Scientific article
UDC 547-314
DOI: 10.52957/2782-1900-2024-5-4-134-141

SELECTIVE MODIFICATION OF TETRAHYDROCHROMENO[2,3-D]PYRIMIDIN-2-ONES

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Keywords:
tetrahydrochromeno[2,3-d]pyrimidin-2-ones, methyl iodide, acetic anhydride, alkylation, acylation

Abstract. *The paper presents the results of the synthesis and characterisation of seven new tetrahydrochromeno[2,3-d]pyrimidin-2-ones derivatives obtained by selective modification of the hydroxyl group at the C-8 position. The authors successfully used alkylation and acetylation reactions to introduce substituents into the molecule. This resulted in a series of new heterocyclic compounds with yields up to 94 %. The authors characterised the obtained compounds by NMR spectroscopy (^{1}H and ^{13}C) and mass spectrometry.*

For citation:
Makarova E.S., Chirkova Zh.V., Uryadova A.M., Karandeeva A.S., Bogdanova N.A. Selective modification of tetrahydrochromeno[2,3-d]pyrimidin-2-ones // *From Chemistry Towards Technology Step-by-Step*. 2024. Vol. 5, Issue 4. P. 134-141. URL: https://chemintech.ru/en/nauka/issue/5563/view

Introduction

Chromeno[2,3-d]pyrimidin-2-ones are heterocyclic compounds containing condensed pyrimidine and dihydropyran rings. Chromeno[2,3-d]pyrimidine derivatives have attracted considerable attention due to their diverse spectrum of biological activities [1-3]. These compounds demonstrate a wide range of pharmacological properties, including antitumour [4, 5], antimicrobial [6], anti-inflammatory [7, 8], antibacterial [9], and antioxidant activities [10]. These activities make them promising substances for the development of new drugs. Therefore, the constant search for new, more effective and selective derivatives of chromeno[2,3-d]pyrimidine remains an urgent task of modern medicinal chemistry.

One of the most effective approaches to modify the structure and, consequently, the properties of chromeno[2,3-d]pyrimidines is the introduction of various substituents into their nucleus [11, 12]. The presence of various functional groups in the molecule of tetrahydrochromeno[2,3-d]pyrimidin-2-one makes it possible to perform targeted

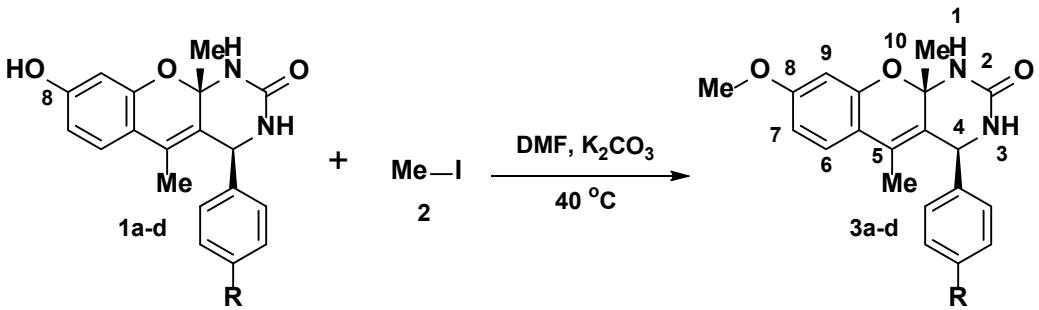
modification of the structure in order to optimise pharmacological properties and reduce toxicity [13]. Particularly, modification of the hydroxyl group [14] often presented in this class of compounds is an effective strategic approach to achieve such purposes. Indeed, changes in the electronic and steric properties of the substituent at the hydroxyl group can significantly affect the interaction of the molecule with biological targets [15].

Alkylation and acylation are fundamental methods for functionalisation of organic molecules. They are determined by their high selectivity, ease of implementation, and also enable targeted modification of physicochemical characteristics and biological activity of compounds. The application of these reactions to chromeno[2,3-d]pyrimidines provides a wide range of possibilities to form libraries of derivatives with diverse structures and potentially improved pharmacological profiles [16].

Main body

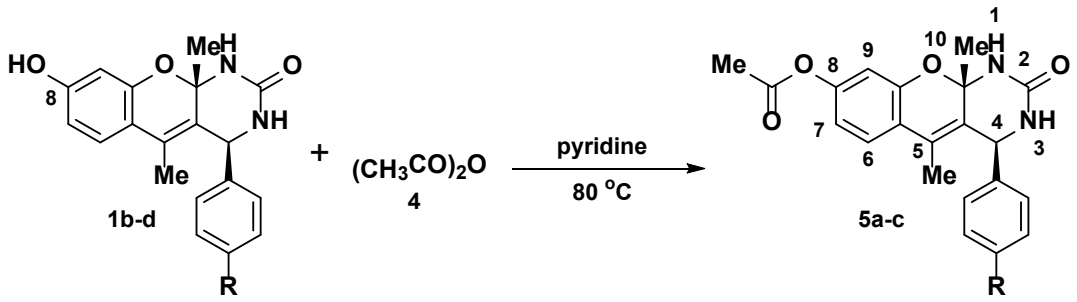
We have used tetrahydrochromeno[2,3-d]pyrimidin-2-ones **1a-d** as starting compounds. The authors synthesised them from the products of the Biginelli reaction and resorcinol according to the procedure [17]. The presence of a hydroxyl group at the C-8 position and two amide groups provides them with convenient substrates for studying modification selectivity. Based on literature data [18], hexahydrochromeno[4,3-d]pyrimidin-2-ones initiate the alkylation reaction selectively on the hydroxyl group. However, acetylation can lead to a diacetylated derivative involving one of the amide groups.

We have chosen methyliodide **2** as the alkyl halide for the alkylation reaction of structures **1a-d**. We performed the reactions in the presence of potassium carbonate in dimethylformamide at 40 °C for 9-12 hours. Subsequently, we obtained new alkylated derivatives of tetrahydrochromeno[2,3-d]pyrimidin-2-ones **3a-d** in up to 84% yield.



1, 3: R = H (**a**), R = Cl (**b**), R = Me (**c**), R = OMe (**d**)

Selective acetylation of the hydroxyl group was achieved using acetic anhydride **4** in the presence of a catalytic amount of pyridine under solvent-free conditions at 80 °C and a reaction time of 1.5-3 hours. This causes the formation of derivatives **5a-c**.



1: R = Cl (**b**), R = Me (**c**), R = OMe (**d**); **5**: R = Cl (**a**), R = Me (**b**), R = OMe (**c**)

The reactions proceeded with good yields from 57 % to 94 %.

Indeed, the alkylation and acylation reactions of tetrahydrochromeno[2,3-d]pyrimidin-2-ones **3a-d** under selected conditions proceed selectively on the hydroxyl group unlike similar reactions of chromeno[4,3-d]pyrimidin-2-ones [18].

Table 1 summarises the reaction conditions and yields for compounds **3a-d** and **5a-c**.

Table 1. Reaction times and yields for products 3 and 5

№	R	Coupling **3**			Coupling **5**		
			Reaction time, h	Yield, %		Reaction time, h	Yield, %
1	H	**a**	9	83			
2	4-Cl	**b**	10	84	**a**	1.7	89
3	4-Me	**c**	12	82	**b**	2	94
4	4-MeO	**d**	11	70	**c**	2.8	57

We purified the obtained compounds **3** and **5** by recrystallisation of isopropyl alcohol and characterised them using modern spectroscopic techniques. We observed the disappearance of the 3330-3300 cm^{-1} signals of the hydroxyl group in the IR spectra of the obtained structures. In the case of acetylated derivatives **5**, the signals of the ester carboxylic group also appeared in the range 1761-1759 cm^{-1}.

^{1}H and ^{13}C NMR spectroscopy demonstrated characteristic signals confirming the successful introduction of the corresponding substituents. Moreover, the appearance of a singlet in the region of 2.27 – 2.29 ppm in the ^{1}H NMR spectrum indicated the presence of an acetyl group in compounds **5**,; a singlet in the region of 3.72 – 3.75 ppm shows the successful introduction of an alkyl fragment in structures **3**.

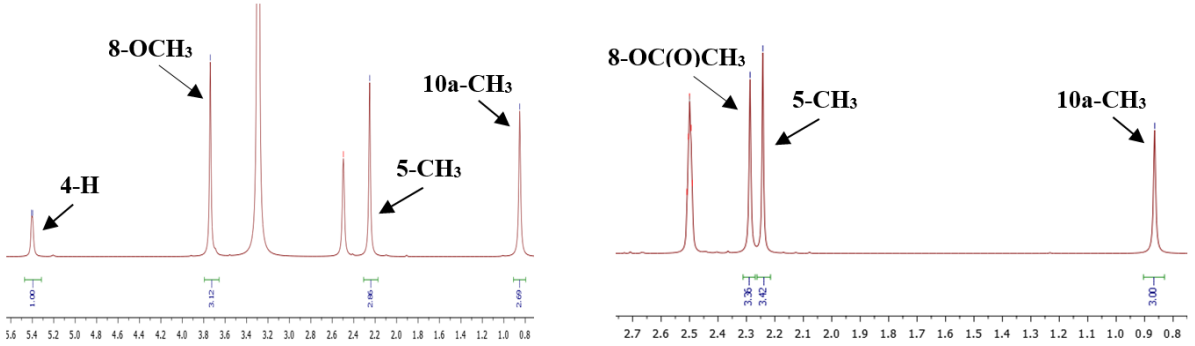


Fig. 1. Fragments of ^{1}H NMR spectra of compounds **3a** (left) and **5a** (right)

Mass spectrometric analysis recorded the molecular masses of the obtained compounds. This further confirmed their structure.

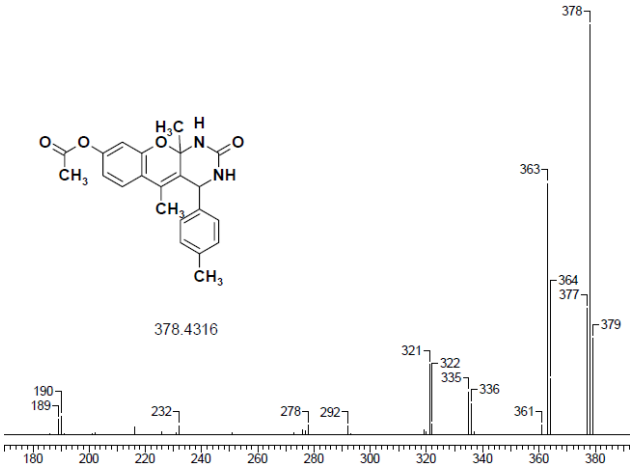


Fig. 2. Mass spectrum fragment of compound **5b**

Conclusions

We have investigated the alkylation and acetylation processes of tetrahydrochromeno[2,3-*d*]pyrimidin-2-ones. Hence, the alkylation reaction in the presence of methyl iodide and potassium carbonate proceeds selectively on the hydroxyl group. We also observed the formation of a monoacylated product at the C-8 position in the case of acetic anhydride acetylation.

Experimental part

We recorded IR spectra in reflected light on a Spectrum Two PerkinElmer spectrometer at 700-4000 cm^{-1}; NMR spectra was recorded 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 ^1H NMR (δ_H = 2.50 ppm) and ^{13}C NMR (δ_C = 39.5 ppm). We used tetramethylsilane signal (IOC RAS, Moscow, Russia) as a marker. We recorded mass spectra on a FINNIGAN MAT.INCOS 50 mass spectrometer at an ionisation voltage of 70 eV and an ionisation chamber temperature of 100-220 °C (IOH RAS, Moscow, Russia). We conducted elemental analysis in the analytical laboratory of INEOS RAS, Moscow, Russia, on a PerkinElmer 2400 unit. We determined the melting temperature using a Büchi M-560 melting point and boiling point apparatus. We monitored the progress of the reaction by thin layer chromatography on Silufol 254 UV plates using hexane-ethyl acetate eluent.

The synthesis methods and physicochemical characterisation of compounds **1a-d** are described in [17].

Methodology for preparation of 3a-d

We heated the reaction mixture containing 1 mmol of tetrahydrochromeno[2,3-*d*]pyrimidin-2-ones **1a-d**, 2 mmol of methyl iodide **2**, 1.3 mmol of anhydrous K_2CO_3 in 2 ml of DMF to 40 °C and stirred for 9-12 h to synthesise compounds **3a-d**. Then we cooled it and poured it into the water; filtered off the residue; then washed it several times with water, and dried it. It was recrystallized in isopropanol.

(4*R,10a*R**)-5,10a-Dimethyl-8-methoxy-4-phenyl-1,3,4,10a-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-2-one (3a).** Yield is 280 mg (83%), T.melt. is 281-283°C. IR-spectrum, ν/cm^{-1}: 3254 (N-H), 1687 (C=O), 1658, 1620, 1492 (C=C), 1378, 1366 (CH_3), 1164 (C-O-C). NMR spectrum ^{1}H (400 MHz, δ, ppm, *J*/Hz): 0.85 (s, 3 H, C(10a)CH_3), 2.25 (s, 3 H, C(5)CH_3), 3.74 (s, 3 H, C(8)OCH_3), 5.40 (d, 1 H, *J* = 4.6, C(4)H), 6.38 (d, 1 H, *J* = 1.8, C(9)H), 6.58 (dd, 1 H, *J* = 8.7, 1.8, C(7)H), 7.22 - 7.36 (m, 6 H, Ph, C(6)H), 7.38 (s, 1 H, N(3)H), 7.41 (s, 1 H, N(1)H). NMR spectrum ^{13}C (100 MHz, δ, ppm): 14.67, 25.96, 52.08, 55.90, 87.00, 102.17, 107.83, 117.50, 124.48, 125.38, 126.12 (2 C), 126.61, 127.64, 129.04 (2 C), 142.55, 153.62, 155.80, 161.03. Mass-spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 336 [M] (100), 335 [M-H]$^-$ (52), 321 [M-15]$^+$ (69), 278 (7), 230 (5), 212 (5), 204 (4), 106 (13), 77 (15), 42 (64). Found (%): C, 71.27; H, 5.97; N, 8.30. $C_{20}H_{20}N_2O_3$. Calculated (%): C, 71.41; H, 5.99; N, 8.33.

(4*R,10a*R**)-5,10a-Dimethyl-8-methoxy-4-chlorophenyl-1,3,4,10a-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-2-one (3b).** Yield is 312 mg (84%), T.melt. is 274-276°C. IR-spectrum, ν/cm^{-1}: 3235 (N-H), 1690 (C=O), 1656, 1620, 1489 (C=C), 1377, 1366 (-CH_3), 1166 (C-O-C), 1097 (C-Cl). NMR spectrum ^{1}H (400 MHz, δ, ppm, *J*/Hz): 0.86 (s, 3 H, C(10a)CH_3), 2.24 (s, 3 H, C(5)CH_3), 3.74 (s, 3 H, C(8)OCH_3), 5.38 (d, 1 H, *J* = 4.2, C(4)H), 6.37 (d, 1 H, *J* = 2.4, C(9)H), 6.58 (dd, 1 H, *J* = 8.8, 2.4, C(7)H), 7.28 (d, 2 H, *J* = 8.2, C(2',6')H), 7.34 (d, 1 H, *J* = 8.6, C(6)H), 7.40 - 7.44 (m, 3 H, C(3',5')H, N(3)H), 7.51 (s, 1 H, N(1)H). NMR spectrum ^{13}C (100 MHz, δ, ppm): 14.69, 26.04, 51.63, 55.89, 86.88, 102.14, 107.86, 117.36, 123.96, 125.80, 126.68, 128.09 (2 C), 129.03 (2 C), 132.26, 141.64, 153.62, 155.64, 161.08. Mass-spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 370 [M] (46), 369 [M-H]$^-$ (15), 355 [M-15]$^+$ (44), 312 (13), 246 (28), 230 (58), 216 (16), 203 (79), 188 (33), 140 (100), 77 (24), 42 (42). Found (%): C, 64.67; H, 5.14; N, 7.52. $C_{20}H_{19}ClN_2O_3$. Calculated (%): C, 64.78; H, 5.16; N, 7.55.

(4*R,10a*R**)-5,10a-Dimethyl-8-methoxy-4-methylphenyl-1,3,4,10a-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-2-one (3c).** Yield is 287 mg (82%), T.melt. is 275-277°C. IR-spectrum, ν/cm^{-1}: 3239 (N-H), 1691 (C=O), 1659, 1620, 1498 (C=C), 1378, 1366 (-CH_3), 1165 (C-O-C). NMR-spectrum ^{1}H (400 MHz, δ, ppm, *J*/Hz): 0.84 (s, 3 H, C(10a)CH_3), 2.23 (s, 3 H, C(5)CH_3), 2.27 (s, 3 H, C(4')CH_3), 3.73 (s, 3 H, C(8)OCH_3), 5.34 (d, 1 H, *J* = 4.1, C(4)H), 6.36 (d, 1 H, *J* = 2.5, C(9)H), 6.57 (dd, 1 H, *J* = 8.6, 2.5, C(7)H), 7.16 (s, 4 H, C(2',3',5',6')H), 7.33 (d, *J* = 8.6, 1 H, C(6)H), 7.40 (s, 1 H, N(3)H), 7.46 (s, 1 H, N(1)H). NMR-spectrum ^{13}C (100 MHz, δ, ppm.): 14.65, 21.26, 26.02, 51.85, 55.87, 86.98, 102.13, 107.76, 117.50, 124.56, 125.12, 126.04 (2 C), 126.56, 129.58 (2 C), 136.68, 139.53, 153.62, 155.77, 160.96. Mass-spectrum (EIY, 70 eV), *m*/*z* (I_{rel}, %): 350 [M] (60), 335 [M-15]$^+$ (51), 292 (4), 226 (14), 203 (24), 188 (13), 146 (7), 120 (100), 77 (13), 42 (36). Found (%): C, 71.84; H, 6.30; N, 7.95. $C_{21}H_{22}N_2O_3$. Calculated (%): C, 71.98; H, 6.33; N, 7.99.

(4*R,10a*R**)-5,10a-Dimethyl-8-methoxy-4-methoxyphenyl-1,3,4,10a-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-2-one (3d).** Yield is 258 mg (70%), T.melt. is 258-260 °C. IR-spectrum, ν/cm^{-1}: 3243 (N-H), 1690 (C=O), 1660, 1617, 1510 (C=C), 1378, 1366 (-CH_3), 1166 (C-O-C). NMR-spectrum ^{1}H (400 MHz, δ, ppm, *J*/Hz): 0.87 (s, 3 H, C(10a)CH_3), 2.23 (s, 3 H, C(5)CH_3), 3.72 (s, 3 H, C(8)OCH_3), 3.73 (s, 3 H, C(4')OCH_3), 5.33 (d, 1 H, *J* = 4.6, C(4)H), 6.37 (d, 1 H, *J* = 2.5, C(9)H), 6.58 (dd, 1 H, *J* = 8.6, 2.5, C(7)H), 6.92 (d, 2 H, *J* = 8.3, C(3',5')H), 7.18 (d, 2 H, *J* = 8.3, C(2',6')H), 7.33 (d, 1 H, *J* = 8.7, C(6)H), 7.35 (s, 1 H, N(3)H),

7.42 (s, 1 H, N(1)H). NMR-spectrum ^{13}C (100 MHz, δ, ppm): 14.57, 26.05, 51.59, 55.74, 55.89, 86.99, 102.16, 107.80, 114.43 (2 C), 117.55, 124.61, 125.00, 126.56, 127.26 (2 C), 134.30, 153.63, 155.75, 158.90, 160.98. Mass-spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 336 [M] (100), 335 [M-H]$^-$ (40), 351 (44), 335 (3), 308 (2,5), 204 (5), 136 (11), 42 (9). Found (%): C, 68.85; H, 6.03; N, 7.61. $C_{21}H_{22}N_2O_4$. Calculated (%): C, 68.84; H, 6.05; N, 7.65.

Methodology for preparation of 5a-c

We added 2 ml of acetic anhydride **4** and 50 μL of pyridine to 1 mmol of tetrahydrochromeno[2,3-*d*]pyrimidin-2-ones **1b-d**, heated to 80 °C, and stirred for 1.5-3 h to synthesise compounds **5a-c**. Then we cooled and poured it into water, filtered off the residue, then washed it several times with water, and dried it. It was recrystallized in isopropanol.

(4*R,10a*R**)-5,10a-Dimethyl-2-oxo-4-(4-chlorophenyl)-1,3,4,10a-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-8-yl acetate (5a).** Yield is 356 mg (89%), T.melt. is 222-224 °C. IR-spectrum, ν/cm^{-1}: 3214 (N-H), 1759 (O-C(=O)CH$_3$), 1678 (C=O), 1658, 1610, 1489 (C=C), 1377, 1367 (-CH$_3$), 1194 (C-O-C), 1091 (C-Cl). NMR-spectrum ^{1}H (400 MHz, δ, ppm, *J*/Hz): 0.86 (s, 3 H, C(10a)CH$_3$), 2.24 (s, 3 H, C(5)CH$_3$), 2.29 (s, 3 H, C(8)COCH$_3$), 5.43 (d, 1 H, *J* = 4.7, C(4)H), 6.64 (d, 1 H, *J* = 2.3, C(9)H), 6.78 (dd, 1 H, *J* = 8.4, 2.3, C(7)H), 7.29 (d, 2 H, *J* = 8.3, C(3',5')H), 7.45 (d, 2 H, *J* = 8.3, C(2',6')H), 7.47 (d, 1 H, *J* = 8.4, C(6)H), 7.54 (s, 1 H, N(1)H), 7.60 (d, 1 H, *J* = 4.6, N(3)H). NMR-spectrum ^{13}C (100 MHz, δ, ppm): 14.69, 21.56, 26.08, 51.89, 87.17, 110.29, 115.35, 122.17, 125.01, 126.06 (2 C), 126.38, 126.89, 129.66 (2 C), 136.82, 139.23, 151.68, 152.97, 155.68, 169.60. Mass-spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 398 [M] (93), 397 [M-H]$^-$ (45), 383 [M-15]$^+$ (79), 356 (71), 341 (100), 298 (24), 232 (16), 216 (43), 189 (40), 140 (31), 43 (57). Found (%): C, 63.14; H, 4.79; N, 6.98. $C_{21}H_{19}ClN_2O_4$. Calculated (%): C, 63.24; H, 4.80; N, 7.02.

(4*R,10a*R**)-5,10a-Dimethyl-2-oxo-4-(4-methylphenyl)-1,3,4,10a-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-8-yl acetate (5b).** Yield is 358 mg (94%), T.melt. is 218-220 °C. IR-spectrum, ν/cm^{-1}: 3222 (N-H), 1761 (O-C(=O)CH$_3$), 1678 (C=O), 1655, 1611, 1495 (C=C), 1372, 1366 (-CH$_3$), 1199 (C-O-C). NMR-spectrum ^{1}H (400 MHz, δ, ppm, *J*/Hz): 0.85 (s, 3 H, C(10a)CH$_3$), 2.24 (s, 3 H, C(5)CH$_3$), 2.28 (s, 6 H, C(4')CH$_3$, C(8)COCH$_3$), 5.38 (d, 1 H, *J* = 4.5, C(4)H), 6.63 (d, 1 H, *J* = 2.3, C(9)H), 6.77 (dd, 1 H, *J* = 8.4, 2.3, C(7)H), 7.29 (d, 2 H, *J* = 8.1, C(3',5')H), 7.45 (d, 2 H, *J* = 8.1, C(2',6')H), 7.46 (d, 1 H, *J* = 8.4, C(6)H), 7.49 (s, 1 H, N(1)H), 7.52 (d, 1 H, *J* = 4.6, N(3)H). NMR-spectrum ^{13}C (100 MHz, δ, ppm): 14.73, 21.56, 21.72, 26.09, 51.67, 87.07, 110.34, 115.43, 122.03, 125.69, 126.29, 126.49, 128.11 (2 C), 129.11 (2 C), 132.35, 141.34, 151.79, 152.94, 155.55, 169.58. Mass-spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 378 [M] (100), 377 [M-H]$^-$ (31), 363 [M-15]$^+$ (61), 335 (10), 321 (17), 292 (2), 232 (2), 190 (5), 120 (12), 43 (33). Found (%): C, 69.71; H, 5.83; N, 7.36. $C_{22}H_{22}N_2O_4$. Calculated (%): C, 69.83; H, 5.86; N, 7.40.

(4*R,10a*R**)-5,10a-Dimethyl-2-oxo-4-(4-methoxyphenyl)-1,3,4,10a-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-8-yl acetate (5c).** Yield is 226 mg (57%), T.melt. is 212-214 °C. IR-spectrum, ν/cm^{-1}: 3220 (N-H), 1759 (O-C(=O)CH$_3$), 1677 (C=O), 1652, 1610, 1507 (C=C), 1378, 1366 (-CH$_3$), 1196 (C-O-C). NMR-spectrum ^{1}H (400 MHz, δ, ppm, *J*/Hz): 0.87 (s, 3 H, C(10a)CH$_3$), 2.24 (s, 3 H, C(5)CH$_3$), 2.27 (s, 3 H, C(8)COCH$_3$), 3.73 (s, 3 H, C(4')OCH$_3$), 5.37 (d, 1 H, *J* = 4.5, C(4)H), 6.63 (d, 1 H, *J* = 2.3, C(9)H), 6.77 (dd, 1 H, *J* = 8.4, 2.3, C(7)H), 6.93 (d, 2 H, *J* = 8.5, C(3',5')H), 7.19 (d, 2 H, *J* = 8.5, C(2',6')H), 7.45 (d, 1 H, *J* = 8.4, C(6)H),

7.47 (s, 1 H, N(1)H), 7.50 (d, 1 H, J = 4.6, N(3)H). NMR spectrum ^{13}C (100 MHz, δ, mmd): 14.64, 21.56, 26.10, 51.61, 55.74, 87.16, 110.29, 114.48 (2 S), 115.34, 122.18, 124.87, 126.36, 126.92, 127.26 (2 S), 133.97, 151.67, 152.96, 155.64, 158.96, 169.60. Mass-spectrum (EI, 70 *eV*), m/*z* (I_{rel}, %): 394 [M] (53), 393 $[M-H]^-$ (6), 351 (5), 337 (5), 232 (3), 190 (10), 136 (91), 60 (11), 43 (100). Found (%): C, 66.87; H, 5.59; N, 7.06. $C_{22}H_{22}N_2O_5$. Calculated (%): C, 66.99; H, 5.62; N, 7.10.

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Received 06.11.2024
Approved 19.11.2024
Accepted 19.11.2024