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SYNTHESIS OF AMINO ACID DERIVATIVES OF HYDRAZONES AND OXIMES OF SPIRODIHYDRO-PYRANOCHROMEN-2-ONES

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Sulfur- and nitrogen-containing derivatives of spirodihydropyranochromen-2-ones at the exocyclic oxygen atom have been synthesized. Modification of the oximes and hydrazones of the spiro-substituted pyranocoumarins with N-substituted amino acids were carried out using activated ester and symmetrical anhydride methods.

Keywords: amino acid derivatives, benzopyran-2-thiones, hydrazones, coumarins, oximes, spirodihydropyranochromen-2-ones.

It is well known that coumarins are an important class of heterocyclic compounds in practice, and possess a broad spectrum of physiological activity. Many of them are promising pharmaceutical substances and have been introduced into medical practice. Derivatives of spirodihydropyranochromen-2-ones, which are practically unstudied to this day [1, 2], are of particular interest in the search for new biologically active substances. The important role of amino acids in vital processes has for a long time stimulated investigations on the search for new biologically active compounds among the natural amino acids, their synthetic analogs, and various compounds containing amino acid residues. It is evident that the introduction into the coumarin system of a fragment with an amino acid structure as a substituent is of interest both for the chemistry of amino acids and of coumarins, and also for the expedient synthesis of new biologically active compounds.

In a continuation of our investigations on the study of the synthesis and properties of spirodihydropyranochromen-2-ones [3], the functionalization of benzopyran bioregulators by introducing pharmacophoric groupings of an amino acid nature into their molecules has been effected in the present work.

The spiro[(7-hydroxychromane)-2,1'-cyclohexane] (**1**) necessary for further conversions was obtained by Kabbe condensation [4, 5] of 2,4-dihydroxyacetophenone with cyclohexanone in the presence of pyrrolidine with subsequent reduction of the resulting spirochroman-4-one under conditions of the Clemmensen reaction [3].

The Pechman condensation of spirochromanol **1** with β-ketoacid esters in the presence of concentrated sulfuric acid led to annelation of the pyran-2-one ring to a spirochromanone with the formation of spirodihydropyranocoumarins **2-7** [3]. To obtain compounds **2-7** ethyl acetoacetate, methyl propionylacetate, methyl 3-oxoheptanoate, ethyl 2-benzylacetoacetate, ethyl cyclopentanone-2-carboxylate, and ethyl cyclohexanone-2-carboxylate respectively were used in the indicated reaction (Scheme 1).

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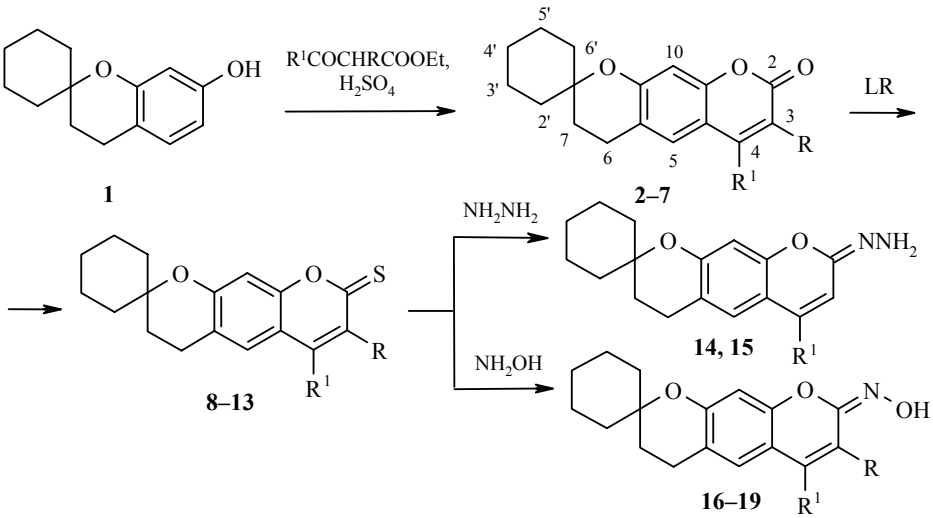
Scheme 1



2, 8, 14 R = H, R^1 = Me; **3, 9, 15** R = H, R^1 = Et; **4, 10, 16** R = H, R^1 = Bu; **5, 11, 17** R = CH_2Ph, R^1 = Me; **6, 12, 18** $RR^1 = (CH_2)_3$; **7, 13, 19** $RR^1 = (CH_2)_4$; LR, Lawesson reagent

The Lawesson reagent was used by us for the thionation of the exocyclic oxygen atom of the benzopyran-2-one system [3, 6, 7]. On heating spirodihydropyranocoumarins **2-7** with a 10% excess of Lawesson reagent in toluene, benzopyran-2-thiones **8-13** were synthesized smoothly and in high yield (Scheme 1). Unlike the colorless initial coumarins **2-7**, compounds **8-13** were bright-yellow substances, the color of which is caused by the presence in their molecules of a C=S grouping.

The hydrazones of spirodihydropyranochromenes **14** and **15** were synthesized by treating alcohol solutions of the appropriate thiones **8** and **9** with hydrazine hydrate [3, 7] (Scheme 1). The oximes of spirodihydropyranochromen-2-ones **16-19** were obtained by the interaction of benzopyran-2-thiones **10-13** with hydroxylamine hydrochloride in pyridine [3, 7] (Scheme 1). The structures of the obtained compounds **14-19** were confirmed by data of elemental analysis and NMR spectroscopy. Signals were present in the ^{1}H NMR spectra of these compounds characteristic of a spirodihydropyranochromene residue. In addition, in the spectra of hydrazones **14** and **15** a two-proton broadened singlet of the amino group was present at 5.60-5.70 ppm, but the spectra of oximes **16-19** were characterized by the presence of a one-proton singlet for the hydroxyl group at 10.00-10.20 ppm.

The active ester method [8], widely used in peptide synthesis, proved to be the most effective for the directed synthesis of amino acid derivatives of the spirodihydro-pyranochromene hydrazones. The N-hydroxysuccinimide esters of N-substituted amino acids [9] were obtained by the interaction of the appropriate N-protected amino acid with N-hydroxysuccinimide (N-HOSu) in the presence of diisopropyl-carbodiimide (DIC) as condensing agent. The activated esters obtained reacted smoothly and in high yield with hydrazones **14** and **15**, forming the corresponding N-acylhydrazones of spirodihydropyranochromen-2-ones **20-27** (Scheme 2), containing residues of DL-2-aminobutyric (**20**, **25**), *trans*-4-(aminomethyl)cyclo-hexanecarboxylic (**22**) and 6-aminohexanoic (**23**) acids, L-2-phenylglycine (**21**, **26**, **27**), and β-alanine (**24**).

The structures of the obtained amino acid derivatives **20-27** were confirmed by data of elemental analysis and NMR spectroscopy. Doubled signals were observed in the ^{1}H NMR spectra of these compounds both for the spirodihydropyranochromene system and for the amino acid fragment as a result of the existence of compounds **20-27** as a mixture of *Z*- and *E*- isomers in almost equal amounts. Signal was also present in the ^{1}H NMR spectra for the hydrazide proton at 8.50-10.40 ppm.

TABLE 1. ^{1}H NMR Spectra of Spirodihydropyranochromen-2-ones **2-7**

Compound	Chemical shifts (400 MHz) in DMSO, δ, ppm (*J*,Hz)						
	R-3	R^{1}-4	H-5 (1H, s)	H-7 (2H, t, *J* = 7.2)	H-6 (2H, t, *J* = 7.2)	H-10 (1H, s)	H-2',3',4',5',6' (10H, m)
2	6.14 (1H, s, H)	2.36 (3H, s, CH_3)	7.48	1.81	2.80	6.70	1.30-1.70
3	6.09 (1H, s, H)	1.22 (3H, t, *J* = 7.2); 2.77 (2H, q, *J* = 7.2) (CH_2CH_3)	7.53	1.81	2.79	6.72	1.30-1.70
4	6.09 (1H, s, H)	0.93 (3H, t, *J* = 7.2); 1.35 (2H, m); 1.62 (2H, m); 2.73 (2H, q, *J* = 7.2) ($CH_2CH_2CH_2CH_3$)	7.53	1.81	2.80	6.72	1.30-1.70
5	3.92 (2H, s); 7.15-7.35 (5H, m) (CH_2Ph)	2.39 (3H, s, CH_3)	7.53	1.80	2.79	6.71	1.30-1.70
6	2.09 (2H, m); 2.73 (2H, t, *J* = 7.2); 3.01 (2H, t, *J* = 7.2) ($CH_2CH_2CH_2$)		7.31	1.81	2.79	6.75	1.30-1.70
7	1.75-1.80 (4H, m); 2.37 (2H, m); 2.76 (2H, m) ($CH_2CH_2CH_2CH_2$)		7.40	1.80	2.80	6.68	1.30-1.70

TABLE 2. ^{1}H NMR Spectra of Spirodihydropyranochromen-2-ones **8-13**

Compound	Chemical shifts (400 MHz) in DMSO, δ, ppm (*J*,Hz)						
	R-3	R^{1}-4	H-5 (1H, s)	H-7 (2H, t, *J* = 7.2)	H-6 (2H, t, *J* = 7.2)	H-10 (1H, s)	H-2',3',4',5',6' (10H, m)
8	6.90 (1H, s, H)	2.36 (3H, s, CH_3)	7.61	1.86	2.85	7.05	1.30-1.70
9	6.90 (1H, s, H)	1.25 (3H, t, *J* = 7.2); 2.79 (2H, q, *J* = 7.2) (CH_2CH_3)	7.64	1.86	2.86	7.00	1.30-1.70
10	6.91 (1H, s, H)	0.92 (3H, t, *J* = 7.2); 1.34 (2H, m); 1.62 (2H, m); 2.72 (2H, q, *J* = 7.2) ($CH_2CH_2CH_2CH_3$)	7.63	1.86	2.84	7.02	1.30-1.70
11	4.40 (2H, s); 7.15-7.30 (5H, m) (CH_2Ph)	2.34 (3H, s, CH_3)	7.66	1.85	2.83	6.92	1.30-1.70
12	2.10 (2H, m); 2.86 (2H, t, *J* = 7.2); 3.11 (2H, t, *J* = 7.2) ($CH_2CH_2CH_2$)		7.42	1.81	2.86	6.93	1.30-1.70
13	1.75-1.80 (4H, m); 2.63 (2H, m); 2.84 (2H, m) ($CH_2CH_2CH_2CH_2$)		7.61	1.85	2.84	6.91	1.30-1.70

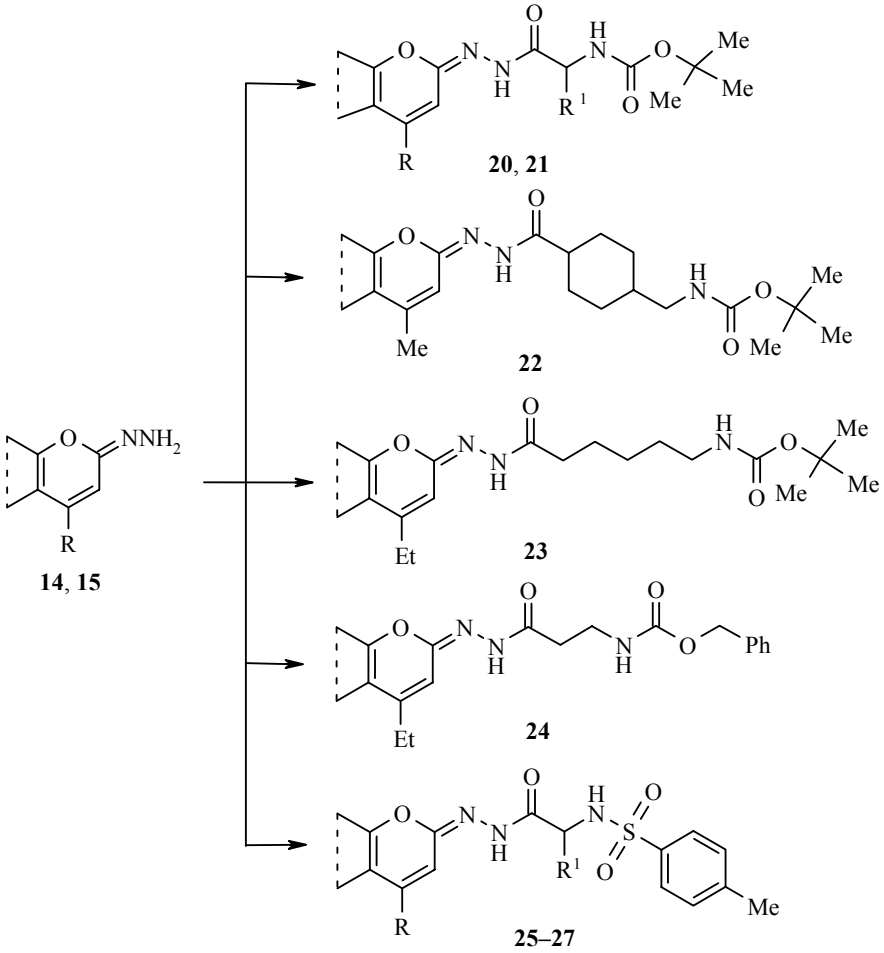
TABLE 3. ^{1}H NMR Spectra of Hydrazones of Spirodihydropyranochromen-2-ones **14, 15**

Com-pound	Chemical shifts (400 MHz) in DMSO, δ, ppm (*J*, Hz)							
	R-3	R^1-4	H-5 (1H, s)	H-7 (2H, t, *J* = 7.2)	H-6 (2H, t, *J* = 7.2)	H-10 (1H, s)	H-2',3',4',5',6' (10H, m)	NH_2 (2H, br. s)
14	5.91 (1H, s, H)	2.06 (3H, s, CH_3)	7.05	1.76	2.69	6.49	1.30-1.70	5.65
15	5.85 (1H, s, H)	1.13 (3H, t, *J* = 7.2); 2.45 (2H, q, *J* = 7.2) (CH_2CH_3)	7.09	1.75	2.68	6.49	1.30-1.70	5.70

TABLE 4. ^{1}H NMR Spectra of Oximes of Spirodihydropyranochromen-2-ones **16-19**

Com-pound	Chemical shifts (400 MHz) in DMSO, d, ppm (*J*, Hz)							
	R-3	R^1-4	H-5 (1H, s)	H-7 (2H, t, *J* = 7.2)	H-6 (2H, t, *J* = 7.2)	H-10 (1H, s)	H-2',3',4',5',6' (10H, m)	N–OH (2H, br. s)
16	5.90 (1H, s, H)	0.93 (3H, t, *J* = 7.2); 1.35 (2H, m); 1.62 (2H, m); 2.73 (2H, q, *J* = 7.2) (CH_2CH_3)	7.19	1.78	2.72	6.50	1.30-1.70	
17	3.86 (2H, s); 7.18-7.35 (5H, m,) (CH_2Ph)	2.15 (3H, s, CH_3)	7.24	1.79	2.73	6.49	1.30-1.70	10.12
18	2.07 (2H, m); 2.63 (2H, t, *J* = 7.2); 2.78 (2H, t, *J* = 7.2) ($CH_2CH_2CH_2$)		7.00	1.78	2.73	6.54	1.30-1.70	10.07
19	1.75-1.80 (4H, m); 2.24 (2H, m); 2.60 (2H, m) ($CH_2CH_2CH_2CH_2$)		7.13	1.78	2.72	6.48	1.30-70	10.07

Scheme 2



20, 25 R = Me, R^1 = Et; **21, 27** R = Et, R^1 = Ph; **26** R = Me, R^1 = Ph

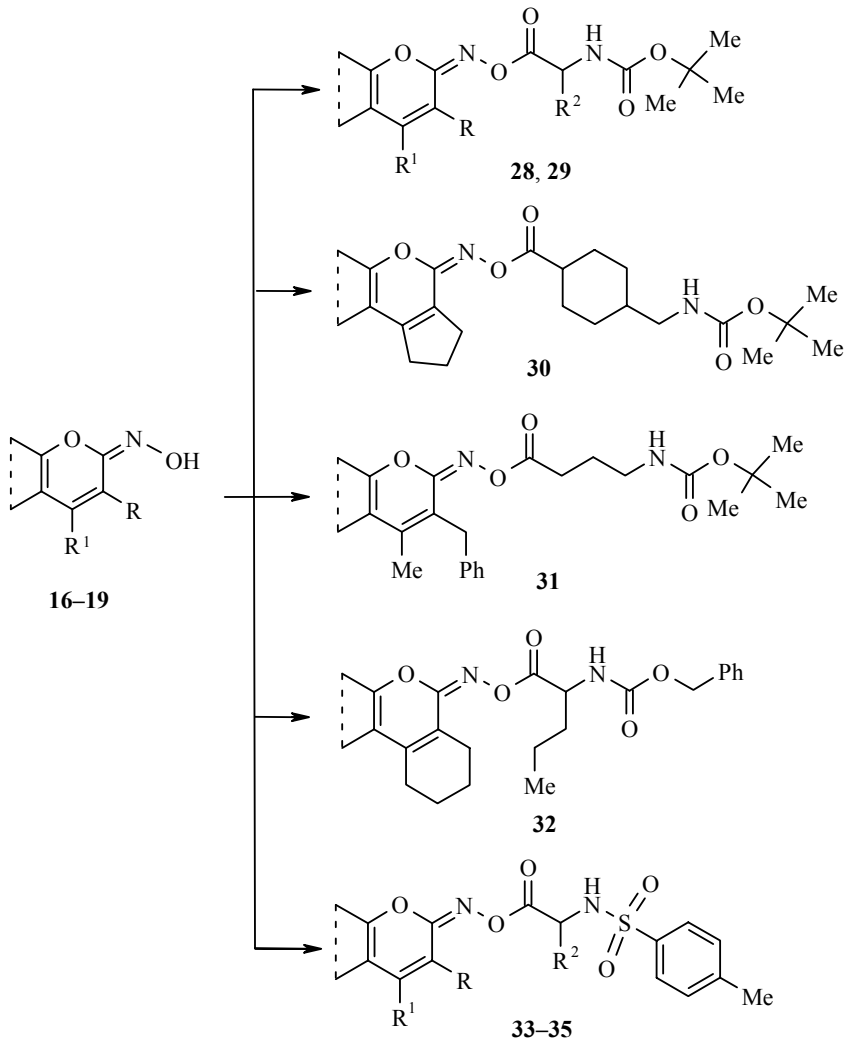
The symmetrical anhydrides method used in peptide synthesis [8] was successfully applied for the acylation of the hydroxyl group of oximes. Symmetrical anhydrides of N-protected amino acids were obtained by the condensation of dicyclohexylcarbodiimide (DCC) with a double quantity of the corresponding N-substituted amino acid in absolute dioxane at 0°C. Treatment of oximes of spirodihydropyranochromenes **16-19** with the obtained symmetrical anhydrides in the presence of catalytic amounts of 4-dimethyl-aminopyridine (DMAP) leads to the formation of O-aminoacylated derivatives **28-35**, modified with residues of DL-aminobutyric (in **28**), *trans*-4-(aminomethyl)cyclohexanecarboxylic (in **30**), and 4-aminobutyric (in **31**) acids, L-2-phenylglycine (in **29**, **33**), DL-2-norvaline (in **32, 34**), and L-phenylalanine (in **35**) (Scheme 3).

Derivatives of hydrazones and oximes of spirodihydropyranochromen-2-ones, modified with residues of amino acids, have been obtained using activated esters and symmetrical anhydrides methods.

EXPERIMENTAL

The progress of reactions and the homogeneity of the obtained compounds was checked by TLC on Merck 60 F254 plates, eluent was chloroform–methanol, 9:1 or 95:5. Melting points were determined on a Kofler heating block. The ^{1}H NMR spectra were recorded on Varian VXR 300 (300 MHz) and Varian Mercury 400 (400 MHz) instruments, internal standard was TMS.

Sheme 3



28 R = H, R^1 = Bu, R^2 = Et; **29** $RR^1 = (CH_2)_4$, R^2 = Ph; **33** R = H, R^1 = Bu, R^2 =Ph;
34 R = CH_2Ph, R^1 = Me, R^2 = Pr; **35** $RR^1 = (CH_2)_4$, $R^2 = CH_2Ph$

The synthesis of spiro[(7-hydroxychromane)-2,1'-cyclohexane] (**1**) was described in [3].

Spirodihydropyranochromen-2-ones 2-7. Conc. H_2SO_4 (40 ml) was added dropwise with vigorous stirring to a solution of spirochromane **1** (10.90 g, 50 mmol) and the appropriate ethyl acetoacetate (50 mmol) in ethanol (20 ml). The reaction mixture was left overnight at room temperature, after which the mixture was poured into ice water (500 ml). The resulting solid was filtered off and crystallized from 2-propanol.

Data of ^{1}H NMR spectroscopy are given in Tables 1.

Spiro[(4-methyl-7,8-dihydropyrano[3,2-*g*]chromen-2-one)-8,1'-cyclohexane] (2). Yield 55%; mp 204-205°C. Found, %: C 75.86; H 7.12. $C_{18}H_{20}O_3$. Calculated, %: C 76.03; H 7.09.

Spiro[(4-ethyl-7,8-dihydropyrano[3,2-*g*]chromen-2-one)-8,1'-cyclohexane] (3). Yield 63%; mp 155-156°C. Found, %: C 76.32; H 7.29. $C_{19}H_{22}O_3$. Calculated, %: C 76.48; H 7.43.

Spiro[(4-butyl-7,8-dihydropyrano[3,2-*g*]chromen-2-one)-8,1'-cyclohexane] (4). Yield 68%; mp 117-118°C. Found, %: C 77.32; H 7.95. $C_{21}H_{26}O_3$. Calculated, %: C 77.27; H 8.03.

Spiro[(4-methyl-3-benzyl-7,8-dihydropyrano[3,2-*g*]chromen-2-one)-8,1'-cyclohexane] (5). Yield 71%; mp 136-137°C. Found, %: C 79.98; H 7.12. $C_{25}H_{26}O_3$. Calculated, %: C 80.18; H 7.00.

Spiro[(2,3,9,10-tetrahydrocyclopenta[*c*]pyrano[3,2-*g*]chromen-4-one)-8,1'-cyclohexane] (6). Yield was 68%; mp 198-199°C. Found, %: C 77.48; H 7.11. $C_{20}H_{22}O_3$. Calculated, %: C 77.39; H 7.14.

Spiro[(1,2,3,4,10,11-hexahydrobenzo[*c*]pyrano[3,2-*g*]chromen-5-one)-9,1'-cyclohexane] (7). Yield 65%; mp 154-155°°C. Found, %: C 77.71; H 7.52. $C_{21}H_{24}O_3$. Calculated, %: C 77.75; H 7.46.

Spirodihydropyranochromen-2-thiones 8-13. A mixture of spirodihydropyranochromen-2-one **2-7** (20 mmol) and Lawesson reagent (2.46 g, 11 mmol) in absolute toluene (50 ml) was boiled for 4 h (the progress of the reaction was checked by TLC). After the end of the reaction the solvent was evaporated, and the oily residue crystallized from aqueous 2-propanol.

Spiro[(4-methyl-7,8-dihydropyrano[3,2-*g*]chromen-2-thione)-8,1'-cyclohexane] (8). Yield 86%; mp 181-182°C. Found, %: C 71.84; H 6.81; S 10.79. $C_{18}H_{20}O_2S$. Calculated, %: C 71.94; H 6.71; S 10.67.

Spiro[(4-ethyl-7,8-dihydropyrano[3,2-*g*]chromen-2-thione)-8,1'-cyclohexane] (9). Yield 90%; mp 176-177°C. Found, %: C 72.49; H 7.11; S 10.15. $C_{19}H_{22}O_2S$. Calculated, %: C 72.57; H 7.05; S 10.20.

Spiro[(4-butyl-7,8-dihydropyrano[3,2-*g*]chromen-2-thione)-8,1'-cyclohexane] (10). Yield 93%; mp 145-146°C. Found, %: C 73.57; H 7.71; S 9.41. $C_{21}H_{26}O_2S$. Calculated, %: C 73.64; H 7.65; S 9.36.

Spiro[(3-benzyl-4-methyl-7,8-dihydropyrano[3,2-*g*]chromen-2-thione)-8,1'-cyclohexane] (11). Yield 88%; mp 182-183°C. Found, %: C 76.99; H 6.62; S 8.28. $C_{25}H_{26}O_2S$. Calculated, %: C 76.89; H 6.71; S 8.21.

Spiro[(2,3,9,10-tetrahydrocyclopenta[*c*]pyrano[3,2-*g*]chromen-4-thione)-8,1'-cyclohexane] (12). Yield 97%; mp 218-219°C. Found, %: C 73.66; H 6.85; S 9.95. $C_{20}H_{22}O_2S$. Calculated, %: C 73.58; H 6.79; S 9.82.

Spiro[(1,2,3,4,10,11-hexahydrobenzo[*c*]pyrano[3,2-*g*]chromen-5-thione)-9,1'-cyclohexane] (13). Yield 95%; mp 178-179°C. Found, %: C 74.15; H 7.08; S 9.51. $C_{21}H_{24}O_2S$. Calculated, %: C 74.08; H 7.10; S 9.42.

Hydrazones of Spirodihydropyranochromen-2-ones 14, 15. Hydrazine hydrate (1 ml, 20 mmol) was added to a solution of thione **8** or **9** (10 mmol) in ethanol (30 ml). The mixture was boiled for 1 h (the progress of the reaction was checked by TLC). After the end of the reaction the mixture was cooled to room temperature, the resulting solid was filtered off, and crystallized from 2-propanol.

Hydrazone of Spiro[(4-methyl-7,8-dihydropyrano[3,2-*g*]chromen-2-one)-8,1'-cyclohexane] (14). Yield 94%; mp 200-201°C. Found, %: C 72.38; H 7.35; N 9.51. $C_{18}H_{22}N_2O_2$. Calculated, %: C 72.46; H 7.43; N 9.39.

Hydrazone of Spiro[(4-ethyl-7,8-dihydropyrano[3,2-*g*]chromen-2-one)-8,1'-cyclohexane] (15). Yield 86%; mp 169-170°C. Found, %: C 72.92; H 7.69; N 8.91. $C_{19}H_{24}N_2O_2$. Calculated, %: C 73.05; H 7.74; N 8.97.

Oximes of Spirodihydropyranochromen-2-ones 16-19. Hydroxylamine hydrochloride (0.84 g, 12 mmol) was added to a solution of thione **10-13** (6 mmol) in absolute pyridine (10 ml). The mixture was maintained at 100°C for 6 h (the progress of the reaction was checked by TLC). After the end of the reaction the mixture was cooled to room temperature, and transferred into 5% acetic acid (100 ml). The resulting solid was filtered off, and crystallized from 2-propanol.

Oxime of Spiro[(4-butyl-7,8-dihydropyrano[3,2-*g*]chromen-2-one)-8,1'-cyclohexane] (16). Yield 88%; mp 175-176°C. Found, %: C 73.78; H 8.02; N 4.12. $C_{21}H_{27}NO_3$. Calculated, %: C 73.87; H 7.97; N 4.10.

Oxime of Spiro[(3-benzyl-4-methyl-7,8-dihydropyrano[3,2-*g*]chromen-2-one)-8,1'-cyclohexane] (17). Yield 94%; mp 243-244°C. Found, %: C 79.95; H 7.05; N 3.65. $C_{25}H_{27}NO_3$. Calculated, %: C 77.09; H 6.99; N 3.60.

Oxime of Spiro[(2,3,9,10-tetrahydrocyclopenta[*c*]pyrano[3,2-*g*]chromen-4-one)-8,1'-cyclohexane] (18). Yield 96%; mp 256-257°C. Found, %: C 73.95; H 7.06; N 4.25. $C_{20}H_{23}NO_3$. Calculated, %: C 73.82; H 7.12; N 4.30.

Oxime of Spiro[(1,2,3,4,10,11-hexahydrobenzo[*c*]pyrano[3,2-*g*]chromen-5-one)-9,1'-cyclohexane] (19). Yield 94%; mp 240-241°C. Found, %: C 74.41; H 7.46; N 4.11. $C_{21}H_{26}NO_3$. Calculated, %: C 74.31; H 7.42; N 4.13.

N-Acylhydrazones of Spirodihydropyranochromen-2-ones 20-27. Diisopropylcarbodiimide (DIC) (0.52 ml, 3.3 mmol) was added with vigorous stirring and cooling (0°C) to a solution of the appropriate N-protected amino acid (3.3 mmol) and N-HOSu (0.38 g, 3.3 mmol) in absolute dioxane (20 ml). The reaction mixture was stirred for 2 h (progress of the reaction was checked by TLC). Hydrazone **14** or **15** (3 mmol) was added to the resulting active ester. The mixture was stirred vigorously at room temperature for 4-6 h (progress of the reaction was checked by TLC). After completion of the reaction the mixture was diluted with water (200 ml), the solid formed was filtered off, and crystallized from 2-propanol.

N-(N-*tert*-Butyloxycarbonyl-DL-2-aminobutyryl)hydrazone of Spiro[(4-methyl-7,8-dihydropyrano-[3,2-*g*]chromen-2-one)-8,1'-cyclohexane] (20). Yield 82%; mp 238-239°C. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz); 0.97 and 1.00 (3H, two t, *J* = 7.2, 3"-CH_3); 1.20-2.00 (14H, m, H-7,2',3'4',5',6',2"); 1.45 and 1.46 (9H, s, $(CH_3)_2$); 2.19 and 2.20 (3H, two s, 4-CH_3); 2.77 (2H, m, H-6); 4.11 (1H, m, H-1'"); 5.09 and 5.36 (1H, two m, CONHC); 5.99 and 6.19 (1H, two s, H-3); 6.56 and 6.71 (1H, two s, H-10); 7.03 and 7.06 (1H, two s, H-5); 8.77 and 9.41 (1H, two s, CONHN). Found, %: C 66.95; H 7.76; N 8.71. $C_{27}H_{37}N_3O_5$. Calculated, %: C 67.06; H 7.71; N 8.69.

N-(N-*tert*-Butyloxycarbonyl-L-2-phenylglycyl)hydrazone of Spiro[(4-ethyl-7,8-dihydropyrano-[3,2-*g*]chromen-2-one)-8,1'-cyclohexane] (21). Yield 68%; mp 231-232°C. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.20-1.85 (14H, m, H-7,2',3',4',5'6',1"); 1.45 and 1.46 (9H, s, $(CH_3)_3$); 2.56 (2H, q, *J* = 7.2, H-1"); 2.74 (2H, m, H-6); 5.29 (1H, m, H-1'"); 5.90 and 6.22 (1H, d, *J* = 7.8, CONHC); 5.97 and 6.19 (1H, two s, H-3); 6.51 and 6.53 (1H, two s, H-10); 7.05 and 7.08 (1H, two s, H-5); 7.30-7.53 (5H, m, C_6H_5); 8.81 and 8.93 (1H, two s, CONHN). Found, %: C 70.55; H 7.16; N 7.75. $C_{32}H_{39}N_3O_5$. Calculated, %: C 70.44; H 7.20; N 7.70.

N-[N-*tert*-Butyloxycarbonyl-*trans*-4-aminomethyl)cyclohexanecarbonyl]hydrazone of Spiro[(4-methyl-7,8-dihydropyrano[3,2-*g*]chromen-2-one)-8,1′-cyclohexane] (22). Yield 82%; mp 268-269°C. ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 0.95-1.80 (21H, m, H-7,2'3',4',5'6',2",3",4",5",6"); 1.39 and 1.41 (9H, s, $(CH_3)_3$); 2.17 and 2.19 (3H, two s, 4-CH_3); 2.32 (1H, m, H-1"); 2.72-2.81 (4H, m, H-6,4"); 6.03 and 6.06 (1H, two s, H-3); 6.59 (1H, m, CONHC); 6.71 and 6.72 (1H, two s, H-10); 7.11 and 7.13 (1H, two s, H-5); 9.78 and 9 96 (1H, two s, CONHN). Found, %: C 69.15; H 8.16; N 8.71. $C_{31}H_{43}N_3O_5$. Calculated, %: C 69.25; H 8.06; N 8.82.

N-(N-*tert*-Butyloxycarbonyl-6-aminohexanoyl)hydrazone of Spiro[(4-ethyl-7,8-dihydropyrano-[3,2-*g*]chromen-2-one)-8,1′-cyclohexane] (23). Yield 72%; mp 185-186°C. ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.22 (3H, t, *J* = 7.2, 2"-CH_3); 1.25-1.80 (18H, m, H-7,2',3',4',5',6',3'",4'",5'"); 1.38 (9H, s, $(CH_3)_3$); 2.57 (4H, m, H-1″,2'"), 2.73 (2H, m, H-6); 2.90 (2H, q, *J* = 7.2, H-6'"); 5.96 and 6.01 (1H, two s, H-3); 6.56 (1H, m, CONHC); 6.71 and 6.72 (1H, two s, H-10); 7.14 and 7.17 (1H, two s, H-5); 9.91 and 10.04 (1H, two s, CONHN). Found, %: C 68.65; H 8.14; N 7.95. $C_{30}H_{43}N_3O_5$. Calculated, %: C 68.54; H 8.24; N 7.99.

N-(N-Benzyloxycarbonyl-β-alanyl)hydrazone of Spiro[(4-ethyl-7,8-dihydropyrano[3,2-*g*]chromen-2-one)-8,1'-cyclohexane] (24). Yield 76%; mp 196-197°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.15-1.20 (3H, m, 2"-CH_3); 1.25-1.75 (10H, m, H-2',3',4',5',6'); 1.78 (2H, t, *J* = 7.2, H-7); 2.46-2.59 (4H, m, H-1",2'"); 2.72 (2H, m, H-6); 3.28 (2H, m, H-3'"); 5.02 and 5.03 (2H, s, OCH_2); 6.01 and 6.07 (1H, two s, H-3); 6.74 and 6.77 (1H, two s, H-10); 7.22 and 7.26 (1H, two s, H-5); 7.28-7.34 (6H, m, CONHC, C_6H_5); 10.30 and 10.32 (1H, two s, CONHN). Found, %: C 69.65; H 6.74; N 8.15. $C_{30}H_{35}N_3O_5$. Calculated, %: C 69.61; H 6.82; N 8.12.

N-[N-(4-Methylbenzenesulfonyl)-DL-2-aminobutyryl]hydrazone of Spiro[(4-methyl-7,8-dihydro-pyrano[3,2-*g*]chromen-2-one)-8,1'-cyclohexane] (25). Yield 69%; mp 208-209°C. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.88 and 0.99 (3H, t, *J* = 7.2, 3"-CH_3); 1.20-1.90 (12H, m, H-7,2',3',4',5',6'); 2.10-2.25 (2H, m, H-2"); 2.20 and 2.22 (3H, two s, 4-CH_3); 2.28 and 2.31 (3H, two s, 4'"-CH_3); 2.27 (2H, m, H-6); 3.75 and 4.63 (1H, two m, H-1'"); 5.34 and 5.60 (1H, d, *J* = 8.4, SO_2NH); 5.99 and 6.13 (1H, two s, H-3); 6.74 and 6.77 (1H, two s, H-10); 7.04 and 7.06 (1H, two s, H-5); 7.18 and 7.23 (2H, two d, *J* = 8.1, H-3'",5'");

7.72 and 7.77 (2H, two d, *J* = 8.1, H-2"",6""); 8.47 and 9.11 (1H, two s, CONHN). Found, %: C 64.69; H 6.52; N 7.85; S 5.98. $C_{29}H_{35}N_3O_5S$. Calculated, %: C 64.78; H 6.56; N 7.82; S 5.96.

N-[N-(4-Methylbenzenesulfonyl)-L-2-phenylglycyl]hydrazone of Spiro[(4-methyl-7,8-dihydropyrano[3,2-*g*]chromen-2-one)-8,1'-cyclohexane] (26). Yield 80%; mp 241-242°C. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.30-1.85 (12H, m, H-7,2',3',4',5',6'); 2.20 and 2.22 (3H, two s, 4-CH_3); 2.30 and 2.33 (3H, two s, 4"'-CH_3); 2.76 (2H, t, *J* = 7.2, H-6); 4.91 and 6.08 (1H, d, *J* = 8.1, H-2"); 5.91 and 5.94 (1H, two s, H-3); 6.02 and 6.11 (1H, d, *J* = 8.4, SO_2NH); 6.44 and 6.48 (1H, two s, H-10); 7.03 (1H, s, H-5); 7.12-7.37 (7H, m, H-3"",5"", C_6H_5); 7.65 (2H, d, *J* = 9.0, H-2"",6""); 8.60 and 8.84 (1H, two s, CONHN). Found, %: C 67.58; H 5.98; N 7.25; S 5.38. $C_{33}H_{35}N_3O_5S$. Calculated, %: C 67.67; H 6.02; N 7.17; S 5.47.

N-[N-(4-Methylbenzenesulfonyl)-L-2-phenylglycyl]hydrazone of Spiro[(4-ethyl-7,8-dihydropyrano[3,2-*g*]chromen-2-one)-8,1'-cyclohexane] (27). Yield 77%; mp 209-210°C. ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.19 and 1.22 (3H, two t, *J* = 7.2, 2″-CH_3); 1.30-1.90 (12H, m, H-7,2',3',4',5',6'); 2.25 and 2.29 (3H, two s, 4"'-CH_3); 2.59 (2H, m, H-1"); 2.75 (2H, m, H-6); 5.33 and 5.86 (1H, d, *J* = 8.4, H-2"); 5.98 and 6.03 (1H, two s, H-3); 6.65 and 6.72 (1H, two s, H-10); 7.12 and 7.14 (1H, two s, H-5); 7.16-7.38 (7H, m, H-3"",5"",C_6H_5); 7.56 and 7.59 (2H, two d, *J* = 9.0, H-2"",6""); 8.27 and 8.47 (1H, d, *J* = 8.7, SO_2NH); 10.37 and 10.40 (1H, two s, CONHN). Found, %: C 68.05; H 6.13; N 7.11; S 5.29. $C_{34}H_{37}N_3O_5S$. Calculated, %: C 68.09; H 6.22; N 7.01; S 5.35.

O-Acyloximes of Spirodihydropyranochromen-2-ones 28-35. Dicyclohexylcarbodiimide (DCC) (0.68 g, 3.3 mmol) was added with vigorous stirring and cooling (0°C) to a solution of the appropriate N-protected amino acid (6.6 mmol) in absolute dioxane (20 ml). The reaction mixture was stirred for 1 h (progress of the reaction was checked by TLC). Oxime **16-19** (3 mmol) and DMAP (5 mg) were added to the resulting symmetrical anhydride. The mixture was stirred vigorously for 8-10 h at room temperature (progress of the reaction was checked by TLC). The solid dicyclohexylurea was filtered off, and the solvent was removed in vacuum. The residue was dissolved in ethyl acetate (50 ml) and treated sequentially in a separating funnel twice with 5% $NaHCO_3$ (50 ml), with water (50 ml), and saturated NaCl solution (50 ml). The organic phase was dried over anhydrous $MgSO_4$, the solvent was removed in vacuum, and the oily residue was crystallized from 2-propanol.

O-(N-*tert*-Butyloxycarbonyl-DL-2-aminobutyryl)oxime of Spiro[(4-butyl-7,8-dihydropyrano-[3,2-*g*]chromen-2-one)-8,1′-cyclohexane] (28). Yield 81%; mp 164-165°C. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.96 (3H, t, *J* = 7.2, 4"-CH_3); 1.04 (3H, t, *J* = 7.2, 3"'-CH_3); 1.25-2.00 (18H, m, H-7,2',3',4',5',6',2",3", 2"'); 1.47 (9H, s, $(CH_3)_3$); 2.73 (2H, t, *J* = 7.2, H-1"'); 2.78 (2H, t, *J* = 7.2, H-6); 4.52 (1H, m, H-1"'); 5.20 (1H, d, *J* = 7.8, NH); 6.19 (1H, s, H-3); 6.75 (1H, s, H-10); 7.14 (1H, s, H-5). Found, %: C 68.49; H 7.94; N 5.35. $C_{30}H_{42}N_2O_6$. Calculated, %: C 68.42; H 8.04; N 5.32.

O-(N-*tert*-Butyloxycarbonyl-L-2-phenylglycyl)oxime of Spiro[(1,2,3,4,10,11-hexahydrobenzo-[*c*]pyrano[3,2-*g*]chromen-5-one)-9,1'-cyclohexane] (29). Yield 70%; mp 161-162°C. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.30-1.80 (16H, m, 2,3,11,2′,3′,4′,5′,6′); 1.45 (9H, s, $(CH_3)_3$); 2.33 and 2.44 (2H, two m, H-4); 2.56 (2H, m, H-1); 2.75 (2H, t, *J* = 7.2, H-11); 5.65 (1H, d, *J* = 7.2, H-1″); 5.75 (1H, d, *J* = 7.8, NH); 6.52 and 6.72 (1H, two s, H-7); 7.02 and 7.07 (1H, two s, H-12); 7.35-7.54 (5H, m, C_6H_5). Found, %: C 71.46; H 7.01; N 4.95. $C_{34}H_{40}N_2O_6$. Calculated, %: C 71.31; H 7.04; N 4.89.

O-[N-*tert*-Butyloxycarbonyl-*trans*-4-(aminomethyl)cyclohexanecarbonyl]oxime of Spiro[(2,3,9,10-tetrahydrocyclopenta[*c*]pyrano[3,2-*g*]chromen-4-one)-8,1'-cyclohexane] (30). Yield 51%; mp 194-195°C. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.95-1.80 (21H, m, 11,2′,3′,4′,5′,6′,2″,3″,4″,5″,6″); 1.46 (9H, s, $(CH_3)_3$); 2.15 (2H, m, H-2); 2.49 (1H, m, H-1″); 2.77 (2H, t, *J* = 7.2, H-10); 2.85 (4H, m, H-3,4″); 3.04 (2H, m, H-1); 4.65 (1H, m, NH); 6.76 (1H, s, H-6); 6.96 (1H, s, H-11). Found, %: C 70.04; H 7.91; N 5.01. $C_{33}H_{44}N_2O_6$. Calculated, %: C 70.19; H 7.85; N 4.96.

O-(N-*tert*-Butyloxycarbonyl-4-aminobutyryl)oxime of Spiro[(3-benzyl-4-methyl-7,8-dihydropyrano[3,2-*g*]chromen-2-one)-8,1'-cyclohexane] (31). Yield 72%; mp 153-154°C. ^{1}H NMR spectrum

(300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.25-1.95 (14H, m, H-7,2',3',4',5',6',3"); 1.45 (9H, s, $(CH_3)_3$); 2.26 (3H, s, 4-CH_3); 2.55 (2H, t, *J* = 7.2, H-2"); 2.77 (2H, t, *J* = 7.2, H-6); 3.23 (2H, m, H-4"); 4.01 (2H, s, H-3); 4.59 (1H, m, NH); 6.74 (1H, s, H-10); 7.15 (1H, s, H-5); 7.16-7.33 (5H, m, C_6H_5). Found, %: C 70.96; H 7.34; N 4.92. $C_{34}H_{42}N_2O_6$. Calculated, %: C 71.06; H 7.37; N 4.87.

O-(N-Benzyloxycarbonyl-DL-norvalyl)oxime of Spiro[1,2,3,4,10,11-hexahydrobenzo[*c*]pyrano-[3,2-*g*]chromen-5-one)-9,1'-cyclohexane] (32). Yield 80%; mp 145-146°C. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.99 (3H, t, *J* = 7.2, 4"-CH_3); 1.27-1.95 (20H, m, 2,3,10,2',3',4',5',6',2",3"); 2.48 (2H, m, H-4); 2.63 (2H, m, H-1); 2.77 (2H, t, *J* = 7.2, H-11); 4.66 (1H, m, H-1'"); 5.14 (2H, s, OCH_2); 5.42 (1H, d, *J* = 7.8, NH); 6.71 (1H, s, H-7); 7.10 (1H, s, H-12); 7.30-7.38 (5H, m, C_6H_5). Found, %: C 71.19; H 7.11; N 4.81. $C_{34}H_{42}N_2O_6$. Calculated, %: C 71.31; H 7.04; N 4.89.

O-[N-(4-Methylbenzenesulfonyl)-L-2-phenylglycyl]oxime of Spiro[(4-butyl-7,8-dihydropyrano-[3,2-*g*]chromen-2-one)-8,1'-cyclohexane] (33). Yield 66%; mp 169-170°C. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.94 (3H, t, *J* = 7.2, 4"-CH_3); 1.30-1.90 (16H, m, H-7,2',3',4',5',6',2"3"); 2.32 (3H, s, 4'"-CH_3); 2.56 (2H, t, *J* = 7.2, H-1'"); 2.77 (2H, t, *J* = 7.2, H-6); 5.30 (1H, d, *J* = 7.8, H-2'"); 5.81 (1H, d, *J* = 7.8, NH); 6.07 (1H, s, H-3); 6.56 (1H, s, H-10); 7.12 (1H, s, H-5); 7.18 (2H, d, *J* = 8.4, H-3'"",5'""); 7.31-7.40 (5H, m, C_6H_5); 7.69 (2H, d, *J* = 8.4, H-2'"",6'""). Found, %: C 68.85; H 6.35; N 4.51; S 5.05. $C_{36}H_{40}N_2O_6S$. Calculated, %: C 68.77; H 6.41; N 4.46; S 5.10.

O-[N-(4-Methylbenzenesulfonyl)-DL-norvalyl]oxime of Spiro[(3-benzyl-4-methyl-7,8-dihydro-pyrano[3,2-*g*]chromen-2-one)-8,1'-cyclohexane] (34). Yield 71%; mp 173-174°C. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.94 (3H, t, *J* = 7.2, 4"-CH_3); 1,25-1.90 (16H, m, H-7,2',3',4',5',6′,2",3"); 2.21 (3H, s, 4-CH_3); 2.26 (3H, s, 4'"-CH_3); 2.78 (2H, t, *J* = 7.2, H-6); 3.90 (2H, s, H-3); 4.20 (1H, m, H-1"); 5.23 (1H, d, *J* = 8.4, NH); 6.67 (1H, s, H-10); 7.12-7.28 (8H, m, H-5,3'"" ,5'"", C_6H_5); 7.70 (2H, d, *J* = 8.4, H-2'"",6'""). Found, %: C 69.19; H 6.55; N 4.32, S 5.09. $C_{37}H_{42}N_2O_6S$. Calculated, %: C 69.13; H 6.59; N 4.36; S 4 99.

O-[N-(4-Methylbenzenesulfonyl)-L-phenylalanyl]oxime of Spiro[(1,2,3,4,10,11-hexahydrobenzo-[*c*]pyrano[3,2-*g*]chromen-5-one)-9,1′-cyclohexane] (35). Yield 73%; mp 198-199°C. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.30-1.90 (16H, m, H-2,3,10,2',3',4',5',6'); 2.32 (3H, s, 4'"-CH_3); 2.43 (2H, m, H-4); 2.62 (2H, m, H-1); 2.78 (2H, t, *J* = 7.2, H-11); 3.24 (3H, m, H-3"); 4.46 (1H, m, H-2″); 5.20 (1H, d, *J* = 8.7, NH); 6.66 (1H, s, H-7); 7.12 (1H, s, H-12); 7.19 (2H, d, *J* = 8.4, H-3'"",5'""); 7.20-7.30 (5H, m, C_6H_5); 7.69 (2H, d, *J* = 8.4, H-2'"",6'""). Found, %: C 69.23; H 6.25; N 4.29; S 4.94. $C_{37}H_{40}N_2O_6S$. Calculated, %: C 69.35; H 6.29; N 4.37; S 5.00.

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