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METHODS OF PROTECTION/DEPROTECTION OF HYDROXY GROUPS IN THE SYNTHESIS OF POLYHYDROXY FLAVONOLS

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The article represents a review of methods for obtaining polyhydroxy flavonols without protection of hydroxy groups, as well as syntheses using methylation, alkylation and benzylation of the initial reagents and, accordingly, demethylation, dealkylation and debenzylation of the final flavonols. It is shown that the most convenient for the synthesis of natural polyhydroxy flavonols and their analogues is the debenzylation reaction using a Pd/C catalyst in tetrahydrofuran, which allows to obtain flavonols containing both hydroxy and methoxy groups. Syntheses using benzylation/debenzylation reactions are easily scaled up, which allows to obtain of large quantities of polyhydroxy flavonols, in addition, the latter do not contain impurities of hydrogen halides, which makes it possible to use the obtained flavonols in the pharmaceutical and food industries.

The syntheses of hydroxy flavonols with a pyrogallol-like structure of the side phenyl ring were carried out, and the natural flavonol fisetin, a promising medicinal product and component of food additives, was obtained through benzylation/debenzylation reactions. effect of ensitrelvir are found in the 1-methyl-1*H*-1,2,4-triazole and 6-chloro-2-methyl-2*H*-indazole fragments.

Keywords: Flavonols, flavonol synthesis, Algar-Flynn-Oyamada reaction, hydroxy group protection.

Introduction

Flavonoids are biologically active substances widespread in plants and fungi [1]. Of greatest interest are the derivatives of 3-hydroxy-2-phenylbenzo-γ-pyrone – flavonols (Figure 1), which are powerful antioxidants, carcinostatics, and have anti-inflammatory properties [2]. Flavonols are also used as complexing agents in the fluorescence analysis of some metal ions; the use of flavonols increases the efficiency of metal ion extraction [3, 4]. In addition, flavonols are convenient models for studying the excited-state intramolecular proton-transer reaction [5].

The greatest biological activity is demonstrated by polyhydroxy derivatives of flavonols containing two to five hydroxy groups. Thus, 5,7,3',4'-tetrahydroxyflavonol (quercetin) is used as a medicine in cardiology and phlebology, the diglucoside (rutinoside) of this compound - rutin is used as a medicinal form of vitamin P [6, 7]. Currently, 7,3',4'-trihydroxyflavonol - fisetin, demonstrating neurotropic activity that supports the survival, differentiation, and functional maintenance of brain cells, is beginning to be used as a medicine [8].

Currently, flavonols for medicinal use are extracted from plant raw materials. The processes of extraction and purification of these compounds are labor-intensive, which determines the high cost of the final product. Therefore, the development of effective and cheap methods for synthesizing polyhydroxyflavonols is currently very relevant.

There are several routes to synthesizing flavonols, the most commonly used being the oxidative cyclization method. Typically, the first step involves synthesizing 2'-hydroxychalcone, which is then followed by the Algar-Flynn-Oyamada cyclization reaction in the presence of hydrogen peroxide [9, 10]. This method is widely used to obtain synthetic derivatives of flavonols containing amino groups, nitro groups, halogens, and to obtain heteroaromatic analogs of flavonols whose side ring is substituted with pyridine, benzadiazole, or thiazole fragments. However, the synthesis of natural flavonols containing a large number of hydroxyl groups is associated with certain difficulties. Condensation of the corresponding hydroxy acetophenones and hydroxy aldehydes is most often carried out in a highly alkaline medium or in a basic solvent. This leads to the dissociation of hydroxy groups, forming unstable anionic forms that are oxidized by atmospheric oxygen and are less active in aldol condensations when obtaining intermediate hydroxy chalcones. The Algar-Flynn-Oyamada reaction is also carried out in an alkaline medium, where the resulting hydroxychalcone anions are oxidized by hydrogen per-

oxide, which is used as a mandatory reagent. In this case, protection of the hydroxy groups is logical, but this protection must occur selectively and not affect the 2'-hydroxy group of acetophenone and the chalcone derivative.

In this article, we briefly reviewed methods for the synthesis of polyhydroxy flavonols containing the pyrogallol-like 3',4'-dihydroxy groups in the side benzene ring, which are most susceptible to oxidation. We also discuss the possibility of obtaining partially methylated derivatives typical for many natural compounds. Basing the information obtained, we carried out regioselective syntheses of 3',4'-R-hydroxyflavonols and the natural flavonol fisetin using the debenzylation reaction. The structures of the obtained flavonols are shown in Table 1.

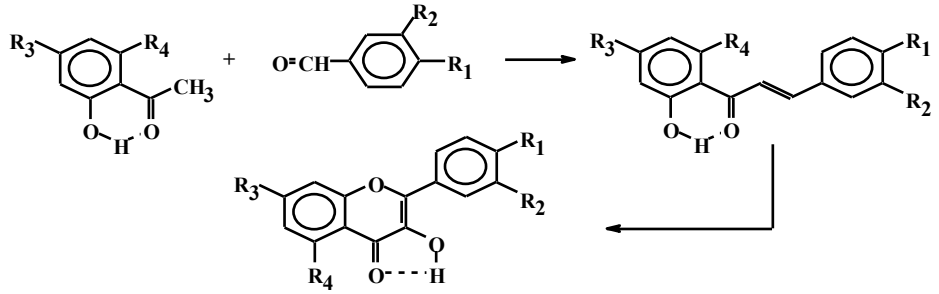
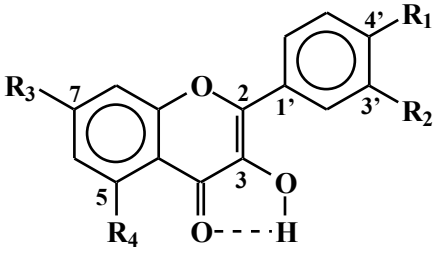


Figure 1. Scheme of flavonols' synthesis according to Algar-Flynn-Oyamada reaction

Table 1. Structures of synthesized flavonol derivatives*



	Substituents			
	R_1 (C4')	**R_2** (C3')	**R_3** (C7)	**R_4** (C5)
flavonol	H	H	H	H
1	OBn	OBn	H	H
2	OH	OH	H	H
3	OBn	OMe	H	H
4	OH	OMe	H	H
5	OMe	OBn	H	H
6	OMe	OH	H	H
7	OBn	OBn	OBn	H
fisetin	OH	OH	OH	H

* OBn – benzyloxy-, OMe – methoxy- substituents.

Matherials and Methods

Commercial reagents were used for the synthesis and physicochemical studies of the flavonol structure. The purification degree of intermediate and final reaction products was controlled using an Agilent 1100 high-performance liquid chromatograph with a SUPELCO Ascentis Express C18 chromatographic column 2.7 μm 4.6 mm x 15 cm.

Identification of compounds was conducted by mass spectrometry using an Agilent LC/MSD SL mass-selective detector. 1H NMR spectra were recorded using Unity Inova 400, Bruker Avance DRX 500 and Bruker Avance III 400 MHz spectrometers in DMSO-d6. 13C NMR spectra were recorded on Bruker Avance DRX 500 and Agilent ProPulse 500 MHz spectrometers at a working frequency of 126 MHz in DMSO-d6. Chemical shifts are presented in δ (ppm) scale. The reaction progress and the individuality of the obtained substances were monitored by TLC on silica gel-coated Polychrome SI F254 plates with a fluorescent detector in a hexane-ethyl acetate 2:1 system. Melting points are performed using Hanon Instruments MP450 Automatic Melting Temperature Controller.

Results and Discussion

Analysis of scientific publications allowed us to identify two strategies for the synthesis of polyhydroxy flavonols (PHF): obtaining final products from the corresponding acetophenones and aldehydes without the protection of hydroxy groups, as well as synthesis with preliminary protection of most hydroxy groups of the starting reagents (except for the 2-hydroxy group of acetophenones). Methylation and benzylation were most frequently used to protect hydroxyl groups.

As noted above, carrying out the reaction in an alkaline medium leads to partial oxidation of both the initial reagents – hydroxy benzaldehydes and acetophenones, the intermediate products – polyhydroxy chalcones, as well as the final flavonols initially formed in the anionic form. Nevertheless, the authors of works [11-13] attempted direct synthesis of hydroxy flavonols without protecting hydroxy groups. The synthesis of flavonols with hydroxy groups in the C3' and C4' positions of the side benzene ring was described in [11]. To prevent oxidation, the synthesis was carried out in a nitrogen atmosphere. The yield of the final compounds was 40-48%. The yield of 3'-hydroxy flavonol obtained in the same synthetical way but in the presence of air decreased to 33% [12]. A compound with an additional 7-hydroxy group was obtained with a lower yield. The authors of [13] performed syntheses of various flavonols in one and two stages, but they failed to reproduce the syntheses of polyhydroxy flavonols described in [11] and [12]. We also failed to reproduce the synthesis of 4'-hydroxyflavonol: the compound was obtained in low yield (<10%), and a high degree of resinification of the final flavonol was observed when carrying out the Algar-Flynn-Oyamada reaction. Also, when purifying the latter by column chromatography on silica gel, the flavonol partially decomposes during the separation process upon contact with the sorbent.

The second method of synthesis is based on selective methylation, ethylation or butylation of hydroxy groups in the initial acetophenones and aldehydes, obtaining alkoxy derivatives of 2'-hydroxychalcone in the first stage of synthesis, with subsequent cyclization of the latter into polyalkoxy flavonols. Depending on the position of the alkoxy groups, the final yield of flavonols is within 15-40%. The last stage of the PHF synthesis is the removal of protective alkyl groups. In this case, a 57% aqueous solution of hydroiodic acid is frequently used for dealkylation of flavonols [14]. The yield of polyhydroxy flavonols in the HI-assisted dealkylation reaction is 40-60%. Demethylation of flavonols with hydroiodic acid is also carried out in solutions of acetic acid [15] or acetic anhydride [16, 17] in the presence of phenol [18] followed by extraction of the reaction mixture with ethyl acetate. In this case, the demethylation yields of reactions are in the range of 50–75%.

Demethylation in aqueous HBr solutions occurs with a yield of approximately 20% [19], in glacial acetic acid and in an inert atmosphere the reaction yield increases to 65% [20]. Demethylation of 3'- and 4'-hydroxy groups of flavonols using HCl in glacial hydrochloric acid has also been described [21], in that case, polyhydroxy flavonols were obtained with a yield of 70–72%.

A less common method used to remove protective alkyl groups is dealkylation with BBr_3 in dry dichloromethane, under an inert gas atmosphere and at –78°C [21] or by heating to 50°C [22]. The yield of dealkylated compounds depends on the location of the protected groups and the presence of other substituents and generally ranges from 50–70%.

All methods for obtaining hydroxy flavonols from initial methylated (alkylated) reagents with subsequent demethylation (dealkylation) of the final compound are characterized by a number of disadvantages – first of all, the difficult purification of flavonols from traces of acetic acid and hydrogen halides. The presence of traces of the latter in polyhydroxyflavonols limits their use as pharmaceuticals and components of food additives. In addition, none of the listed methods allows regioselective demethylation of flavonols. Since natural flavonoids can simultaneously have hydroxy and methoxy groups, it is not possible to obtain such compounds using the above dealkylation methods. Even if the molecule contains different protective fragments, such as methoxy, butoxy or benzyloxy groups, the use of the above methods leads to their complete and non-selective removal.

Comparison of the synthetical methods showed that the most convenient is the protection of hydroxy groups of the initial reagents with benzyl residues, as well as the debenzylation of finally obtained benzyloxy flavonols. As noted above, the benzyl group can be removed with hydrohalic acids in concentrated acetic acid. For weaker acid HCl, it is necessary to heat the reaction mixture to boiling [21, 23], the reaction with stronger HBr occurs at room temperature [24]. The yields of the debenzylation reaction are 45-70% and 60-80%, respectively, depending on the location of the benzyloxy groups in the molecule. Benzyloxy groups are also removed with $TiCl_4$ [25] with a hydroxyflavonols' yield of 64%, and trifluoroacetic acid in the presence of thioanisole as a catalyst [26, 27] with yields of debenzylated compounds of 30-60%.

The use of the BBr3 reagent in dichloromethane [21] is non-selective and results in the removal of not only benzyloxy but also any other alkoxy substituents. In addition, the yield of debenzylated derivatives for various compounds can vary widely from 30 to 95%.

Recently, the removal of benzyl fragments by catalytic hydrogenation in the presence of a Pd/C catalyst, metallic palladium adsorbed on a carbon carrier, has become widespread [28, 29]. The use of palladium compounds as a catalyst, for example, Pd(OH)2/C, is undesirable in the case of polyhydroxyflavonols since it leads to the formation of colored flavonol-palladium complexes [30]. Pd/C catalysts are renewable, non-toxic, used in the food and pharmaceutical industries, and therefore are most suitable for the synthesis of analogs of natural flavonols.

Tetrahydrofuran, methanol, ethanol, ethyl acetate, or their mixtures in various ratios are used as solvents in debenzylation reactions [31–34]. However, when scaling up reactions to 1–10 grams, the reproducibility of the methods with MeOH [35, 36], EtOAc [37], and EtOH [38, 39] turned out to be low, with yields of 30–40%. This is due to the extremely low solubility of benzyloxy derivatives of flavonols in the indicated solvents. The best reproducibility during the scaling up of syntheses was noted when using tetrahydrofuran [40] as a solvent. In our experiments, the use of 10–20 volume equivalents of tetrahydrofuran relative to the starting materials provided high yields in the range of 75–95%.

Taking into account the possibility of carrying out regioselective synthesis using debenzylation reactions of flavonols, we obtained compounds with different arrangements of hydroxy and methoxy groups and also synthesized the natural flavonol fisetin with the protection of hydroxyls by benzyl groups with subsequent debenzylation reaction. Typical methods of flavonol synthesis are described below. The results of physicochemical studies of the structure of the obtained compounds are given in Tables 2-4.

General Procedure for the Synthesis of Chalcones. Under a nitrogen atmosphere, a suspension of NaH (6.5 mmol, 60% dispersion in mineral oil) in DMF (20 mL) was cooled to 0 °C. A solution of 2'-hydroxyacetophenone (5 mmol) was then added dropwise, and the mixture was stirred at 0 °C for 10 minutes. Subsequently, a solution of the corresponding benzaldehyde (5 mmol) in DMF (10 mL) was added dropwise, and the reaction was allowed to proceed at room temperature for 2 hours. The reaction mixture was then gradually acidified with glacial acetic acid until pH 4. The resulting precipitate was collected by filtration, washed with MeOH (10 mL), and used in the next stage without further purification.

Table 2. Melting points and mass-spectra of synthesized flavonols, yields of flavonol synthesis stages.

flavonols	Mass spectra (m/z, %)	$T_{m.p.}$, ºC	Yield, %			
			Claisen-Schmidt condensation	AFO*	Debenzylation	All stages
1	451 ([M+H]$^+$, 74), 473 ([M+Na]$^+$, 26)	146-158	90 %	74 %	–	67 %
2	271 ([M+H]$^+$, 88), 293 ([M+Na]$^+$, 4)	253-291	90 %	74 %	86 %	57 %
3	375 ([M+H]$^+$, 100)	153-155	98 %	67 %	–	66 %
4	285 ([M+H]$^+$, 100)	242-253	98 %	67 %	90 %	59 %
5	375 ([M+H]$^+$, 88), 397 ([M+Na]$^+$,12)	197-208	96 %	68 %	–	65 %
6	285 ([M+H]$^+$, 94), 307 ([M+Na]$^+$, 6)	207-208	96 %	68 %	90 %	59 %
7	557 ([M+H]$^+$, 100)	158-159	88%	65%	-	57%
fisetin	287 ([M+H]$^+$, 100)	329-331	88%	65%	85%	49%

* AFO – the yield of Flynn-Algar-Oyamada reaction

General Procedure for the Synthesis of Flavonols. A suspension of chalcone (6 mmol) in MeOH (50 mL) was treated with a 15% solution of KOH (15 mmol) and stirred at -15 °C for 10 minutes. A 30% H_2O_2 solution (18 mmol) was then added dropwise, and the reaction was allowed to proceed at room temperature for 2.5 hours. The reaction mixture was subsequently acidified with glacial acetic acid until pH 2. The precipitate was collected by filtration, and washed with MeOH (20 mL) to afford the pure product.

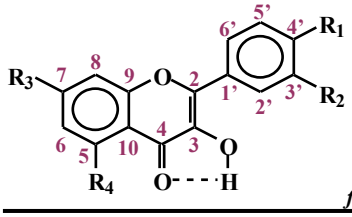
General Procedure for Debenzylation. The debenzylation reaction was carried out by dissolving the target compound in THF (10–20 volEq.) in the presence of 10% Pd/C (0.1 weq.). The mixture was stirred under a hydrogen atmosphere at room temperature for 12 hours. Upon completion, the catalyst

was removed by filtration through a silica gel, and the solvent was evaporated under reduced pressure to yield the deprotected product.

Conclusions

As shown by the analysis of the methods for hydroxy group protection in the synthesis of flavonols, the best results are obtained using benzylation of the initial reagents and subsequent debenzylation of the reaction products.

Table 3. ^{13}C-NMR signals of synthesized flavonol

Atom numbering in ^{13}C NMR spectra	Comp.	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
	*1*	145.2	138.4	172.6	124.7	124.0	133.4	118.3	154.3	121.9
	2	146.6	138.4	172.9	125.2	124.9	133.8	118.6	154.8	121.8
	3	145.3	138.3	172.6	124.7	124.5	133.4	118.3	154.3	121.2
	4	145.9	138.0	172.5	124.4	124.6	133.3	118.3	154.3	121.8
	5	145.3	138.3	172.6	113.0	124.7	133.4	118.3	154.4	121.3
	6	145.9	138.0	172.5	124.4	124.6	133.3	118.3	154.3	121.8
	7	146.3	137.8	172.8	124.0	125.1	133.1	115.0	155.0	158.2
	fisetin	145.5	137.6	172.4	122.9	124.3	134.1	116.0	156.7	162.7

Comp.	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'	(CH_3)	C (CH_2)	C (Ph*)
1	121.2	113.7	147.7	149.8	113.7	124.4	–	70.4, 69.9	137.0, 136.8, 128.4, 127.9, 127.8, 127.6
2	122.8	116.1	145.6	148.1	115.8	120.5	–	–	–
3	123.5	112.7	147.4	150.6	111.7	121.9	55.6	70.2	136.9, 128.4, 128.1, 128.9
4	122.3	111.7	147.4	148.7	115.5	121.3	55.7	–	–
5	121.2	111.3	148.7	149.3	124.4	123.9	55.7	69.8	136.7, 128.4, 127.9, 127.8
6	122.1	111.5	149.7	149.2	114.7	121.0	-	71.2	128.0, 127.7, 127.1
fisetin	122.8	115.3	145.5	146.7	115.3	116.5	-	-	-

Table 4. ^{1}H-NMR signals of synthesized flavonols

Flavonols	H-5	H-6	H-7	H-8	H-2'	H-5'	H-6'	H (OH)	H (CH_2)	H (Ph*)	H (CH_3)
1	8.09 (d)	7.83 – 7.70 (m)	7.83 – 7.70 (m)	7.54 – 7.28 (m)	7.94 (s)	7.25 (d)	7.87 (d)	9.52 (s)	5.22 (d)	7.54 –7.28 (m)	–
2	7.9 (dd)	7.43 (t)	7.72 – 7.65 (m)	7.79 – 7.72 (m)	7.79 – 7.72 (m)	6.91 (d)	7.61 (dd)	9.39 (m)	–	–	–
3	8.09 (d)	7.51– 7.36 (m)	7.51 – 7.36 (m)	7.80 – 7.73 (m)	7.51 – 7.36 (m)	7.22 (d)	7.80– 7.73 (m)	9.48 (s)	5.17 (s)	7.88 –7.80 (m), 7.51 – 7.36 (m)	3.85 (s)
4	8.09 (d)	7.44 (t)	7.80 – 7.73 (m)	7.80 – 7.73 (m)	7.83 (s)	6.96 (d)	7.80– 7.73 (m)	9.55 (m)	–	–	3.86 (s)
5	8.10 (d)	7.94 – 7.87 (m) and 7.84 –7.72 (m)		7.84 – 7.72 (m)	7.49 – 7.38 (m)	7.17 (d)	7.94 – 7.87 (m)	9.50 (s)	5.18 (s)	7.49 –7.38 (m), 7.34 (t)	3.86 (s)
6	8.11 (dd)	7.45 (t)	7.73 – 7.60 (m)	7.83 – 7.73 (m)	7.83 – 7.73 (m)	7.10 (d)	7.73 – 7.60 (m)	9.29 – 9.21 (m)	–	–	3.86 (s)
7	8.05	7.15 (d)	-	7.22 (s)	6.94 (s)	7.12 (d)	7.35-7.39 (m)	10.3	5.26	7.48-7.30 (m)	–
fisetin	7.90 (d)	7.52 (t)	-	7.67-6.64 (m)	7.62-6.58 (m)	6.95 (d)	6.85-6.87 (m)	9.49 (s) 10.72 (s)	-	-	-

* Phenyl ring of benzyl moiety

Debenzylation using a Pd/C catalyst in tetrahydrofuran provides a high yield of polyhydroxy flavonols – 86-90%; the synthesis method is successfully scaled up, the catalyst is easily regenerated, and the resulting final products do not contain traces of halogens, which allows them to be used in the pharmaceutical and food industries. Debenzylation also allows one to obtain flavonols with different arrangements of hydroxy- and methoxy- groups, which is important in the synthesis of natural compounds. The results presented in the article confirm the possibility of synthesizing flavonols with various substituents in the side phenyl fragment, as well as the possibility of successfully synthesizing fisetin using benzylation/debenzylation reactions.

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References

1. Hao, B.; Yang, Zh.; Liu, H.; Liu, Yu; Wang Sh. Advances in Flavonoid Research: Sources, Biological Activities, and Developmental Prospectives. Current Issues in Molecular Biology. 2024, 46(4), 2884-2925. https://doi.org/10.3390/cimb46040181.
2. Panche, A.N.; Diwan, A.D.; Chandra, S.R. Flavonoids: an overview. Journal of Nutritional Science. 2016, 5, art.num e47. https://doi.org/10.1017/jns.2016.41
3. Roshal, A.D. Complexation of flavonoids: Spectral phenomena, regioselectivity, interplay with charge and proton transfer. The Chemical Record. 2024, 4 (2), art. num. e202300249. https://doi.org/10.1002/tcr.202300249.
4. Demidov, O.O.; Krasnopyorova, A.V.; Yukhno, G.D.; Efimova, N.V.; Roshal, A.D. Flavonol assisted extraction of divalent and trivalent metal ions. Functional Materials. 2024, 31(4), 601–608, https://doi.org/10.15407/fm31.04.601.
5. Roshal, A.D.; Organero, J.A.; Douhal, A. Tuning the mechanism of proton-transfer in a hydroxyflavone derivative. Chemical Physics Letters, 2003, 379, 53-59. https://doi.org/10.1016/j.cplett.2003.08.008
6. Yang, D.; Wang, T.; Long, M.; Li, P. Quercetin: Its Main Pharmacological Activity and Potential Application in Clinical Medicine. Oxidative Medicine and Cellular Longevity, 2020, art. num. 2020:8825387. https://doi.org/10.1155/2020/8825387.
7. Ganeshpurkar, A.; Saluja, A.K. The Pharmacological Potential of Rutin. Saudi Pharmaceutical Journal, 2016, 25(2), 149–164. https://doi.org/10.1016/j.jsps.2016.04.025.
8. Elwan, A.H.; El-Masry, S.M.; Habib, D.A.; Zewail, M. An insight into fisetin, the miraculous multifaceted flavonol: Paving the road for enhanced delivery through promising pharmaceutical nano-formulations. Journal of Drug Delivery Science and Technology, 2024, 101 (Part B), art. num. 106292, https://doi.org/10.1016/j.jddst.2024.106292.
9. Algar, J.; Flynn, J.P. A New Method for the Synthesis of Flavonols. Proceedings of the Royal Irish Academy. Section B: Biological, Geological, and Chemical Science. 1934, XLII, 1-8.
10. Oyamada, T.J. A new general method for the synthesis of the derivatives of flavonol. Bulletin of the Chemical Society of Japan, 1934, 55, 1256–1261. https://doi.org/10.1246/bcsj.10.182.
11. Ma, M.-L.; Li, M.; Gou, J.-J.; Ruan, T.-Y.; et al. Design, synthesis and biological activity of flavonoid derivatives as selective agonists for neuromedin U 2 receptor. Bioorganic & Medicinal Chemistry. 2014, 22(21), 6117–6123. https://doi.org/10.1016/j.bmc.2014.08.038.
12. Ferrari, G.V.; Pappano, N.B.; Montaña, M.P.; Garcıa, N.A.; Debattista, N.B. Synthesis of 3,3′-Dihydroxyflavone and Apparent Formation Constants of Flavonoid−Ga(III) Complexes. Journal of Chemical & Engineering Data, 2010, 55(9), 3080–3083. https://doi.org/10.1021/je901091f.
13. Gunduz, S.; Goren, A.C.; Ozturk T. Facile Syntheses of 3-Hydroxyflavones. Organic Letters. 2012, 14(6), 1576–1579. https://doi.org/10.1021/ol300310e.
14. Sobottka, A.M.; Werner, W.; Blaschke, G.; Kiefer, W.; et al. Effect of Flavonol Derivatives on the Carrageenin-Induced Paw Edema in the Rat and Inhibition of Cyclooxygenase-1 and 5-

Lipoxygenase in Vitro. Archiv der Pharmazie. 2020, 333 (7), 205–210 https://doi.org/10.1002/1521-4184(20007)333:7<205::aid-ardp205>3.0.co;2-y
15. Shaw, B.L.; Simpson, T.H. Chelate systems. Part II. Journal of the Chemical Society 1952, 5027–5032. https://doi.org/10.1039/jr9520005027
16. Gupta, S.R.; Seshadri T.R. Survey of anthoxanthins. Part VI. Colouring matter of tamarix troupii. Constitution of the aglycone and its synthesis. Journal of the Chemical Society. 1954, 3063–3065. https://doi.org/10.1039/jr9540003063
17. Ahluwalia, V.K.; Seshadri T.R. Synthetic experiments in the benzopyrone series. Proceedings of the Indian Academy of Sciences – Section A. 1954, 39 (6), 296–300. https://doi.org/10.1007/bf03048703
18. Sagareishvili, T.G.; Alaniya, M.D.; Tsitsishvili, V.G.; Kemertelidze, E.P. Micranthoside – A new glycoside from Eupatorium micranthum. Chemistry of Natural Compounds. 1981, 17, 225–230. https://doi.org/10.1007/BF00568507
19. Shih, T.-L.; Chou, C.-E.; Liao, W.-Y.; Hsiao C.-A. Copper-mediated trimethylsilyl azide in amination of bromoflavonoids to synthesize unique aminoflavonoids. Tetrahedron. 2014, 70 (23), 3657–3664, https://doi.org/10.1016/j.tet.2014.04.022
20. Lindel, Th.; Mende S. Synthesis of morin and morin derivatives. US Patent 2020/0308131 A1, 2020, C07D 311/28.
21. Sousa, J.L.C.; Proença, C.; Freitas, M.; Fernandes, E.; Silva, A.M.S. New polyhydroxylated flavon-3-ols and 3-hydroxy-2-styrylchromones: synthesis and ROS/RNS scavenging activities. European Journal of Medicinal Chemistry. 2016, 119, 250–259. https://doi.org/10.1016/j.ejmech.2016.04.057
22. Ahn, M.; Park, S.E.; Choi, J.; Choi, J. et al. Synthesis and biological evaluation of flavonoid-based IP6K2 inhibitors. Journal of Enzyme Inhibition and Medicinal Chemistry, 2023, 38 (1), art.# 2193866, https://doi.org/10.1080/14756366.2023.2193866
23. Qin, C.X.; Chen, X.; Hughes, R.A.; Williams, S.J.; Woodman, O.L. Understanding the Cardioprotective Effects of Flavonols: Discovery of Relaxant Flavonols without Antioxidant Activity. Journal of Medicinal Chemistry. 2008, 51 (6), 1874–1884. https://doi.org/10.1021/jm070352h
24. Serdiuk, I.E.; Roshal, A.D.; Błażejowski, J. Origin of Spectral Features and Acid–Base Properties of 3,7-Dihydroxyflavone and Its Monofunctional Derivatives in the Ground and Excited States. The Journal of Physical Chemistry A. 2016, 120 (25), 4325–4337. https://doi.org/10.1021/acs.jpca.6b03290
25. Ranga Rao, R.; Tiwari, A. K.; Prabhakar Reddy, P.; Suresh Babu, K.; et al. Synthesis of antihyperglycemic, α-glucosidase inhibitory, and DPPH free radical scavenging furanochalcones. Medicinal Chemistry Research. 2011, 21 (6), 760–774. https://doi.org/10.1007/s00044-011-9583-7
26. Venkateswararao, E.; Son, M.-J.; Sharma, N.; Manickam, M.; et al. Exploration of Pharmacophore in Chrysosplenol C as Activator in Ventricular Myocyte Contraction. ACS Medicinal Chemistry Letters. 2015, 6 (7), 758–763 https://doi.org/10.1021/acsmedchemlett.5b00043
27. Yap, S.; Woodman, O. L.; Crack, P. J.; Williams, S. J. Synthesis of a hypoxia-targeted conjugate of the cardioprotective agent 3′,4′-dihydroxyflavonol and evaluation of its ability to reduce ischaemia/reperfusion injury. Bioorganic & Medicinal Chemistry Letters. 2011, 21 (17), 5102–5106. https://doi.org/10.1016/j.bmcl.2011.03.040
28. Xie, J.; Xu, H.; Zhang, Q.; Wu, Z.; et al. Semi-Synthesis of Flavonoid Glycosides and Their Anti-Inflammatory and Antitumor Activities towards Triple Negative Breast Cancer. Chemistry & Biodiversity. 2023, 20 (2), art. num e202200899. https://doi.org/10.1002/cbdv.202200899
29. Jian, J.; Fan, J.; Yang, H.; Lan, P.; et al. Total Synthesis of the Flavonoid Natural Product Houttuynoid A. Journal of Natural Products. 2018, 81 (2), 371–377. https://doi.org/10.1021/acs.jnatprod.7b00791
30. Docampo-Palacios, M. L.; Alvarez-Hernández, A.; Adiji, O.; Gamiotea-Turro, D.; Valerino-Diaz, A. B.; et al. Glucuronidation of Methylated Quercetin Derivatives: Chemical and Biochemical Approaches. Journal of Agricultural and Food Chemistry. 2020, 68 (50), 14790–14807. https://doi.org/10.1021/acs.jafc.0c04500
31. Jian, J.; Fan, J.; Yang, H.; Lan, P.; et al. Total Synthesis of the Flavonoid Natural Product Houttuynoid A. Journal of Natural Products. 2018, 81 (2), 371–377. https://doi.org/10.1021/acs.jnatprod.7b00791

32. Kim, S.; Li, Y.; Lin, L.; Sayasith, P. R.; et al. Synthesis and Biological Evaluation of 4′-Substituted Kaempfer-3-ols. The Journal of Organic Chemistry. 2020, 85 (6), 4279–4288. https://doi.org/10.1021/acs.joc.9b03461
33. Horie, T.; Tsukayama, M.; Kawamura, Y.; Seno, M.; et al. Studies of the Selective O-Alkylation and Dealkylation of Flavonoids. XI. A New Convenient Method for Synthesizing 3,5,7-Trihydroxy-8-methoxyflavones from 7-Hydroxy-3,5,8-trimethoxyflavones. Bulletin of the Chemical Society of Japan. 1988, 61 (2), 441–447. https://doi.org/10.1246/bcsj.61.44
34. Chiruta, C.; Schubert, D.; Dargusch, R.; Maher, P. Chemical Modification of the Multitarget Neuroprotective Compound Fisetin. Journal of Medicinal Chemistry. 2011, 55 (1), 378–389. https://doi.org/10.1021/jm2012563
35. Mei, Q.; Wang, C.; Zhao, Z.; Yuan, W.; et al. Synthesis of icariin from kaempferol through regioselective methylation and para-Claisen–Cope rearrangement. Beilstein Journal of Organic Chemistry. 2015, 11, 1220–1225. https://doi.org/10.3762/bjoc.11.135
36. Nguyen, V.-S.; Shi, L.; Li, Y.; Wang, Q.-A. Total Synthesis of Icaritin via Microwave-assistance Claisen Rearrangement. Letters in Organic Chemistry. 2014, 11 (9), 677–681. https://doi.org/10.2174/15701786110914090310392 7
37. Sheng, X.; Jia, X.-Y.; Tang, F.; Wang, Y.; et al. The total synthesis of (±)-sanggenol F. Tetrahedron. 2017, 73 (25), 3485–3491. https://doi.org/10.1016/j.tet.2017.05.022
38. Kan, T.; Hiza, A.; Tsukaguchi, Y.; Ogawa, T.; et al. Synthetic Studies of Fisetin, Myricetin and Nobiletin Analogs and Related Probe Molecules. Heterocycles. 2014, 88 (2), 1371–1396. https://doi.org/10.3987/com-13-s(s)107
39. He, L.; Zhou, Z.; Fang, Z.; Jin, H.; et al. Selective Monomethylation of Quercetin. Synthesis. 2010, 23, 3980–3986. https://doi.org/10.1055/s-0030-1258310
40. Estévez-Sarmiento, F.; Said, M.; Brouard, I.; León, F.; et al. 3′-Hydroxy-3,4′-dimethoxyflavone blocks tubulin polymerization and is a potent apoptotic inducer in human SK-MEL-1 melanoma cells. Bioorganic & Medicinal Chemistry. 2017, 25 (21), 6060–6070. https://doi.org/10.1016/j.bmc.2017.09.043

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О. Демидов, О. Рошаль. Методи захисту/зняття захисту гідроксильних груп при синтезі полігідроксифлавонолів

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У статті представлено огляд методів одержання полігідроксифлавонолів без захисту гідроксигруп, а також синтезів із застосуванням метилювання, алкілування та бензилювання вихідних реагентів і, відповідно, деметилювання, деалкілування та дебензилювання кінцевих флавонолів. Показано, що найбільш зручною для синтезу природних полігідроксифлавонолів та їх аналогів є реакція дебензилювання з використанням Pd/C каталізатора в тетрагідрофурані, що дозволяє отримати флавоноли, що містять як гідрокси-, так і метоксигрупи. Синтези з використанням реакцій бензилювання/дебензилювання легко масштабуються, що дозволяє отримувати великі кількості полігідроксифлавонолів, крім того, останні не містять домішок галогеноводнів, що дає можливість використовувати отримані флавоноли у фармацевтичній та харчовій промисловості.

Проведено синтези гідроксифлавонолів з пірогалол-подібною структурою бічного фенільного циклу. З використанням реакцій бензилювання/дебензилювання отримано природний флавонол фізетин – перспективний лікарський засіб та компонент харчових добавок.

Ключові слова:*.флавоноли, синтез флавонолів, реакція Алгара-Флінна-Оямади, захист гідроксигруп.*

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