



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.

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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, C₂₀) (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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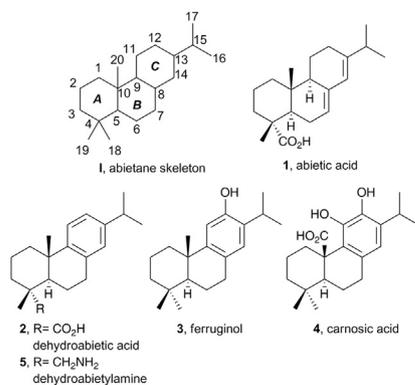


Fig. 1. Abietane numbering system and abietanes 1–5.

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 anti-pepsin activities were evaluated as a preliminary evaluation of anti-ulcer 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 anti-pepsin activity. Among the tested compounds, the salts of 12-sulfodehydroabietic acid (6a–b) (Fig. 2) were found to exhibit remarkably high anti-pepsin activity (92–96% inhibition at 100 mg/kg) without aldosterone-like activity shown by other anti-ulcer agents. Further research on the molecule 6a (12-sulfodehydroabietic acid monosodium salt) has led to the development of the drug ecabec[®] (ecabec 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 (IC₅₀ > 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 pneumoniae*. 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),

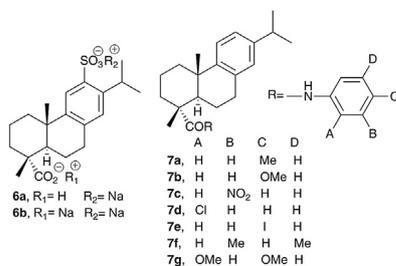


Fig. 2. Antiulcer DHA derivatives 6–7.

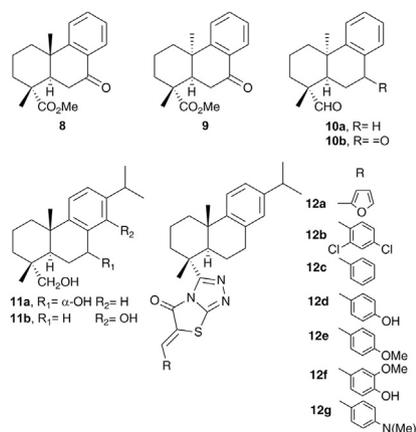


Fig. 3. Antifungal DHA derivatives 8–12.

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 fumigatus* 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. fumigatus*, *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*.

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.*

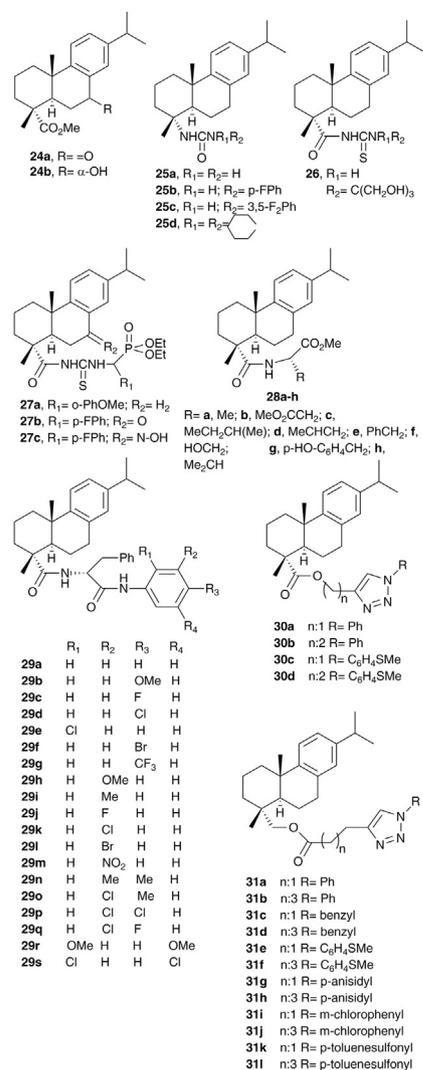
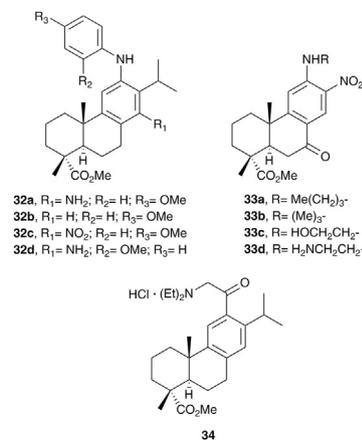


Fig. 6. Antitumour DHA derivatives 24–31.

8.1 μ M (SK-BR-3), respectively. Furthermore, all derivatives were shown to possess high selective cytotoxic activities for leukaemia cells, since they exhibited only weak cytotoxicity against normal lymphocyte cell line RPMI1788. In connection with this research, Zhang et al. described the synthesis and antitumour activities of novel dipeptide derivatives, compounds **29a–s** (Fig. 6), derived from DHA (**2**) [29]. The antitumour activity screening indicated that many compounds showed moderate to high levels of inhibition activities against NCI-H460 (lung), HepG2 (liver), SKOV3 (ovarian), BEL-7404 (liver), HeLa (cervical) and HCT-116 (colon) cancer cell lines and that some displayed more potent inhibitory activities than commercial anticancer drug 5-FU. The mechanism of representative compound **29b** was studied which demonstrated that it induced apoptosis in HeLa cells through a mitochondrial pathway. Recently, Pertino et al. reported on the synthesis and anti-proliferative activity of some novel triazole derivatives of DHA (**2**), compounds **30a–d** and **31a–l** (Fig. 6) [30]. The best results were obtained for compound **31a** which presented an IC₅₀ value of 6.1 μ M in the SK-MES-1 cell line derived from metastatic site. Under the same experimental conditions, the IC₅₀ value of etoposide was 1.83 μ M.

The redox properties of several diarylamines (e. g. **32a–d**) (Fig. 7) derived from DHA (**2**) have been investigated by cyclic

Fig. 7. Antioxidant DHA derivatives **32–33** and sedative and antipyretic DHA derivative **34**.

voltammetry, and their free radical scavenging activity was tested by reduction of the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical [31]. Compounds **32a**, **32c** and **32d** with lower oxidation potential proved to be as active as isopropylidiphenylamine (IPPD) and superior to *tert*-butylhydroxytoluene (BHT). In order to probe the antioxidant effect of a series of methyl 12-imino-13-nitro dehydrodeisopropylbiolate derivatives (**33a–d**) (Fig. 7), the metal ion binding abilities on Cu²⁺ and Fe²⁺ of these derivatives were studied using fluorescence quenching method [32]. The results indicated that each compound showed obvious chelation activity with the binding constants (*K*_A) of the 10² L mol⁻¹ order of magnitude, which implied its potential pharmacology application as antioxidant by the inhibition of Fenton reaction through chelation with Cu²⁺ and Fe²⁺. Compound **33b** has the strongest chelation activity with Cu²⁺, while **33d** has the strongest chelation activity with Fe²⁺, respectively.

The biological activity of a series of amino derivatives of DHA (**2**) (e. g. **34**) (Fig. 7) has been studied. Compound **34** produces a calming effect, anxiolytic activity, and antipyretic action comparable with that of the reference drug analgin in mice [33].

In order to explore novel scaffolds for large-conductance calcium-activated K⁺ channel openers (BK channels), Ohwada et al. selected the aromatic ring of DHA (**2**) for structural modification. Well-characterised BK channel openers could be used to treat acute stroke, epilepsy, and bladder overactivity. There is some evidence for the utility of BK channel openers in the treatment of asthma, hypertension, gastric hypermotility and psychoses. Thus, this research group has investigated a number of derivatives, compounds **35–38** (Fig. 8), as BK channel openers. For example, the early studies found that 12,14-dichlorodehydroabiatic acid (**35**) showed a remarkable increase of the BK channel-opening activities [34]. Later on, the discovery of the hexahydrodibenzazepinone moiety with BK channel-opening activity was reported [35]. In this study, it was concluded that substitution with a phenyl-bearing alkynyl group on the lactam amide, compound **36**, was critical for activity. A series of ureas and thioureas (e. g. **37**) were also synthesised and studied as BK channel openers. Compound **37** increased the ionic current by 240% of control current at a concentration of 30 μ M [36]. Studies to improve the activity of lead compound **35** were also carried out. Thus, it was discovered that oxime ether derivatives (e. g. **38**) of the benzylic ketone of 12,14-dichlorodehydroabiatic acid (**35**) were potent and effective BK channel openers [37,38]. Compound **38** was approximately twice as potent as the standard compound NS1619 and its mechanism of action has been studied [39].

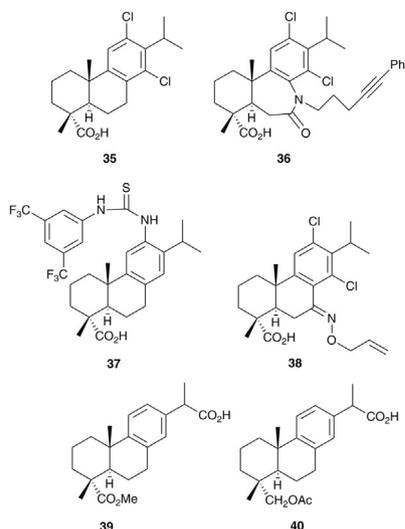


Fig. 8. BK channel openers based on DHA derivatives 35–38 and anti-inflammatory derivatives 39 and 40.

The study of Li and McChesney in 1992 described the synthesis and potential anti-inflammatory activity of DHA (2) derivatives. In this work, compounds 39 and 40 (Fig. 8) demonstrated weak anti-inflammatory activity [40].

2.2. Dehydroabietylamine derivatives

Dehydroabietylamine (5, DHAA) (Fig. 1), also called leelamine, is a synthetic primary amine having a tricyclic structure which is obtained as a part of a mixture of amines prepared from rosin. This compound and its derivatives are widely used in the fields of paper-making, and chemical industries due to its properties as resolving agent, surfactant, dye and pharmaceutical [41]. DHAA (5) and some

derivatives have been patented as antibacterials and anticancer agents [42,43]. One of the early studies on antimicrobial activity of DHAA (5) found that several peptoid derivatives (e. g. 41–42) (Fig. 9) were also active in the range 3–12 $\mu\text{g}/\text{mL}$ against a panel of Gram-positive and Gram-negative bacteria, which included isolates which were resistant to known antibiotics [44]. The antimicrobial activity of these compounds was generally slightly more potent against Gram-positive than Gram-negative isolates. The activity against *S. aureus* was rapid, bactericidal, and independent of protein synthesis. Compound 42a protected *S. aureus*-infected mice in a simple infection model. The antibacterial activity of DHAA (5) against *B. subtilis* and *S. aureus* as well as two fungi strains (*Poria placenta* and *Rhizopus oryzae*) has also been reported [45]. DHAA (5) showed strong activity against the two bacteria, and presented fairly similar antibiotic activity against fungus of *R. oryzae* but little activity against fungus of *P. placenta*. Several quaternary ammonium salts (43–44) (Fig. 9) obtained from DHAA (5) displayed antibacterial activity against *S. aureus* and *E. coli* with MIC values in the range of 7.81–31.25 $\mu\text{g}/\text{mL}$ for *S. aureus*, and 250–500 $\mu\text{g}/\text{mL}$ for *E. coli* [46]. It was also found that the ammonium salts with N,N-dimethyl groups had stronger activity than those with N,N-diethyloxyl groups. Other derivatives of DHAA (5), such as schiff base derivatives (45a–h) (Fig. 9), obtained by reaction of the amino group have shown antibacterial activity against *S. aureus*, *B. subtilis* and *E. coli* [47]. All the compounds exhibited bactericidal activity. Compound 45c derived from Cl-substituted benzaldehyde was the most active towards *B. subtilis*, and compound 45d derived from fluorinated benzaldehyde, toward *S. aureus*. The most active agent toward *E. coli* was compound 45a derived from unsubstituted benzaldehyde. The bactericidal activity of ring B derivatives of DHAA (5) such as 12-nitro-dehydroabietylamine (46a) and 12,14-dinitro-dehydroabietylamine (46b) has also been reported [48]. Both compounds had strong bactericidal activity against *E. coli*, *S. aureus* and *P. fluorescens*.

Recently, DHAA (5) has been studied for treating melanoma showing a novel mechanism of action. It was 4.5-fold more effective at inhibiting cultured melanoma cell survival than normal cells, with average IC_{50} values of 2 and 9.3 μM , respectively [49]. It also inhibited the growth of preexisting xenografted melanoma tumours by an average of 60% without affecting animal body weight or blood markers of major organ function. The potent biological profile of DHAA (5) has spurred the synthesis of a number of derivatives (47–56) (Fig. 10) for studying their antitumour properties. For example, a series of novel α -aminophosphonate derivatives, compounds 47a–j (Fig. 10), have been synthesised by Rao et al. and evaluated for their antitumour activities against SMMC7721 liver cancer cells [50]. Compounds 47d and 47f exhibited higher activities even at very low concentrations, and the inhibition ratios reached 75% and 79% at 0.1 μM , respectively. The inhibition ratio of compound 47i reached 99% after 72 h incubation. The derivatives with a fluorine atom and a nitro group fused to the benzene ring exhibited higher activities. The same authors have reported that dehydroabietylamine derivative 48a (TBIDOM) (Fig. 10) exhibited significant antiproliferative effects by induction of apoptosis in SMMC7721 liver cancer cells. Its mechanism may be related to the decrease in the expression of anti-apoptotic protein, Bcl-2, accompanied by a drop in the mitochondrial membrane potential and the activation of caspase-3, that led to apoptotic body formation and finally apoptosis [51]. Similarly, dehydroabietylamine-fluorobenzaldehyde derivative 48b (Fig. 10) displayed a significant inhibitory effect on the growth of SMMC7721 cells in a dose- and time-dependent manner ($\text{IC}_{50} = 44.5 \mu\text{M}$) [52]. Also, compound 48b could significantly reduce tumour weight in the H22 solid tumour mouse model *in vivo*. A series of Schiff bases, compounds 49a–e (Fig. 10), derived from 12-amino-N-acetyldehydroabietylamine

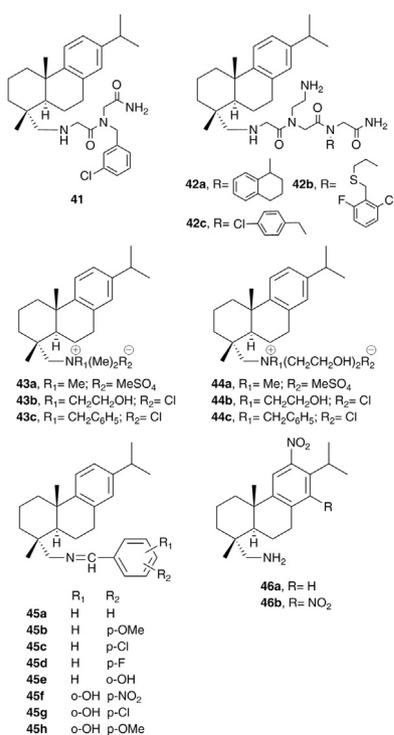


Fig. 9. Antimicrobial DHAA derivatives 41–46.

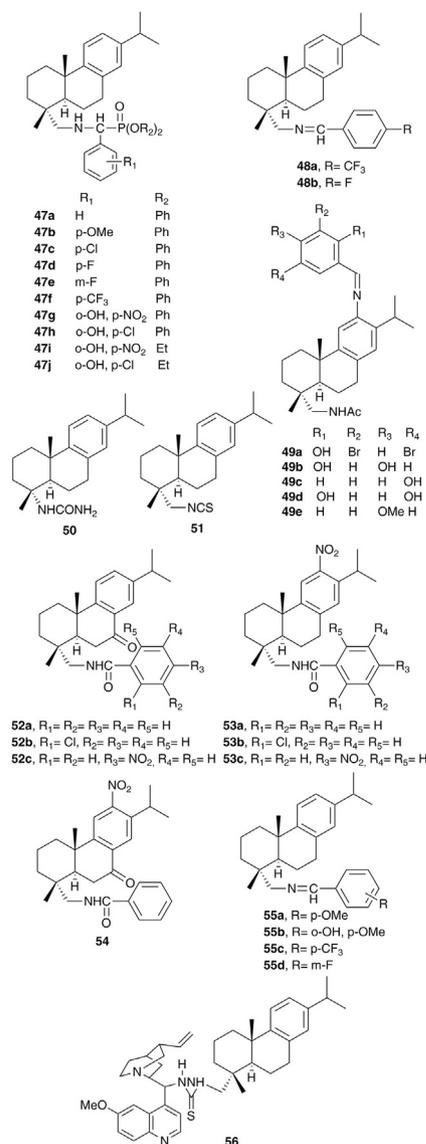


Fig. 10. Antitumour DHAA derivatives 47–56.

have been synthesised and evaluated for their antitumour activities on Hey-1B ovarian cancer cell line [53]. The IC₅₀ values were in the range of 15–20 μg/mL. The urea derivative **50** (Fig. 10) showed a significant dose-dependent and time-dependent inhibition of growth of human hepatoma HepG2 cells (IC₅₀ = 3.81 μM) [54]. It possibly has its effect by inhibition of glycolysis and glycolysis-dependent ATP depletion. The isothiocyanate derivative **51** (Fig. 10) at concentrations ca. 1 μM displayed dose-dependent and selective cytotoxicity to endometrial cancer cells in comparison to other cancer cell lines [55]. Lin et al. have prepared several benzamide derivatives, compounds **52a–c** and **53a–c** (Fig. 10), with a carbonyl group at C-7 on ring B or a nitro group at C-12 on ring C and evaluated the influence of these groups on the cytotoxicity against PC-3 (prostate) and Hey-1B (ovarian) cancer cell lines [56]. The results showed that the presence of either a carbonyl or a nitro group increased the cytotoxic activity. Among these compounds, **52a** and **53a–c** showed good cytotoxicities against PC-3 cancer cells (IC₅₀ = 5.7–8.2 μg/mL) and Hey-1B cancer cells (IC₅₀ = 11.3–16.0 μg/mL). These researchers also carried out a screening of 73 dehydroabietylamine derivatives as potential candidate inhibitors of the growth of liver cancer cells. In this study, N-benzoyl-12-

nitrodehydroabietylamine-7-one (**54**) (Fig. 10) demonstrated to have significant growth inhibitory activity in the human liver cancer cell line, HepG2 (IC₅₀ = 67.86 μg/mL) [57]. Further research confirmed that this compound effectively induced apoptosis and inhibited HepG2 cell proliferation by blocking DNA synthesis. However, another study of this research group showed that one or two nitro groups in ring C of DHAA (**5**) together with aromatic imines gave highly cytotoxic compounds to normal human hepatocyte (L02) cells [58]. Recently, Rao et al. screened a series of imines, amides and ureas with a dehydroabietyl skeleton for their antitumour activities against SMMC7721 (liver), A549 (lung), C6 (glioma) and MCF-7 (breast) cancer cell lines [59]. Imines **55a–d** (Fig. 10) possess noticeable antitumour activity against SMMC7721, A549, C6 and MCF-7 cancer cells, with lowest IC₅₀ values of 6.65, 0.75, 0.81, and 10.65 μM, respectively. The antitumour activity of DHAA (**5**) against two bladder cancer cell lines (EJ and 5637), one prostate cancer cell line (PC-3), one cervical cancer cell line (HeLa) and one human T-cell leukaemia cancer cell line (Jurkat) was improved with the attachment of quinidine via thiourea bond [60]. Thus, compound **56** (Fig. 10) exhibited broad spectrum of activity (IC₅₀ = 2.07–3.21 μM) against the tested cancer cell lines with little toxicity to normal cells, and induced apoptosis mainly through mitochondrial-dependent pathway.

But the biological properties of DHAA (**5**) derivatives go beyond antimicrobial and antitumour activities. For example, the anti-inflammatory activity of four derivatives of DHAA (**5**), compounds **57–60** (Fig. 11), has also been described. These compounds were found to be active as topical inflammation inhibitors as demonstrated in the tetradecanoylphorbol acetate induced ear oedema assay [61].

The derivative N-benzoyl-dehydroabietylamine-7-one (**61**) (Fig. 11) has been found to possess certain androgen receptor binding activity with IC₅₀ value of 83.8 μM [62]. And the imine derivative **62** (Fig. 11) displayed tyrosine kinase inhibitory activity (FGFR1, IC₅₀ = 1.20 μM) [63]. The antioxidative activity of derivative **63** (Fig. 11), which resulted from merging gallic acid and DHAA (**5**) through an amide bond, has also been reported [64]. Compound **63**

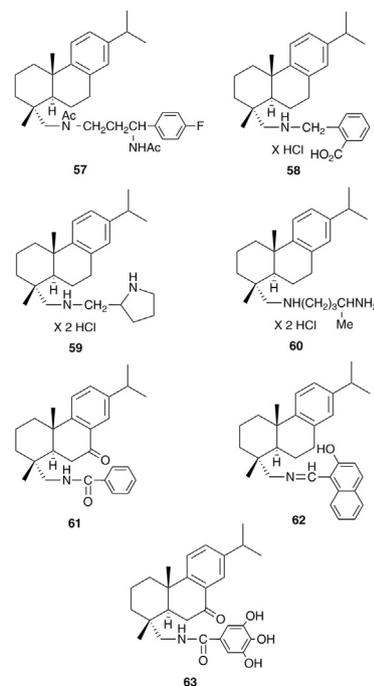


Fig. 11. Other bioactive DHAA derivatives 57–63.

was tested for the ability on scavenging superoxide anion radical and 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical. The results indicate that the inhibitory rate of superoxide anion radical by **63** was 38.18% which is twice as much as that of L-ascorbic acid (18.35%) and its capacity on scavenging DPPH radical ($IC_{50} = 2 \text{ mg/L}$) is much better than L-ascorbic acid ($IC_{50} = 236 \text{ mg/L}$).

In addition, DHAA (**5**) is a known inhibitor of pyruvate dehydrogenase kinase (PDK) which could have utility as a therapy for diabetes, ischaemia, lactic acidosis and cardiac insufficiency [65].

2.3. Ferruginol derivatives

Ferruginol (**3**) (Fig. 1) is an abietane diterpenoid that occurs in plants belonging to the *Podocarpaceae*, *Cupressaceae*, *Lamiaceae* and *Verbenaceae* families among others. This abietane has attracted much attention since it has exhibited promising bioactivities, such as antifungal and antimicrobial [66], cardioactive [67], antioxidative [68], antileishmanial and nematocidal [69]. In addition, ferruginol (**3**) has recently shown antitumour activity against prostate cancer [70], cytotoxicity against human pancreatic tumour cell lines [71], as well as anti-inflammatory activity [72]. This diterpene has also shown a strong protective effect in animal gastric ulcer models [73]. However, it has demonstrated high cytotoxicity which has led to the study of semisynthetic derivatives with lower toxicity. For example, Rodriguez et al. prepared a series of semisynthetic derivatives of ferruginol (**3**), compounds **64a–i** (Fig. 12), and assessed their gastroprotective effects in the HCl/ethanol-induced gastric lesion model in mice, as well as cytotoxicity in human gastric adenocarcinoma (AGS) and human lung fibroblasts (MRC-5) cells [74]. At 20 mg/kg, the greatest gastroprotective effects were provided by compounds **64a**, **64e**, **64f**, **64h**, and **64i**, all of which were as active as the reference drug lansoprazole at 20 mg/kg, reducing gastric lesions by 69, 76, 67, 72 and 61%, respectively. Compounds that showed the greatest cytotoxicity towards AGS cells were ferruginol (**3**), the corresponding formate **64b**, acetate **64c**, propionate **64d**, **64e**, **64f**, **64g**, and **64i** ($IC_{50} = 18–44 \text{ }\mu\text{M}$). Ferruginol (**3**) and compounds **64b–g**, and **64i** were the most toxic compounds against fibroblasts ($IC_{50} = 19–56 \text{ }\mu\text{M}$), with a correlation to AGS cells. The best activity/cytotoxicity ratio was found for compound **64h**, with a lesion index comparable with lansoprazole at 20 mg/kg and cytotoxicity $>1000 \text{ }\mu\text{M}$ towards MRC-5 and AGS cells, respectively. Later on, this research group described the synthesis and evaluation of several new semisynthetic ester derivatives of ferruginol (**3**), compounds **65a–g** (Fig. 12), using the same gastric model in mice and cell lines

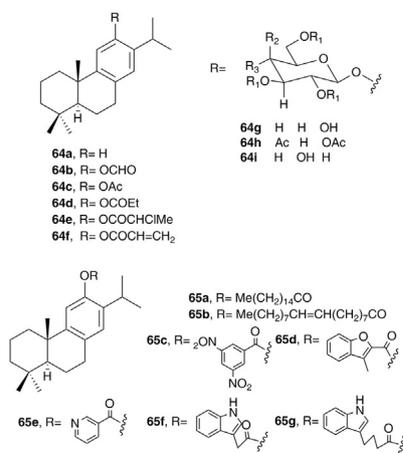


Fig. 12. Antiulcer ferruginol derivatives **64** and **65**.

[75]. Thus, the best gastroprotective effect was elicited by ferruginyl nicotinate (**65e**), reducing the lesion index by 71%, while the derivatives ferruginyl palmitate (**65a**), ferruginyl oleate (**65b**), ferruginyl 3,5-dinitrobenzoate (**65c**), ferruginyl 3-methylbenzofuran-2-carbonyl ester (**65d**), ferruginyl indoleacetate (**65f**) and ferruginyl indolebutyrate (**65g**) reduced the lesions by 50–66%. The most promising compounds were **65c**, **65e** and **65f**, presenting a gastroprotective effect higher or similar to that of ferruginol (**3**) but with a high selectivity towards the tumour AGS cells. Among these three products, the most selective towards AGS cells was **65f**, followed by **65e**, and **65c** (IC_{50} values of 12, 22, and 29 μM , respectively). The cytotoxicity of the above cited compounds towards fibroblasts was $>1000 \text{ }\mu\text{M}$.

The antitumour activity of sugiol (**66**) (Fig. 13), a ferruginol related diterpenoid, and several β -amino alcohol analogues, compounds **67a–d** (Fig. 13), has been reported [76]. In this work, these compounds were evaluated against three human solid tumour cell lines A2780 (ovarian), SW1573 (lung) and WiDr (colon) and showed more potent activities (IC_{50} values in the range 1.5–6.7 μM) than the parent compound **66** (IC_{50} values in the range 23–50 μM).

Gigante et al. prepared four catechols, compounds **68a–d** (Fig. 13) from abietic acid and evaluated several biological activities, including antifungal, antitumour, antiviral and inhibition of nitric oxide (NO) production [77]. Compounds **68a** and **68d** exhibited potent antifungal activity against dermatophytes *Microsporum canis*, *Trichophyton mentagrophytes* and *Epidermophyton floccosum*, being more potent ($MIC = 13.1–210.0 \text{ }\mu\text{M}$) than the control drug fluconazole ($MIC = 52.2–208.9 \text{ }\mu\text{M}$). Catechols **68a–d** were potent inhibitors of NO production ($IC_{50} = 5.2–18.5 \text{ }\mu\text{M}$) and also displayed moderate antitumour activity. Compound **68a** was found to have antiherpetic activity and moderate anti-HIV activity ($EC_{50} = 275 \text{ }\mu\text{M}$). Later on, this research group demonstrated the potential application of compound **68a** as antioxidant [78].

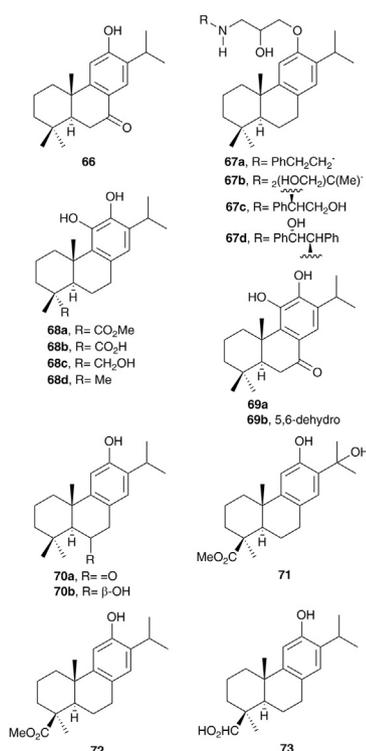


Fig. 13. Bioactive ferruginol derivatives **66–73**.

Tada et al. developed a synthetic route to (+)-ferruginol (**3**) and the corresponding enantiomer (–)-ferruginol. Using this methodology, this research group prepared various oxidised abietanes, including catechols **69a** and **69b** (Fig. 13), 6-oxoferruginol (**70a**) and 6 β -hydroxyferruginol (**70b**) (Fig. 13) and evaluated their antimicrobial activity against methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) [79]. Compounds **69–70** showed potent activity with MIC values of 4–8 $\mu\text{g}/\text{mL}$ against MRSA and 4–16 $\mu\text{g}/\text{mL}$ against VRE. Non-natural (–)-ferruginol showed stronger activity than natural (+)-ferruginol (**3**).

Recently, Sánchez-Moreno et al. reported on the antileishmanial activity (*Leishmania infantum* and *Leishmania braziliensis*) of several phenol abietanes related to ferruginol (**3**), compounds **71–73** (Fig. 13) [80]. These compounds were more active ($\text{IC}_{50} = 14.0\text{--}31.6 \mu\text{M}$) and less toxic than the reference drug glucantime.

2.4. Carnosol and carnosic acid derivatives

Carnosol (CS, **74**) (Fig. 14) and carnosic acid (CA, **4**) (Fig. 1) are found in the popular Lamiaceae herbs, sage (*Salvia officinalis*) and rosemary (*Rosmarinus officinalis*). Both possess an o-diphenol structure (catechol) which undergoes oxidation easily and provides potent antioxidant activity. The early studies on biological activity of derivatives of these abietanes considered particularly the antioxidant activity. For example, Nakatani et al. reported on the antioxidant activity of compounds **74b–d**, **75a–b** and **76b–e** (Fig. 14) derived from carnosol (**74**) and rosmanol (**76a**), a related catechol, respectively [81]. In general, when the phenol is fully substituted there is a decrease in activity while mono-substituted derivatives were as strong antioxidants as the parent compounds. Preparative-scale incubations of CA (**4**) with *Nocardia* sp. led to the isolation of derivatives **77** and **78** (Fig. 14), which were evaluated for antioxidant activity using the DPPH free-radical scavenging assay

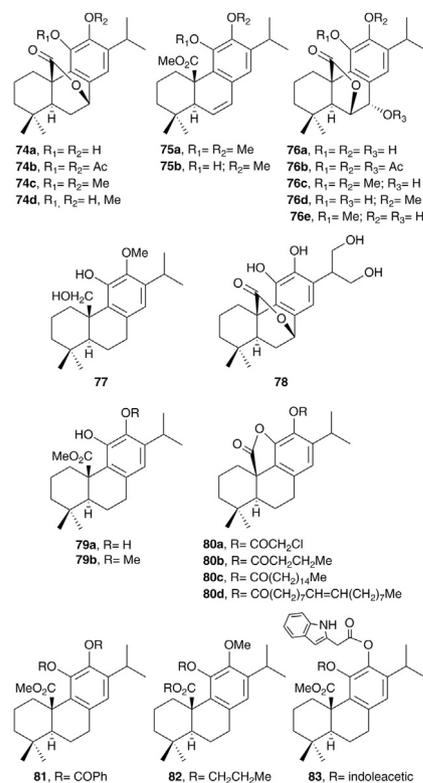


Fig. 14. Bioactive carnosic acid derivatives **74–83**.

[82]. Both compounds showed activities similar to that of tocopherol and CA (**4**).

Takeya et al. prepared several semisynthetic derivatives from CA (**4**), including compounds **79a–b** (Fig. 14), and examined the cytotoxic activity using P388 murine leukaemia cells [83]. Substitution of the phenol groups decreased the cytotoxicity, compound **79b** ($\text{IC}_{50} = 5.9 \mu\text{g}/\text{mL}$), but the free hydroxyl groups along with the ester group at C-20, compound **79a** ($\text{IC}_{50} = 0.6 \mu\text{g}/\text{mL}$), gave more potent activity than CA (**4**) ($\text{IC}_{50} = 1.2 \mu\text{g}/\text{mL}$). In another study, compound **79b** also showed cytotoxicity against breast (MCF-7) cancer cell line ($\text{IC}_{50} = 69 \mu\text{M}$) as well as activity against *Mycobacterium tuberculosis* (MIC = 28 μM), being more potent than carnosol (**74**) [84].

The gastroprotective activity of carnosic acid (**4**) derivatives has also been reported. For example, Schmeda-Hirschmann et al. described the synthesis and evaluation of a series of γ -lactone derivatives (e. g. **80a–d**) (Fig. 14) of carnosic acid (**4**) in the HCl/ethanol-induced gastric lesion model in mice, as well as cytotoxicity in human gastric adenocarcinoma (AGS) and human lung fibroblasts (MRC-5) cells [85]. Compounds **80a–d** showed the highest gastroprotective effect (65–82% lesion reduction), however, compound **80a** was more cytotoxic ($\text{IC}_{50} = 130 \mu\text{M}$ for MRC-5 and 103 μM for AGS) than compounds **80c** and **80d**, which presented IC_{50} values of >1000 μM against MRC-5 cells and >1000 and 822 μM toward AGS cells, respectively. Later on, this research group reported on the gastroprotective effect of further derivatives of carnosic acid (**4**), compounds **81–83** (Fig. 14). At 10 mg/kg, compounds **81–83** were more effective preventing gastric lesions (73–78% lesion reduction) than the reference drug lansoprazole at the same dose (64% lesion reduction). These compounds showed the best gastroprotective effect combines with the lowest cytotoxicity [86]. Their mechanism of action has also been studied, which includes protection against cell damage induced by sodium taurocholate, increase in glutathione content, stimulation of prostaglandin E₂ synthesis and cell proliferation [87].

3. Conclusion

A number of derivatives of natural aromatic abietanes have been synthesised and studied for biological properties. The encouraging findings warrant further interesting studies in this area of research, which could provide with novel chemotherapeutics and chemical probes.

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