AMINO-ACID DERIVATIVES OF 3-PHENOXYCHROMONES

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Peptide-chemistry methods have produced various amino-acid conjugates of 3-phenoxychromones in which 7-hydroxychromone is bound to the amino acid by the C- or N-terminus.

Key words: flavonoids, 3-phenoxychromones, amino-acid derivatives.

Flavonoids are a large and structurally unique group of compounds that is widely distributed in nature. They occur in varying quantities in almost all higher plants and are exceedingly rare in microorganisms and insects. In addition to natural flavonoids, derivatives in which a phenyl substituent is bound to the chromone ring through an O atom are sometimes encountered. Such compounds are called phenoxychromones. The commonest phenoxychromone in nature is capillarisin, which was isolated from extracts of *Artemisia capillaris* Herba [1]. At present, about ten compounds based on the 2-phenoxychromone moiety have been isolated from natural sources. The roots of *Glycyrrhiza aspera*, which are widely used in Chinese folk medicine, yielded glyasperin E, the only 3-phenoxychromone isolated from a natural source [2].

Flavonoids undergo various biochemical transformations and participate in several physiological processes owing to their high biological activity that is due to the presence of several pharmacophores. Therefore, our goal was to modify 3-phenoxychromone derivatives by addition to them of amino acids.

The amino-acid derivatives of 3-phenoxychromones were synthesized by two methods. The first is based on formation of an ester of the amino acids and phenolic compounds. In our opinion, a more suitable and convenient synthesis of 7-O-aminoacylchromones is the reaction of 7-hydroxychromones and symmetric anhydrides of N-substituted amino acids because the reaction occurs under mild conditions and has no side reactions [3, 4].

The symmetric anhydrides of N-substituted amino acids are prepared by reaction of dicyclohexylcarbodiimide (DCC) with two equivalents of an N-substituted amino acid in absolute THF at 0°C. The amino group is blocked using a *t*-butyloxycarbonyl (Boc) protecting group. 7-Hydroxy-3-phenoxychromones **1**, **2**, and **3** were acylated with symmetric anhydrides $(BocNHCHRCO)_2O$ in absolute THF in the presence of catalytic amounts of 4-dimethylaminopyridine (DMAP) at low temperature (0°C). The products were N-substituted 7-O-aminoacyl-3-phenoxychromones **4**-**27**, the molecules of which include glycine (**4**-**6**), L-alanine (**7**-**9**), L-valine (**10**-**12**), L-leucine (**13**-**15**), L-isoleucine (**16**, **17**), L-methionine (**18**-**20**), L-proline (**21**, **22**), L-phenylalanine (**23**, **24**), L-tyrosine (**25**, **26**), and L-tryptophane (**27**).

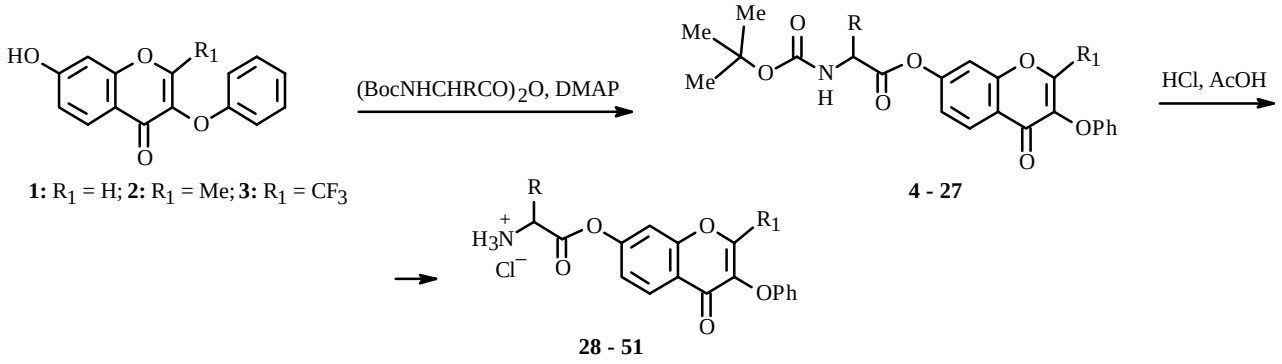

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TABLE 1. Physicochemical Constants of N-Substituted 7-O-aminoacyl-3-phenoxychromones **4**-**27**

Compound	Empirical formula	Yield, %	mp, °C	PMR spectrum, $CDCl_3$, δ, ppm									
				Chromone protons				Phenoxyl protons					7-O-Amino-acid protons
				2-R_1, s	5-H, d	6-H, dd	8-H, d	2-H, m	3-H, m	4-H, m	5-H, m	6-H, m	
4	$C_{22}H_{21}NO_7$	82	146	8.02 (H)	8.31	7.00	7.08	7.30	7.20	7.20	7.20	7.30	Boc NH CH_2 1.48; 5.14; 4.19
5	$C_{23}H_{23}NO_7$	89	135	2.43 (Me)	8.24	6.95	7.00	7.30	7.15	7.15	7.15	7.30	Boc NH CH_2 1.48; 5.15; 4.19
6	$C_{23}H_{20}F_3NO_7$	74	121	– (CF_3)	8.22	6.95	7.00	7.30	7.20	7.20	7.20	7.30	Boc NH CH_2 1.49; 5.08; 4.22
7	$C_{23}H_{23}NO_7$	86	151	8.02 (H)	8.30	7.02	7.08	7.30	7.20	7.20	7.20	7.30	Boc NH CH CH_3 1.49; 5.06; 4.55; 158
8	$C_{24}H_{25}NO_7$	81	146	2.43 (Me)	8.26	6.97	7.06	7.30	7.15	7.15	7.15	7.30	Boc NH CH CH_3 1.48; 5.08; 4.55; 158
9	$C_{24}H_{22}F_3NO_7$	79	132	– (CF_3)	8.21	6.98	7.08	7.30	7.20	7.20	7.20	7.30	Boc NH CH CH_3 1.48; 5.04; 4.54; 157
10	$C_{25}H_{27}NO_7$	81	132	8.02 (H)	8.28	7.02	7.08	7.35	7.20	7.20	7.20	7.35	Boc NH CH CH $(CH_3)_2$ 1.48; 5.05; 4.47; 2.32; 1.11; 1.05
11	$C_{26}H_{29}NO_7$	79	126	2.43 (Me)	8.26	6.95	7.01	7.30	7.20	7.20	7.20	7.30	Boc NH CH CH $(CH_3)_2$ 1.48; 5.08; 4.47; 2.32; 1.13; 1.06
12	$C_{26}H_{26}F_3NO_7$	72	118	– (CF_3)	8.23	6.98	7.01	7.30	7.20	7.20	7.20	7.30	Boc NH CH CH $(CH_3)_2$ 1.49; 5.07; 4.43; 2.31; 1.12; 1.07
13	$C_{26}H_{29}NO_7$	85	136	8.02 (H)	8.29	7.02	7.08	7.35	7.20	7.20	7.20	7.35	Boc NH CH CH_2 CH $(CH_3)_2$ 1.47; 4.96; 4.54; 1.78; 1.78; 1.02
14	$C_{27}H_{31}NO_7$	78	122	2.43 (Me)	8.26	6.95	7.01	7.30	7.20	7.20	7.20	7.30	Boc NH CH CH_2 CH $(CH_3)_2$ 1.47; 4.96; 4.54; 1.78; 1.78; 1.02
15	$C_{27}H_{28}F_3NO_7$	73	109	– (CF_3)	8.23	6.95	7.02	7.30	7.20	7.20	7.20	7.30	Boc NH CH CH_2 CH $(CH_3)_2$ 1.48; 4.98; 4.54; 1.77; 1.77; 1.03
16	$C_{26}H_{29}NO_7$	75	125	8.49 (H)	8.22	7.05	7.09	7.30	7.20	7.20	7.20	7.30	Boc NH CH CH (CH_3) CH_2 CH_3* 1.36; 6.57; 4.36; 2.10; 1.10; 1.66; 0.99
17	$C_{27}H_{28}F_3NO_7$	71	106	– (CF_3)	8.22	6.95	7.02	7.30	7.20	7.20	7.20	7.30	Boc NH CH CH (CH_3) CH_2 CH_3 1.47; 5.05; 4.48; 2.05; 1.05; 1.35; 1.05
18	$C_{25}H_{27}NO_7S$	86	139	8.03 (H)	8.28	7.00	7.09	7.30	7.20	7.20	7.20	7.30	Boc NH CH CH_2 CH_2S CH_3 1.48; 5.21; 4.66; 2.68; 2.27; 2.15
19	$C_{26}H_{29}NO_7S$	81	131	2.45 (Me)	8.24	6.95	7.01	7.30	7.20	7.20	7.20	7.30	Boc NH CH CH_2 CH_2S CH_3 1.48; 5.28; 4.66; 2.67; 2.26; 2.15
20	$C_{26}H_{26}F_3NO_7S$	79	123	– (CF_3)	8.22	6.95	7.02	7.30	7.20	7.20	7.20	7.30	Boc NH CH CH_2 CH_2S CH_3 1.48; 5.24; 4.68; 2.68; 2.28; 2.16
21	$C_{27}H_{27}NO_7$	72	85	2.43 (Me)	8.23	6.90	7.00	7.30	7.20	7.20	7.20	7.30	Boc N CH_2 CH_2 CH_2 CH COO 1.48; 3.59; 1.6–2.3; 4.51
22	$C_{27}H_{24}F_3NO_7$	75	69	– (CF_3)	8.23	6.96	7.02	7.30	7.20	7.20	7.20	7.30	Boc N CH_2 CH_2 CH_2 CH COO 1.48; 3.59; 1.6–2.3; 4.55
23	$C_{29}H_{27}NO_7$	88	164	8.01 (H)	8.28	7.00	7.10	7.30	7.20	7.20	7.20	7.30	Boc NH CH CH_2 Ph 1.46; 5.08; 4.80; 3.24; 7.35
24	$C_{30}H_{26}F_3NO_7$	86	153	– (CF_3)	8.19	7.01	7.11	7.30	7.20	7.20	7.20	7.30	Boc NH CH CH_2 Ph 1.45; 5.07; 4.80; 3.23; 7.33
25	$C_{34}H_{35}NO_{10}$	74	179	8.02	8.27	7.00	7.10	7.30	7.20	7.20	7.20	7.30	Boc NH CH CH_2 (4-$BocOC_6H_4$) 1.46; 5.06; 4.79; 3.23; 1.57; 7.22
26	$C_{35}H_{34}F_3NO_{10}$	71	160	– (CF_3)	8.18	7.00	7.10	7.30	7.20	7.20	7.20	7.30	Boc NH CH CH_2 (4-$BocOC_6H_4$) 1.47; 5.11; 4.75; 3.22; 1.57; 7.25
27	$C_{31}H_{28}N_2O_7$	72	172	8.00 (H)	8.21	6.90	6.99	7.30	7.20	7.20	7.20	7.30	Boc NH CH CH_2 Indol NH 1.46; 5.15; 4.82; 3.44; 7.1– 7.6; 8.29

TABLE 2. Physicochemical Properties of 7-O-Aminoacyl-3-phenoxychromone Hydrochlorides **28-51**

Compound	Empirical formula	Yield, %	mp, °C	PMR spectrum, δ, ppm, DMSO-d_6									
				Chromone protons				Phenoxyl protons					7-O-Amino-acid protons
				2-R_1, s	5-H, d	6-H, dd	8-H, d	2-H, m	3-H, m	4-H, m	5-H, m	6-H, m	
28	$C_{17}H_{14}ClNO_5$	85	229	8.77 (H)	8.19	7.41	7.68	7.30	7.00	7.00	7.00	7.30	Cl H_3N CH_2 8.90; 4.14
29	$C_{18}H_{16}ClNO_5$	91	216	2.39 (Me)	8.10	7.25	7.45	7.20	7.00	7.00	7.00	7.20	Cl H_3N CH_2 8.95; 4.12
30	$C_{19}H_{13}F_3ClNO_5$	79	195	– (CF_3)	8.15	7.45	7.82	7.30	7.15	7.15	7.15	7.30	Cl H_3N CH_2 8.85; 4.16
31	$C_{18}H_{16}ClNO_5$	88	212	8.78 (H)	8.20	7.44	7.76	7.30	7.00	7.00	7.00	7.30	Cl H_3N CH CH_3 8.91; 4.43; 1.62
32	$C_{19}H_{18}ClNO_5$	87	205	2.39 (Me)	8.10	7.25	7.45	7.20	7.00	7.00	7.00	7.20	Cl H_3N CH CH_3 8.99; 4.43; 1.61
33	$C_{19}H_{15}F_3ClNO_5$	83	192	– (CF_3)	8.18	7.49	7.88	7.30	7.15	7.15	7.15	7.30	Cl H_3N CH CH_3 8.91; 4.42; 1.63
34	$C_{20}H_{20}ClNO_5$	86	209	8.79 (H)	8.18	7.44	7.78	7.30	7.10	7.10	7.10	7.30	Cl H_3N CH CH $(CH_3)_2$ 9.00; 4.18; 2.39; 1.14
35	$C_{21}H_{22}ClNO_5$	88	201	2.40 (Me)	8.10	7.25	7.45	7.20	7.00	7.00	7.00	7.20	Cl H_3N CH CH $(CH_3)_2$ 8.98; 4.17; 2.41; 1.14
36	$C_{21}H_{19}F_3ClNO_5$	76	196	– (CF_3)	8.18	7.50	7.93	7.30	7.15	7.15	7.15	7.30	Cl H_3N CH CH $(CH_3)_2$ 9.04; 4.15; 2.37; 1.14
37	$C_{21}H_{22}ClNO_5$	85	198	8.77 (H)	8.18	7.43	7.75	7.30	7.05	7.05	7.05	7.30	Cl H_3N CH CH_2 CH $(CH_3)_2$ 8.96; 4.25; 2.13; 1.51; 1.09
38	$C_{22}H_{24}ClNO_5$	79	189	2.39 (Me)	8.08	7.25	7.46	7.20	7.00	7.00	7.00	7.20	Cl H_3N CH CH_2 CH $(CH_3)_2$ 8.98; 4.24; 2.00; 1.59; 1.05
39	$C_{22}H_{21}F_3ClNO_5$	83	192	– (CF_3)	8.19	7.50	7.93	7.30	7.15	7.15	7.15	7.30	Cl H_3N CH CH_2 CH $(CH_3)_2$ 9.04; 4.26; 1.90; 1.90; 1.00
40	$C_{21}H_{22}ClNO_5$	82	196	8.78 (H)	8.18	7.47	7.79	7.30	7.05	7.05	7.05	7.30	Cl H_3N CH CH (CH_3) CH_2 CH_3 8.98; 4.22; 2.08; 1.03; 1.35; 1.03
41	$C_{22}H_{21}F_3ClNO_5$	86	189	– (CF_3)	8.16	7.48	7.89	7.30	7.15	7.15	7.15	7.30	Cl H_3N CH CH (CH_3) CH_2 CH_3 8.92; 4.24; 2.05; 1.05; 1.35; 1.05
42	$C_{20}H_{20}ClNO_5S$	76	218	8.78 (H)	8.20	7.46	7.79	7.30	7.05	7.05	7.05	7.30	Cl H_3N CH CH_2 CH_2 S CH_3 9.00; 4.46; 2.76; 2.34; 2.11
43	$C_{21}H_{22}ClNO_5S$	70	209	2.38 (Me)	8.09	7.25	7.45	7.20	7.00	7.00	7.00	7.20	Cl H_3N CH CH_2 CH_2 S CH_3 9.05; 4.47; 2.76; 2.32; 2.12
44	$C_{21}H_{19}F_3ClNO_5S$	78	206	– (CF_3)	8.10	7.45	7.65	7.30	7.10	7.10	7.10	7.30	Cl H_3N CH CH_2 CH_2 S CH_3 8.90; 4.46; 2.74; 2.34; 2.12
45	$C_{21}H_{20}ClNO_5$	79	215	2.33 (Me)	7.84	6.95	7.02	7.30	7.05	7.05	7.05	7.30	Cl H_3N CH_2 CH_2 CH_2 CH COO 9.10; 3.18; 1.91; 1.91; 4.22
46	$C_{21}H_{17}F_3ClNO_5$	81	206	– (CF_3)	8.10	7.45	7.68	7.30	7.10	7.10	7.10	7.30	Cl H_3N CH_2 CH_2 CH_2 CH COO 9.00; 3.19; 1.95; 1.95; 4.28
47	$C_{24}H_{20}ClNO_5$	90	226	2.39 (Me)	8.08	7.25	7.46	7.20	7.00	7.00	7.00	7.20	Cl H_3N CH CH_2 Ph 9.11; 4.55; 3.35; 7.39
48	$C_{25}H_{19}F_3ClNO_5$	86	208	– (CF_3)	8.19	7.42	7.62	7.30	7.10	7.10	7.10	7.30	Cl H_3N CH CH_2 Ph 9.14; 4.60; 3.35; 7.42
49	$C_{24}H_{20}ClNO_6$	88	206	8.76 (H)	8.15	7.32	7.45	7.30	7.10	7.10	7.10	7.30	Cl H_3N CH CH_2 (4-HOC_6H_4) 9.00; 4.46; 3.25; 9.55; 7.20; 6.79
50	$C_{25}H_{19}F_3ClNO_6$	79	200	– (CF_3)	8.13	7.38	7.64	7.30	7.10	7.10	7.10	7.30	Cl H_3N CH CH_2 (4-HOC_6H_4) 8.98; 4.49; 3.35; 9.49; 7.20; 6.76
51	$C_{27}H_{23}ClNO_5$	62	229	8.76 (H)	8.08	7.32	7.64	7.30	7.10	7.10	7.10	7.30	Cl H_3N CH CH_2 Indol NH 9.06; 4.50; 3.37; 7.0-7.4; 11.19

TABLE 3. Physicochemical Properties of N-(3-Phenoxychromonyl-7-hydroxyacetyl)amino Acid Derivatives **58**-**70**

Compound	Empirical formula	Yield %	mp, °C	PMR spectrum, δ, ppm										
				Chromone protons				Phenoxyl protons						Amino-acid protons
				2-R_1, s	5-H, d	6-H, dd	7-OCH_2CO, s	8-H, d	2-H, m	3-H, m	4-H, m	5-H, m	6-H, m	CONH	
58	$C_{22}H_{21}NO_7$	73	118	2.37 (Me)	7.98	7.12	4.76	7.29	7.18	6.98	6.98	6.98	7.18	8.63	CH_2 COO CH_2 CH_3 3.91; 4.13; 1.19
59	$C_{21}H_{19}NO_7$	69	106	7.99 (H)	8.23	6.95	4.62	7.00	7.30	7.06	7.06	7.06	7.30	7.32	CH (COOCH_3) CH_3 4.70; 3.79; 1.49
60	$C_{23}H_{23}NO_7$	66	95	7.99 (H)	8.23	6.95	4.64	7.00	7.30	7.06	7.06	7.06	7.30	7.32	CH (COOCH_3) CH $(CH_3)_2$ 4.68; 3.77; 2.23; 0.95
61	$C_{24}H_{25}NO_7$	64	89	7.98 (H)	8.20	6.95	4.62	7.02	7.30	7.05	7.05	7.05	7.30	7.34	CH (COOCH_3)CH_2 CH $(CH_3)_2$ 4.68; 3.75; 1.64; 1.64; 0.95
62	$C_{25}H_{27}NO_7$	61	81	2.41 (Me)	8.16	6.90	4.61	6.95	7.30	7.00	7.00	7.00	7.30	7.32	CH (COOCH_3)CH_2 CH $(CH_3)_2$ 4.69; 3.75; 1.65; 1.65; 0.93
63	$C_{24}H_{25}NO_7$	59	86	7.98 (H)	8.23	6.95	4.63	7.00	7.30	7.05	7.05	7.05	7.30	7.36	CH (COOCH_3) CH (CH_3) CH_2 CH_3 4.68; 3.76; 1.98; 0.96; 1.35; 0.93
64	$C_{23}H_{23}NO_7S$	62	123	7.99 (H)	8.23	6.95	4.64	7.00	7.30	7.05	7.05	7.05	7.30	7.36	CH (COOCH_3)CH_2 CH_2 S CH_3 4.86; 3.78; 2.52; 2.18; 2.08
65	$C_{24}H_{25}NO_7S$	68	113	2.41 (Me)	8.17	6.92	4.63	6.97	7.30	7.00	7.00	7.00	7.30	7.32	CH (COOCH_3)CH_2 CH_2 S CH_3 4.82; 3.78; 2.52; 2.18; 2.08
66	$C_{27}H_{23}NO_7$	69	126	7.98 (H)	8.20	6.90	4.58	7.00	7.30	7.00	7.00	7.00	7.30	7.35	CH (COOCH_3) CH_2 Ph 5.07; 3.76; 3.16; 7.28
67	$C_{27}H_{28}NO_8$	75	132	8.65 (H)	7.98	7.00	4.71	7.05	7.30	7.00	7.00	7.00	7.30	8.56	CH (COOCH_3) CH_2 (4-HOC_6H_4) 4.94; 3.63; 2.93; 9.24; 7.00; 6.66
68	$C_{23}H_{23}NO_7$	61	145	2.36 (Me)	7.96	6.95	4.88	7.00	7.30	7.00	7.00	7.00	7.30	8.35	CH (COOH) CH $(CH_3)_2$ 4.78; 12.5; 1.85; 0.97
69	$C_{24}H_{25}NO_7$	66	131	2.35 (Me)	7.96	6.95	4.67	7.00	7.30	7.00	7.00	7.00	7.30	8.22	CH_2 CH_2 CH_2 COOH 3.18; 1.68; 2.17; 12.10
70	$C_{26}H_{29}NO_7$	62	136	2.35 (Me)	7.98	6.95	4.66	7.00	7.30	7.00	7.00	7.00	7.30	8.20	CH_2 CH_2 CH_2 CH_2 CH_2 COOH 3.13; 1.2-1.8; 2.18; 12.00

Solvent: DMSO-d_6 – **58, 67**–**70**; $CDCl_3$ – **59**–**66**.

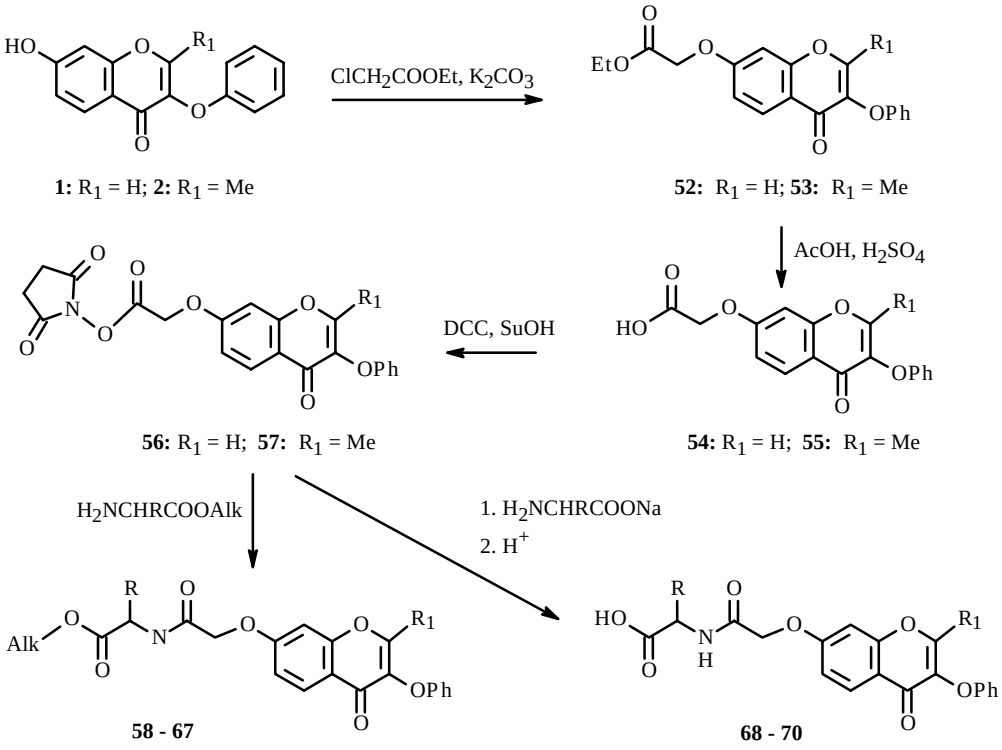
The PMR spectra of the synthesized compounds **4**-**27** contain signals for the chromone ring, the amino acid moiety, and the protecting group. A strong 9H singlet for the protons of the Boc group appears at 1.4-1.5 ppm. The signal of the amide appears at 5.0-5.2 ppm (using $CDCl_3$ solvent) or 6.5-6.7 ppm (acetone-d_6). The physicochemical properties and PMR data for the N-substituted 7-O-aminoacyl-3-phenoxychromones **4**-**27** are given in Table 1.

Hydrochlorides of 7-O-aminoacyl-3-phenoxychromones **28**-**51** were prepared via acidolysis of the corresponding Boc-derivatives by 3 M dry HCl in glacial acetic acid. The PMR spectra of **28**-**51** contain signals of the chromone and the amino-acid moieties. However, in contrast with the spectra of the starting Boc-derivatives, signals of the protecting group are absent. A signal for the protonated amino group near 9 ppm is observed instead of the amide signals. The physicochemical constants and PMR data of the hydrochlorides of 7-O-aminoacyl-3-phenoxychromones **28**-**51** are given in Table 2.

The second method for amino-acid modification of 3-phenoxychromones is based on activated esters. This method is widely used in peptide synthesis [5]. Alkylation of 7-hydroxy-3-phenoxychromones **1** and **2** by ethylchloroacetate in acetone in the presence of potash produces 7-ethoxycarbonylmethoxy-3-phenoxychromones **52** and **53**. Acidolysis of the ester group in these compounds by a mixture of glacial acetic and conc. H_2SO_4 gives the corresponding acids **54** and **55**. The carboxyl group is activated using N-hydroxysuccinimide esters, which are highly reactive and do not give racemized products [6]. The N-hydroxysuccinimide esters of 7-carboxymethoxy-3-phenoxychromones **56** and **57** were prepared in high yields by the reaction of the corresponding acids **54** and **55** with N-hydroxysuccinimide (SuOH) in absolute dioxane using DCC as the condensing agent [7, 8]. The PMR spectra of the activated esters **56** and **57** contain a 4H singlet at 2.9 ppm that is characteristic of the

succinimide.

Condensation of activated esters **56** and **57** with alkyl esters of the corresponding amino acids ($H_2NCHRCOOAlk$) in absolute THF at 0°C forms the amino-acid derivatives **58**-**67**. The ethyl esters of glycine (to give **58**) and methyl esters of L-alanine (**59**), L-valine (**60**), L-leucine (**61**, **62**), L-isoleucine (**63**), L-methionine (**64**, **65**), L-phenylalanine (**66**), and L-tyrosine (**67**) were used. The PMR spectra of **58**-**67** contain signals of the amino acid, chromone ring, and amide bond in the range 7.3-7.4 ppm (in $CDCl_3$) or 8.5-8.6 ppm (DMSO-d_6).



1: R_1 = H; **2:** R_1 = Me

52: R_1 = H; **53:** R_1 = Me

56: R_1 = H; **57:** R_1 = Me

54: R_1 = H; **55:** R_1 = Me

58 - 67

68 - 70

Reaction of activated ester **57** with sodium salts of amino acids ($H_2NCHRCOONa$) in THF—H_2O at room temperature followed by acidolysis gives amino-acid derivatives of 7-carboxymethoxy-2-methyl-3-phenoxychromone **68**-**70** with a free carboxyl group. Derivatives of L-valine (**68**), L-phenylalanine (**69**), and γ-aminobutyric acids (**70**) were obtained. The PMR spectra of **68**-**70** in DMSO-d_6 contain signals of the chromone, amino acid, and amide bond at 8.2-8.4 ppm and the carboxyl group at 12-13 ppm. The physicochemical constants and PMR data of the amino-acid derivatives of 7-carboxymethoxy-3-phenoxychromones **58**-**70** are given in Table 3.

EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC on Silufol UV-254 plates using $CHCl_3$—CH_3OH mixtures (9:1 and 95:5) as eluent. PMR spectra were measured on a Varian VXR-300 in DMSO-d_6, acetone-d_6, and $CDCl_3$ (TMS internal standard). Elemental analyses of all compounds corresponded to those calculated.

Starting 7-hydroxy-3-phenoxychromones **1**-**3** were prepared according to the literature methods [9, 10].

N-Substituted 7-O-Aminoacyl-3-phenoxychromones 4-27. A solution of the appropriate N-Boc-amino acid (9 mmol) in absolute THF (50 mL) was cooled to 0°C, stirred vigorously, and treated with DCC (0.92 g, 4.5 mmol). The reaction mixture was cooled for 1 h, treated with the corresponding 7-hydroxychromone (**1**, **2**, or **3**, 4 mmol) and DMAP (20 mg), and stirred and cooled (0°C) for 0.5-1 h (completion of the reaction was determined by TLC). The precipitated dicyclohexylurea was filtered off. The solvent was removed under vacuum. The oil was dissolved in ethylacetate (50 mL) and treated successively in a separatory funnel with $NaHCO_3$ solution (5%, 2×50 mL), water (50 mL), and saturated NaCl solution (50 mL). The organic layer was dried over anhydrous $MgSO_4$. The solvent was removed under vacuum. The solid was crystallized from propan-2-ol. Yields and constants of **4**-**27** appear in Table 1.

Hydrochlorides of 7-O-Aminoacyl-3-phenoxychromones 28-51. A cooled solution of 7-O-(N-Boc-aminoacyl)chromone (**4-27**, 2 mmol) in absolute THF (5 mL) was treated with a cooled (0°C) solution (3 M, 10 mL) of dry HCl in glacial acetic acid. The reaction mixture was stirred for 0.5-1 h (completion of the reaction was determined by TLC), treated with absolute ether (100 mL), and held at 0°C for 1 h. The precipitate was filtered off and dried under vacuum over NaOH. Yields and constants of obtained hydrochlorides **28-51** appear in Table 2.

7-Ethoxycarbonylmethoxy-3-phenoxychromones 52 and 53. A hot solution of 7-hydroxychromone (**1** or **2**, 50 mmol) in absolute acetone (100 mL) was stirred vigorously, treated with freshly calcined potash (20.7 g, 150 mmol) and ethylchloroacetate (5.9 mL, 55 mmol), held at 50-60°C with vigorous stirring for 3-4 h (completion of the reaction was determined by TLC), cooled, transferred into ice water (500 mL), and acidified until the pH was 5-6. The precipitate was filtered off and crystallized from propan-2-ol (75%).

7-Ethoxycarbonylmethoxy-3-phenoxychromone 52: $C_{19}H_{16}O_6$, yield 88%, mp 175°C. PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.32 (3H, t, CH_3), 4.30 (2H, q, CH_2), 4.73 (2H, s, $OOCCH_2O$-7), 6.87 (1H, dd, J = 2.0, 8.0, H-6), 7.00 (1H, d, J = 2.0, H-8), 7.05 (2H, m, H-2 and H-6 of phenoxyl), 7.27 (3H, m, H-3, H-4, and H-5 of phenoxyl), 7.96 (1H, s, H-2), 8.18 (1H, d, J = 8.0, H-5).

7-Ethoxycarbonylmethoxy-2-methyl-3-phenoxychromone 53: $C_{20}H_{18}O_6$, yield 87%, mp 164°C. PMR spectrum [300 MHz, $(CD_3)_2CO$, δ, ppm, J/Hz]: 1.28 (3H, t, CH_3 of ethoxycarbonyl), 2.38 (3H, s, CH_3-2), 4.25 (2H, q, CH_2), 4.93 (2H, s, $OOCCH_2O$-7), 6.95 (1H, dd, J = 2.0, 8.0, H-6), 7.05 (1H, d, J = 2.0, H-8), 7.15 (2H, m, H-2 and H-6 of phenoxyl), 7.30 (3H, m, H-3, H-4, and H-5 of phenoxyl), 8.01 (1H, d, J = 8.0, H-5).

7-Carboxymethoxy-3-phenoxychromones 54 and 55. A mixture of ester **52** or **53** (40 mmol), glacial acetic acid (30 mL), and conc. H_2SO_4 (10 mL) was held at 60-80°C for 2-3 h (completion of the reaction was determined by TLC), cooled, and transferred into ice water (300 mL). The precipitate was filtered off and crystallized from aqueous propan-2-ol.

7-Carboxymethoxy-3-phenoxychromone 54: $C_{17}H_{12}O_6$, yield 85%, mp 218°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 4.90 (2H, s, $OOCCH_2O$-7), 6.95 (1H, dd, J = 2.0, 8.0, H-6), 7.00 (2H, m, H-2 and H-6 of phenoxyl), 7.05 (1H, d, J = 2.0, H-8), 7.40 (3H, m, H-3, H-4, and H-5 of phenoxyl), 8.01 (1H, d, J = 8.0, H-5), 8.64 (1H, s, H-2), 13.0 (1H, s, COOH).

7-Carboxymethoxy-2-methyl-3-phenoxychromone 55: $C_{18}H_{14}O_6$, yield 92%, mp 204°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.36 (3H, s, CH_3-2), 4.88 (2H, s, $OOCCH_2O$-7), 6.95 (1H, dd, J = 2.0, 8.0, H-6), 7.05 (1H, d, J = 2.0, H-8), 7.10 (2H, m, H-2 and H-6 of phenoxyl), 7.30 (3H, m, H-3, H-4, and H-5 of phenoxyl), 7.95 (1H, d, J = 8.0, H-5), 13.0 (1H, s, COOH).

N-Hydroxysuccinimide Esters of 7-Carboxymethoxy-3-phenoxychromones 56 and 57. A cooled solution of **54** or **55** (20 mmol) and N-hydroxysuccinimide (2.54 g, 22 mmol) in absolute dioxane (50 mL) was treated with DCC (4.12 g, 20 mmol) and held for 1-2 h with vigorous stirring at 0°C (completion of the reaction was determined by TLC). The precipitate of dicyclohexylurea was filtered off. The solvent was removed under vacuum. The oil was crystallized from propan-2-ol.

N-Hydroxysuccinimide ester of 7-carboxymethoxy-3-phenoxychromone 56: $C_{21}H_{10}NO_8$, yield 79%, mp 159°C. PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.88 (4H, s, CH_2CH_2 of N-hydroxysuccinimide), 5.09 (2H, s, $OOCCH_2O$-7), 6.87 (1H, dd, J = 2.0, 8.0, H-6), 7.00 (1H, d, J = 2.0, H-8), 7.05 (2H, m, H-2 and H-6 of phenoxyl), 7.26 (3H, m, H-3, H-4, and H-5 of phenoxyl), 7.98 (1H, s, H-2), 8.22 (1H, d, J = 8.0, H-5).

N-Hydroxysuccinimide ester of 7-carboxymethoxy-2-methyl-3-phenoxychromone 57: $C_{22}H_{12}NO_8$, yield 74%, mp 148°C. PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.36 (3H, s, CH_3-2), 2.85 (4H, s, CH_2CH_2 of N-hydroxysuccinimide), 5.04 (2H, s, $OOCCH_2O$-7), 6.95 (1H, dd, J = 2.0, 8.0, H-6), 7.03 (1H, d, J = 2.0, H-8), 7.10 (2H, m, H-2 and H-6 of phenoxyl), 7.30 (3H, m, H-3, H-4, and H-5 of phenoxyl), 8.01 (1H, d, J = 8.0, H-5).

Esters of N-(7-Carbonylmethoxy-3-phenoxychromone)-amino Acids 58-67. A suspension of the corresponding alkylamino-acid hydrochloride (3.5 mmol) in absolute THF (20 mL) was vigorously stirred and cooled to 0°C, treated dropwise with triethylamine (0.42 mL, 3.5 mmol), and vigorously stirred for 30 min. The precipitate of triethylamine hydrochloride was filtered off. The filtrate was treated with activated ester **56** or **57** (3 mmol) in absolute THF (10 mL), vigorously stirred for 2 h at 0°C, and held at room temperature for 10-12 h. The solvent was removed under vacuum. The solid was dissolved in ethylacetate (50 mL) and treated in a separatory funnel successively with H_2SO_4 (1 N, 50 mL), water (50 mL), $NaHCO_3$ solution (5%, 50 mL), water (30 mL), and saturated NaCl solution (50 mL). The organic layer was dried over anhydrous $MgSO_4$. The solvent was removed under vacuum. The oil was crystallized by treatment with diethylether. Yields and physicochemical constants of prepared compounds **58-67** appear in Table 3.

N-(7-Carbonylmethoxy-2-methyl-3-phenoxychromone)amino Acids 68-70. A solution of the appropriate amino

acid (3.5 mmol) in NaOH solution (7 mL, 0.5 M, 3.5 mmol) was treated with activated aster **57** (1.27 g, 3 mmol) in THF (10 mL), vigorously stirred for 1 h at room temperature (completion of the reaction was determined by TLC), treated with distilled water (100 mL), and acidified until the pH was 5-6. The precipitate was filtered off and crystallized from aqueous propan-2-ol. Yields and physicochemical constants of compounds **68**-**70** appear in Table 3.

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