ESTUDO FITOQUÍMICO DAS RAÍZES DA ESPÉCIE *Homalolepis suffruticosa* (Simaroubaceae) E AVALIAÇÕES DE ATIVIDADES BIOLÓGICAS

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CAMPOS DOS GOYTACAZES - RJ
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Orientador: Prof. Dr. Ivo José Curcino Vieira
Co-orientador: Prof. Dr. Raimundo Braz-Filho

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B671 Boeno, Samyra Imad da Silva.

ESTUDO FITOQUÍMICO DAS RAÍZES DA ESPÉCIE *Homalolepis suffruticosa* (Simaroubaceae) E AVALIAÇÕES DE ATIVIDADES BIOLÓGICAS / Samyra Imad da Silva Boeno. - Campos dos Goytacazes, RJ, 2021.

116 f. : il.
Inclui bibliografia.

Tese (Doutorado em Produção Vegetal) - Universidade Estadual do Norte Fluminense Darcy Ribeiro, Centro de Ciências e Tecnologias Agropecuárias, 2021. Orientador: Ivo Jose Curcino Vieira.

1 . quassinoides. 2. triterpenos. 3. fitoquímica. 4. malária. 5. Simaroubaceae. I. Universidade Estadual do Norte Fluminense Darcy Ribeiro. II. Título.

CDD - 630

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Aprovada em 02/07/2021

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AGRADECIMENTOS

Primeiramente agradeço a Deus, pela força e sustentação no decorrer de todos os desafios e obstáculos que surgiram ao longo desses 4 anos de doutorado. Foram muitos, mas Deus esteve sempre comigo.

Agradeço ao meu esposo Eliersio que foi essencial no apoio emocional durante essa jornada. Eu não teria conseguido sem você e meu amorzinho Nicolas, sempre me ajudando a renovar as energias para continuar seguindo em frente. As sessões de risadas com você, meu filho, foi e tem sido a melhor das terapias. Marido, seu carinho e ombro amigo foram imprescindíveis para me dar força na caminhada. Teria sido impossível sem vocês!

Também sou grata pelo constante apoio e incentivo da minha mãe Leila, você é uma amiga na qual eu sei que sempre vou poder contar. Ao meu pai Merialdo também... obrigada por fazerem parte da minha vida e estarem presentes me apoiando sempre que preciso.

Ao professor Ivo José Curcino Vieira agradeço muitíssimo pelas oportunidades fornecidas; ao professor Raimundo Braz-Filho pelos ensinamentos de RMN; e à Professora Sarah O'Connor por ter me recebido na Max Planck.

Aos Professores das bancas para defesa do projeto, qualificação e defesa final: Milena, Daniela, Antônio Sérgio, Milena e Almir... agradeço grandemente pelas contribuições para melhorar meu trabalho.

Aos amigos de laboratório na UENF: Michel, Noemi, Mayara, Lara, Thalya, Fabíola, Renata, Mariah... e também do Instituto Max Planck, que são muitos,

pelos conhecimentos compartilhados, parceria na obtenção de resultados e amizade.

Aos parceiros nos experimentos envolvendo RMN, agradeço primeiramente ao Professor Braz e Márcio (UENF) e também à Yoko (Instituto Max Planck). Aos parceiros do massas, agradeço ao Marcelo (UENF) e também à Délia e Maritta (Instituto Max Planck).

Pelos ensaios biológicos que contribuíram grandemente com as publicações apresentadas aqui, agradeço à Professora Alaíde Braga, Maria Fernanda Alves, Douglas costa, Sanderson Dias e Michele Frazão.

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RESUMO

BOENO, Samyra Imad da Silva; D.Sc.; Universidade Estadual do Norte Fluminense Darcy Ribeiro; julho de 2021; ESTUDO FITOQUÍMICO DAS RAÍZES DA ESPÉCIE *Homalolepis suffruticosa* (Simaroubaceae) E AVALIAÇÕES DE ATIVIDADES BIOLÓGICAS; Orientador: D.Sc. Ivo José Curcino Vieira.

Uma característica marcante da família Simaroubaceae é o sabor amargo de seu córtex, devido à produção de quassinoides e alcaloides, compostos estes de grande importância biológica. Diante disso, objetivou-se nessa pesquisa o isolamento e identificação dos metabólitos secundários de *Homalolepis suffruticosa,* espécie pertencente à família Simaroubaceae, e investigar se a espécie e compostos isolados possuem atividade antimicobacteriana e/ou antimalárica. Das raízes de *H. suffruticosa* foi isolado e identificado um novo triterpeno, Milemaronol, juntamente com chaparrinona, escopoletina, 5-metoxicantin-6-ona, eurileno, hispidol A, hispidol B, nilocitina, α-diidronilocitina, β-diidronilocitina, e teurileno. Neste trabalho foi avaliado os efeitos antiplasmódicos e citotóxicos do extrato metanólico das raízes e compostos isolados de *H. suffruticosa* contra a cepa de *Plasmodium falciparum* W2 resistente à cloroquina; e atividade antimicobacteriana contra as cepas de *Mycobacterium tuberculosis* H37Rv e M299 e as atividades citotóxicas. Os resultados sustentam a história etnofarmacológica dessa espécie de Simaroubaceae como antimaláricos e foi aqui relatada pela primeira vez. Em relação à atividade antimicobacteriana, o novo composto intilulado Milemaronol, apresentou a melhor relação atividade

versus citotoxicidade contra as cepas de *Mycobacterium tuberculosis* H37Rv e M299 dentre os onze compostos avaliados, isolados da mesma espécie vegetal.

ABSTRACT

BOENO, Samyra Imad da Silva; D.Sc.; North Fluminense State University Darcy Ribeiro; março de 2018; PHYTOCHEMICAL STUDY OF THE ROOTS OF THE *Homalolepis suffruticosa* SPECIES (SIMAROUBACEAE); Advisor: D.Sc. Ivo José Curcino Vieira.

A highlight feature of the Simaroubaceae family is the bitter taste of its cortex, due to the production of quassinoids and alkaloids, compounds with great biological importance. Therefore, the aim of this research was to isolate and identify the secondary metabolites of *Homalolepis suffruticosa*, a species belonging to the Simaroubaceae family, and investigate if the specie and isolated compounds have antimycobacterial and / or antimalarial activity. From the roots of *H. suffruticosa*, a new triterpene, Milemaronol, was isolated and identified, together with chaparrinone, scopoletin, 5-methoxycanthin-6-one, eurylene, hispidol A, hispidol B, nilocitine, α-dihydronilocitine, β-dihydronilocitine, and teurilene. In this reserarch, the antiplasmodic and cytotoxic effects of the methanolic extract of the roots and compounds isolated from *H. suffruticosa* against the chloroquine-resistant strain of *Plasmodium falciparum* W2 were evaluated; and antimycobacterial activity against strains of *Mycobacterium tuberculosis* H37Rv and M299 and cytotoxic activities. The results support the ethnopharmacological history of the specie of Simaroubaceae as antimalarial and was reported here for the first time. Regarding antimycobacterial activity, the new compound named Milemaronol, showed the best activity versus cytotoxicity ratio against

Mycobacterium tuberculosis H37Rv and M299 strains among the eleven compounds evaluated, isolated from the same plant species.

1. INTRODUÇÃO

A curiosidade do homem juntamente com o desenvolvimento da ciência e da tecnologia ao logo do tempo culminaram na produção de fármacos a partir de produtos naturais de plantas; e posteriormente, fármacos sintéticos. Logo, observa-se a grande importância da pesquisa científica sobre produtos naturais, devido às descobertas de entidades químicas ativas (Jr et al., 2006).

Neste contexto, muitas espécies da família Simaroubaceae vem sendo usadas na medicina popular, por seus benefícios biológicos observados (Arriaga et al., 2002); e por esse motivo, pesquisas químicas e biológicas com espécies desta família vem sendo realizadas.

Uma característica marcante da família Simaroubaceae é o sabor amargo de seu córtex (Almeida et al., 2007); isso devido à produção de substâncias amargas, tais como os quassinoides, compostos naturais encontrados exclusivamente em plantas da família em questão (Polonsky, 1973).

Entre as propriedades farmacológicas dos quassinoides, podemos encontrar: anticâncer (Ozeki et al., 1998; Ye et al., 2015); antimalárico (Dou et al., 1996; Muhammad et al., 2004; Silva et al., 2009); herbicida (Jiwajinda et al., 2001); antialimentação e inibição do crescimento de pragas (Kubo et al., 1992; Lidert et al., 1987; Polonsky et al., 1989); inseticida (Fang et al., 2015); larvicida (Silva et al., 2009); antileishmania (Muhammad et al., 2004); antiviral (Okano et al., 1996; Pierré et al., 1980; Yan et al., 2010); anti-inflamatório (Hall et al., 1983); amebicida (Wright et al., 1988) e anticomplemento (Zhan et al., 2019).

Além dos quassinoides, também são encontrados alcaloides na família Simaroubaceae, compostos estes também amargos e de grande interesse biológico (Kuo et al., 2003; Noldin, 2005).

Dentro da família Simaroubaceae, destaca-se o gênero *Homalolepis*, recentemente segregado de *Simaba*. *Homalolepis* compreende 28 espécies vegetais, com distribuição predominantemente extra-amazônica (Devecchi, 2017). Diversos trabalhos científicos relatam os efeitos biológicos apresentados pelas espécies agora pertencentes ao gênero *Homalolepis*. Como exemplo, pode-se citar a citotoxicidade (Ozeki et al., 1998) e a atividade antimalárica (Oliveira et al., 2015) apresentadas pela espécie *Homalolepis cedron*.

Dentre as espécies pertencentes ao gênero em questão, a espécie *Homalolepis suffruticosa*, muito utilizada popularmente na região do triângulo mineiro como anti-helmíntico (Barbosa, 2012), se mostrou atrativa para estudo fitoquímico/biológico. Isso se deve ao potencial químico-farmacológico da família e gênero aqui descritos, somado a escassez de artigos científicos publicados sobre a espécie.

Diante disto, a presente pesquisa objetiva isolar e identificar os metabólitos secundários da espécie *Homalolepis suffruticosa,* e descobrir se a espécie e compostos possuem atividade antimicobacteriana e/ou malárica.

2. REVISÃO DE LITERATURA

2.1 Família Simaroubaceae

A família Simaroubaceae possui 22 gêneros e pouco mais de 100 espécies (Clayton et al., 2007). Essa família tem distribuição principalmente pantropical; com algumas espécies de *Brucea, Castela, Holacantha, Ailanthus* e *Picrasma* subtropicais, e outras de *Ailanthus altissima, Picrasma quassioides* e *Leitneria floridan* crescendo em climas temperados (Clayton, 2011). No continente Africano existe maior representatividade de gêneros de Simaroubaceae, porém a diversidade de espécies é significativamente maior na região neotropical (Clayton, 2011).

Como já introduzido anteriormente, quando o assunto é família Simaroubaceae, não se pode deixar de fora seu marcador taxonômico, os quassinoides (Saraiva et al., 2006), ou seja, substâncias amargas que vem demonstrando grande valor farmacológico.

Neste contexto, Chan et al., 1986 publicaram o grande potencial antimalárico de quassinoides isolados de *Eurycoma longifolia.* Eurycomalactone (**1 -** CI_{50} = 0,21 µg/ml), Eurycomanone (**2 -** CI_{50} = 0,11 µg/ml) e Eurycomanol (**3 -** CI_{50} = 0,28 µg/ml) apresentaram valores de CI_{50} contra uma cepa tailandesa multirresistente (K-1) de *Plasmodium falciparum* comparável ou até melhor que a Cloroquina (CI_{50} = 0,21 µg/ml) (Figura 1).

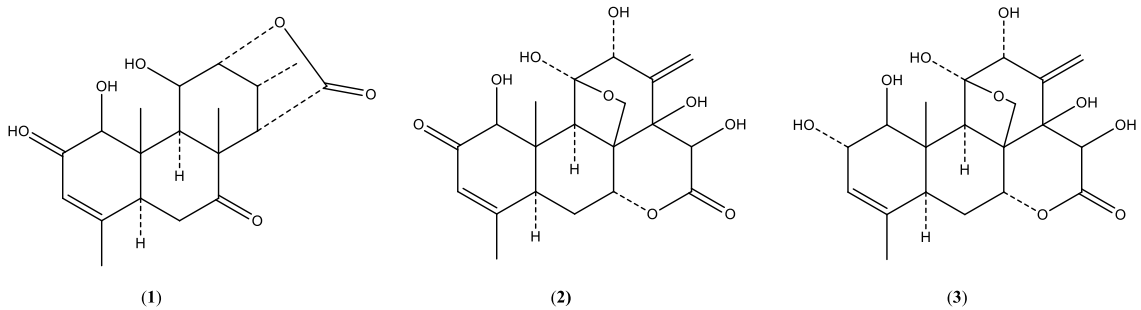


Figura 1: Quassinoides isolados da espécie vegetal *Eurycoma longifolia*: (1) Eurycomalactone; (2) Eurycomanone e (3) Eurycomanol.

Além dos quassinoides, também tem sido encontrado outras classes de substâncias biologicamente interessantes nas espécies desta família, como por exemplo, triterpenos e alcaloides.

Neste contexto, Morita et al., 1993a isolaram quatro triterpenos, derivados do esqualeno, da espécie *Eurycoma longifolia*: eurileno (**4**), 14-diacetileurileno (**5**), peróxido de longileno (**6**) e teurileno (**7**); sendo apenas este último (**7**) já isolado anteriormente, a partir da alga vermelha *Laurencia obtusa* (Suzuki et al., 1985). Os quatro triterpenos isolados desta espécie de Simaroubaceae apresentaram atividade citotóxica contra células KB, com valores de CI_{50} = >100 µg/mL, 0,52 µg/mL, 5,3 µg/mL, 7,0 µg/mL para os compostos **4**, **5**, **6** e **7,** respectivamente (Morita et al., 1993a). Os compostos **6** e **7**, com o terceiro anel tetrahidrofurano no centro da molécula, foram mais potentes em relação à **4**, que tem o anel central clivado. Curiosamente, apesar da clivagem do anel central em **5**, essa molécula mostrou a atividade mais potente. Aparentemente, o anel central de tetrahidrofurano em **6** e **7**, ou o anel central formado por ligação de hidrogênio intramolecular em **5**, pode ser um requisito estrutural para a potência da atividade (Morita et al., 1993ª) (Figura 2).

Como exemplo da atividade de alcaloides na família Simaroubaceae, estudos realizados por Kuo et al., 2003, demonstraram citotoxicidade significativa dos compostos 9-metoxicantin-6-ona e canthin-6-ona contra linhagens celulares de câncer de pulmão humano (A-549) e de mama humano (MCF-7).

Pesquisas que levaram a conhecimentos como o mencionado acima, só foram possíveis porque benefícios biológicos foram observados anteriormente,

através do uso de plantas pertencentes à família Simaroubaceae na medicina popular.

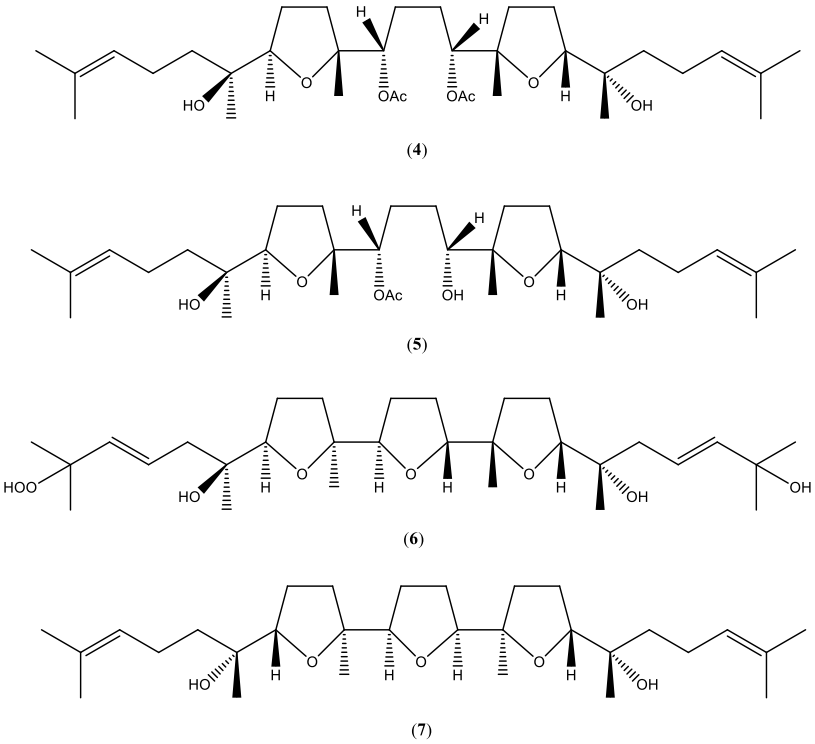


Figura 2: Triterpenos isolados da espécie *Eurycoma longifolia*: (4) Eurileno; (5) 14-diacetileurileno; (6) Peróxido de longileno e (7) Teurileno.

Para exemplificar, a pesquisa de Oliveira et al. 2015 se encaixa perfeitamente. Esses autores observaram o uso de diversas espécies de plantas, incluindo a espécie *Homalolepis cedron* (Planch.). Devecchi & Pirani (synon. *Simaba cedron* Planch) como antimalárico por membros de uma comunidade quilombola na Amazônia. Decidiram então testar a atividade antimalárica dessas plantas e notaram que a espécie *Homalolepis cedron*, pertencente à família Simaroubaceae, foi uma das três mais efetivas, entre onze plantas testadas, com maior atividade contra o parasita da malária humana.

Logo, desde a observação do uso de plantas da família Simaroubaceae de forma empírica pelos cientistas, pesquisas químicas e biológicas com as espécies da família vem sendo realizadas. E conforme virá a seguir, as espécies

da família em questão apresentam efeitos biológicos muito amplos, além dos efeitos citotóxicos e antimaláricos já mencionados anteriormente.

Neste contexto, Poljuha et al., 2017 demonstraram atividade antibacteriana e antifúngica equivalente aos antibióticos usados como padrão de extratos de *Ailanthus altissima*. O extrato de acetona das folhas foi tão ativo contra *Escherichia coli* (CMI = 0,04 mg/mL) quanto o controle positivo gentamicina (CMI = 0,0 mg/mL). Ambos os extratos de acetona e metanol: diclorometano tiveram uma atividade maior contra os fungos *Candida albicans* (CMI = 0,0 mg/mL) do que a droga usada como padrão anfotericina B (CMI = 0,1 mg/mL). Esses resultados tornam essa espécie de Simaroubaceae um recurso valioso para a atividade antimicrobiana, o que torna esta espécie interessante para futuras investigações e possível aplicação farmacêutica.

Algumas espécies da família Simaroubaceae também foram testadas quanto à atividade contra larvas do mosquito *Aedes aegypti*, um transmissor de diversas doenças ao homem, tais como a dengue, o zika vírus, a febre amarela e a chikungunya. Resultados mostraram que os extratos das espécies *Picrolemma sprucei, Simaba polyphylla, Simaba* sp. e *Simarouba amara*, a concentrações de 500 µg/mL, causaram mortalidade em larvas de *Aedes aegypti* (Pohlit et al., 2004). Extratos do tronco e raiz de *Picrolemma sprucei* apresentaram 57% e 74% de atividade contra larvas de *Aedes aegypti*, respectivamente; Enquanto os extratos dos galhos de *Simaba polyphylla*, *Simaba* sp. e *Simarouba amara* causaram 100%, 70% e 37% de mortalidade das larvas do mosquito (Pohlit et al., 2004).

Outro efeito biológico promissor demonstrado por uma espécie da família Simaroubaceae, é o potencial anti-inflamatório da espécie *Quassia borneensis*. Extratos de hexano, clorofórmio e aquoso da espécie já mencionada, apresentaram efeitos inibidores na produção de óxido nítrico pelos macrófagos (células RAW 264.7), conforme demonstrado por Kamarulzaman et al., 2017. Os melhores efeitos foram exibidos pelo extrato de clorofórmio da raiz, com inibição de 97.64% da produção de óxido nítrico, enquanto o controle positivo (indometacina) inibiu 45.12%.

Em relação ao potencial antioxidante de Simaroubaceae, Santhosh et al., 2016 observaram atividade antioxidante a partir da espécie *Simarouba glauca*. Os extratos de acetato de etila e éter de petróleo desta espécie mostraram atividade

antioxidante significativa, de forma dependente da dose. Contudo, o extrato de acetato de etila revelou-se mais eficaz. Pelo ensaio de Atividade Antioxidante Total, os valores de CI_{50} foram 1000 µg e 2000 µg para os extratos de acetato de etila e éter de petróleo respectivamente; sendo o CI_{50} da vitamina C (usada como padrão) igual a 700 µg. Já pelo Método de Eliminação de Radicais Hidroxila, os extratos de acetato de etila e éter de petróleo demonstraram CI_{50} = 1120 µg e 1320 µg respectivamente; sendo CI_{50} da vitamina C igual a 700 µg (Santhosh et al., 2016).

Os extratos de clorofórmio, hexano e aquoso da espécie *Quassia borneensis* também demonstraram atividade antioxidante (Kamarulzaman et al., 2017). Os melhores resultados foram observados pelo extrato de clorofórmio na ausência e presença de células de leucemia HL-60, onde os valores referentes ao Poder Antioxidante Férrico de Redução foram 125,45 µM $FeSO_4.7H_2O$ e 181,55 µM $FeSO_4.7H_2O$, respectivamente. Enquanto o Poder Antioxidante Férrico de Redução do controle negativo (células HL-60 não tratadas) foi de 0.62 µM $FeSO_4.7H_2O$.

Tratando-se da atividade antiproliferativa de espécies da família em questão, extratos de clorofórmio, hexano e aquoso de *Quassia borneensis* exibiram efeitos sobre células HL-60 (células de leucemia); sendo os melhores resultados apresentados pelo extrato de clorofórmio do tronco, com CI_{50} = 5,0 µg/mL, enquanto que o medicamento quimioterápico etoposídeo demonstrou CI_{50} = 2,4 µg/mL (Kamarulzaman et al., 2017). Desta forma, os autores demonstraram o potencial quimioterápico da espécie.

2.2 **Gênero *Homalolepis***

Homalolepis é um gênero que recentemente foi segregado de *Simaba*, com base em aspectos moleculares e morfológicos (Devecchi, 2017). Enquanto que *Simaba* atualmente compreende aproximadamente 10 espécies distribuídas apenas na região Amazônica, *Homalolepis* compreende 28 espécies com distribuição predominantemente extra-amazônica (Devecchi, 2017).

As espécies do gênero *Homalolepis* são distribuídas principalmente na América do Sul tropical, com uma espécie que se estende para a América Central. A maioria das espécies ocorre no Brasil dentro dos domínios do Cerrado

(17 spp.) e da Mata Atlântica (10 spp.), sendo algumas encontradas nos domínios da Caatinga e da Amazônia ou em outros países (Devecchi et al., 2018).

Em relação às atividades biológicas apresentadas por espécies do gênero em questão, quatro quassinoides isolados da espécie *Homalolepis cedron* mostraram citotoxicidade significante, *in vitro*, contra células de leucemia P-388; sendo esses quassinoides: Cedronolactona A (**8**) com CI_{50} = 0,0074 µg/mL, simalikalactona D (**9**) com CI_{50} = 0,0055 µg/mL, chaparrinona (**10**) com CI_{50} = 0,92 µg/mL e glaucarubolona (**11**) com CI_{50} = 1,4 µg/mL (Ozeki et al., 1998) (Figura 3).

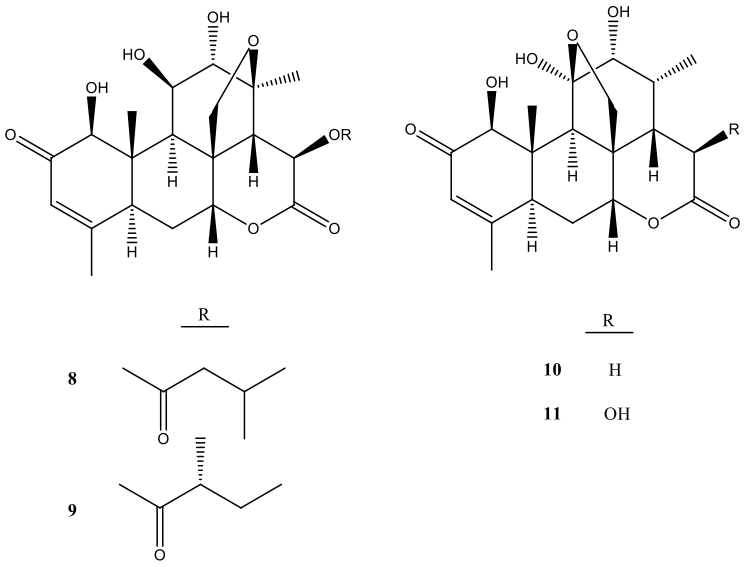
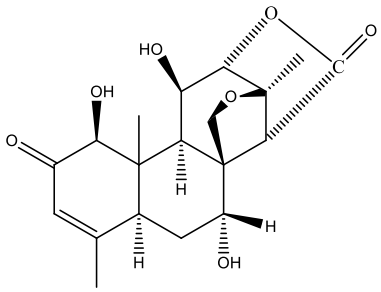


Figura 3: Quassinoides isolados da espécie *Homalolepis cedron*: (8) Cedronolactona; (9) Simalikalactona; (10) Chaparrinona e (11) Glaucarubolona.

Em contrapartida, o quassinoide cedronina (**12**), também isolado da espécie *Homalolepis cedron*, apresentou baixa citotoxicidade contra células do carcinoma bucal humano (CI= 4 µg/mL) quando comparado aos quassinoides C_{20} biologicamente ativos (Moretti et al., 1994) (Figura 4).



(12)

Figura 4: Quassinoide cedronina (12) isolado da espécie *Homalolepis cedron*.

Entretanto, a cedronina (C_{19}) demonstrou atividade *in vitro* contra cepas de *Plasmodium falciparum* (CI_{50} = 0,25 µg/mL), sendo o CI_{50} do antimalárico cloroquina igual a 0,38 µg/mL. No mesmo estudo, a cedronina também apresentou atividade *in vivo* contra o *Plasmodium vinkei* (CI_{50} = 1,8 mg/kg) com valores de CI_{50} do controle positivo cloroquina igual a 0,5 mg/kg (Moretti et al., 1994).

O estudo de Oliveira et al., 2015 já descrito anteriormente, onde dentre as onze plantas medicinais testadas contra cepas do *Plasmodium falciparum*, *H. cedron* foi uma das três com maior atividade antimalárica, confirmando o potencial antimalárico da espécie vegetal em questão.

Tratando-se da espécie *Homalolepis ferruginea*, resultados revelados por Noldin, 2005 e Almeida et al. 2011 demonstraram que esta planta é uma fonte promissora de compostos antiulcerogênicos. Tanto os extratos metanólicos, quanto os alcaloides isolados, do tipo cantinona, foram efetivos no combate a úlcera gástrica, e ainda apresentaram significante atividade antinociceptiva em ratos (Noldin, 2005). Além da atividade biológica mencionada, a espécie em questão também apresenta boa atividade antioxidante (acima de 60% de inibição), de acordo com estudos realizados por Simão et al., 2013.

2.3 Quassinoides

Quassinoides são compostos encontrados exclusivamente em plantas da família Simaroubaceae, por isso são considerados o marcador taxonômico da

família (Almeida et al., 2007). São triterpenoides degradados, derivados da série eufol / tirucalol; geralmente bastante oxigenados e possuem lactonas em seus esqueletos básicos. Raramente possuem mais que uma ligação dupla (Almeida et al., 2007).

Esses compostos possuem grande importância biológica, como já descrito anteriormente. Dentre as propriedades farmacológicas apresentadas pelos mesmos, encontram-se: anticâncer (Ozeki et al., 1998; Ye et al., 2015); antimalárico (Dou et al., 1996; Muhammad et al., 2004; Silva et al., 2009); herbicida (Jiwajinda et al., 2001); antialimentação e inibição do crescimento de pragas (Kubo et al., 1992; Lidert et al., 1987; Polonsky et al., 1989); inseticida (Fang et al., 2015); antibacteriano (Wong et al., 2019); larvicida (Silva et al., 2009); antileishmania (Muhammad et al., 2004); antiviral (Okano et al., 1996; Pierré et al., 1980; Yan et al., 2010); anti-inflamatório (Hall et al., 1983); amebicida (Wright et al., 1988) e anticomplemento (Zhan et al., 2019).

Neste contexto, os quassinoides brusatol (**13**), bruceantinol (**14**), bruceina A (**15**) e bruceantarina (**16**) (Ye et al., 2015) apresentaram atividades antitumorais promissoras, com resultados ainda melhores que o controle positivo utilizado (Figura 5).

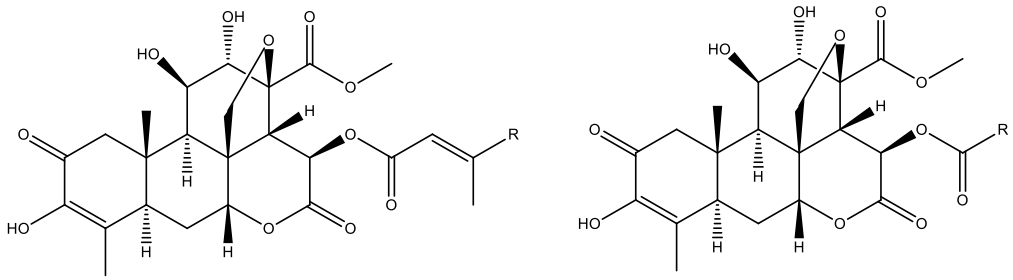
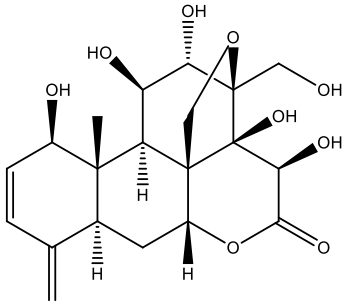


Figura 5: Quassinoides: (13) Brusatol; (14) Bruceantinol; (15) Bruceina e (16) Bruceantarina.

Esses quatro quassinoides, dos dezoito avaliados com uma fração diosfenol (3-hidroxi-3-en-2-ona), apresentaram atividades inibitórias potentes

contra duas linhagens celulares de câncer de mama: em primeiro lugar, aquela com valores de CI_{50} entre 0,063-0,182 µM, testado contra MCF-7 (controle positivo com CI_{50} = 0,880 µM) e, em segundo lugar, aquele com 0,081-0,238 µM, testado contra MDA-MB-231 (controle positivo com CI_{50} = 0,261 µM) (Ye et al., 2015). Segundo os autores, os quassinoides que não contêm a porção 3-hidroxi-3-en-2-ona, assim como o bruceeno A (**17**), apresentaram fraca atividade antitumoral contra as linhagens testadas (Figura 6).



(**17**)

Figura 6: Quassinoide Bruceeno A (17).

Juntamente com a atividade antitumoral muito conhecida dos quassinoides, tem-se o potencial antimalárico desses compostos.

Sendo assim, conforme resultados apresentados por Chan et al., 2004, os seguintes quassinoides isolados da espécie *Eurycoma longifolia*: eurycomanone (**18**), 13,21-dihydroeurycomanone (**19**), 13α (21) –epoxyeurycomanone (**20**) e eurycomalactone (**21**) mostraram um maior nível de atividade antimalárica contra a cepa Gombak A do parasita da malária humana *Plasmodium falciparum* (CI_{50} = 0,23 , 0,29, 0,45 e 1,56 µg / mL, respectivamente) em comparação com a cloroquina (CI_{50} = 2,50 µg / mL). Esses quassinoides foram respectivamente 8,66, 6,83 e 4,58 vezes mais potentes do que a cloroquina contra a cepa Gombak A (Chan et al., 2004) (Figura 7).

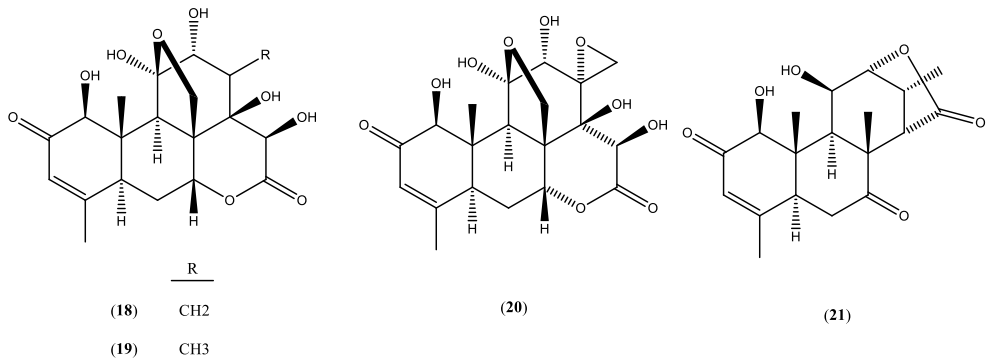


Figura 7: Quassinoides isolados da espécie *Eurycoma longifolia*: (18) Eurycomanone; (19) 13,21-dihydroeurycomanone; (20) 13α (21) – epoxyeurycomanone e (21) eurycomalactone.

Além das muito conhecidas atividades antitumoral e antimalárica dos quassinoides, existem diversos outros estudos científicos que chamam a atenção para possíveis outros fins de uso para esses compostos.

Dentre esses estudos, Wong et al., 2019 demonstraram boas atividades antibacterianas de alguns quassinoides contra a bactéria gram positiva *Bacillus subtilis*. Enquanto o antibiótico Ampicilina mostrou CMI = 0,8 µM, os quassinoides (16R)-methoxyjavanicin B (**22**), (16S)-methoxyjavanicin B (**23**) e picrajavanicin B (**24**) tiveram valores de CMI iguais a 1.6 µM, 1.6 µM e 3.1 µM, respectivamente (Figura 8).

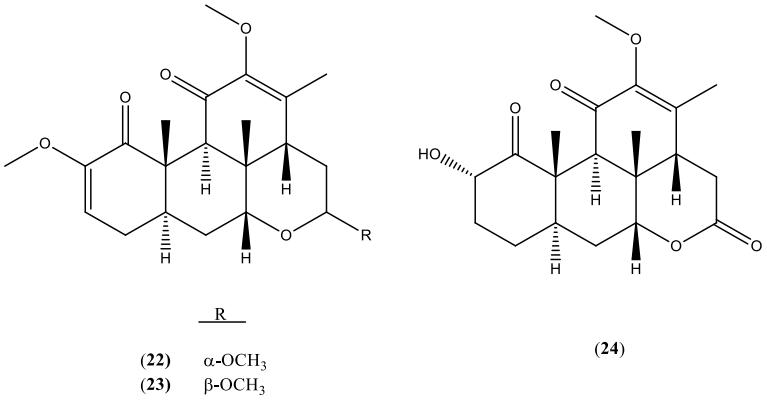


Figura 8: Quassinoides: (22) (16R)-methoxyjavanicin B; (23) (16S)-methoxyjavanicin B e (24) Picrajavanicin B.

3. TRABALHOS

3.1 Trabalho 1: Antimycobacterial Activity of Milemaronol, a New Squalene-Type Triterpene, and Other Isolate?[1]**

Atividade antimicobacteriana do Milemaronol, um novo triterpeno do tipo esqualeno e outro isolado?

[1] **Trabalho publicado no periódico Natural Product Communications, volume 15(5), páginas 1–6, no ano 2020, doi: 10.1177/1934578X20925589 fará parte da tese a ser apresentada à UENF.**

Abstract

A new triterpene, named milemaronol (**1**), was isolated from *Homalolepis suffruticosa* Engl., Simaroubaceae, along with 10 known metabolites, chaparrinone (**2**), scopoletin (**3**), 5-methoxycanthin-6-one (**4**), eurylene (**5**), hispidol A (**6**), hispidol B (**7**), nilocitine (**8**), α-dihydronylocytine (**9**), β-dihydronylocytine (**10**), and teurilene (**11**). These compounds were characterized based on their spectral data, mainly 1D (^{1}H, ^{13}C-APT) and 2D (^{1}H-^{1}H-COSY, NOESY, HSQC, HMBC) NMR and their mass spectra (HR-ESI-MS), in comparison with data from the literature. Compounds **1** to **6**, **8**, and **9** were evaluated for their antimycobacterial activity against 2 strains (H37Rv and M299).

Keywords: Simaroubaceae, triterpenes, quassinoid, alkaloids, *Mycobacterium*

3.1.1. INTRODUCTION

The family Simaroubaceae contains 117 reported species of trees, whose characteristic is the bitter taste of their cortex.[1,2] This can be attributed to the presence of quassinoids, which is also considered a taxonomic marker of this family.[3] The genus *Homalolepis* turcz., recently segregated from *Simaba* Aub., comprises 28 species, spread mainly in tropical South America.[2]

Besides the quassinoids, other types of triterpenes, alkaloids, and other classes of compounds were also observed.[4] These compounds showed many biological activities like antibacterial,[5,6] anticancer,[7,8] antileishmanial [9-11]; antiviral,[12-14] and others.[11,15-19]

Thus, in view of the high biological potential of the compounds of the Simaroubaceae, a phytochemical study of the roots of *Homalolepis suffruticosa* was carried out, during which a new unusual squalene triterpene, named milemaronol (**1**), was characterized and 10 known compounds were identified; their antimycobacterial and cytotoxicity activities were evaluated.

3.1.2. RESULTS AND DISCUSSION

Elaboration of the MeOH and *n*-hexane extracts of the roots of *H. suffruticosa* through classical chromatographic methods resulted in the isolation of 11 compounds, **1** to **11**, whose

structures are shown in Figure 1. A new triterpenoid, named milemaronol,[1] along with 10 known compounds, chaparrinone (**2**),[20] scopoletin (**3**),[21] 5-methoxycanthin-6-one (**4**),[22] eurylene (**5**),[23] hispidol A (**6**),[24] hispidol B (**7**),[24] nilocitine (**8**),[25] α-dihydronylocitine (**9**),[26] β-dihydronilocitine (**10**),[27] and *meso*-teurilene (**11**),[23] was characterized based on their ^{1}H- and ^{13}C-NMR spectral data, especially 2D-NMR, and by comparison of the mass spectral data with the literature values.

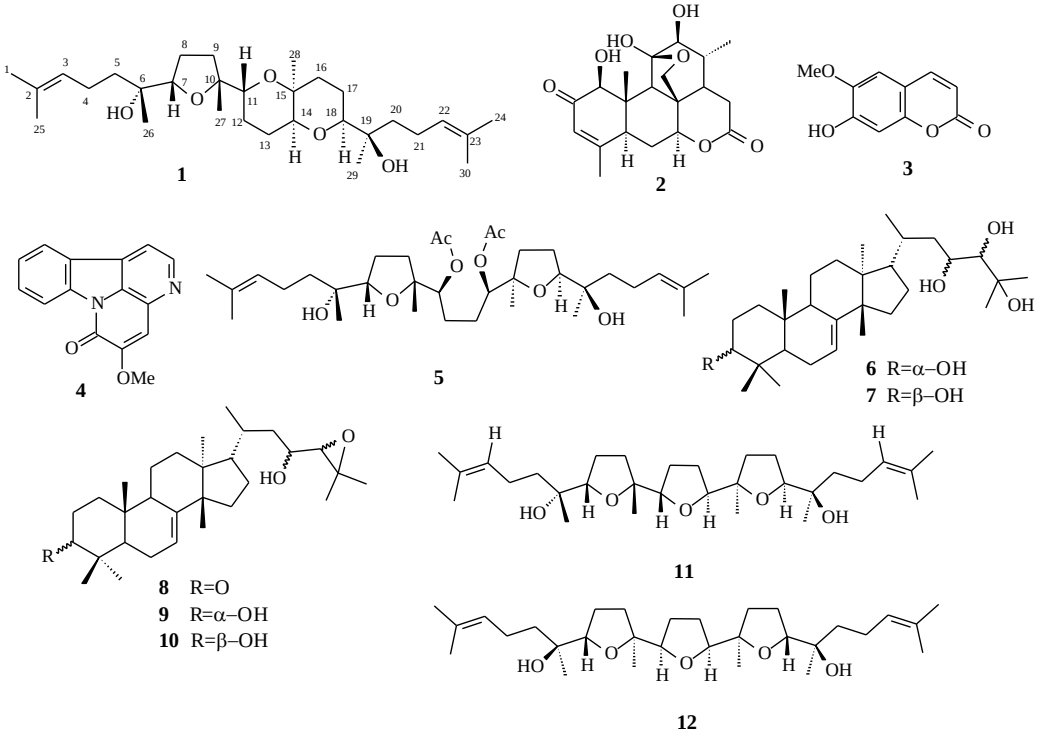


Figure 1. Compounds isolated from roots of *H. suffruticosa* (**1**-**11**) and Teurilene (**12**).

Milemaronol (**1**) was isolated as an yellow oil. Its HRESI-MS showed peaks due to the presence of a sodium ion at *m/z* 515.3606 ([M+Na]+, calc. *m/z* 515.3712) and a potassium ion at *m/z* 531.3481 ([M+K]+, calc. *m/z* 531.3452) (Supplemental Scheme 1S). These data, combined with the information obtained by 1D and 2D NMR spectral analysis, were used to deduce the molecular formula $C_{30}H_{52}O_5$, indicating 5 degrees of unsaturation (2 C=C bonds and 3 rings).

The ^{13}C-APT-NMR spectrum of **1** revealed signals corresponding to 30 carbon atoms, including 6 quaternary [C_6: 2 sp^2 (double bond) and 4 sp^3 linked to oxygen atoms], 6 methines [$(CH)_6$: 4 sp^3 carbinolics and 2 sp^2 olefinics at δC 124.8 and 124.5], 10 methylenes [$(CH_2)_{10}$], and 8 methyls [$(CH_3)_8$ including 4 linked to sp^2 carbon atoms (2 at δ_C 25.7 and 2 at δ_C 17.6)]. ^{1}H NMR spectral analysis of **1** showed 2 triplet signals in the region of the olefinic hydrogens at δ_H

5.11 (H-3, t, 6.7) and 5.14 (H-22, t,7.1); 4 double doublet signals in the region of carbinolic hydrogens δ_H 3.90 (H-7, dd, 7.8, 5.0), 3.69 (H-18, dd, 11.5, 3.9), 3.71 (H-11, dd, 12.1, 1.9), and 3.55 (H-14, dd, 7.6, 5.0); and 4 singlet signals corresponding to methyl groups linked to sp^2 carbon atoms at δ_H 1.71 (3H-24), δ_H 1.69 (3H-1), δ_H 1.64 (3H-25), and δ_H 1.62 (3H-30). All ^1H and ^{13}C chemical shifts are assigned in Table 1.

The location of these 2 C=CH bonds was established through analysis of the HMBC spectrum, which revealed cross-peaks of δ_C 131.3 (C-2) with 3H-1 (δ_H 1.69, 2 J_{CH}), 3H-25 (δ_H 1.64, 2 J_{CH}), and 2H-4 (δ_H 2.08, 3 J_{CH}) and δ_C 131.9 (C-23) with 3H-24 (δ_H 1.71, 2 J_{CH}), 3H-30 (δ_H 1.71, 2 J_{CH}), and 2H-21 (δ_H 2.03, 1.78, 3 J_{CH}). Additional HMBC couplings via 3 JCH of CH-3 (δ_C 124.8) with 2H-5 (δ_H 2.08) and CH-22 (δ_C 124.5) with 2H-20 (δ_H 1.90, 1.75) confirmed the terminal units (Me2C=CHCH2-CH2-5 and Me2C=CH-CH2-CH2-20). The tetrahydrofuran ring was observed based on the carbon shift of C-10 (δ_C 85.2) with cross-peak with H-7 (δ_H 3.90), 2H-9 (δ_H 2.25 and 1.48), H-11 (δ_H 3.71), and 3H-27 (δ_H 1.14). This allowed to recognize the identical unit from C-1 to C-10 of **11**, confirmed by comparative analysis of spectral data.[23]

In the region of the carbinolic carbons of **1**, signals were observed at δ_C 73.8 (C-6) and δ_C 73.2 (C-19), which displayed correlations in the HMBC spectrum with methyl groups 3H-26 (δ_H 1.24) and 3H-29 (δ_H 1.31), and 2 carbinolic hydrogens H-7 (δ_H 3.90, dd, 7.8, 5.0) and H-18 (3.69, dd, 11.5, 3.9), which showed a system with a methyl linked to a carbinolic carbon previously observed in the equivalent spectra of eurylene and teurilene.[23] Moreover, in the region of the carbinolic carbons, signals were observed at δ_C 84.4 (CH-7), 85.2 (C-10), 75.1 (CH11), 78.0 (CH-14), 75.9 (C-15), and 72.9 (C-18), corresponding to an ether function.

Table 1. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR Data of Compound **1**, in $CDCl_3$, Including HSQC and HMBC (2 J_{HC} and 3 J_{HC}). δ in ppm and *J* (in Parentheses) in Hz.

	1		
C	δ_c	δ_H	HMBC
1	25.7	1.69, s	3, 25
2	131.3	-	1, 4, 25
3	124.8	5.11, t (6.7)	1, 4, 5, 25
4	22.3	2.08 (m)	3
5	38.6	1.58 (m), 1.48 (m)	26
6	73.8	-	7, 26
7	84.4	3.90, dd (7.8, 5.0)	9, 26
8	26.0	2.08 (m), 1.90 (m)	9
9	31.2	2.25 (m), 1.48 (m)	11, 27
10	85.2	-	7, 9, 11, 27
11	75.1	3.71, dd (12.1, 1.9)	27
12	20.3	2.03 (m), 1.80 (m)	14
13	27.2	1.82 (m), 1.60 (m)	12
14	78.0	3.55, dd (7.6, 5.0)	13, 28
15	75.9	-	28
16	38.1	1.55 (m), 1.40 (m)	28
17	24.7	1.90 (m), 1.75 (m)	18
18	72.9	3.69, dd (11.5, 3.9)	14, 29
19	73.2	-	18, 29
20	35.1	1.90 (m), 1.75 (m)	21, 29
21	22.5	2.03 (m), 1.78 (m)	22
22	124.5	5.14, t (7.1)	20, 21, 24, 30
23	131.9	-	21, 24, 30
24	25.7	1.71, s	22, 30
25	17.6	1.64, s	1, 3
26	24.6	1.24, s	
27	24.9	1.14, s	
28	23.2	1.20, s	-
29	17.8	1.31, s	18, 20
30	17.6	1.62, s	22, 24

The location of this unit linked to C-11 (δ_C 75.1) was deduced by heteronuclear interaction of this nonprotonated carbon with 3H-27 (δ_H 1.14, 3 J_{CH}). The other terminal unit involving carbon atom C-19 was linked to CH-18 [δ_C 72.9/δ_H 3.69 (dd, J = 11.5, 3,9)] by correlation (3 J_{CH}) of this methinic carbon with 3H-29 (δ_H 1.31) and H-14 (δ_H 3.55). The HMBC correlation (3 J_{CH}) of CH-14 (δ_C 78.0) with 3H-28 (δ_H 1.20) and the 3H-28 with CH2- 16 (δ_C 38.1) allowed us to postulate the presence of 2 pyran rings, 2-alkyl-octahydro-4a-methyl-6-alkylpyrano[3,2-b]pyran (**1**). This deduction is in agreement and does not deny the necessary biogenetic arguments involving squalene as a precursor.

Finally, 2 tetrahydropyran rings formed by the ether bond CH-11/C-15 and CH-14/CH-18 attached to the tetrahydrofuran ring between C-10/CH-11 were established from the HMBC

spectrum which exposed cross-peaks of δ_H 3.55 (H-14, dd, 7.6, 5.0) with CH-18 (δ_C 72.9) and CH_2-12 (δ_C 20.3); δ_H 1.20 (3H-28, s) with CH-14 (δ_C 78.0), C-15 (δ_C 75.9), and CH_2-16 (δ_C 38.1); δ_H 2.03 (1Ha-12) and 1.80 (1Hb-12) with CH_2-13 (δ_C 27.2); and δ_H 3.71 (H-11, dd, 12.1, 1.9) with CH-9 (δ_C 31.2) and C-10 (δ_C 85.2). The complete assignment of the ^1H and ^{13}C signals of **1** was successfully performed with the use of the HSQC and ^1H-^1H COSY spectra (Figure 1; Table 1).

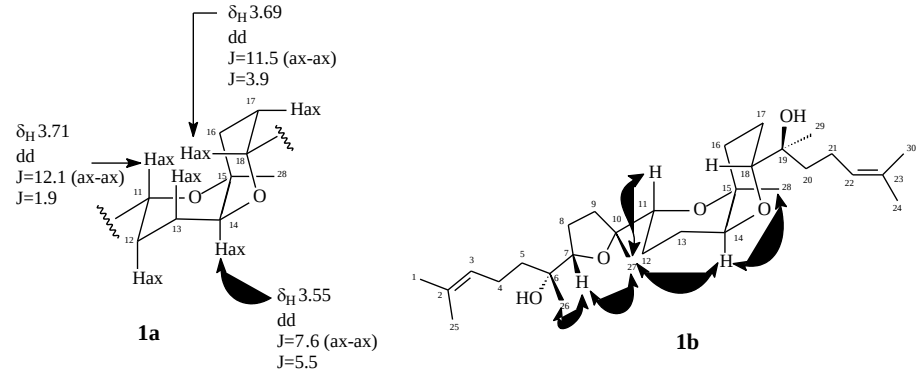


Figure 2. Important ^1H-^1H-NOESY correlations for Milemaronol (**1**).

The relative stereochemistry of **1** was determined from the coupling constants of the relevant hydrogens and from the observed ^1H-^1H-NOESY spectra. The values corresponding to vicinal interaction (3 $J_{H,H}$) between hydrogens H-11ax (J = 12.1 Hz, axial-axial interaction with H-12ax), H-14 (J = 7.6 Hz, axial-axial interaction with H-13ax), and H-18 (J = 11.5 Hz, axial-axial interaction with H-17ax) are consistent with the relative configuration shown in **1** and **11** (Table 1). In accordance with these observations, the NOESY spectrum of **1** showed cross-peaks assigned to dipolar interaction (spatial proximity, Figure 2) of 3H-26 (δ_H 1.24) with H-7 (δ_H 3.90); 3H-27 (δ_H 1.14) with H-7 (δ_H 3.90), H-11 (δ_H 3.71), and H-14 (δ_H 3.55); and 3H-28 (δ_H 1.20) with H-14 (δ_H 3.55).

The antimycobacterial activity against *Mycobacterium tuberculosis* strains H37Rv and M299, and cytotoxic activities of compounds **1** to **6**, **8**, and **9** were evaluated; the results are shown in Table 2. Compounds **2** and **5** showed excellent growth inhibition of 2 Mycobacterial strains, but revealed toxicity in viable cells. Compounds **4**, **6**, and **9** yielded a good response in the inhibition of both strains, but high cytotoxicity. On the other hand, compound **1** showed the best result, being sensitive to both mycobacteria and presenting low cell toxicity (Table 2).

Table 2. Antimycobacterial activities of compounds **1**-**6**, **8** and **9**.

	MIC_{50}		IC_{50}
	H37Rv	**M299**	**MTT**
1	42.12 ± 0.7	64.38 ± 0.8	307.7 ± 0.1
2	3.0 ± 1.2	7.6 ± 1.4	3.95 ± 1.0
3	≥500	≥500	≥ 500
4	30.4 ± 0.5	34.86 ± 0.3	46.9 ± 0.1
5	1.4 ± 0.9	2.0 ± 0.6	40.1 ± 0.7
6	14.6 ± 1.9	7.2 ± 1.9	3.37 ± 0.3
8	≥500	253.8 ± 1,0	79.5 ± 0.1
9	25.54 ± 0.7	24.42 ± 0.7	51,6 ± 0,2
Rifampicin	0.2 ± 0.1	1.1 ± 0.1	-

3.1.3. MATERIAL AND METHODS

3.1.3.1.General experimental procedures

Column chromatography (CC) was performed on silica gel 60 (0.063-0.200 mm, Merck), and *n*-hexane (98.5%), methanol (99.8%), ethyl acetate (99.5%), and dichloromethane (99.5%) were used as mobile phase solvents, purchased from Synth (São Paulo, Brazil). 1D and 2D NMR analysis was performed on a 500 MHz Bruker Ascend 500 NMR spectrometer operating at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR. Deuterated chloroform ($CDCl_3$), tetradeuterated methanol (CD_3OD), and pyridine (pyridine-d_5), containing TMS (tetramethylsilane) as an internal standard, were used. HR-ESI-MS were obtained on a micrOTOF-Q II Bruker Daltonics mass spectrometer, with the use of the positive ion mode of analysis.

3.1.3.2. Plant material

Roots of *Homalolepis suffruticosa* were collected in September 2017, in the Araguari city, Minas Gerais. The specie was identified by the taxonomist José Rubens Pirani, from the Universidade de São Paulo (USP). A voucher specimen (HUENF-10840) was deposited in the herbarium of the Universidade Estadual do Norte Fluminense Darcy Ribeiro (UENF).

3.1.3.3. Extraction and isolation

H. suffruticosa roots were dried and powdered. The extraction was performed firstly with hexane (CH, 20.5 g) and then with methanol (CM, 23.4 g). Methanolic extract (23.4 g) was fractionated in a silica gel chromatography column using CH_2Cl_2:MeOH solvents in polarity gradient, obtaining nine fractions (CM1-CM9). The CM4 fraction was similarly rechromatographed, generating ten fractions (CM4.1-CM4.10). Chaparrinone (**2**) and scopoletin (**3**) were identified in fractions CM4.7 and CM4.4, respectively. The fraction CM4.8 was also chromatographed with the hexane:acetone eluent system, generating seventeen fractions (CM4.8.1-CM4.8.17), and the fractions CM4.8.3 (30.3 mg) and CM4.8.11 were identified as the compounds milemaronol (**1**) and 5-metoxicantin-6-ona (**4**), respectively.

The hexane extract (CH, 20.5 g) was fractionated by silica gel chromatography column with a gradient of hexane:acetone to yield fourteen fractions (CH1-CH14). The CH5 fraction was similarly rechromatographed, yielding nine fractions (CH5.1-CH5.9). Nilocitine (**8**) was identified in the fraction CH5.3 (4,5 mg). The CH8 fraction (1.9 g) was subjected to chromatography column with CH_2Cl_2:MeOH as eluents, yielding ten fractions (CH8.1-CH8.10). In the CH8.5 fraction a precipitate was observed, which was recrystallized and identified as eurylene (**5**). Still in fraction CH8.5, it was chromatographed with hexane: EtOAc yielding the α-dihydronylocytin (**9**) and β-dihydronylocytin (**10**) in mixture. The CH10 fraction (1,461 g) was chromatographed with hexane: EtOAc, obtaining eight fractions (CH 10.1-CH10.8). Compounds Hispidol A (**6**) and Hispidol B (**7**) were identified as a mixture in CH10.3 (24.9 mg) and compound **6** was isolated in CH10.4 (14.5 mg). The *meso*-teurilene (**11**) was isolated from CH12 fraction (29.1 mg).

3.1.3.4. Culture of Mycobacteria and evaluation of bacterial growth

Two strains of *Mycobacterium tuberculosis* were used in this study (a virulent laboratory strain H37Rv, ATCC 27294 and a highly virulent Mtb strain Beijing M299, isolated from a TB patient in Mozambique), which were evaluated for virulence in a previous study.[28] Middlebrook 7H9 broth, containing 10% dextrose albumin complex (ADC), 0.5% glycerol and 0.05% Tween-80 was used to mycobacterial strains growth at 37ºC, under conditions of containment of Biosafety 3. The MTT assay was performed to quantify bacterial growth[29] and the procedures were described by Ventura et al. [30] The samples were analyzed by optical density at 570 nm. For

negative control, untreated bacterial suspensions were used, while for positive control rifampicin was applied.

3.1.3.5. Evaluation of cytotoxicity by MTT assay

RAW 264.7 macrophages were treated with compounds at concentrations of 4, 20, 100 and 500 µg/mL. After 24h, the levels of cytotoxicity of the samples were assessed using mitochondrial functionality using the MTT method and compared to negative (macrophages stimulated by LPS) and positive (macrophages stimulated by LPS and treated with 1% Triton X-100) controls. Values are reported as mean ± standard deviation, and different groups were considered significant according to $p < 0.001$ (***), $p < 0.01$ (**) and $p < 0.05$ (*).

3.1.4. ACKNOWLEDGMENT

The authors are grateful to Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro, to CNPq, and to CAPES (Finance Code 001).

3.1.5. DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

3.1.6. FUNDING

The author(s) received no financial support for the research, authorship, and/or publication of this article.

3.1.7. REFERENCES

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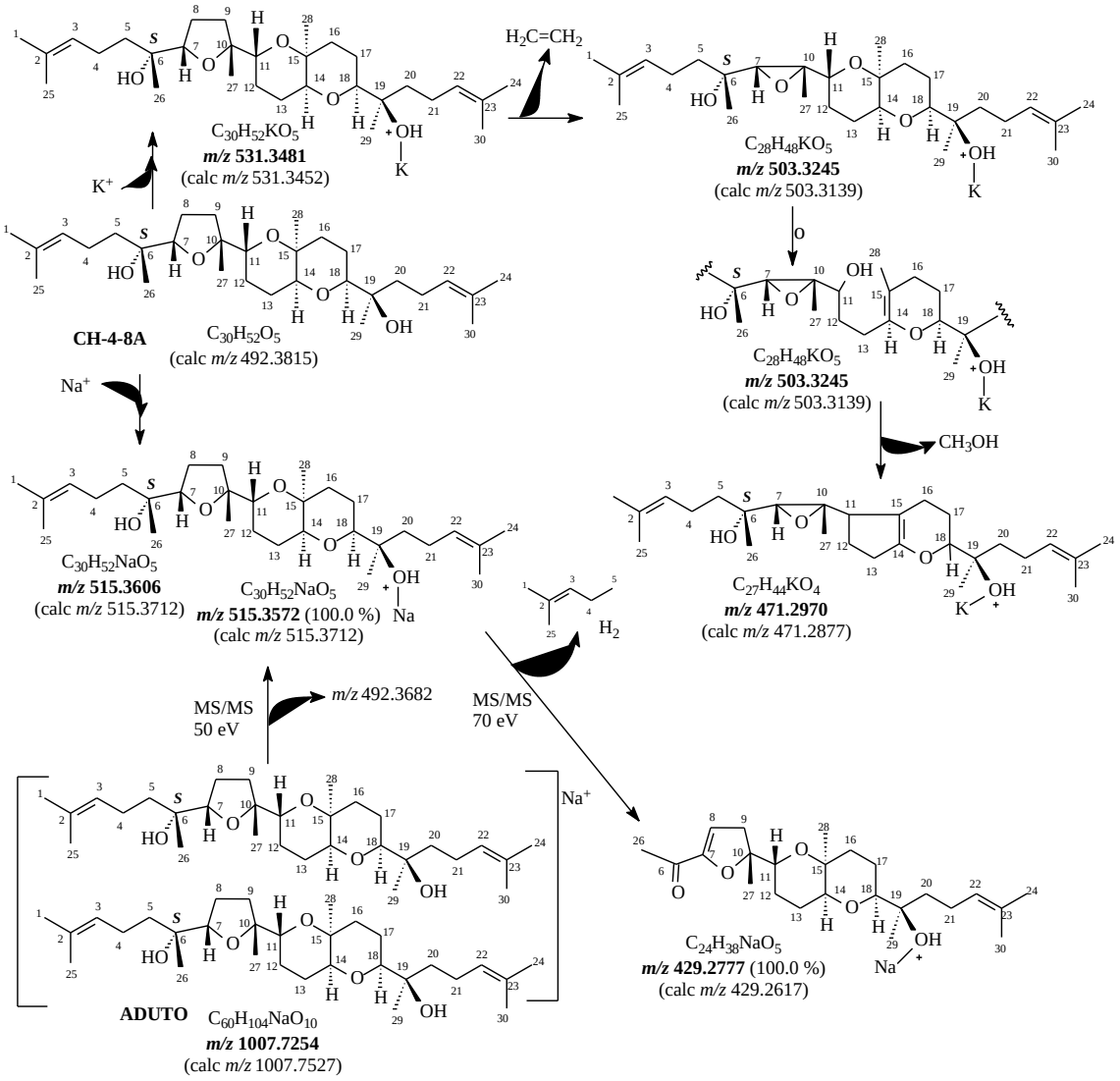
3.1.8. SUPPLEMENTAL ONLINE MATERIAL



Scheme 1S. Proposed fragmentation mechanisms of **1,** only peaks revealed by HRESI-MS and classified as principals.

Table S1. ^{13}C (125 MHz) NMR data for 2-8, in $CDCl_3$ as solvent and chemical shifts (δ, ppm)

Position	**2**	**3**	**4**	**5**	**6**	**7**	**8**
	δ_c	δ_c	δ_c	δ_c	δ_c	δ_c	δ_c
1	83.1, CH	-	113.9, CH	25.7, CH_3	31.1, CH_2	37.3, CH_2	38.6, CH_2
2	197.6, C	162.6, C	145.9, CH	131.6, C	25.1, CH_2	27.7, CH_2	34.9, CH_2
3	124.7, CH	111.2, CH	136.9, C	124.5, CH	75.6, CH	79.3, CH	216.9, C
4	163.8, C	144.7, CH	109.9, CH	22.1, CH_2	37.0, C	39.0, C	47.9, C
5	42.0, CH	108.5, CH	154.6, C	37.3, CH_2	44.3, CH	50.6, CH	52.4, CH
6	25.3, CH_2	145.7, C	155.4, C	72.0, C	23.6, CH_2	23.9, CH_2	24.4, CH_2
7	78.6, CH	151.6, C	139.2, C	86.6, CH	118.0, CH	118.0, CH	118.0, CH
8	45.6, C	102.6, CH	117.6, CH	25.7, CH_2	145.9, C	145.6, C	145.7, C
9	43.7, CH	150.0, C	130.6, CH	34.9, CH_2	48.6, CH	48.9, CH	48.5, CH
10	44.7, C	111.1, C	125.9, CH	83.8, C	34.4, C	34.9, C	35.0, C
11	109.2, C	-	122.7. CH	78.1, CH	17.8, CH_2	18.1, CH_2	18.2, CH_2
12	78.6, CH	-	125.3, C	26.8, CH_2	33.7, CH_2	34.0, CH_2	33.6, CH_2
13	30.9, CH	-	129.5, C	27.0, CH_2	43.4, C	43.6, C	43.6, C
14	41.6, CH	-	127.6, C	77.6, CH	51.0, C	53.4, C	51.2, C
15	29.2, CH_2	-	-	83.6, C	33.9, CH_2	33.9, CH_2	34.0, CH_2
16	172.1, C	-	-	34.2, CH_2	28.0, CH_2	28.7, CH_2	28.8, CH_2
17	11.6, CH_3	-	-	25.5, CH_2	53.9, CH	53.8, CH	53.3, CH
18	21.5, CH_3	-	-	84.4, CH	21.1, CH_3	21.8, CH_3	21.8, CH_3
19	8.9, CH_3	-	-	72.7, C	12.2, CH_3	13.1, CH_3	12.8, CH_3
20	-	-	-	37.5, CH_2	33.4, CH	33.7, CH	33.6, CH
21	-	-	-	22.1, CH_2	18.1, CH_3	18.9, CH_3	19.9, CH_3
22	-	-	-	124.5, CH	40.8, CH_2	40.5, CH_2	40.7, CH_2
23	-	-	-	131.6, C	68.6, CH	69.7, CH	69.3, CH
24	-	-	-	25.7, CH_3	75.4, CH	75.0, CH	68.4, CH
25	-	-	-	17.6, CH_3	73.3, C	74.4, C	60.3, C
26	-	-	-	24.2, CH_3	25.8, CH_3	27.6, CH_3	19.8, CH_3
27	-	-	-	22.5, CH_3	25.1, CH_3	27.2, CH_3	24.9, CH_3
28	-	-	-	22.8, CH_3	27.2, CH_3	27.7, CH_3	24.5, CH_3
29	-	-	-	24.0, CH_3	21.0, CH_3	14.7, CH_3	21.6, CH_3
30	70.8, CH_2	-	-	17.6, CH_3	26.5, CH_3	26.2, CH_3	27.4, CH_3
31	-	-	-	171.0, C	-	-	-
32	-	-	-	21.2, CH_3	-	-	-
33	-	-	-	170.8, C	-	-	-
34	-	-	-	21.1, CH_3	-	-	-
OMe	-	55.4, CH_3	57.0, CH_3	-	-	-	-

Table S2. ^{13}C (125 MHz) NMR data for 9-11, in $CDCl_3$ as solvent and chemical shifts (δ, ppm)

Position	**9**	**10**	**11**
	δ_c	δ_c	δ_c
1	37.2, CH_2	37.6, CH_2	25.7, CH_3
2	28.8, CH_2	28.8, CH_2	131.1, C
3	76.3, CH	79.2, CH	125.0, CH
4	37.4, C	38.9, C	22.3, CH_2
5	44.5, CH	50.6, CH	38.6, CH_2
6	23.9, CH_2	23.9, CH_2	73.0, C
7	118.1, CH	118.5, CH	84.3, CH
8	145.9, C	145.6, C	25.3, CH_2
9	53.3, CH	48.9, CH	30.6, CH_2
10	34.7, C	34.9, C	85.3, C
11	18.0, CH_2	18.1, CH_2	85.2, CH
12	33.9, CH_2	33.9, CH_2	29.5, CH_2
13	43.5, C	43.6, C	29.5, CH_2
14	51.3, C	51.2, C	85.2, CH
15	33.7, CH_2	33.7, CH_2	85.3, C
16	25.4, CH_2	25.5, CH_2	17.7, CH_3
17	51.3, CH	50.6, CH	30.6, CH_2
18	13.0, CH_3	13.1, CH_3	25.3, CH_2
19	19.8, CH_3	19.8, CH_3	84.3, CH
20	33.5, CH	33.6, CH	73.0, C
21	21.8, CH_3	21.8, CH_3	38.6, CH_2
22	40.7, CH_2	40.8, CH_2	22.3, CH_2
23	69.3, CH	69.3, CH	125.0, CH
24	68.5, CH	68.5, CH	131.1, C
25	60.3, C	60.3, C	25.7, CH_3
26	19.9, CH_3	19.9, CH_3	24.3, CH_3
27	24.9, CH_3	24.9, CH_3	23.5, CH_3
28	27.2, CH_3	27.8, CH_3	23.5, CH_3
29	14.7, CH_3	14.1, CH_3	24.3, CH_3
30	27.8, CH_3	27.6, CH_3	17.6, CH_3

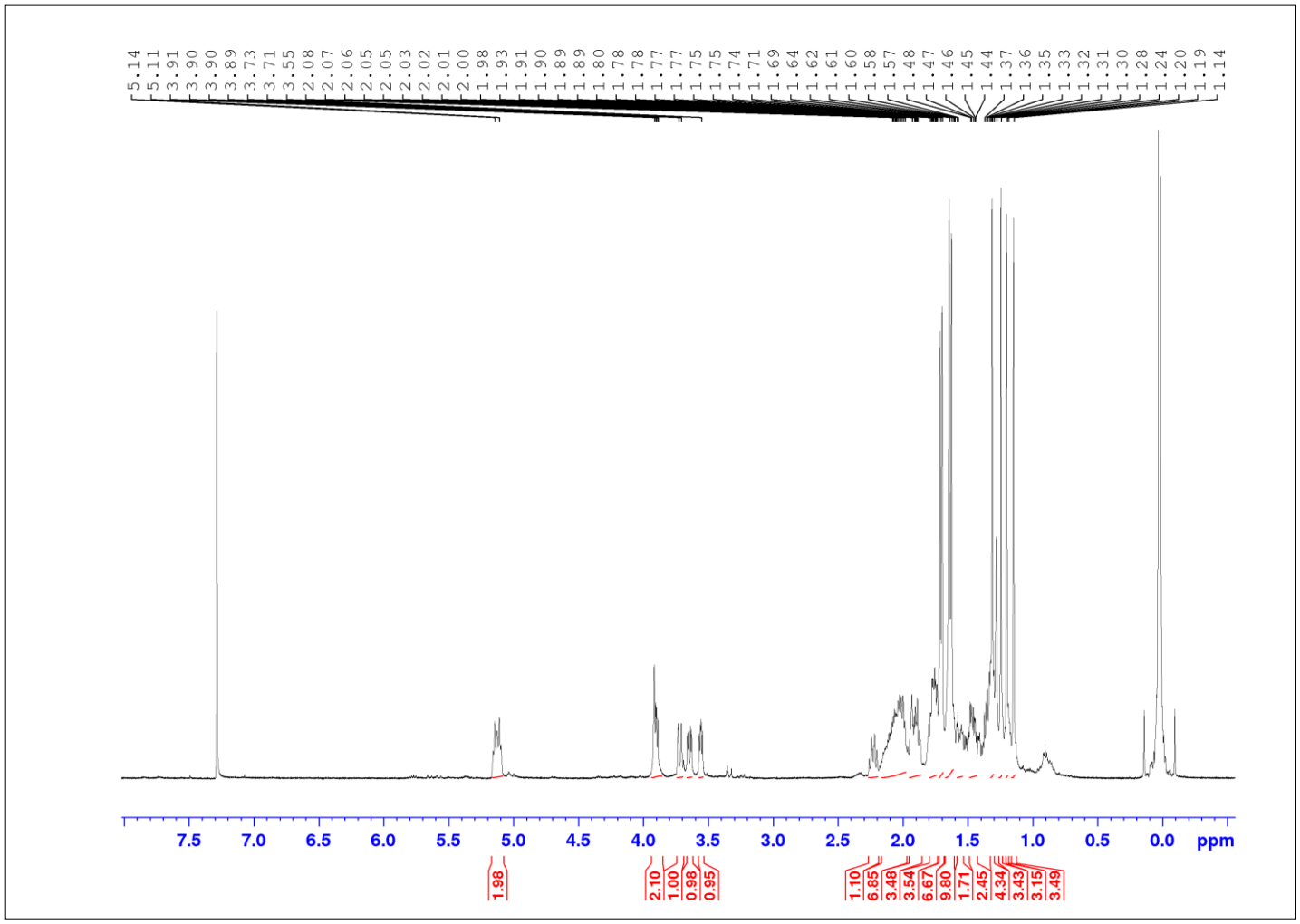


Figure 1S. ^{1}H-NMR spectrum (500MHz, $CDCl_3$) of compound **1**.

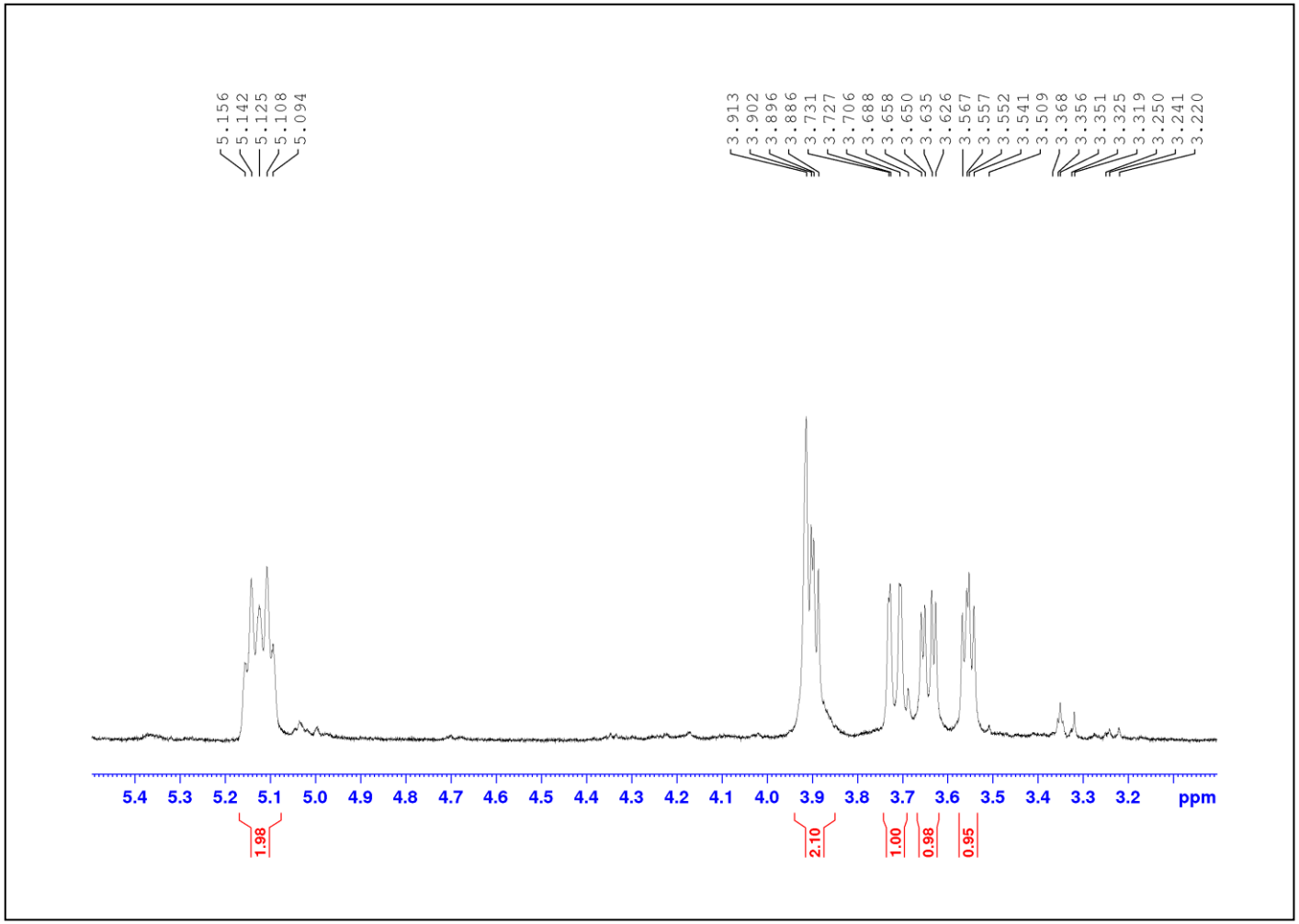


Figure 2S. Expansion of the ^{1}H NMR spectrum (500 MHz, $CDCl_3$) between δ_H 3.0 to 5.5 ppm of compound **1**.

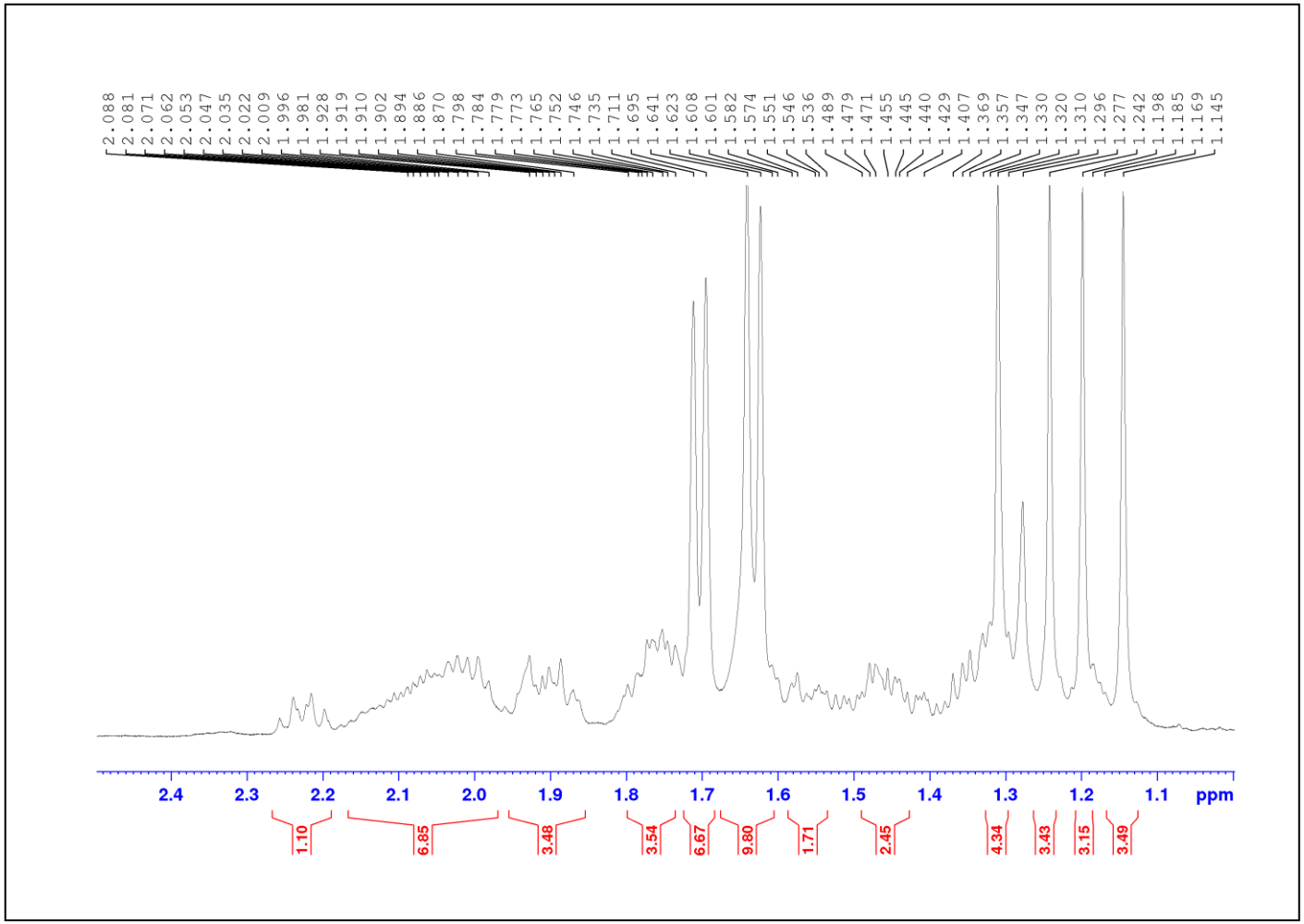


Figure 3S. Expansion of the ^{1}H NMR spectrum (500 MHz, $CDCl_3$) between δ_H 1.0 to 2.4 ppm of compound **1**.

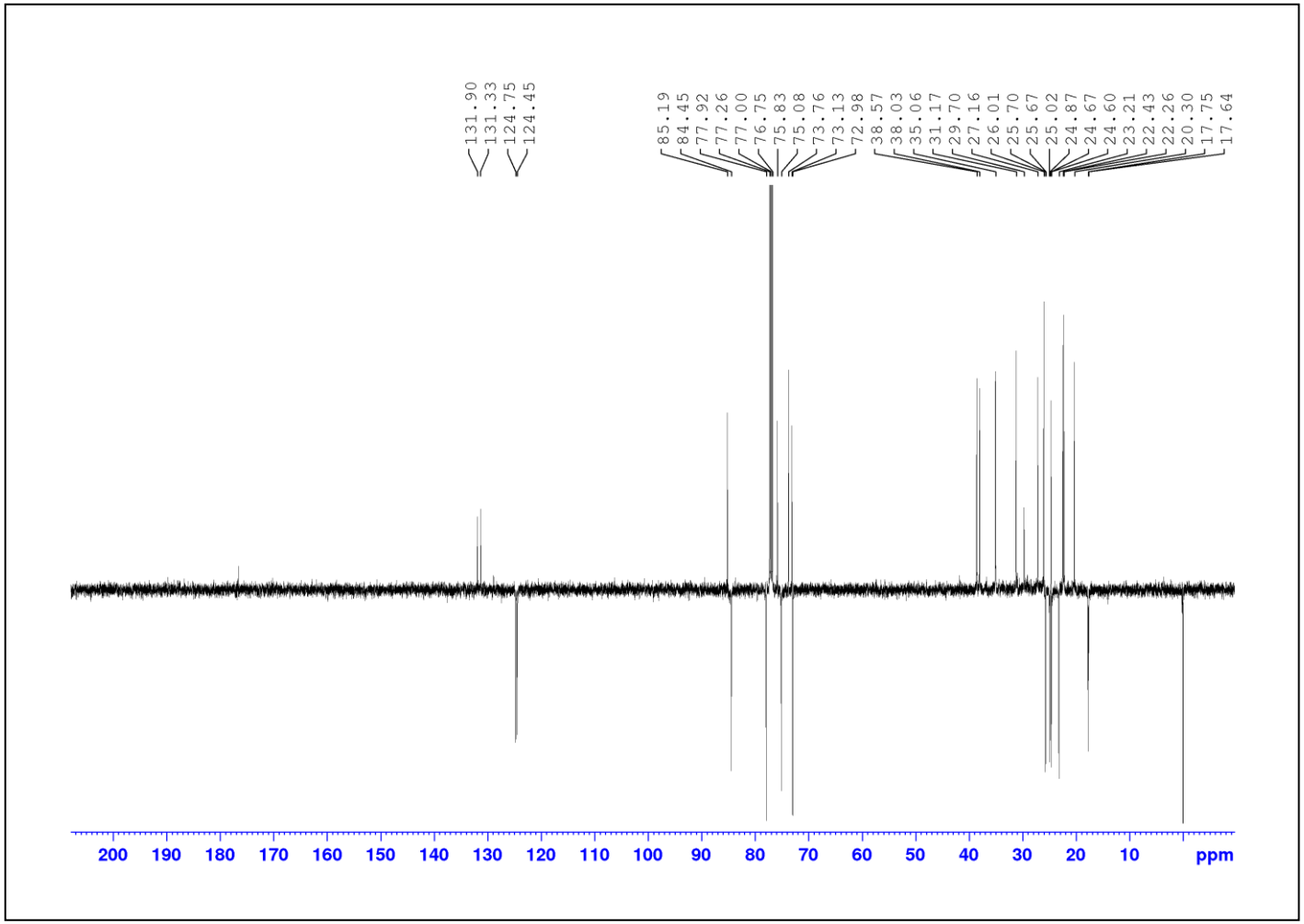


Figure 4S. ^{13}C-APT NMR spectrum (125 MHz, $CDCl_3$) of compound **1**.

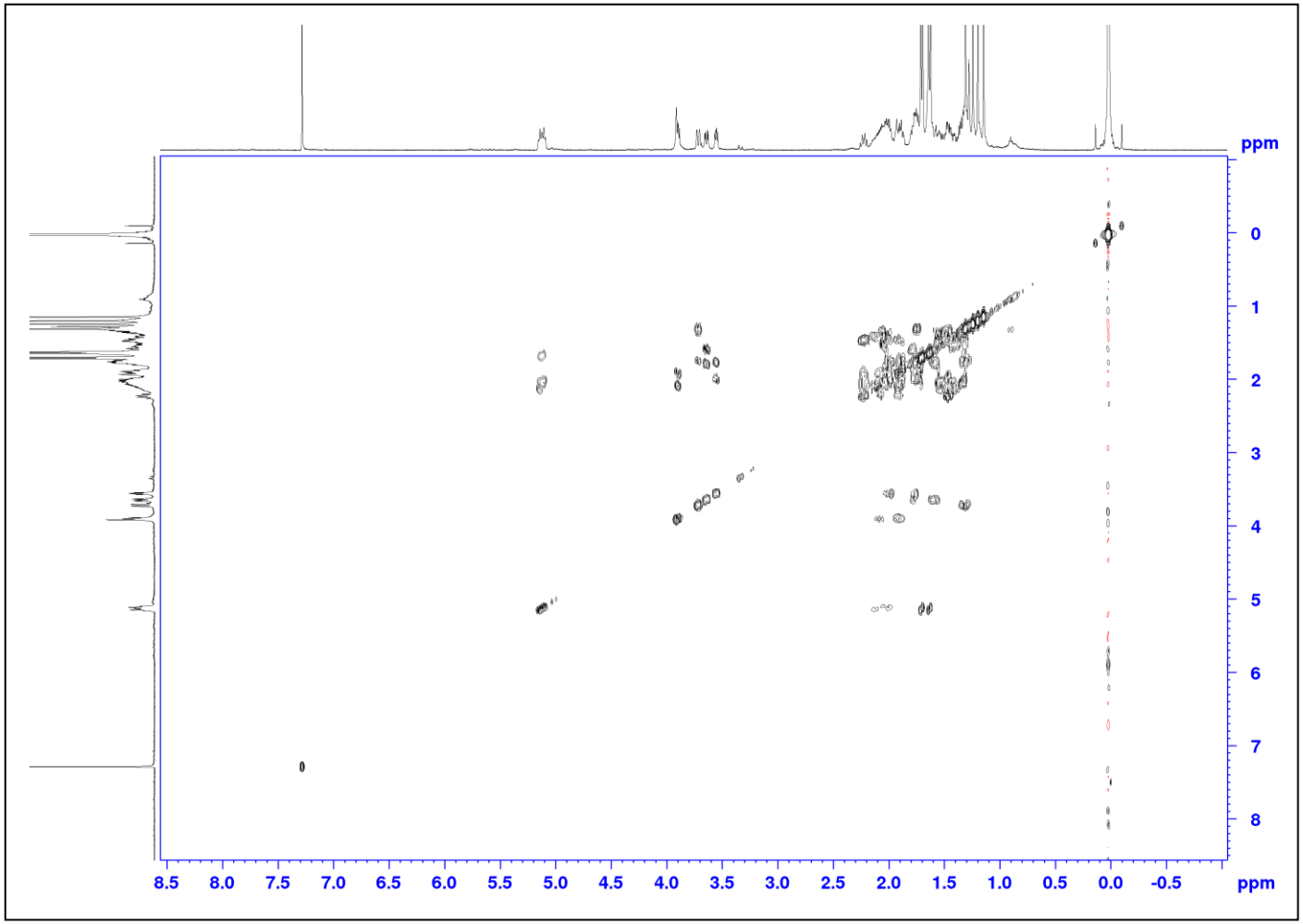


Figure 5S. ^{1}H-^{1}H COSY NMR spectrum (500 MHz, $CDCl_3$) of compound **1**.

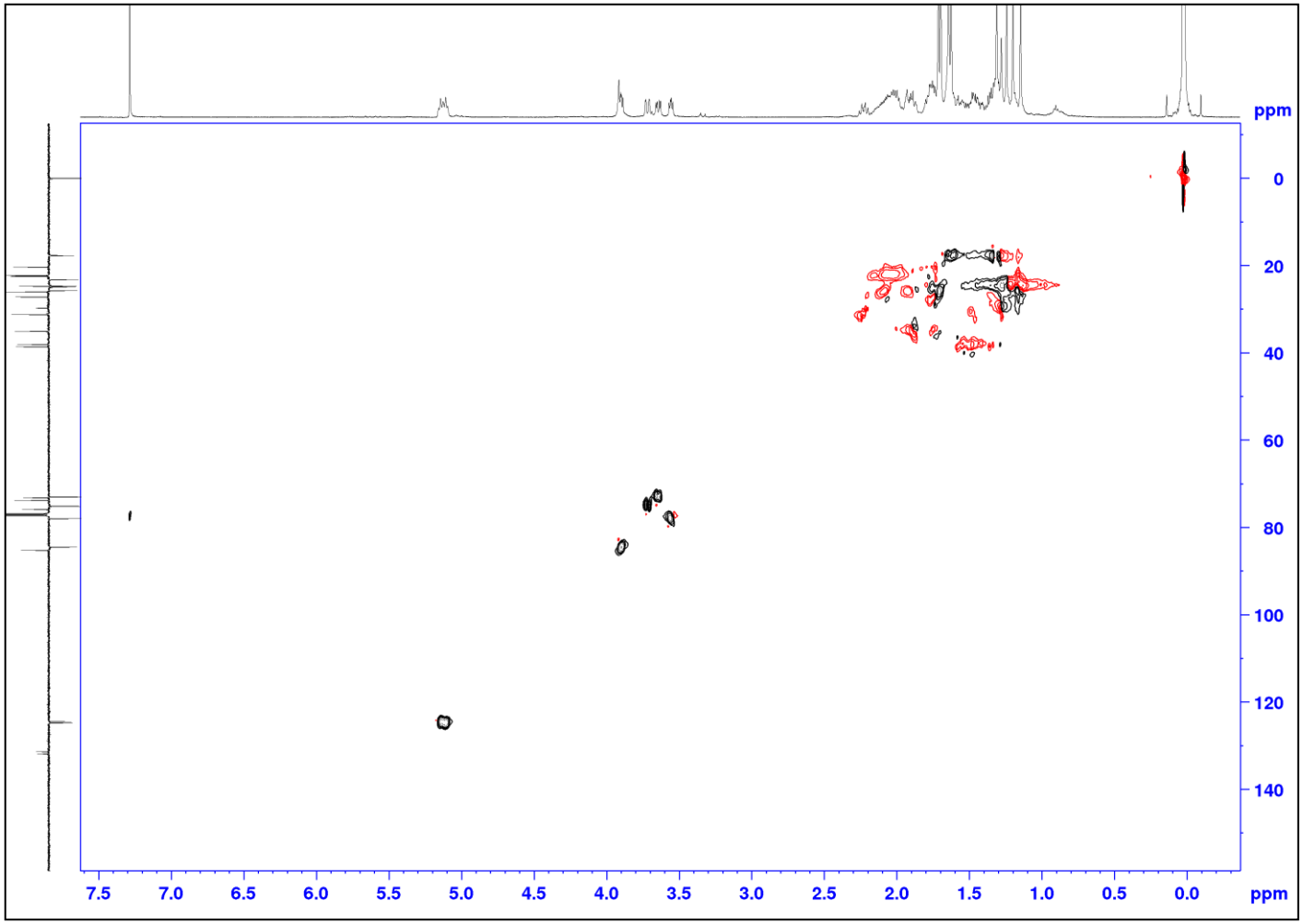


Figure 6S. HSQC NMR spectrum (500 and 125 MHz, $CDCl_3$) of compound **1**.

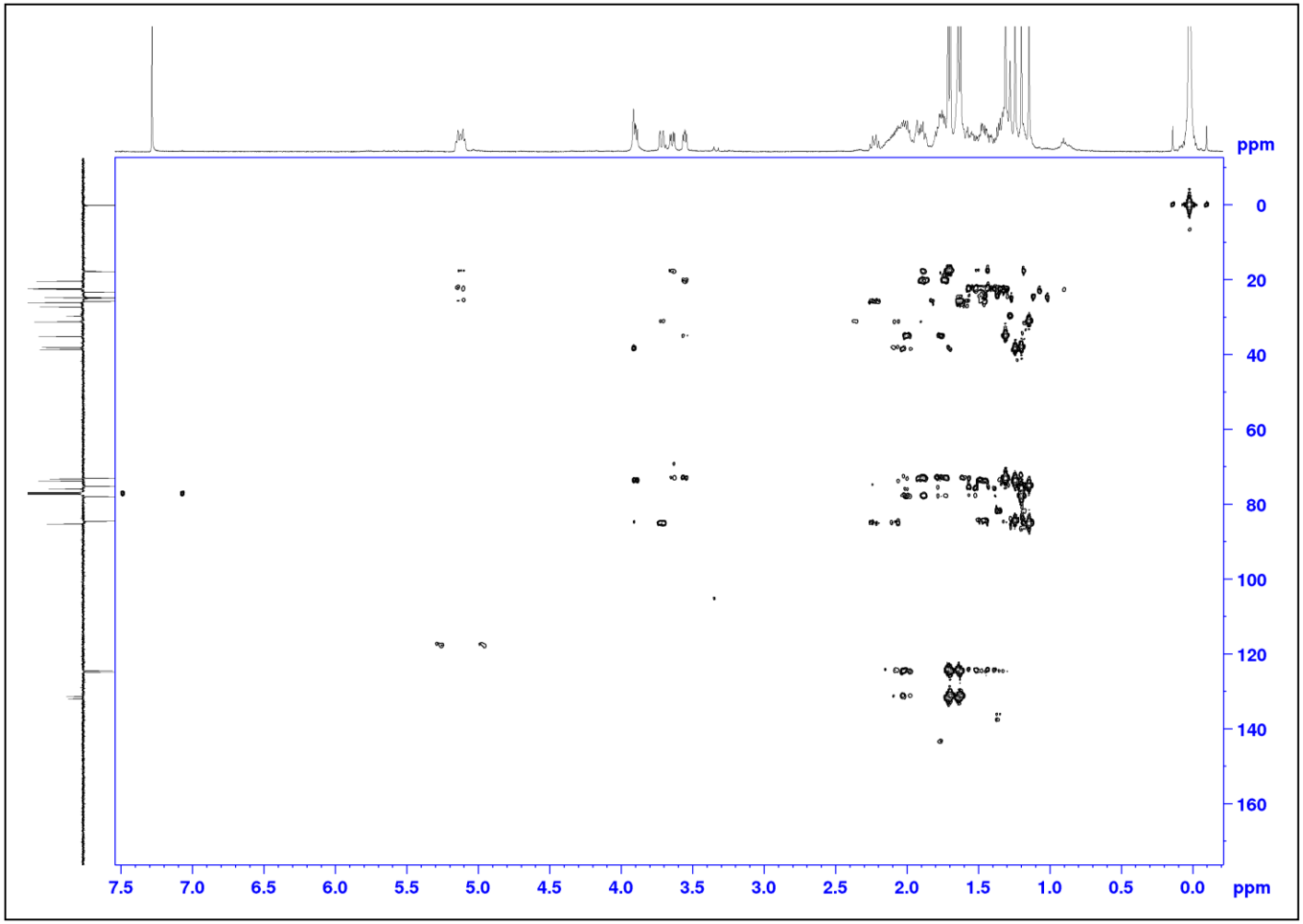


Figure 7S. HMBC NMR spectrum (500 and 125 MHz, $CDCl_3$) of compound **1**.

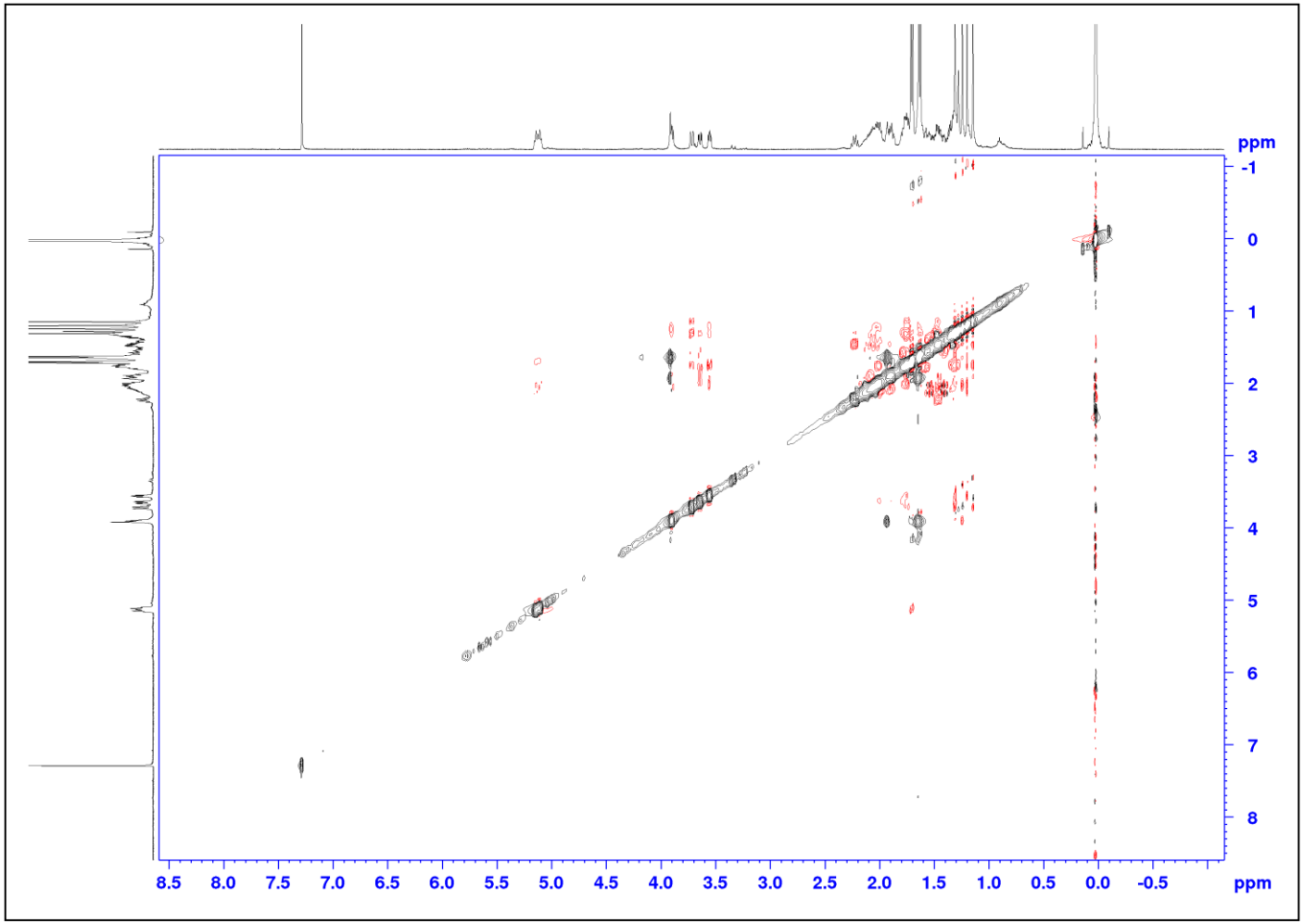


Figure 8S. ^{1}H-^{1}H NOESY NMR spectrum (400 MHz, $CDCl_3$) of compound **1**.

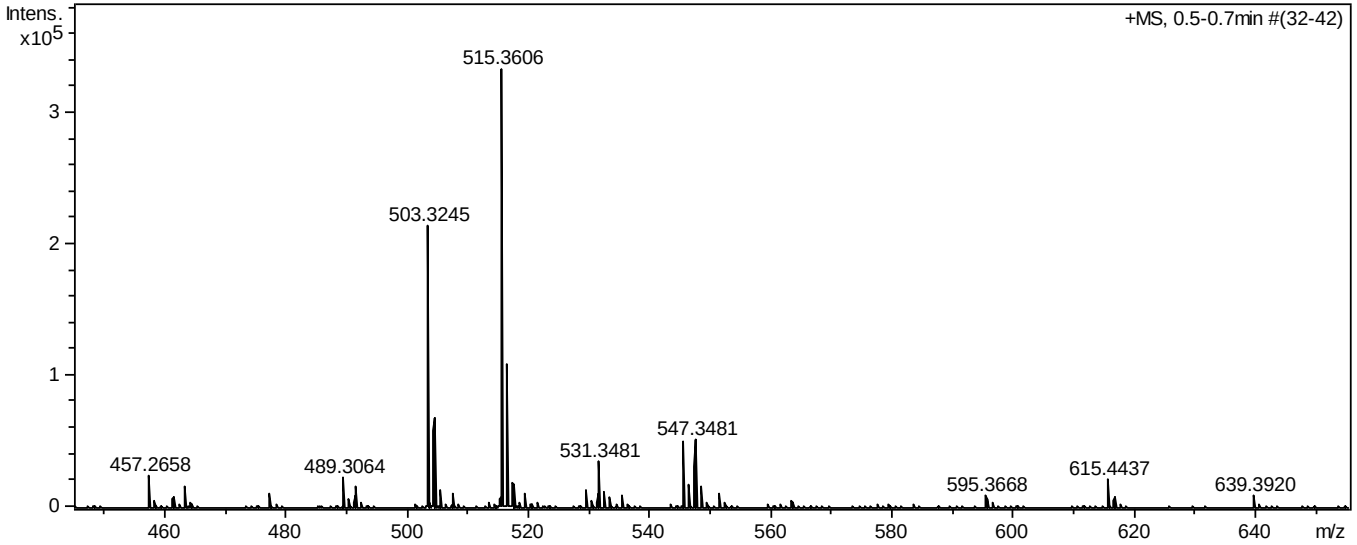


Figure 9S. HR-ESI-MS spectrum of compound **1**.

3.2. Trabalho 2: BIOLOGICAL ACTIVITY AND ^{13}C NMR SPECTRAL DATA OF SKELETON TYPE C_{20} QUASSINOIDS (1985-2019)[1**]

ATIVIDADE BIOLÓGICA E DADOS ESPECTRAIS DE RMN 13C DE QUASSINOIDES TIPO C20 DE ESQUELETO (1985-2019) [1**]

[1] **Trabalho publicado como capítulo do livro Studies in Natural Products Chemistry, volume 68, páginas 97-166, do ano 2021, doi: 10.1016/B978-0-12-819485-0.00011-6 fará parte da tese a ser apresentada à UENF.**

Abstract: Quassinoids are secondary metabolites that characteristically belong to Simaroubaceae family. These compounds have called attention because they are responsible for a wide range of biological activities, many of them are extremely promising. The great majority of isolated quassinoids have basic skeleton C_{20}. Therefore, this review aims to discuss the biological activities and compile the ^{13}C NMR spectra data of quassinoids isolated after 1985, skeletal type C_{20}. The conclusion is that many C_{20} quassinoids appear to be promising antitumor and antimalarial agents. Besides that, different studies report several other biological activities of these compounds, as insecticidal, larvicidal, antileishmanial, antiviral, anti-inflammatory activities, among others. From the data compilation it is concluded that 154 quassinoids were isolated and identified in the period between 1985 up to the present time and that there are eight types of skeletons that are more frequent for the ring A of quassinoids, and also eight different ring C skeletons. About the rings B and D, it is observed the variation to C-15, which usually has no substituents, oxidated by a free hydroxyl group, as well as the esterification of the hydroxyl group.

3.2.1. INTRODUCTION

The most notorious feature of the Simaroubaceae family is the bitter taste of its cortex [1]. Many species of this family have been known for their bittertasting compounds, in which case the quassinoids are responsible for such characteristics [2].

In this context, quassinoids are secondary metabolites, which are of great pharmacological importance. They are characteristic of the Simaroubaceae family and are considered chemotaxonomic markers of this family [3,4]. Among the pharmacological properties of quassinoids, we can find: anticancer

[5,6] and antimalarial [7–9]; herbicidal [10]; antifeedant and growth inhibition of pests [11–13]; insecticidal [14]; larvicide [9]; antileishmanial [7]; antiviral [15–17]; anti-inflammatory [18]; amoebicidal [19]; and anticomplement [20].

Quassinoids are modified triterpenoids, derived from the euphol/tirucallol series. They contain in their basic skeleton, highly oxygenated lactones with a variable amount of hydroxyl, esterified hydroxyl, carbonyl, methoxyl, and carbomethoxyl groups [21]. The quassinoids may be divided into distinct groups according to the number of carbon atoms present in their basic skeletons, C18, C19, C20, C22, and C25 (**Fig. 4.1**). It is observed that most isolated compounds contain C20 skeleton type [1].

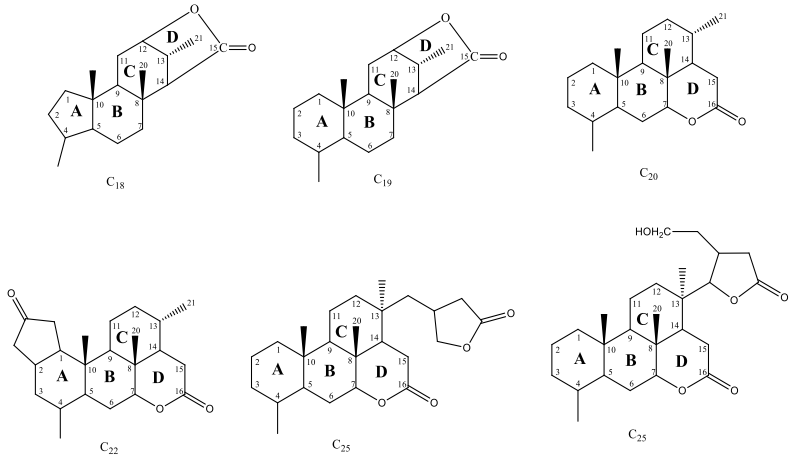


Figure 4.1 Basic skeletons of quassinoids.

The biosynthesis of quassinoids begins with squalene epoxide cyclization, resulting in Δ7-tirucallol (20S) or Δ7-euphol (20R), which undergo oxidative reactions [22]. After the formation of apoeuphol/apotirucallol, the isomerization of the double bond in the ring D is followed by epoxidation and oxidation reactions. The ring D is cleaved by oxidation, via the Baeyer-Villiger. After that, the opening and the relactonization of the γ-lactone are observed. The resulting 7α-hydroxyl group undergoes oxidation of the 17-hydroxyl, while one of the methyl groups at C-4 is lost. This, then, leads to the basic skeleton of simarolide (C25). The cleavage of the C-13/C-17 bond results in the formation of C22 and C20 quassinoids, while C19 compounds require the additional loss of the carbon atom C-16. Eventually, the C19 loss of one carbon atom in ring A forms C18 skeleton [3,22,23]. The biosynthesis is summarized in **Fig. 4.2**.

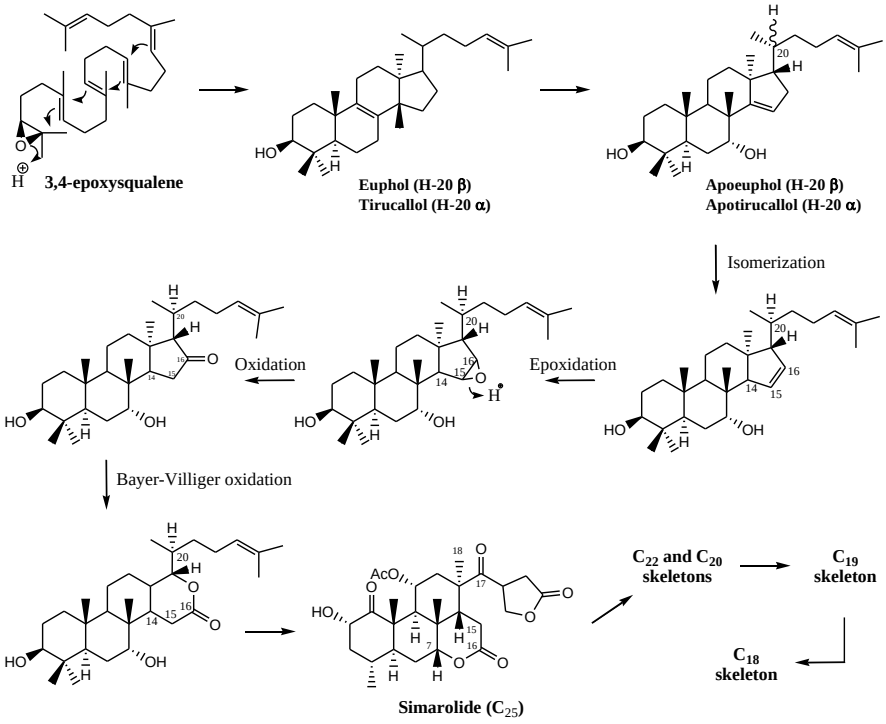


Figure 4.2 Quassinoids biosynthetic pathway.

Due to their importance, some excellent reviews about quassionoids and the Simaroubaceae family were published over the years. The book's sections "Quassinoid Bitter Principles I" and "Quassinoid Bitter Principles II" were collected in 1973 and 1985, respectively [2,24]. A comprehensive review of "quassinoids: structural diversity, biological activity and synthetic studies" was published in 2006 [21]. In addition, the comprehensive review "occurrence and biological activity of quassinoids in the last decade" has also been written [1]. Most recently, in 2014, "Simaroubaceae family: botany, chemical composition and biological activities" was published [25].

In agreement with reviews and papers on quassinoids, there are common factors between their skeletons, which can be grouped in order to minimize the difficulties of structural determinations of C20 skeleton-type quassinoids. Therefore, this review aims to compile and discuss the spectral data of the ^{13}C NMR of quassinoids with C20 skeleton-type isolated after the year of 1985, as well as the biological activities of these compounds.

3.2.2. DESCRIPTION AND ^{13}C NMR DATA OF C_{20} SKELETAL- TYPE QUASSINOIDS

After 1985, more than 100 C20 skeletal-type quassinoids, isolated from various species of the Simaroubaceae family, have been identified, as shown in **Table 4.1** and in **Figure 4.3**.

Table 4.1 C_{20}-type quassinoids known up to the present, with their respective vegetal species from where they have been isolated, and its bibliographical references.

Nº	Quassinoids	Species	Reference
1	13*α*(21)-Epoxyeurycomanone	*Eurycoma longifolia*	[26]
2	15-Acetyl-13*α*(21)-epoxyeurycomanone	*Eurycoma longifolia*	[26]
3	12,15-diacetyl-13*α*(21)-epoxy-eurycomanone	*Eurycoma longifolia*	[26]
4	12-Acetyl-13,21-dihydroeurycomanone	*Eurycoma longifolia*	[26]
5	ailantinol B	*Ailanthus altissima*	[27]
6	shinjulactone M	*Ailanthus altissima*	[28]
7	peninsularinone	*Castela peninsulares*	[29]
8	iandonone	*Eurycoma harmandiana*	[30]
9	14-Hydroxychapparinone	*Hannoa chlorantha*	[31]
10	15-*O*-*β*-D-glycopyranosyl-21-hydroxyglaucarubolone	*Hannoa klaineana*	[32]
11	15-*O*-*α*-D-xylofuranosyl(1→ 6)-*β*-D-glycopyranosyl-21-hydroxyglaucarubolone	*Hannoa klaineana*	[32]
12	altissinol A	*Ailanthus altissima*	[33]
13	altissinol B	*Ailanthus altissima*	[33]
14	14-*epi*-13,21-dihydroeurycomanone	*Eurycoma longifolia*	[34]
15	12,15-*O*,*O*-diacetyl-13,21-dihydroeurycomanone	*Eurycoma longifolia*	[34]
16	1-*epi*-holacanthone	*Castela polyandra*	[35]
17	1-*epi*-glaucarubolone	*Castela polyandra*	[35]
18	1-*epi*-5-*iso*-glaucarubolone	*Castela polyandra*	[35]
19	javanicolide B	*Brucea javanica*	[36]
20	bruceanol-A	*Brucea antidysenterica*	[37]
21	bruceanol-B	*Brucea antidysenterica*	[37]
22	bruceanol-C	*Brucea antidysenterica*	[38]
23	bruceanol-D	*Brucea antidysenterica*	[39]
24	yadanziolide A	*Brucea javanica*	[40]
25	yadanziolide B	*Brucea javanica*	[40]
26	yadanziolide C	*Brucea javanica*	[40]
27	indaquasin C	*Quassia indica*	[41]
28	gutolactone	*Simaba guianensis*	[42]
29	15-*O*-benzoyl-brucein D	*Soulamea amara*	[43]
30	cedronolactone A	*Simaba cedron*	[6]
31	samaderine Z	*Simaba cedron*	[44]
32	simalikalactone D	*Simaba cedron*	[45]
33	simalikalactone E	*Quassia amara*	[46]
34	bruceanol-E	*Brucea antidysenterica*	[39]
35	bruceanol-G	*Brucea antidysenterica*	[47]
36	bruceanol-H	*Brucea antidysenterica*	[47]
37	6*α*-Acetoxy-14,15β-dihydroxyklaineanone	*Eurycoma longifolia*	[26]
38	6*α*-acetoxy-15β-hydroxyklaineanone	*Eurycoma longifolia*	[26]
39	15*β*-Acetyl-14-hydroxy-klaineanone	*Eurycoma longifolia*	[26]
40	12-*epi*-11-dehydroklaineanone	*Eurycoma longifolia*	[10]
41	yadanziolide T	*Brucea mollis*	[48]
42	yadanziolide U	*Brucea mollis*	[48]
43	6*α*,14,15*β*-trihydroxyklaineanone	*Eurycoma longifolia*	[34]
44	indaquassin F	*Quassia indica*	[41]
45	ailantinol E	*Ailanthus altissima*	[49]
46	chaparramarine	*Castela tortuosa*	[13]
47	ailantinol A	*Ailanthus altissima*	[27]

48	ailantinol D	*Ailanthus altissima*	[50]
49	vilmorinine A	*Ailanthus vilmoriniana*	[51]
50	vilmorinine B	*Ailanthus vilmoriniana*	[52]
51	vilmorinine C	*Ailanthus vilmoriniana*	[52]
52	vilmorinine D	*Ailanthus vilmoriniana*	[52]
53	vilmorinine E	*Ailanthus vilmoriniana*	[52]
54	vilmorinine F	*Ailanthus vilmoriniana*	[52]
55	15-*O*-acetyl-glaucarubol	*Castela polyandra*	[35]
56	15-*O*-acetyl-$\Delta^{4,5}$-glaucarubol	*Castela polyandra*	[35]
57	$\Delta^{4,5}$-glaucarubol	*Castela polyandra*	[35]
58	shinjulactone N	*Ailanthus altissima*	[28]
59	ailantinol C	*Ailanthus altissima*	[50]
60	3,4-dihydro excelsin	*Ailanthus excels*	[53]
61	casteloside A	*Castela tortuosa*	[54]
62	casteloside B	*Castela tortuosa*	[54]
63	casteloside C	*Castela tortuosa*	[55]
64	iandonoside A	*Eurycoma harmandiana*	[30]
65	iandonoside B	*Eurycoma harmandiana*	[30]
66	13*β*,18-dihydroeurycomanol	*Eurycoma longifolia*	[56]
67	eurycomanol-2-*O*-*β*-D-glycopyranoside	*Eurycoma longifolia*	[57]
68	13,18-dehydro-6*α*-senecioyloxychaparrin	*Simaba multiflora*	[58]
69	12-dehydro-6*α*-senecioyloxychaparrin	*Simaba multiflora*	[58]
70	orinocinolide	*Simaba orinocensis*	[7]
71	20-hydroxyyadanzigan	*Brucea javanica*	[20]
72	castelalin	*Castela tortuosa*	[59]
73	javanicolide D	*Brucea javanica*	[60]
74	quassinoid 3	*Eurycoma longifolia*	[61]
75	indaquasin D	*Quassia indica*	[41]
76	indaquasin E	*Quassia indica*	[41]
77	shinjulactone L	*Ailanthus altissima*	[62]
78	ailantinol F	*Ailanthus altissima*	[49]
79	shinjuglycosides E	*Ailanthus altissima*	[63]
80	shinjuglycosides F	*Ailanthus altissima*	[63]
81	11-*O*-*trans*-*p*-coumaroyl amarolide	*Castela texana*	[8]
82	dihydrojavanicin Z	*Picrasma javanica*	[64]
83	nigakilactone P	*Picrasma quassioides*	[65]
84	nigakilactone O	*Picrasma ailanthoides*	[66]
85	picrajavanins A	*Picrasma javanica*	[67]
86	picrajavanins B	*Picrasma javanica*	[67]
87	6*α*-acetoxypicrasine B	*Soulamea fraxinifolia*	[68]
88	picrasinoside A	*Picrasma ailanthoides*	[69]
89	bruceanol-F	*Brucea antidysenterica*	[39]
90	bruceantinoside C	*Brucea antidysenterica*	[70]
91	yadanzioside N	*Brucea javanica*	[71]
92	javacinoside B	*Brucea javanica*	[60]
93	picrasinoside H	*Picrasma ailanthoides*	[72]
94	picrasinol D	*Picrasma ailanthoides*	[73]
95	picrasinoside C	*Picrasma ailanthoides*	[69]
96	picrasinol B	*Picrasma ailanthoides*	[69]
97	*β*-dihydronorneoquassin	*Picrasma crenata*	[74]
98	*α*-hemiacetaljanicin Z	*Picrasma javanica*	[64]
99	*β*-hemiacetaljanicin Z	*Picrasma javanica*	[64]
100	javanicin Z	*Picrasma javanica*	[64]
101	picrasinol C	*Picrasma ailanthoides*	[75]
102	javacinoside I	*Picrasma javanica*	[76]
103	javacinoside J	*Picrasma javanica*	[76]
104	javacinoside K	*Picrasma javanica*	[76]
105	javacinoside L	*Picrasma javanica*	[76]
106	12-*α*-hydroxy-13,18-dehydroparain	*Quassia Amara*	[77]
107	picrasinoside D	*Picrasma ailanthoides*	[69]
108	picrasinoside E	*Picrasma ailanthoides*	[69]
109	picrasinoside F	*Picrasma ailanthoides*	[69]
110	picrasinoside G	*Picrasma ailanthoides*	[69]
111	picrasinol A	*Picrasma ailanthoides*	[69]
112	picraqualide F	*Picrasma quassioides*	[65]
113	nigakilactone Q	*Picrasma quassioides*	[65]

114	quassialactol	*Quassia Amara*	[8]
115	11-*α*-*O*-(*β*-D-glucopyranosyl)-16-*α*-*O*-methylneoquassin	*Quassia Amara*	[77]
116	1-*α*-*O*-methylquassin	*Quassia Amara*	[77]
117	16-*β*-*O*-methylneoquassin	*Picrasma crenata*	[78]
118	16-*β*-*O*-ethylneoquassin	*Picrasma crenata*	[78]
119	picrasinoside B	*Picrasma ailanthoides*	[69]
120	yadanzioside M	*Brucea javanica*	[71]
121	yadanzioside O	*Brucea javanica*	[71]
122	yadanzioside F	*Brucea javanica*	[40]
123	yadanzioside J	*Brucea javanica*	[40]
124	bruceoside D	*Brucea javanica*	[79]
125	bruceoside E	*Brucea javanica*	[79]
126	bruceoside F	*Brucea javanica*	[79]
127	javanicoside D	*Brucea javanica*	[60]
128	javanicoside E	*Brucea javanica*	[60]
129	javanicoside F	*Brucea javanica*	[60]
130	javacinoside C	*Brucea javanica*	[60]
131	javanicolide H	*Brucea javanica*	[80]
132	yadanzioside K	*Brucea javanica*	[71]
133	yadanzioside P	*Brucea javanica*	[81]
134	yadanzioside I	*Brucea javanica*	[40]
135	yadanzioside L	*Brucea javanica*	[40]
136	bruceoside C	*Brucea javanica*	[82]
137	bruceantinol B	*Brucea javanica*	[83]
138	bruceine J	*Brucea javanica*	[83]
139	javanicolide E	*Brucea javanica*	[17]
140	javanicolide F	*Brucea javanica*	[17]
141	quassinoid A	*Ailanthus excels*	[53]
142	quassinoid B	*Ailanthus excels*	[53]
143	bruceanic acid B	*Brucea antidysenterica*	[84]
144	bruceanic acid C	*Brucea antidysenterica*	[84]
145	bruceanic acid D	*Brucea antidysenterica*	[84]
146	bruceanic acid E	*Brucea javanica*	[80]
147	bruceanic acid F	*Brucea javanica*	[80]
148	bruceanic acid E methyl ester	*Brucea javanica*	[80]
149	javanic acid A	*Brucea javanica*	[80]
150	javanic acid B	*Brucea javanica*	[80]
151	javanicin	*Brucea javanica*	[85]
152	javanicolide C	*Brucea javanica*	[60]
153	ailanquassin A	*Eurycoma longifolia*	[34]
154	bruceene A	*Brucea javanica*	[5]

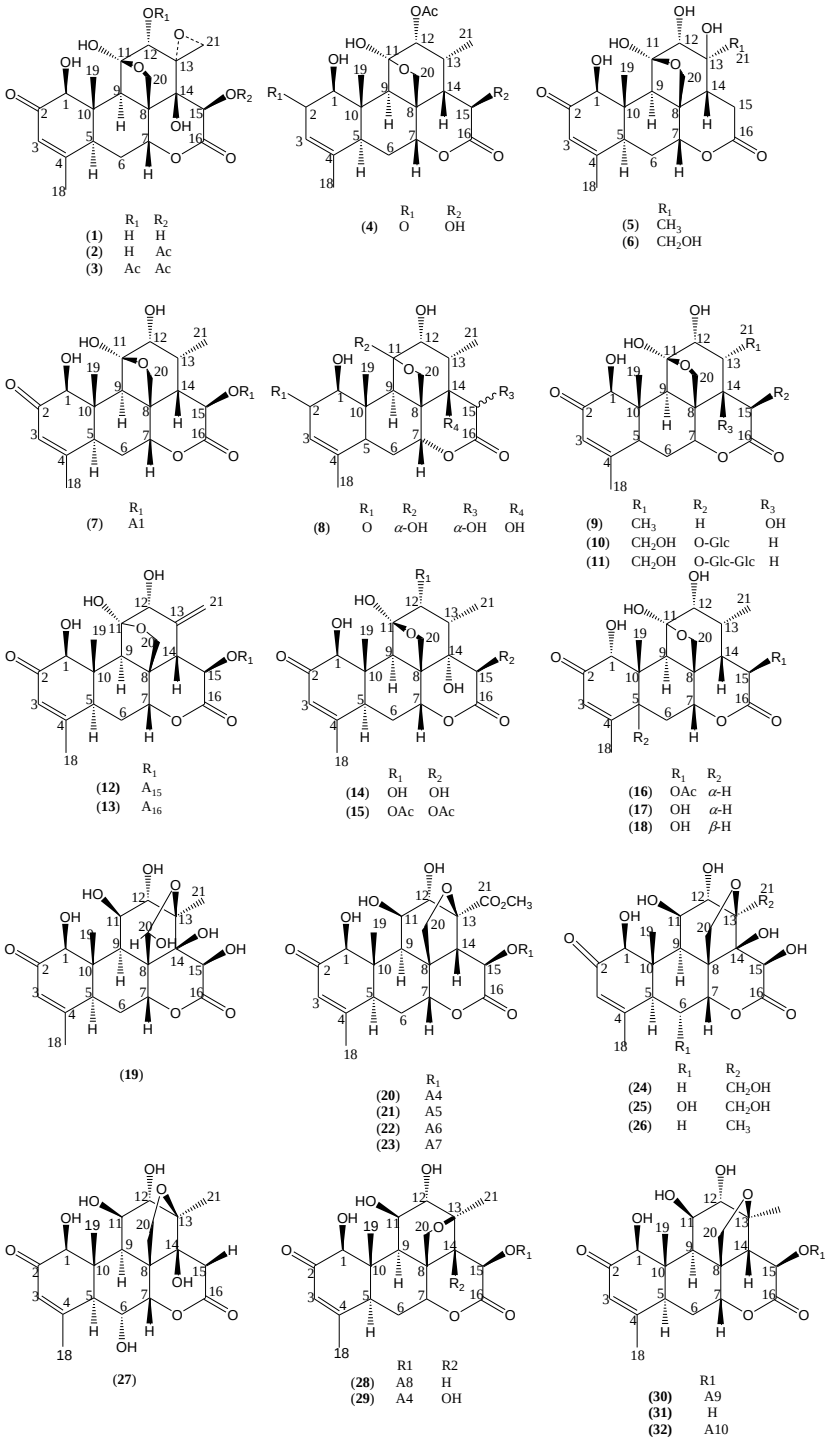
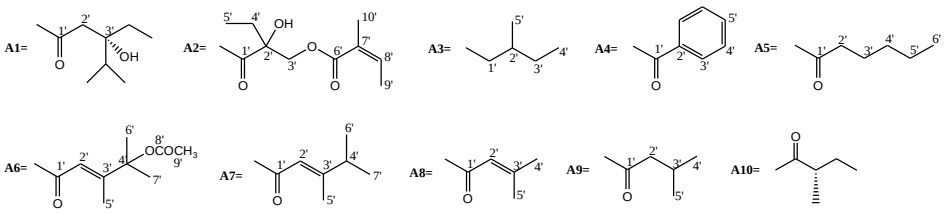
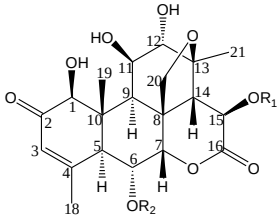
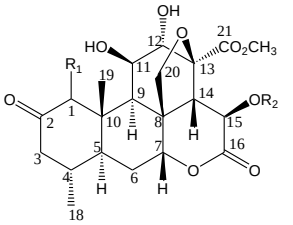


Figure 4.3 Structure of compounds **1–154**

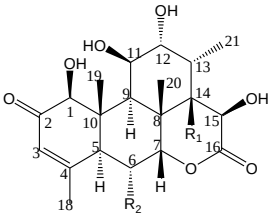




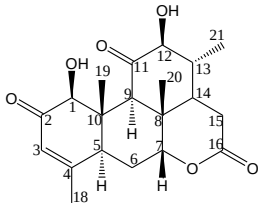
	R_1	R_2
(33)	A10	A11



	R_1	R_2
(34)	β-OH	A7
(35)	β-OH	A6
(36)	O	A7



	R_1	R_2
(37)	OH	OAc
(38)	H	OAc
(39)	OH	H_2



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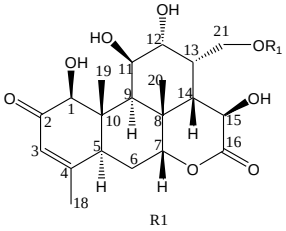
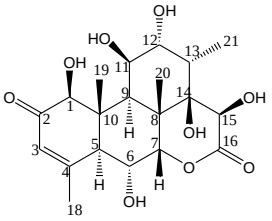
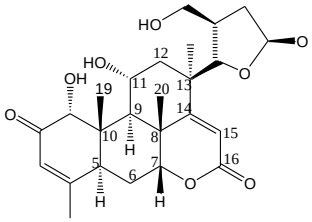


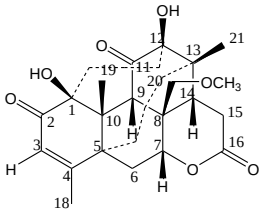
	R1
(41)	H
(42)	Glc



(43)



(44)



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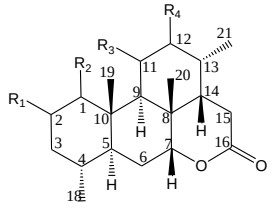
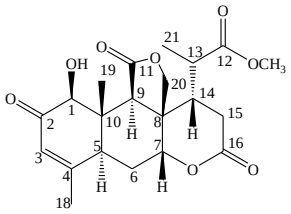
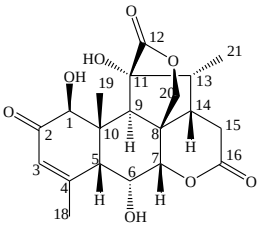


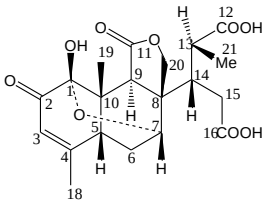
	R_1	R_2	R_3	R_4
(46)	O	α-OH	O	α-OH



(47)



(48)



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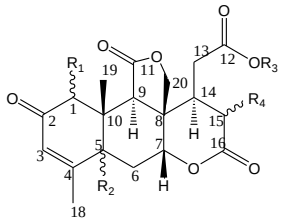
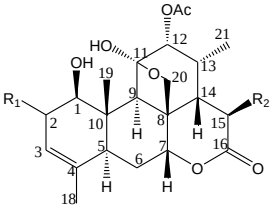
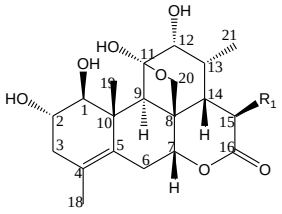


	R_1	R_2	R_3	R_4
(50)	βOH	αH	Me	β-Me
(51)	βOH	αH	H	β-Me
(52)	αOH	αH	H	β-Me
(53)	βOH	βH	H	β-Me
(54)	βOH	βH	H	α-Me

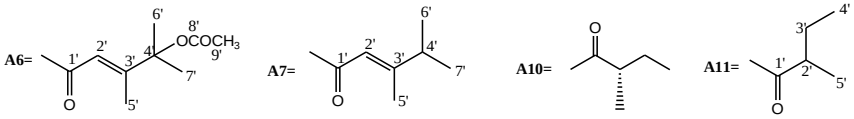


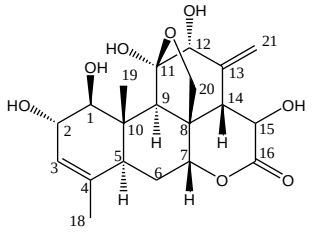
	R_1	R_2
(55)	β–OH	OAc



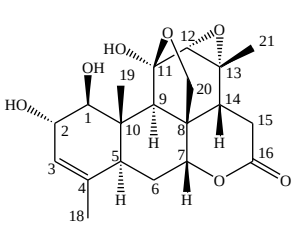
	R_1
(56)	OAc
(57)	OH

Figure 4.3 Continued

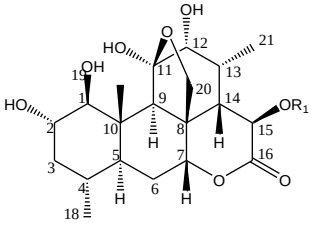




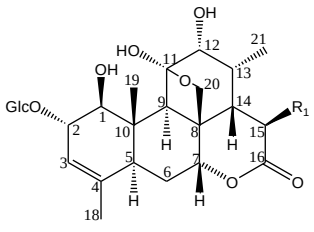
(**58**)



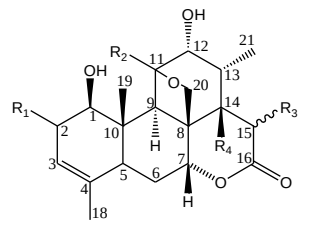
(**59**)



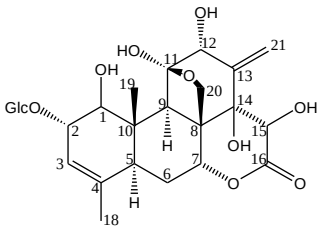
	R1
(**60**)	A11



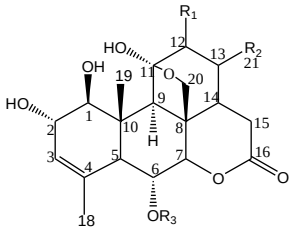
	R1
(**61**)	H
(**62**)	OH



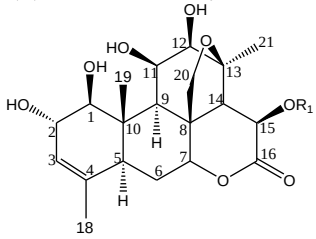
	R1	R2	R3	R4
(**63**)	α-OH	α-O-Glc	H	H
(**64**)	α-O-Glc	α-OH	α-OH	H
(**65**)	α-O-Glc	α-OH	α-OH	OH
(**66**)	α-OH	α-OH	β-OH	OH



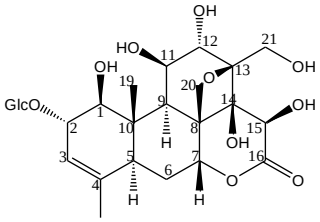
(**67**)



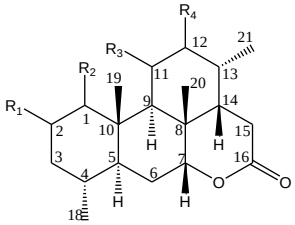
	R1	R2	R3
(**68**)	α-OH	CH_2	A8
(**69**)	O	α-CH_3	A8



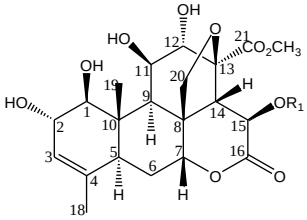
	R1
(**70**)	A11



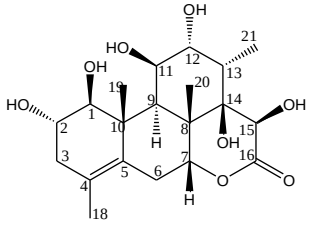
(**71**)



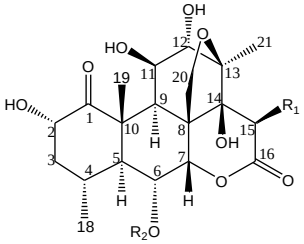
	R1	R2	R3	R4
(**72**)	α-OH	α-OH	O	β-OH



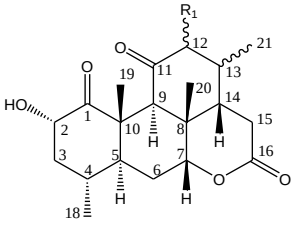
	R1
(**73**)	A12



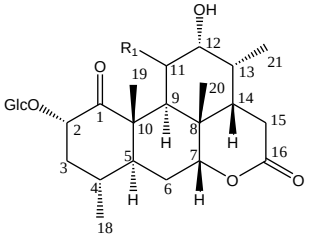
(**74**)



	R1	R2
(**75**)	H	A17
(76)	OH	A17



	R1	R2
(**77**)	β-OAc	α-CH_3
(**78**)	OH	CH_3



	R1
(**79**)	α-OH
(**80**)	O

Figure 4.3 Continued

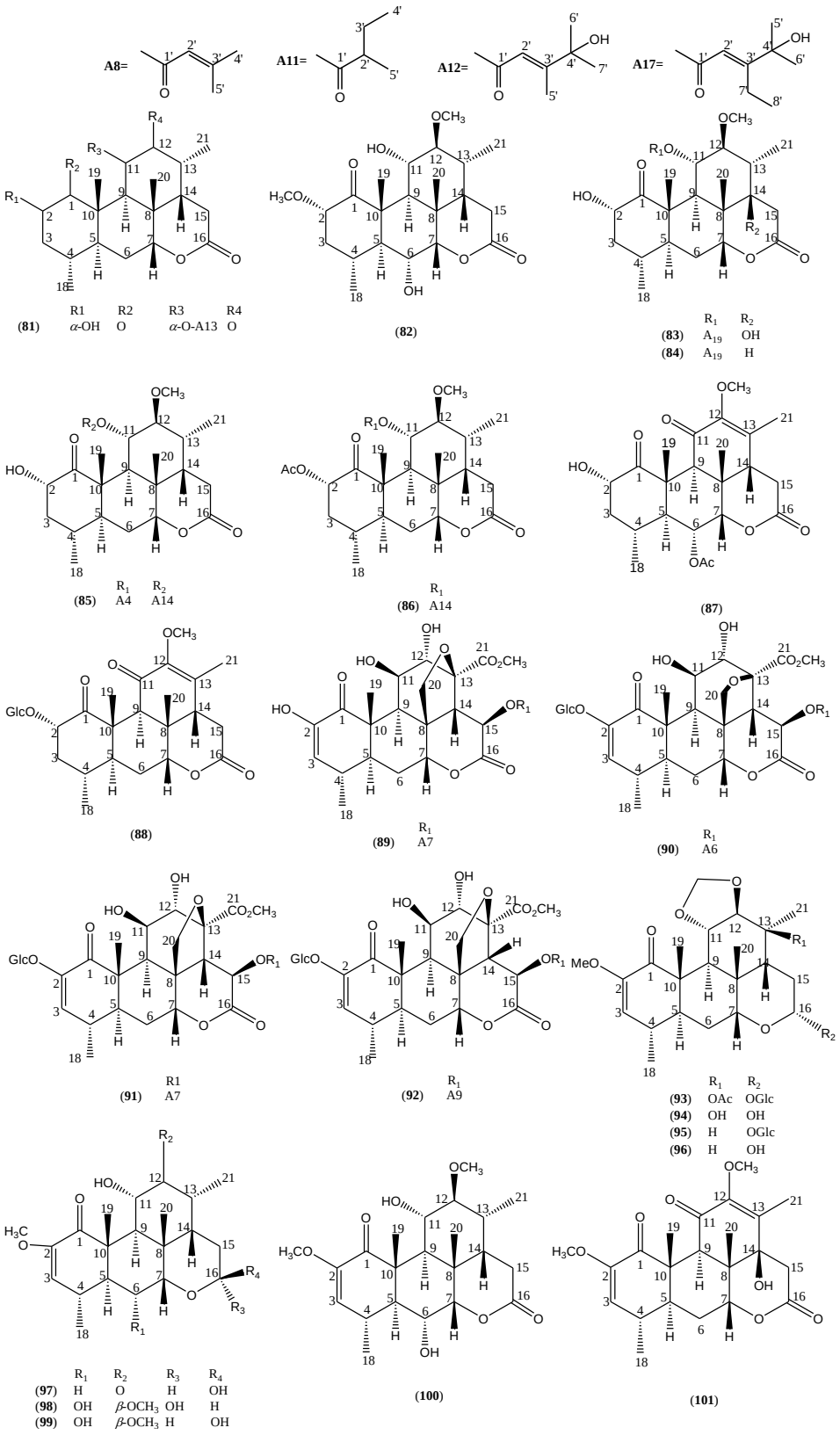
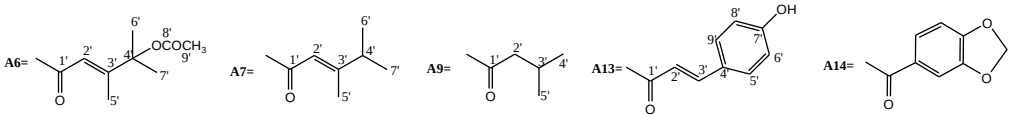
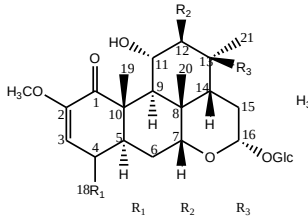
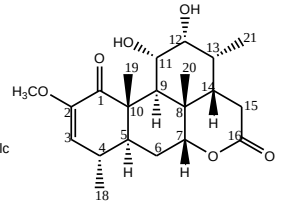


Figure 4.3 Continued

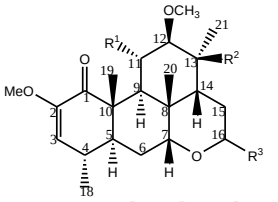




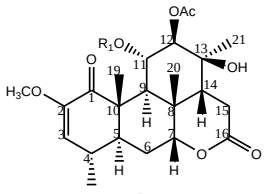
	R_1	R_2	R_3
(**102**)	O	OCH_3	H
(**103**)	α-CH_3	OAc	OH
(**104**)	H, H	OAc	OH
(**105**)	α-CH_3	OH	OH



(**106**)

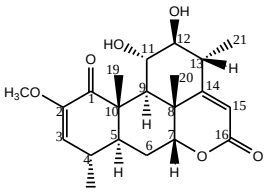


	R_1	R_2	R_3
(**107**)	OAc	H	O-Glc
(**108**)	OAc	OH	O-Glc
(**109**)	OH	H	O-Glc
(**110**)	OH	OH	O-Glc
(**111**)	OAc	H	OH

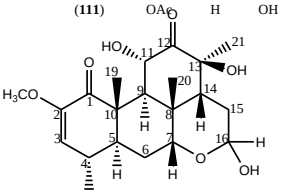


R_1

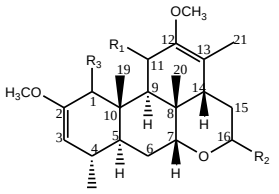
(**112**) 3,4-methyienedioxybenzoyl



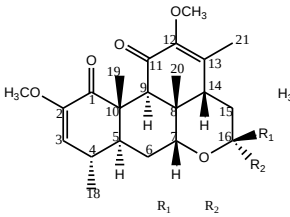
(**113**)



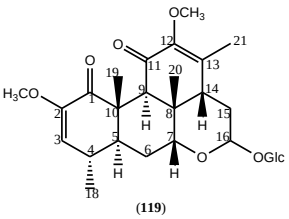
(**114**)



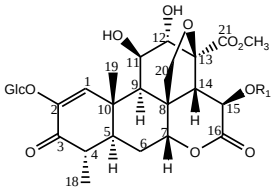
	R_1	R_2	R_3
(**115**)	β-O-Glc	β-OCH_3	O
(**116**)	O	O	β-OCH_3



	R_1	R_2
(**117**)	OCH_3	H
(**118**)	OC_2H_5	H



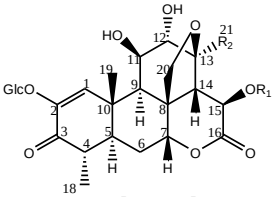
(**119**)



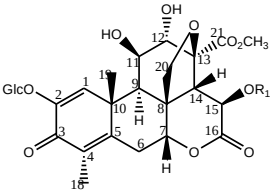
R_1

(**120**) A4

(**121**) A15

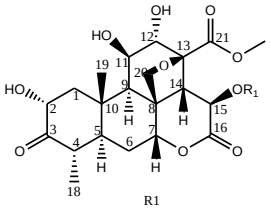


	R_1	R_2
(**122**)	$COCH_3$	CO_2CH_3
(**123**)	A16	CO_2CH_3
(**124**)	A8	COOH
(**125**)	A9	COOH
(**126**)	A6	COOH
(**127**)	A17	CO_2CH_3
(**128**)	A6	CO_2CH_3
(**129**)	A	CO_2CH_3



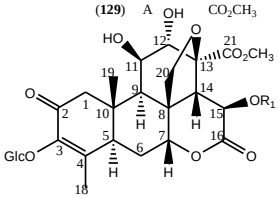
R_1

(**130**) A8



R1

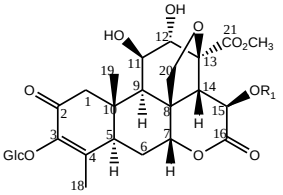
(**131**) A8



R_1

(**132**) A15

(**133**) A7



R1

(**134**) $COCH_3$

(**135**) A12

Figure 4.3 Continued

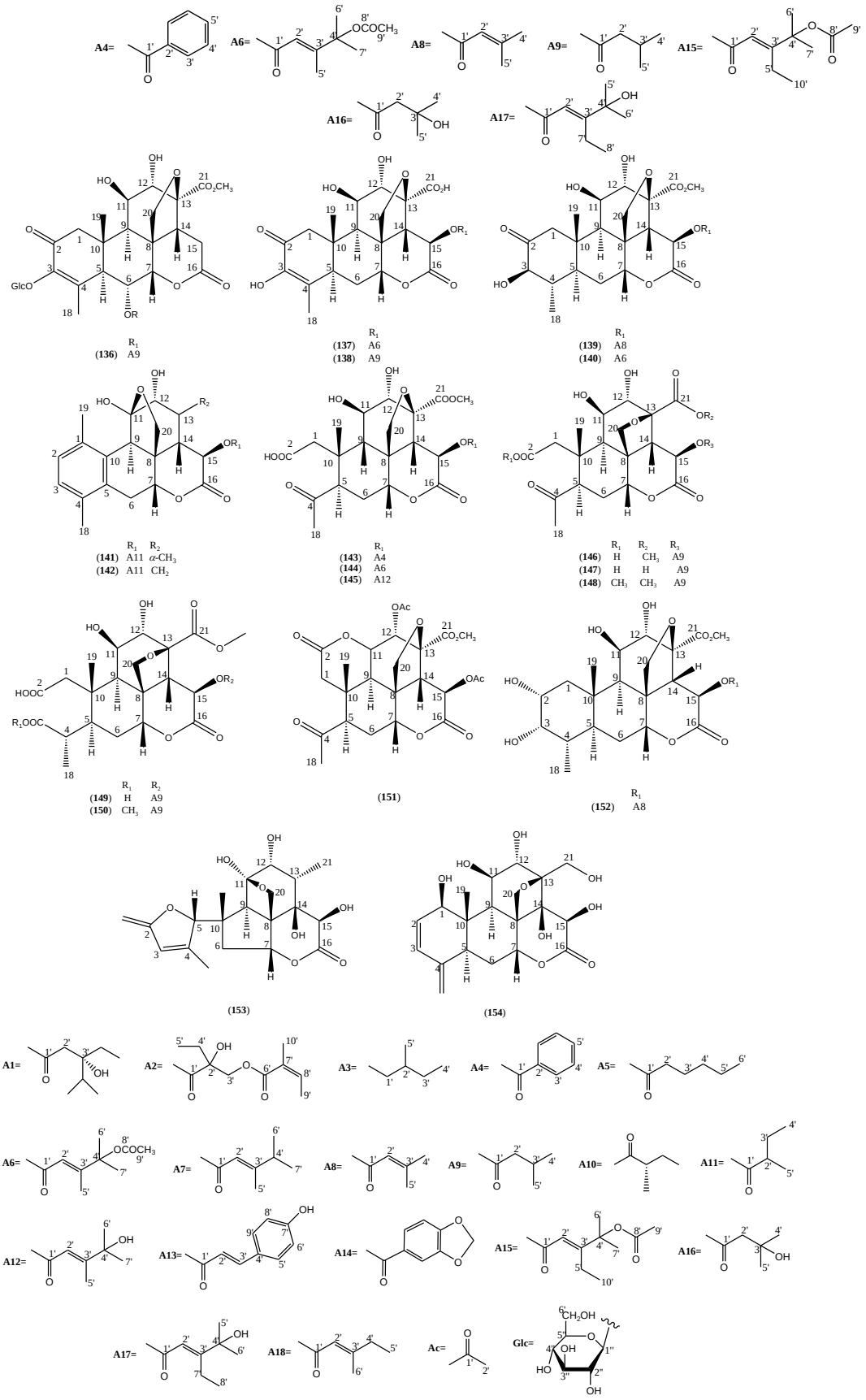


Figure 4.3 Continued

Table 4.2 shows the NMR ^{13}C spectral data of all structures cited above.

Table 4.2 NMR 13C spectral data of the 1–154 compounds, except of those which did not have their data reported in the literature.

Carbons	Compounds/δC (ppm)							
	1[I]	2[I]	3[I]	4[I]	5[I]	6[I]	7[I]	8[I]
C								
2	197.3	197.1	196.8	179.1	197.6	197.5	197.4	197.4
4	162.4	162.0	161.9	161.2	162.3	162.3	162.3	162.2
8	53.5	54.0	53.7	50.5	46.5	46.3	46.0	49.9
10	45.8	45.7	45.7	45.4	45.3	45.3	45.6	45.7
11	109.6	109.5	107.3	108.8	110.7	110.5	110.7	110.1
13	-	-	-	-	74.2	75.8	-	-
14	75.4	74.9	74.7	76.2	-	-	-	76.6
16	173.8	169.8	169.7	172.4	170.2	170.1	168.4	171.9
Ac	-	168.3	167.8	170.5	-	-	-	-
Ac	-	-	170.2	-	-	-	-	-
CH								
1	84.5	84.3	84.2	84.2	84.6	84.6	84.3	84.8
3	126.1	126.3	126.2	125.9	126.3	126.2	126.2	126.2
5	42.2	42.1	41.8	42.6	42.6	42.6	42.2	42.5
7	75.6	76.4	76.2	73.1	78.2	78.3	75.4	70.9
9	48.4	48.8	50.1	46.6	44.8	45.3	45.4	45.3
12	81.7	81.2	80.8	80.2	83.0	80.7	78.6	78.7
13	59.2	58.9	57.0	33.1	-	-	32.7	41.1
14	-	-	-	-	49.0	46.3	48.1	-
15	71.4	72.1	70.8	74.3	-	-	80.0	75.9
CH_2								
6	25.5	25.3	25.3	25.1	26.1	26.1	25.9	25.9
15	-	-	-	-	31.8	31.0	-	-
20	66.8	66.5	66.7	71.5	71.0	70.9	71.3	67.7
21	46.5	45.5	45.1	-	-	66.5	-	-
CH_3								
18	22.4	22.4	22.3	22.5	22.4	22.4	15.5	22.4
19	10.4	10.4	10.3	9.3	10.7	10.6	8.3	10.6
21	-	-	-	9.4	26.2	-	10.7	10.1
Ac	-	20.6	20.4	21.1		-	-	-
Ac	-	-	20.9	-	-	-	-	-
Side chain								
1’	-	-	-	-	-	-	172.0	-
2’	-	-	-	-	-	-	34.7	-
3’	-	-	-	-	-	-	70.8	-
4’	-	-	-	-	-	-	29.6	-
5’	-	-	-	-	-	-	40.9	-
6’	-	-	-	-	-	-	17.5	-
7’	-	-	-	-	-	-	17.2	-
8’	-	-	-	-	-	-	22.3	-

[I] C_5D_5N (pyridine), [II] CD_3OD, [III] DMSO-d_6, [IV] $CDCL_3$

Table 4.2 Continued

Carbons	Compounds/δ_C (ppm)							
	9[I]	9[III]	10[I]	11[I]	12[II]	13[I]	14	16[I]
C								
2	197.6	197.2	197.23	197.3	198.8	72.4	197.4	198.9
4	163.2	162.6	162.50	162.5	165.0	134.6	161.5	160.7
8	51.6	49.5	46.79	46.9	48.5	47.7	50.8	47.2
10	46.2	44.5	45.49	45.5	46.3	42.0	45.6	45.8
11	110.5	108.3	110.49	110.6	110.1	110.5	110.4	112.2
13	-	-	-	-	142.8	144.3	-	
14	75.3	74.4	-	-	-	-	78.3	-
16	171.0	169.7	170.82	170.6	168.2	167.7	172.3	168.1
Ac	-	-	-	-	-	-	-	169.7
CH								
1	85.2	82.7	84.40	84.5	84.1	83.3	84.3	79.6
3	126.6	124.9	126.07	126.1	126.0	127.2	125.9	125.2
5	41.3	41.0	46.20	46.3	43.0	41.8	42.7	41.9
7	76.1	73.5	75.63	75.4	79.9	79.5	72.9	77.0
9	48.1	46.0	42.32	42.4	46.1	45.8	46.4	36.3
12	79.0	76.8	78.38	79.2	80.8	80.6	81.3	78.6
13	38.9	36.8	41.22	41.2	-	-	32.7	33.1
14	-	-	47.95	47.5	52.3	52.1	-	36.1
15	-	-	79.22	80.0	70.7	68.9	73.8	72.0
CH_2								
6	26.5	24.8	26.54	26.6	26.3	26.7	25.2	26.1
15	38.9	36.8	-	-	-	-	-	-
20	67.4	65.3	71.16	71.2	72.7	72.7	71.4	70.7
21	10.9	9.6	61.59	61.7	122.6	120.5	-	-
CH_3								
18	22.9	22.3	22.33	22.4	22.9	21.2	22.5	22.1
19	10.7	9.5	10.56	10.6	10.1	10.7	9.4	14.3
20	-	-	-	-	-	-	-	-
21	-	-	-	-	-	-	10.3	15.2
Ac	-	-	-	-	-	-	-	20.8
Side chain								
1’	-	-	-	110.9	173.6	175.2	-	-
2’	-	-	-	77.0	78.3	41.4	-	-
3’	-	-	-	76.5	69.7	27.0	-	-
4’	-	-	-	78.5	29.6	11.8	-	-
5’	-	-	-	64.9	7.9	16.8	-	-
6’	-	-	-	-	169.3	-	-	-
7’	-	-	-	-	129.3	-	-	-
8’	-	-	-	-	139.4	-	-	-
9’	-	-	-	-	14.4	-	-	-
10’	-	-	-	-	12.1	-	-	-
Glucose							-	-
1’’	-	-	104.15	103.9	-	-	-	-
2’’	-	-	76.93	77.0	-	-	-	-
3’’	-	-	78.38	77.5	-	-	-	-
4’’	-	-	71.84	71.8	-	-	-	-
5’’	-	-	77.21	77.2	-	-	-	-
6’’	-	-	63.00	75.1	-	-	-	-

[I] C_5D_5N (pyridine), [II] CD_3OD, [III] DMSO-d_6, [IV] $CDCL_3$

Table 4.2 Continued

Carbons	Compounds/δC (ppm)							
	17[I]	18[I]	19[I]	20[IV]	21[IV]	22[IV]	23[I]	24[I]
C								
2	199.0	197.2	198,2	196.7	196.9	196.9	198.4	198.4
4	160.9	162.8	163,4	163.0	162.9	163.1	163.0	163.5
8	49.6	49.3	52,9	45.8	45.7	45.5	48.4	45.7
10	46.7	47.3	48,7	47.6	47.5	47.5	46.5	50.7
11	112.4	110.9	-	-	-	-	-	-
13	-	-	85,9	82.9	82.8	82.2	82.6	83.0
14	-	-	82,4	-	-	-	-	70.7
16	174.1	172.7	174,8	166.7	166.9	167.0	167.4	174.9
21	-	-	-	172.0	172.4	172.1	171.3	-
CH								
1	80.2	83.3	82.7	80.7	80.6	80.5	83.1	84.6
3	125.3	124.1	125	124.3	124.3	124.2	125.2	124.9
5	41.8	42.1	43,4	43.5	43.5	43.5	43.8	43.6
7	77.1	77.6	77,6	81.3	81.1	81.2	83.9	83.8
9	36.7	46.7	46	42.8	42.7	42.6	42.7	48.6
11	-	-	75,4	72.7	72.5	72.4	75.5	70.6
12	78.4	80.2	81,1	75.8	75.8	75.7	75.9	75.4
13	33.5	32.8	-	-	-	-	-	-
14	36.2	37.8	-	51.4	51.5	51.3	50.0	-
15	68.4	68.3	70,5	67.4	66.5	66.4	68.6	64.7
20	-	-	98,1	-	-	-	-	-
CH_2								
6	26.5	25.5	27,6	28.6	28.5	28.5	28.5	28.0
20	72.3	71.9	-	73.3	73.3	73.3	78.6	78.3
21	-	-	-	-	-	-	-	79.1
CH_3								
18	22.2	23.2	22,1	22.5	22.5	22.6	22.2	11.5
19	14.3	16.3	11,6	11.6	11.5	11.6	11.5	22.2
21	16.2	22.9	20,1	-	-	-	-	-
Side chain								
1’	-	-	-	164.8	171.9	165.2	166.0	-
2’	-	-	-	128.7	33.6	111.9	113.5	-
3’	-	-	-	128.5	31.2	169.5	168.4	-
4’	-	-	-	130.0	24.2	82.7	38.2	-
5’	-	-	-	133.8	22.2	14.6	16.7	-
6’	-	-	-	-	13.8	26.0	20.7	-
7’	-	-	-	-	-	26.3	20.7	-
8’	-	-	-	-	-	164.7	-	-
9’	-	-	-	-	-	21.6	-	-

[I] C_5D_5N (pyridine), [II] CD_3OD, [III] DMSO-d_6, [IV] $CDCL_3$

Table 4.2 Continued

Carbons	Compounds/δ_C (ppm)							
	25[I]	26[I]	27[I]	28[IV]	30	31	32	33
C								
2	198.2	198.4	198.2	197.4	198.4	200.7	197.6	196.5
4	166.4	161.6	166.3	163.6	162.9	166.3	162.6	163.0
8	49.2	37.7	48.0	47.7	46.6	43.8	45.8	46.1
10	51.2	38.3	51.1	45.8	48,3	47.5	47.7	50.4
13	83.3	82.0	83.3	80.4	81.2	83.1	81.7	80.0
14	70.9	70.5	81.3	-	-	-	-	-
16	174.7	174.9	170.6	-	168.7	176.2	167.6	166.5
21	-	-	-	-	-	-	169.5	
CH								
1	84.3	85.5	83.2	81.6	82.9	83.9	81.3	81.8
3	126.9	125.0	126.6	124.2	125.1	126.0	124.5	126.5
5	44.6	44.6	49.2	43.5	43.7	45.6	43.4	45.9
6	68.2	-	68.3	-	-	-	-	69.1
7	83.8	82.6	84.8	83.2	84.3	85.7	81.7	82.8
9	51.1	49.7	45.1	42.4	43.0	44.5	42.4	41.1
11	70.0	70.5	74.4	79.3	75.5	76.7	74.3	74.2
12	75.5	76.2	81.7	74.3	80.1	81.8	75.1	79.8
14	-	-	-	52.3	53.1	57.3	52.3	52.7
15	64.6	73.2	-	66.8	68.9	68.0	67.8	67.3
16	-	-	-	168.2	-	-	-	-
CH_2								
6	-	28.0	-	28.3	28.3	30.0	28.2	-
15	-	-	38.1	-	-	-	-	-
20	78.6	79.7	69.7	71.7	72.3	73.7	73.0	70.9
21	83.8	-	-	-	-	-	-	-
CH_3								
18	12.5	15.0	27.1	22.6	22.1	23.4	22.4	26.1
19	27.1	22.0	12.4	22.8	11.4	12.3	11.3	12.5
21	-	19.5	17.6	11.4	23.9	24.8	-	22.8
Side chain								
1’	-	-	-	165.0	171.6	-	170.7	175.2
2’	-	-	-	114.7	43.4	-	20.5	41.3
3’	-	-	-	160.1	25.9	-	-	16.7
4’	-	-	-	20.6	22.4	-	-	26.7
5’	-	-	-	27.6	22.4	-	-	11.7
1’’	-	-	-	-	-	-	-	176.2
2’’	-	-	-	-	-	-	-	41.3
3’’	-	-	-	-	-	-	-	15.6
4’’	-	-	-	-	-	-	-	27.2
5’’	-	-	-	-	-	-	-	11.5

[I] C_5D_5N (pyridine), [II] CD_3OD, [III] DMSO-d_6, [IV] $CDCL_3$

Table 4.2 Continued

Carbons	Compounds/δ_C (ppm)							
	34[I]	35[I]	36[I]	37[I]	38[I]	39[I]	41[I]	42[I]
C								
1	-	-	212.2	-	-	-	-	-
2	209.5	209.4	-	199.1	199.4	199.3	200.0	200.0
4	-	-	-	163.8	163.9	164.4	165.4	165.4
8	48.7	48.7	46.5	44.4	39.1	45.2	39.3	39.4
10	47.0	47.0	44.7	51.3	50.7	48.9	49.5	49.4
11	-	-	-	-	-	73.9	-	-
13	82.5	82.3	83.0	-	-	-	-	-
14	-	-	-	77.1	57.1	77.9	-	-
16	167.1	168.3	167.0	175.0	173.0	169.2	175.2	175.2
21	171.3	171.3	171.5	-	-	-	-	-
Ac	-	-	-	170.3	170.4	170.8	-	
CH								
1	83.9	83.9	-	85.8	85.9	84.3	85.2	85.2
2		-	73.1	-	-	-	-	-
3	-	-	-	127.4	127.3	124.7	125.2	125.2
4	32.1	32.1	32.6	-	-	-	-	-
5	44.7	44.7	38.7	45.6	46.3	43.3	43.8	43.8
6	-	-	-	69.1	68.9	-	-	-
7	83.8	83.6	83.6	81.3	83.5	81.8	84.3	84.2
9	43.2	43.2	34.7	42.5	39.8	45.4	43.2	43.1
11	75.7	75.7	76.4	73.6	72.9	-	74.3	74.3
12	76.0	75.9	78.5	77.9	76.4	77.2	74.4	73.4
13	-	-	-	35.8	26.9	36.4	37.3	35.4
14	50.5	51.0	50.2	-	-	-	52.8	53.5
15	68.5	69.0	68.6	70.0	66.7	75.0	68.0	68.0
CH_2								
3	47.5	47.5	45.3	-	-	-	-	-
6	29.5	29.5	29.5	-	-	26.1	26.6	26.6
20	73.2	73.2	73.9	-	-	-	-	-
21	-	-	-	-	-	-	64.0	71.8
CH_3								
18	19.8	19.8	20.0	24.4	23.8	22.3	22.8	22.8
19	12.6	12.6	14.4	13.2	13.6	11.6	12.3	12.4
20	-	-	-	17.7	24.1	17.7	25.7	25.6
21	-	-	-	13.8	16.2	13.6	-	-
Ac	-	-	-	21.3	21.3	21.1	-	-
Side chain								
1’	166.2	165.8	166.0	-	-	-	-	-
2’	113.5	113.6	113.5	-	-	-	-	-
3’	168.4	169.6	168.2	-	-	-	-	-
4’	38.1	82.5	38.2	-	-	-	-	-
5’	16.7	14.5	16.7	-	-	-	-	-
6’	20.7	25.8	20.7	-	-	-	-	-
7’	20.7	26.4	20.7	-	-	-	-	-

[I] C_5D_5N (pyridine), [II] CD_3OD, [III] DMSO-d_6, [IV] $CDCL_3$

Table 4.2 Continued

Carbons	Compounds/δ_C (ppm)							
	43	44[I]	45[I]	46[I]	47[I]	48[I]	49[I]	50[I]
C								
1	-	78.8	88.4	-	-	-	94.9	-
2	200.8	198.2	195.9	210.5	197.5	197.1	192.6	197.5
4	169.3	161.8	167.5	-	160.3	157.5	166.4	160.3
5	-	-	52.2	-	-	-	-	-
8	44.9	39.5	49.5	35.5	45.8	42.2	49.3	-
10	49.6	43.9	55.6	50.4	45.0	44.0	40.9	45.7
11	73.8	-	211.2	215.9	175.6	79.2	177.5	45.0
12	-	-	94.5	-	172.8	172.8	178.5	172.7
13	-	44.9	55.1	-	-	-	-	175.5
14	78.1	164.7	-	-	-	-	-	-
16	176.6	170.5	174.8	169.0	172.3	170.8	176.2	172.2
CH								
1	86.3	-	-	82.1	84.7	80.5	-	84.7
3	127.3	125.2	127.2	-	126.9	126.4	120.1	126.9
4	-	-	-	-	-	-	-	-
5	51.7	37.1	-	26.9	40.6	52.8	39.9	40.9
6	66.4	-	-	-	-	70.5	-	-
7	85.9	78.6	65.6	70.8	75.7	80.4	72.1	75.6
9	43.4	49.1	54.1	42.8	54.3	53.5	46.6	54.3
11	-	65.8	-	-	-	-	-	-
12	77.9	-	-	74.9	-	-	-	-
13	36.0	-	-	40.5	36.9	53.1	39.7	-
14	-	-	40.9	48.0	40.9	45.5	42.2	40.6
15	71.1	117.5	-	-	-	-	-	36.9
CH_2								
3	-	-	-	47.9	-	-	-	-
4	-	-	-	29.1	-	-	-	-
6	-	24.8	31.4	48.9	26.0	-	26.1	26.0
12	-	43.1	-	-	-	-	-	-
13	-	-	-	-	-	-	-	31.3
15	-	-	33.1	29.0	31.4	36.1	32.9	-
20	-	-	61.1	-	69.4	77.3	70.5	69.4
CH_3								
18	26.2	22.1	22.6	18.6	22.2	22.8	23.1	22.2
19	13.0	13.8	13.8	13.1	10.7	16.8	17.7	10.7
20	17.5	21.8	-	21.6	-	-	-	-
21	13.2	24.4	14.1	10.6	10.7	14.3	16.9	13.7
OCH3	-	-	-	-	52.2	-		54.3
Side chain								
1’	-	86.3	-	-	-	-	-	-
2’	-	38.1	-	-	-	-	-	-
3’	-	64.4	-	-	-	-	-	-
4’	-	32.1	-	-	-	-	-	-
5’	-	176.7	-	-	-	-	-	-

[I] C_5D_5N (pyridine), [II] CD_3OD, [III] DMSO-d_6, [IV] $CDCL_3$

Table 4.2 Continued

Carbons	Compounds/δ_C (ppm)							
	51[I]	52[I]	53[I]	54[I]	55[I]	56[IV]	57[I]	58[I]
C								
2	197.5	196.9	198.1	198.3	-	-	-	-
4	160.5	159.9	160.9	161.0	134.6	128.7	129.6	134.4
5						127.1	127.5	-
8	-	44.9	46.2	30.0	47.8	48.1	49.9	45.7
10	45.8	42.3	43.0	42.8	45.6	45.7	48.1	41.7
11	45.0	176.7	174.7	175.2	110.8	109.6	111.1	110.2
12	176.0	174.9	174.4	170.0	-	-	-	-
13	174.8	-	-	-	-	-	-	148.6
16	172.5	172.3	172.4	171.5	168.1	167.3	173.8	173.0
Ac					169.7	170.3	-	-
CH								
1	84.6	76.0	75.2	74.8	83.3	82.1	83.5	83.1
2	-	-	-	-	72.4	66.9	67.0	72.3
3	126.8	125.6	124.9	124.8	126.8	-	-	126.7
5	41.0	34.6	47.2	47.3	41.7	-	-	41.5
7	75.8	76.4	79.5	79.1	78.8	78.9	79.4	78.6
9	54.3	48.3	45.7	46.2	45.2	48.0	49.6	47.1
12	-	-	-	-	79.8	78.9	80.2	80.7
13	-	-	-	-	32.7	31.7	32.9	-
14	40.6	41.6	32.2	35.1	41.4	43.6	44.3	55.5
15	-	37.0	-	-	71.3	71.4	71.8	67.8
CH_2								
3	-	-	-	-	-	40.4	41.5	-
6	26.0	26.1	30.8	31.5	25.6	27.4	28.4	25.5
13	32.0	32.2	31.4	34.5	-	-	-	-
15	31.3	-	36.7	40.8	-	-	-	-
20	69.7	72.8	67.5	67.3	70.2	69.7	68.6	72.2
21	-	-	-	-	-	-	-	120.2
CH_3								
18	22.2	22.2	22.3	22.4	20.9	19.4	19.8	20.9
19	10.7	14.8	18.1	18.0	10.7	14.4	16.2	10.5
21	13.9	13.7	14.9	15.2	15.1	17.9	18.6	-
Ac	-	-	-	-	20.8	21.1	-	-

[I] C_5D_5N (pyridine), [II] CD_3OD, [III] DMSO-d_6, [IV] $CDCL_3$

Table 4.2 Continued

Carbons	Compounds/δC (ppm)							
	59[I]	61[I]	61[II]	62[I]	62[II]	63[I]	64[I]	65[I]
C								
4	134.4	136.1	137.5	136.1	137.6	128.8	135.7	135.5
5				-	-	128.1	-	-
8	44.9	46.3	47.2	47.5	48.4	46.3	44.8	50.0
10	41.5	41.6	42.3	42.0	42.5	44.7	42.3	42.3
11	107.4	110.7	110.7	111.0	110.9	114.0	110.9	110.3
13	59.0	-	-	-	-	-	-	-
14	-	-	-	-	-	-	48.5	76.6
16	169.6	170.5	173.7	174.3	175.6	169.5	171.2	172.0
CH								
1	82.8	82.7	82.7	82.7	82.8	83.1	82.8	82.8
2	72.0	84.2	84.2	84.2	84.2	68.0	83.7	83.8
3	127.1	124.7	124.9	124.7	124.8	-	124.9	124.8
5	41.5	41.8	42.4	41.4	42.1	-	41.6	41.2
7	78.7	79.7	80.6	80.5	79.9	79.5	79.3	71.5
9	45.2	44.3	45.0	45.6	46.2	48.5	45.9	44.8
12	68.0	79.0	80.2	80.5	80.9	79.3	78.3	78.8
13	-	31.7	32.4	33.2	33.6	31.3	31.9	41.4
14	43.5	42.8	43.1	49.7	49.7	42.4	-	-
15	-	30.6	30.6	68.8	69.3	-	65.4	76.1
CH_2								
3	-	-	-	-	-	39.9	-	-
6	25.5	26.0	26.5	26.1	26.5	28.6	26.0	25.7
15	28.6	-	-	-	-	30.3	-	-
20	72.8	-	-	-	-	73.8	72.3	67.9
CH_3								
18	21.3	21.1	21.3	21.1	21.2	20.2	21.1	21.1
19	10.8	10.4	10.4	10.9	10.6	17.7	10.7	10.9
20	-	71.8	72.5	71.9	72.5	-	-	-
21	21.9	13.2	13.0	16.3	15.7	12.9	13.0	10.1
Side chain								
1’	-	106.4	105.6	-	-	-	-	-
2’	-	76.2	75.7	-	-	-	-	-
3’	-	78.7	78.1	-	-	-	-	-
4’	-	71.7	71.6	-	-	-	-	-
5’	-	78.6	78.0	-	-	-	-	-
6’	-	62.8	62.8	-	-	-	-	-
Glucose								
1’’	-	-	-	106.4	105.5	98.2	106.3	106.2
2’’	-	-	-	76.2	75.7	75.5	76.2	76.3
3’’	-	-	-	78.8	78.1	78.3	78.6	78.5
4’’	-	-	-	71.7	71.6	71.6	71.6	70.7
5’’	-	-	-	78.5	78.0	74.4	78.5	78.5
6’’	-	-	-	62.8	62.7	62.7	62.7	62.7

[I] C_5D_5N (pyridine), [II] CD_3OD, [III] DMSO-d_6, [IV] $CDCL_3$

Table 4.2 Continued

Carbons	Compounds/δ_C (ppm)							
	66[I]	67[I]	67[III]	68[I]	69[I+IV]	70[IV]	71	72
C								
4	135.42	-	134.8	134.8	134.5	135.4	135.3	-
8	52.76	52.8	51.2	46.8	47.5	44.1	49.6	40.5
10	41.81	42.5	-	45.3	45.7	46.5	-	41.7
11	110.46	109.6	107.8	110.9	108.5	-	-	211.0
12	-	-	-	-	207.9	-	-	-
13	-	147.9	146.0	-	-	80.9	83.5	-
14	76.49	79.4	77.7	147.7	-	-	-	-
16	174.73	173.8	172.2	169.1	168.5	167.7	174.1	173.1
CH								
1	83.79	84.0	83.1	83.9	83.6	81.5	79.6	74.3
2	72.78	82.5	79.9	73.0	72.5	73.1	84.3	68.0
3	126.83	-	124.0	130.1	129.7	123.6	123.9	-
4	-	-	-	-	-	-	-	29.7
5	41.30	41.3	-	44.9	44.3	43.0	42.1	38.1
6	-	-	-	68.1	67.7	-	-	-
7	75.62	71.7	69.9	80.0	79.0	84.3	-	84.8
9	47.00	47.8	46.1	43.6	40.7	42.2	-	48.3
11	-	-	-	-	-	74.8	-	-
12	79.69	81.0	79.1	81.0	-	78.9	82.6	77.9
13	42.23	-	-	-	50.4	-	-	39.9
14				48.1	43.6	52.6	-	46.3
15	71.96	76.5	75.0	-	-	67.9	-	-
CH_2								
3	-	-	-	-	-	-	-	38.9
6	25.65	25.5	24.4	-	-	28.3	-	27.2
15	-	-	-	35.2	28.9	-	-	28.3
20	67.40	68.0	66.9	72.0	72.7	72.7	-	-
21	-	120.1	118.9	118.2	-	-	-	-
CH_3								
18	21.15	21.3	20.9	24.8	24.9	21.1	-	20.1
19	10.98	10.8	9.8	11.8	10.2	12.0	-	15.5
20	-	-	-	-	-	-	-	24.4
21	13.97	-	-	-	11.8	23.4	-	15.2
Side chain								
1’	-	-	-	167.0	166.0	175.7	-	-
2’	-	-	-	116.6	116.4	41.3	-	-
3’	-	-	-	158.8	159.2	27.0	-	-
4’	-	-	-	27.3	27.7	11.9	-	-
5’	-	-	-	20.5	20.7	16.7	-	-
Glucose								
1’’	-	106.2	105.3	-	-	-	-	-
2’’	-	76.1	74.0	-	-	-	-	-
3’’	-	78.6	76.6	-	-	-	-	-
4’’	-	71.9	70.2	-	-	-	-	-
5’’	-	78.5	76.2	-	-	-	-	-
6’’	-	62.7	60.9	-	-	-	-	-

[I] C_5D_5N (pyridine), [II] CD_3OD, [III] DMSO-d_6, [IV] $CDCL_3$

Table 4.2 Continued

Carbons	Compounds/δ_C (ppm)							
	73[I]	74[I]	75[I]	76[I]	77[IV]	78[IV]	79[I]	80[I]
C								
1	-	-	214.8	214.6	212.4	213.2	216.9	211.4
4	134.3	124.7	-	-	-	-	-	-
5	-	132.0	-	-	-	-	-	-
8	46.7	47.1	47.8	50.4	-	37.1	50.4	50.2
10	44.6	44.5	53.1	53.1	-	48.0	35.9	39.2
11	-	-	-	-	201.5	191.0	-	209.4
13	82.5	-	84.2	82.3	-	125.2	-	-
14		77.6	81.3	85.3	-	-	-	-
16	168.4	176.1	170.1	174.5	168.9	169.1	171.1	169.8
21	171.4	-	-	-	-	-	-	-
Ac	-	-	-	-	169.8	-	-	-
CH								
1	82.3	82.9	-	-	-	-	-	-
2	73.2	67.7	70.6	70.5	69.9	69.8	75.7	75.8
3	126.5	-	-	-	-	-	-	-
4	-	-	28.7	28.6	27.8	28.2	29.0	28.2
5	43.3	-	51.6	51.3	48.8	47.0	32.8	39.3
6	-	-	72.4	72.0	-	-	-	-
7	84.3	70.9	81.7	81.1	81.8	81.9	75.7	77.1
9	43.2	46.6	38.8	38.3	38.6	45.6	32.5	46.8
11	75.9	74.4	73.6	73.8	-	-	82.6	-
12	75.7	82.8	81.9	81.9	77.6	142.9	70.8	81.9
13	-	36.6	-	-	45.3	-	47.8	47.3
14	50.9	-	-	-	47.3	46.9	45.4	44.2
15	68.4	77.9	-	70.8	-	-	-	-
CH_2								
3	-	41.1	49.2	49.0	-	47.5	45.1	46.6
6	28.6	28.5	-	-	-	26.1	26.9	27.0
15	-	-	38.3	-	-	31.5	29.9	28.1
20	74.1	-	70.4	70.0	-	-	-	-
CH_3								
18	21.0	14.2	22.2	22.2	18.3	18.3	18.5	18.3
19	12.3	16.1	17.6	17.6	15.1	14.8	13.3	15.6
20	-	19.8	-	-	23.6	23.2	14.3	15.1
21	-	19.6	17.7	19.4	15.0	15.2	21.6	23.6
Ac	-	-	-	-	20.5	-	-	-
Side chain								
1’	166.6	-	167.3	167.2	-	-	-	-
2’	112.9	-	128.8	128.8	-	-	-	-
3’	168.1	-	139.2	139.2	-	-	-	-
4’	73.1	-	14.4	14.3	-	-	-	-
5’	28.9	-	12.1	12.1	-	-	-	-
Glucose								
1’’	-	-	-	-	-	-	103.3	103.8
2’’	-	-	-	-	-	-	76.2	76.3
3’’	-	-	-	-	-	-	78.6	78.6
4’’	-	-	-	-	-	-	71.4	71.4
5’’	-	-	-	-	-	-	78.2	78.3
6’’	-	-	-	-	-	-	62.7	62.8

[I] C_5D_5N (pyridine), [II] CD_3OD, [III] DMSO-d_6, [IV] $CDCL_3$

Table 4.2 Continued

Carbons	Compounds/δ_C (ppm)							
	81[I]	82	83	84	85[I]	86[IV]	89[I]	90[I]
C								
1	214.4	213.7	214.7	214.6	208.1	207.6	201.5	199.7
2	-	-	-	-	-	-	146.3	146.4
8	35.7	35.8	40.1	35.6	35.9	35.7	48.4	46.7
10	50.3	51.6	49.3	49.2	50.6	49.9	47.0	48.9
12	203.7	-	-	-	-	-	-	-
13	-	-	-	-	-	-	83.0	82.9
14	-	-	74.8	-	-	-	-	-
16	168.7	170.1	168.8	170.0	170.0	169.2	167.3	168.1
21	-	-	-	-	-	-	171.3	171.5
CH								
2	70.9	79.5	69.9	69.9	73.0	71.8	-	-
3							120.8	124.9
4	29.1	30.5	28.6	28.6	28.9	28.8	31.0	31.5
5	48.2	53.8	47.8	47.7	48.0	47.1	44.5	36.8
6	-	68.6	-	-	-	-	-	-
7	81.9	88.1	79.0	82.4	82.2	82.4	83.2	82.9
9	37.3	36.3	37.0	35.7	36.0	35.5	37.2	44.1
11	75.4	72.6	72.8	73.3	73.9	73.0	75.3	75.1
12	-	88.1	86.2	85.5	85.9	85.7	76.5	76.2
13	43.1	34.9	43.1	35.1	35.0	34.9	-	-
14	47.5	45.6	-	45.1	45.3	45.2	50.7	50.8
15	-	-	-	-	-	-	68.9	69.2
CH_2								
3	49.6	46.5	48.9	48.9	42.9	42.8	-	-
6	26.9	-	25.9	26.3	26.6	26.3	28.8	28.7
15	29.2	28.7	36.2	28.0	28.3	27.9	-	-
20	-	-	-	-	-	-	73.8	73.6
CH_3								
18	18.5	22.5	18.3	18.3	18.5	18.5	15.0	14.5
19	13.0	14.4	13.8	13.5	13.3	13.3	19.5	18.9
20	21;5	21.5	15.0	21.9	21.8	22.1	-	-
21	10.6	14.6	10.2	14.3	14.4	14.3	-	-
Side chain								
1’	166.5	-	123.5	123.7	130.3	-	166.0	165.9
2’	114.2	-	104.1	110.4	130.1	-	113.6	113.5
3’	146.6	-	143.4	143.3	128.6	-	168.4	169.5
4’	126.2	-	140.1	139.9	133.4	-	38.2	82.3
5’	130.9	-	148.2	148.8	128.6	-	16.7	14.5
6’	116.7	-	110.4	104.1	130.1	-	20.7	26.4
7’	161.5	-	165.2	165.3	164.9	-	20.7	25.7
8’	116.7	-	102.4	102.3	-	-	-	163.7
9’	130.9	-	-	-	-	-	-	21.4
1’’	-	-	-	-	125.4	124.1	-	-
2’’	-	-	-	-	110.6	110.3	-	-
3’’	-	-	-	-	148.1	147.4	-	-
4’’	-	-	-	-	151.8	151.5	-	-
5’’	-	-	-	-	108.1	107.6	-	-
6’’	-	-	-	-	126.5	126.2	-	-
7’’	-	-	-	-	165.6	165.4	-	-
8’’	-	-	-	-	102.2	101.6	-	-
Glucose	-	-	-	-	-	-		
1’’	-	-	-	-	-	-	-	100.7
2’’	-	-	-	-	-	-	-	74.6
3’’	-	-	-	-	-	-	-	79.0
4’’	-	-	-	-	-	-	-	71.4
5’’	-	-	-	-	-	-	-	78.6
6’’	-	-	-	-	-	-	-	62.3

[I] C_5D_5N (pyridine), [II] CD_3OD, [III] DMSO-d_6, [IV] $CDCL_3$

Table 4.2 Continued

Carbons	Compounds/δ_C (ppm)							
	91[I]	92[I]	93	94[I]	97[IV]	98	100	101[I]
C								
1	199.6	199.6	198.7	199.0	202.8	206.2	205.0	197.5
2	146.4	146.2	149.1	149.3	148.1	148.0	147.8	148.5
8	46.7	46.7	39.9	40.0	35.7	38.2	36.8	43.8
10	48.9	48.8	47.9	47.6	48.2	50.4	49.9	46.9
11	-	-	-	-	74.9	-	-	192.0
12	-	-	-	-	211.3	-	-	148.8
13	83.0	83.0	83.9	74.3	42.5	-	-	141.8
14	-	-	-	-	-	-	-	75.1
16	168.2	168.1	-	-	-	98.2	170.0	169.3
21	171.1	171.2	-	-	-	-	-	-
CH								
3	125.5	124.8	115.2	115.2	117.4	120.5	120.4	117.0
4	31.6	31.4	32.3	32.3	31.8	33.3	32.9	31.4
5	36.9	44.0	44.3	44.5	43.5	50.8	49.7	43.8
6	-	-	-	-	-	68.9	68.5	-
7	83.0	83.1	77.3	78.3	69.2	83.9	87.8	79.8
9	44.2	37.1	38.1	38.6	39.6	37.8	37.0	50.1
11	75.1	75.1	75.2	76.1	-	74.7	74.1	-
12	76.3	76.2	84.5	85.4	-	89.6	88.5	-
13			-	-	-	35.1	34.9	-
14	50.9	50.8	47.5	54.3	44.3	48.2	44.6	-
15	68.8	68.9	-	-	-	-	-	-
16	-	-	99.1	91.4	91.2	-	-	-
CH_2								
6	28.8	28.6	32.1	26.3	25.4	-	-	26.1
15	-	-	-	31.3	26.5	31.3	28.7	40.0
20	73.7	71.4	26.0	-	-	-	-	-
CH_3								
18	14.5	18.8	19.2	19.4	19.3	23.8	23.7	19.2
19	18.9	14.4	13.0	13.4	12.0	14.5	14.3	12.8
20	-	-	23.0	-	21.5	21.2	23.7	16.5
21	-	-	22.6	26.1	10.4	15.4	14.5	11.0
Side chain								
1’	166.0	171.9	-	-	-	-	-	-
2’	113.6	43.3	-	-	-	-	-	-
3’	167.2	25.9	-	-	-	-	-	-
4’	38.1	22.5	-	-	-	-	-	-
5’	16.7	22.4	-	-	-	-	-	-
6’	20.7	-	-	-	-	-	-	-
7’	20.7	-	-	-	-	-	-	-
Glucose								
1’’	100.9	100.5	100.7	-	-	-	-	-
2’’	74.7	74.6	75.1	-	-	-	-	-
3’’	78.9	78.6	78.9	-	-	-	-	-
4’’	71.5	71.4	71.5	-	-	-	-	-
5’’	78.6	78.9	78.3	-	-	-	-	-
6’’	62.5	62.4	62.7	-	-	-	-	-

[I] C_5D_5N (pyridine), [II] CD_3OD, [III] DMSO-d_6, [IV] $CDCL_3$

Table 4.2 Continued

Carbons	Compounds/δ_C (ppm)							
	102[I]	103[I]	104[I]	105[I]	106[IV]	112	113	114[IV]
C								
1	200.5	206.5	205.9	206.6	208.2	199.0	204.2	203
2	166.6	148.5	149.4	148.6	147.5	148.5	148.0	147.9
4	195.2	-	-	-	-	-	-	-
8	37.0	38.6	39.7	38.7	35.8	36.5	39.2	37.0
10	49.6	48.8	48.8	49.7	46.0	46.6	47.4	48.5
11	-	-	-	-	75.6	-	-	-
12	-	-	-	-	77.1	-	-	210.9
13	-	75.4	75.4	75.8	-	75.7	38.5	78.8
14	-	-	-	-	-	-	168.4	-
16	-	-	-	-	169.3	169.4	164.4	-
CH								
3	109.2	118.5	112.4	118.5	115.8	114.2	119.0	118.3
4	-	32.2	29.4	32.2	30.8	31.8	32.1	31.9
5	51.8	44.7	37.7	44.6	43.2	43.5	43.1	43.3
7	77.5	77.8	78.0	78.2	82.6	81.8	78.0	68.7
9	42.3	40.0	40.4	39.3	42.5	36.5	42.9	41.6
11	71.6	69.3	69.2	70.8	-	69.4	72.7	71.1
12	88.9	81.4	81.5	80.3	-	77.2	82.9	-
13	34.0	-	-	-	146.1	-	-	-
14	48.9	53.2	53.3	52.3	44.5	48.9	-	48.3
15	-	-	-	-	-	-	111.6	-
16	98.8	98.6	98.4	99.6	-	-	-	90.6
CH_2								
6	-	-	-	-	-	-	25.0	25.1
15	27.8	31.5	29.4	31.9	31.5	29.7	-	28.1
CH_3								
18	-	19.1	-	19.2	20.9	19.5	19.6	19.3
19	16.6	12.9	11.6	13.0	12.5	12.5	12.2	12.4
20	22.0	24.0	24.0	24.1	18.8	23.3	20.5	23.0
21	15.3	26.0	26.1	26.9	114.3	25.8	13.4	22.7
Side chain								
1’	-	-	-	-	-	124.2	-	-
2’	-	-	-	-	-	109.8	-	-
3’	-	-	-	-	-	147.7	-	-
4’	-	-	-	-	-	151.7	-	-
5’	-	-	-	-	-	108.2	-	-
6’	-	-	-	-	-	126.3	-	-
7’	-	-	-	-	-	166.1	-	-
8’	-	-	-	-	-	101.7	-	-
Glucose							-	-
1’’	100.4	100.4	100.2	100.1	-	-	-	-
2’’	75.3	75.2	75.2	75.2	-	-	-	-
3’’	78.4	78.1	78.2	78.3	-	-	-	-
4’’	71.5	71.6	71.7	71.6	-	-	-	-
5’’	78.6	78.3	78.9	78.9	-	-	-	-
6’’	62.7	62.9	63.0	62.9	-	-	-	-

[I] C_5D_5N (pyridine), [II] CD_3OD, [III] DMSO-d_6, [IV] $CDCL_3$

Table 4.2 Continued

Carbons	Compounds/δ_C (ppm)							
	115 [I]	116 [IV]	117 [I]	118 [II]	120 [I]	121 [I]	122 [I]	123 [I]
C								
1	193.1	70.3	198.6	201.5	-	-	-	-
2	148.0	150.9	148.6	149.1	148.8	148.8	148.8	148.9
3					194.5	194.6	194.5	194.5
8	38.2	37.1	38.5	39.6	46.9	46.6	46.6	46.8
10	40.1	41.9	46.6	47.5	39.7	39.6	39.6	39.6
11	90.8	192.0	193.2	195.5	-	-	-	-
12	139.9	139.8	140.3	143.6	-	-	-	-
13	148.2	147.5	148.7	149.5	82.7	82.6	82.7	82.7
16	95.7	168.9	97.7	97.4	168.0	168.0	168.0	168.1
21	-	-	-	-	171.2	171.1	171.3	171.2
CH								
1					129.4	129.6	129.5	129.5
3	116.5	104.4	116.5	118.6	-	-	-	-
4	31.3	30.9	31.6	32.6	43.9	43.9	43.9	43.8
5	45.8	44.9	44.5	45.7	40.8	40.4	40.6	40.7
7	68.1	82.8	69.4	70.6	83.7	83.4	83.6	83.6
9	46.3	46.0	46.5	47.4	41.4	41.4	41.4	41.4
11	-	-	-	-	73.5	73.5	73.4	73.5
12	-	-	-	-	76.1	76.0	76.1	76.0
14	49.6	48.8	44.3	45.4	50.7	50.3	50.5	50.5
15	-	-	-	-	69.3	68.6	68.8	68.7
CH_2								
6	25.1	25.2	25.9	26.5	30.1	30.0	30.0	30.0
15	29.6	30.7	31.0	32.2	-	-	-	-
20	-	-	-	-	73.8	73.6	73.7	73.7
CH_3								
18	19.3	19.0	19.5	19.8	12.6	12.5	12.6	12.5
19	12.7	12.7	13.0	13.3	18.0	18.0	18.0	17.9
20	19.4	19.2	22.0	22.4	-	-	-	-
21	13.1	15.1	15.2	15.4	-	-	-	-
Side chain								
1’	106.4	-	-	-	165.3	165.2	169.7	170.7
2’	78.6	-	-	-	130.4	113.8	20.6	48.6
3’	77.4	-	-	-	130.2	169.5	-	69.2
4’	77.0	-	-	-	128.7	82.7	-	29.7
5’	75.4	-	-	-	133.6	22.0	-	29.8
6’	59.9	-	-	-	128.7	26.2	-	-
7’	-	-	-	-	130.2	26.5	-	-
8’	-	-	-	-	-	168.6	-	-
9’	-	-	-	-	-	21.7	-	-
10’	-	-	-	-	-	14.6	-	-
Glucose								
1’’	-	-	-	-	102.0	102.0	102.0	102.1
2’’	-	-	-	-	74.7	74.6	74.7	74.7
3’’	-	-	-	-	78.8	78.8	78.8	78.8
4’’	-	-	-	-	71.4	71.3	71.3	71.4
5’’	-	-	-	-	78.5	78.4	78.5	78.5
6’’	-	-	-	-	62.4	62.4	62.4	62.4

[I] C_5D_5N (pyridine), [II] CD_3OD, [III] DMSO-d_6, [IV] $CDCL_3$

Table 4.2 Continued

Carbons	Compounds/δ_C (ppm)							
	124[I]	125[I]	126[I]	127[I]	128[I]	129[I]	130[I]	131[I]
C								
2	148.4	148.8	148.8	148.9	148.9	148.9	148.9	-
3	194.6	194.6	194.7	194.5	194.5	194.5	180.2	212.1
4	-	-	-	-	-	-	131.9	-
5	-	-	-	-	-	-	155.6	-
8	46.7	46.7	46.7	46.6	46.7	46.6	46.7	46.4
10	39.7	39.6	39.7	39.6	39.6	39.5	44.3	38.5
13	82.5	82.6	82.7	82.6	82.7	82.6	83.0	82.7
16	168.2	168.4	168.4	168.2	168.2	168.3	167.6	168.2
21	-	-	-	171.2	171.2	171.2	170.9	171.4
CH								
1	129.3	129.2	129.4	129.3	129.1	129.3	128.6	-
2								72.3
4	41.4	41.4	41.4	41.4	41.4	41.4	-	42.1
5	43.8	43.7	43.8	43.8	43.7	43.8	-	48.3
7	83.7	83.8	83.6	83.5	83.8	83.5	84.8	83.7
9	40.6	40.7	40.6	40.4	40.6	40.6	41.5	43.0
11	73.2	73.3	73.2	73.6	73.6	73.5	75.8	73.7
12	76.7	76.6	76.8	76.1	75.9	76.0	76.2	75.9
14	50.2	50.2	50.2	50.4	50.2	50.3	49.4	51.2
15	68.3	68.5	69.0	68.4	68.2	68.5	68.4	68.4
21	173.5	173.4	173.4	-	-	-	-	-
CH_2								
1	-	-	-	-	-	-	-	48.0
6	30.1	30.1	30.1	30.0	30.0	30.0	32.7	30.8
20	73.8	73.7	73.7	73.7	73.7	73.7	72.9	74.0
CH_3								
18	12.6	12.6	12.6	12.5	12.5	12.6	11.2	11.4
19	18.0	17.9	18.0	17.9	17.9	17.9	24.0	16.3
Side chain								
1’	174.0	174.0	162.6	166.0	167.5	165.8	165.6	165.2
2’	116.3	43.3	113.9	112.6	36.8	114.3	115.9	115.9
3’	157.7	25.6	169.5	168.3	39.5	163.7	158.6	158.4
4’	26.9	22.4	82.3	73.5	83.8	33.6	27.0	20.1
5’	20.1	22.5	14.5	29.3	22.2	11.7	20.1	27.0
6’	-	-	25.8	29.2	23.5	18.8	-	-
7’	-	-	-	22.9	14.5	-	-	-
8’	-	-	-	15.0	170.0	-	-	-
9’	-	-	-	-	22.1	-	-	-
Glucose								
1’’	101.9	101.9	101.9	102.1	102.0	102.0	101.8	-
2’’	74.7	74.7	74.7	74.7	74.7	74.7	74.7	-
3’’	78.5	78.5	78.5	78.6	78.5	78.5	78.5	-
4’’	71.2	71.2	71.2	71.3	71.3	71.4	71.7	-
5’’	78.9	78.9	78.9	78.9	79.0	78.9	78.9	-
6’’	62.3	62.3	62.3	62.3	62.3	62.3	62.3	-

[I] C_5D_5N (pyridine), [II] CD_3OD, [III] DMSO-d_6, [IV] $CDCL_3$

Table 4.2 Continued

Carbons	Compounds/δ_C (ppm)							
	132[I]	133[I]	134[I]	135[I]	136[I]	137	138	139[IV]
C								
2	193.6	193.6	193.6	193.6	194.1	194.5	194.6	209.2
3	148.0	147.9	146.8	146.6	148.0	145.8	145.8	-
4	146.6	146.7	148.0	147.9	146.8	130.4	130.5	-
8	46.0	46.0	46.0	46.0	46.3	46.3	46.0	45.7
10	40.8	40.9	40.8	40.8	39.7	42.2	42.1	42.3
13	82.6	82.7	82.7	82.7	82.8	84.0	83.4	81.2
16	168.0	168.2	168.0	168.2	167.2	169.5	169.3	167.1
21	-	171.3	171.3	171.2	170.9	172.1	178.2	171.9
CH								
3	-	-	-	-	-	-	-	79.8
4	-	-	-	-	-	-	-	40.8
5	43.4	43.4	43.4	43.4	48.1	43.2	43.2	43.2
6	-	-	-	-	78.8	-	-	-
7	83.4	83.4	83.5	83.4	83.2	84.9	85.1	82.2
9	41.9	42.1	42.1	42.1	-	42.8	42.8	42.2
11	73.0	73.1	72.9	73.0	73.3	71.1	70.9	71.2
12	75.9	75.9	76.0	76.0	75.6	78.5	78.5	75.8
14	50.2	50.5	50.3	50.5	42.5	51.3	51.6	51.2
15	68.4	68.3	68.7	68.3	-	67.7	67.4	65.7
CH_2								
1	51.1	51.5	51.0	51.1	51.0	50.2	50.2	50.2
6	29.3	29.4	29.3	29.4	-	30.1	30.1	29.1
15			-	-	27.7	-	-	-
20	73.5	73.6	73.5	73.6	73.3	74.4	-	73.6
CH_3								
18	15.2	15.3	15.3	15.3	16.8	13.4	13.4	16.19
19	15.8	15.9	15.8	15.9	26.5	16.0	16.1	16.14
Side chain								
1’	165.7	165.8	169.8	166.4	-	166.9	173.5	164.4
2’	113.5	113.5	20.6	112.8	116.0	114.4	43.5	114.0
3’	169.5	167.2	-	168.2	158.6	164.0	26.4	160.9
4’	82.3	38.1	-	73.2	20.1	84.0	22.7	27.6
5’	14.3	16.7	-	28.9	27.0	26.5	22.7	20.5
6’	25.8	20.7	-	28.9	-	26.7	-	-
7’	26.3	20.7	-	15.5	-	14.9	-	-
8’	163.4	-	-	-	-	171.8	-	-
9’	21.4	-	-	-	-	21.7	-	-
Glucose								
1’’	104.8	104.9	104.8	104.9	105.1	-	-	-
2’’	75.6	76.1	75.9	75.9	76.3	-	-	-
3’’	78.5	78.6	78.5	78.6	78.2	-	-	-
4’’	71.5	71.6	71.5	71.6	71.0	-	-	-
5’’	78.3	78.4	78.3	78.4	77.9	-	-	-
6’’	62.8	62.9	62.8	62.9	62.2	-	-	-

[I] C_5D_5N (pyridine), [II] CD_3OD, [III] DMSO-d_6, [IV] $CDCL_3$

Table 4.2 Continued

Carbons	Compounds/δ_C (ppm)							
	140[IV]	141[IV]	142[IV]	143[I]	144[I]	145[I]	146[I]	147[I]
C								
1	-	135.5	136.2	-	-	-	-	-
2	209.2	-	-	177.3	176.9	177.2	174.7	174.7
4	-	134.9	135.1	211.3	209.9	211.5	210.4	210.6
5	-	130.9	130.9	-	-	-	-	-
8	45.7	47.5	47.4	46.7	46.5	46.2	46.5	46.5
10	42.3	127.3	127.0	40.5	40.5	40.2	40.4	40.4
11	-	108.9	109.0	-	-	-	-	-
12	-	-	-	-	-	-	-	-
13	81.2	-	141.9	83.1	82.9	83.1	82.9	82.9
14	-	-	-	-	-	-	-	-
16	167.0	168.2	167.6	168.2	168.3	168.3	168.1	168.4
21	171.6	-	-	171.3	171.2	171.0	171.1	174.7
CH								
2	-	129.5	130.0	-	-	-	-	-
3	79.8	129.0	129.5	-	-	-	-	-
4	40.8	-	-	-	-	-	-	-
5	43.2	-	-	36.6	38.2	40.2	49.8	49.8
7	82.2	74.4	75.2	76.7	76.7	76.5	83.0	83.2
9	42.1	46.6	52.4	36.5	36.2	36.0	36.3	36.5
11	71.3	-	-	73.5	73.6	73.4	73.7	73.8
12	75.7	78.1	79.6	83.7	83.4	82.7	76.5	77.1
13	-	32.3	-	-	-	-	-	-
14	51.2	40.8	41.2	50.2	50.0	49.8	49.9	49.9
15	66.2	69.5	70.3	69.6	69.0	68.6	68.5	68.7
CH_2								
1	50.2	-	-	45.1	44.8	45.0	42.6	42.6
6	29.1	26.4	30.8	29.8	29.8	29.5	29.8	29.8
20	73.6	71.2	71.0	73.7	73.7	73.0	73.5	73.6
21	-	-	124.0	-	-	-	-	-
CH_3								
18	16.18	19.4	19.8	32.2	32.1	32.0	31.7	31.8
19	16.15	20.6	21.0	19.8	19.9	19.6	19.9	19.9
21	-	13.6	-	-	-	-	-	-
Side chain								
1’	164.6	176.2	176.7	165.8	166.0	166.7	165.5	165.8
2’	111.8	37.4	38.0	130.4	113.5	112.6	116.0	116.4
3’	165.2	30.5	27.0	130.2	169.6	168.2	158.4	157.6
4’	82.3	11.5	11.9	128.8	82.4	73.2	20.1	20.0
5’	14.5	16.0	16.8	133.7	14.5	15.3	27.0	26.8
6’	26.1	-	-	-	25.7	28.5	-	-
7’	26.1	-	-	-	26.4	28.6	-	-
8’	169.6	-	-	-	163.7	-	-	-
9’	21.6	-	-	-	21.4	-	-	-

[I] C_5D_5N (pyridine), [II] CD_3OD, [III] DMSO-d_6, [IV] $CDCL_3$

Table 4.2 Continued

Carbons	Compounds/δ_C (ppm)						
	148[I]	149[I]	150[I]	151	152[I]	153	154[II]
C							
2	172.8	174.5	174.1	171.4	-	172.7	-
3	-	179.5	177.4	-	-	-	-
4	210.1	37.7	37.8	207.9	-	170.1	145.3
8	46.4	46.4	46.4	43.5	46.5	63.3	51.3
10	39.0	42.1	42.0	37.2	39.0	47.1	44.7
11	-	-	-	-	-	111.1	-
13	82.9	82.9	82.9	80.8	82.7	-	84.7
14	-	-	-	-	168.3	75.4	83.6
16	167.3	168.1	168.2	168.7	171.5	174.5	176.5
21	171.2	-	-	157.9	-	-	
CH							
1	-	-	-	-	-	-	77.3
2	-	-	-	-	68.3	-	131.5
3	-	-	-	-	74.8	119.0	131.1
4	-	-	-	-	34.2	-	-
5	52.5	38.2	37.6	46.8	38.5	92.2	41.1
7	82.9	83.4	83.4	79.3	84.4	82.2	80.5
9	35.3	35.9	36.3	35.5	43.7	46.9	46.6
11	73.6	74.4	74.4	74.8	73.5	-	75.6
12	75.9	76.7	76.7	73.3	76.0	81.5	78.0
13	-	-	-	-	-	43.5	-
14	48.8	48.6	49.0	52.6	50.4	-	-
15	69.1	69.4	68.7	66.3	68.3	71.1	70.7
CH_2							
1	41.4	41.7	41.6	44.3	41.1	-	-
6	28.9	28.9	28.9	28.5	29.6	46.1	29.3
20	74.0	171.2	171.2	70.2	74.1	68.7	70.9
21	-	-	-	-	-	-	64.7
CH_3							
18	29.0	15.4	14.8	20.0	16.6	16.2	112.6
19	23.6	19.8	19.6	19.5	16.0	18.4	11.5
21	-	-	-	-	-	13.1	-
Side chain							
1’	165.7	166.0	168.2	-	165.3	-	-
2’	116.0	116.0	116.1	-	116.0	-	-
3’	158.4	158.5	158.2	-	158.2	-	-
4’	20.1	20.0	20.1	-	27.0	-	-
5’	27.0	26.9	27.0	-	20.1	-	-

[I] C_5D_5N (pyridine), [II] CD_3OD, [III] DMSO-d_6, [IV] $CDCL_3$

Some quassinoids show common structural factors, which will be summarized here in order to facilitate the structural determinations of these compounds, as follows.

3.2.2.1. Characterization of rings: A ring

The C_{20} skeletal-type quassinoids have shown a numerous variety of structural types for the A ring. In **Figure 4.4**, the main variations for the A ring are displayed, which are found in C_{20}-type quassinoids, with their respective chemical displacements.

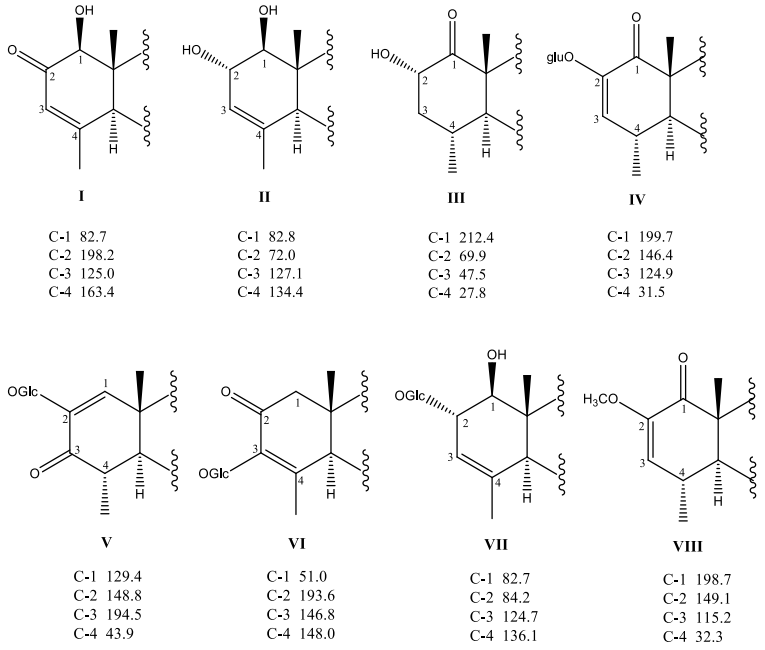


FIG. 4.4 Main structural types of the A ring of C20-type quassinoids.

In this context, the 13*α*(21)-epoxyeurycomanone (**1**), 15-acetyl-13*α*(21)-epoxyeurycomanone (**2**), and 12,15-diacetyl-13*α*(21)-epoxy-eurycomanone (**3**) quassinoids, which are examples with A ring-type 1, have been easily identified through typical chemical displacements of the ^{13}C NMR, as displayed in **Figure 4.2.** This type of ring contains a carbonyl group in C-2 carbon atom and α,β-unsaturated at C-3 and C-4, which also happens with IV, V, VI, and VIII ring types. The A ring-type IV, with a carbonyl group at the C-1 carbon atom, and α,β-unsaturated at the C-2 and C-3 carbon atoms, are present in the quassinoids bruceantinoside C (**90**), yadanzioside N (**91**), and javacinoside B (**92**). At the same time, the ring V, with a carbonyl group at the C-3 carbon atom and α,β-unsaturated at the C-2 and C-1 carbon atoms, appears in yadanzioside M (**120**), yadanzioside O (**121**), and yadanzioside F (**122**) quassinoids.

The quassinoids yadanzioside I (**134**), yadanzioside L (**135**), and bruceoside C (**136**) contain the VI ring type, with the carbonyl group at C-2, and α,β-unsaturated at the carbon atoms C-3 and C-4. Additionally, the quassinoids picrasinoside H (**93**), picrasinol D (**94**) and picrasinoside C (**95**) contain the ring-type VIII, with the carbonyl group at the carbon atom C-1 and the α,β-unsaturated at the carbon atoms C-2 and C-3.

Within this framework, the quassinoids shinjulactone N (**58**), ailantinol C (**59**), and javanicolide D (**73**) are examples which contain the A ring-type II, while the quassinoids indaquasin D (**75**), shinjulactone L (**77**), and ailantinol F (**78**) contain ring A

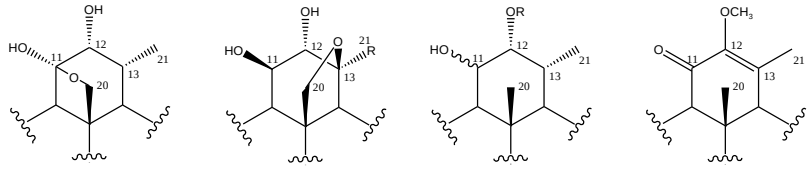
type III. Finally, the VII type ring is present in the quassinoids casteloside A (**61**), casteloside B (**62**), and iandonoside A (**64**).

3.2.2.2. Characterizations of C ring

Among the structural varieties of the C ring in C_{20}-type quassinoids, the eight displayed in **Figure 4.5** are the most frequent ones. The C ring-type I, found in structures 1-*epi*-holacanthone (**58**), 1-*epi*-glaucarubolone (**77**) and 1-*epi*-5-iso-glaucarubolone (**78**), among others, contains the formation of the tetrahydrofuranic ring-type C-20-*O*-C-11, with the formation of the hemiacetal in C-11. This pattern may be characterized by the presence of the signal in δ_C 112 at the spectrum of the NMR ^{13}C, relating to C-11.

Nonetheless, the ones bearing rings type II, such as the quassinoids bruceanol-A (**47**), bruceanol-C (**48**), indaquasin D (**61**), indaquasin E (**62**), bruceoside D (**124**), bruceoside E (**125**), bruceoside F (**126**), bruceanic acid E (**146**), bruceanic acid E methyl ester (**148**), and also the C-20 methyl undergo oxidation to form the tetrahydrofuranic at carbon C-13. When the tetrahydrofuranic ring is type C-20-*O*-C-13, the signal in δ_C 112 is not present in the spectrum. Instead, a signal for quaternary carbon appears at approximately δ_C 80ppm.

On the other hand, the ones which do not present tetrahydrofuronic ring formation are the C ring- type III, represented by quassinoids 6*α*-acetoxy-14,15*β*-dihydroxyklaineanone (**37**), 6*α*-acetoxy-15*β*-hydroxyklaineanone (**38**), 15*β*-acetyl-14-hydroxy-klaineanone (**39**), *α*-hemiacetaljanicin Z (**98**), *β*-hemiacetaljanicin Z (**99**), and javanicin Z (**100**); and type IV with unsaturation in C-12/C-13, found in the compounds 16-*β*-*O*-methylneoquassin (**117**) and 16-*β*-*O*-ethylneoquassin (**118**).



I

C-11 112.2
C-12 78.6
C-13 33.1
C-20 70.7
C-21 15.2

II

C-11 72.7
C-12 75.8
C-13 82.9
C-20 73.3
C-21 172.0

III

C-11 73.6
C-12 77.9
C-13 35.8
C-20 17.7
C-21 13.8

VI

C-11 193.2
C-12 140.3
C-13 148.7
C-20 22.0
C-21 15.2

Figure 4.5 Main structural types of C ring present in C_{20}-type quassinoids.

3.2.2.3. Characterization of B and D rings

The functionalization at the carbon atom C-15, present in quassinoids 6*α*-acetoxy-14,15*β*-dihydroxyklaineanone (**37**), 15-*O*-acetyl-△4,5-glaucarubol (**56**), and ailantinol B (**5**), may be determined by the chemical displacement of the carbonilic carbon C-16. A chemical displacement at approximately δ_C 173 for the carbon C-16 indicates the presence of a free hydroxyl group attached to the carbon C-15. However, when the hydroxyl of the C-15 is esterified, the signal to C-16 is approximately δ_C 167.

3.2.3. BIOLOGICAL ACTIVITIES

3.2.3.1. Antitumor activity

Many quassinoids, such as bruceanols A (**20**), B (**21**), C (**22**), D (**23**), E (**34**), and F (**89**), which were isolated from the *Brucea antidysenterica* Mill [37–39,47], have been tested and have shown potent antitumor activities against an array of tumor cell lines. A good example would be the bruceanol-C (**37**) tested against KB epidermoid carcinoma cells (ED_{50}<0.04μg/mL), A-549 lung carcinoma cells (ED_{50}=0.48μg/mL), colon tumor HCT-8 (ED_{50}=0.40μg/mL), and P-388 murine lymphocytic leukemia (ED_{50}=0.56μg/mL) [38].

At the same time, the bruceanols G (**35**) and H (**36**) showed activity against three tumor cell lines: SK-MEL-5 (melanoma), COLO-205 (colon cancer), and KB cells (nasopharyngeal carcinoma) [47]. These compounds were marginally cytotoxic against the cell line of the melanoma, with values of ED_{50} of 4.08 and 6.37μM, respectively. However, only the bruceanol-G (**40**) was highly active against cell lines COLO-205 and KB, with values of ED_{50} of 0.44 and 0.55μM, respectively [47].

In accordance with Toyota et al. [84], who tested the cytotoxic activity of a quassinoid against murine lymphocytic leukemia P-388 cells, the quassinoid bruceanic acid D (**145**), isolated from the wood of the species *Brucea antidysenterica*, was highly cytotoxic against these cells, with ED_{50}=0.77μg/mL.In addition, other four quassinoids isolated from the species *Simaba cedron* were also cytotoxic against P-388 murine lymphocytic leukemia, through MTT colorimetric assay [6]. These quassinoids are: cedronolactone A (**30**), with IC_{50}=0.0074 μg/mL; simalikalactone D (**32**), with IC_{50}=0.0055 μg/ mL; chaparrinone, with IC_{50}=0.92 μg/mL; and glaucarubolone, with IC_{50}=1.4 μg/mL [6].

As far as the antileukemic activity of quassinoids is concerned, the yadanziosides F (**122**), I (**134**), J (**123**), and L (**135**), isolated from the seeds of *Brucea javanica* Merr, have also shown *in vivo* activity against P-388 murine lymphocytic leukemia [40].

Besides showing cytotoxicity against P-388 murine lymphocytic leukemia (ED_{50}<5.11μg/mL), the quassinoid bruceoside C (**136**), isolated from the fruits of *B. javanica*, has also shown interesting activities against other types of cell lines [82]. For instance, the bruceoside C (**136**) showed values of ED_{50}<0.1μg/mL when tested against human nasopharyngeal epidermoid carcinoma (KB). When tested against human lung carcinoma (A-549), it showed values of ED_{50}<0.44μg/mL; against melanoma (RPMI), the values were ED_{50}<0.1μg/mL, and against CNS carcinoma (TE-671) the values were ED_{50}<0.29μg/mL [82].

The quassinoids brusatol, bruceantinol, bruceine A, and bruceantarin [5] also showed promising antitumoral activities, yielding better results than the positive control used. These four quassinoids, out of the eighteen evaluated with a diosphenol moiety (3-hydroxy-3-en-2-one), showed potent inhibitory activities against two cell lines of breast cancer: first the one with IC_{50} values between 0.063 and 0.182μM, tested against MCF-7 (positive control with IC_{50}=0.880μM) and second the one with 0.081–0.238μM, tested against MDA-MB-231 (positive control with IC_{50}=0.261μM) [5]. According to the authors previously mentioned, the quassinoids which do not contain the portion 3-hydroxy-3-en-2-one, as well as the bruceine A (**154**), showed weak antitumor activity against the tested cell lines.

In connection with the above, the quassinoid isobrucein B, isolated from *Picrolemma sprucei*, was first considered very toxic to *Artemia franciscana*. In a further experiment, when it was tested through MTT assay, it showed a very potent cytotoxic activity against four types of human tumor cells [9]: SF295 (glioblastoma), with values of IC_{50} for isobrucein B of 0.027μg/mL; MDA-MBA345 (melanoma), with values of 0.027μg/mL; HCT-8 (colon) with values of 0.024μg/mL; and HL-60 (leukemia) with values of 0.027μg/mL (Silva et al. [9]).

Similarly, chaparrinone, glaucarubolone, and holacantone, isolated from *Castela texana*, showed potent cytotoxicity, without selectivity, against leukemia cells (IC_{50}=1.80μg/mL for chaparrinone, IC_{50}=0.60μg/mL for glaucarubolone, and IC_{50}=1.00μg/mL for holacantone). Furthermore, they were also potent against KB epidermoid carcinoma cells (IC_{50}=1.20μg/mL for chaparrinone, IC_{50}=1.00μg/mL for glaucarubolone, and IC_{50}=0.50μg/mL for holacantone). When tested against BT-549 breast

cancer cells, these quassinoids showed values of IC_{50}=0.80μg/mL for chaparrinone, 0.40μg/mL for glaucarubolone, and 0.30μg/mL for holacantone. Finally, when tested against SK-OV-3 ovarian carcinoma cells, these quassinoids were equally potent, with values of IC_{50}=0.50μg/mL for chaparrinone, 0.80μg/mL for glaucarubolone, and 0.50μg/mL for holacantone [8].

According to these authors, studies on the structure–activity relationships of quassinoids suggest that an α,β-unsaturated ketone in A ring and an oxymethylene bridge in ring C are usually considered necessary for antitumor activities [8]. On the other hand, other compounds tested by Dou et al. [8], which include the 11-*O*-trans-p-coumaroyl amarolide (**81**), did not show cytotoxicity in their highest concentration tested (10μg/mL).

From this perspective, Wang et al. [33] also connected the increase in cytotoxic activity to the presence of α,β-unsaturated ketone in A ring and also to a methylenoxy bridge between the C-8 and C-11. The evaluated quassinoids which showed this pattern, among them the altissionol A (**12**), were the most potent inhibitors of human hepatoma cells Hep3B and HepG2. According to these authors, the hydrogenation of the A ring, as well as the cleavage of the methylenoxy bridge between C-8 and C-11, could decrease the cytotoxic activities of quassinoids, as the tested quassinoids showing this pattern were almost inactive in those cell lines tested. These authors also suggest that the quassinoids Ailanthone and 6α-tigloyloxychaparrinone may be new potential candidates for the development of anticancer agents from natural products [33].

Miyake et al. [34], similarly associated the presence of α,β-unsaturated ketone in ring A of quassinoids to the cytotoxicity of these compounds. The most potent quassinoids studied by them, such as the eurycomalactone, 14,15*β*-dihydroxyklaineanone and 13,21-dihydroeurycomanone, showed high cytotoxicity related to the highly metastatic human fibrosarcoma HT-1080 cell line (IC_{50}=0.93–1.1μM) [34]. These results were higher than the results from the positive control used, 5-fluorouracil (IC_{50}=5.2μM).

In these conditions, the compounds javanicolide H (**131**), bruceoside A, bruceines B, D, E, H, bruceantinoside A, dehydrobrusatol and javanicolide E (**104**) have also shown cytotoxicity against five human tumor cell lines (HCT-8, HepG2, BGC-823, A549, and SKVO3), whose IC_{50} values ranged from 0.12 to 9.3μM [80].

On the other hand, the quassinoids 13*α*(21)-epoxyeurycomanone (**1**), 15-acetyl-13*α*(21)-epoxyeurycomanone (**2**), 12,15-diacetyl-13*α*(21)-epoxyeurycomanone (**3**), 12-acetyl-13,21-dihydroeurycomanone (**7**), 15*β*-acetyl-14-hydroxyklaineanone (**39**), 6*α*-acetoxy-14,15*β*-dihydroxyklaineanone (**37**), and 6*α*-acetoxy,15β(3)-hydroxyklaineanone

(**38**) showed moderate antileukemic activity against P-388 cell lines (IC_{50}=14.0, 6.6, 7.2, 0.94, 7.8, 12.0, and 15.0μg/mL, respectively) [26].

Likewise, javanicolides B (**19**) [36], C (**152**) and D (**73**) [60], isolated from the seeds of *B. javanica*, showed weak cytotoxicity against P-388 murine leukemia cells (IC_{50}=8, 10, and 18μg/mL, respectively). Javanicosides A, B, C, D (**127**), E (**128**), and F (**129**) showed no activity [36,60] and neither did vilmorinine A (**49**), isolated from the *Ailanthus vilmoriniana* (IC_{50}>100μg/mL) [51].

In this regard, none of the quassinoids isolated by Xu et al. [65] have shown cytotoxicity (IC_{50}>50μM) against MCF-7, A-549, and HepG2 cell lines. The quassinoids tested in the study mentioned are the following: nigakilactone P (**83**), picraqualide F (**112**), nigakilactone Q (**113**), desbenzoylpicrajavanin A, nigakilactone O (**84**), nigakilactone A, nigakilactone B, nigakilactone F, nigakilactone K, nigakilactone I, picrasin A [65].

It has currently been shown that ailanthone (isolated from *Ailanthus altissima*), with a concentration of 0.5μM, restrained acute myeloid leukemia (AML) cells growth, migration, and invasion. The anti-AML functions of ailanthone were through upregulation of miR-449a, and deactivation of Notch and PI3K/AKT signaling pathways [86].

The bruceine D, one of the quassinoids isolated from *B. javanica* fruit, showed anticancer activity against nonsmall cell lung cancer H460 and A549 cells through JNK activation with IC_{50} values of 0.5 and 0.6μmol/L, respectively [87].

Recently, the C_{20} quassinoids isoailanthone, 2-dihydroailanthone, ailanthone and 12-dihydroisoailanthone showed cytotoxic effects on cultures of three tumor cells (human hepatoma cells SMMC-7721, human brain glioma U-251 cells, human gastric adenocarcinoma AGS cells) similarly to positive control (cisplatin) [88]. In addition, compounds brujavanol A and B showed significant *in vitro* cytotoxicity against human oral cavity cancer (KB) cells with IC_{50} values of 1.30 and 2.36μg/mL, respectively [89].

3.2.3.2. Antimalarial activity

Many species of the family Simaroubaceae, which have been reported to express quassinoids, have been used by the "folk" medicine as antimalarials. The species *Simaba cedron*, for instance, has been pointed out as one of the most popular plants used as antimalarial by members of a "quilombola" community in the Amazon, with high incidence of malaria [90].

The *Eurycoma longifolia* Jack is a species from the Simaroubaceae family, which is often used by the people of Southeast Asia for intermittent fever (malaria) and contains several quassinoids with C_{20} skeleton type [91,92]. The isolated quassinoids of this species,

such as the eurycomanone, 13,21-dihydroeurycomanone, 13*α*(21)-epoxyeurycomanone and eurycomalactone have shown a higher level of antimalarial activity against the Gombak A strain of the human malaria parasite *Plasmodium falciparum* (IC_{50}=0.23, 0.29, 0.45, and 1.56μg/mL, respectively) when compared to the chloroquine (IC_{50}=2.50μg/mL). These quassinoids were, respectively, 8.66, 6.83, and 4.58 times more potent than the chloroquine against the Gombak A strain [92].

Against this background, the quassinoid eurycomanol-2-*O*-*β*-D-glycopyranoside (**67**), isolated from the roots of *E. longifolia*, showed moderate activity against the human malaria parasite *P. falciparum*, with IC_{50} of 1.590μg/mL [57]. The activity of the quassinoid eurycomanol with values of IC_{50} (1.544_0.137μg/mL) was comparable to the eurycomanol-2-*O*-*β*-Dglycopyranoside (**84**) [57].

Silva et al. [9] have also reported interesting antimalarial results for the quassinoid isobrucein B, which surmounts positive controls of quinine and chloroquine. This quassinoid showed *in vitro* activity against the human malaria parasite, with a value of IC_{50}=0.001μg/mL, while quinine and chloroquine showed values of IC_{50}=0.06 and 0.082μg/mL, respectively [9].

In this framework, the quassinoid simalikalactone E (**33**), of the *Quassia amara*, was seven times more active (IC_{50}=1.2μM) than the primaquine related compound (IC_{50}=8.9μM) against gametocytes of *P. falciparum*, which is the fundamental stage for the transmission to the mosquitos [46]. The compound *in vivo* inhibited the growth of the *Plasmodium vinckei* petteri (murine malaria) in 50% to 1 and 0.5mg/kg of body weight/day, through oral or intraperitoneal administrations, respectively [46].

Other three quassinoids from the roots of the *E. longifolia* Jack were evaluated in terms of antimalarial activity against nine strains of *P. falciparum*, obtained from patients infected with choroquine-resistant malaria [93]. The results indicated that the eurycomanol, eurycomanol 2-*O*-β-D-glucopiranoside and the 13β,18-dihydroeurycomanol showed antimalarial activity with values of IC_{50} of 1.231–4.899, 0.389–3.498, and 0.504–2.343μM, respectively, compared with 0.323–0.774μM for the chloroquine [93].

The *Simaba guianensis* is another species of the Simaroubaceae family, which is commonly used for fevers. From its bitter bark, the following antimalarial quassinoids were isolated: gutolactone (**28**) (IC_{50}=4.0 ng/mL for the Indochina W-2 strain and IC_{50}=4.1 ng/mL for the Sierra Leone D-6 strain) and simalikalactone D (**144**) (IC_{50}=1.6 ng/mL for Indochina W-2 strain and IC_{50}=1.5 ng/mL for the Sierra Leone D-6 strain). Their antimalarial activity was similar or even better than the antimalarials used as patterns [42].

The isobrucein B also showed antimalarial activity, which exceeded the positive control—its *in vitro* activity against the human malaria parasite (*P. falciparum*) showed a value of IC_{50}=0.001μg/mL, while the quinine and chloroquine showed values of IC_{50}=0.06 and 0.082μg/mL, respectively [9].

In this respect, the quassinoid called simalikalactone E (**33**), isolated from *Q. amara*, showed excellent antiplasmodial activity against three *P. falciparum* strains. The IC_{50} value obtained was in the range of most antimalarials commercially available tested under similar conditions, and varied from 24 to 68nM [46]. Against the gametocytes of *P. falciparum*, the fundamental stage for the transmission to the mosquitoes, compound 154 was seven times more active (IC_{50}=1.2μM) than the primaquine reference compound (IC_{50}=8.9μM) [46]. *In vivo*, the simalikalactone E (**33**) inhibited the growth of murine malaria of the *P. vinckei* petteri in 50% to 1 and 0.5mg/kg of body weight/day, through oral or intraperitoneal administration, respectively [46]. Hence, Cachet et al. [46] conclude that the contribution of the quassinoids as a source of antimalarial molecules needs to be reexamined.

The quassinoids chaparrinone, glaucarubolone, and holacantone, isolated from *C. texana*, have also shown high antimalarial activity (chaparrinone—IC_{50}=0.25μg/mL against *P. falciparum* clone D6 and 0.20μg/mL against the W2; glaucarubolone—0.125μg/mL against the clone D6 and 0.20μg/mL against the clone W2; holacantone—0.010 μg/mL against the clone D6 and 0.012μg/mL against the clone W2) [8].

In this sense, orinocinolide (**70**) and simalikalactone D (**32**), isolated from the bark of the *Simaba orinocensis* roots, have been equally potent against the clones of *P. falciparum* D6 (IC_{50}=3.27 and 8.53ng/mL, respectively) and W2 (IC_{50}=3.0 and 3.67ng/mL, respectively) [7]. However, the quassinoid 11-*O*-trans-p-coumaroyl (**81**), isolated from *C. texana*, showed moderate antimalarial activity without potent cytotoxicity [8]. The bruceine D has recently shown excellent antiplasmodial activity against the *P. falciparum* strains (IC_{50}=0.58μg/mL) [89].

3.2.3.3. Insecticidal activity

Another important characteristic of quassinoids is the insecticidal activity. Fang et al. [14] tested the quassinoids perforalactone A and B, isolated from the plant *Harrisonia perforata*, which have shown significant insecticidal activity against the agricultural pest *Aphis medicaginis* Koch, with values of LC_{50} of 86.4 and 7.23μM, respectively. Yet, these quassinoids have not shown activity against the chewing insects *Spodoptera exigua* (Hubner) and *Mythimna separata* Walker.

In this context, several studies have also shown the potential of quassinoids as pest antifeedant agents [11]. Polonsky et al. [12], when testing quassinoids against the aphid *Myzus persicae*, confirmed the antifeedant activity of quassinoids: isobrucein A and B, bruceine B and C, glaucarubinone, and quassin. Isobrucein A was efficient in a concentration of 0.01%, while the other quassinoids reduced the feeding rates in concentrations up to 0.05%.

In addition, Kubo et al. [13] verified the growth inhibitory activity of three quassinoids isolated from the bark of *Castela tortuosa* in lepdopterous insects. The chaparrinone showed a stronger inhibitory activity against the larvae of the insect *Heliothis virescens* (the tobacco larva); the chaparramarine (**70**) showed moderate inhibitory activity while the chaparrine showed a weaker activity.

Similarly, some species of the Simaroubaceae family, known by the bioproduction of quassinoids, have also shown larvicidal activity against the larvae of the *Aedes aegypti* mosquito. As an example, Pohlit et al. [94], pointed out the larvicidal activity of the *P. sprucei*, *Simaba polyphylla* and *Simarouba amara*. In order to corroborate the results of the previously mentioned study regarding the larvicidal activity of the species *P. sprucei*, Silva et al. [9], have tested two isolated quassinoids C_{20} of this species against the third larval stage of the *A. aegypti*. The quassinoids isobrucein B and neosergeolide showed values of IC_{50}=3.2 and 4.4μg/mL, respectively [9].

3.2.3.4. Other biological activities

It has come to knowledge that other studies have reported different biological activities of the quassinoids in addition to the most commonly observed antitumoral, antimalarial, and insecticidal activities, such as the hypoglycemic effect [95], spermatogenesis increase [96], antiangiogenic [97], anticomplement [20], antiviral [15,16], herbicidal [98], antileishmanial [7], anti-inflammatory [18], and amoebicidal [19].

In that respect, according to Noorshahida et al. [95], seeds of *B. javanica* (L.) Merr (Simaroubaceae) are recommended by traditional practitioners for the treatment of *diabetes mellitus*. So, during investigation, the authors concluded that bruceines D and E, isolated from this specie, reduced blood glucose concentration, which is comparable to glibenclamide, and they might act as an insulin secretagogue [95].

E. longifolia Jack (Simaroubaceae) is also a medicinal plant used in folk medicine. It is popularly considered as a traditional remedy to improve the male libido, sexual prowess, and fertility [96]. Eurycomanone, the highest concentrated quassinoid in the root extract of *E. longifolia*, enhanced testosterone steroidogenesis at the Leydig cells

by inhibiting aromatase conversion of testosterone to estrogen. At a high concentration, it may also involve phosphodiesterase inhibition, according to Low et al. [96]. The authors of the study still state that the quassinoid Eurycomanone may be worthily used for further development as a phytomedicine to treat testosterone-deficient idiopathic male infertility and sterility [96].

Recently, aqueous extract of *E. longifolia* roots, which is rich in quassinoids, caused significant reductions in mounting, intromission, and ejaculation latencies and increased penile erection index in male rats. Furthermore, it increased total body weight and relative weights of seminal vesicles and prostate. Lastly, it significantly increased the total and free serum testosterone and brain cortical and hippocampal dopamine content [99].

Moreover, *E. longifolia* is used as a traditional medicine for the treatment of a variety of angiogenesis-related diseases including cancer, obesity, rheumatoid arthritis, and psoriasis [100]. In this context, Al-Salahi et al. [97], demonstrated that the antiangiogenic activity of TAF273 (partially purified quassinoid-rich fraction of *E. longifolia* root extract) may happen due to its inhibitory effect on endothelial cell proliferation, differentiation, and migration, which could be attributed to the high content of quassinoids in *E. longifolia*. HPLC characterization showed that TAF273 is enriched with eurycomanone, 13α(21)-epoxyeurycomanone (1) and eurycomanol [97].

Another biological activity of quassinoids is the anticomplement activity, according to Zhan et al. [20]. 20-Hydroxyyadanzigan (**71**), yadanzigan, bruceine F, bruceine E, yadanziolide A (**24**), and bruceine D showed potent anticomplement activity with values of CH_{50} and AP_{50} of 0.032–0.075 and 0.061–0.181mg/mL, respectively.

From another point of view, Feo et al. [98] suggested a possible use of the quassinoids ailanthinone and chaparrine, isolated from the *A. altissima* Swingle, as natural herbicides. It is due to the fact that the quassinoids showed good allopathic activity against seeds of radish (*Raphanus sativus* L. cv. "Saxa"). 12-*epi*-11-dehydroklaineanone (**40**), isolated from the leaves of *E. longifolia*, have also shown moderate activity as a plant growth inhibitor against cucumber seedlings [10].

Besides that, some quassinoids have also shown potent antiviral activity. For instance, against the antitobacco mosaic virus (TMV), the quassinoids brusatol, brucein B, bruceoside B, yadanzioside I (**134**), yadanzioside L (**135**), bruceine D, yadanziolide A (**24**), and aglycone of yadanziolide D were more efficient (value of IC_{50} in the range of 3.42–5.66μM) than the ningnanmycin positive control (IC_{50}=117.3μM) [17].

Another good example of important biological activity is the simalikalactone D (**32**), which is also active against the oncogenic virus of *Rous Sarcoma* [15]; and shinjulactone C appears as an anti-HIV (EC_{50}= 10.6mM) [16].

The *B. javanica* has also shown potential lipolytic activity, as brucein A (**1**), brucein B (**2**), brucein C (**3**), 30-hydroxybrucein A (**37**), brusatol (**38**), and bruceantinol (**39**) are the main compounds that contribute to the activity at concentrations lower than 160nM [101].

These quassinoids were evaluated for their antitumor activity, as an Epstein barr virus early antigen (EBV-EA). Yadanzioside M (**120**), Bruceantinoside A, Yadanzioside G, Yadanzioside A, and Bruceoside A, all isolated from *B. javanica* showed intermediate activity [102].

In addition to the biological activities already described, there are also studies reporting the activity of the quassinoids against the protozoa *Leishmania donovani* (simalikalactone D—32, com IC_{50}=0.035μg/mL) [7], anti-inflammatory activity (brusatol) [18], and amoebicidal activity (bruceantine) [19].

3.2.4. CONCLUDING REMARKS

In this study, biological activities and data of ^{13}C NMR of C_{20} skeleton-type quassinoids have been discussed, in order to provide information which may be useful regarding possible biological applications of these compounds, as well as to distinguish different types of skeletons in their structural elucidations.

In terms of biological activities of C_{20} skeleton-type quassinoids, it was concluded that many of them appear to be promising antitumor and antimalarial agents. In addition to that, there are studies that report a number of other biological activities of these compounds, which may be interesting, as herbicidal, antifeedant, pests growth inhibition, insecticidal, larvicidal, antileishmanial, antiviral, anti-inflammatory, amoebicidal, and anticomplement. It is emphasized that the amount of publications about quassinoids as antitumoral and antimalarial agents is higher, compared to other biological activities.

During this study, it has been made an inventory of all quassinoids isolated from the year 1985 up to the present, and 154 compounds were found. Regarding the diversity found for the rings of the 154 compounds, it was observed that eight skeletons were more frequent for rings type A and other eight skeletons for rings type C. It was observed that the α,β-unsaturated hydroxyl frequently occurs at type A ring while at type C ring, it is common to find the formation of tetrahydrofuranic ring-type C-20-*O*-C-11 or C-20-*O*-C-13, with hemiacetal formation at C-11 or C-13, respectively. Concerning rings B and D,

the oxidation of the carbon atom C-15 is frequently seen, which is usually found without substituents or oxidated by a hydroxyl group, or the esterification of this hydroxyl group.

3.2.5. AKNOWLEDGMENTS

The authors are grateful to Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ) for granting a research fellowship, to Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Coordenação de Aperfeiçoamento de Pessoal de Ensino Superior (CAPES) for research fellowships.

3.2.6. REFERENCES

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3.3. Trabalho 3: Antiplasmodial activity and cytotoxicity of roots *Homalolepis suffruticosa* methanol extract and constituents isolated [1]**

Atividade antiplasmodial e citotoxicidade do extrato metanólico de raízes de Homalolepis suffruticosa e seus constituintes isolados [1]**

[1] ****Este trabalho foi submetido ao periódico *Journal of Ethnopharmacology*.**

Abstract

Ethnopharmacological relevance

Malaria is one dangerous parasitic disease in endemic countries all over the world. The ethnopharmacological approach to investigate plants traditionally used to treat malaria has been very fruitfull for guiding the discovery of new antimalarial hits. Different species of Simaroubaceae family have already been extensively investigated. However *Homalolepis suffruticosa* (syn. *Simaba suffruticosa* and *Quassia suffruticosa*), closely related to other antimalarial plants of the Simaroubaceae family, has not yet been investigated for its phytochemical composition and antimalarial potential.

Aim of the study

To assess the antiplasmodial and cytotoxicity effects of *Homalolepis suffruticosa* roots methanol extract and of the isolated compounds.

MATERIALS AND METHODS

H. suffruticosa roots methanol extract and of six isolate compounds were evaluated against chloroquine-resistant *Plasmodium falciparum* W2 strain by *Pf*LDH method and cytotoxicity in HepG2 cells by the MTT assay.

RESULTS

H. suffruticosa methanol extract, which showed high *in vitro* antiplasmodial activity (IC_{50} 1.88 ± 0.56 µg/ml) and moderate cytotoxicity (CC_{50} 41.93 ± 2.30 µg/ml), resulting in good selectivity index (SI = 22.30). The six compounds isolated and the mixtures of metabolites disclosed high to moderate antiplasmodial activity (IC_{50}

0.0548 ± 0.0083 µg/ml to 26.65 ± 2.40 µg/ml) and cytotoxicity was in the range of CC_{50} 0.62 ± 0.33 µg/ml to 56.43 ± 2.54 µg/ml.

CONCLUSIONS

Taken together, the antiplasmodial activity and cytotoxicity of the roots methanol extract of *H. suffruticosa* and its isolated compounds support the ethnopharmacological history of this Simaroubaceae species as antimalarials and is here firstly reported. Among the metabolites isolated, 5-metoxycantin-6-one, an indole alkaloid, was shown to be the most potent compounds.

Keywords: Malaria; Ethnopharmacoly; Simaroubaceae; Phytochemical analyses; Dereplication; UPLC-DAD-ESI-MS/MS.

3.3.1. INTRODUCTION

Malaria is still a major global health problem, affecting a large population of the world, in endemic tropical and subtropical regions. The WHO (World Health Organization), has estimated 229 million cases of malaria and 409 000 deaths occurred worldwide, in 2019 (WHO, 2020). Most of the malaria cases and deaths (93% and 94% respectively) were in the African Region. For thousands of years, traditional herbal remedies have been used to treat malaria and plant remedies afforded the most important antimalarial drugs, quinine, from the bark of *Cinchona* trees (Rubiaceae), native to the South American Andes, and artemisinin, the active compound from the Chinese *Artemisia annua* L.. Quinine, an aminoquinoline alkaloid, was isolated in 1820 and became a template for the synthesis of chloroquine, the most widely used antimalarial drug, as well as for

other synthetic quinolines, like chloroquine, amodiaquine, mefloquine and primaquine (Tse et al., 2019). However, chloroquine became of limited use due to the worldwide *P. falciparum* resistance that started at the 1960s (WHO, 2020). The most recently antimalarial approved by the FDA is tafenoquine, a new synthetic aminoquinoline structurally related to quinine that was firstly isolated 200 years ago (Lu and Derbyshire, 2020).

Artemisinin was isolated in China from *Artemisia annua* L., in 1972, by Chinese researchers under the leadership of Tu Youyou who was awarded with the 2015 Nobel Prize in Medicine for the discovery of this antimalarial sesquiterpene lactone. Artemisinin and its derivatives artemether, artesunate and dihydroartemisinin, have been initially used as a single drug in itself and are currently used, in nearly all endemic countries, in the form of artemisinin-based combination therapy (ACT) (Ashley et al., 2005). Besides quinine and artemisinins, another drug introduced in malaria chemotherapy is atovaquone which was developed after lapachol, a naphthoquinone from *Handroanthus impetiginosus* (Mart. ex DC.) Mattos (syn. *Tabebuia impetiginosa* (Mart. ex DC.) Standl., *T. avellanedae* Lorentz ex Griseb.) popularly known in Brazil as pau-d´arco and ipê-roxo, with an international nomination of red lapacho (Castellanos et al., 2009; Baggish and Hill, 2002). However, the resistance of *P. falciparum* and *P. vivax* to available antimalarial drugs, including artemisinins and ACTs, points to the need of intensive research for new drugs, particularly those with new mechanisms of action (Tse et al., 2019). A successful approach has been by exploring the biodiversity potential, particularly on the basis of ethnopharmacologial data on plants of medicinal applications. This strategy led to the discovery of currently clinical antimalarials. Indeed, the isolation of quinine from the barks of *Cinchona* plants and artemisinin from the leaves of *Artemisia annua* represent the best

examples of drug discovery from ethnopharmacological studies (Cragg and Newman, 2013).

Homalolepis Turcz. is a neotropical genus recently reestablished as a segregate from *Simaba* Aubl. (Simaroubaceae), based on molecular and morphological grounds (Devecchi et al., 2018). The *Homalolepis* genus comprises 28 species, mainly distributed in tropical South America, with one species extending to Central America. Most species occur within the Cerrado and Atlantic forest biomes, in Brazil (Devechi et al., 2018; Barbosa et al., 2011). The Simaroubaceae family is known as a source of quassinoids, a class of bitter tasting natural products derived from triterpenes degradation (Gray et al., 1988), disclosing relatively complex and highly oxygenate structures (Jolad et al., 1981). Since the 1970s, this group of natural products have attracted attention because of their two major pharmacological activities, mainly the anticancer and antimalarial potential (Houël et al. in 2013). Other classes of natural products frequently occurring in the Simaroubaceae family are triterpenes, β-carboline and canthinone alkaloids (Vieira, 1995; Barbosa et al., 2011; Alves et al., 2014).

Homalolepis cedron (Engl.) Devecchi & Pirani (Simaroubaceae) is the presently accepted name for *Simaba cedron* Planchon. Under the designation of *S. cedron* a wide distribution is found in tropical America, including Brazil, Asia and West Africa and is a known medicinal plant used for various purposes including treatment of malaria and fevers. For members of a “quilombola” community in the Brazilian Amazon region it is popularly known as *pau-para-tudo* (“stick for everything”). Its aqueous bark extract disclosed a good *in vitro* activity (IC_{50} 1.6 µg/mL) against *P. falciparum* (W2 clone) by the [^{3}H]-hypoxanthine incorporation assay, but the active constituents were not isolated (Oliveira et al., 2015). *S. cedron* is still named *Quinquina de Cayenne*, being one of the numerous drugs

called 'falsa quina' (fake quine) used against malaria in South and Central America (Moretti et al., 1994). Other Simaroubaceae species of bitter taste, like *Quassia amara* L., are also used as traditional medicine against fever (Bertani et al., 2006). Therefore, not only the *Simaba* and *Quassia* genera, but also different plant species of various genus from the Simaroubaceae family are ethnopharmacologically known as antimalarials (Milliken, 1997; François et al., 1998; Muhammad et al., 2004; Almeida et al., 2007; Alves et al., 2014).

In the course of our ethnopharmacological directed research on antimalarial natural products, we performed an evaluation of the *in vitro* antiplasmodial activity and cytotoxicity of *Homalolepis suffruticosa* (Engl.) Devecchi & Pirani (syn. *Simaba suffruticosa* (Engl.) and *Quassia suffruticosa* (Engl.) Noot.) (Flora do Brasil, 2020) (Simaroubaceae). The *in vitro* antiplasmodial evaluation by the quantification of the parasite lactate dehydrogenation (*Pf*LDH) and of the cytotoxicity to HepG2 cells (MTT) are reported here. As far as we know, this is first report on phytochemical composition, antiplasmodial and cytotoxic effects relative to *H. suffruticosa* that, closely related to other antimalarial Simaroubaceae species used in traditional and folk medicine.

3.3.2. METHODS AND MATERIALS

3.3.2.2. Phytochemical analyses

Plant material, preparation of roots methanol extract, chromatographic fractionation and isolation were previously performed by Boeno et al. (2020). The phytochemistry of the roots methanol extract of *H. suffruticosa* collected in the municipality of Araguari, state of Minas Gerais, Brazil, afforded a new triterpene, named milemaronol, along with others known metabolites, scopoletin, 5-methoxycanthin-6-one, eurylene, hispidol A, hispidol B, *α*-dihydronylocytine, *β*-

dihydronylocytine, and *meso*-teurilene. All of these compounds were characterized based on their spectral data, mainly 1D (^{1}H, ^{13}C-APT) and 2D (^{1}H-^{1}H-COSY, NOESY, HSQC, HMBC) NMR and their mass spectra (HR-ESI-MS) (Boeno et al., 2020).

3.3.2.2. In vitro bioassays

3.3.2.2.1. Antiplasmodial activity

Plasmodium falciparum W2 clone, which is chloroquine-resistant and mefloquine-sensitive, was kept in a continuous culture at 37 ºC in human erythrocytes, as described (Trager & Jensen, 1976). Evaluation of the *in vitro* antiplasmodial activity of the methanol extract and isolated compounds were performed by the quantification of the parasitic enzyme lactate dehydrogenase (*Pf*LDH) (Makler et al., 1998). Initially, the samples were screened for the percentage of parasite growth inhibition (% GI) at the fixed concentrations of 25 and 50 µg/ml, in two experiments that were independently performed in triplicates. Posteriorly, different concentrations of extract and more the bioactive isolated compounds were assayed for determination of the 50% inhibitory concentration of parasites (IC_{50}), as it is routinely performed in our laboratory at Faculdade de Farmácia, UFMG. Chloroquine diphosphate salt (≥ 98.5 % purity, Sigma-Aldrich®) was the standard antimalarial drug (Borgati et al., 2017; Gontijo et al., 2019).

3.3.2.2.2. Cytotoxicity assay

HepG2 cells (human hepatoblastoma cells) were obtained from Cell Bank of Rio de Janeiro (RJ, Brazil). The cells were plated and incubated at 37 ºC and 5% CO_2 for 24 h. When the cells reached 75 – 80% confluency, they were treated for 24 h with different concentrations of the extract and isolated compounds. After incubation, the cytotoxicity of the substances was assessed by the colorimetric

MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay with modifications (Mosman, 1983; Nascimento, et al*.,* 2020). Each experiment was performed in triplicate and all experiments included a solvent control (dimethyl sulfoxide). Data shown represent means ± standard deviation (SD) values.

3.3.2.3. Statistical analyses

All data were expressed as means ± standard deviations of triplicate measurements. Statistical significance of the antiplasmodial activity and of the cytotoxicity assays were determined by one-way analysis of variance (Tukey post hoc testing for parametric analysis of variance), using the software Sigma Plot 12.5 with $\alpha = 0.05$ (Systat, 2013).

3.3.2. RESULTS AND DISCUSSION

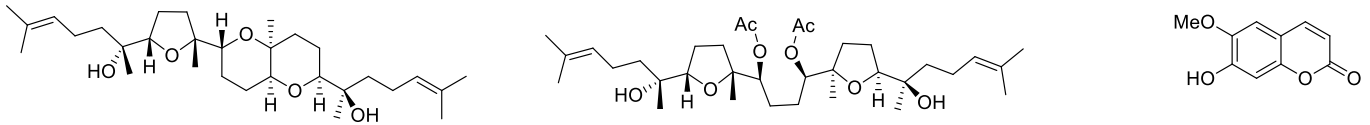
The roots methanol extract of *H. suffruticosa,* six of the compounds isolated and the two mixtures were evaluated for *in vitro* antiplasmodial activity and cytotoxicity (Table 1) here discriminated: milemaronol, scopoletin, 5-methoxycanthin-6-one, eurylene, hispidol A and *meso*-teurilene as well the mixtures of hispidol A plus hispidol B, *α*-dihydronylocitine plus *β*-dihydronylocitine (Figure 1) (Boeno et al., 2020). Thus, samples disclosing percentage of parasite growth inhibition (% GI) > 50% in the concentration of 50 µg/ml were assayed for determination of the IC_{50} (Table 1). All the samples, except the terpene eurylene and the coumarin scopoletin, caused high inhibition of the parasite growth at the concentration of 50 µg/ml with GI > 50%, in both the experiments. In the concentration of 25 µg/ml, six out of the nine samples assayed were active (GI > 50%) (Table 1). The GI for milemaronol, 5-methoxycanthin-6-one and *meso*-teurilene, reached, in some experiments to values > 90%.

So, evaluation of the *in vitro* IC_{50} antiplasmodial activity was determined for the *H. suffruticosa* extract and six active samples. In the primary screening (Table 1) the GI > 50% and then the IC_{50} were determined for *P. falciparum* (W2). IC_{50} values were in the range of 26.65 ± 2.40 to 0.0548 ± 0.0083 µg/ml (Table 1). The methanol extract showed a good antiplasmodial activity with an IC_{50} of 1.88 ± 0.56 µg/ml. The mixtures of hispidol A + hispidol B, and *α*-dihydronylocitine + *β*-dihydronylocitine were shown to be moderately active with IC_{50} values of 24.58 ± 1.79 and 26.65 ± 2.40 µg/ml, respectively. The squalene-type triterpenes milemaronol and *meso*-teurilene disclosed good activity (IC_{50} 7.89 ± 1.95 and 10.80 ± 1.49 µg/ml, respectively) and the indole alkaloid 5-methoxycanthin-6-one with IC_{50} 0.0548 ± 0.0083 µg/ml was about 2 times more potent than chloroquine control (IC_{50} 0.125 ± 0.03 µg/ml), however, it is 184 times more cytotoxic than the control (Table 1). The IC_{50} titers determined for eurylene and *meso*-teurilene were higher (lower activity) than the expected when the respective % GI > 80% are considered (Table 1). However, a good correlation was observed for the roots methanol extract of *H. suffruticosa* with GI > 80% and IC_{50} 1.88 ± 0.56 µg/ml.

Table 1. Percentage of growth inhibition (% GI) and fifty percent inhibitory concentration (IC_{50}) of *Plasmodium falciparum* (W2), fifty percent cytotoxicity concentration (CC_{50}) of HepG2 cells, and selectivity index (SI) of different samples from roots of *Homalolepis suffruticosa*.

Samples	Antiplasmodial Activity			Cytotoxicity	SI
	% Growth Inhibition		IC_{50}(µg/ml)	CC_{50} (µg/ml)	
	[50 µg/ml]	[25 µg/ml]			
Methanol extract	92.5 ± 7.7^{AB}	88.0 ± 9.9^{AB}	1.88 ± 0.56^{B}	41.93 ± 2.30^{D}	22.30
Milemaronol	84.5 ± 0.7^{B}	80.5 ± 6.3^{B}	10.80 ± 1.49^{C}	51.03 ± 0.61^{E}	4.75
Scopoletin	32.5 ± 3.5^{C}	22.5 ± 3.5^{D}	-	-	-
5-Methoxycanthin-6-one	91.0 ± 5.6^{AB}	87.5 ± 6.3^{AB}	0.0548 ± 0.008^{A}	0.62 ± 0.33^{A}	11.31
Eurylene	10.5 ± 2.1^{D}	8.5 ± 0.7^{E}	-	-	-
Hispidol A	80.0 ± 5.6^{B}	50.0 ± 4.2^{C}	-	-	-
Hispidol A Hispidol B	95.5 ± 3.5^{A}	49.0 ± 7.0^{C}	24.58 ± 1.79^{D}	26.83 ± 1.40^{C}	1.09
α-Dihydronylocitine β-dihydronylocitine	79.5 ± 0.7^{B}	43.5 ± 3.5^{C}	26.65 ± 2.40^{D}	14.87 ± 1.38^{B}	0.56
meso-Teurilene	89.0 ± 5.6^{B}	76.5 ± 4.9^{B}	7.89 ± 1.95^{B}	56.43 ± 2.54^{E}	7.15
*Chloroquine diphosphate salt	97.5 ± 0.7^{A}	94.5 ± 0.7^{A}	0.125 ± 0.03^{A}	114.00 ± 4.20^{F}	912.00

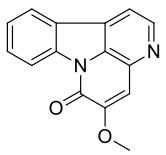
Note: % Growth Inhibition and IC_{50} were determined by the *Pf*LDH method; CC_{50} were determined by the MTT assay. Means (± SD, n = 3) followed by different letters were significantly different within columns (Tukey test's, α = 0.05). Statistical analyses of parasitemia reduction at 50.0 and 25.0 µg/mL were performed separately for each concentration. *Positive control.



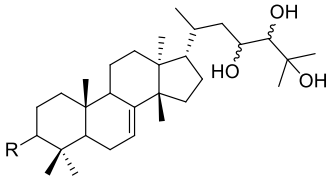
Milemaronol

Eurylene

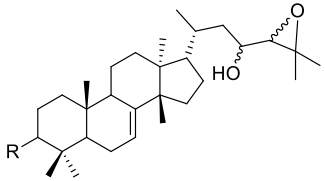
Scopoletin



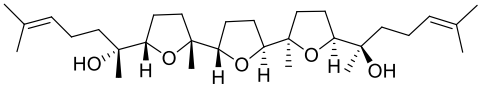
5-Methoxycanthin-6-one



Hispidol A (R = α-OH)
Hispidol B (R = β-OH)



Nilocitine (R = O)
α-Dihydronylocitine (R = α-OH)
β-Dihydronylocitine (R = β-OH)



meso-Teurilene

Figure 1. Chemical structures of isolated compounds from roots methanol extract of *Homalolepis suffruticosa* evaluated to antiplasmodial activity and cytotoxic effect

It is worth highlighting the high antiplasmodial activity in chloroquine-resistant *P. falciparum* W2 strain, followed by moderate cytotoxicity in HepG2 cells observed for the *H. suffruticosa* extract (Table 1). This antiplasmodial effect is a support to the use of *H. suffruticosa* and species taxonomically closed *Simaba* and *Quassia* genera as traditionally used as antimalarials. Interestingly, as observed for *Quinquina de Cayenne,* popular name of *Simaba cedron* and *Quassia amara*, *H. suffruticosa* (syn. *Simaba suffruticosa* and *Quassia suffruticosa*) besides *Simaba ferruginea* , are known as *calunga* (Gazoni et al., 2018; Flora do Brasil, 2020; GBIF, 2020), and all of them have similar ethnopharmacological use of the Simaroubaceae antimalarial species (Milliken, 1997). Indeed, despite the multiplicity of species, their geographic distribution range, and therefore the extreme cultural diversity that underlies their use, there is a marked homogeneity in the uses made of Simaroubaceae species (Houël et al., 2013).

Concerning the cytotoxicity effect, the CC_{50} titers to HepG2 cells for the *H. suffruticosa* extract and the six isolated bioactive compounds as observed in the primary screening (Table 1) showed that three of them (methanol extract, milemaronol and *meso*-teurilene) were moderately cytotoxic (CC_{50} 41.93 ± 2.30, 51.03 ± 0.61 and 56.43 ± 2.54 µg/ml, respectively), the two mixtures hispidol A plus hispidol B and α-dihydronylocitine plus β-dihydronylocitine were more cytotoxic (CC_{50} 26.83 ± 1.40 and 14.87 ± 1.38 µg/ml, respectively) and 5-methoxycanthin-6-one showed the highest cytotoxicity (C_{50} 0.62 ± 0.33 µg/ml). As a consequence, the selectivity indexes were favorable (SI > 10) for the methanol extract (SI = 22.30) and 5-methoxycanthin-6-one (SI = 11.31) that, although being the most cytotoxic of the active samples, disclosed a SI > 10 because of its high potent antiplasmodial effect (IC_{50} 0.0548 ± 0.0083 µg/ml) against the chloroquine resistant *P. falciparum* (W2 clone). *Meso*-teurilene and milemaronol showed

reasonable selectivities to parasites (SI 7.15 and 4.75, respectively) while scopoletin and eurylene were inactives (GI < 50%) and, therefore, their IC_{50} and CC_{50} were not determined (Table 1). The squalene type triterpene polyethers are generally marine metabolites with significant structural and pharmacological diversity. Approximately 40 polyether triterpenes from red algae of the genus *Laurencia* were reported until 2014 (Ji and Wang, 2014). Recently, three rare squalene type polyethers were isolated from *H. suffruticosa* and were full chemically characterized (Boeno et al., 2020).

Once again, the good antiplasmodial activity disclosed for the *H. suffruticosa* roots methanol extract is demonstrated by a favorable SI > 20 that might be related to the presence of highly active compounds as quassinoids and canthin-6-ones. In this sense, the cytotoxic effects of quassinoids and canthin-6-one alkaloids were previously highlighted (Vieira and Braz-Filho, 2006; Jiang et al, 2008; Houël et al., 2013; Dejos et al., 2014; Gazoni et al., 2018). Given the high cytotoxicity observed for the isolated 5-methoxycanthin-6-one, and taking into account the moderate cytotoxic effect of the *H. suffruticosa* extract, that was approximately 67 times less than the isolated 5-methoxycanthin-6-one, the phytochemical constitution of this extract, either in the structural diversity and/or content of the compounds detected, points out as the next stage for the standardization and validation of this extract to further investigation on the development of a phytomedicine. Indeed, although highly antiplasmodial compounds were isolated, the limited use of Simaroubaceae species may be direct related to the known cytotoxicity of the quassinoids, impairs any commercial development of antimalarial treatment based on the use of those molecules, especially for C_{20} quassinoids (Bertani et al., 2012; Oliveira et al., 2015). The moderate cytotoxicity of the *H. suffruticosa* methanol extract in HepG2 cells, which

has a prominent expression of several key enzymes in the xenobiotic metabolism of phase I and II clinical assays (Stampar et al., 2020), that are important in hepatic metabolization of drugs, together with significant antiplasmodial activity in chloroquine-resistant *P. falciparum* W2 strain, encourages the continuation on antimalarial studies with *H. suffruticosa*.

3.3.4. CONCLUSIONS

The antiplasmodial effect for the roots methanol extract of *H. suffruticosa* corroborates with previously reports for different Simaroubaceae species pointed out as antimalarial agents of traditional medicinal plants. The LC-DAD-MS dereplication as well as the antiplasmodial and cytotoxicity evaluations for *H. suffruticosa*, are reported here for the first time. The lower activity of the squalene-like triterpenes *meso*-teurilene and milemaronol, whose antiplasmodial activity is here also firstly reported, might be highlighted as new antimalarial hits. The isolated active metabolites support the quality control analyses of the plant drug in the case of a phytomedicine development. Thus, the phytochemical composition and ethnopharmacological history of *Homalolepis* and *Simaba* species, which are used in the Brazilian Amazonia for treatment of malaria and fevers, combined with moderate cytotoxicity of the roots methanol extract, is a motivation for further investigation of *H. suffruticosa* aiming the sustainable development of phytomedicines that would benefit the local people.

3.3.5. ACKNOWLEDGEMENTS

To Conselho Nacional de Desenvolvimento Científico e Tecnológico – CNPq, for a senior research fellowship to ABO; to Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – CAPES for Postdoctoral fellowship to DCG; to

Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro – FAPERJ, and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - CAPES (Finance Code 001).

3.3.6. CONFLICT OF INTEREST

The authors declare to have no conflict of interest.

3.3.7. REFERENCES

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4. RESUMO E CONCLUSÕES

Com a compilação de dados de espectros de ^{13}C RMN de todos os quassinoides do tipo C_{20} isolados após 1985 apresentados neste trabalho, foi possível contribuir com informações que poderão ser úteis no ponto de vista quimiotaxonômico. Também pôde ser observado, através da apresentação de resultados de diversos estudos, que os quassinoides C_{20} parecem ser agentes antitumorais e antimaláricos promissores, além de várias outras atividades biológicas relatadas.

Neste trabalho foram avaliados os efeitos antiplasmódicos e citotóxicos do extrato metanólico de raízes e compostos isolados de *Homalolepis suffruticosa* (família Simaroubaceae - família conhecida pela bioprodução de quassinoides). Em conjunto, a atividade antiplasmódica e a citotoxicidade destes sustentam a história etnofarmacológica dessa espécie de Simaroubaceae como antimaláricos e foi aqui relatada pela primeira vez.

Também foi descrito aqui os dados espectrais de um novo triterpeno (Milemaronol), além de outros dez metabólitos isolados da espécie *H. suffruticosa* (família Simaroubaceae). O novo metabólito, intitulado Milemaronol, apresentou a melhor relação atividade *versus* citotoxicidade contra as cepas de *Mycobacterium tuberculosis* H37Rv e M299 dentre os onze compostos avaliados, isolados da mesma espécie vegetal.

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