Synthetic Derivatives of Aromatic Abietane Diterpenoids and Their Biological Activities

ARTICLE *in* EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY · OCTOBER 2014

Impact Factor: 3.45 · DOI: 10.1016/j.ejmech.2014.10.023

1 AUTHOR:

Miguel A. González
University of Valencia
52 PUBLICATIONS **532** CITATIONS

SEE PROFILE

European Journal of Medicinal Chemistry 87 (2014) 834–842

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Mini-review

Synthetic derivatives of aromatic abietane diterpenoids and their biological activities

Miguel A. González

Departamento de Química Orgánica, Universidad de Valencia, E-46100 Burjassot, Valencia, Spain

ARTICLE INFO

Article history:
Received 26 August 2014
Received in revised form
6 October 2014
Accepted 9 October 2014
Available online 13 October 2014

Keywords:
Abietane
Diterpenoid
Dehydroabietic acid
Ferruginol
Dehydroabietylamine
Carnosic acid

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

E-mail address: Miguel.A.Gonzalez@uv.es.

http://dx.doi.org/10.1016/j.ejmech.2014.10.023
0223-5234/

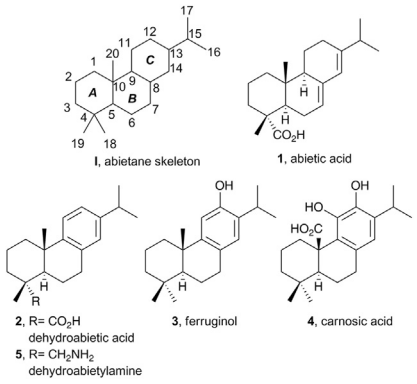

Fig. 1. Abietane numbering system and abietanes **1**–**5**.

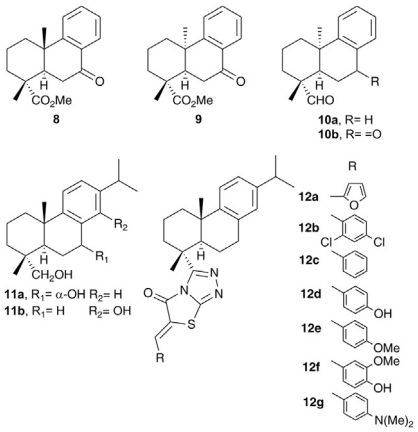

Fig. 3. Antifungal DHA derivatives **8**–**12**.

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*.

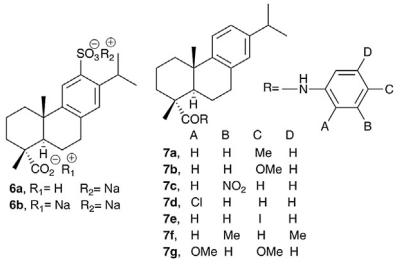

Fig. 2. Antiulcer DHA derivatives **6**–**7**.

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.*

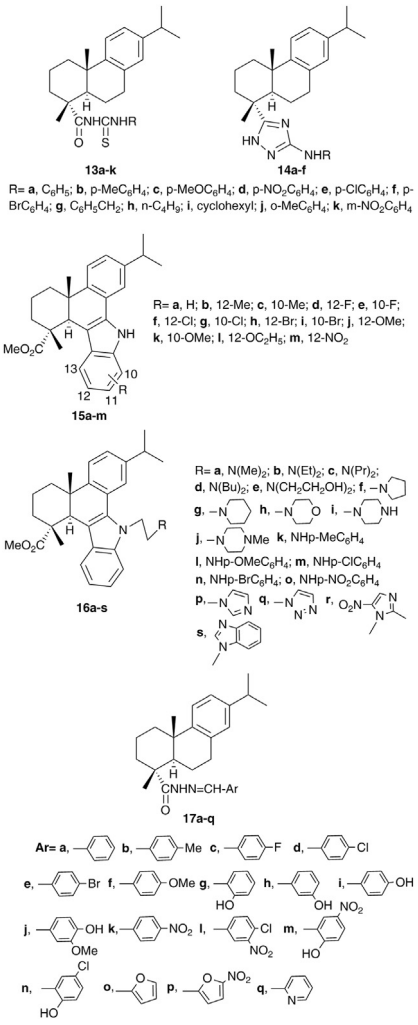

Fig. 4. Antimicrobial DHA derivatives **13**–**17**.

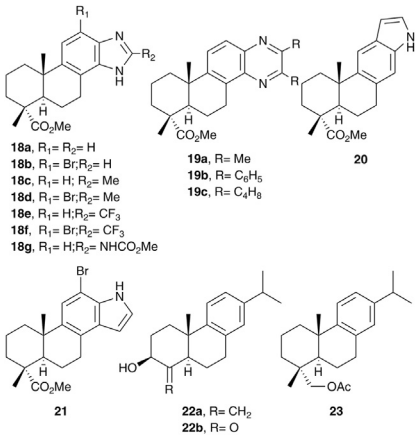

Fig. 5. Antiviral DHA derivatives **18**–**23**.

subtilis, *S. aureus*, *E. coli*, and *P. fluorescens*). Among the tested compounds, compound **17p** (MIC = 1.9 μg/mL) exhibited good antibacterial activity against *S. aureus* and *B. subtilis* comparable to positive control (amikacin, MIC = 0.9 μg/mL). Compounds **17l**, **17n** and **17p** also showed strong inhibitions (3.9–7.8 μg/mL) against the Gram-negative strains *E. coli* and *P. fluorescens*.

The antiviral activity of DHA (**2**) derivatives has also been studied. For example, Fonseca et al. described the synthesis of novel heterocycles (Fig. 5), such as benzimidazoles (**18a**–**g**), quinoxalines (**19a**–**c**), and indoles **20** and **21** as potential antiviral agents [20]. Biological evaluation showed that compounds **18b**, **18e**, **19c**, and **21** inhibited both varicella-zoster virus (VZV) and cytomegalovirus (CMV) replication at a concentration ca. 5- to 10-fold lower than the cytotoxic concentration, when tested in human embryonic lung cells. The potencies of **18a**, **18b**, **18d**, **18e**, **19c**, **20** and **21** as anti-VZV agents were comparable to that of acyclovir (IC_{50} = 0.3–3.0 μg/mL), while the potencies of **18a**, **18b**, **18e**, **19c** and **21** as anti-CMV agents were comparable to that of ganciclovir (IC_{50} = 0.9–1.5 μg/mL). However, all these derivatives were not active against herpes simplex virus (HSV-1 and HSV-2), vaccinia virus, vesicular stomatitis virus, Coxsackie viruss B4, respiratory syncytial virus, and human immunodeficiency virus at a concentration of 400 pg/mL. Two different studies confirmed anti-herpetic activity for DHA (**2**) derivatives. Firstly, Tagat et al. reported that A-ring hydroxylated compounds **22a** and **22b** (Fig. 5) show HSV-2 inhibitory activity and concluded that they interfere with an early event in viral replication [21]. And secondly, Gonzalez et al. described that dehydroabietinol acetate **23** (Fig. 5) showed significant anti-herpetic activity of broad spectrum [13,22].

DHA (**2**) has exhibited strong inhibitory effects on Epstein–Barr virus early antigen (EBV-EA) activation induced by 12-O-tetradecanoylphorbol-13-acetate (TPA) and was selected to examine effects on *in vivo* two-stage mouse skin carcinogenesis. It exhibited high activity in this antitumour-promoting test [23]. Two oxidation products of methyl abietate, compounds **24a** and **24b** (Fig. 6), have displayed weak cytotoxicity against KB cells (IC_{50} = 4.5 and 5.8 μg/mL, respectively) [24]. Rao et al. reported a cytotoxicity study on liver cancer cells (SMMC7721) of a number of N,N'-substituted ureas (*e. g.* **25a**–**d**) (Fig. 6) synthesised from DHA (**2**) [25]. Their IC_{50} values were between 8.8 and 14.2 μM. The change of N′-substituted groups resulted little difference to the cytotoxicity activities of ureas, which indicated that the cytotoxicity of this kind of ureas depend strongly on the tricyclic hydrophenanthrene structure. Later on, these authors described the synthesis and antitumour activities of several acylthioureas (*e. g.* **26**) (Fig. 6) on liver cancer cells (SMMC7721) and lung cancer cells (A549) [26]. Compound **26** exhibited higher inhibition ratio against A549 than SMMC7721 (82.89% and 61.72%, respectively). Its IC_{50} was 6.44 μM for A549 and 6.84 μM for SMMC7721. Recently, Zhang et al. continued this research on thioureas and studied novel α-aminophosphonates dehydroabietic acid derivatives (*e. g.* **27a**–**c**) (Fig. 6) against several human cancer cell lines, including NCI-H460 (lung), A549 (lung), HepG2 (liver) and SKOV3 (ovarian) [27]. Compound **27a** exhibited the best antitumour activity on NCI-H460 with IC_{50} of 3.33 μM and demonstrated better cytotoxic inhibition than 5-fluorouracil (5-FU) in all tested cell lines. Its apoptosis-inducing activity on NCI-H460 cells was studied and the results revealed that this compound showed clear cell apoptosis inducing effects. Also, C7-functionalised derivative **27c** exhibited high level of antitumour activities against the tested cancer cell lines and demonstrated to be more potent compared with the commercial anticancer drug 5-FU. This compound induced cell apoptosis in A549 cells. The cytotoxic activities of several amino acid-conjugate derivatives of DHA (**2**), compounds **28a**–**h** (Fig. 6), against four human cancer cell lines (HL60, leukaemia), (A549, lung), (AZ521, stomach) and (SK-BR-3, breast) have been reported [28]. All compounds showed cytotoxicity against HL60 cells with IC_{50} values in the range of 2.3–37.3 μM. In addition, most of the derivatives exhibited moderate cytotoxicity against the other cancer cell lines. Among the derivatives, l-tyrosine derivative **28g** exhibited potent activities against the four cancer cell lines with IC_{50} values of 2.3 (HL60), 7.1 (A549), 3.9 (AZ521), and

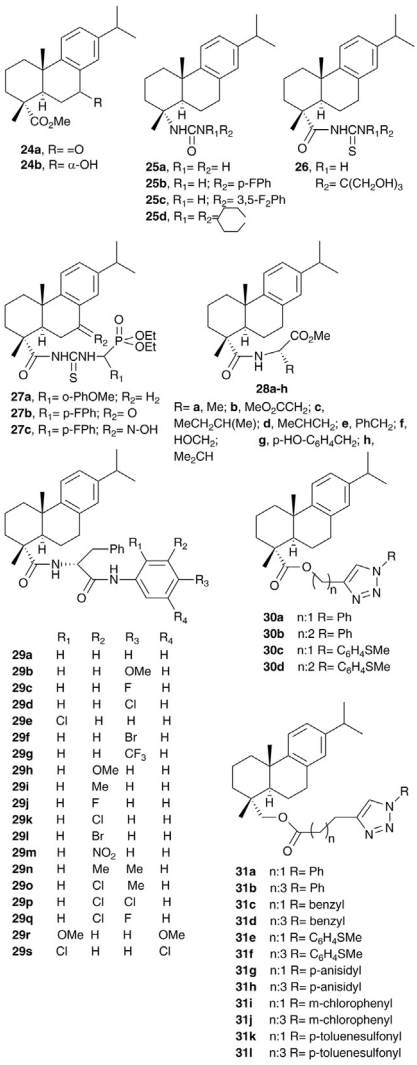

Fig. 6. Antitumour DHA derivatives **24**–**31**.

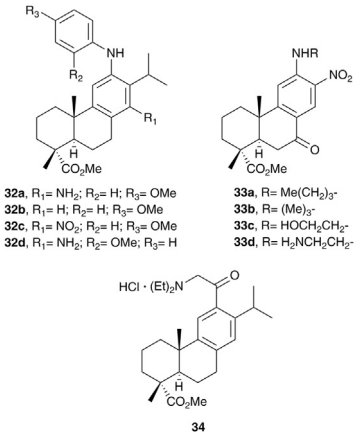

Fig. 7. Antioxidant DHA derivatives **32**–**33** and sedative and antipyretic DHA derivative **34**.

8.1 μM (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 antiproliferative 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 IC_{50} value of 6.1 μM in the SK-MES-1 cell line derived from metastatic site. Under the same experimental conditions, the IC_{50} value of etoposide was 1.83 μM.

The redox properties of several diarylamines (*e. g.* **32a**–**d**) (Fig. 7) derived from DHA (**2**) have been investigated by cyclic 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 isopropyldiphenylamine (IPPD) and superior to *tert*-butylhydroxytoluene (BHT). In order to probe the antioxidant effect of a series of methyl 12-imino-13-nitro dehydrodeisopropylabietate derivatives (**33a**–**d**) (Fig. 7), the metal ion binding abilities on Cu^{2+} and Fe^{2+} 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 10^2 L mol^{-1} order of magnitude, which implied its potential pharmacology application as antioxidant by the inhibition of Fenton reaction through chelation with Cu^{2+} and Fe^{2+}. Compound **33b** has the strongest chelation activity with Cu^{2+}, while **33d** has the strongest chelation activity with Fe^{2+}, 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-dichlorodehydroabietic 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 μM [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-dichlorodehydroabietic 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].

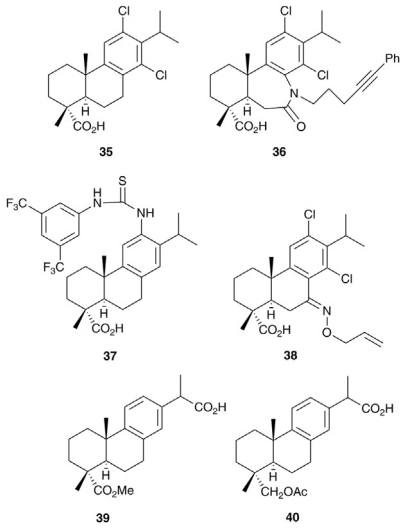

Fig. 8. BK channel openers based on DHA derivatives **35**–**38** and anti-inflammatory derivatives **39** and **40**.

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

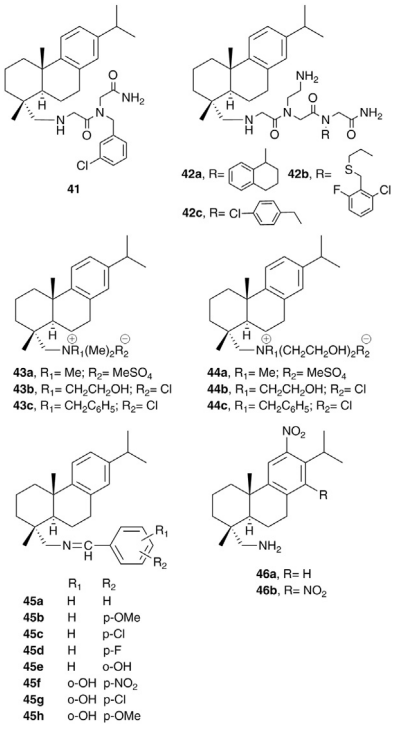

Fig. 9. Antimicrobial DHAA derivatives **41**–**46**.

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 μg/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 μg/mL for *S. aureus*, and 250–500 μg/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-flurobenzaldehyde derivative **48b** (Fig. 10) displayed a significant inhibitory effect on the growth of SMMC7721 cells in a dose- and time-dependent manner ($IC_{50} = 44.5$ μM) [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

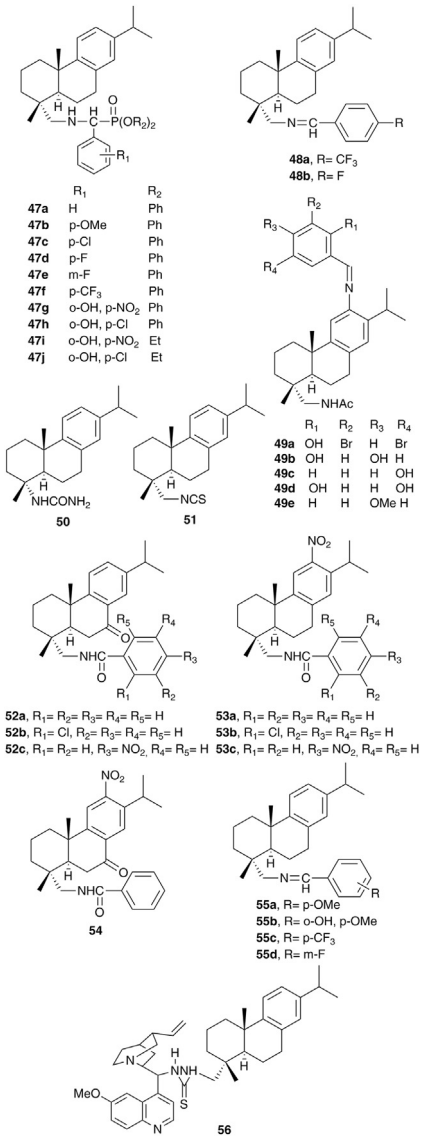

Fig. 10. Antitumour DHAA derivatives **47**–**56**.

have been synthesised and evaluated for their antitumour activities on Hey-1B ovarian cancer cell line [53]. The IC_{50} 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 (IC_{50} = 3.81 μM) [54]. It possibly has its effect by inhibition of glucolysis and glucolysis-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 (IC_{50} = 5.7–8.2 μg/mL) and Hey-1B cancer cells (IC_{50} = 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 (IC_{50} = 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 IC_{50} 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 (IC_{50} = 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 IC_{50} value of 83.8 μM [62]. And the imine derivative **62** (Fig. 11) displayed tyrosine kinase inhibitory activity (FGFR1, IC_{50} = 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**

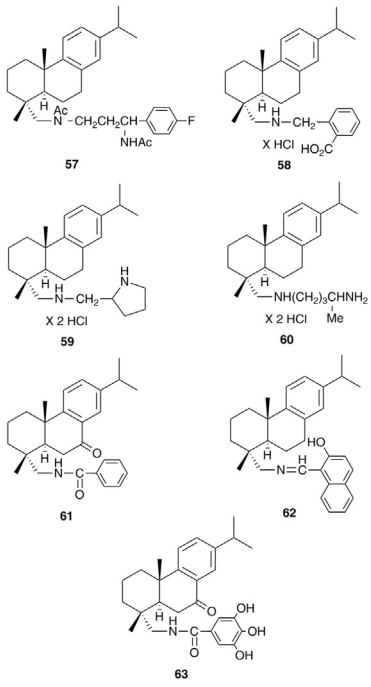

Fig. 11. Other bioactive DHAA derivatives **57**–**63**.

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 mg/L) is much better than L-ascorbic acid (IC_{50} = 236 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 nematicidal [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 μM). Ferruginol (**3**) and compounds **64b**–**g**, and **64i** were the most toxic compounds against fibroblasts (IC_{50} = 19–56 μM), 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 μM 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 [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 μM.

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 μM) than the control drug fluconazole (MIC = 52.2–208.9 μM). Catechols **68a**–**d** were potent inhibitors of NO production (IC_{50} = 5.2–18.5 μM) and also displayed moderate antitumour activity. Compound **68a** was found to have antiherpetic activity and moderate anti-HIV activity (EC_{50} = 275 μM). Later on, this research group demonstrated the potential application of compound **68a** as antioxidant [78].

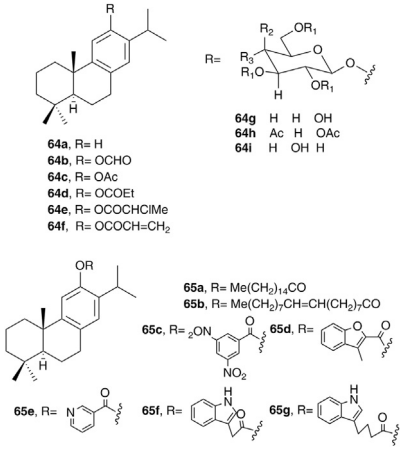

Fig. 12. Antiulcer ferruginol derivatives **64** and **65**.

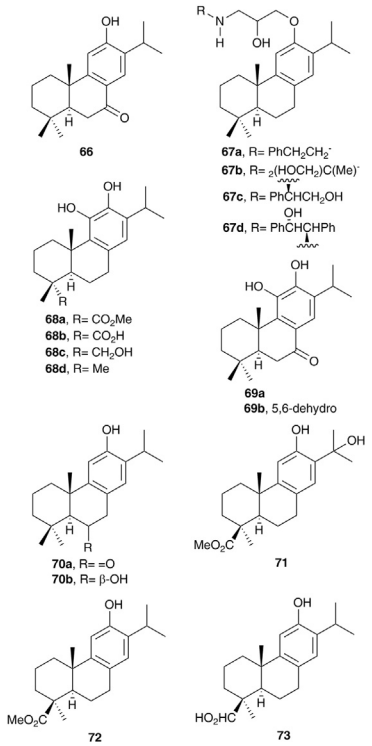

Fig. 13. Bioactive ferruginol derivatives **66**–**73**.

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 6β-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 μg/mL against MRSA and 4–16 μg/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 (IC_{50} = 14.0–31.6 μM) 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 [82]. Both compounds showed activities similar to that of tocopherol and CA (**4**).

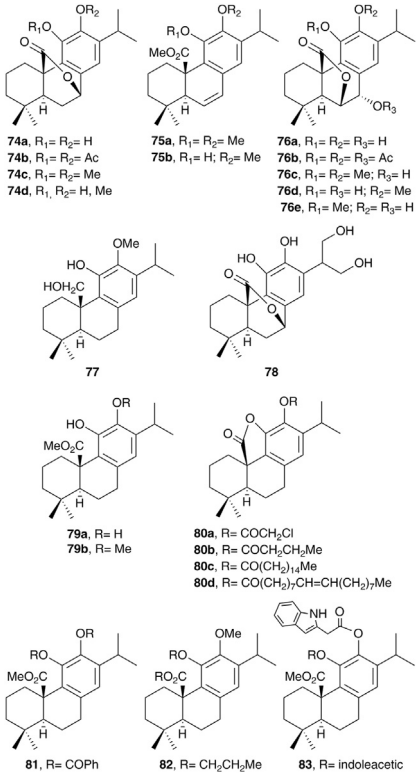

Fig. 14. Bioactive carnosic acid derivatives **74**–**83**.

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** (IC_{50} = 5.9 μg/mL), but the free hydroxyl groups along with the ester group at C-20, compound **79a** (IC_{50} = 0.6 μg/mL), gave more potent activity than CA (**4**) (IC_{50} = 1.2 μg/mL). In another study, compound **79b** also showed cytotoxicity against breast (MCF-7) cancer cell line (IC_{50} = 69 μM) 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 (IC_{50} = 130 μM 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 E_2 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.

Acknowledgements

Financial support from the Universidad de Valencia is gratefully acknowledged.

References

[1] D.J. Newman, G.M. Cragg, J. Nat. Prod. 75 (2012) 311–335.
[2] J.R. Hanson, Nat. Prod. Rep. 30 (2013) 1346–1356 and preceding contributions of the author.
[3] A. San Feliciano, M. Gordaliza, M.A. Salinero, J.M. Miguel del Corral, Planta Med. 59 (1993) 485–490.
[4] L.F. Fieser, W.P. Campbell, J. Am. Chem. Soc. 60 (1938) 159–170.
[5] C.W. Brandt, L.G. Neubauer, J. Chem. Soc. (1939) 1031–1037.
[6] (a) G.C. Harris, J. Am. Chem. Soc. 70 (1948) 3671–3674;
(b) T. Norin, B. Winell, Acta Chem. Scand. 26 (1972) 2289–2296;
(c) A. Ulubelen, M. Miski, T.J. Mabry, J. Nat. Prod. 44 (1981) 119–124.
[7] N. Okamura, Y. Fujimoto, S. Kuwabara, A. Yagi, J. Chromatogr. A 679 (1994) 381–386.
[8] H. Wada, S.-I. Kodato, M. Kawamori, T. Morikawa, H. Nakai, M. Takeda, S. Saito, Y. Onoda, H. Tamaki, Chem. Pharm. Bull. 33 (1985) 1472–1487.
[9] B. Sepúlveda, L. Astudillo, J.A. Rodríguez, T. Yañez, C. Theoduloz, G. Schmeda-Hirschmann, Pharmacol. Res. 52 (2005) 429–437.
[10] S. Savluchinske-Feio, M.J. Marcelo Curto, B. Gigante, J.C. Roseiro, Appl. Microbiol. Biotechnol. 72 (2006) 430–436.

[11] S. Savluchinske-Feio, B. Gigante, J.C. Roseiro, M.J. Marcelo Curto, J. Microbiol. Methods 35 (1999) 201–206.
[12] B. Gigante, A.M. Silva, M.J. Marcelo Curto, S. Savluchinske-Feio, J.C. Roseiro, L.V. Reis, Planta Med. 68 (2002) 680–684.
[13] M.A. González, D. Pérez-Guaita, J. Correa-Royero, B. Zapata, L. Agudelo, A. Mesa-Arango, L. Betancur-Galvis, Eur. J. Med. Chem. 45 (2010) 811–816.
[14] B. Zapata, M. Rojas, L. Betancur-Galvis, A.C. Mesa-Arango, D. Pérez-Guaita, M.A. González, Med. Chem. Comm. 4 (2013) 1239–1246.
[15] X.-T. Xu, X.-L. Ma, W.-G. Duan, L. Chen, B. Cen, Q.-J. Mo, J.-Y. Wang, Holzforschung 67 (2013) 107–112.
[16] G.-F. Su, L.-N. Huo, R. Chen, F.-L. Zhao, Y.-F. Guan, Acta Chim. Sin. 66 (2008) 2717–2724.
[17] W. Gu, S. Wang, Eur. J. Med. Chem. 45 (2010) 4692–4696.
[18] W. Gu, C. Qiao, S.-F. Wang, Y. Hao, T.-T. Miao, Bioorg. Med. Chem. Lett. 24 (2014) 328–331.
[19] W. Gu, R. Wu, S. Qi, C. Gu, F. Si, Z. Chen, Molecules 17 (2012) 4634–4650.
[20] T. Fonseca, B. Gigante, M.M. Marques, T.L. Gilchrist, E. De Clercq, Bioorg. Med. Chem. 12 (2004) 103–112.
[21] J.R. Tagat, D.V. Nazareno, M.S. Puar, S.W. McCombie, A.K. Ganguly, Bioorg. Med. Chem. Lett. 4 (1994) 1101–1104.
[22] L.S. Agudelo-Gómez, L.A. Betancur-Galvis, M.A. González, Pharmacologyonline 1 (2012) 36–42.
[23] R. Tanaka, H. Tokuda, Y. Ezaki, Phytomedicine 15 (2008) 985–992.
[24] S. Prinz, U. Müllner, J. Heilmann, K. Winkelmann, O. Sticher, E. Haslinger, A. Hüfner, J. Nat. Prod. 65 (2002) 1530–1534.
[25] X. Rao, Z. Song, L. He, W. Jia, Chem. Pharm. Bull. 56 (2008) 1575–1578.
[26] X.-P. Rao, Y. Wu, Z.-Q. Song, S.-B. Shang, Z.-D. Wang, Med. Chem. Res. 20 (2011) 333–338.
[27] (a) X.-C. Huang, M. Wang, Y.-M. Pan, G.-Y. Yao, H.-S. Wang, X.-Y. Tian, J.-K. Qin, Y. Zhang, Eur. J. Med. Chem. 69 (2013) 508–520;
(b) X.-C. Huang, M. Wang, Y.-M. Pan, X.-Y. Tian, H.-S. Wang, Y. Zhang, Bioorg. Med. Chem. Lett. 23 (2013) 5283–5289.
[28] M. Ukiya, T. Kawaguchi, K. Ishii, E. Ogihara, Y. Tachi, M. Kurita, Y. Ezaki, M. Fukatsu, Y. Kushi, T. Akihisa, Chem. Biodiv. 10 (2013) 1260–1268.
[29] X.-C. Huang, M. Wang, H.-S. Wang, Z.-F. Chen, Y. Zhang, Y.-M. Pan, Bioorg. Med. Chem. Lett. 24 (2014) 1511–1518.
[30] M.W. Pertino, V. Verdugo, C. Theoduloz, G. Schmeda-Hirschmann, Molecules 19 (2014) 2523–2535.
[31] M.A. Esteves, N. Narender, M.J. Marcelo-Curto, B. Gigante, J. Nat. Prod. 64 (2001) 761–766.
[32] K. Wang, X. Liu, X. Yi, H. Wang, Y. Zhang, Y. Pan, Med. Chem. Res. 21 (2012) 2494–2500.
[33] I.A. Tolmacheva, A.V. Tarantin, A.A. Boteva, L.V. Anikina, Y.B. Vikharev, V.V. Grishko, A.G. Tolstikov, Pharm. Chem. J. 40 (2006) 489–493.
[34] T. Ohwada, T. Nonomura, K. Maki, K. Sakamoto, S. Ohya, K. Muraki, Y. Imaizumi, Bioorg. Med. Chem. Lett. 13 (2003) 3971–3974.
[35] T. Tashima, Y. Toriumi, Y. Mochizuki, T. Nonomura, S. Nagaoka, K. Furukawa, H. Tsuru, S. Adachi-Akahane, T. Ohwada, Bioorg. Med. Chem. 14 (2006) 8014–8031.
[36] Y.-M. Cui, E. Yasutomi, Y. Otani, T. Yoshinaga, K. Ido, K. Sawada, T. Ohwada, Bioorg. Med. Chem. Lett. 18 (2008) 5201–5205.
[37] Y.-M. Cui, E. Yasutomi, Y. Otani, T. Yoshinaga, K. Ido, K. Sawada, M. Kawahata, K. Yamaguchi, T. Ohwada, Bioorg. Med. Chem. Lett. 18 (2008) 6386–6389.
[38] Y.-M. Cui, E. Yasutomi, Y. Otani, K. Ido, T. Yoshinaga, K. Sawada, T. Ohwada, Bioorg. Med. Chem. 18 (2010) 8642–8659.
[39] G. Gessner, Y.-M. Cui, Y. Otani, T. Ohwada, M. Soom, T. Hoshi, S.H. Heinemann, PNAS 109 (2012) 3552–3557.
[40] W.-S. Li, J.D. McChesney, J. Pharm. Sci. 81 (1992) 646–651.
[41] X. Rao, Z. Song, H. Gao, Chem. Bull. 69 (2006) 168–172.
[42] P.C. De Vissier, G.J. Platenburg, J.T. Van Dissel, WO 2008016300 A2, 2008.
[43] G.P. Robertson, C.D. Raghavendragowda, S.V. Madhunapantula, O.F. Kuzu, G.S. Inamdar, US Patent 20120141578 A1, 2012.
[44] B. Goodson, A. Ehrhardt, S. Ng, J. Nuss, K. Johnson, M. Giedlin, R. Yamamoto, W.H. Moos, A. Krebber, M. Ladner, M.B. Giacona, C. Vitt, J. Winter, Antimicrob. Agents Chemother. 43 (1999) 1429–1434.
[45] Y. Li, Chin. J. Struct. Chem. 27 (2008) 1089–1092.
[46] Y. Wang, C. Yang, Y. Zhou, Z. Song, Nat. Prod. Res. Dev. 10 (1998) 59–63.
[47] X. Rao, Z. Song, A.B. Radbil', B.A. Radbil', Russ. J. Appl. Chem. 80 (2007) 1373–1375.
[48] S. Zhang, Z. Lin, J. Chem. Ind. Eng. (China) 60 (2009) 3077–3081.
[49] R. Gowda, S.V. Madhunapantula, O.F. Kuzu, A. Sharma, G.P. Robertson, Mol. Cancer Ther. 13 (2014) 1679–1689.
[50] X. Rao, Z. Song, L. He, Heteroat. Chem. 19 (2008) 512–516.
[51] F. Li, L. He, Z. Song, J.-C. Yao, X.-P. Rao, H.-T. Li, J. Pharm. Pharmacol. 60 (2008) 205–211.
[52] L. Liu, F. Li, L. He, X.-P. Rao, Z.-Q. Song, Chin. Pharm. J. 48 (2013) 269–274.
[53] S. Zhang, Z. Lin, Chin. J. Pharm. 41 (2010) 566–579.
[54] J.X. Xie, L. He, L.-Y. Zhang, X.-P. Rao, Z.-Q. Song, J. China Pharm. Univ. 41 (2010) 160–165.
[55] T.C. Horan, M.A. Zompa, C.T. Seto, K.K. Kim, R.G. Moore, T.S. Lange, Investig. New Drugs 30 (2012) 1460–1470.
[56] Y. Chen, Z.-X. Lin, A.-M. Zhou, Nat. Prod. Res. 26 (2012) 2188–2195.
[57] L.-Y. Lin, Y.-L. Bao, Y. Chen, L.-G. Sun, X.-G. Yang, B. Liu, Z.-X. Lin, Y.-W. Zhang, C.-L. Yu, Y. Wu, Y.-X. Li, Chem. Biol. Interact. 199 (2012) 63–73.
[58] C.-X. Liu, Z.-X. Lin, X. Yu, Z. Lu, A.-M. Zhou, Y.-L. Bao, Pharmazie 68 (2013) 861–865.
[59] X. Rao, X. Huang, L. He, J. Song, Z. Song, S. Shang, Comb. Chem. High Throughput Screen. 15 (2012) 840–844.
[60] Y. Xing, W. Zhang, J. Song, Y. Zhang, X. Jiang, R. Wang, Bioorg. Med. Chem. Lett. 23 (2013) 3868–3872.
[61] W.W. Wilkerson, W. Galbraith, I. DeLucca, R.R. Harris, Bioorg. Med. Chem. Lett. 3 (1993) 2087–2092.
[62] Y. Chen, Z.-X. Lin, Chem. Ind. For. Prod. 29 (2009) 121–124.
[63] T.-T. Zhou, L. He, M. Yang, L.-Y. Zhang, J.-G. He, X.-P. Rao, Chin. J. Nat. Med. 11 (2013) 506–513.
[64] Z. Lu, C. Liu, X. Yu, Z. Lin, Chin. J. Org. Chem. 33 (2013) 562–567.
[65] T.D. Aicher, R.E. Damon, J. Koletar, C.C. Vinluan, L.J. Brand, J. Gao, S.S. Shetty, E.L. Kaplan, W.R. Mann, Bioorg. Med. Chem. Lett. 9 (1999) 2223–2228.
[66] J. Becerra, C. Flores, J. Mena, P. Aqueveque, J. Alarcón, M. Bittner, V. Hernández, M. Hoeneisen, E. Ruiz, M. Silva, J. Chil. Chem. Soc. 47 (2002) 151–157.
[67] A. Ulubelen, H. Birman, S. Oksuz, G. Topcu, U. Kolak, A. Barla, W. Voelter, Planta Med. 68 (2002) 818–821.
[68] M. Ono, M. Yamamoto, C. Masuoka, Y. Ito, M. Yamashita, T. Nohara, J. Nat. Prod. 62 (1999) 1532–1537.
[69] V. Samoylenko, D.C. Dunbar, M.A. Gafur, S.I. Khan, S.A. Ross, J.S. Mossa, F.S. El-Feraly, B.L. Tekwani, J. Bosselaers, I. Muhammad, Phytother. Res. 22 (2008) 1570–1576.
[70] M. Bispo de Jesus, W.F. Zambuzzi, R.R. Ruela de Sousa, C. Areche, A.C. Santos de Souza, H. Aoyama, G. Schmeda-Hirschmann, J.A. Rodríguez, A.R.M. de Souza Brito, M.P. Peppelenbosch, J. den Hertog, E. de Paula, C.V. Ferreira, Biochimie 90 (2008) 843–854.
[71] M. Fronza, R. Murillo, S. Slusarczyk, M. Adams, M. Hamburger, B. Heinzmann, S. Laufer, I. Merfort, Bioorg. Med. Chem. 19 (2011) 4876–4881.
[72] H.L. Chen, K.W. Lin, K.H. Gan, J.P. Wang, S.J. Won, C.N. Lin, Fitoterapia 82 (2011) 219–224.
[73] J.A. Rodriguez, C. Theoduloz, T. Yañez, J. Becerra, G. Schmeda-Hirschmann, Life Sci. 78 (2006) 2503–2509.
[74] C. Areche, J.A. Rodriguez, I. Razmilic, T. Yañez, C. Theoduloz, G. Schmeda-Hirschmann, J. Pharm. Pharmacol. 59 (2007) 289–300.
[75] M. Espinoza, L.S. Santos, C. Theoduloz, G. Schmeda-Hirschmann, J.A. Rodriguez, Planta Med. 74 (2008) 802–808.
[76] I. Córdova, L.G. León, F. León, L. San Andrés, J.G. Luis, J.M. Padrón, Eur. J. Med. Chem. 41 (2006) 1327–1332.
[77] B. Gigante, C. Santos, A.M. Silva, M.J.M. Curto, M.S.J. Nascimento, E. Pinto, M. Pedro, F. Cerqueira, M.M. Pinto, M.P. Duarte, A. Laires, J. Rueff, J. Gonçalves, M.I. Pegado, M.L. Valdeira, Bioorg. Med. Chem. 11 (2003) 1631–1638.
[78] G.C. Justino, C.F. Correia, L. Mira, R.M.B. Dos Santos, J.A.M. Simões, A.M. Silva, C. Santos, B. Gigante, J. Agric. Food Chem. 54 (2006) 342–348.
[79] Z. Yang, Y. Kitano, K. Chiba, N. Shibata, H. Kurokawa, Y. Doi, Y. Arakawa, M. Tada, Bioorg. Med. Chem. 9 (2001) 347–356.
[80] I. Ramírez-Macías, C. Marín, R. Chahboun, F. Olmo, I. Messouri, O. Huertas, M.J. Rosales, R. Gutierrez-Sánchez, E. Alvarez-Manzaneda, M. Sánchez-Moreno, Mem. Inst. Oswaldo Cruz 107 (2012) 370–376.
[81] R. Inatani, N. Nakatani, H. Fuwa, Agric. Biol. Chem. 47 (1983) 521–528.
[82] M. Hosny, H.A. Johnson, A.K. Ueltschy, J.P.N. Rosazza, J. Nat. Prod. 65 (2002) 1266–1269.
[83] Y. Aoyagi, Y. Takahashi, Y. Satake, K. Takeya, R. Aiyama, T. Matsuzaki, S. Hashimoto, T. Kurihara, Bioorg. Med. Chem. 14 (2006) 5285–5291.
[84] A.A. Hussein, J.J.M. Meyer, M.L. Jimeno, B. Rodríguez, J. Nat. Prod. 70 (2007) 293–295.
[85] M.W. Pertino, C. Theoduloz, J.A. Rodriguez, T. Yañez, V. Lazo, G. Schmeda-Hirschmann, J. Nat. Prod. 73 (2010) 639–643.
[86] C. Theoduloz, M.W. Pertino, J.A. Rodriguez, G. Schmeda-Hirschmann, Planta Med. 77 (2011) 882–887.
[87] C. Theoduloz, M.W. Pertino, G. Schmeda-Hirschmann, Molecules 19 (2014) 581–594.