Pergamon

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Bioorganic & Medicinal Chemistry Letters 13 (2003) 881–884

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Synthesis and Anticancer Effect of Chrysin Derivatives

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Received 15 October 2002; accepted 12 December 2002

Abstract—A series of chrysin derivatives, prepared by alkylation, halogenation, nitration, methylation, acetylation and trifluoromethylation, were tested in vitro against human gastric adenocarcinoma cell line (SGC-7901) and colorectal adenocarcinoma (HT-29) cells. Among these derivatives of chrysin, 5,7-dimethoxy-8-iodochrysin **3** and 8-bromo-5-hydroxy-7-methoxychrysin **11** have the strongest activities against SGC-7901 and HT-29 cells, respectively. 5,7-Dihydroxy-8-nitrochrysin **12** were found to have strong activities against both SGC-7901 and HT-29 cells.

Introduction

Flavonoids are a broad class of polyphenolic secondary metabolites abundant in plants and in various common foods such as apples, onions, tea and red wine. Apart from their important biological roles in nitrogen fixation and chemical defense, flavonoids possess a broad range of pharmacological properties including anti-oxidant, anti-cancer, anti-viral and anti-inflammatory properties.[1] Chrysin, a naturally wide distributed flavonoid, has been reported to have many different biological activities such as anti-oxidant,[2] anti-virus,[3] anti-diabetogenic activity[4] and anti-anxiolytic effect.[5] Furthermore, chrysin has demonstrated anti-cancer activities. Chrysin can inhibit the metabolism of the carcinogen benzo[α]pyrene by hamster embryo cells in tissue culture[6] and markedly augment the cytotoxicity of TNF (tumor necrosis factor-α).[7] Chrysin is also found to have tyrosinase inhibitory activity,[8] and moderate aromatase inhibitory activity.[9] It can also inhibit the estradiol-induced DNA synthesis.[10] In order to improve the biological activities of chrysin, a number of its derivatives had been prepared.[1,4,11] Such as C-isoprenylated hydrophobic derivatives of chrysin are potential P-glycoprotein (Pgp) modulators in tumor cells.[12] Herein, we described the synthesis of chrysin derivatives and their anti-cancer activities against human gastric adenocarcinoma cell line (SGC-7901) and colorectal adenocarcinoma (HT-29) cells.

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Chemistry

The readily available Chrysin **1** was the starting material for the preparation of chrysin derivatives. Treatment of chrysin **1** with CH_3I in the presence of K_2CO_3 gave 5,7-dimethoxychrysin **2**. Iodination of **2** with ICl in the presence of acetic acid in DMSO provided 5,7-dimethoxy-8-iodochrysin **3**. Considerable attention has been given to trifluoromethyl-containing organic compounds as agrochemical and pharmaceutical agents due to their unique properties arising from altered electron density, acidity and lipophilicity.[13] Accordingly, we were interested in the synthesis of trifluoromethylated chrysins. Treatment of **3** with $FSO_2CF_2CO_2Me$[14] in the presence of CuI in DMF afforded 5,7-dimethyl-8-trifluoromethylchrysin **4** (Scheme 1).

A mixture of **1**, acetic anhydride (used as both reactant and solvent) and a drop of pyridine was heated at reflux temperature for 7 h to provide 5,7-diacetoxychrysin **5**. However, when the reaction mixture was stirred at room temperature, 5-hydroxy-7-acetoxychrysin **6** was obtained. Iodination of **5** and **6** with ICl gave the same product 6,8-diiodo-5-hydroxy-7-acetoxychrysin **7**. Trifluoromethylation of **7** with $FSO_2CF_2CO_2Me$/CuI afforded 6,8-ditrifluoromethyl-5-hydroxy-7-acetoxychrysin **8** (Scheme 2).

Treatment of chrysin **1** with ICl gave 6,8-diiodo-5,7-dihydroxychrysin **9**. The reaction of **1** with Br_2/H_2O provided 6,8-dibromo-5,7-dihydroxychrysin **10**. However, bromination of **2** with Br_2/H_2O resulted in no reaction and **2** was recovered. Fortunately, bromination

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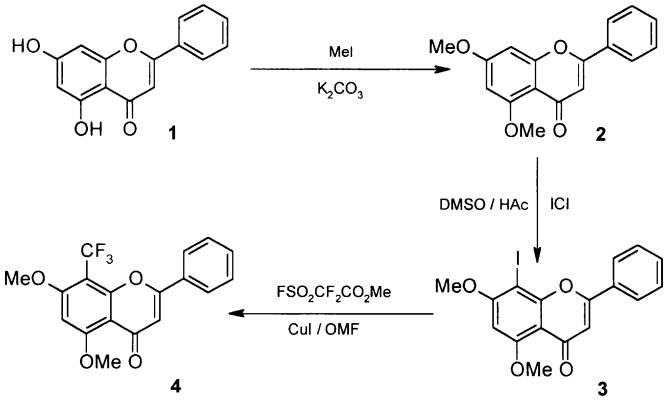
doi:10.1016/S0960-894X(02)01081-8

of **2** with *N*-bromosuccinimide (NBS) afforded 8-bromo-5-hydroxy-7-methoxychrysin **11** (Scheme 3).

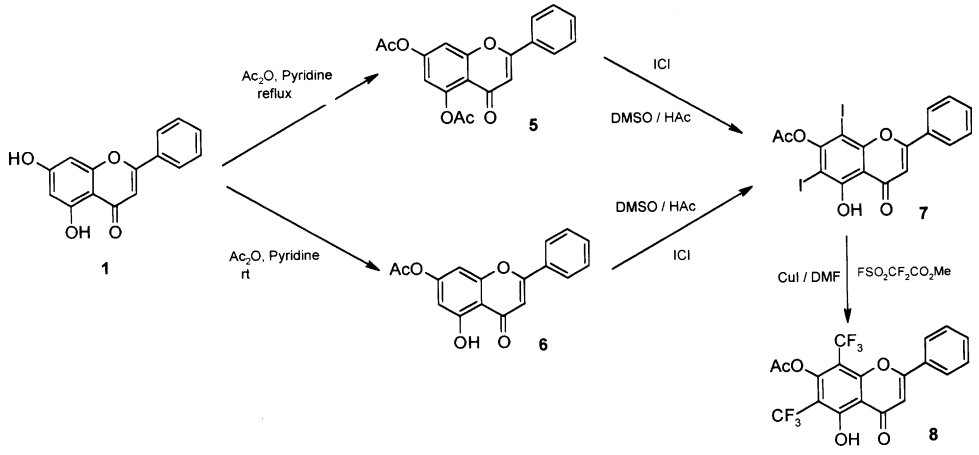
Several years ago, Li et al. reported that treatment of flavone with iodine-cerium(IV)ammonium nitrate (I_2/CAN) in anhydrous CH_3CN gave 3-iodoflavone.[15] However, when we extended Li's reaction conditions to chrysin **1**, the reaction was very complicated and the separation of the reaction mixture by column chromatography proved very tedious. Fortunately, when acetic acid was used as the solvent instead of CH_3CN, the reaction of **1** with I_2/CAN gave 5,7-dihydroxy-8-nitrochrysin **12**. Under the same reaction conditions, 5,7-dimethoxychrysin **2** was converted into 8-iodo-5-hydroxy-7-methoxy-6-nitrochrysin **13** (Scheme 4).

Biological Activity

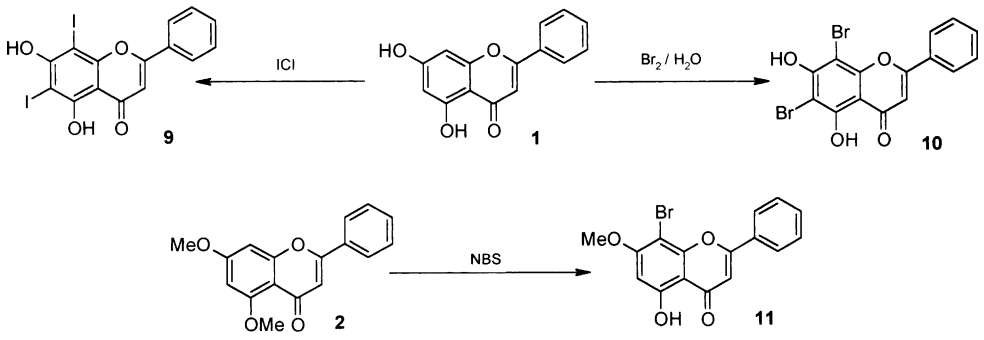
All the above compounds were tested for their in vitro anticancer activities against SGC-7901 and HT-29 cells by MTT-based assay. The assays were performed in 96-well plates essentially as described by Mosmann.[16] The IC_{50} concentration represents the concentration which



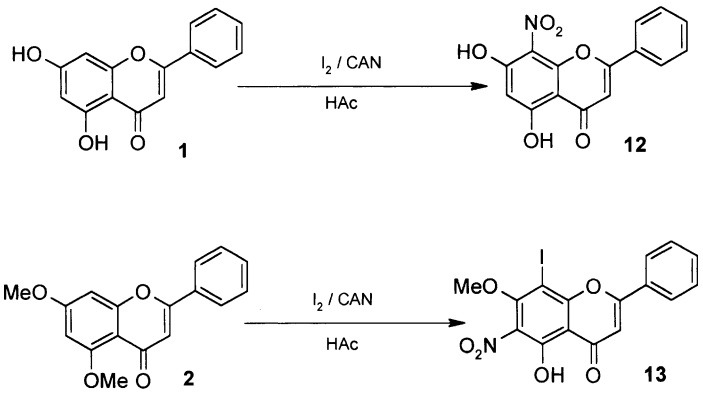
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

results in a 50% decrease in cell growth after 6 days incubation. The given values are mean values of three experiments.

Results and Discussion

The pharmacological results were summarized in Table 1 for anti-HT-29 and anti-SGC-7901 cells respectively. It appeared that these closely related molecules did not display a remarkable difference in cytotoxicity. As shown in Table 1, we disclosed that compounds **2**, **3**, **5**, **6**, **7**, **9**, **10**, **11** and **12** showed stronger cytotoxicity towards SGC-7901 cells than chrysin, and compounds **2**, **3**, **4**, **5**, **7**, **8**, **11**, **12** and **13** had better inhibitory activities to HT-29 cells than chrysin. 8-Bromo-5-hydroxy-7- methoxychrysin **11** was identified as the most potent anti-HT-29 tumor cells and 5,7-dimethoxy-8-iodochrysin **3** showed the most significant activity to SGC-7901 tumor cells. Although general structure–activity relationship of the chrysin derivatives to anticancer effect was not elucidated from these data, the following points were noteworthy: (1) The 8-substituted chrysin derivatives (**3**, **11** and **12**) had stronger activities against both SGC-7901 and HT-29 tumor cells. (2) The 6,8-dihalo substituted chrysin derivatives (**9** and **10**) showed better inhibitory activities against SGC-7901 cells than against HT-29 cells. While the other 6,8-disubstituted chrysin derivatives (**8** and **13**) were more efficient for inhibition of HT-29 cells than for SGC-7901 cells.

Table 1. In vitro cytotoxicity against the SGC-7901 and HT-29 cell lines

Compd	SGC-7901 (IC_{50} μM)	HT-29 (IC_{50} μM)
1	5.8	3.1
2	3.7	2.0
3	2.2	2.6
4	5.9	2.3
5	4.5	2.6
6	3.6	3.8
7	4.2	3.0
8	8.6	2.9
9	2.9	4.4
10	5.1	4.0
11	2.5	1.9
12	2.8	2.3
13	6.4	2.3

In conclusion, we have synthesized a series of chrysin derivatives.[17] The preliminary biological activities screening tests indicated that 8-bromo-5-hydroxy-7-methoxychrysin **11** was identified as the most potent anti-HT-29 tumor cells and 5,7-dimethoxy-8-iodochrysin **3** showed the most significant activity against SGC-7901 tumor cells.

Acknowledgements

We thank the National Natural Science Foundation of China and the Ministry of Education of China for financial support.

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17. All the new compounds were characterized by detailed spectroscopic analysis. **7** MS (EI, 70 ev) *m*/*z*: 548; IR υ_{max} (cm^{-1}, KBr): 1774 (C=O), 3068 (OH); ^1H NMR (300 MHz, DMSO-d_6): 3.293 (3H, s), 7.285 (1H, s), 7.596 (3H, m), 8.159 (2H, m), 13.949 (1H, s). **8** MS (EI, 70 ev) *m*/*z*: 432; IR υ_{max} (cm^{-1}, KBr): 1791 (C=O); ^{19}F NMR (300 MHz) −55.541, −56.692; ^1H NMR (300 MHz, DMSO-d_6): 3.363 (3H, s), 7.277 (1H, s), 7.702 (3H, m), 8.152 (2H, m). **11** MS (EI, 70 ev) *m*/*z*: 347; IR υ_{max} (cm^{-1}, KBr): 1660 (C=O), 3067 (OH); ^1H NMR (300 MHz, DMSO-d_6): 3.968 (3H, s), 7.062 (1H, s), 7.601 (3H, m), 8.116 (2H, m), 13.575 (1H, s). Anal. calcd for $C_{16}H_{11}BrO_4$: C, 55.36, H, 3.19; found C, 55.53, H, 3.40. **12** MS (EI, 70 ev) *m*/*z*: 299; IR υ_{max} (cm^{-1}, KBr): 1656 (C=O), 3068 (OH); ^1H NMR (300 MHz, DMSO-d_6): 6.356 (1H, s), 7.148 (1H, s), 7.579 (3H, m), 7.948 (2H, m). ^{13}C NMR (300 MHz, DMSO-d_6): 98.875 (C-6), 103.124 (C-10), 105.923 (C-3), 121.422 (C-8), 126.357 (C-2′,6′), 129.279 (C-3′,5′), 129.880 (C-1′), 132.527(C-4′), 149.897 (C-9), 157.961 (C-5), 162.714 (C-2), 163.160 (C-7), 181.235 (C-4). Anal. calcd for $C_{15}H_9NO_6$: C, 60.20, H, 3.03, N, 4.68; Found C, 59.79, H, 3.21, N, 4.65. **13** MS (EI, 70 ev) *m*/*z*: 439; ^1H NMR (300 MHz, $CDCl_3$): 4.115 (3H, s), 6.866 (1H, s), 7.570 (3H, m), 7.852 (2H, m), 14.219 (1H, s).