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Review

Pyrrolizines: Promising scaffolds for anticancer drugs

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ABSTRACT

Pyrrolizine derivatives constitute a class of heterocyclic compounds which can serve as promising scaffolds for anticancer drugs. The unique antitumor properties of mitomycin C inspired chemists to develop different pyrrolizine systems and assess their potential antitumor activities against a wide variety of cancer types. Here we review the different classes of pyrrolizines that possess anticancer potency, with an emphasis on their structure activity relationships, in an effort to pave the way for further development in this promising area of research.

Contents

1. Introduction

Pyrrolizines are hetrocyclic systems consisting of two fused five memebered rings with one nitrogen atom at the ring junction; the parent compound of this class is 3*H*-pyrrolizine **1** (Fig. 1).[1] Although pyrrolizine does not appear to occur naturally, many of its derivatives have been isolated from plants[2] and animals.[3]

Pyrrolizidine constitutes the main skeleton of over 660 alkaloids identified in 6000 plants worldwide.[4] These alkaloids are biosynthesized by plants as secondary metabolites against herbivores.[5] Pyrrolizidine alkaloids are known to cause hepatotoxicity and genotoxicity because they form reactive pyrrolic metabolites that can bind to DNA, forming DNA- and DNA–protein-cross-links.[6,7]

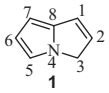

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Figure 1. Structure and numbering system of 3*H*-pyrrolizine **1**.

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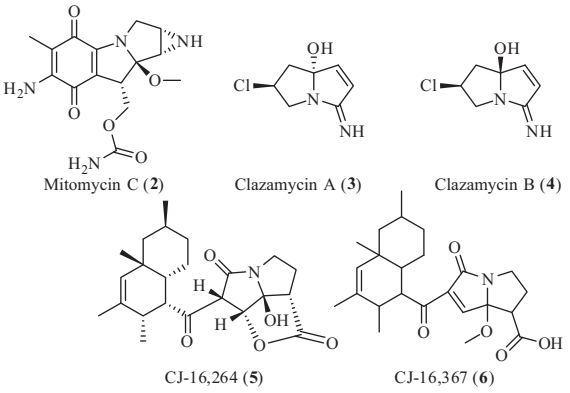


Figure 2. Antitumor antibiotics **2**–**6**.

However, pyrrolizidine alkaloids are beyond the scope of this review.

Pyrrolizines and pyrrolizidine alkaloids are challenging synthetic targets that have attracted the attention of many synthesis groups because of the unique structural features and interesting biological activity.[8–10] Pyrrolizine analogues are of interest to medicinal chemists, because of their biological and pharmacological activities. The pyrrolizine ring constitutes a scaffold for many compounds with diverse biological roles as antitumor[11–13] and anti-inflammatory agents.[14–16]

One of the early discovered antitumor drugs is mitomycin C **2** (Fig. 2), which was isolated from *Streptomyces caespitosus* or *Streptomyces lavendulae* and has antitumor antibiotic activity. It is used to treat upper esophageal carcinoma, anal cancers, breast cancers, and superficial bladder tumors.[17–19] Mitomycin C **2** is believed to act as a good DNA alkylator which can cross-link DNA with high efficiency and specificity.[20,21] It was demonstrated that mitomycins and structurally similar drugs cross-link the exocyclic amino groups of deoxyguanosine residues at the sequence 5′-d(CG) in duplex DNA.[22] Other interesting antitumor antibiotics are clazamycin A **3** and clazamycin B **4**. Both compounds are natural pyrrolizidines isolated from microorganisms, the only known pyrrolizidines that contain a chlorine substituent attached to the pyrrolizidine ring.[23] Two other well known antibiotics that have a pyrrolizidinone skeleton are CJ-16,264 **5** and CJ-16,367 **6** (Fig. 2).[24]

The structural similarity of these compounds shows clearly the importance of the pyrrolizine scaffold as a key nucleus in the synthesis of antitumor drugs. This review summarizes the efforts of medicinal chemists in the search for new pyrrolizine derivatives of potential antitumor activity with an emphasis on their structure activity relationship (SAR) and general synthetic protocols for the major pyrrolizine classes.

2. Pyrrolizines with anticancer activities

2.1. Substituted pyrrolizines

Novel pyrrolizines **7**–**10** (Fig. 3) were synthesized and tested against mammary cancer cell line (MCF-7) and were found to have higher antitumor activity against breast cancer than the drug doxorubicin. The *p*-methoxy benzylidene derivative **9** was found to be the most active compound with an IC_{50} of 16 nM.[25] Compound **7** was easily synthesized by stirring 2-(pyrrolidin-2-ylidene)malononitrile **11**, morpholine, and formaldehyde at room temperature for 24 h (Scheme 1). Compounds **8a**–**b**, **9**, and **10** were obtained by reacting **7** with isocyanates or isothiocyanates, different acylating agents, and *p*-substituted benzaldehydes respectively.[25]

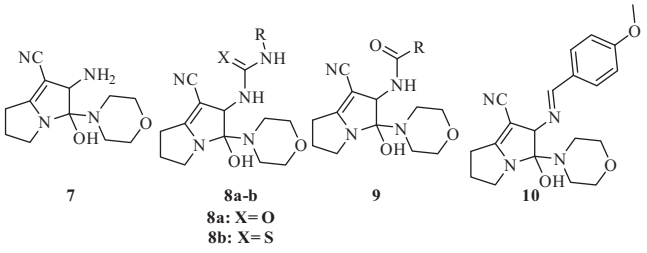
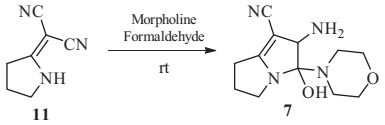


Figure 3. Substituted pyrrolizines **7**–**10**.



Scheme 1. Synthesis of pyrrolizine **7**.

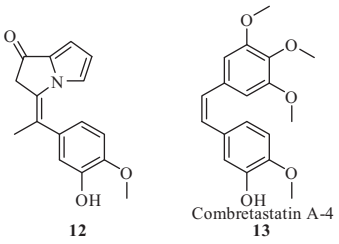


Figure 4. Phenethylidenepyrrolizinones (**12**) and combretastatin A-4 (**13**).

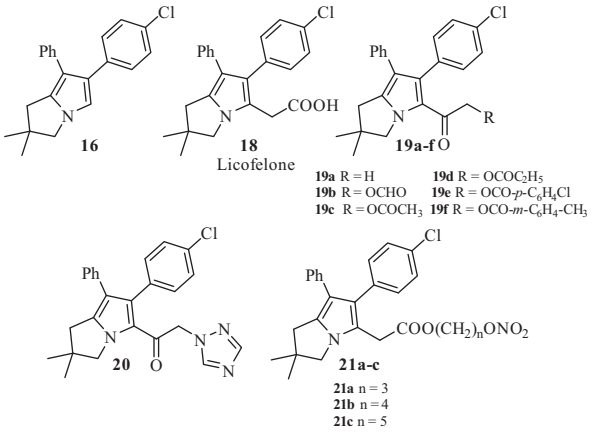


Figure 5. Licofelone (**18**) and licofelone derivatives (**16**, **19**–**21**).

Phenethylidenepyrrolizinone **12** (Fig. 4) has a significant cytotoxicity in human KB cells (IC_{50} = 70 nM). However, the activity of **12** was diminished by replacing either the *m*-OH or the *p*-OMe with other substituents. The structural similarity between **12** and combretastatin A-4 **13** is remarkable and may provide an explanation for this loss of activity.[26]

Licofelone **18** (Fig. 5) was developed as an anti-inflammatory drug and it is currently in clinical trials. This drug showed promising anti-tumor activity by enhancing apoptosis in prostate cancer cells as well as HCA-7 colon cancer cells through the mitochondrial pathway.[27,28] Moreover, it was identified as a dual 5-LOX/COX inhibitor of both small intestinal and colon tumorigenesis in APC$^{Min/+}$ mice.[29] This drug has great potential for preventing and treating colon cancer, but it has yet to be explored.