Review

Allobetulin and Its Derivatives: Synthesis and Biological Activity

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Abstract: This review covers the chemistry of allobetulin analogs, including their formation by rearrangement from betulin derivatives, their further derivatisation, their fusion with heterocyclic rings, and any further rearrangements of allobetulin compounds including ring opening, ring contraction and ring expansion reactions. In the last part, the most important biological activities of allobetulin derivatives are listed. One hundred and fifteen references are cited and the relevant literature is covered, starting in 1922 up to the end of 2010.

Keywords: triterpene; allobetulin; rearrangement; biological activity

1. Introduction

Triterpenes and triterpenoids are numerous and widely distributed in Nature. Biosynthetically, they are derived from squalene. Earlier studies have focused on the isolation and structural elucidation of the compounds, and there is still a lot of ongoing research in this area that has been regularly reviewed by Connolly and Hill [1]. During recent years, several interesting biological properties were found for this class of compounds, which in combination with their low toxicities lead to an increased research
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effort [2,3]. More particularly, the oleanane group displays a number of significant pharmacological activities. Allobetulin (2) and its derivatives, obtained from the readily available lupane betulin (1), form a part of the oleanane group.

In this review, we summarize the chemistry of allobetulin analogs including: (1) their formation by rearrangement from betulin derivatives, (2) their further derivatisation, (3) their fusion with heterocyclic rings, and (4) the further rearrangements of allobetulin including ring opening, ring contraction and ring expansion reactions. In the final part (5), the most important biological activities of the allobetulin derivatives mentioned in sections 1–4 are listed.

There are also a number of allobetulin derivatives that are isolated from plant extracts. For a recent example see [4]. These will not be treated in this review. We also did not cover the chemistry of the ring contracted or seco-derivatives of allobetulin, other than their formation from allobetulin derivatives.

2. Betulin-Allobetulin Rearrangement

In 1922, Schulze and Pieroh reported that when betulin (1) was heated in formic acid, an unexpected formate ester product resulted, that gave an isomeric product after saponification that was named allobetulin (2) (Scheme 1) [5]. At that time, very little was known about the structure of (allo)-betulin due to the lack of adequate characterisation techniques, but the authors were able to conclude that the obtained product was a monoalcohol, containing an ether function and an otherwise strongly rearranged structure as compared to the dialcohol betulin (1). Dischendorfer et al. determined the correct molecular bruto formula of 2 not much later [6]. In the following years several authors carried out similar rearrangements and prepared derivatives of allobetulin (2), but breakthroughs regarding its structure came only after the work of Davy [7] who oxidized the acetate of allobetulin to the corresponding 28-oxo derivative, and then saponified it to the alcohol and oxidized this compound to oxyallobetulone (3). The latter was identical to a product (“ketone-lactone-A”) derived by rearrangement of betulonic acid. Only recently was an X-ray structure of allobetulin (2) reported [8].

Scheme 1. Rearrangement of betulin (1) to allobetulin (2).

Various acidic conditions have been applied for this transformation, which is now known to belong to the class of Wagner-Meerwein rearrangements. Hydrobromic acid in chloroform [9], sulfuric acid in acetic acid [10], concentrated hydrochloric acid in ethanol [11,12] and even the highly toxic dimethyl sulfate [13] have been used for the transformation of 1 to 2 in moderate to good yields. The yield can be substantially improved by using acid reagents adsorbed on solid supports. Li et al. used “solid
acids” such as sulfuric acid or tosic acid on silica, Montmorillonite K10 and KSF, bleaching clays and kaolinite to obtain allobetulin and its derivatives in close to quantitative yield [14]. Pichette et al. have used ferric nitrate or ferric chloride absorbed on silica gel or alumina to convert betulin (1) into allobetulin (2) in excellent yield. Longer reaction times lead to the formation of allobetulone (4) or A-ring contracted products, respectively [15]. Ferric chloride hydrate itself (not supported) was also used for a larger scale reaction (approx. 5 g, 92% yield) [16]. Trifluoroacetic acid [17] or bismuth triflate (via triflic acid liberated by hydrolysis) [18] also give excellent results for this transformation. Russian researchers, including patent literature, mention the use of diluted sulfuric acid [19] and orthophosphoric acid [20] to combine the process of extraction of 1 from birch bark and rearrangement to 2. This rearrangement can in fact be seen as an interesting undergraduate laboratory experiment [21].

Simple derivatives of betulin, such as betulone, 3-acetylbetulin, and betulinic acid have been transformed by the above methods to the corresponding allobetulin analogs allobetulone (4), 3-acetoxyallobetulin (5), and 28-oxoallobetulin (6). Betulinic acid is slower to rearrange in comparison to other betulin analogs and may give substantial amounts of side products. 28-Oxoallobetulin (6) may be prepared more effectively in two steps by rearrangement of the 3-acetylated betulinic acid, followed by hydrolysis [22]. As mentioned earlier, rearrangement of betulonic acid or its methyl ester [23] affords triterpene 3, which can be reduced back to 6 (Figure 1) [24].

![Figure 1. Structures of triterpenes 3-6.](image)

Another example is the preparation of 3-amino-28-oxoallobetulin (7) after attempted trifluoroacetic acid deprotection of the corresponding Boc-protected betulinic acid derivative [25]. Treatment of betulin (1) with bromine was reported to give a good yield of the dibromoallobetulin (8) [26]. The structure of rearrangement product 8 was proven by X-ray crystallography. However, this good yield is difficult to reproduce so an efficient procedure towards this interesting product is still lacking. Pradhan
et al. likewise reported on the formation of the 3-acetylated 28-oxo analogs of 8 after treatment of the corresponding betulin derivative with N-bromosuccinimide in DMSO (Figure 2) [27-29].

**Figure 2.** Structures 7 and 8.

![Figure 2](image)

Davy *et al.* prepared an interesting enol ether analog 10 of allobetulin via rearrangement (20% sulfuric acid in acetic acid) of the acetyl derivative of betulone (9). Ozonolysis of compound 10 afforded 28-oxoallobetulone (3), proving the enol ether structure (Scheme 2) [30].

**Scheme 2.** Rearrangement of ketone 9 to enol ether 10.

![Scheme 2](image)

In the recent work of Czuk *et al.*, allobetulin homologues 12 were prepared in almost quantitative yields by trifluoroacetic acid induced rearrangement of secondary alcohols 11 that were prepared from 3-acetylated betulinic aldehyde by aldol condensation reactions (Scheme 3) [31].

**Scheme 3.** Rearrangement of alcohols 11 to allobetulin homologues 12.

![Scheme 3](image)

R = COOEt, COCH₂COOEt
The naturally occurring 23-hydroxybetulin (13, obtained from the bark of Sorbus aucuparia L.) was transformed to the diformate 14a (R = CHO) by an adaptation of the Schulze-Pieroh procedure [11]. Removal of the formate lead to 23-hydroxyallobetulin (14b, R = H). Oxidation of the latter with Jones reagent lead to formation of the norketone 15, after decarboxylation of the intermediate ketoacid. The latter compound was used as a means to functionalize the B-ring, and 19β,28-epoxy-18α-olean-5-ene derivatives such as the interesting unsaturated allobetulone analog 16 were obtained after a bromination, dehydrobromination and methylation sequence (Figure 3) [32].

Figure 3. Structures of compounds 13-16.

3. Simple Functionalisation Reactions of Allobetulin Analogs

Allobetulin (2) can be simply oxidized to the synthetically valuable allobetulone (4) by chromium(VI) reagents [2,33,34], Swern reaction [35] or sodium hypochlorite [36]. As mentioned previously, 4 can also be prepared in a one-pot procedure from betulin (1) [15].

Figure 4. Structures of compounds 17-19.

17a,b X = NOH, Y = H₂, O
18 X = N-NHPh, Y = H₂
19a
19b
Allobetulone (4) was used to prepare the usual ketone analogues, such as the oxime 17a,b (X = NOH, Y = H₂ or O) [5,37], and the phenylhydrazone 18 (X = N-NHPh) [5]. Epimeric spiro compounds 19a,b were obtained (as a 1:2 mixture) from 4 by hetero-Diels-Alder cycloaddition reaction with benzoyl ketene generated in situ from 5-phenyl-2,3-dihydrofuran-2,3-dione (Figure 4). The two isomers 19a,b were isolated and characterized by X-ray crystallography [38]. The effect of the substituents on the cumulene and aryl fragments on the stereoselectivity was studied [39].

3-Acetoxyallobetulin (5) was oxidized to the lactone 6 with CrO₃ in acetic acid [5,40], similarly 3 was prepared starting from allobetulone (4) [6]. Zhang et al. succeeded to oxidize allobetulin (2) directly to 28-oxoallobetulone (3, 87% yield), using sodium periodate/ruthenium trichloride as the reagent [41]. The selective reduction of lactone 3 to 28-oxoallobetulin (6) is another viable alternative to prepare this compound [24].

Base catalyzed oxidation of allobetulone (4) with oxygen as the reagent affords the 2-hydroxy enone derivative of allobetulin (20) [34,40,42,43]. Similarly, the oximes 21a,b (X = H₂, O) are prepared from 4 or 3 via condensation with isoamyl nitrite reagent [32]. Forster reaction of 21a gave the corresponding 2-diazoallobetulone (21c, Scheme 4) [42].

Scheme 4. Oxidation and oximation of ketones 3,4.

Ethylenedithioketal 22a (X = S, Y = H₂) was prepared from allobetulone (4) and reduced to allobetulane (23) with Raney nickel [44]. The 28-oxyallobetulone ketal 22b (X = Y = O) was prepared in 86% yield from triterpene 3 and ethylene glycol [41]. Other ketals were also prepared from allobetulone (4) [45]. Allobetulenones 24a,b that are of importance as biomarkers were prepared from allobetulin (2, X = H₂) or 28-oxoallobetulin (6, X = O) via tosylation in pyridine and elimination of toluenesulfonic acid [14]. The alkene 24a is known from older work by the name of γ-allobetulin [46,47]. This alkene 24a was subjected to the Prins reaction, leading to the alcohol 24c (R = CH₂OH) [48]. Interestingly, allobetulone (4) was isomerized to the 2-keto triterpene 25 in the presence of sulfur and morpholine (Figure 5) [49].
Aldol condensation reactions of allobetulone (4) with benzaldehydes and heterocyclic aldehydes lead to the α,β-unsaturated ketones 26 [6,50]. Similarly, Claisen condensations of 4 with formate and oxalic esters have been used to prepare the synthetically useful 1,3-diketones 27 or their enol tautomers (Figure 6) [16,51-53]. The formyl derivative 27 (R = H) was converted into the 2-fluoro-methylidene derivative by treatment with DAST [54].
phenylselenic anhydride oxidation of allobetulone 4 [39] and was used as a Michael acceptor for cyanide anion (Figure 7) [41].

**Figure 7.** Structures of triterpenes 28-30.

Addition of acetylide to allobetulone (4) affords a monoacetylene 31 [63]. Trimethylsilyl cyanide addition to 4 followed by reduction yields aminoalcohol 32 [35]. A dimeric bis(allobetulenyl) sulfide 33 (X = S) is isolated after treatment of allobetulone (4) with Lawesson’s reagent [64] the corresponding diselenide 33 (X = Se2) was isolated after attempted dehydrogenation of 4 with selenium dioxide [59]. Enol acetates and ethers 34 were also prepared starting from allobetulone (4) (Figure 8) [65,66].

**Figure 8.** Structures of triterpenes 31-34.

A remarkable photolytic transformation (Barton reaction) of 2-nitrite 35, derived from the ketone 25 after reduction and esterification with nitrosyl chloride, lead to the formation of two regioisomeric
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aldoximes 36 (40%) and 37 (40%) [67-69]. The remotely functionalized (C-25 and C-26) oximes 36a and 37a were further converted into nitriles 36b and 37b (Scheme 5).

Scheme 5. Photolysis of nitrite 35.

![Scheme 5](image)

Simple ester derivatives 38 of allobetulin (2) or its 28-oxo analog 6 may be prepared via acylation of the 3-βOH function [5,70,71]. Acylation with cyclic anhydrides leads to monoacidic ester derivatives with improved water solubilities [71]. Alternatively, R groups containing ionic functionalities (ammonium, sulfonate) or polyethylene glycol solubilizers are attached [72]. Next to acylation, sulfonylation and phosphorylation reactions were also described [71]. The oximes 17a,b may also be used to prepare O-acylated derivatives 39 [37,73].

Enamines 40 are prepared from the enol acetate 34 (R = Ac) by epoxidation and condensation with primary or secondary amines. The reaction involves an oxidation, probably effected by adventitious oxygen [67]. 2-Alkylaminomethylene derivatives 41 of allobetulone (4) were prepared from the Claisen ester condensation product 27 (R = H) and primary amines (Figure 9) [53].

Figure 9. Structures of triterpenes 38-41.
Glycosides and saponins with allobetulin (2) or its 28-oxo derivative 6 as aglycones were prepared by reacting the 3β-hydroxy function with sugar derivatives, such as glycals [74-78] or a large collection of trichloroacetimidates [22,79-81]. This modification, see for instance glycoside 42 [78], saponin 43 [79] and the glycoside derivative of 20a [40], greatly enhances water solubility and hence influences the biological properties (Figure 10).

Figure 10. Structures of triterpene saponins 42 and 43.

4. Ring Fusion to the A-Ring of Allobetulin

2,3-Epoxides may be formed by ring closure of the corresponding bromohydrins, available from reduction of 2-bromoallobetulones 28 (X = Br), by epoxidation of alkene 24a [59,82] or by oxidation reactions of enol acetate 34 (R = Ac) as mentioned above [66]. The main feature of these epoxides is their propensity for ring opening reactions with nucleophiles [52,61]. Interestingly, 2α,3α-epoxide 44 on treatment with a methyl Grignard reagent underwent rearrangement (see also next part 3) before addition of the organometal, affording nor-A alcohol derivative 45. The 2β,3β-isomeric epoxide underwent a similar rearrangement/addition sequence (Scheme 6) [83].

Scheme 6. Ring opening of epoxide 44 with Grignard reagent to afford 45.

Allobetulone (4) and its substituted derivatives are the starting point for the annelation of allobetulin with heterocyclic rings. For instance, Fischer indole synthesis starting from arylhydrazine and ketone 4 gave the fused indole 46 [84,85]. 2-Hydroxyenone 20a was condensed with diamines such as 1,2-
diaminobenzene and 1,2-ethylenediamine to give the corresponding (benzo)pyrazine derivatives 47 (Figure 11) [43,45,49,86].

**Figure 11. Structures of fused triterpenes 46 and 47.**

Hantzsch type synthesis starting from the α-bromoallobetulone (28a, R = Br) and thiourea gave an aminothiazolo fused triterpene 48 [87]. Condensation of the 1,3-dicarbonyl derivatives 27, prepared by Claisen ester condensation of 4, with hydrazine or hydroxylamine gave pyrazoles 49 or isoxazoles 50, respectively [51]. In the case of alkylhydrazines two isomeric pyrazoles with [b] and [c] fusion are formed (Figure 12) [88].

**Figure 12. Structures of fused triterpenes 48-50.**

5. Further Rearrangements of Allobetulin, Including Ring Contractions and Ring Expansions

Often, the rearrangement of betulin (1) to allobetulin (2) is accompanied with the formation of the dehydrated, isomeric “apoallobetulins”. The latter have a variety of structures and can also be obtained from isolated allobetulin (2) by treatment with different acidic reagents. The structure of the δ-allobetulin 51 obtained by treatment of allobetulin (2) with PCl₅ or phosphorous pentoxide at 0 °C [5,6,15] was shown later by ozonolysis to have an exocyclic double bond [89]. The so-called α-apoallobetulin 52 has an endocyclic double bond and is formed on treatment of betulin (1) with Fuller’s earth [6,89]. More recently, different solid acids such as Montmorillonite K10 have successfully transformed 1, 2 or even the δ–isomer 51 to mixtures of 52 and the “rearranged α-apoallobetulin” [47] 53. In general, the amount of 53 in the mixture increases at higher temperatures. 28-Oxo derivatives of 52 and 53 are formed accordingly from betulinic acid or 28-oxoallobetulin (6)
Silica- or alumina supported FeCl₃ hydrate gave a similar mixture (55:45 ratio) of 52 and 53 on extended reaction of betulin (1), via allobetulin (2) [16]. The reaction of allobetulin (2) with PCl₅ has been reinvestigated and was shown to lead directly to 52 at slightly higher temperatures (5–10 °C). At −10–0 °C, the expected 51 was formed [47]. The highest yields and selectivities of apoallobetulin isomers were obtained on treatment of betulin (1) with bismuth triflate. The relative amount of catalyst is important. Thus, heating 1 with 20 mol% catalyst for 40 h at reflux in dichloromethane gave 98% yield of 52. On the other hand, heating of 1 or 52 for 8–15 h in the same solvent with 50 mol% bismuth triflate gave the isomer 53 almost quantitatively (96–98% yield) (Figure 13) [19].

Figure 13. Structures of apoallobetulins 51-53.

Treatment of allobetulin (2) with acid chlorides in high boiling solvents leads to rearranged and ring opened diacylated products 54a, that can be saponified to the so-called “heterobetulin” 54b, which has an ursane framework [9,47,90,91]. “Alloheterobetulin” 55 is a ring closed isomer of the latter which can be obtained after treatment of 54b with tolenesulfonic acid [92]. A remarkable rearrangement/O,C-diacylation was recently reported to occur (55% yield of 56) when allobetulin (2) was treated with acetic anhydride and a few drops of perchloric acid (Figure 14) [93].

Figure 14. Structures of ring opened allobetulin derivatives 54-56.

The Baeyer-Villiger oxidation of allobetulone (4) was investigated by different groups under different circumstances [40,94,95]. With MCPBA in dichloromethane, the main product (83%) is the ring-expanded lactone 57a. Other peracids (performic, peracetic) give similar results. However, reaction of 4 with MCPBA in the presence of acid (acetic + sulfuric) leads to the formation of a nor-
lactone 57b. The 3,4-seco derivatives 58a,b were obtained in good yield either from 57a by alkaline hydrolysis or directly from 4, carrying out the oxidation in methanol with a trace amount of sulfuric acid [95]. Larger amounts of acid (0.15%) lead to the formation of the 2α-hydroxyallobetulone 28c in good yield (86%) (Figure 15) [65].

Figure 15. Structures of A-seco derivatives 57 and 58.

The Beckmann rearrangement of allobetulin oxime 17a, induced by TsCl/pyridine or phosphoryl chloride, gave rise to the formation of a lactam 59a (major product) and a 3,4-seco-triterpene nitrile 60 (minor product). The lactam 59a could be transformed into the nitrile 60 on extended heating [96,97]. Upon Schmidt reaction of methyl betulonate or Beckmann rearrangement (POCl3) of its oxime, the 28-oxo derivatives 59b and 60b were formed after two consecutive rearrangements [98]. Other 2,3-seco-derivatives were prepared via Beckmann fragmentation of allobetulin derivatives (Figure 16) [33,45,99,100].

Figure 16. Structures of ring expanded and ring opened triterpenes 59 and 60.

The dibromoallobetulin 29 underwent a quasi-Favorskii rearrangement on treatment with base, leading to the ring contracted product 61a. Oxidative decarboxylation of the latter with lead tetraacetate gave the norketone 62 [45,56,96,101]. The latter is an interesting starting material that was used in many follow-up reactions that will not be discussed here. Benzilic acid rearrangement of diketone 20a gives the same hydroxyacid 61a. The photochemical Wolff rearrangement of diazo compound 21c gave the ring contracted carboxylic acid 61b (Figure 17) [45].
Dischendorfer reported oxidation of the A-ring of 28-oxoallobetulone 3 to “allobetulinic acid” which formed a cyclic anhydride 63 [102, 103]. This seco-derivative 63 was recently used to prepare spirocyclic derivatives 64 after treatment with benzylamines and oxalyl chloride [104]. Recently, the diacid analog of 63 was prepared by ozonolysis of the Claisen ester condensation product of 3 (i.e. the 3-oxo analog of 27) [105]. This procedure has some similarity with earlier work by Ruzicka, who used chromic acid to prepare the diacid from hydroxymethyleneallobetulone (27, R = H) or directly from allobetulin (2) (Scheme 7) [106].

**Scheme 7. Spirocyclic triterpenes 64.**

The nearly insoluble lactone 65 was formed in low yield (24%) on oxidation of allobetulone (4) with chromic acid. Treatment of 65 with diazomethane gave the 1,2-seco derivative 66 in good yield (Figure 18) [107].

**Figure 17. Structures of A-ring contracted triterpenes 61 and 62.**

**Figure 18. Structures of oxidized triterpenes 65 and 66.**
Another obvious position for ring cleavage is the lactone bridge of 28-oxoallobetulin derivatives. This bridge is quite stable towards saponification, but LiAlH₄ reduction of the 3β-acetoxy derivative of 5 [108] or 28-oxoallobetulone (3) [25,30,109] gives a germanicanetriol derivative 67 which was further transformed to different germanicanes by selective acylation, oxidation and dehydration reactions [108,109]. The lactone ring of the protected 28-oxoallobetulone 22b was reductive cleaved with LiAlH₄ and after deprotection, 28-acetylation, dehydration with POCl₃, saponification, and stepwise oxidation, moronic acid (68) and the reduced morolic acid 69 were obtained (Figure 19) [41]. In general, allobetulin and its derivatives are important starting materials for the synthesis of rare germanicanes and olean-18(19)-ene triterpenoids.

**Figure 19.** Structures of triterpenes 67-69.

Treatment of allobetulin (2) with sodium iodide/acetyl chloride at reflux in acetonitrile lead to the formation of iodinated diacetate 70 [110]. Treatment of allobetulin (2) or its 3-acetate with POCl₃ in refluxing pyridine similarly gave dialkene 71 or the corresponding acetate 72 (Figure 20) [16].

**Figure 20.** Structures of triterpenes 70-72.

### 6. Biological Properties of Allobetulin Analogs

The biological properties of betulin, betulinic acid and its derivatives are well known [2] and often activity studies of allobetulin derivatives are found back in the literature together with or in comparison to their betulin isomers. A wide spectrum of biological properties have been reported, including antiviral, antifeedant, immunotropie, antibacterial, antifungal, and anti-inflammatory activities, cytotoxicity and inhibition of glycogen phosphorylase activities.
6.1. Antiviral properties

In 1995, it was found that allobetulin (2) itself showed moderate inhibitory activity against the influenza B virus [111]. It was claimed in the patent literature that different derivatives of allobetulin, including 2 and its 3-O-acylated and phosphorylated derivatives, 4, 30a, 32, exhibited significant antiviral activity and could be used to treat herpes virus (HSV-herpes simplex virus) infection [35]. Also in 2002, compound 3 was shown in cell culture to inhibit influenza A growth while being inactive against HSV and the enterovirus ECHO-6 [112]. Somewhat later, allobetulin derivatives 3, 6, and different O-acylated oximes 39 were tested against several viruses such as HSV, influenza and ECHO-6 [24,37]. In fact, the non-acetylated oxime 17a had the largest effect against influenza virus A, while being only moderately active against enterovirus ECHO-6 and inactive with respect to HSV. The N-acetylated oximes 39 had a moderate activity towards HSV, but were inactive against the other viruses [37]. It was confirmed that 28-oxoallobetulone (3) strongly inhibited the influenza virus, but did not influence HSV reproduction [24]. Rearranged product 56 showed only moderate inhibition of the Papilloma virus [93].

6.2. Antifeedant properties

In 1990, Lugemwa et al. reported high antifeedant activity against the bollworm larvae, *Heliothis zea*, for the glycoside derivative of 30a. Simple allobetulin derivatives such as 2, 20a and 30a itself were not active. The antifeedant property was selective and the glycoside did not display high activity against either the Colorado potato beetle (*Leptinotarsa decemlineata*) or the fall armyworm (*Spodoptera frugiperda*) [40].

6.3. Immunotropic activities

Different 2-substituted allobetulone derivatives, including the formyl analog 27 (R = H) and different condensation products with amines 41 were screened [53]. In fact, compounds 27 and 41 (R = iPr) had the most promising activity combined with low toxicity. In later work it was shown that these compounds had high biological activity on chronic administration and that their immunosuppressive activity was the result of toxic effect on the lymphocytes [113].

6.4. Antibacterial and antifungal activities

Compounds 2 and 3 were taken into a screening of 32 betulin derivatives against *Chlamydia pneumoniae*. Allobetulin (2) was equal to betulin (1) in antichlamydial activity (48%), but 28-oxoallobetulone (3) was inactive [114].

6.5. Anti-inflammatory and anti-ulcer properties

Biological tests on mice with the carrageenan and formalin edema models showed that acylated derivatives of allobetulin (2) possessed anti-inflammatory activity comparable to ortophen (diclofenac) [71,115]. Moderate antiulcer activity of 3 and 3-O-acylated allobetulin derivatives were observed in mice [112,115].
6.6. Cytotoxicity

The cytotoxicity of pyrazine and quinoloxaline derivatives of allobetulin (47) was tested against a T-lymphoblastic leukemia cell line and found to be lower than the fused triterpene analogs based on unrearranged betulin or betulinic acid [86]. Pichette et al. did a study on the cytotoxicity of betulin- and allobetulin-derived 3β-O-monoestersosidic saponins (such as 42) with higher hydrosolubility and better pharmacokinetics. In vitro anticancer activity of saponins derived from 2 and 6 showed that the bioactivity for these glycosides was only moderate (IC₅₀ 30–40 μM/L), as compared to the corresponding betulinic acid derivatives (IC₅₀ 7.3–10.1 μM/L) [23]. The in vitro toxicity of 67 (human lung carcinoma or human colorectal adenocarcinoma assay) was comparable to that of betulinic acid or 5-fluorouracil [108]. Chacotrioside saponins such as 43 were fourfold superior to betulinic acid against human breast (MCF7) and prostate (PC-3) adenocarcinomas cell lines. Moreover, chacotriosides bearing non-polar functions at the C-28 position had a haemolytic activity against red blood cells [80]. Allobetulin derivatives 12 with 28-functionality were reported by Czuk et al. to have moderate cytotoxicity [31].

6.7. Inhibition of glycogen phosphorylase

Morolic acid (69) (IC₅₀ 70.3 μM/L), its 3-epimer (IC₅₀ 34.5 μM/L) and 3-O-acetylated derivative (IC₅₀ 32.7 μM/L) were shown to cause moderate inhibitory activity against rabbit muscle glycogen phosphorylase [41].

7. Conclusions

Allobetulin and its analogues are easily accessible starting from the corresponding betulin derivatives. Although a large structural variety of allobetulin analogs is already available by functionalisation, ring fusion to the A ring, further rearrangements, ring contractions, ring expansions, and ring cleavages, there is still much chemical space unexplored. Further investigations are certainly worthwhile because of the interesting bioactivities.

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