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Preparation of indolequinones and their applications in organic synthesis

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1. Introduction

Indolequinones constitute an important class of compounds that possess interesting properties. They have been reported to be powerful anticancer natural products such as Murrayaquinone A (**1**),[1–5] Exiguamine A (**2**),[6] BE 10988 (**3**),[7] and dipyrrolobenzoquinone (+)-terreusinone (**4**)[8] (Fig. 1). They are also key precursors for the synthesis of many useful medicinal compounds including Lymphostin (**5**),[9] Discorhabdin C (**6**),[10] E09 (**7**),[11] or the marine alkaloid Tsitsikammamines A (**8**)[12,13] (Fig. 2). In synthetic medicinal chemistry, they are usually referred to as effective prodrugs.[14–17] Additionally, their cytotoxicities result from their unique structures; the relationship between their structures and activities has been investigated in vivo and in vitro.[18–20] Therefore, to advance

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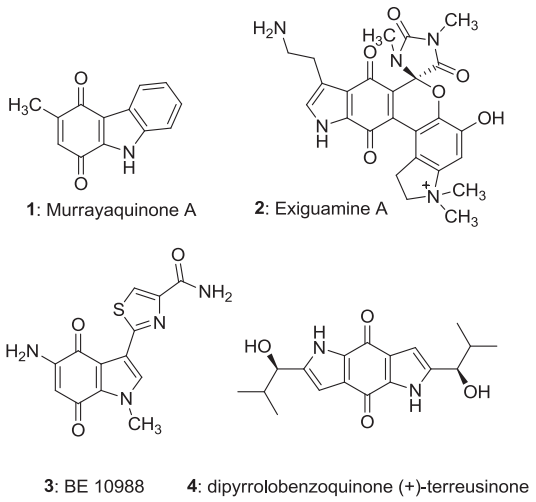


Fig. 1. Natural products containing indolequinone structures.

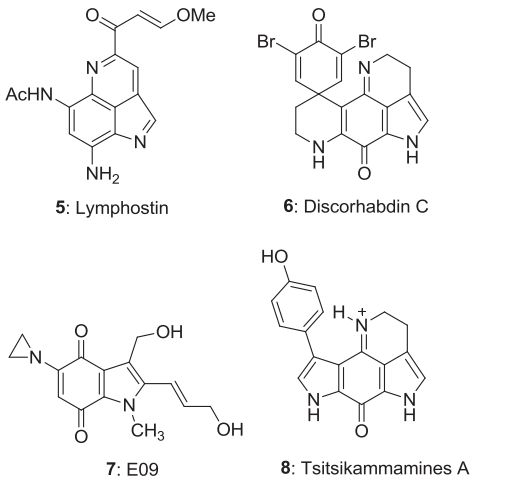


Fig. 2. Medicinal compounds synthesized from indolequinone precursors.

the understanding of the mechanism of their biological activities, it is required to create a diverse library of indolequinones. This task has attracted synthetic chemists over the last few decades. However, there has not been a full review of their preparation methods. This report summarizes the beautiful work on the synthesis of indolequinones and their related compounds including latest developments.

Indolequinones can be classified into two types of compounds based on their quinone structures: *p*-indolequinones (indole-4,7-diones) and *o*-indolequinones (indole-4,5- or 6,7-diones). Since the applications of *p*-indolequinones are dominant in synthetic organic chemistry, in this report, the methodology development for *p*-indolequinone synthesis will be in focus. The related compounds, which *p*-quinone structures are incorporated in their carbazole skeletons, will also be included. The methods were categorized into three general groups: oxidation of indoles, cyclization of quinones, and other methods.

2. Oxidation of indoles

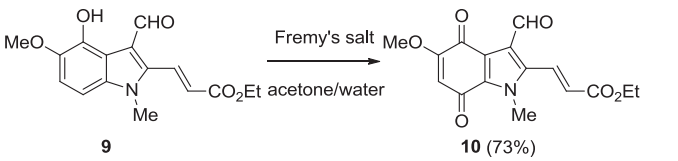
Usually, the oxidation of indoles is accomplished by using metal salts and complexes as single electron transfer agents. In addition, other reagents including inorganic acids, hypervalent iodines, bromine, DDQ, and air were also used. This section contains three sub-categories: Oxidation by Fremy's salt, by other metal reagents, and by other reagents.

2.1. Oxidation by Fremy's salt

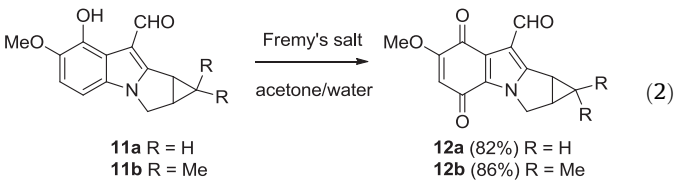
In methodology development of indolequinone synthesis, Fremy's salt [$K_2NO(SO_3)_2$] is considered to be the most powerful tool utilized. Moreover, the use of this salt accounts for the major portion to construct indolequinones in natural product syntheses and medicinal chemistry.

The oxidizing properties of Fremy's salt as a single electron transfer agent have been investigated and well established.[21] In general, two starting materials can be used to synthesize *p*-quinones by oxidation: phenol and aniline derivatives.[21] Thus, Fremy's salt has been readily applied to *p*-indolequinone synthesis using indoles as starting materials that have a hydroxyl or an amino group on the fused benzene ring.

2.1.1. Oxidation of indoles with hydroxyl group. One of the most famous indolequinones is the anticancer agent E09 (**7**). During the effort to improve the synthesis of this agent, Cotterill et al. succeeded in preparing the key indolequinone **10** as a building block in good yield by oxidation of 4-hydroxyindole **9** using Fremy's salt (Eq. 1).[11] Other well-known synthetic medicinal compounds are cyclopropamitosenes **12**. The synthesis of **12** from **11** to construct the *p*-quinone structure was accomplished with Fremy's salt oxidation by Moody and co-workers (Eq. 2).[22,23] An extension to a wide variety of analogs of cyclopropamitosene **12** was also achieved for bioactivity screening.[23]



(1)



(2)

Besides synthetic anticancer agents, indolequinones also appear as important precursors for many natural products (Figs. 1 and 2). Murrayaquinone A (**1**) was obtained after the treatment of **13a** with Fremy's salt in acetone–water in 40% yield, while its substituent-free derivative **14** was obtained in better yield (85%) from **13b** (Eq. 3).[1,24] Fillion and co-workers also demonstrated the effect of bromine substituent on indole oxidation by Fremy's salt. The starting material without bromine (**15a**) underwent Fremy's salt oxidation to give **16a** in 83% yield (Eq. 4), while **15b** gave only 77% of **16b** (Eq. 5).[25–27] When the reaction was performed in a phosphonate buffer solution, the yield of Murrayaquinone A (**1**) was improved drastically (Eq. 6).[2–5] A similar result, 83% of Murrayaquinone A (**1**) from **15c**, was obtained by Miki et al. (Eq. 7).[28] These results showed that the same compound **1** was obtained under the same condition from the different starting materials, which have hydroxyl group at 1 or 4-position on the carbazole. These reaction conditions also worked well for the total synthesis of sponge alkaloid Exiguamine A (**2**).[6] The preparations of indolequinones **18** and **20** from **17** and **19** are shown in Eqs. 8 and 9, respectively. Along with potassium dihydrophosphate, sodium dihydrophosphate can also serve as a buffer medium for Fremy's salt oxidation (Eq. 8 and 9).[29]

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