

The Skeleton Construction and Pharmaceutical Activity of Coumarins

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Abstract—Coumarins are oxygen-containing heterocyclic compounds, which is an important type of compounds in the discovery of bioactive molecules. Some work on the synthesis of bioactive coumarins has been done by other groups. Meanwhile, many synthetic methodologies have been put forward to construct skeleton of coumarins. Results: herein, typical methods constructing coumarin and its derivatives along with multifarious biological activity compounds in vitro and in vivo are summarized, which is of value for design, synthesis and biological application of coumarins.

Keywords—Coumarin; heterocyclic compound; synthesis; methodology; biological activity.

I. INTRODUCTION

Coumarins are well known as a kind of compounds containing a benzo- α -pyrone mother structure (Fig. 1, type 1), all of which mostly come from the plants of the Rutaceae and Umbelliferae [1]. The first naturally occurring compound was isolated in 1820 [2]. Coumarins are separated into four categories: simple coumarins, furanocoumarins, pyranocoumarins, and the pyrone-substituted coumarins. The simple coumarins consist of a benzene ring modified by hydroxyl, alkoxy or alkyl groups and an α -pyrone ring. The furanocoumarins, of which the coumarin nucleus are attached by a five-membered furan ring, are divided into the linear furanocoumarins and the angular furanocoumarins. The pyranocoumarins is similar to the furanocoumarins, but five-membered furan ring is replaced with a six-membered pyran ring, and the pyrone-substituted coumarins are one with substituents in the pyrone ring. These phyto-chemical derivatives, some interesting

oxygen-containing heterocyclic compounds, exhibit the extensive biological activities due to biogenetical physiological active substance, 7-hydroxycoumarin (Fig. 1, type 2) [3]. To date, all the studies have indicated that coumarins possess a variety of biological activities, such as: anti-inflammatory[4], antimicrobial[5], anti-viral[6], anti-oxidant[7], antinociceptive[8], anti-tumor[9], antiasthmatic [10], antidepressant [11], anti-HIV [12], antituberculosis [13], anti-Alzheimer [8], anti-influenza [14], antihyperlipidemic [15]. Due to their wide application in fragrance, agrochemical industries and pharmaceutical field, designing and synthesizing novel and potential coumarin derivatives is particularly important. In this paper, based on our recent study on coumarins, we summarize and analyze typical synthetic methodologies, including Knoevenagel, Perkin, Wittig and Horner-Wittig, Pechmann, Ponndorf, Baylis–Hillman, Wittig and Reformatsky methodology, Claisen rearrangement, as well as the Houben-Hoesch reactions, also give a brief introduction of coumarin derivatives on their biological activities.

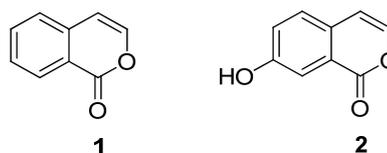
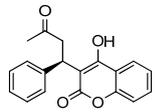
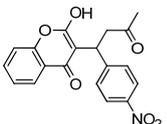
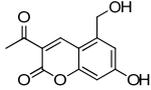
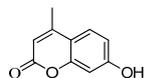
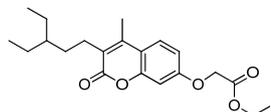
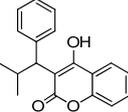
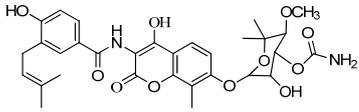
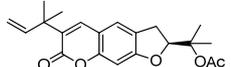
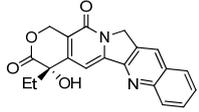
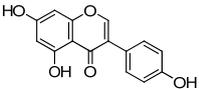
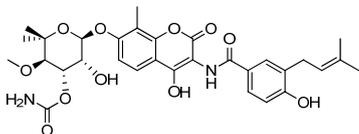


Figure 1. The skeleton of coumarin and umbelliferone.

TABLE I. COUMARIN DERIVATIVES AS DRUGS OR ON THEIR WAY TO CLINICS.

Coumarin	Time	Author	Structure	Pharmacological Activity
1	1954	Holford, Nicholas HG		Anticoagulant [27]
2	2009	Goldfarb, David Scott		Anticoagulant [28]
3	1974	Kiangsu Luminescent Bacteria Research Unit		Antibiotics [29]
4	1931	S. Bonfils, G. Madesclaie		Choleretic and antispasmodic [30]
5	1966	O. Kraupp, et al.		Coronary disease [31]
6	1957	Enders, Edgar		Anti-HIV activity [32]
7	1958	Uvarov, Olga Assignee		Antibiotic [33]
8	2014	B. Xu, L. Wang		Antiviral activity [6]
9	1960	Lerchen, Hans-Georg		Topoisomerase inhibitors [34]
10	N. M. Dean, M. Kanemitsu, A. L. Boynton		Genistein influences multiple biochemical functions in living cells [35]	
11	1955	Hoekserma, et al		Antibiotics [33]

IV. CONCLUSIONS

In this review, we show all the classical synthetic methods of coumarins, of which, two reactions, Knoevenagel, Peckmann, have higher frequency used for synthesis of coumarins; and also pharmacological profiles of coumarins with various bioactivities, in particular, their physiological, bacteriostatic and anti-tumor activities. Some compounds were proposed as clinical therapeutic agents. We have made our efforts to compile most of these classical methods and enumerate

several important compounds used in clinic and on their way to clinics in the history of exploiting coumarins, which provides an important reference for further research on coumarins.

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