SYNTHESIS OF 1-PHENYL-3-(CHROMON-3-YL)-2-PROPEN-1-ONE DERIVATIVES: A NEW GROUP OF BIOLOGICALLY ACTIVE COMPOUNDS

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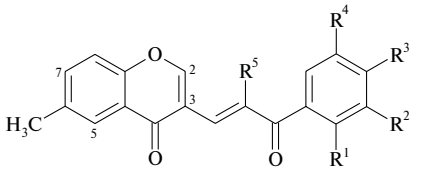
There are numerous published data showing evidence of a broad spectrum of pharmacological activity inherent in 1,3-diphenylpropenone (chalcone) derivatives [1]. By substituting the residues of various heterocycles for one or both benzene nuclei in the chalcone molecule, it is possible not only to introduce an additional pharmacophore into the base structure, but to modify more significantly (as compared to simple functionalization of the benzene nucleus) the character of electron density distribution on the propenone fragment. In our opinion, selection of the chromon-3- yl residue can simultaneously increase the antiallergic activity and decrease the toxicity of chalcone derivatives [2 – 4].

In accordance with this prognosis, we have synthesized a series of 1-phenyl-3-(6-methylchromon-3-yl)-2-propen-1-one derivatives (I – XVI) of the general structural formula



I –XVI

With substituents R^1 – R^5 listed in Table 1.

A conventional method for the synthesis of chalcones employs the base-catalyzed Claisen – Schmidt condensation. We have used an alternative variant of the reaction between reagents offered by the acid catalysis. The synthesis was conducted in anhydrous acetic acid in the presence of a catalytic amount of perchloric acid (method A). Under these conditions, the reactions of 3-formyl-6-methylchromone with substituted acetophenones yield chalcones I – XI (Table 1).

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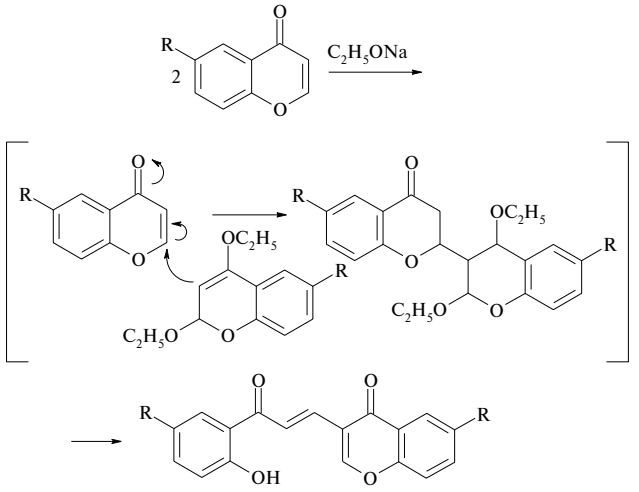
TABLE 1. The Yields and Some Physicochemical Properties of 1-Phenyl-3-(6-methylchromon-3-yl)-2-propen-1-one Derivatives

Compound	R^1	R^2	R^3	R^4	R^5	M.p., °C	Yield, %	IR spectrum (vaseline oil): ν, cm^{-1}
I	H	H	H	H	H	163 – 164	73	1665, 1630, 1595, 1010
II	CH_3	H	CH_3	H	H	181 – 182	75	1666, 1640, 1600, 980
III	H	H	Ph	H	H	193 – 195	62	1670, 1630, 1590, 1005
IV	H	H	OH	H	H	239 – 240	54	1670, 1610, 1570, 985
V	H	*t*-Bu	OH	*t*-Bu	H	205 – 207	48	1665, 1630, 1600, 990
VI	H	H	OCH_3	H	H	176 – 177	62	1660, 1640, 1600, 990
VII	H	H	F	H	H	159 – 161	76	1670, 1635, 1600, 990
VIII	H	H	Cl	H	H	195 – 197	71	1670, 1630.1600, 985
IX	H	Cl	Cl	H	H	225 – 226	85	1665, 1640, 1605, 980
X	H	H	Br	H	H	204 – 205	78	1670, 1595, 1530, 1010
XI	H	H	NO_2	H	H	253 – 254	82	1670, 1630, 1590, 985
XII	OH	H	H	H	H	196 – 197	63	1653, 1613, 987
XIII	OH	H	H	CH_3	H	208 – 209	65	1653, 990
XIV	OH	H	H	OCH_3	H	211 – 213	68	1626, 1600, 980
XV	OH	H	H	Cl	H	243 – 244	73	1640, 1627, 974
XVI	OH	H	H	H	CH_3	131 – 132	58	1653, 1627, 1600

Since the endocyclic carbonyl group of 3-formylchromone is a stronger acceptor of proton than is the formyl group occurring in the side chain [5], we may suggest that an active intermediate in the acid-catalyzed reactions of chromone-3-carboxaldehyde with acetophenones is the pyrylium salts. In connection with this, we have studied the interaction of the reagents in a mixture of triethylorthoformate and 70% perchloric acid. This reaction proceeds with the formation of perchlorates of 3-(1-(R-benzoyl)-2-ethylene)-4-ethoxy-6-methylchromylium salts, the hydrolysis of which leads with a quantitative yield to the target products (method B). This method was used for the synthesis of chalcones I, II, VI, VIII, and XI.

Our attempts at conducting the condensation of 3-formylchromone with *ortho*-hydroxyacetophenones by method A were unsuccessful, apparently because of the decrease in the nucleophilicity of ketone as the result of formation of an intramolecular hydrogen bond. Using method B leads to the formation of cyclization products, 2- (6-methylchromon-3-yl)chromones. The method for the synthesis of chromone analogs of *ortho*-hydroxychalcone described in [6] is based on the dimerization of 2,3-unsubstituted chromones in an alkaline medium. Unfortunately, this method is characterized by the limited possibility of varying substituents $R^1 – R^5$, which is explained by certain features of the reaction chemistry.

In this context, we decided to convert the initial 2-hydroxyacetophenones into 2,2-difluoro-4-methylbenzo-[e]-1,3,2-dioxaborine derivatives [7]. Reactions of these derivatives with 6-methylchromone-3-carboxaldehyde in acetic acetic led to a quantitative yield of 1-(6-methylchromon-3-yl)-2-(2,2-difluorobenzo-[e]-1,3,2-dioxaborin-4-yl)ethylene derivatives. Treatment of the latter compounds with sodium hydrocarbonate in ethanol allowed us to obtain the target products XII – XVI (method C).

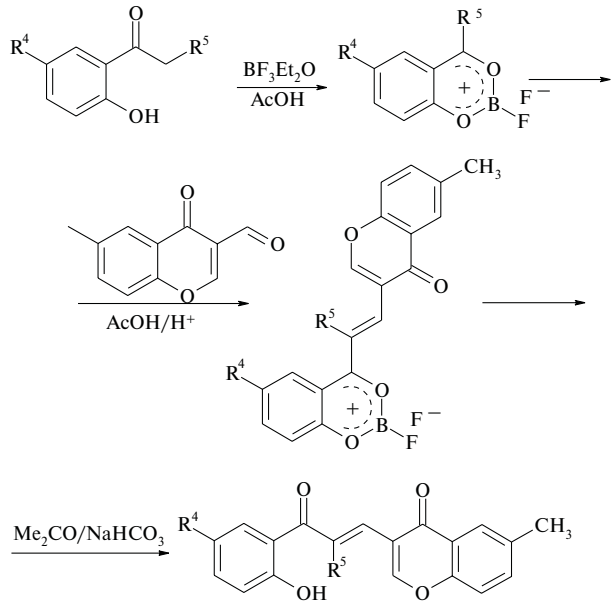


In the IR spectra of the synthesized compounds, the highest frequency band in the characteristic absorption range of 1700 – 1500 cm $^{-1}$ was assigned to stretching vibrations of the carbonyl group in the propenone fragment. As is known, the introduction of electron donor substituents at positions 4 or 4′ of the chalcone molecule leads to a shift of the electron density toward the carbonyl group and decreases polarization of this group, which is accompanied by a decrease in the frequency and integral intensity of the stretching vibrations ν(C=O); electron acceptors substituted at the same positions produce the opposite effect [8]. This behavior was observed for the absorption band in the region of 1670 – 1650 cm $^{-1}$.

The stretching vibrations of the carbonyl group in the chromone cycle were manifested at 1640 – 1620 cm $^{-1}$. This decrease in the ν(C=O) frequency as compared to the value (1660 cm $^{-1}$) in unsubstituted chromone can be explained by the increase in contribution of the betaine pyrylium moiety to the ground state of the chromone molecule.

The intense band in the region of 1600 cm $^{-1}$ was attributed to the stretching vibrations of the vinylene group of the propenone fragment. The medium-intensity band in the region of 1000 – 980 cm $^{-1}$, characteristic of the out-of-plane bending vibrations of disubstituted ethylene derivatives, is evidence of the transoidal configuration of the synthesized compounds. The intensity of the band due to the stretching vibrations of an exocyclic double bond was significantly greater as compared to the ν(C=O) intensity, which is evidence in favor of the *s-cis* arrangement of the carbonyl and vinylene groups.

The ^{1}H NMR spectra of the synthesized compounds contain two doublets in the intervals of 8.6 – 8.7 and 7.4 – 7.5 ppm, which is a manifestation of the AB system of vinylene protons. The value of the spin – spin coupling constant, J_{ab} = 15.5 ± 0.3 Hz (typical of the *trans*-disubstituted ethylenes), is indicative of the E-configuration of the chromone analogs of chalcone.



XII – XVI

As is known, the chemical shifts of olefin protons in 4,4′-disubstituted chalcones depend linearly on the electron properties of subsitituents and are described by the Hammett equation [1]. However, variation of substituents in the benzene ring of compounds I – XI did not significantly influence the chemical shifts of olefin protons, which is evidence of the weak electron interaction in the 1-phenylpropenone fragment. This can be explained by the phenyl ring being displaced out of the plane of the molecule.

The proton in position 2 of the chromone nucleus shows up as a narrow singlet in the region of 8.1 – 8.2 ppm. Such a significant descreening can be explained by the localization at C_2 of a positive charge appearing due to the electron acceptor properties of the substituent in position 3.

The signal from proton at C_5 is also shifted toward weaker fields (δ = 8.06 – 8.21 ppm), which is explained by the character of the electron density distribution in the molecule and by the magnetic anisotropy of the *peri*-carbonyl group of the heterocycle. This signal has the form of a doublet with *meta* constants J = 2.6 Hz.

Table 2 presents a computer-predicted pharmacological activity spectrum of the synthesized compounds. The prognosis was obtained using the PASS program (Version 4.2, 1996). The high probability (79 – 92%) of antiallergic activity manifestations confirms the expediency of combining the benz-γ-pyrone and 1-phenylpropen-2-one fragments in the same structure. The probability of manifestation of histamine receptor blocking activity is much lower (26 – 51%). In our opinion, of special interest is the prediction of GABAergic and tranquilizer properties. Taking into account that the synthesized compounds involve no nitrogen-containing substituents, numerical estimates of the probability of manifestation of these activity types are rather high (67 – 73 and 30 – 47%, respectively). The ability of flavones (chrysin, apigenin, and related synthetic derivatives) to interact with benzodiazepine receptors of the brain and produce an anxiolytic effect comparable with that of diazepam [9] is known. This is also indicative of the promising search for new neurotropic agents in the series of 1-phenyl-3-(6-methylchromon-3-yl)-2-propen-1-one derivatives.

EXPERIMENTAL PART

The ^{1}H NMR spectra were measured on a Bruker WP-300 spectrometer with a working frequency of 300 MHz. The samples were studied as solutions in deuterated chloroform with a concentration of 0.3 – 0.5 mole/liter; the internal standard was HMDS or $CDCl_3$. The IR absorption spectra in a 600 – 3600 cm^{-1} range were recorded on Specord 74-IR and Specord 75-IR spectrophotometers using samples prepared as suspensions in Vaseline oil. The course of reactions was monitored and the purity of the reaction products was checked by TLC on Silufol UV-254 plates eluted in toluene – hexane (9 : 1), butanol – acetic acid – water (5 : 3 : 2), and toluene – ethanol (9 : 1) systems; the spots were revealed under UV irradiation.

The initial acetophenones were synthesized by acylating benzenes according to the Friedel – Crafts reaction [10]; 6-methylchromone-3-carboxaldehyde was obtained as described in [11].

1-Phenyl-3-(6-methylchromon-3-yl)-2-propen-1-one derivatives (I – XI).

Method A. To a mixture of 1.88 g (10 mmole) of 6-methylchromone-3-carboxaldehyde and 10 mmole of the corresponding acetophenone, dissolved on heating in 10 ml of glacial acetic acid, was added 0.03 ml of a 70% perchloric acid solution. The reaction mixture was heated for 30 – 60 min at 80 – 90°C and cooled. The precipitate was separated by filtration and washed with 20 ml of hexane. The obtained ketone was recrystallized from *n*-butanol or benzene.

Method B. To a mixture of 1.88 g (10 mmole) of 6-methylchromone-3-carboxaldehyde and 10 mmole of the corresponding acetophenone, dissolved in 10 ml of freshly distilled triethylorthoformate, was added 1 ml of a 70% perchloric acid solution. The reaction mixture was heated for 15 min on a water bath and allowed to stand for 1 – 3 h at room temperature. The precipitate was separated by filtration and washed with 30 ml of dry diethyl ether. The obtained 3-(1-(R-benzoyl)-2-ethylene)-4-ethoxy-6-methylchromylium perchlorate was crystallized from glacial acetic acid. To 1.0 g of this perchlorate dissolved on heating in 15 ml of acetone was added dropwise 5 ml of a 20% aqueous solution of sodium acetate. The target chalcone, which precipitated on cooling, was separated by filtration, washed with water, dried, and recrystallized from toluene.

1-(2-Hydroxyphenyl)-3-(6-methylchromon-3-yl)-2-propen-1-one derivatives (XII – XVI).

TABLE 2. Biological Activity Spectrum Predicted for 1-Phenyl-3-(6-methylchromon-3-yl)-2-propen-1-one Derivatives

Compound	Probability of activity manifestations, %						
	Antiallergic	GABAergic	Antioxidant	Analeptic	Tranquilizer	Respiratory analeptic	Antihistamine
I	92	72	51	65	42	60	51
II	92	72	51	65	42	60	51
III	85	66	51	55	30	50	31
IV	87	67	63	66	28	60	42
V	88	63	65	61	28	55	43
VI	90	68	49	65	40	62	49
VII	84	75	33	58	47	53	36
VIII	86	68	36	58	35	54	42
IX	77	70	27	51	36	44	28
X	81	70	39	54	36	49	37
XI	86	73	46	59	35	55	35
XII	88	69	64	61	25	55	40
XIII	88	69	64	61	25	55	40
XIV	84	65	63	58	–	54	36
XV	79	67	39	48	30	39	26
XVI	71	64	46	67	–	59	27

Method C. To 1.88 g (10 mmole) of 6-methylchromone-3-carboxaldehyde dissolved on heating in 15 ml of acetic acid was added 10 mmole of the corresponding 2,2-difluoro-4-methylbenzo-[e]-1,3,2-dioxaborine derivative and the reaction mixture was heated for 30 – 60 min at 80 – 90°C and cooled. The precipitated 1-(6-methylchromon-3-yl)-2-(2,2-difluoro-4-methylbenzo-[e]-1,3,2-dioxaborin-4-yl)ethylene was separated by filtration, washed with ether, and dissolved in 20 ml of ethanol. To the hot solution was added dropwise 5 ml of a 20% aqueous solution of sodium hydrocarbonate. The target compound precipitating on cooling was separated by filtration, washed with water, dried, and recrystallized from ethanol.

The biological activity spectrum was predicted using the PASS 4.2 (1996) program developed by V. V. Poroikov and D. A. Filimonov.

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