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Mini-review

Synthetic derivatives of aromatic abietane diterpenoids and their biological activities

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ABSTRACT

Naturally occurring aromatic abietane diterpenoids (dehydroabietanes) exhibit a wide range of biological activities. A number of synthetic studies aimed at modifying the abietane skeleton in order to obtain new potential chemotherapeutic agents have been reported. In this study, the biological activities of synthetic derivatives of aromatic abietane diterpenoids are reviewed.

1. Introduction

Natural products have played a dominant role in the drug discovery efforts for the treatment of human diseases [1]. Abietanes are a family of naturally occurring diterpenoids that have been isolated from a variety of terrestrial plant sources. During the last three decades, many new members of this family of natural products have been isolated and described in several specific reviews on naturally occurring diterpenoids by Professor Hanson [2]. These compounds exhibit a wide variety of interesting biological activities, which has generated significant interest from the medicinal and pharmacological communities. The biological activities of natural abietane acids and their derivatives have been reviewed up to 1992 [3]. In this review, our attention is focused on diterpenoids characterised by tricyclic structures having the abietane (**I**, C_{20}) (Fig. 1) carbon framework and an aromatic ring C.

Aromatic abietanes comprised the largest group of components of naturally occurring abietanes. They possess an aromatic ring C and a different degree of oxygenation at several positions. This group of abietanes is exemplified by dehydroabietic acid (**2**) and ferruginol (**3**) which were discovered more than seventy years ago [4,5]. Both structures were assigned based on chemical data. Dehydroabietic acid (**2**) was initially obtained from chemical studies starting from abietic acid (**1**), later, it was found in resin or extracts of conifers [6]. Ferruginol (**3**) was firstly isolated in 1939 from the resin of the Miro tree (*Podocarpus ferrugineus*), endemic to New Zealand [5]. Another typical aromatic abietane is carnosic acid (**4**), which is found in the popular Lamiaceae herbs, sage (*Salvia officinalis*) and rosemary (*Rosmarinus officinalis*) [7]. Dehydroabietylamine (**5**), an abietane diterpenic amine derived from abietic acid (**1**), is the main component of disproportionated rosin amine. The diterpenoid skeleton present in these abietanes has been the object of derivatisation in screening for new potential chemotherapeutic agents. In this study, the biological activities of dehydroabietic acid, ferruginol, carnosic acid and dehydroabietylamine derivatives are reviewed.

2. Biological activities of aromatic abietane derivatives

2.1. Dehydroabietic acid derivatives

Over the past few years, a lot of research has been committed to the synthesis of dehydroabietic acid (**2**, DHA) derivatives. Dehydroabietic acid (**2**) displays not only antiulcer and antimicrobial properties but also antitumour effects. Modifications in rings B and C as well as manipulation of the carboxyl group at C-18 of DHA (**2**) have been studied in order to enhance its properties. In one of the early studies aimed at searching for new antiulcer agents with a broad cytoprotective effect, Wada et al. prepared more than

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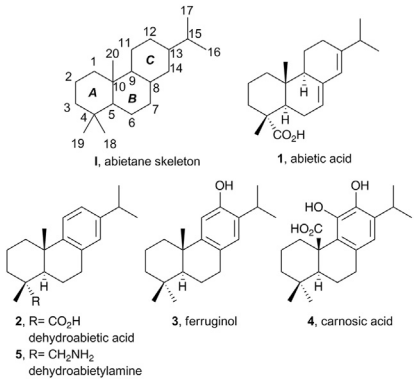

Fig. 1. Abietane numbering system and abietanes **1**–**5**.

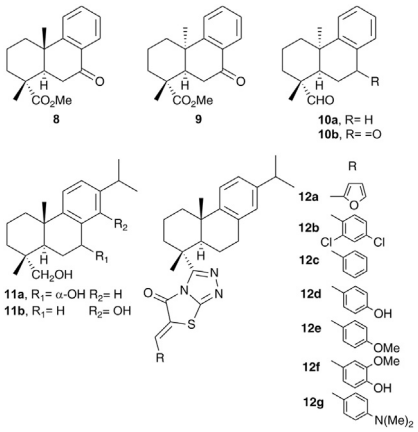

Fig. 3. Antifungal DHA derivatives **8**–**12**.

seventy derivatives of DHA (**2**), introducing a hydrophilic residue (amino, carbamoyl, carbamate, ureide, sulfonyl, or sulfamoyl) onto the lipophilic dehydroabietane skeleton [8]. The antisecretory and antipepsin activities were evaluated as a preliminary evaluation of antiulcer activity. The results obtained showed that DHA (**2**) has a moderate antisecretory action (22% inhibition of secretion at an intraperitoneally dose of 30 mg/kg in rats) and had no antipepsin activity. Among the tested compounds, the salts of 12-sulfodehydroabietic acid (**6a**–**b**) (Fig. 2) were found to exhibit remarkably high antipepsin activity (92–96% inhibition at 100 mg/kg) without aldosterone-like activity shown by other antiulcer agents. Further research on the molecule **6a** (12-sulfodehydroabietic acid monosodium salt) has led to the development of the drug ecabet® (ecabet sodium) for the treatment of reflux oesophagitis and peptic ulcer disease. The gastroprotective and cytotoxic effect of a series of DHA (**2**) derivatives at C-18 has been reported [9]. In this study, DHA (**2**) presented a dose-related gastroprotective effect on HCl/EtOH-induced gastric lesions in mice (59% inhibition at 100 mg/kg). The aromatic amide derivatives **7a**–**g** (Fig. 2) showed a strong gastroprotective activity (67–85% inhibition of gastric lesions) with low cytotoxicity (IC_{50} > 1000 μM) for both fibroblasts (MRC-5) and human epithelial gastric cell line (AGS).

The antimicrobial activity of resin acid derivatives has been reviewed up to 2006, including some DHA (**2**) derivatives [10]. For example, C-13 deisopropylated compounds **8** and **9** (Fig. 3) were the most active inhibiting the growth of several filamentous fungi (*Actinomucor harzii*, *Cladosporium cucumerinum*, *Mucor racemosus*, *Rhizopus arrhizus*, *Rhizopus stolonifer*, and *Syncephalastrum racemosum*) and also the Gram-positive bacterium *Staphylococcus aureus* [11]. Both compounds did not inhibit the growth of Gram-negative bacteria, *Escherichia coli* and *Klebsiella pneumonia*. However, in combination, those two compounds (**8** and **9**) inhibited the growth of those organisms suggesting a synergistic effect. The presence of an aldehyde group, compounds **10a** and **10b** (Fig. 3), seemed to be important for the antiyeast activity against *Candida albicans*, *Candida kruzei* and *Candida parapsilosis* [12]. More recently, González et al. demonstrated that DHA (**2**) (MIC = 39.7 μg/mL against *Aspergillus terreus*) and dehydroabietane **11a** (Fig. 3) (MIC = 50 and 63 μg/mL against *Aspergillus fumigates and Aspergillus niger*, respectively) possess anti-*Aspergillus* activity [13]. These authors also described anti-*Aspergillus* activity for the phenol **11b** (Fig. 3) (MIC = 25, 25 and 50 μg/mL against *A. fumigates*, *A. terreus and A. niger*, respectively) [14]. A series of DHA (**2**) derivatives bearing 1,2,4-triazolo-thiazolidinone moieties, compounds **12a**–**g** (Fig. 3), have been synthesised and tested at 50 μg/mL for antifungal activity against *Fusarium oxysporum*, *Alternaria solani*, *Physalospora piricola*, *Cercospora arachidicola* and *Fusarium graminearum* [15]. With the exception of **12c**, all compounds were most effective against *F. graminearum*, being compound **12d** the most potent with inhibition ratio of 70.9%. Compound **12c** showed the greatest inhibition ratio of 51.9% against *F. oxysporum*, and compound **12e** displayed the greatest inhibition ratio of 56.8% against *P. piricola*.

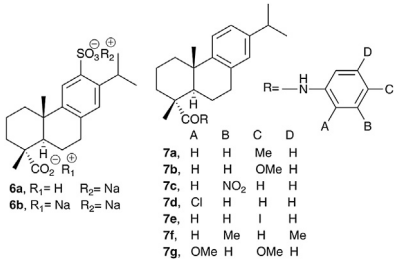

Fig. 2. Antiulcer DHA derivatives **6**–**7**.

Other antimicrobial studies include the synthesis of some thioureas, compounds **13a**–**k** (Fig. 4), and the corresponding 1,2,4-triazolo-aniline derivatives **14a**–**f** (Fig. 4), which were tested against *Bacillus subtilis* and *E. coli* [16]. Compounds **13j**, **13e**, **13f** and **14b** possess antibacterial activity against *B. subtilis* at a test concentration (for **13j**: 50 mg/mL; for **13e**, **13f**, **14b**: 100 mg/mL) while compounds **13b**, **13h**, **13i** and **14e** possess antibacterial activity against *E. coli* at a test concentration of 100 mg/mL.

A series of novel dibenzo-carbazole derivatives of DHA (**2**), compounds **15a**–**m** (Fig. 4), were synthesised and tested against four bacteria (*B. subtilis*, *S. aureus*, *E. coli*, and *Pseudomonas fluorescens*) and three fungi (*Trichophyton rubrum*, *C. albicans* and *A. niger*) [17]. Among the compounds tested, **15d**, **15e**, **15f** and **15m** exhibited pronounced antibacterial activities and **15e** and **15m** also showed moderate antifungal activities. Particularly, **15d** exhibited stronger antibacterial activity against *B. subtilis* (MIC = 1.9 μg/mL) comparable to positive control (amikacin, MIC = 0.9 μg/mL). Later on, the same authors reported the synthesis and antimicrobial evaluation of N-substituted dibenzo-carbazole derivatives of DHA (**2**), compounds **16a**–**s** (Fig. 4) [18]. Some of the synthesised compounds displayed pronounced antimicrobial activity against four bacteria (*B. subtilis*, *S. aureus*, *E. coli*, and *P. fluorescens*) with low MIC values ranging from 0.9 to 15.6 μg/mL. Among them, compounds **16j** and **16r** exhibited potent inhibitory activity comparable to reference drug amikacin. These authors have also described the synthesis and antibacterial evaluation of new N-acylhydrazone derivatives, compounds **17a**–**q** (Fig. 4), from DHA (**2**) [19]. The compounds were evaluated against four microbial strains (*B.*