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Fluorine-Containing Chrysin Derivatives: Synthesis and Biological Activity

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Abstract

Chrysin, a flavonoid, has played a great role in the fields of anticancer, antibacterial, and antiviral drug discovery. A large number of chrysin derivatives have been synthesized recently. The fluorine atom represents an important substituent group for a great number of natural products and pharmaceuticals. Taking into account the importance of both chrysin and the fluorine atom in medicinal chemistry, the synthesis of fluorine-containing chrysin derivatives has gained great interest. Chemically, the synthetic methods for these new chrysin derivatives have also been developed rapidly. In recent years, research on their synthesis has been focused on speeding up the reaction process by changing the catalyst. Biologically, the purpose of introducing fluorine into chrysin was to improve its lipophilicity, but today it is mainly focused on the enhancement and improvement of either its anticancer or antimicrobial activities by incorporating the special properties of fluorine atoms. In this review, synthetic methods for the introduction of fluorine atoms into chrysin are summarized, and their anticancer, antibacterial, antiviral, and hypoglycemic effects are discussed.

Keywords

chrysin derivatives, fluorine, synthetic methods, biological activity

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Flavonoids have attracted much attention because of their wide distribution in nature and their various pharmacological effects.[1] Flavonoids can be further divided into flavonols, flavones, flavanones, flavanols, isoflavonoids, flavonoid glycosides, and flavonolignans. Flavone is an important scaffold for medicinal chemistry. Chrysin (5,7-dihydroxyflavone) (Figure 1), a flavone, has been shown to have various biological properties, such as anticancer,[2] antimutagenic,[3] antibacterial,[4] antioxidant,[5] anti-inflammatory,[6] and neuroprotective activities.[7] However, chrysin has low water solubility, poor absorption, and rapid metabolism after glycosylation,[8] which deems it to be difficult to pass through the intestinal/hepatic barrier.[9] Various attempts have been made to synthesize chrysin derivatives, such as introduction of functional groups such as halogens,[10] methoxide,[11] amino acids, and metal ions,[12] aiming to increase its pharmacological properties.[13] For instance, Mannich base derivatives of chrysin showed moderate inhibitory effects against Hela (cervical), A549 (lung), SGC-7901 (gastric), HCT-116 (colon), and K562 (leukemia) cell lines.[10] Bromochrysins are other synthesized derivatives of chrysin that presented activity against HL-60 and HT-29 cells,[11] and the iodol-chrysin derivatives are active against SW-579 tumor cells.[12]

Incorporation of the fluorine atom into compounds can impact their solubility and lipophilicity, and affect their biological potency. However, many marketed drugs contain fluorine atoms, and many of the newly synthesized compounds have introduced fluorine atoms to improve their properties. In the field of pharmaceutical chemistry, 80% of fluorine atoms in fluorinated compounds exist in the form of fluorine aryl, simple fluoroalkyl, and aromatic trifluoromethyl.[14] Fluorine is a strongly electronegative element located at the distal end of the first line of the periodic table with small volume and small atomic mass. These properties make the fluorocarbon bond highly polarized and also make the fluorocarbon bond very strong, which can prevent drug metabolism. The introduction of fluorine atoms into the compounds has the following effects: (1) Affecting the liposolubility of compounds.[15] A

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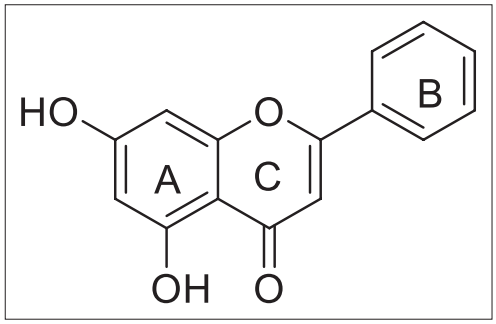
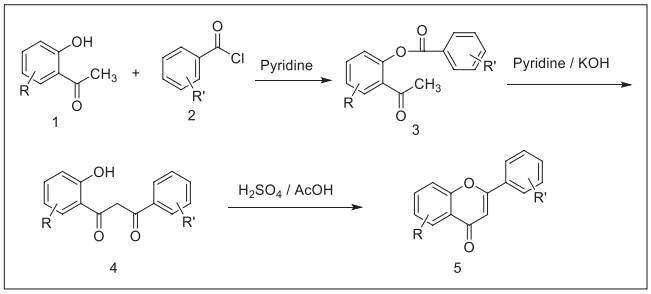


Figure 1. Molecular structure of chrysin.



Scheme 1. Baker-Venkataraman methodology.

large number of statistical analyses based on the effects of fluorine substituents on lipophilic properties show that a single fluorine substituent increases lipophilicity by an average of 0.17 units.[16] However, some studies have shown that this is not the case with aromatically substituted fluorine. Like aryl cyclofluorination, the lipophilicity of the CF_3 group was slightly increased by using fluorinated hydrogen in a methyl substituted group, and the substituent group was transformed into a strong electron absorbent group. Some studies have also shown that fluorination of simple alkyl chains can lead to reductions in lipophilicity; however, the examples were limited. (2) Influencing compound pKa.[17] Trifluoromethanesulfonamide is much more potent than methanesulfonamide in inhibiting carbonic anhydrase. (3) Affecting drug metabolism.[18] Fluorine can prevent oxidative metabolism of aromatic and aliphatic sites, which is not only used to reduce the metabolic oxidation rate but also successfully prevents the production of active metabolites related to specific toxicity, aromatics, and reactivity. (4) Affecting the binding of molecules to proteins.[16] (5) Molecular conformation change.[19]

In consideration of the importance of both fluorine atoms and chrysin in medicinal chemistry, the synthesis of chrysin derivatives containing fluorine has gained attention. With this goal, the Baker-Venkataraman rearrangement reaction[20] and Claisen-Schmidt methodology[21] have become the most widespread approach. In a number of publications, synthetic ways have focused on changing the catalysts and conditions[22] to make the reaction faster, safer, and more efficient. In this paper, recent observations on chrysin derivatives are reviewed. The effects of fluorine-substituted chrysin and the biological activity of these compounds are discussed.

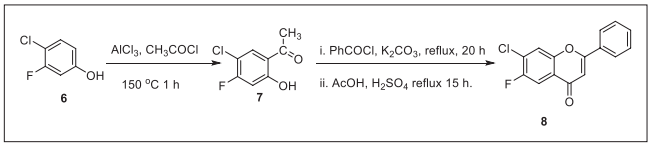
Synthesis of Fluorinated Chrysin

Introducing the Fluorine Atom in the A Ring of the Chrysin Bicyclic System

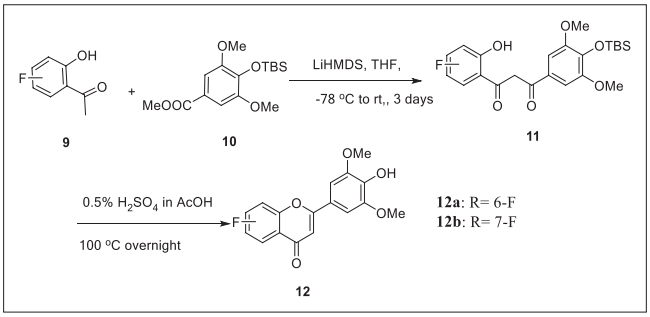
The Baker-Venkataraman reaction is the most common methodology used to incorporate fluorine atoms into chrysin and is a classical method for the synthesis of chrysin derivatives by introducing either fluorine atoms or trifluoromethyl groups into the chrysin derivatives (Scheme 1). The Baker-Venkataraman rearrangement reaction converts 2-hydroxyacetophenone to benzoyl ester[23] and then rearranges to form 1,3-diphenylpropane 1,3-diketone. Cyclization gives flavonoids under acidic conditions. 3-Choro-4-fluorophenol (**6**) was first converted into a benzoyl ester and then treated with base, forming a 1,3-diketone. Treatment of this diketone with acid leads to the generation of compound **8**[24] (Scheme 2). Similarly, compounds **12a** and **12b** were obtained through the Baker-Venkataraman reaction (Scheme 3). Lithium hexamethyldisilazide (LiHMDS) was added to a solution of methyl 4-*O*-tert-butyldimethylsilyl-3,5-dimethoxybenzoate and fluorinated acetophenone (4'-fluoro-2'-hydroxyacetophenone or 5'-fluoro-2'-hydroxyacetophenone) in tetrahydrofuran (THF). The product was dissolved in 0.5% H_2SO_4 in AcOH and the acidic solution was stirred at 100°C for 3 hours. This led to fluorinated chrysin derivatives **12a** and **12b** in 52% to 71% yields.[23,25]

ICl-induced cyclization provides a simple, highly efficient approach to obtain chrysin derivatives in good yields through just 2 procedures. This process is run under mild conditions and tolerates various functional groups. Syntheses of fluorinated chrysin derivatives based on ICl-induced cyclization are convenient (Scheme 4). First, the 2-methoxyaryl-containing alkynones are prepared. There are 2 ways to achieve this. First is the palladium/copper-catalyzed Sonogashira coupling of an acid chloride with a terminal acetylene at either room temperature or 50°C. Second is the addition of lithium acetylide to an aldehyde, followed by oxidation of the resulting secondary alcohol by activated MnO_2. Generally, the requisite alkynones are obtained in 66% to 98% yields by these straightforward approaches.[26]

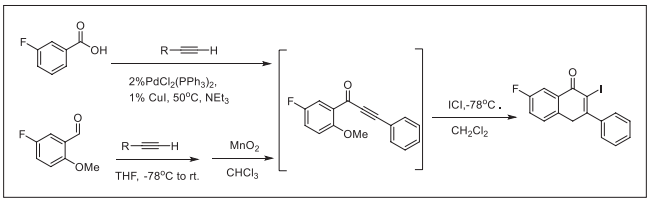
The direct fluorination method is modified by using chrysin as the raw material. Compound **16** (Scheme 5),



Scheme 2. Synthesis of 7-choro-6-fluorinated chrysin derivative **8**.



Scheme 3. Synthesis of monofluorinated 3',5'-dimethyl-4'-hydroxychrysin derivative **12**.



Scheme 4. ICl-induced synthesis of chrysin analogs.

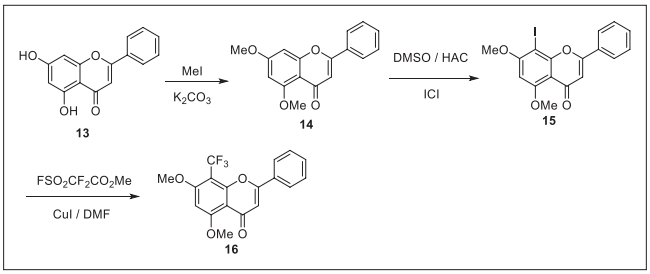
5,7-dimethyl-8-trifluoromethylchrysin, can be produced by a substitution reaction. Iodine was introduced into chrysin, the starting material, followed by fluoromethylation.[27] When the intermediate product is 5,7-diacetoxychrysin, the reaction with trifluoromethylation in $FSO_2CF_2CO_2Me/CuI$ will obtain 6,8-ditrifluoromethyl-5-hydroxy-7-acetoxychrysin.

The above method is to obtain the target product by using fluorinated raw material to synthesize chrysin.

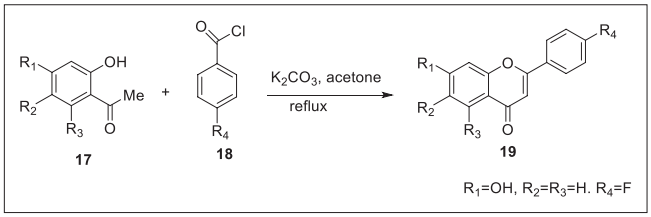
Introducing a Fluorine Atom Into the B Ring of the Chrysin Bicyclic System

A great number of chrysin derivatives bearing fluorine atoms in the B ring have been synthesized by Baker-Venkataraman and Claisen-Schmidt methodologies. Many new reactions on prepared fluorinated chrysin have been developed.

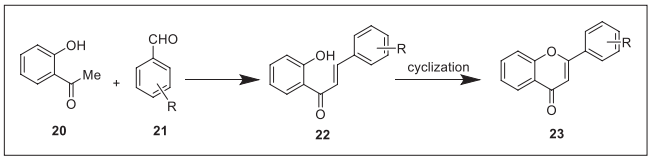
The Baker-Venkataraman method is the most commonly used one for the synthesis of chrysin derivatives by introducing fluorine atoms into acetophenone to synthesize chrysin



Scheme 5. Synthesis of 5,7-dimethoxy-8-trifluoromethylchrysin **16**.



Scheme 6. K_2CO_3 catalyzed synthesis of fluorinated chrysin **19**.

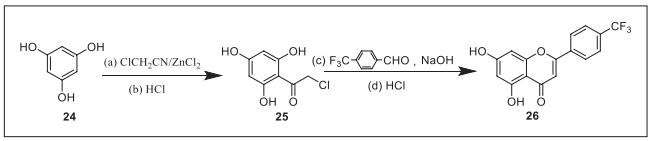


Scheme 7. Claisen-Schmidt methodology.

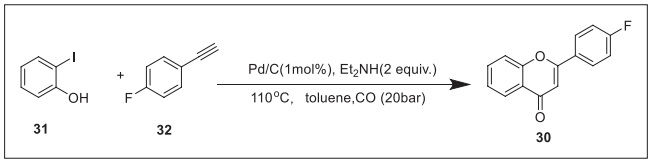
fluorinated on its B ring. Baker-Venkataraman methodology has been improved by Chee et al to obtain flavones in excellent yield in a single step.[28] 2-Hydroxy-acetophenone (**17**) with aroyl chloride (**18**) in the presence of K_2CO_3 and acetone afforded chrysin derivatives with a moderate yield of 60% (Scheme 6).

The well-known Claisen-Schmidt methodology to synthesize fluorinated chrysin appears to be an important approach. 2'-Hydroxy-acetophenone and benzaldehyde are used as raw materials to produce chalcone under alkaline conditions and then under basic conditions, followed by their oxidative cyclization to flavone[21] (Scheme 7). Fluorine atoms were introduced into flavonoids by changing the substituents of benzaldehyde (Scheme 8). Various Lewis acid/base catalysts have been utilized for this oxidative cyclization and $ZnCl_2$ is one of them.[27] Phloroglucinol with chloroacetonitrile followed by hydrolysis with HCl gas provided ketone **25**. The cyclization reaction of benzaldehyde under alkaline conditions was carried out. Fluorinated chrysin was produced by introducing fluorine atoms into the starting material, obtaining the final compound **26** (4'-trifluoromethylchrysin).

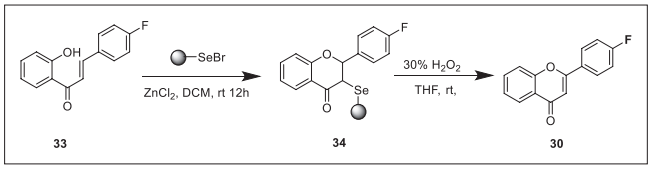
Limited by the long reaction time of the Claisen-Schmidt method, many scholars obtained substituted chrysin derivatives by optimizing the synthetic method of chrysin, for example, compound **30** (4'-fluorinated chrysin). The fluorinated 2-hydroxychalcones derived from the Claisen-Schmidt reaction between acetophenones and salicylaldehyde underwent oxidative cyclization on heating in the presence of catalytic iodine. This methodology changes the starting material in which the formation of chalcone is easier with high yields and the



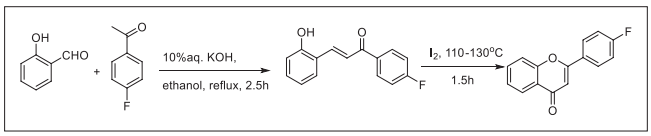
Scheme 8. Synthesis of 4'-trifluoromethoxylchrysin.



Scheme 9. Flavones from salicylaldehyde and acetophenone derivatives.



Scheme 10. Synthesis of 4'-fluorinated chrysin derivative.

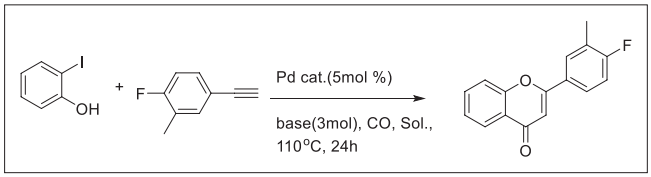


Scheme 11. Palladium-catalyzed cyclocarbonylation of *o*-iodophenol with phenyl acetylene.

reaction is environmental friendly and devoid of organic solvents and metal catalysts[29] (Scheme 9).

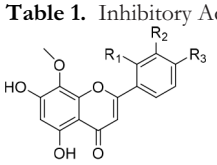
In addition, there are many methods for the synthesis of chrysin, especially by changing the catalyst to achieve the purpose of selective substitution and to increase the yield and reduce the reaction time. Another synthesis of 4'-fluorinated chrysin catalyzed by Pd/C is typical[30] (Scheme 10). The reaction was carried out in toluene at 110°C under positive CO (20 Bar) pressure employing different bases. In addition, there are still many similar reactions to obtain 4'-fluorinated chrysin. Yang et al[31] reported a highly efficient and selective palladium catalyzed ligand-free cyclocarbonylation reaction of *o*-iodophenols with terminal acetylenes under CO pressure in an ionic liquid medium. A phosphonium salt ionic liquid as the reaction medium enhances the efficiency of the cyclo-carbonylation reaction (Scheme 11).

Huang et al reported a special and interesting methodology to obtain chrysin in good yields, which is a resin supported solid-phase synthesis catalyzed by $ZnCl_2$[32] (Scheme 12). The reaction first occurs by Lewis acid-mediated



Scheme 12. Synthesis of 4'-fluorinated chrysin derivative.

Table 1. Inhibitory Activities of Chrysin Derivatives (IC_{50}, μM).



35

No.	R_1	R_2	R_3	A549	HepG2
35a (control)	H	H	H	15.8	19
35b	Br	H	F	ND	33.5
35c	H	H	F	ND	43.9
35d	H	F	H	ND	59.4

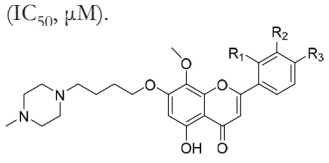
polystyrene-supported selenium-induced intramolecular cyclization of chalcones and followed by oxidative cleavage of the selenium resins. The reaction has several advantages such as mild reaction conditions, being odorlessness, good yields, and easy purification techniques.

Biological Activity of Fluorine-Containing Chrysin

Anticancer Activity

As already mentioned, chrysin has been shown to inhibit proliferation and induce apoptosis, and is more potent than the other tested flavonoids against leukemia cells.[33] The mechanism includes antitumor cell proliferation,[34] tumor cell apoptosis,[35] and reversing multidrug resistance of the tumor cell and antigene mutation.[36] Activation of apoptosis is the key molecular mechanism responsible for the anticancer activities of chrysin. Zhang et al showed that chrysin effectively inhibited the growth of HeLa cells by apoptosis induction and downregulated the proliferating cell nuclear antigen.[37] However, chrysin sensitized tumor necrosis factor (TNF)α-induced apoptosis in tumor cells and such sensitization is probably associated with the inhibitory effect on nuclear factor kappa-B (NF-κB)

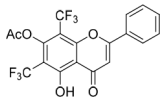
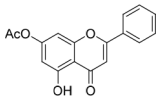
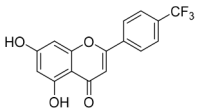
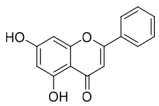
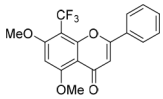
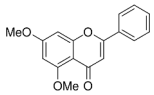
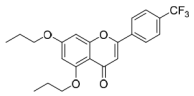
Table 2. Inhibitory Activities of Piperazine-Chrysin Derivatives (IC_{50}, μM).



36

No.	R_1	R_2	R_3	A549	HepG2
36a (control)	H	H	H	1.74	1.07
36b	H	H	CF_3	2.89	2.40
36c	H	H	F	2.22	2.81
36d	Br	H	F	2.98	2.13
36e	H	F	H	2.09	1.95

Table 3. In Vitro Cytotoxicity of Chrysin Derivatives Against SGC-7901 (IC_{50}, μM).

No.	Molecular structure	SGC-7901	Control	SGC-7901
37		8.1		3.6
38		6.6		5.8
39		5.9		3.7
40		2.7		

activation.[38] Woo et al showed that chrysin induced apoptosis in association with the activation of caspase-3, involving the inactivation of either protein kinase B (Akt) or protein kinases B signaling in human leukemia cells.[39]

To improve the potency and physico-chemical properties of chrysin, fluorinated derivatives of it have been obtained. Wang et al[40] have synthesized a series of such derivatives fluorinated on the B ring and evaluated their proliferation activity against HepG2 cells (Table 1). Compound **35a** exhibited the highest activity against HepG2 cells, with an IC_{50} value of 19 μM, higher activity than those of **35b** to **35d**. This showed that the effect of fluorine substitution on the B ring was relatively negative on HepG2 cells.

Chrysin was further modified by Bian et al,[41] and on the basis of the study of Wang et al,[40] the B ring modification of compound **36** was used to evaluate the proliferative activity of

Table 4. Inhibitory Activities of Chrysin Derivatives (IC_{50}, μM).

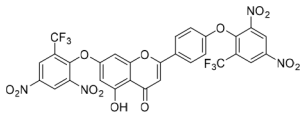
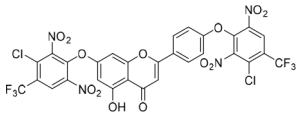
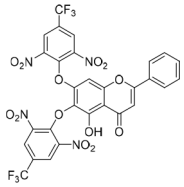
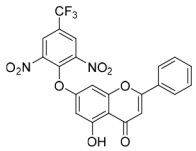
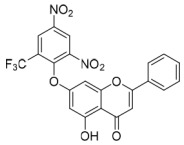
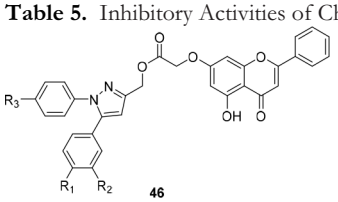
No.	Molecular structure	MCF-7	Hela	KSP
41		5.2 ± 0.48	4.9 ± 0.44	0.027 ± 0.0018
42		4.8 ± 0.45	4.3 ± 0.39	0.023 ± 0.001
43		5.1 ± 0.56	5.3 ± 0.52	0.038 ± 0.0030
44		14.9 ± 1.24	13.9 ± 1.37	0.13 ± 0.02
45		15.6 ± 1.38	14.6 ± 1.36	0.12 ± 0.01

Table 5. Inhibitory Activities of Chrysin Derivatives (IC_{50}, μM).



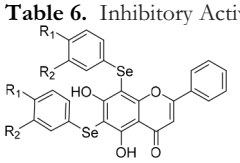
46

No.	R_1	R_2	R_3	MCF-7	A549	Hela
46a (control)	H	H	H	3.47 ± 1.02	3.23 ± 0.88	2.41 ± 0.37
46b	F	H	H	3.82 ± 0.92	12.04 ± 0.95	>100
46c	F	H	CF_3	17.8 ± 1.52	4.62 ± 0.57	>100
46d	H	F	H	9.02 ± 1.01	40.16 ± 2.07	2.81 ± 0.77
46e	CF	H	H	11.02 ± 0.9	8.02 ± 0.86	6.61 ± 1.02
46f	H	CF_3	H	8.01 ± 1.03	6.68 ± 0.66	4.33 ± 0.32

anticancer cells (Table 2). This showed that the introduction of a piperazine group resulted in a significant increase in the inhibitory activity of A549 and HepG2. By comparing Tables 1 and 2, it was found that compound **36a** had a good antiproliferation effect on A549 and HepG2 cells. Although the activities of compounds **36b** to **36e** are not as good as that of control compound **36a**, they are much higher than that of compounds **35b** and **35c**, which also shows that piperazine has a good substitution effect.

Zheng et al enhanced the liposolubility and anticancer ability of chrysin by introducing trifluoromethyl into the A and B rings of chrysin (Table 3).[42] They synthesized the following fluorine compounds by the Baker-Venkataraman method and studied their antigastric cancer effects. It was shown that the trifluoromethyl substituents of 5,7-dipropoxy-4'-trifluoromethylchrysin (compound **40**) made it the most potent agent compared with the other compounds. Compound **37**, 6,8-ditrifluoromethyl-7-acetatechrysin, showed slight activity with an IC_{50} value of 8.06 μM. When the research group continued to study the substitution of trifluoromethyl chrysin, it was found that compound **40**, with the fluorine atom in the B ring, had the best antigastric cancer cell activity. However, the mechanism of introducing fluorine atoms to increase anticancer activity was not shown.

Table 6. Inhibitory Activities of Se-Chrysin Derivatives (IC_{50}, μM).



47

No.	R_1	R_2	A549
47a (control)	H	H	>50
47b	F	H	19.19
47c	H	CF_3	>50

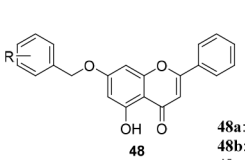
The kinesin spindle protein (KSP) has recently gained significant attention as a novel biological target for anticancer therapy. Kinesin spindle protein plays a critical role in centrosome separation and the formation and maintenance of the bipolar spindle.[43] Inhibition of KSP in proliferating tumor cells leads to the failure of centrosome separation and consequently irregular formation of a monopolar spindle, ultimately resulting in cell death. Dong et al used compounds with trifluoromethylphenyl groups in the A and B rings of chrysin, and their inhibitory effects on KSP and the antiproliferation effects were evaluated (Table 4).[44] They evaluated the antiproliferative activities of compounds **41** to **45** against MCF-7 (human breast cancer cell lines) and Hela cells.

Among the tested compounds, chrysin derivatives showed remarkable anticancer activities, and compound **42** displayed the most potent inhibitory activity (IC_{50} = 4.8 μM for MCF-7 and IC_{50} = 4.3 μM for Hela). Specifically, the target compounds showed obvious inhibitory activity for KSP with IC_{50} values between 0.023 and 0.170 μM. In particular, compound **42** showed potent inhibitory activity against KSP. The antiproliferative properties of the synthesized compounds could be explained by their ability to inhibit KSP activity through the mitotic phenotype. After analysis of the docking results, it was found that many interactions between compound **42** and the protein residues in the binding site might play a crucial role in its KSP inhibitory activities.

In addition, Shen-Zhen Ren et al designed and synthesized a series of 1, 5-diarylpyrazole and chrysin derivatives, and evaluated their inhibitory activity against Cyclo-xygen-ase (COX)-1 and COX-2[45] (Table 5). However, the effect of fluorine substitution on the compounds on 5-diarylpyrazole was not obvious. Compound **46a** was a control compound and compounds **46b** to **46f** showed slight antiproliferative activity, which is comparable with the positive drug.

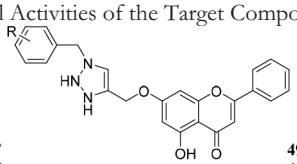
Selenium compounds due to their chemical properties are being used in selective reactions[46] and asymmetric catalysis.[47] Besides, the number of biological activities associated with the lack of toxicity is also an attractive feature of this class of

Table 7. In Vitro Antibacterial Activities of the Target Compounds (minimum inhibitory concentration [MIC]: μg/mL).



48

48a: R= 2-F
48b: R= 3-F
48c: R= 4-F



49

49a: R=2-F
49b: 3-F
49c: 4-F

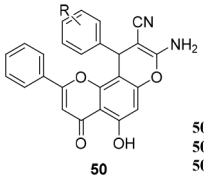
	Microorganisms					
	Gram positive			Gram negative		
No.	*Bacillus subtilis*	*Staphylococcus epidermidis*	*Staphylococcus. aureus*	*Pseudomonas aeruginosa*	*Escherichia coli*	*Klebsiella pneumoniae*
48a	25	25	50	50	50	50
48b	50	25	25	50	50	50
48c	50	12.5	50	25	50	50
49a	12.5	12.5	25	12.5	25	50
49b	12.5	12.5	6.25	12.5	25	50
49c	6.25	12.5	6.25	6.25	6.25	50

compound.[48] Sergio et al found that the use of ultrasonic (US) irradiation in the synthesis of new chrysin derivatives by a simple and effective methodology utilizing CuI as catalyst gave good to excellent yields (60%-89%).[49] Fluorinated Se-chrysin exhibited better anti-A549 cell activity than its unsubstituted compounds (Table 6). Using an in vitro assay, compound **47b**, semisynthetic 6,8-bis(*o*-tolylselanyl)-chrysin, presented the most potent antioxidant activity.

Antibacterial and Antiviral Activity

FabH, proteins from both Gram-positive and Gram-negative bacteria, are highly conserved at the sequence and structural level,[50] and can regulate the fatty acid biosynthesis rate by an initiation pathway. It is reported that chrysin exhibited antibacterial activities as FabH inhibitors.[51] Xin et al synthesized a series of chrysin derivatives[52] that displayed excellent activities greater than the natural parent chrysin, while some were even more potent than the positive drug penicillin (Table 7). Compound **49c** showed 4-fold higher activity (with a MIC value of 6.25 μg/mL) than that of chrysin against *Bacillus subtilis* and penicillin. Moreover, the molecular model for the binding between **49c** and the active site of *Escherichia coli*, β-ketoacyl-acyl carrier protein synthase III (*E. coli* FabH), was provided on the basis of the computational docking results. Compound **50b** showed excellent antibacterial and antifungal activity with inhibitory zones >20 mm[53] (Table 8). The antibacterial activities of these compounds were evaluated by in vitro assay against *Pseudomonas aeruginosa* (ATCC 27853) and *E. coli* (ATCC 25922) as examples of Gram-negative bacteria, and *Bacillus licheniformis* (ATCC 14580) and *Staphylococcus aureus* (ATCC 25923) as examples of Gram-positive bacteria. These compounds were also evaluated for their in vitro activity against *Candida albicans* (ATCC 76615) and *Fusarium oxysporum* (ATCC 16417); compound **50b** showed the best docking scores with appreciable binding energy values, which also exactly correlated with the experimental antibacterial activity.[53]

Table 8. Inhibition Zone Diameters (mm) and MIC (mg/mL) of Chrysin Derivatives.



50

50a: R=H
50b: R=3-F, 4-CH_3
50c: R=4-CH_3

	Gram-negative bacteria		Gram-positive bacteria		Fungi	
No.	*Pseudomonas aeruginosa*	*Escherichia coli*	*Bacillus licheniformis*	*Staphylococcus aureus*	*Candida albicans*	*Fusarium oxysporum*
50a (control)	25 (12.5)	23 (12.5)	21 (12.5)	25 (6.25)	23 (3.12)	22 (12.5)
50b	21 (25)	23 (12.5)	22 (12.5)	24 (6.25)	22 (3.12)	21 (25)
50c	20 (25)	21 (25)	21 (25)	22 (6.25)	21 (3.12)	22 (25)

Table 9. Cyclin-Dependent Kinase 9 Ligand Binding Energies (kcal/mol) and Anti-Human Cytomegalovirus Effect (EC_{50}, nM).

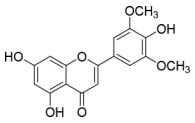
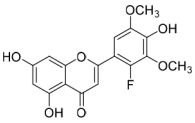
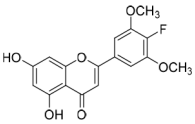
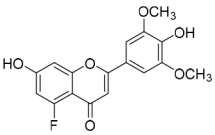
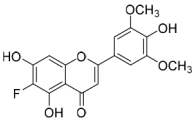
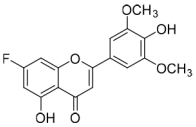
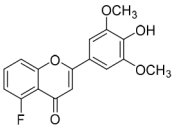
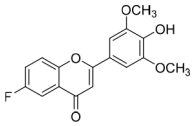
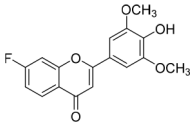
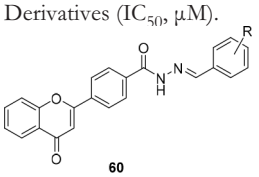
No.	Molecular structure	Lowest value	HCMV (EC_{50})
51 (control)		−5.77	54.25
52		−5.58	
53		−5.94	
54		−6.06	
55		−6.19	
56		−5.91	
57		−5.97	
58		−7.04	0.126
59		−6.72	

Table 10. α-Glucosidase Inhibition Activity of Flavone Hydrazone Derivatives (IC_{50}, μM).



60

No.	R	IC_{50}
61 (control)	Acarbose	860.23 ± 6.10
60a	2'-F	17.1 ± 0.24
60b	3'-F	22.8 ± 1.23
60c	4'-F	19.4 ± 0.20

Human cytomegalovirus (HCMV) is present in a majority of the population worldwide and is a ubiquitous viral pathogen.[54] Chrysin was modified by Kazuhiro et al and the binding energy of the modified compound to cyclin-dependent kinase (CDK) 9 was measured[23] (Table 9). By analyzing the binding energy of the compounds to the target proteins, the binding ability of the compounds can be roughly obtained and the ability of the compounds for promoting cancer cells can be inferred and verified by the measurement of EC_{50} values. The study illustrated that the compounds with fluorine atoms at the 6 and 7 positions of the chrysin derivative A ring had the best effect (compounds **58** and **59**), and the binding energy with CDK9 was the highest, while the EC_{50} value of the compound

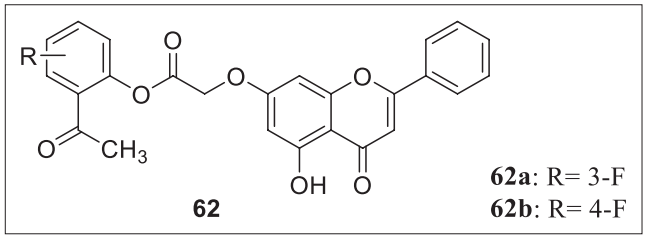


Figure 2. Structure of chrysin derivatives as potential immunosuppressive agents.

to the HCMV of cancer cells was 0.126 μM, which was 200 times that of chrysin derivatives. At the same time, the binding energies of compounds (compounds **54** and **55**) substituted at other positions of ring A to CDK9 are more effective than those of chrysin derivatives. This was due to the creation of strong intermolecular interactions between the 6F-chrysin derivative and the amino acids near the binding site of CDK9.

Hypoglycemic Activity

Chrysin hydrazone derivatives were synthesized by Syahrul et al[55] (Table 10). The introduction of fluorine atoms in the flavonoid hydrazone was shown to result in good inhibition of α-glucosidase. An α-glucosidase inhibitor can delay the release of glucose into the blood and regulate blood glucose. Compounds **60a** to **60c** exhibited high inhibitory effect on α-glucosidase, with IC_{50} values of 17.1, 22.8, and 19.4 μM, respectively. Compared with the control compound, acarbose (IC_{50} = 860.2 ± 6.1 μM), compound **60a** showed a good inhibitory effect on α-glucosidase.

Other Activity

Lv et al synthesized a series of novel chrysin derivatives (Figure 2) and evaluated their immunosuppressive activity in the search for potential immunosuppressive agents.[56] Synthesized compounds with halogen substitutions in the R_3-position on the phenyl ring of the salicylic acid derivatives showed higher activity than others, with IC_{50}s ranging from 0.78 to 6.82 μM (Table 11). Specifically, compound **62a** showed better activity than **62b**, but was not as good as the control compounds.

Table 11. In Vitro Cytotoxicity to Lymph Node Cells and Inhibitory Effects of the Synthetic Compounds on Lymph Node Cells Costimulated by CD3/CD28.

No.	R	IC_{50}, μM	CC_{50}, μM
62 (control)	H	264.9	28.5
62a	3-F	389.3	6.8
62b	4-F	318.7	40.3

Discussion

Among the above compounds, **36e** showed good anti-A549 and anti-HepG2 cell activities. The main reason for the good effect of compound **58** on HCMV cells was its good binding effect with the target proteins, thus inhibiting cell proliferation. The good antiproliferation activity of compound **40** also indicated that the introduction of CF_3 and an alkoxy group on the aromatic rings could improve the liposolubility of the compounds to some extent, but the effects of specific targets and changes of fluorine sites on the liposolubility of the compounds are still to be studied.

Conclusion

Fluorinated chrysin showed many pharmacological activities, including anti-A549, HepG2, HCMV, and SGC-7901, which indicated that fluorine-containing compounds had multiple pharmacological properties, thus warranting further study of fluorine modification of chrysin. This review aims to enhance our understanding of the synthesis and pharmacological effects of chrysin fluoride substitution, in addition to the Baker-Venkataraman methodology for the synthesis of chrysin. The known synthetic method for chrysin is focused on increasing the reaction rate and yield by changing the catalyst, while improving the safety and environmental friendliness of the reaction. Most of these studies are focused on Pd/C and metal catalysis. At the same time, it is a common method to accelerate the reaction by US, ultraviolet, and other physical methods. The pharmacological activity and the antitumor and antiproliferative activity of chrysin were improved by the fluorine substitution of its skeleton and branched chain. In particular, branched fluorine substituents and CF_3 substitutions on the maternal ring were used, such as for compound **40**. At the same time, this improves its antibacterial and antivirus ability. In addition, we found that fluorine atoms have different effects when they are substituted in the chrysin A and B rings. However, there is a lack of discussion on the mechanism of action of chrysin, so it is necessary to discuss the pharmacological effects of fluorine substitution at different sites of the molecule and the effects of fluorine atoms and CF_3 on chrysin in the future.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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