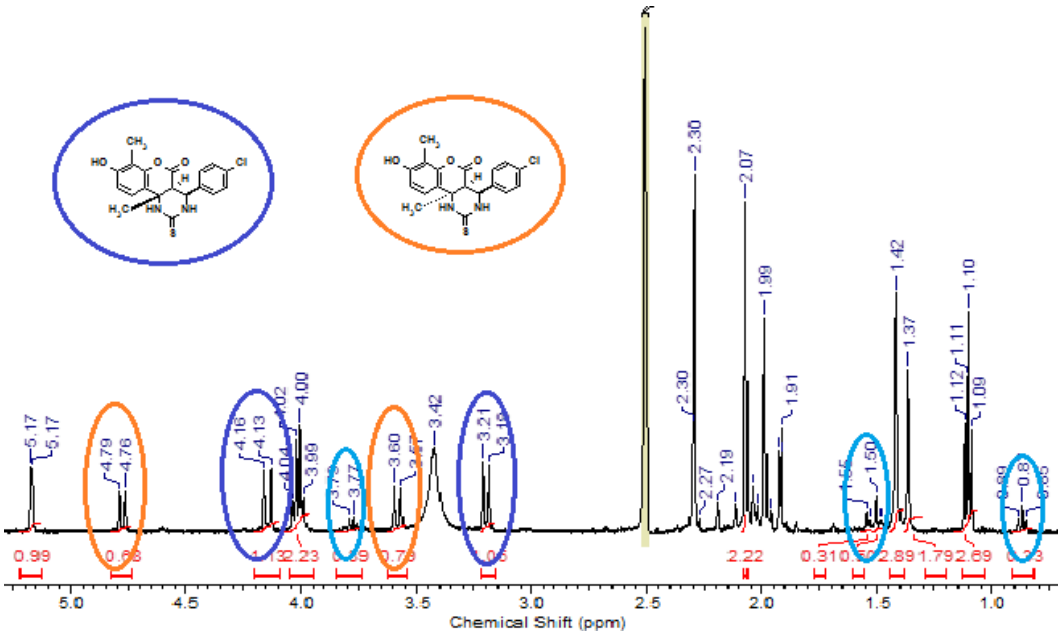


Fig. 5. Fragment of NMR spectra of the reaction mixture after 8 hours when 3,4b was obtained: **blue** colored signals (4*R**,4a*S**,10b*R**)-8-hydroxy-7,10b-dimethyl-2-thio-4-(4-chlorophenyl)-1,2,3,4,4a,10b-hexahydro-5*H*-chromeno[4,3-*d*]pyrimidin-5-one **3b** ; **orange** (4*R**,4a*S**,10b *SR**)-8-hydroxy-7,10b-dimethyl-2-thio-4-(4-chlorophenyl)-1,2,3,4,4a,10b-hexahydro-5*H*-chromeno[4,3-*d*]pyrimidin-5-one **4b**; **blue** - intermediate products

A similar dependence of product accumulation is observed in the case of 2-methylresorcinol. However, target products **3b** and **4b** are accumulated at a ratio of 2:1, while intermediates **B** are only recorded in trace amounts, and it is difficult to clearly determine their ratio (Fig. 4, 5).

To determine the graphical dependence of the diastereomer accumulation, the hydrogen atom signal (doublet at 5.17 ppm) at the aromatic substituent of the starting dihydropyrimidinedione **1** was chosen as a marker signal; its integral was equalled to 1 and the diastereomers **3** and **4** were determined by it. The ratio of diastereomers **3a**/**4a** was found as 3:1 and that of diastereomers **3b**/**4b** as 2:1. This relationship remained for a long time without significant changings (Table 1, Fig. 6).

Table 1. Values of product proton peaks integrals in ^{1}H NMR spectra

Time, hours	Signal intensity			
	3a	**4a**	**3b**	**4b**
0,00	0,00	0,00	0,00	0,00
1,00	0,02	0,00	0,01	0,00
2,00	0,05	0,01	0,03	0,01
3,00	0,12	0,04	0,06	0,03
3,50	0,18	0,06	0,08	0,05
4,50	0,35	0,14	0,14	0,07
5,00	0,41	0,15	0,17	0,08
5,50	0,45	0,18	0,18	0,10
6,00	0,69	0,25	0,28	0,14
6,50	0,87	0,31	0,30	0,17
7,00	1,62	0,58	0,51	0,27
7,50	2,41	0,91	0,68	0,40
8,00	7,00	2,30	1,13	0,65

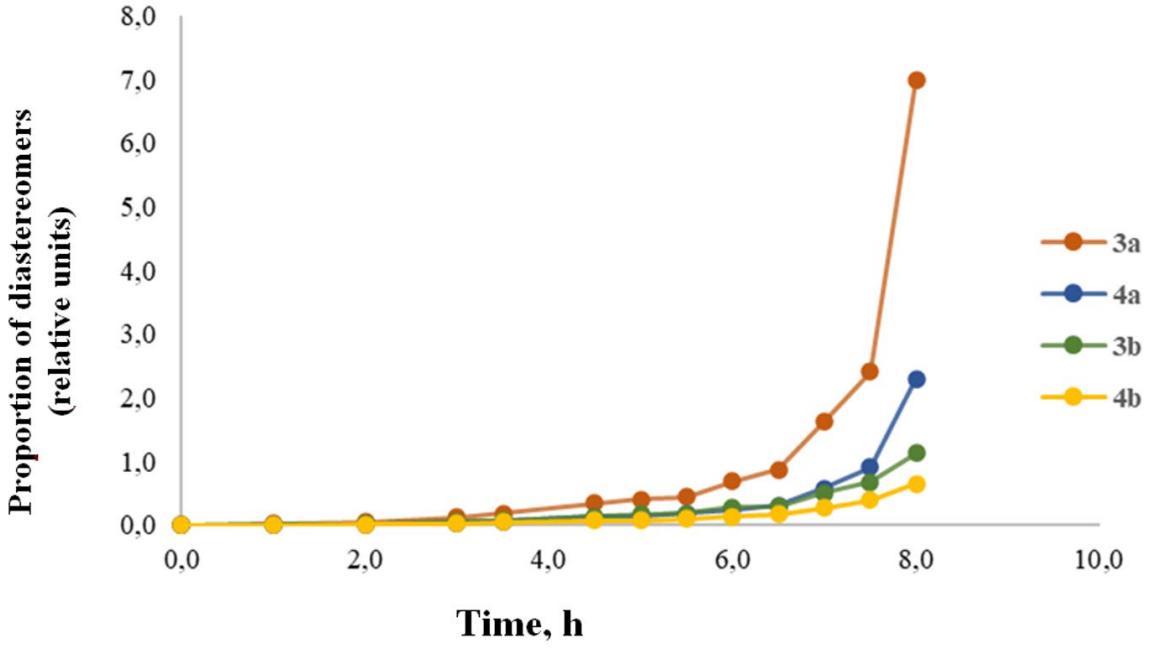


Fig. 6. Graph of the accumulation of diastereomers 3 and 4

Despite the different dynamics of the product accumulation, it was not possible to isolate pure diastereomer **4a** due to its good solubility in the most solvents. However, when the reaction was carried out with 2-methylresorcinol (a less soluble compound), with increasing of synthesis time it was possible to fix the second diastereomer **4b** as an impurity up to 20-40 %.

Experimental part

We recorded IR spectra in reflected light on a Fourier Transform Infrared Spectrum Two PerkinElmer spectrometer at 700-4000 cm^{-1}. NMR spectra were registered on the apparatus Bruker DRX-400 for solutions in DMSO-d_6 at 30 °C. Solvent residual proton signals in ^1H NMR (δ_H= 2.50 ppm) or in ^{13}C (δ_C 39.5 ppm) were the reference for the chemical shift readout, tetramethylsilane signal was used as the marker (N. D. Zelinsky Institute of Organic Chemistry Russian Academy of Sciences, Moscow). Mass spectra were recorded on a FINNIGAN MAT.INCOS 50 chromato-mass spectrometer at an ionisation voltage of 70 eV and an ionisation chamber temperature of 100-220 °C (N. D. Zelinsky Institute of Organic Chemistry Russian Academy of Sciences, Moscow). Elemental analysis was carried out in the analytical laboratory of INEOS RAS (A.N. Nesmeyanov Institute of Organoelement Compounds of Russian Academy of Sciences, Moscow) on a PerkinElmer 2400. The melting point was determined by Büchi M-560 melting point and boiling point apparatus.

A mixture of pyrimidintione **1** (1 mmol), 1,3-benzenediol **2a,b** (1.1 mmol), AcOH (2 ml) and $MeSO_3H$ 0.040 ml ($6.16\text{-}10^{-4}$ M) was stirred at 100 °C for 4-12 h. The precipitate was filtered from the hot solution and recrystallised from EtOH. A mixture of diastereomers **3a,b** and **4a,b** was obtained and air-dried.

To obtain pure compounds **3a,b** we added 0.020 mL $MeSO_3H$ ($3.08\text{-}10^{-4}$ M) to 1 mL AcOH (0.001 mol) of mixture of diastereomers **3a,b** and **4a,b** and stirred at 100 °C for 20-40 min. The resulting substance was filtered from the hot solution, washed with EtOH and air-dried.

(4*R,4a*S**,10b*R**)-8-hydroxy-7,10b-dimethyl-2-thio-4-(4-chlorophenyl)-1,2,3,4,4a,10b-hexahydro-5*H*-chromeno[4,3-d]pyrimidin-5-one (3a)** Yield 270 mg (72%), m.p. 292–294 °C. NMR ^1H (400 MHz, δ, ppm, *J*/Hz): 1.42 (s, 3H, Me), 3.18 (d, ^3J = 10.8, 1H, H-4a), 4.07 (d, ^3J = 10.8, 1H, H-4), 6.52 (d, ^4J = 2.5, 1H, H-7), 6.71 (dd, ^3J = 8.3, ^4J =2.5, 1H, H-9), 6.89 (d, ^3J = 8.8, 2H, H-3',5'), 7.17 (d, ^3J = 8.8, 2H, H-2',6'), 7.27 (d, *J* = 8.3, 1H, H-10), 8.37 (s, 1H, 3-NH), 9.21 (s, 1H, 1-NH), 9.94 (s, 1H, OH). NMR ^{13}C (100 MHz, δ, ppm): 27.50, 50.65, 53.44, 53.72, 103.56, 112.53, 119.22, 126.56, 128.32 (2 C), 129.51 (2 C), 132.96, 136.94, 148.16, 158.40, 165.22, 175.84. IR spectrum (ν/cm^{-1}, vaseline oil): 3367, 3192, 1773, 1620, 1216, 1146. Mass spectrum (EI, 70 eV), *m*/*z* (I_{ratio}, (%)): 376 (6), 374 (17), 237 (12), 177 (88), 148 (49), 139 (100), 102 (24), 77 (32).

(4*R,4a*S**,10b*S**)-8-hydroxy-7,10b-dimethyl-2-thio-4-(4-chlorophenyl)-1,2,3,4,4a,10b-hexahydro-5*H*-chromeno[4,3-d]pyrimidin-5-one (4a).** NMR ^1H (400 MHz, δ, ppm, *J*/Hz): 1.37 (s, 3H, Me), 3.67 (d, ^3J = 10.8, 1H, H-4a), 4.78 (d, ^3J = 10.8, 1H, H-4), 6.46 (d, ^4J = 2.5, 1H, H-7), 6.64 (dd, ^3J = 8.3, ^4J =2.5, 1H, H-9), 7.38 d, ^3J = 8.8, 2H, H-3',5'), 7.48 (d, ^3J = 8.8, 2H, H-2',6'), 7.82 (d, *J* = 8.3, 1H, H-10), 8.92 (s, 1H, 3-NH), 9.73 (s, 1H, 1-NH), 9.87 (s, 1H, OH). Found (%): C, 57.46; H, 4.01; N, 7.45. $C_{18}H_{15}ClN_2O_3S$. Calculated (%): C, 57.68; H, 4.03; N, 7.47.

(4*R,4a*S**,10b*R**)-8-hydroxy-7,10b-dimethyl-2-thio-4-(4-chlorophenyl)-1,2,3,4,4a,10b-hexahydro-5*H*-chromeno[4,3-*d*]pyrimidin-5-one (3b)** Yield 245 mg (62 %), m.p. 320–322 °C, NMR ^1H (400 MHz, δ, ppm, *J*/Hz): 1.41 (s, 3H, 10b-Me), 2.06 (s, 3H, 7-Me), 3.19 (d, *J* = 10.8, 1H, H-4a), 4.14 (d, *J* = 10.8, 1H, H-4), 6.74 (d, *J* = 8.5, 1H, H-9), 7.09 (d, *J* = 8.5,

1H, H-10), 7.30 (d, *J* = 8.1, 2H, H-3',5'), 7.42 (d, *J* = 8.1, 2H, H-2',6'), 8.53 (s, 1H, 3-NH), 9.26 (s, 1H, 1-NH), 9.85 (s, 1H, OH). NMR ^{13}C (100 MHz, δ, ppm): 8.47, 27.41, 50.57, 53.63, 53.67, 111.33, 112.26, 119.29, 122.74, 128.35 (2 C), 129.47 (2 C), 132.93, 137.13, 146.38. 156.17, 165.28, 175.85. IR spectrum (ν/cm^{-1}, vaseline oil): 3366, 3184, 1773, 1615, 1601, 1216, 1075. Mass spectrum (EI, 70 eV), *m*/*z* (I_{ratio}, (%)):390 (8), 388 (25), 237 (19), 199 (17), 191 (67), 165 (25), 162 (49), 140 (96), 138 (100), 11 (20), 102 (39), 77 (70). Found (%): C, 58.73; H, 4.39; N, 7.17. $C_{19}H_{17}ClN_2O_3S$. Calculated (%): C, 58.68; H, 4.41; N, 7.20.

(4*R,4a*S**,10b*S**)-8-hydroxy-7,10b-dimethyl-2-thio-4-(4-chlorophenyl)-1,2,3,4,4a,10b-hexahydro-5*H*-chromeno[4,3-*d*]pyrimidin-5-one (4b)** NMR ^{1}H (400 MHz, δ, ppm, *J*/Hz): 1.36 (s, 3H, 10b-Me), 1.98 (s, 3H, 7-Me), 3.57 (d, *J* = 11.0, 1H, H-4a), 4.77 (d, *J* = 11.0, 1H, H-4), 6.66 (d, *J* = 8.5, 1H, H-9), 7.38 (d, *J* = 8.1, 2H, H-3',5'), 7.47 (d, *J* = 8.1, 2H, H-2',6'), 7.62 (d, *J* = 8.5, 1H, H-10), 8.57 (s, 1H, 3-NH), 8.85 (s, 1H, 1-NH), 9.78 (s, 1H, OH). NMR spectrum ^{13}C (100 MHz, δ, ppm): 8.49, 25.17, 47.05, 52.44, 53.22, 110.38, 112.01, 119.46, 121.11, 127.86 (2 C), 130.67 (2 C), 132.39, 138.63, 147.24, 155.88, 165.80, 176.05.

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