

Biologically Active Quassinoids and Their Chemistry: Potential Leads for Drug Design

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Abstract: Quassinoids are highly oxygenated triterpenes, which were isolated as bitter principles from the plants of *Simaroubaceae* family. Their synthesis has attracted much attention because of the wide spectrum of their biological properties. The most prevalent quassinoids have C-20 picrasane skeleton, some known as bruceolides as they were isolated from the genus *Brucea*, which showed marked antileukemic and antimalarial activities.

Keywords: Quassinoids, semi-synthesis, total synthesis, biological activities, SAR, antileukemic and antimalarial activities.

INTRODUCTION

Quassinoids refer to the group of compounds as the bitter principles of the *Simaroubaceae* family [1], and chemically they are degraded triterpenes. According to their basic skeleton, quassinoids are categorized into five distinct groups, C-18, C-19, C-20, C-22 and C-25 types shown in Fig. (1) [2]. Among them C-20 quassinoids have especially been the subject of extensive investigations to dig their biological activities partially due to the discovery in the early 1970s by National Cancer Institute that some of these compounds possess marked antileukemic activity [3]. The C-20 quassinoids can be further classified into two types, tetracyclic and the pentacyclic. The tetracyclic variety does not have oxygenation at C-20, while the pentacyclic quassinoids possess additional oxygenation at C-20 that allows for the formation of an additional ring. As studies on these compounds progress, however, other groups, especially C-19 quassinoids, have recently received more attention [4,5]. Many of these quassinoids display a wide range of biological activities *in vitro* and/or *in vivo*, including antitumor, antimalarial, antiviral, anti-inflammatory, antifeedant, insecticidal, amoebicidal, antiulcer and herbicidal activities.

CHEMISTRY: ISOLATION AND STRUCTURE ELUCIDATION

At the present, quassinoids are found solely in various species of the *Simaroubaceae* family, such as *Brucea antidysenterica* Mill, *Brucea javanica* Merr, *Simaba amara*, *Picrasma ailanthoides*, *Pierreodendron kerstingii*, and *Ailantluts grandis*. All of these species belong to the *Simarouboidae* subfamily of *Simaroubaceae*, and some, in particular, have been used clinically for centuries. Originally,

the collective bitter substances contained in such plants were termed *quassin*, after a man by the name of Quassi, who treated fever with the bark of these plants.

The first two quassinoids isolated and structures elucidated were quassin (1) and neoquassin (2) shown in Fig. (2), both of the C-20 type. These two compounds were isolated by Clark's group [7] as early as 1930s, however, the structure elucidation was not completed until the early 1960s, when Valenta and his co-workers applied modern physical techniques like NMR [8]. A number of genera of the *Simaroubaceae* family have then been investigated and many individual bitter components have been isolated and structure-elucidated. All these *Simaroubaceae* constituents are chemically related to quassin and are thus named as quassinoids [9]. Research in the area of quassinoids has intensified since the recognition of the quassin structure and of the quassinoids antileukemic activity.

The research and application of quassinoids continued to extend through the 1990's with the isolation and structure elucidation of many new compounds. Today, over 150 quassinoids have been isolated and fully characterized, and dozens of them have been found that do not fall into any of the basic quassinoid skeletal configurations shown in Fig. (1). In 1995 Grieco and group isolated a C-19 quassinoid from *Castela polyandra*, which they named as (+)-polyandrol (3) [4]. Tonkawa *et al.* found similar compounds in *Eurycoma longifolia* and isolated eurylactone A (4) and eurylactone B (5), along with two known C-19 quassinoids [10]. These atypical quassinoids do not possess a six-member A-ring, while the B-ring is lessened to a five-member ring. Aono *et al.* isolated another similar compound from *Ailanthus malabarica* in 1994, named as ailanquassin A (6), along with ailanquassin B, a novel C-20 quassinoid (7) [11]. In conjunction with seven known C-20 quassinoids extracted from the leaves of *Eurycoma longifolia*, Morita *et al.* [12] has isolated another kind of unusual C-19 quassinoid, 6-dehydroxylongilactone (8), and a new C-19 quassinoid, 7- α -hydroxyeurycomalactone (9). Two compounds lacking a C-ring, ailantinol A (10) and ailantinol B (11), were recently isolated by Kobuta's group [13] from

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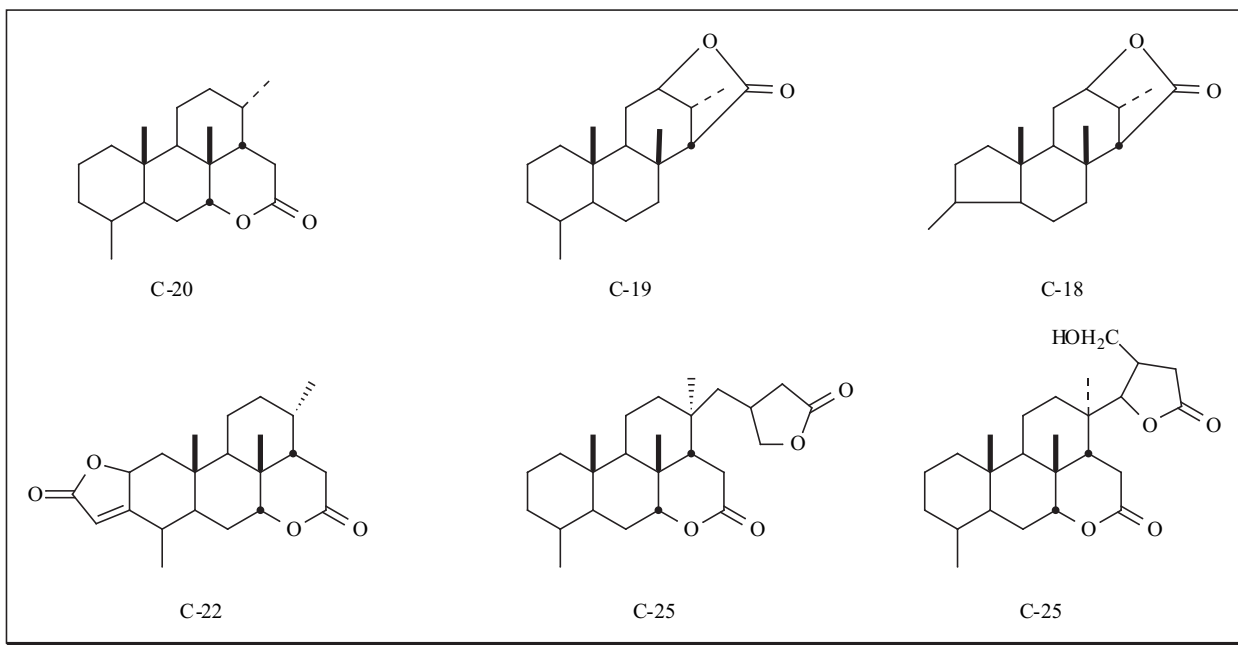


Fig. (1). Skeleton of quassinoids.

Ailanthus altissima. Other quassinoids isolated and structurally elucidated in this period were summarized in Table I (12-64) [14-37] in terms of their botanical source, type of quassinoid and the corresponding references, and their structures were shown in Fig. (3).

With the isolation and characterization of novel quassinoids, their bioactivities have also been well noted. Francois *et al.* [38] isolated four novel quassinoids (65-68) from *Hannoa chlorantha* and were tested for their antimalarial and cytotoxic activities to found 15-desacetylundulatone (67) as the most active compound in antimalarial assay. Takeya *et al.* [39] isolated four new quassinoids, cedronolactones A-D (69-72), from the wood of *Simaba cedron*. Cedronolactone A (69) was shown to exhibit a significant *in vitro* cytotoxicity (IC_{50} 0.0074 μ g/mL) against P-388 cells. Further investigations led them to isolate another novel pentacyclic C-19 quassinoid, cedronolactone E (73), from the wood of *Simaba cedron*, which were found to show a weak cytotoxic activity (IC_{50} 51 μ g/mL) against P-388 murine leukemia cells [40]. This same group isolated vilmorinone A (74) from the cortex of *Ailanthus vilmoriniana* [41], however, this quassinoid did not show any cytotoxic activity at the maximum tested dose

(IC_{50} >100 μ g/mL). Further investigations led them to isolate five more novel quassinoids, vilmorinone B-F (75-79) from the cortex of *Ailanthus vilmoriniana* [42].

The efforts from Takeya *et al.* led to the isolation and identification of three novel quassinoids, euryconolactones A-C (80-82) [43] having unique structural features, from the roots of a Malaysian plant *Eurycoma longifolia* Jack. Euryconolactone B (81) is the most potent compound among them with an IC_{50} value of 23 μ g/mL against P-388 cells. Further investigations led them to isolate three other novel quassinoids, euryconolactones D-F (83-85) shown in Fig. (3) [44] from the same plant *Eurycoma longifolia* Jack (Table I).

Grieco *et al.* [45] isolated six new C-20 quassinoids, 1-*epi*-holacanthone (86), 15-*O*-acetylglaucaurubol (87), 15-*O*-acetyl- $\Delta^{4,5}$ -glaucaurubol (88), 1-*epi*-5-*iso*-glaucaurubolone (89), 1-*epi*-glaucaurubolone (90) and $\Delta^{4,5}$ -glaucaurubol (91) and one new C-19 quassinoid, 15-*O*-acetyl-5-(*S*)-polyandrol (92) along with holacanthone (93) [46], 5-(*R*)-polyandrol (94) [47], glaucaurubolone (95) [48], glaucaurubol (96) [49] and niloticin (97) [50] from the twigs and thorns of *Castela polyandra*. The C-25 quassinoids 20-(*R*)- and 20-(*S*)-

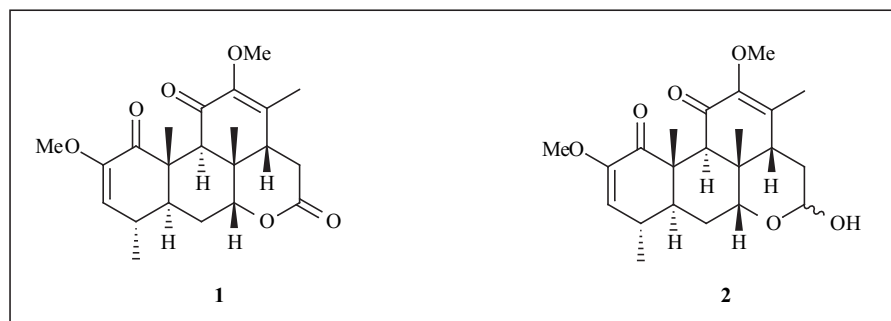


Fig. (2). Quassin (1) and neoquassin (2) are the first two quassinoids that were isolated and structures elucidated.

Table I. Novel Quassinoids and their Plant Sources

Source	Type of Quassinoid	Chemical Constituents	Ref.
<i>Castela polyandra</i> (Crucifixion)	C-19	(+)-polyandrol (3)	4
	C-19	15- <i>O</i> -acetyl-5(<i>S</i>)-polyandrol (92)	45
	C-19	5(<i>R</i>)-polyandrol (94)	47
	C-20	1- <i>epi</i> -holacanthone (86)	45
	C-20	15- <i>O</i> -acetylglaucaurubol (87)	45
	C-20	15- <i>O</i> -acetyl- $\Delta^{4,5}$ -glaucaurubol (88)	45
	C-20	1- <i>epi</i> -5- <i>iso</i> -glaucaurubolone (89)	45
	C-20	1- <i>epi</i> -glaucaurubolone (90)	45
	C-20	$\Delta^{4,5}$ -glaucaurubol (91)	45
	C-20	holacanthone (93)	46
	C-20	glaucaurubolone (95)	48
	C-20	glaucaurubol (96)	49
C-25	niloticin (97)	50	
<i>Eurycoma longifolia</i> (Ali's walking stick)	C-19	eurylactone A (4), B (5)	10
	C-19	6-dehydroxylongilactone (8)	12
	C-19	58-60, 6- α -hydroxyeurycomalactone (62)	35-37
	C-19	longilactone (63)	35-37
	C-19	longilactone (115)	56
	C-19	6-dehydro longilactone (116)	56
	C-20	61, 4,15- β -dihydroxyklaineaneone (64)	35-37
	C-20	7- α -hydroxyeurycomalactone (9)	12
	C-20	11-dehydroklaineaneone (117)	57
	C-20	12- <i>epi</i> -11-dehydroklaineaneone (118)	57
	C-20	15 β -hydroxyklaineaneone (119)	12
	C-20	14,15 β -dihydroxyklaineaneone (120)	50
C-20	15 β - <i>O</i> -acetyl-14-hydroxyklaineaneone (121)	58	
<i>Ailanthus malabarica</i> (White Bean)	C-20	ailanquassin A (6), B (7)	11
<i>Ailanthus altissima</i> (Tree of Heaven)	C-20	ailantinal A (10), B (11)	13
<i>Castela tortuosa</i> (Texan goatbush)	C-20	castelatin (12)	14
	C-20	castelosides A (48), B (49)	30
	C-20	chaparramarin (50)	30
	C-20	castelalene-11- <i>O</i> - β - <i>D</i> -glucopyranoside (54)	32
<i>Simaba guianensis</i> (Guianensis)	C-25	gutolactone (13)	15
<i>Brucea antidysenterica</i> (Woinos meleta)	C-25	bruceanols D (14), E (15), F (16)	16
	C-25	bruceanols G (17), H (18)	17
<i>Harrisonia perforate</i> (Kon-tah)	C-20	perforaquassins A (19), B (20), C (21)	18
<i>Brucea javanica</i> (Brucea)	C-25	bruceoside C (22)	19
	C-25	bruceosides D (32), E (33), F (34)	25
<i>Picrasma ailanthoides</i> (Indian Quassia wood)	C-20	picrasinoside H (23)	20
	C-20	picrasinol D (27)	23
	C-20	picrasinol C (55)	33
<i>Picrasma javanica</i> B1 (Quassia wood)	C-20	picrajavanins A (24), B (25)	21
<i>Castela peninsularis</i> (Crucifixion Thorn)	C-25	peninsularinone (26)	22
<i>Eurycoma longifolia</i> (Pasak bumi)	C-20	pasakbumins A (28), B (29), C (30), D (31)	24
<i>Picrasma javanica</i> (Kho diep)	C-20	javanicin Z (35), dihydrojavanicin Z (36), hemiacetaljavanicin Z (37)	26
	C-20		26
	C-20	javanicinosides I (44), J (45), K (46), L (47)	29
<i>Quassia indica</i> (Bitter wood)	C-20	samaderines X (38), Y (39), Z (40)	27
	C-20	indaquassin X (41)	27
	C-19	2- <i>O</i> -glucosylsamaderine C (42)	27
<i>Castela texana</i> (Texan goatbush)	C-20	11- <i>O</i> - <i>trans</i> - <i>p</i> -coumaroylamarolide (43)	28
<i>Quassia amara</i> (Surinam Quassia)	C-20	11- α - <i>O</i> -(β - <i>D</i> -glucopyranosyl)-16- α - <i>O</i> -methylneoquassin (51)	31
	C-20	1- α - <i>O</i> -methylquassin (52)	31
	C-20	12- α -hydroxy-13,18-dehydroparain (53)	31
	C-20		31

(Table I). contd.....

Source	Type of Quassinoid	Chemical Constituents	Ref.
<i>Hannoa chlorantha</i> *	C-20	14-hydroxychaparrinone (56)	34
	C-20	chaparrinone (65)	38
	C-20	14-hydroxychaparrinone (66)	38
	C-20	15-desacetylundulatone (67)	38
	C-20	6- α -tigloyloxyglaucarubol (68)	38
<i>Quassia multiflora</i> (Dew berry/ Wine berry)	C-20	6- α -hydroxychaparrinone (57)	35
<i>Simaba cedron</i> (Cedron)	C-25	cedronolactone A (69)	39
	C-19	cedronolactones B-D (70-72)	39
	C-19	cedronolactone E (73)	40
	C-22	nilocitin (122)	59
	C-22	dihydronilocitin (123)	59
	C-22	piscidinol (124)	59
	C-22	bourjutinolone A (125)	59
	C-20	glaucarubolol (126)	59
<i>Ailanthus vilmoriniana</i> (Tree of Heaven)	C-20	vilmorinone A (74)	41
	C-20	vilmorinone B-F (75-79)	42
<i>Eurycoma longifolia</i> Jack (Malaysian Ginseng)	C-19	euryconolactones A, E-F (80, 84-85)	43-44
	C-18	euryconolactones B-D (81-83)	43-44
<i>Simaba cuneata</i> (Simaba)	C-25	20(R)- and 20(S)-simarolides (98-99)	51
<i>Picrasma crenata</i> (Picrasma)	C-20	16- β -O-methylneoquassin (100)	52
	C-20	16- β -O-ethylneoquassin (101)	52
<i>Samadera indica</i> (Samadera)	C-20	indaquassin C (103)	54
	C-19	samaderins C (104), B (105)	54
	C-18	samaderin A (106)	54
<i>Eurycoma harmandiana</i> Pierre (Tongkat Ali)	C-20	iandonosides A (108), B (109)	55
	C-20	iandonone (111)	55

* common name not available

simarolide epimers (**98-99**) were isolated from *Simaba cuneata* by Fernandes *et al.* [51] and their structures were elucidated. Krebs *et al.* [52] re-investigated the Brazilian plant *Picrasma crenata* to isolate two quassinoids, 16- β -O-methyl- (**100**) and 16- β -O-ethylneoquassin (**101**). The phytochemical analysis of two collections of a new species (accession number SAC-2825) has yielded a novel quassinoid, 2'-acetoxylglaucarubin (**102**), apart from other natural products [53]. Govindachari *et al.* [54] isolated four quassinoids, indaquassin C (**103**), samaderins C (**104**), B (**105**) and A (**106**), from the seeds of *Samadera indica*, and were tested to find them having significant antifeedant activity (0.5 $\mu\text{g}/\text{cm}^2$). Yamasaki *et al.* [55] isolated eight quassinoids from the roots of *Eurycoma harmandiana* Pierre, among which three are unusual quassinoids, iandonosides A (**108**) and B (**109**) and iandonone (**111**) and the other five quassinoids, (**107, 110, 112-114**) are reported previously [11,30,56]. Jiwajinda *et al.* [57] reported some novel quassinoids from the leaves of *Eurycoma longifolia* as plant growth inhibitors. These quassinoids include longilactone (**115**), 6-dehydro longilactone (**116**) [56], 11-dehydroklaineane (**117**), 12-*epi*-11-dehydroklaineane (**118**) [57], 15 β -hydroxyklaineane (**119**), 14,15 β -dihydroxyklaineane (**120**) and 15 β -O-acetyl-14-hydroxyklaineane (**121**) [12,50,58]. Quassinoids from *Simaba cedron* were isolated by Vieira *et al.* [59], which include nilocitin (**122**), dihydronilocitin (**123**), piscidinol

(**124**), bourjutinolone A (**125**), glaucarubolol (**126**) and glaucarubolone (**127**) shown in Fig. (1).

BIOSYNTHESIS OF QUASSINIDS

All quassinoids are believed to be biosynthesized through the triterpenoid biogenetic pathway [1], similar to that of the limonoids, another group of naturally occurring terpenoids. The isolation of three new quassinoids, perforaquassin A (**19**), B (**20**), C (**21**), and a new limonoid, perforin A (**128**) from the same *Simaroubaceae* plant by Kamiuchi *et al.* [18], and the successful conversion of the Geduin salt (**129**), a limonoid, to merogedunin (**130**), a quassinoid-like skeletal compound by Okogun and Orisadipe [60] support this relation shown in Fig. (4). Schematized in Fig. (5) is the formation of the quassinoids from the proto-triterpene, apo-euphol or its C-20 epimer, apo-tirucallol.

The biosynthetic process begins with the degradation of triterpenes including the loss of a methyl group at C-4 and the four carbon atoms at the end of the side chain. A Bayer-Villiger-like oxidation leads to the cleavage of the bond between C-16 and C-17, making it possible to form a δ -lactone ring through the C-16 carbonyl with the 7 α -hydroxy group, the common moiety in most of the C-20 quassinoids. Further introduction of an oxygen atom at

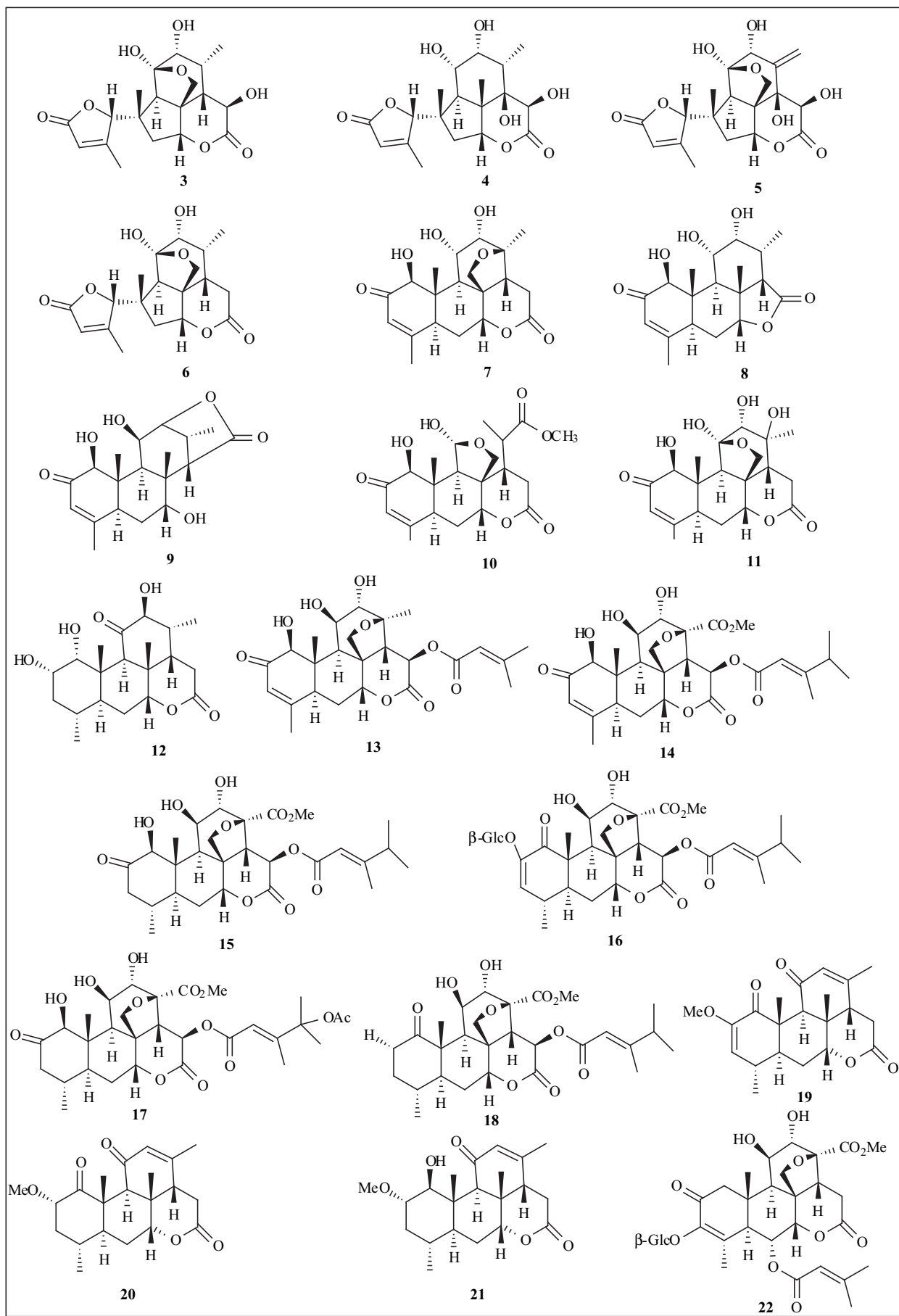
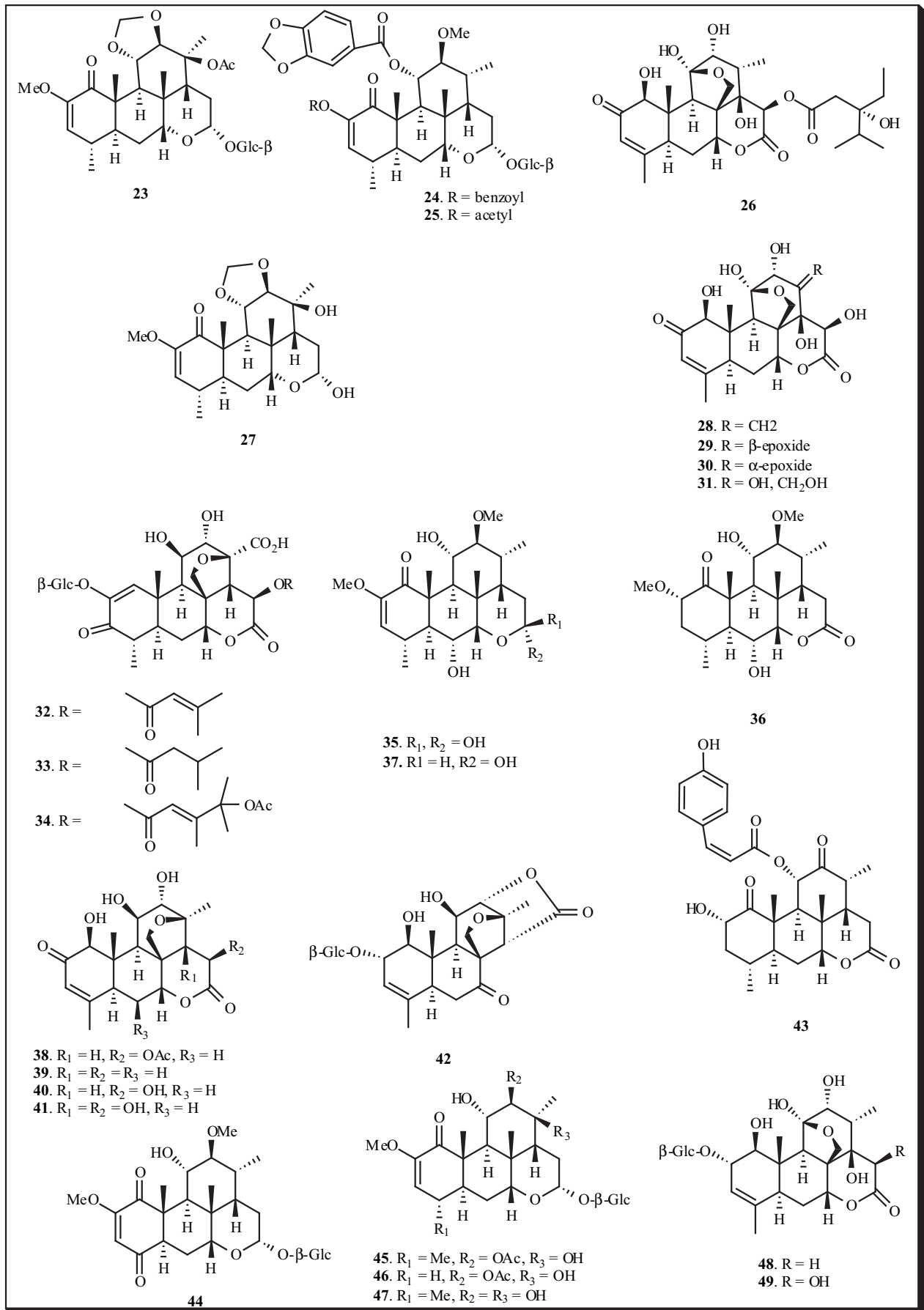


Fig. (3). contd.....



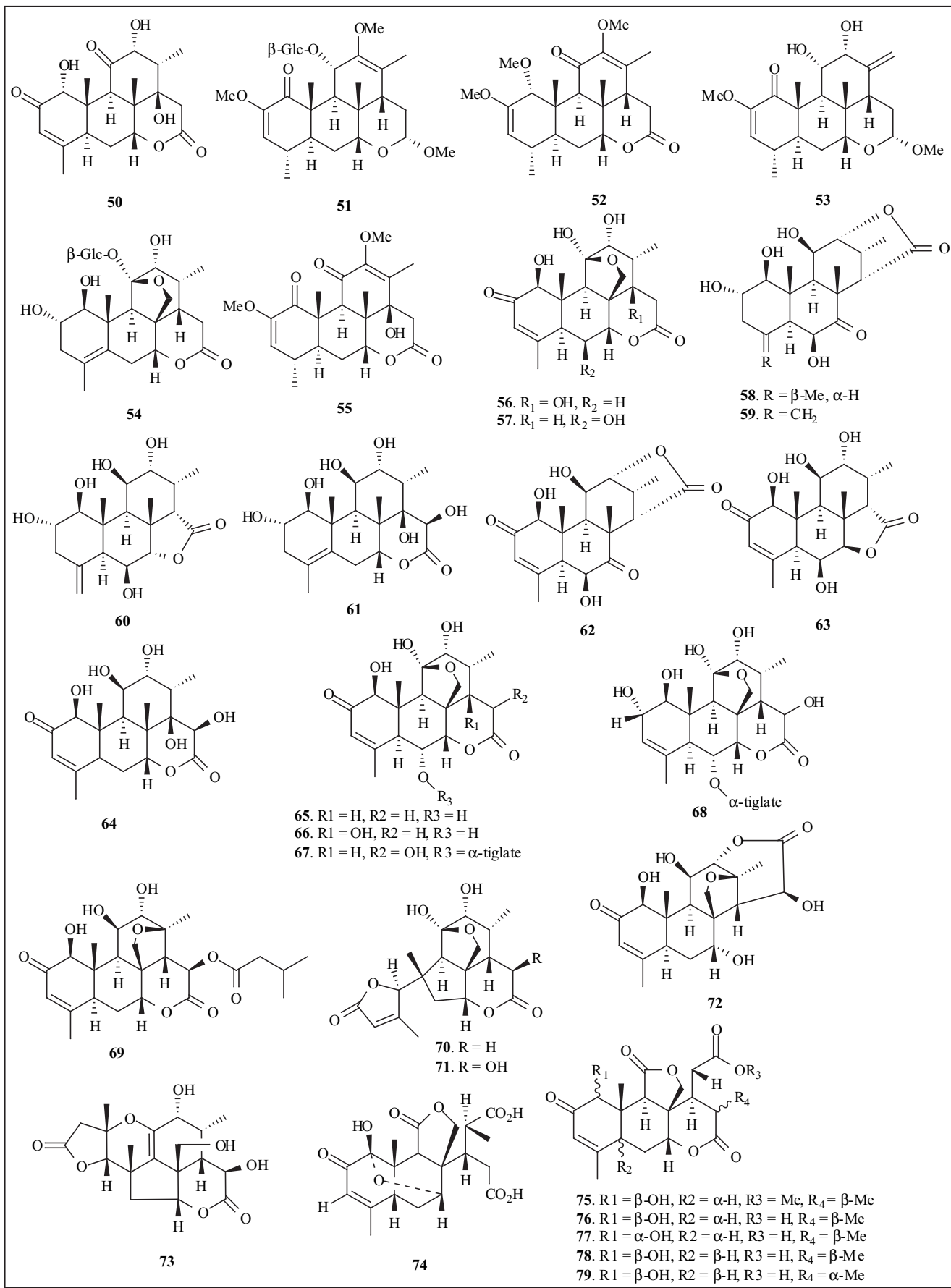
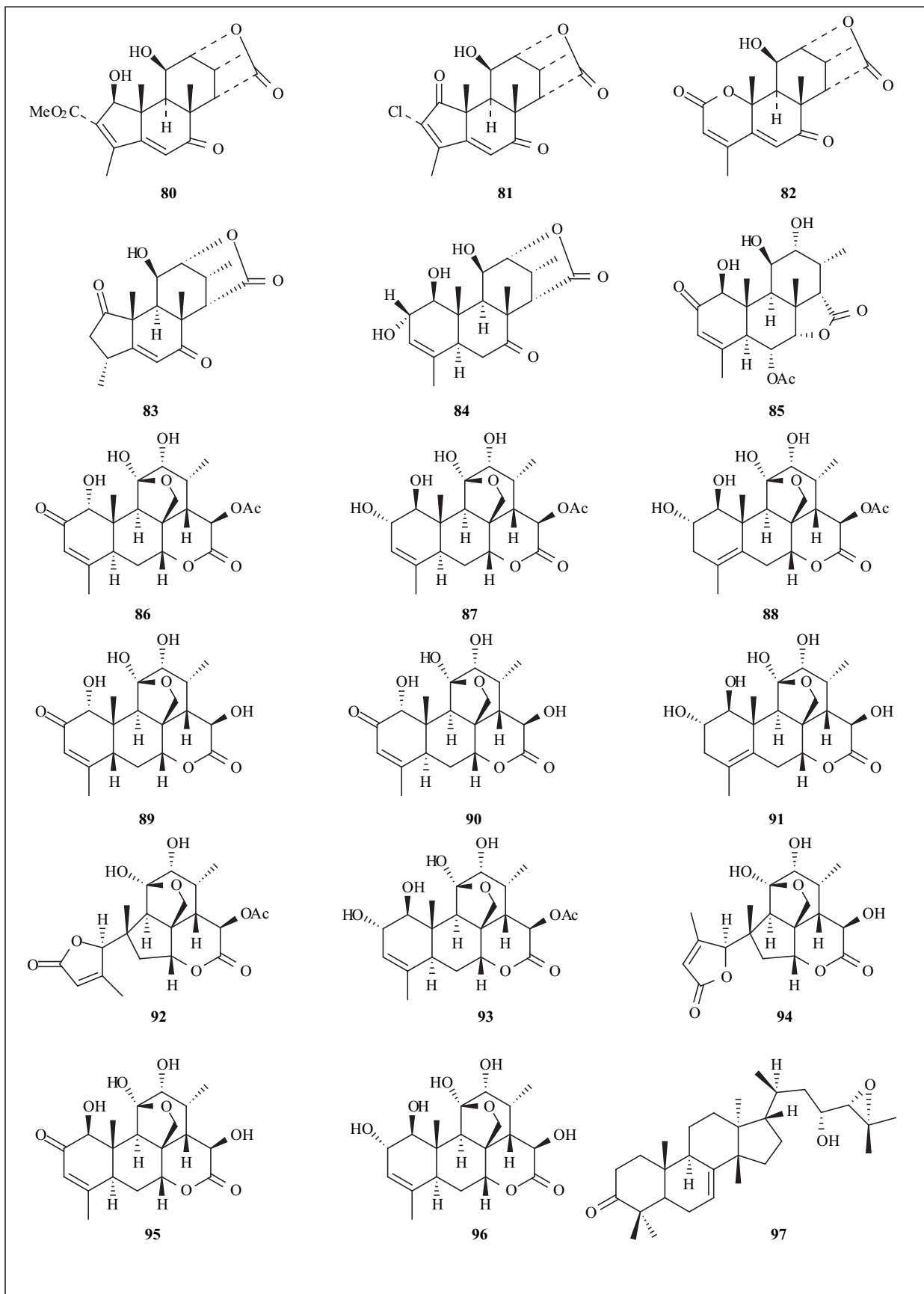


Fig. (3). contd.....



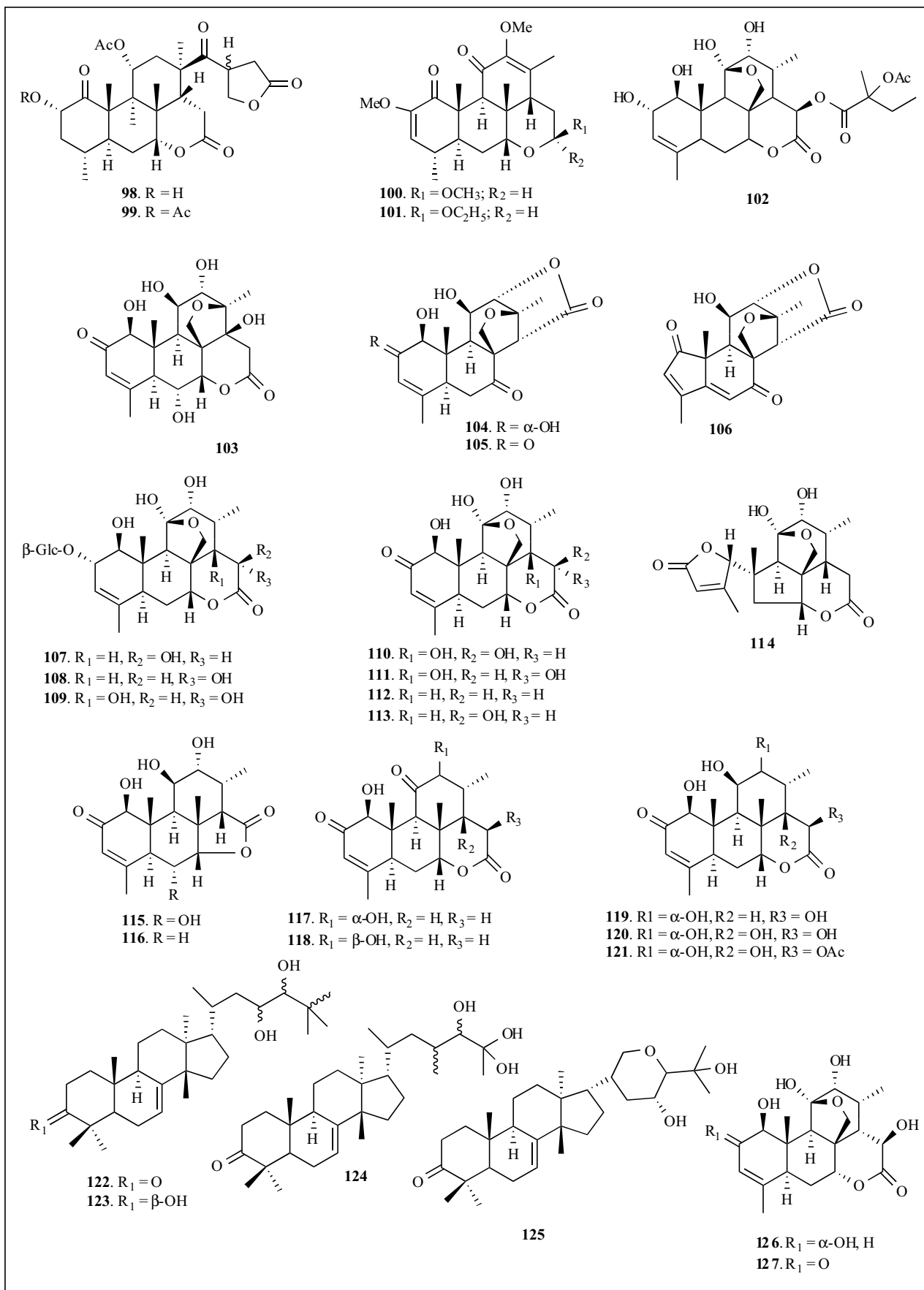


Fig. (3). Structures of novel quassinoids.

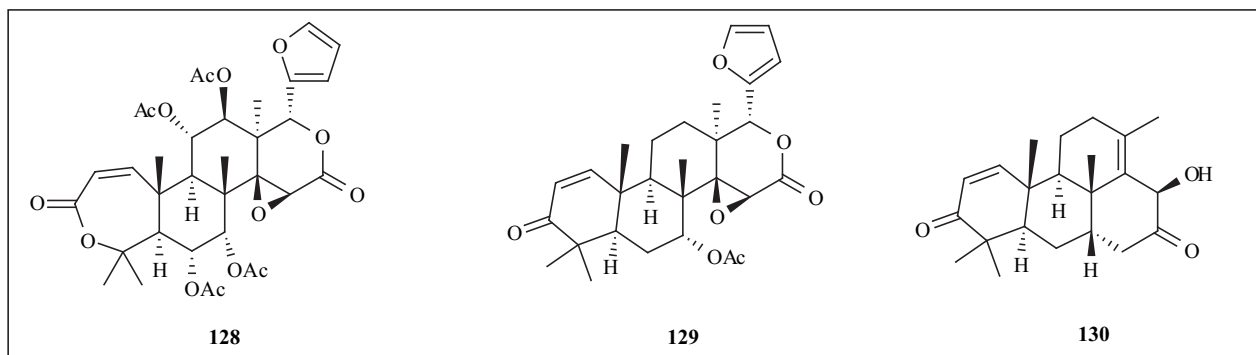


Fig. (4). Structures of limonoids and quassinoids that support the fact that both these groups undergo the similar biosynthetic pathway. It primarily involves degradation of triterpenes (loss of a C-4 methyl group and side chain), followed by oxidative cleavage of C-16 and C-17 bond that allows δ -lactone formation, the moiety in most of the C-20 quassinoids.

allows the cleavage of the C-13/C-17 bond, resulting in the formation of most C-20 and C-19 quassinoids.

SEMISYNTHESIS OF QUASSINOIDS

Semisynthesis of a natural product usually is an alternative source for biologically active compounds found

in lower content in nature. Arguably, the most successful example of semisynthesis of quassinoids is the conversion of bruceoside A (**131**), a compound easily obtained from *Brucea javanica* Biomass [3], into bruceantin (**132**) shown in Fig. (6), a compound difficult to obtain in quantity for clinical trials that displays very potent antileukemic activity [61]. Bruceoside A upon hydrolysis gives the compound **133**, which can then be esterified to afford a mixture of

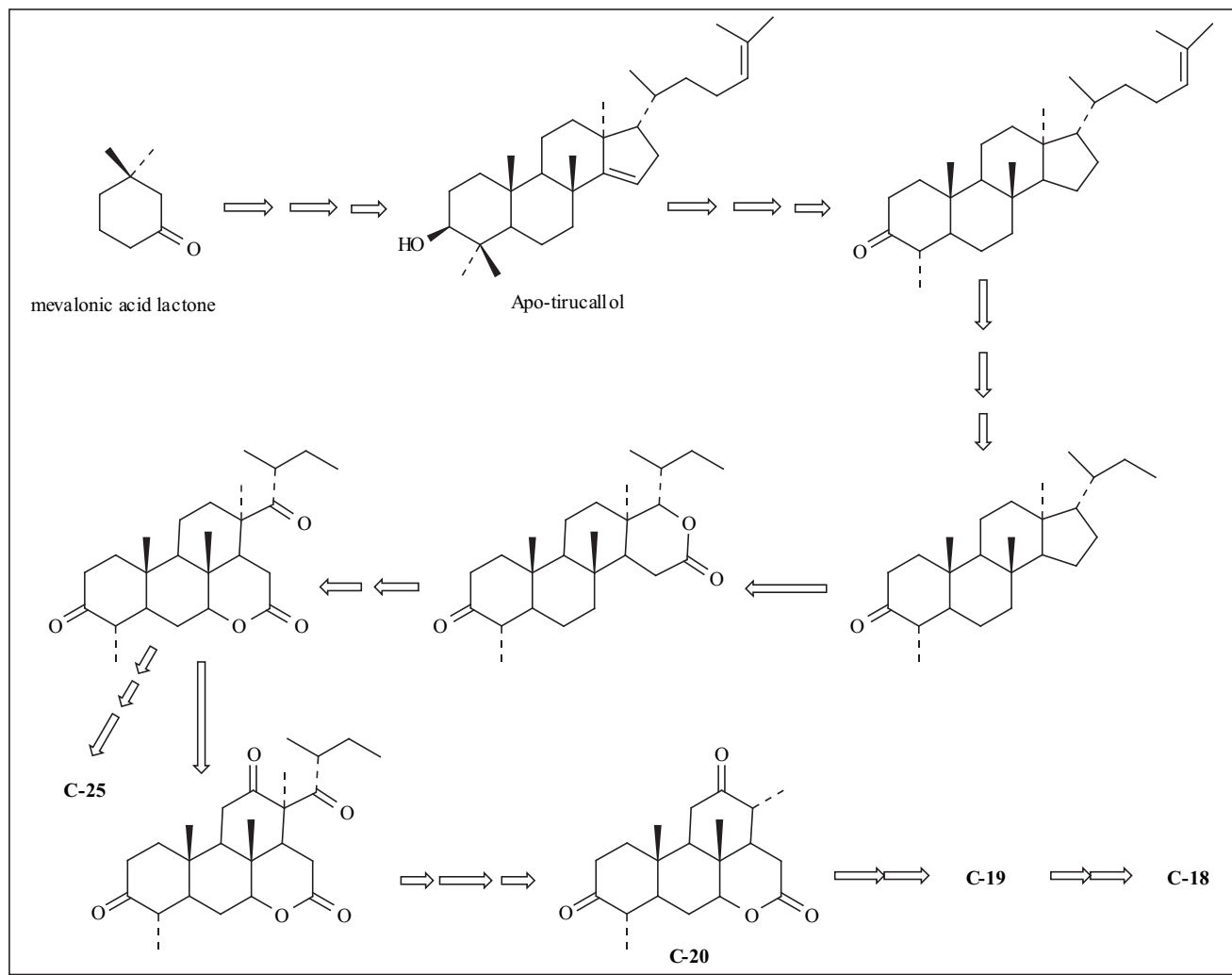


Fig. (5). Proposed biosynthetic pathway of quassinoids.

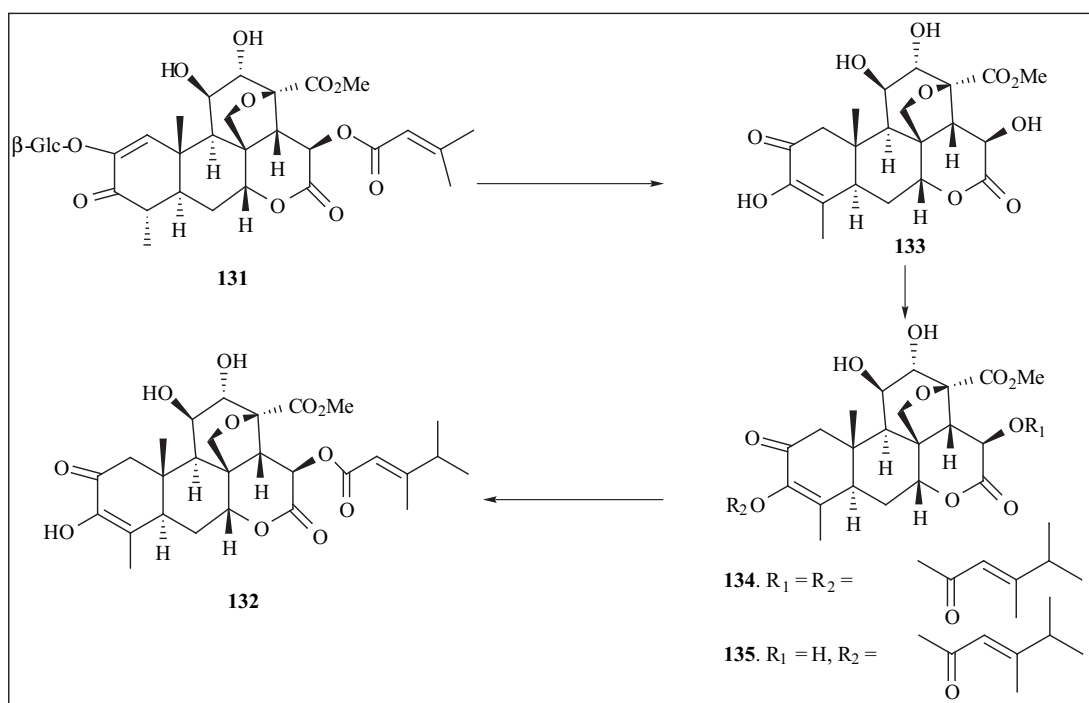


Fig. (6). Semisynthesis of bruceantin from bruceoside A.

compounds **134** and **135**. The compound **135** can be further esterified to get **134**, and the subsequent selective hydrolysis of C-3 ester gives bruceantin (**132**) in a 40% yield. This semisynthetic procedure established an alternate source of bruceantin to ensure a continuing supply for clinical trials. Another application is to convert the biologically inactive chaparrin (**136**) to the potent antileukemic agent glaucarubolone (**137**) shown in Fig. (7) [62].

Semisynthesis also plays a major role in the structural modification of natural products leading to the discovery more active compounds. The structural modification of quassinoids has been applied to the structural activity relationship and structure elucidation studies for novel quassinoids. One such discovery exploiting these methods is that esterification of the C-15 hydroxyl group of deacetylated isobrucein B may significantly improve its antitumor promoting activity [63].

TOTAL SYNTHESIS OF QUASSINOIDS

The wide spectra of biological activities and the complexity of the structures of quassinoids have challenged

the chemists for over two decades to attempt total synthesis of these compounds. In 1980 Grieco completed the total synthesis of quassin, the first quassinoid prepared completely synthetically. Since then the list of total syntheses has slowly been increasing as shown in Fig. (8) to include (\pm)-amarolide [65], (\pm)-klaianone (**113**) [66], (\pm)-castelanolide [67], (\pm - [68] and (-)-chaparrinone (**138**) [69], (\pm - [70] and (-)-bruceantin (**132**) [71], (+)-picrasane B [72], (+)- Δ^2 -picrasane B [71], (\pm)-shinjudilactone C [73] and shinjulactone D [72], (\pm)-holacanthone [74], (\pm - [73] and (-)-glaucarubolone [69], (+)-simalikalactone D (**142**) [75], (\pm)-shinjudilactone [76], (+)-quassamarin [77], (+)-glaucarunone (**140**) [68], (\pm)-samaderin B [78], (+)-quassin (**1**) [79], (\pm)-14 β ,15 β -dihydroxyklaianone [80], (-)-peninsularinone [81] and most recently, (+)-*des*-D-chaparrinone [82].

The synthesis of bruceantin by Grieco's group is a primary example of the total synthesis of quassinoids [70] shown in Fig. (9). The synthesis commences with protection of the hydroxymethyl group of a tricyclic ketone (**144**) at C-8, followed by carbomethoxylation to afford compound **145**. The α,β -unsaturated double bond can be introduced by selenylation and elimination of benzeneselenic acid to afford tricyclic enone (**146**), which can be converted to compound

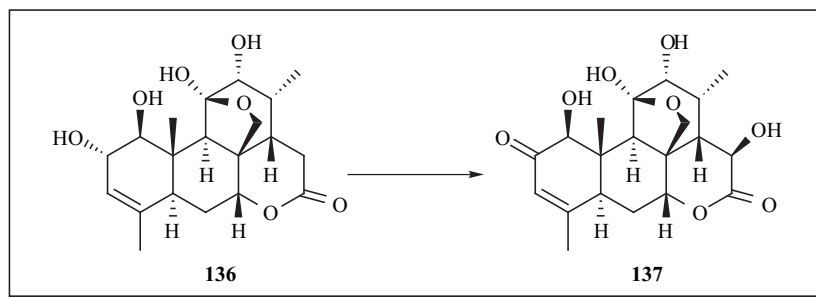


Fig. (7). Semisynthesis of chaparrin from glaucarubolone.

147 by the introduction of two-carbon unit and cleavage of protecting group. Bromination of **147**, followed by heating with collidine yields compound **149**, which can be quantitatively converted to a tetracyclic ketone (**150**). Introduction of the *trans* diaxial diol unit into the C-ring was achieved *via* an eight-step sequence to produce compound (**154**), which is ready to form the D-ring. Upon selective protection, oxidation, reduction and deprotection, triol (**156**) is obtained, which then is transformed *via* a four-step sequence into a pentacyclic lactol (**157**). From compound **157** the pentacyclic ketone (**160**) is prepared through elimination, oxidation and hydrolysis. Acylation of **160**, followed by consequence oxidation gave compound **162**, which upon deprotection of two hydroxy groups at C-ring gives crystalline racemic bruceantin (**132**).

BIOLOGICAL ACTIVITIES

Since the discovery of potent antileukemic activity of bruceantin [83], studies about the biological activities of quassinoids have increased enormously. Besides bruceantin, many quassinoids display various biological activities *in vitro* and/or *in vivo* including antitumor, antimalarial, antiviral, anti-inflammatory, antifeedant, insecticidal, amoebicidal, antiulcer, and herbicidal activities.

Antitumor Activity

The antitumor activity is one of the most impressive medicinal properties of quassinoids and has been well researched [19,25,84-86]. Many quassinoids display antitumor activity in different potencies (Table II), bruceantin (**132**), bruceantinol (**163**), glaucarubinone (**140**), and simalikalacton D (**142**) are among the most potent.

The mechanism of the action is believed to be that quassinoids can inhibit the protein synthesis by inhibition of the ribosomal peptidyl transferase activity [87-90] leading to the termination of the chain elongation. Bruceantin (**132**) and brusatol (**164**) were used to investigate the details of

protein synthesis inhibition. Both compounds can inhibit poly (U)-directed polyphenylalanine synthesis with runoff ribosomes. However, they did not inhibit formation of the 40S and 80S initiation complex, but did inhibit the reaction of puromycin with initiation complex containing [³⁵S]-Met-tRNA_f. The data suggests that quassinoids inhibits the peptidyl transferase elongation reaction of protein synthesis, but can do so only after one round of protein synthesis has been completed. Kupchan [91] proposed another plausible mechanism in which the A-ring enone acts as a Michael acceptor for biological nucleophiles shown in Fig. (10).

Recent studies have provided evidence in support of this hypothesis [92]. A free hydroxyl group at C-1 or C-3 was found to enhance biological activity, presumably due to intramolecular hydrogen bonding between the hydroxyl and the oxygen of the enone, thus further activating the enone towards nucleophilic attack. Bruceantin once had been introduced into phase II clinical trials as a candidate anticancer drug [93]; however, it has been withdrawn due to lack of significant efficacy [94]. Bruceanol D (**14**) showed potent *in vitro* cytotoxicity in five human tumor cell lines [16]. Their ED₅₀s (mg/mL) is 0.08 (KB), 0.55 (A-549), 0.09 (HCT-8), 0.09 (P-388), 0.08 (TE-671), and 0.09 (RPMI-7951). A recent report from Kitagawa's group [27] showed that samaderines X (**38**), Y (**39**), Z (**40**), B (**170**), C (**171**), E (**172**) and indaquassin X (**41**), C (**173**) exhibit *in vitro* cytotoxicity (IC₅₀: 0.02 - 1.00 mg/mL against KB cells).

Antimalarial Activity

It has been considered as a great discovery that several quassinoids possess potent antimalarial activity (Table III), especially the activity against the chloroquine-resistant *Plasmodium falciparum* [95,96]. IC₅₀'s of bruceantin and glaucarubinone are at nM level and are much more potent than that of chloroquine. The mechanism of the action is also the inhibition of the protein synthesis [97]. However, it seems to be different from that of cytotoxicity, since some

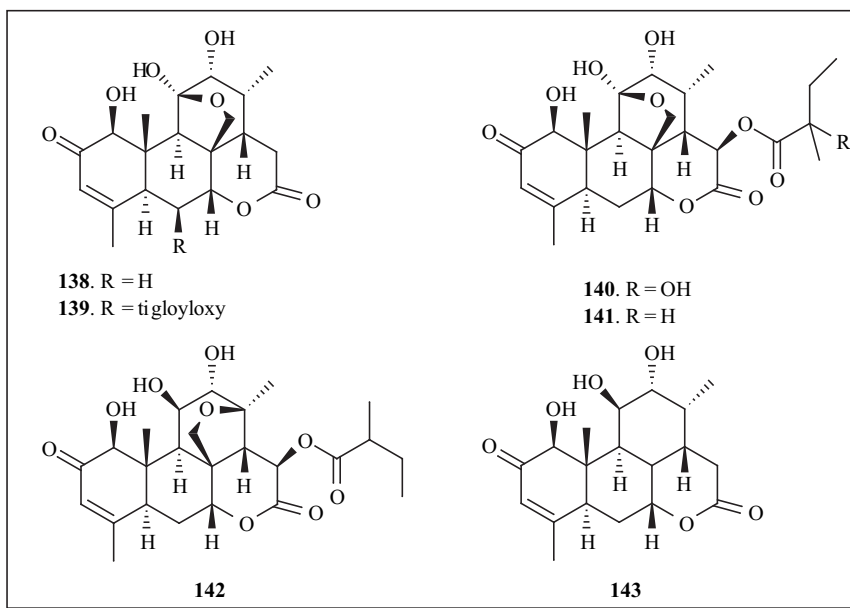


Fig. (8). Structures of the quassinoids whose total synthesis is known.

quassinoids have shown greater selectivity against *P. falciparum* than against KB cells [98]. For instance, the cytotoxic activity of glaucarubinone against KB cells is 285 times of its activity against *P. falciparum*. This result suggests that it may be a possible way to develop more selective quassinoid derivatives in the future [99].

Kirby *et al.*[97] utilized the incorporation of [³H]-isoleucine into acid-insoluble products as the index of protein synthesis and the incorporation of [³H]-hypoxanthine into acid-insoluble products as the index of nucleic acid synthesis to determine the inhibition activities of several quassinoids on both syntheses. According to the results, all

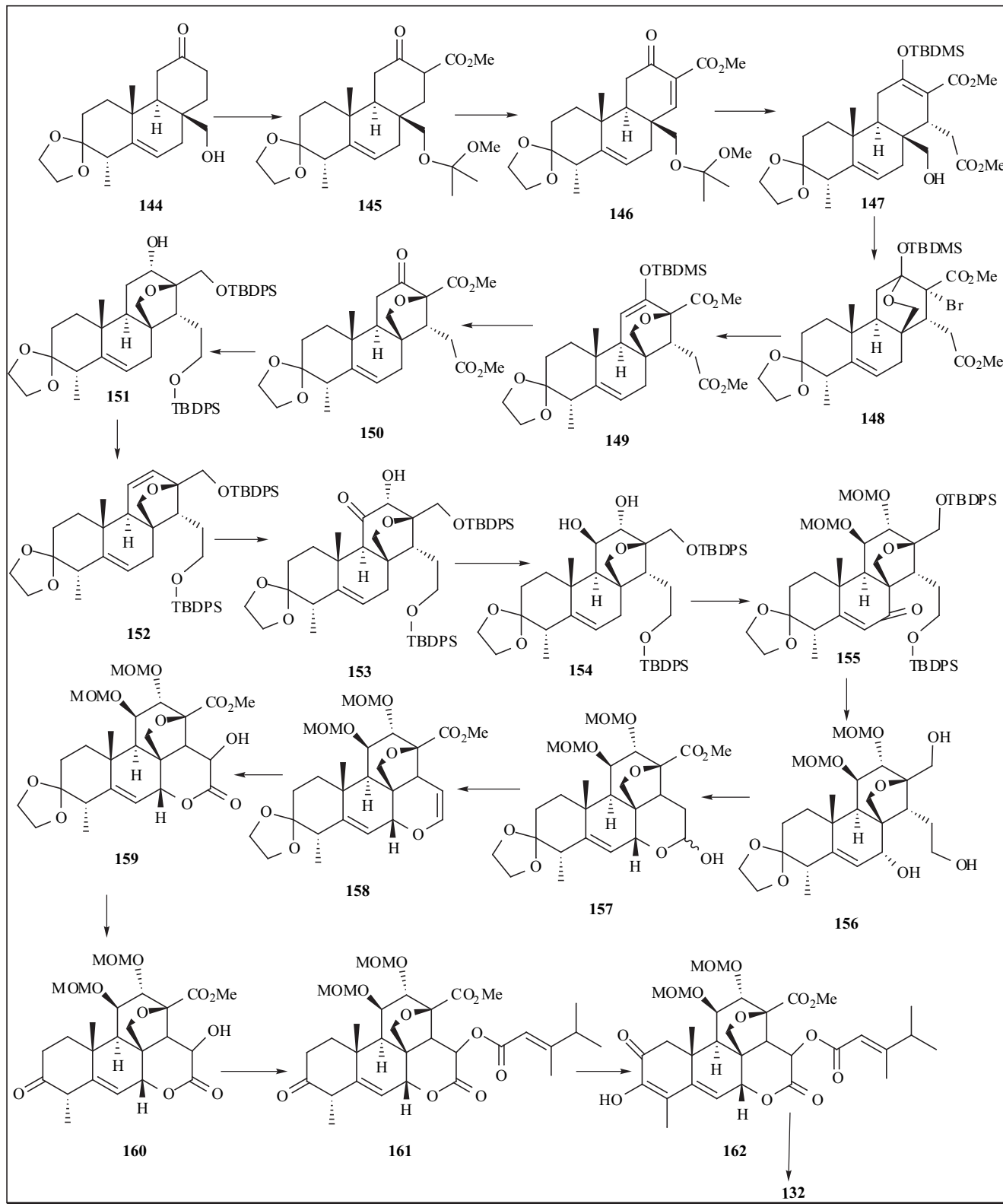


Fig. (9). Total synthesis of bruceantin.

Table II. Antileukemic Activity of Various Quassinoids

Quassinoids	Optimal dose (mg/kg)	T/C
Glaucarubinone (140)	0.25	177
Ailanthinone (141)	2.00	148
Tigloyloxy-6 α -chaparrinone (139)	0.60	163
Simalikalactone D (142)	1.00	198
Bruceantin (132)	0.50	220
Bruceantinol (163)	1.00	238

quassinoids tested inhibited protein synthesis more rapidly than nucleic acid synthesis in the *P. falciparum* infected human erythrocytes. The inhibition on nucleic acid synthesis was observed following the failure of protein synthesis. In the malaria parasite, as in eukaryote model, quassinoids are rapid and potent inhibitors of protein synthesis, most likely due to effects upon the ribosome rather than upon nucleic acid metabolism [97]. Studies have shown that the chance of cross-resistance of malaria between quassinoids and chloroquine is less, since chloroquine did not affect protein synthesis. Quassinoids may be presumed to act upon the malaria parasite through a fundamentally different mechanism to that of chloroquine [97]. Using the inhibition of incorporation of [³H]-hypoxanthine as an index, Ekong *et al.* [100] has proven that a chloroquine-sensitive strain of *P. falciparum* and a chloroquine-resistant strain did not differ in their sensitivities to the quassinoids; therefore, these triterpenoids offer a promising source for the development of new antimalarial drugs against chloroquine-resistant malaria.

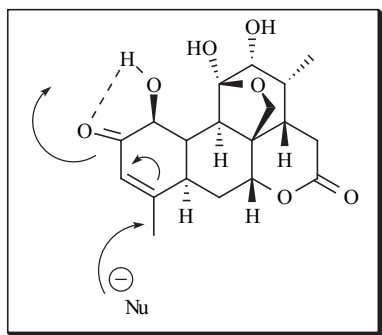


Fig. (10). Plausible mechanism of action of quassinoids in which the A-ring enone acts as a Michael acceptor for biological nucleophiles [91].

Antifeedant and Insecticidal Activity

In contrast to other activities of quassinoids, quassin (**1**), which is inactive in most other biological activities, is relatively active as an aphid antifeedant agent and is not phytotoxic at the concentration of 0.05% [101]. Quassin, as well as several other quassinoids, are also active against Mexican Bean Beetle and the southern armyworm. Recently it has been found that isobrucein B (**169**) has high potency in both antifeedant and insecticidal activities against the diamondback moth [102].

Other Biological Activities

Certain quassinoids display *in vitro* antiviral activity, but usually at relatively high concentration. For instance, simalikalactone D is active against the oncogenic Rous Sarcoma virus at as high as 0.10 mg/mL only [103]. However, a recent report showed that some quassinoids possessed anti-HIV activity. Among the eighteen quassinoid glycosides and nine quassinoids tested, the shinjulactone C (**175**) demonstrated the highest anti-HIV activity ($EC_{50} = 10.6$ mM) with a therapeutic index of greater than 25 [104]. Quassinoids were also reported to possess anti-inflammatory activity [105].

Several quassinoids were potent inhibitors of induced inflammation and arthritis in rodents. Brusatol (**164**) showed promising activity *in vivo* study. At the dose of 0.25 mg/kg it was as effective as indomethacin at the dose of 10 mg/kg. Samaderines X (**38**) and B (**105**) were found to exhibit significant anti-inflammatory activity, which inhibited the exudate volume by 79 and 78% respectively at dose of 1 mg/kg [27]. Amoebicidal activity is another property of quassinoids [106]. Bruceantin is the most potent amoebicide among the quassinoids examined [107]. Excelsin (**176**) as well as a few other quassinoids have been tested for herbicidal activity. Upon administration of excelsin at 20 g/acre, it totally controlled the growth of *Chenopodium album* and *Amaranthus retroflexus* on soybean in a pot experiment. Antiulcer activity of certain quassinoids was also reported recently. Four tested quassinoids, pasakbumins A (**28**), B (**29**), C (**30**), and D (**31**) showed up to 92.4% inhibition at dose 1.0 mg/kg [24].

STRUCTURE-ACTIVITY RELATIONSHIP (SAR)

Most of the structure-activity relationship studies were carried out about antitumor activity. The general structural requirements for optimal cytotoxicity and solid tumor selectivity based on various SAR studies shown in Fig. (12). For example, analogs that lack the A-ring enone exhibit significant loss of potency and complete loss of solid tumor selectivity. A free hydroxyl at C-1 or C-3 was found to enhance biological activity, presumably due to intramolecular hydrogen bonding between the hydroxyl and the oxygen of the enone, thus further activating the enone towards nucleophilic attack [108]. Moreover, substituting the C-1 hydroxyl of glaucarubolone with a C-1 methyl ether results in complete loss of cytotoxicity. Grieco and Valeriotte

Table III. Antimalarial Activity of Various Quassinoids

Quassinoids	<i>P. falciparum</i> (IC ₅₀ mM)	KB cells (IC ₅₀ mM)	Selectivity
Ailanthinone (141)	0.0190	0.914	48.11
Bruceantin (132)	0.0015	0.015	10.00
Bruceine A (165)	0.0210	0.188	8.95
Bruceine B (166)	0.0230	0.115	5.00
Bruceine C (167)	0.0090	0.037	4.11
Bruceine D (174)	0.0370	2.820	76.20
Brusatol (164)	0.0060	0.196	32.67
Glaucarubinone (140)	0.0080	2.280	285.00

[92], as well as others [109], have further addressed SAR in the C-, D- and E-rings of C-20 type quassinoids. For the c-ring, it has been found that any deviation from the oxygenation pattern found in the parent quassinoids of glaucarubolone, chaparrinone or bruceantin results in decreased biological activity. The D-ring lactone has also been shown to be essential for biological activity. A chaparrinone analog lacking the D-ring is biologically inactive [110]. A glaucarubolone analog with the D-ring lactone reduced to the tetrahydropyran displays moderate cytotoxicity, but lacks any solid tumor selectivity. Reduction of the D-ring lactone to the corresponding lactol

results in loss of cytotoxicity and no solid tumor selectivity. Also, lipophilic ester side chains at C-15 appear to be important for both potency and spectrum of response. Apparently, the lipophilic side chain aids in transport across cell membranes [92]. Finally, the E-ring also appears to be important for biological activity. Analogs that lack an E-ring (e.g. klaineanone) retain cellular cytotoxicity, however have no solid tumor selectivity. Quassinoids that have an E-ring which either forms a hemiketal bridge between C-8 and C-11 (e.g. chaparrinone), or forms an epoxymethano bridge from C-8 to C-13 (e.g. simalikalactone D), demonstrate both cytotoxicity and solid tumor selectivity.

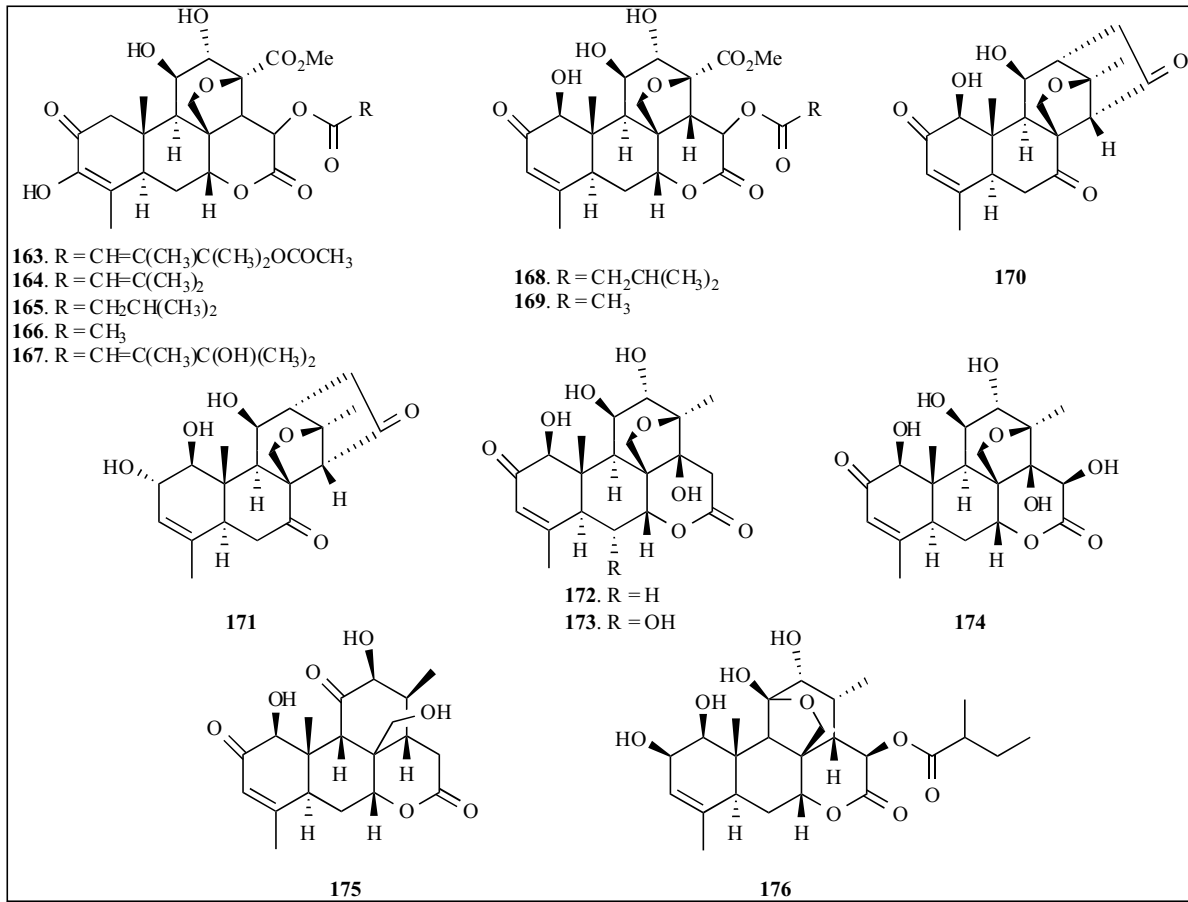


Fig. (11). Some of the biologically active quassinoids.

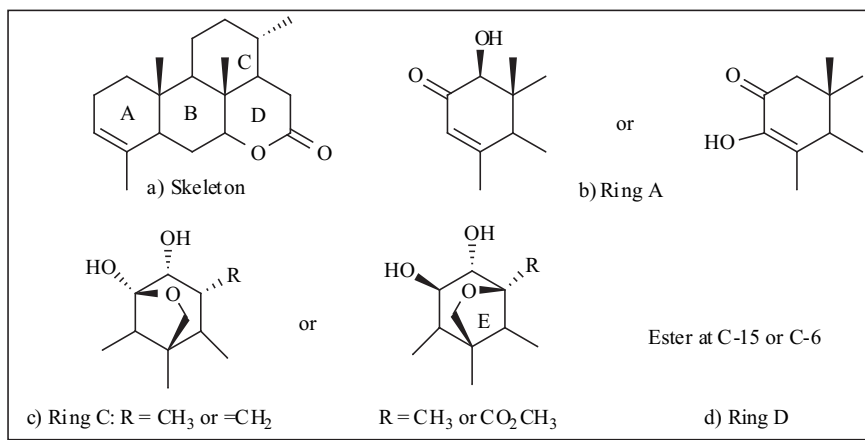


Fig. (12). Structural requirements for antileukemic activity of bruceantin.

Wall and Wani [111] have suggested that the E-ring slightly flattens the C-ring and holds the quassinoid in a rigid, biologically active conformation. These results suggest some general structural requirements for optimal cytotoxicity and solid tumor selectivity, which include: a) a four ring skeleton with a lactone D-ring; b) an α,β -unsaturated ketone and an α -hydroxyl group next to the carbonyl in the A-ring; c) two free hydroxyl groups and an oxygen-methylene bridge in the C-ring; and d) an ester group at either C-15 or C-6. The structural requirements for antimalarial activity are relatively similar and the structure in A-ring and C-15 ester group seems more important. However, since these are based on the natural products and some of their semisynthesis derivatives, the structural variation may be not enough to draw an accurate conclusion. As a matter of fact, not all compounds possessing potent activities meet these structural requirements. For example, samaderin X doesn't possess a D-ring and ester side chain at all, but it is still an active compound with an IC₅₀ 0.07 mg/mL against KB cells [27].

QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP (QSAR) STUDY

So far only two reports have been published about QSAR study on quassinoids antitumor activity [112,113]. A quantitative electronic structure-activity relationship (QESAR) technique and the alternating conditional expectations (ACE) method have been employed. Total 28 quassinoids were used as data set and cytotoxic activity of these quassinoids (ED₅₀) were used as biological activity index. A ten-descriptor model was obtained ($r^2 = 0.85$, $S = 1.26$, and $F = 10.0$). The results showed that the net charges at atoms C₁, C₂, C₄, C₆, C₁₀, O₁₁, C₁₂, C₁₃, C₁₅, and lactone O are important to activity. It is in agreement with the previous SAR results, however, it reveals that oxide bridge in ring C seems not to be related to the biological activity.

CONCLUSION AND FUTURE PROSPECTS

Quassinoids possess a wide spectrum of biological activities, some of which have been well researched and

documented. The antitumor activity of quassinoids is definite, but most of the compounds are too toxic to be clinically used. Investigating the new sources of natural products to isolate more potent and less toxic quassinoids and structurally modifying the known compounds to retain activity and lower toxicity are still the best possible ways to develop new anticancer drugs of this class. Other discovered biological activities do not always parallel their cytotoxicity, offering a promising potential for the separation of the useful activities from the toxicity. Structural modification and synthesis of partial analogs may give the answer. Any further applications, such as antiulcer and anti-HIV applications, need to be further investigated.

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