

Synthesis of 8-Triazolo-chrysin Analogs Through Click Reaction

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Flavonoids are natural polyphenol compounds of plant origin and exhibit various biological activities such as anti-inflammatory, anti-oxidant, and anti-tumor activities.^{1,2} Chrysin (5,7-dihydroxyflavone) is a naturally occurring flavonoid that possesses a very broad spectrum of biological activities.³⁻⁶ Chrysin has been known as a PPAR-agonist which results in down regulation of the key pro-inflammatory enzymes, inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2).⁷ Based on the chemical structures and anti-inflammatory activities of several natural flavonoids (Figure 1), we speculated that the substituent at 6- or 8-position of A-ring seems to play a very important role to possess strong anti-inflammatory activity. Therefore, we have synthesized various chrysin derivatives (Figure 1) and found that introduction of a substituent at 6- and/or 8-

position is tolerable to bioactivity.⁸⁻¹² The results also implied that the electronic and steric parameters of the substituent seemed to play more important roles to bioactivity regardless the number and position of substituents. As a continuing study, chrysin analogs carrying 8-heteroaryl groups were synthesized and found that the chrysin analog with 4-pyridinyl group at 8-position exhibited promising anti-inflammatory activities both *in vitro* and *in vivo* screenings.^{13,14} Based on these results, we designed chrysin analogs bearing nitrogen-containing heterocycles like 1,2,3-triazoles as congeners of 8-pyridinyl group.

1,2,3-Triazoles were reported to possess various biological activities in pharmaceutical¹⁵⁻¹⁹ and agrochemical products.^{20,21} These results may imply that electron withdrawing character of nitrogen in 1,2,3-triazole increases the binding interaction with active sites of receptors and exhibits excellent bio-activities to various targets. 1,4-Functionalized 1,2,3-triazoles can be easily generated from azides and alkynes through Click reaction (Figure 2).^{22,23} Herein, we report a concise synthesis of 8-(1,2,3-triazolo)chrysin analogs (Scheme 1).

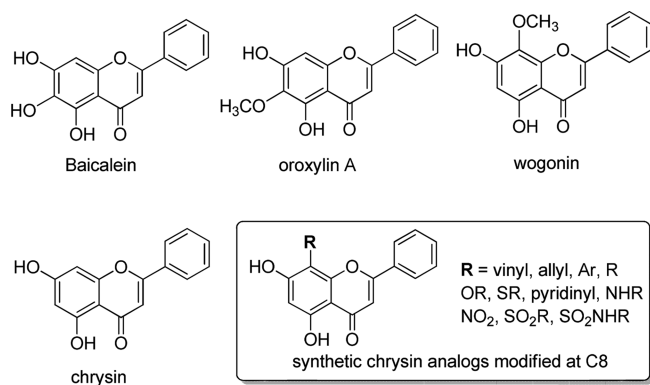


Figure 1. Structures of natural and synthetic flavonoids.

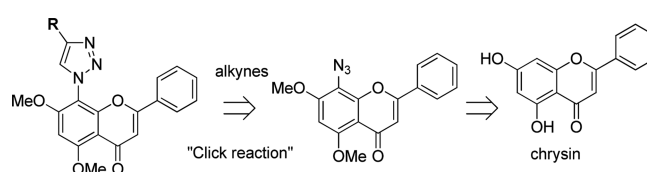
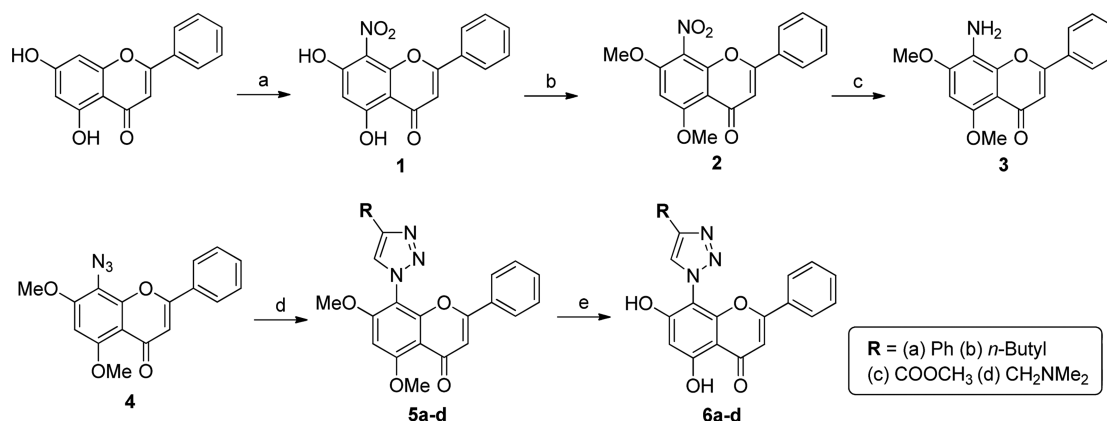


Figure 2. Retrosynthesis of 8-triazolo-chrysin analogs.



Scheme 1. Reagent and conditions: (a) HNO₃, AcOH, 78% (b) Me₂SO₄, acetone, 90% (c) Na₂S₂O₄, acetone-water, 98% (d) HCl, NaNO₂, NaN₃, water, 54-85% (e) BBr₃, CH₂Cl₂, 45-81%.

Experimental Section

As shown in Scheme 1, 8-azido-5,7-dimethoxyflavone (**4**), a key intermediate, was prepared from a commercially available purchased chrysin *via* 4 steps in excellent overall yields. Nitration of chrysin with 60% HNO₃ in AcOH gave 5,7-dihydroxy-8-nitroflavone **1**. Methylation of compound **1** with Me₂SO₄ and K₂CO₃ in acetone gave 5,7-dimethoxy-8-nitroflavone (**2**).¹² Reaction of nitroflavone **2**, Na₂S₂O₄, acetone in water at room temperature for 1 h gave the reduced product, 8-amino-5,7-dimethoxyflavone **3**. After stirring the reaction mixture of aminoflavone **3** and *c*-HCl in water (0.5 M) were stirred at room temperature for 30 min., to this reaction mixture was added the aqueous NaNO₂ solution and the reaction mixture was stirred at 0 °C for 1 h, which gave diazonium salt form. 8-Azido-5,7-dimethoxyflavone (**4**) was obtained by stirring the resulting mixture for an additional 1 h at room temperature and treating with reaction at room temperature for 1 h after slowly adding NaN₃ solution in water.²² Click reaction between 8-azido-flavones **4** and alkynes in a catalytic amount of Cu(OAc)₂ in CH₃CN gave 1,2,3-triazole compounds **5a-d** in 54-85% yields, respectively.^{22,23} Demethylation of compound **5a-d** with BBr₃ in CH₂Cl₂ gave 8-substituted 5,7-dihydroxyflavones **6a-d** in 45-81% yields, respectively.²⁴

In summary, a concise and efficient synthesis of 8-(1,2,3-triazolo)chrysin analogs from chrysin and alkynes as starting materials in five steps with 25-36% overall yields, respectively, is described. Click reaction was proved as an materials for introducing 1,2,3-triazole substructures. Our result is being applied to synthesize chrysin analogs with 1,2,3-triazoles for SAR study and the results will be reported.

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- ¹H and ¹³C data of 8-triazolochrysin analogs **6a-d**: 5,7-Dihydroxy-8-(4-phenyl-1H-1,2,3-triazol-1-yl)flavone (**6a**): ¹H-NMR (400 MHz, DMSO) δ 13.00 (s, 1H, 5-OH), 11.97 (s, 1H, 7-OH), 8.93 (s, 1H, triazole ring), 7.97-7.99 (d, 2H, *J* = 7.4 Hz, H_{2'}, H_{6'}), 7.66-7.68 (d, 2H, *J* = 7.6 Hz, H₂-Ph, H₆-Ph) 7.48-7.53 (m, 3H, H_{3'}, H_{4'}, H_{5'}), 7.36-7.41 (t, 3H, *J* = 7.6 Hz, H₃-Ph, H₄-Ph, H₅-Ph), 7.10 (s, 1H, H₃), 6.53 (s, 1H, H₆); ¹³C-NMR (100 MHz, DMSO) δ 182.0 (C-4), 163.3 (C-2), 162.1 (C-7), 160.2 (C-9), 152.6 (C-5), 146.5 (C-4-triazole), 132.6 (C-5-triazole), 130.9 and 130.5 (C-1' and C-1-Ph), 129.4 (C-3', C-5', C-3-Ph, C-5-Ph), 128.5 (C-4-Ph), 126.4 (C-2', C-6'), 125.7 (C-2-Ph, C-6-Ph), 125.4 (C-4'), 106.0 (C-3), 105.5 (C-10), 104.0 (C-6), 99.1 (C-8). 5,7-Dihydroxy-8-(4-butyl-1H-1,2,3-triazol-1-yl)flavone (**6b**): ¹H-NMR (400 MHz, CDCl₃) δ 12.96 (s, 1H, 5-OH), 8.16 (s, 1H, triazole ring), 7.64-7.66 (d, 2H, *J* = 7.4 Hz, H_{2'}, H_{6'}), 7.56-7.60 (t, 1H, *J* = 7.4 Hz, H_{4'}), 7.44-7.48 (t, 2H, *J* = 7.6 Hz, H_{3'}, H_{5'}), 7.12 (s, 1H, H₃), 6.48 (s, 1H, H₆), 2.76-2.80 (t, 2H, *J* = 7.5 Hz, -CH₂-butyl), 1.66-1.74 (m, 2H, -CH₂-butyl), 1.36-1.45 (m, 2H, -CH₂-butyl), 0.92-0.96 (t, 3H, *J* = 7.4 Hz, CH₃); ¹³C-NMR (100 MHz, DMSO) δ 182.1 (C-4), 163.1 (C-2), 161.8 (C-7), 160.4 (C-9), 152.7 (C-5), 147.0 (C-4-triazole), 132.7 (C-1'), 130.5 (C-4'), 129.4 (C-3', C-5'), 126.4 (C-2', C-6'), 125.7 (C-5-triazole), 105.88 and 105.83 (C-3 and C-10), 103.9 (C-6), 99.0 (C-8), 31.7, 24.9, 21.9 (3xCH₂ in butyl), 14.1 (CH₃). 5,7-Dihydroxy-8-(4-methoxycarbonyl-1H-1,2,3-triazol-1-yl)flavone (**6c**): ¹H-NMR (400 MHz, DMSO) δ 13.20 (s, 1H, 5-OH), 9.04 (s, 1H, triazole ring), 7.65-7.67 (d, 2H, *J* = 7.5 Hz, H_{2'}, H_{6'}), 7.55-7.59 (t, 1H, *J* = 7.3 Hz, H_{4'}), 7.47-7.51 (t, 2H, *J* = 7.3 Hz, H_{3'}, H_{5'}), 7.17 (s, 1H, H₃), 6.85 (s, 1H, H₆), 3.92 (s, 3H, CH₃); ¹³C-NMR (100 MHz, DMSO) δ 182.2 (C-4), 163.7 (-COOCH₃), 163.2 (C-2), 162.0 (C-7), 160.6 (C-9), 151.9 (C-5), 132.9 (C-4-triazole, C-1'), 130.4 (C-4'), 129.6 (C-3', C-5'), 126.5 (C-2', C-6'), 106.1 and 105.5 (C-3 and C-10), 104.4 (C-6), 96.4 (C-8), 57.7 (CH₃). 5,7-Dihydroxy-8-(4-methylamino-1H-1,2,3-triazol-1-yl)flavone (**6d**): ¹H-NMR (300 MHz, CDCl₃) δ 13.07 (s, 1H -OH), 7.92 (s, 1H, triazole ring), 7.33-7.53 (m, 5H, H_{2'}, H_{6'}, H_{3'}, H_{5'}, H_{4'}), 6.66 (s, 1H, H₃), 6.49 (s, 1H, H₆), 3.86 (s, 2H, -CH₂), 3.08 (s, 6H, 2 x Me). ¹³C-NMR (100 MHz, DMSO) δ 182.2 (C-4), 163.2 (C-2), 162.0 (C-7), 160.6 (C-9), 151.9 (C-5), 132.9 (C-4-triazole, C-1'), 130.4 (C-4'), 129.6 (C-3', C-5'), 126.5 (C-2', C-6', C-5-triazol), 106.1 and 105.5 (C-3 and C-10), 104.4 (C-6), 96.4 (C-8), 63.2 (N-CH₂), 45.9 (N-CH₃).