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Synthesis of 8-Triazolochrysin 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 pharmaceutical[15-19] 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 bioactivities 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).

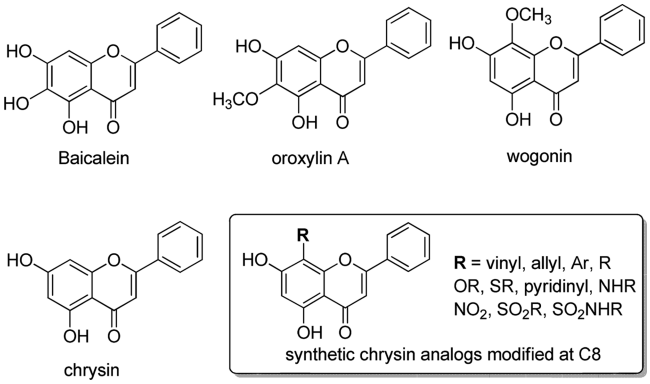


Figure 1. Structures of natural and synthetic flavonoids.

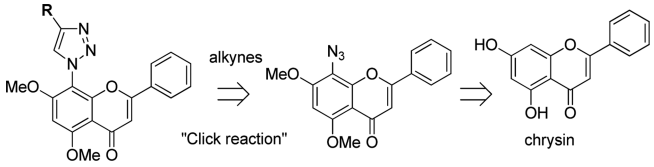
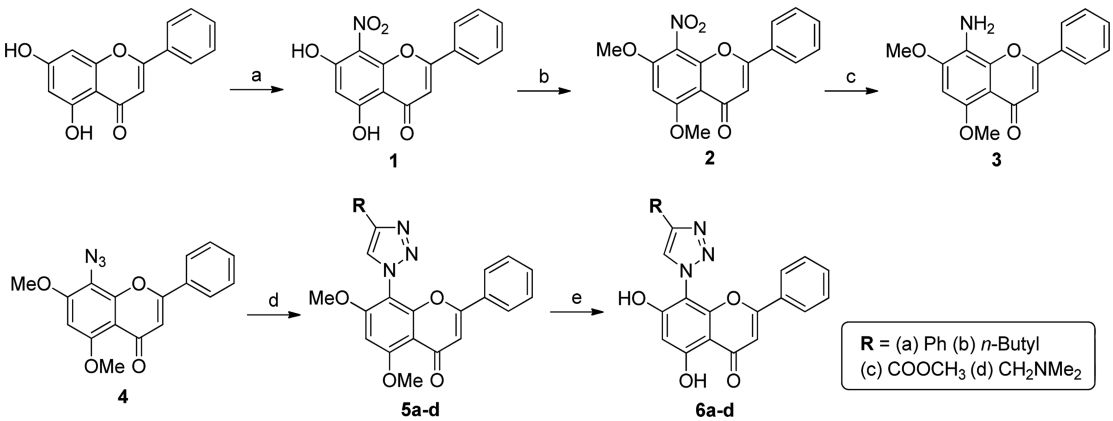


Figure 2. Retrosynthesis of 8-triazolochrysin analogs.



Scheme 1. Reagent and conditions: (a) HNO_3, AcOH, 78% (b) Me_2SO_4, acetone, 90% (c) $Na_2S_2O_4$, acetone-water, 98% (d) HCl, $NaNO_2$, NaN_3, water, 54-85% (e) BBr_3, CH_2Cl_2, 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% HNO_3 in AcOH gave 5,7-dihydroxy-8-nitroflavone **1**. Methylation of compound **1** with Me_2SO_4 and K_2CO_3 in acetone gave 5,7-dimethoxy-8-nitroflavone (**2**).[12] Reaction of nitroflavone **2**, $Na_2S_2O_4$, 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 $NaNO_2$ solution and the reaction mixture was stirred at 0 °C for 1 h, which gave diazonium salt form. 8-Azido-5,7-dimethoxy flavone (**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 NaN_3 solution in water.[22] Click reaction between 8-azido-flavones **4** and alkynes in a catalytic amount of $Cu(OAc)_2$ in CH_3CN gave 1,2,3-triazole compounds **5a-d** in 54-85% yields, respectively.[22,23] Demethylation of compound **5a-d** with BBr_3 in CH_2Cl_2 gave 8-substituted 5,7-dihydroxy-flavones **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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24. ^{1}H and ^{13}C data of 8-triazolochrysin analogs **6a-d**: *5,7-Dihydroxy-8-(4-phenyl-1H-1,2,3-triazol-1-yl)flavone (**6a**):* ^{1}H-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, H2', H6'), 7.66-7.68 (d, 2H, *J* = 7.6 Hz, H2-Ph, H6-Ph) 7.48-7.53 (m, 3H, H3', H4', H5'), 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); ^{13}C-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**):* ^{1}H-NMR (400 MHz, $CDCl_3$) δ 12.96 (s, 1H, 5-OH), 8.16 (s, 1H, triazole ring), 7.64-7.66 (d, 2H, *J* = 7.4 Hz, H2', H6'), 7.56-7.60 (t, 1H, *J* = 7.4 Hz, H4'), 7.44-7.48 (t, 2H, *J* = 7.6 Hz, H3', H5'), 7.12 (s, 1H, H3), 6.48 (s, 1H, H6), 2.76-2.80 (t, 2H, *J* = 7.5 Hz, -CH_2-butyl), 1.66-1.74 (m, 2H, -CH_2-butyl), 1.36-1.45 (m, 2H, -CH_2-butyl), 0.92-0.96 (t, 3H, *J* = 7.4 Hz, CH_3); ^{13}C-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 (3xCH_2 in butyl), 14.1 (CH_3). *5,7-Dihydroxy-8-(4-methoxycarbonyl-1H-1,2,3-triazol-1-yl)flavone (**6c**):* ^{1}H-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, H2', H6'), 7.55-7.59 (t, 1H, *J* = 7.3 Hz, H4'), 7.47-7.51 (t, 2H, *J* = 7.3 Hz, H3', H5'), 7.17 (s, 1H, H3), 6.85 (s, 1H, H6), 3.92 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO) δ 182.2 (C-4), 163.7 (-COOCH$_3$), 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-triazole), 106.1 and 105.5 (C-3 and C-10), 104.4 (C-6), 96.4 (C-8), 57.7 (CH_3). *5,7-Dihydroxy-8-(4-methylamino-1H-1,2,3-triazol-1-yl)flavone (**6d**):* ^{1}H-NMR (300 MHz, $CDCl_3$) δ 13.07 (s, 1H –OH), 7.92 (s, 1H, triazole ring), 7.33-7.53 (m, 5H, H2', H6', H3', H5', H4'), 6.66 (s, 1H, H3), 6.49 (s, 1H, H6), 3.86 (s, 2H, -CH_2), 3.08 (s, 6H, 2 x Me). ^{13}C-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*-CH_2), 45.9 (*N*-CH_3).