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Communications

Synthesis of Heterocyclic Baicalein Derivatives

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Flavonoids are widely distributed in plant kingdom and they belong to the secondary metabolites of plants. Their diverse structures (Figure 1) combined with variety of biological activities such as *anti*-cancer, *anti*-inflammatory, *anti*-viral, apoptosis and *anti*-oxidation drew much attention during last decades.[1-4] The importance of Baicalein derivatives in terms of their biological activities was more clearly exemplified by recent reports. Thus, Chung *et al.*[5] reported that Baicalein **4** affects the pharmacokinetics of Tamoxifen which is the agent of choice for treating and preventing breast cancer. Also more recently Kim *et al.*[6] reported the suppressing effect for the NF-κB signaling pathway for the Baicalein derivatives. So, it was envisioned that the expansion of chemical synthesis of Baicalein derivatives containing a heterocyclic ring is highly warranted. Since a bioisosterism[7,8] is a lead modification approach to attenuate toxicity and/or improve the biological properties of the compounds, we decided to substitute the benzene moiety of 2-position of Baicalein **4** by a heterocyclic ring such as thiophene or furan to test their biological activities. Furthermore Kim *et al.*[9] reported a practical synthetic method of Baicalein **4** due to the interests from many research groups

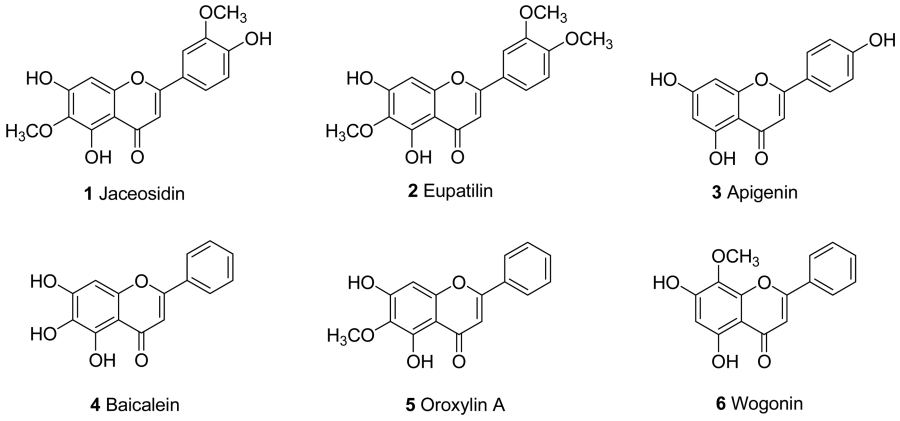
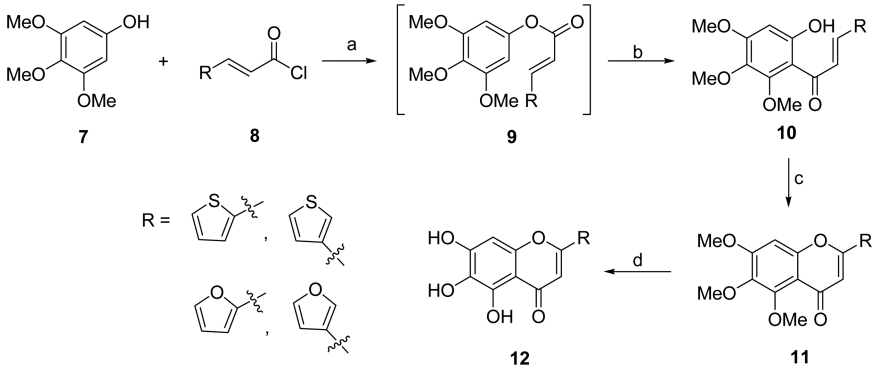
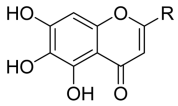


Figure 1. Chemical structures and some bioactive flavonoids.



Scheme 1. Reagents and reaction conditions: (a) cat. DMAP, toluene, 110 °C, 20 min; (b) 1.1 eq. $BF_3 \cdot Et_2O$, 110 °C, 2 h, 60-75% from **7**; (c) cat. I_2, DMSO, 120 °C, 2 h, 75-92%; (d) 0.1eq. Tetrabutylammonium iodide (TBAI), 47% HBr, reflux, 18 h, 65-74%.

Table 1. Analytical data for the heterocyclic Baicalein derivatives **12**



Entry	R	^{1}H-NMR (CD_3OD, 400 MHz)	^{13}C-NMR (CD_3OD, 100 MHz)	mp (°C)	ESI-MS (*m/z*)
1		δ 6.50 (s, 1H), 6.79 (s, 1H), 7.27 (m, 1H), 7.95 (d, *J* = 5.2 Hz,1H), 8.00(d, *J* = 3.2 Hz, 1H)	δ 93.79, 102.82, 116.14, 129.00, 129.38, 129.66, 131.87, 134.00, 147.08, 149.32, 153.50, 158.91, 181.58	dec. > 200	277.2 (M+1)
2		δ 6.56 (s, 1H), 6.81 (s, 1H), 7.74 (m, 2H), 8.42 (m, 1H)	δ 93.91, 104.00, 104.15, 125.49, 128.29, 128.35, 129.22, 133.52, 147.02, 149.57, 153.46, 159.51, 182.20	dec. > 200	277.3 (M+1)
3		δ 6.40 (s, 1H), 6.42 (s, 1H), 6.60 (dd, *J* = 3.6, 3.3 Hz, 1H), 7.14 (d, *J* = 3.6 Hz, 1H), 7.69 (d, *J* = 3.2 Hz, 1H)	δ 93.01, 103.12, 105.84, 113.82, 114.63, 130.79, 147.36, 147.80, 148.09, 151.59, 154.79, 157.26, 183.89	179	261.4 (M+1)
4		δ 6.43 (s, 1H), 6.52 (s, 1H), 6.91 (d, *J* = 6.2 Hz, 1H), 7.66 (d, 1H), 8.26 (s, 1H)	δ 94.95, 104.95, 108.59, 121.50, 130.47, 130.61, 137.82, 145.19, 146.29, 151.89, 154.73, 161.15, 184.00	dec. > 200	261.3 (M+1)

in testing the activities of Baicalein **4**. So, with the important concept of heterocyclic Baicalein derivatives due to the possible bioactivities exhibited by them and the synthetic technology to construct the Baicalein ring system in hand, we carried out synthetic efforts to prepare several heterocyclic Baicalein derivatives **12** (Scheme 1).

The key intermediate **8** were prepared by Knovenegal condensation of commercially available aldehydes with malonic acid followed by chlorination of the corresponding acids with thionyl chloride with no incidence. Condensation of 3,4,5-trimethoxyphenol **7** with acid halides **8** provided compounds **9** in almost quantitative yields. It was noticed that the addition of catalytic amount of DMAP is crucial for good results. Without isolation of the compounds **9** (the completion of reaction is checked by TLC), the reaction mixture was subjected to Fries rearrangement by adding 1.1 eq. of $BF_3{\cdot}Et_2O$ and then refluxing the reaction mixture for 2h followed by aqueous workup to get compound **10** in 60-75% yields. Ring closure of chalcones **10** to flavonoids **11** was accomplished by the published procedure[9] in 75-92% yields. The final step of demethylation on flavonoids **11** was carried out successfully by the published procedure[10] in 65-74% purified yields. The analytical data for the final compounds **12** were summarized in Table 1.

As a conclusion we prepared several Baicalein derivatives containing thiophene and furan ring, and their expected biological activity test is waiting.

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