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Polyprenylated benzophenone derivatives from *Clusia burle-marxii* and their chemotaxonomic significance

Caline G. Ferraz [a,b,c,**], Maria do C.C. Silva [b], David A.S.G. Pereira [c], Brenno V.V. Caldas [a], Rafael Mattos [a], Vivian V.G. Oliveira [a], Eberson M.J. Andrade [a], Ana C.F. Soares [d], Franceli da Silva [d], Frederico G. Cruz [a], Paulo R. Ribeiro [b,*]

[a] Centro de Ciências Exatas e Tecnológicas – CETEC, Universidade Federal do Recôncavo da Bahia, Rua Rui Barbosa, no710, 44.380-000, Cruz das Almas, Brazil
[b] Metabolomics Research Group, Departamento de Química Orgânica, Instituto de Química, Universidade Federal da Bahia, Rua Barão de Jeremoabo s/n, 40170-115, Salvador, Brazil
[c] Grupo de Estudos de Substâncias Naturais Orgânicas, Instituto de Química, Universidade Federal da Bahia, Rua Barão de Jeremoabo s/n, 40170-115, Salvador, Brazil
[d] Universidade Federal do Recôncavo da Bahia, R. Rui Barbosa, 710, Cruz das Almas, BA, Brazil

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ABSTRACT

Six polyprenylated benzophenone derivatives (1–6) with the central bicyclo[3.3.1]nonane-2,4,9-trione core were isolated from *Clusia burle-marxii* trunks. Despite their highly conserved structural characteristics, this is the very first time that these polyprenylated benzophenone derivatives are isolated from a single plant species, highlighting the biochemical plasticity of *Clusia burle-marxii* to produce such unique class of bioactive compounds. Compounds 1, 2, and 6 are reported for the first time in *Clusia burle-marxii*, whereas compounds 3, 4 and 5 are reported for the first time in the Clusiaceae family. Their structures were established by careful analysis of spectroscopic data, including ^{1}H NMR, ^{13}C NMR, and 2D-NMR (COSY, NOESY, HSQC, HMBC). These polyprenylated benzophenone derivatives have the potential to be used as chemosystematics biomarkers for the family Clusiaceae. Their putative biosynthesis pathway is also discussed.

1. Subject and source

Clusia is one of the most representative genera of the Clusiaceae family and it comprises about 300–400 species of neotropical distribution, especially in Central and South America. *Clusia* species are important sources of type-A polyisoprenylated benzophenones skeletons (PPBS) (Anholeti et al., 2015), which present very complex and diverse chemical structures. Nevertheless, the most representative benzophenones in Clusia species are the bicyclo[3.3.1]nonane-2,4,9-trione derivatives (type-A PPBS) and simple 2,4,6-trihydroxybenzophenone derivatives (BBS) (Anholeti et al., 2015). Type-A PPBS show a diverse panel of biological activities, such as antimicrobial (Azebaze et al., 2008; Kumar et al., 2013; Monzote et al., 2011; Rubio et al., 1999b; Wu et al., 2014), cytotoxic (Júnior et al., 2013; Kumar et al., 2013; Nugroho et al., 2018; Wu et al., 2014), topoisomerase I inhibitors (Di Micco et al., 2019), immunomodulatory (Cen et al., 2015; Schobert and Biersack, 2019), and antioxidant activity (Kumar et al., 2013; Ramirez et al., 2019; Wu et al., 2014).

C. burle-marxii trunk was collected at Mucugê city (Bahia state, Brazil). A voucher specimen (ALCB-61584) was deposited in the Herbarium Alexandre Leal Costa at Federal University of Bahia. Herein, we have described the isolation and structural identification of six type-A polyisoprenylated benzophenones derivatives from *Clusia burle-marxii*, as well as we have discussed their biological activities, occurrence, putative biosynthesis pathway, and chemotaxonomic significance.

2. Previous work

There is only a single study describing the isolation of polyprenylated benzophenone derivatives from *Clusia burle-marxxi*. In this study, the isolation of three polyprenylated benzophenone derivatives with a tetracyclo[8.3.1.0^{3,11}.0^{5,10}]tetradecane core skeleton was reported (Ferraz

* Corresponding author.
** Corresponding author. Metabolomics Research Group, Departamento de Química Orgânica, Instituto de Química, Universidade Federal da Bahia, Rua Barão de Jeremoabo s/n, 40170-115, Salvador, Brazil.
E-mail addresses: califerraz@gmail.com (C.G. Ferraz), pauloribeiro@ufba.br, paulodc3@gmail.com (P.R. Ribeiro).

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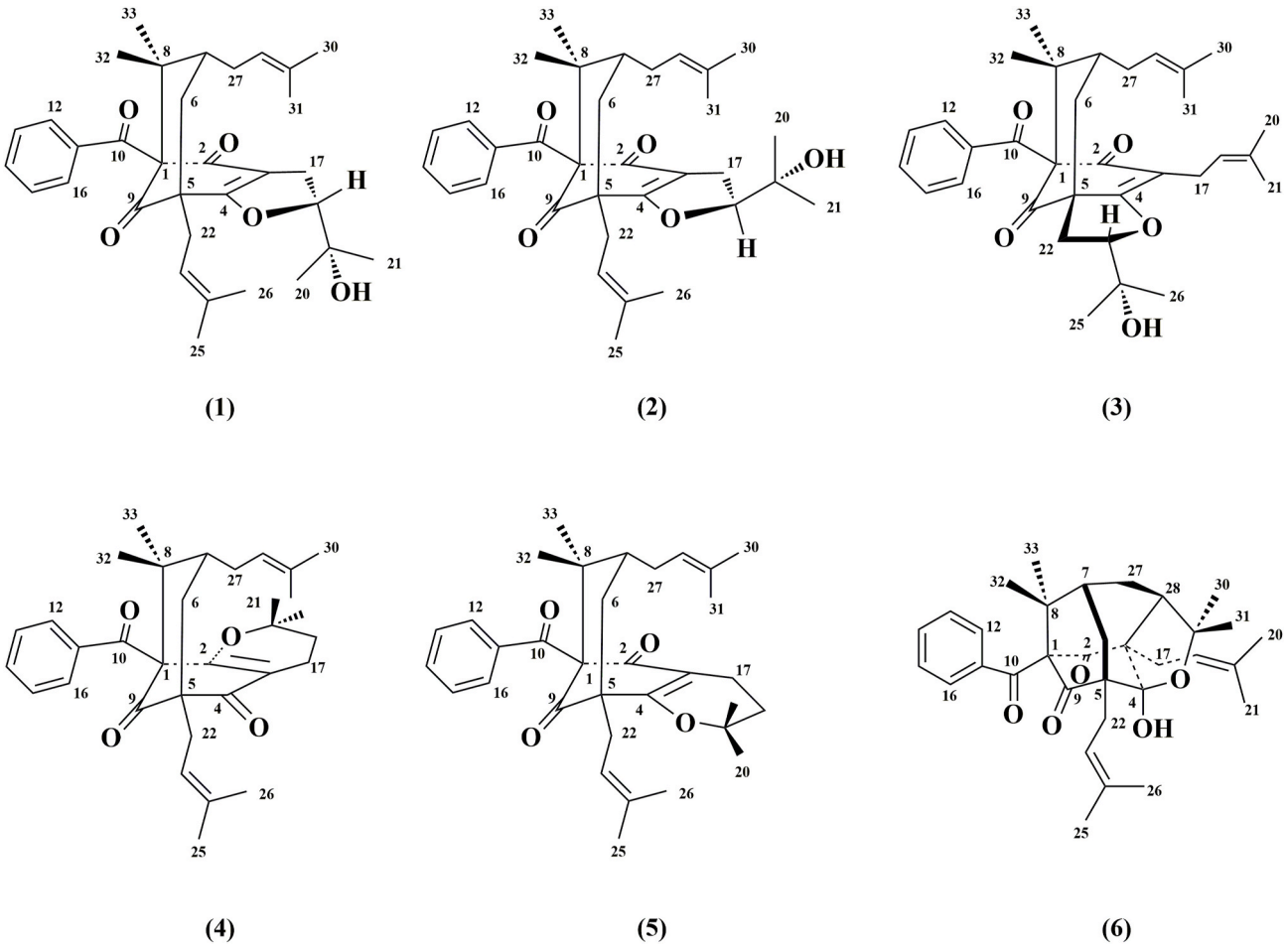

Fig. 1. Chemical structures of polyprenylated benzophenone derivatives with the central bicyclo[3.3.1]nonane-2,4,9-trione core from *Clusia burle-marxii*.

et al., 2019). The isolation of flavonoids, steroids, terpenoids, xanthones, and biphenyls from *Clusia burle-marxxi* has also been reported (Ribeiro et al., 2011, 2019).

3. Present study

Six sophisticated polyprenylated benzophenone derivatives (**1**–**6**) with the central bicyclo[3.3.1]nonane-2,4,9-trione core were isolated from hexane extract of *Clusia burle-marxii* trunks (Fig. 1). Detailed information on the fractionation and isolation of these compounds is provided (Supplementary material and methods). The presence of the central bicyclo[3.3.1]nonane-2,4,9-trione core was inferred by a very characteristic set of signals in the ^{13}C NMR spectra. Frequently, the bicyclo[3.3.1]-nonane-2,4,9-trione core undergo enolization, which leads to great variation in the ^{13}C NMR signals at positions C-2 and C-4 (Table S1) (Anholeti et al., 2015; Ciochina and Grossman, 2006; Gao et al., 2016). A wide range of substitution patterns is observed at positions C-1, C-3, C-5, and C-7, which includes isoprenoid units, such as prenyl, geranyl, or their isomers (Anholeti et al., 2015; Ciochina and Grossman, 2006; Rubio et al., 1999a). Position C-8 often bares two methyl groups, whereas position C-6 does not undergo any substitution. The existence of two prenyl groups were inferred by the presence of two olefinic protons signals between 4.97 and 5.60 ppm and protons signals from four methyl groups between 1.45 and 1.84 ppm. This later region is often characteristic of proton signals from methyl groups bonded to sp^2 carbons. Careful analysis of the HMBC correlations allowed us to undoubtedly place these prenyl groups at positions C-3, C-5, or C-7 (Tables S1–S6). Aromatic proton signals observed between 7.00 and 7.90 ppm, along with their HMBC correlations to the well-conserved carbon signal around 193 ppm suggested that all six polyprenylated benzophenone derivatives isolated from *Clusia burle-marxii* possessed a benzoyl moiety (Tables S1–S6). The connection of this benzoyl moiety to C-1 of the central bicyclo[3.3.1]nonane-2,4,9-trione core and its relative configuration was established by careful analysis of the NOESY correlations between H-23 and the aromatic proton signals (Table S1). Protons signals from four additional methyl groups were observed between 0.28 and 1.41 ppm, which is often characteristic of proton signals from methyl groups bonded to sp^3 carbons. The ^{13}C NMR spectrum suggested the presence of two carbonyl groups between 187.7 and 209.4 ppm attributed to positions 2, 4 or 9 of the central bicyclo[3.3.1]nonane-2,4,9-trione core. From those, higher field carbon signals (greater than 200 ppm) were assigned to the non-conjugated carbonyl group at C-9, whereas lower field carbon signals (between 180 and 200 ppm) were assigned to α,β-unsaturated carbonyl groups at either C-2 or C4. Although these polyprenylated benzophenone derivatives show highly conserved structural features, this is the very first time that they are isolated from a single plant species. Unique NMR characteristics of each compound that allowed us to undoubtedly identify them are presented in Supplementary Material and Methods.

These polyprenylated benzophenone derivatives show a great panel of biological activities. Compounds **1** and **2** showed mild antibacterial activity against *Staphylococcus aureus* (Matsuhisa et al., 2002), whereas compound **1** also showed strong cytotoxic activity against HeLa tumor cells, as well as strong antimicrobial activity against *Streptococcus mutans*, *Streptococcus sobrinus*, *Streptococcus oralis*, *Staphylococcus aureus*, and *Actinomyces naeslundii* (Castro et al., 2009). Compound **5** showed significant antimicrobial and antifungal activity against *Streptomyces chartrensis*, *Streptomyces violochromogenes*, *Shigella sonnei*, *Candida*

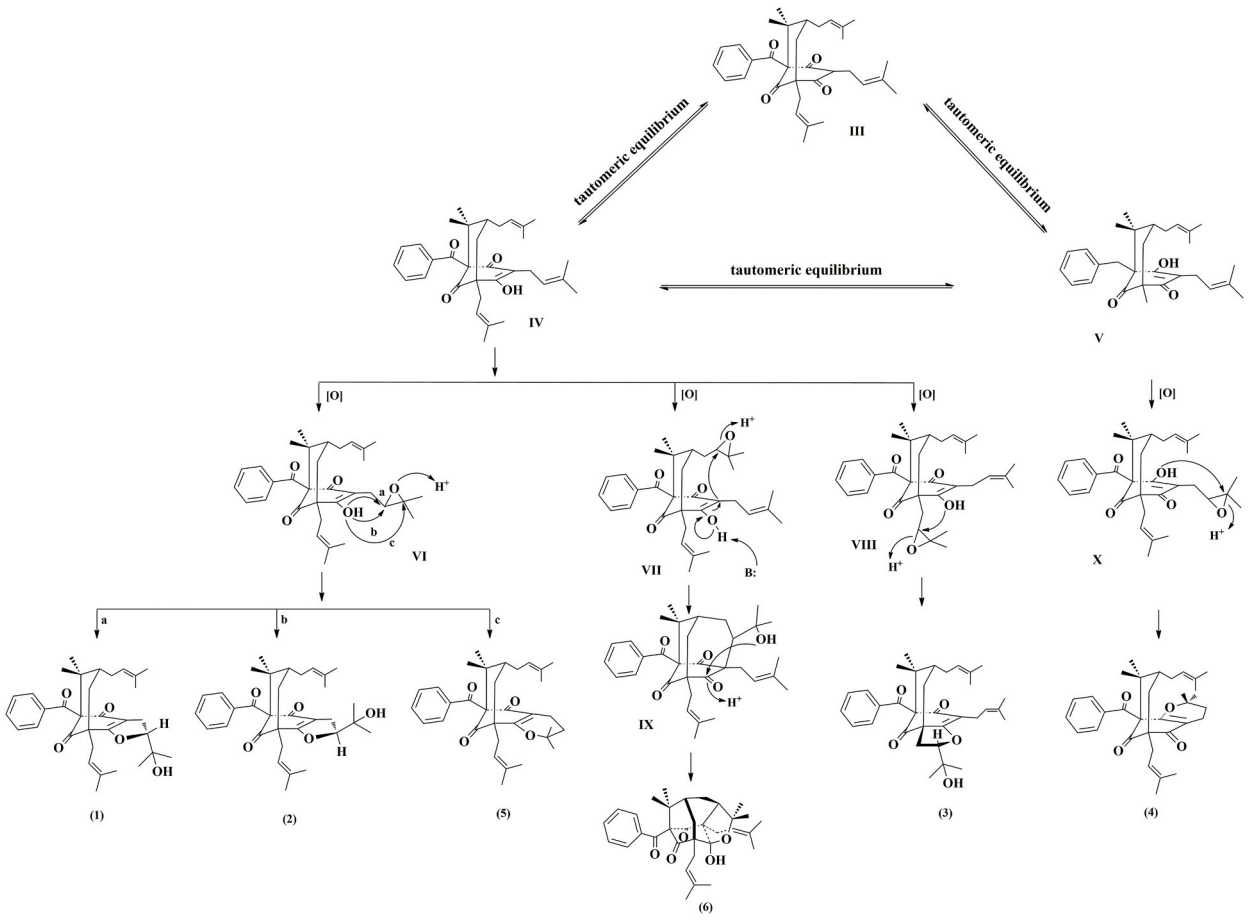

Fig. 2. Putative biosynthesis pathway of Polyprenylated benzophenone derivatives with the central bicyclo[3.3.1]nonane-2,4,9-trione core from *Clusia burle-marxii*.

albicans, *C. parapsilosis*, *C. tropicalis*, and *Pseudomonas aeuruginosa* (Rubio et al., 1999a).

4. Chemotaxonomic importance

The biosynthesis of compounds **1**–**6** begins with the intermediate I, which is a keto-enol equilibrium derivative of 2,4,6-trihydroxybenzophenone. Intermediate I undergo three successive enzyme-catalyzed prenylation on the phloroglucinol moiety to produce intermediate II. The concerted attack of one of the geminal prenyl groups of intermediate II to a prenyl pyrophosphate unit produces intermediate III (Figure S1) (Ciochina and Grossman, 2006; Hu and Sim, 1999).

Intermediate III putatively exists in a tautomeric equilibrium with intermediates IV (nemorosone) and V. Epoxidation of the prenyl group at C-3 produces intermediate VI, at C-7 produces intermediate VII, and C-5 produces intermediate VIII. Intramolecular cyclization of intermediate VI may occur between 4-OH and C-18 or C-19 (Fig. 2). Intramolecular cyclization between 4-OH and C-18 produces a five-membered ring with two possible stereochemistry (epimers) resulting in compounds **1** and **2**, whereas intramolecular cyclization between 4-OH and C-19 produces a six-membered ring resulting in compound **5**. Intramolecular cyclization of VIII between 4-OH and C-23 produces a five-membered ring resulting in compounds **3** (Fig. 2) (Tian et al., 2016; Xiao et al., 2007). Intramolecular cyclization of intermediate VII forms intermediate IX, which shows a tricyclo[4.3.1.1]undecanetrione core. The proximity of the carbonyl (C-4) and the hydroxyl group (29-OH) favors the hemiketal formation to the novel rigid 5-oxatetra-cyclo [7.3.1.$0^{3,7}$.$0^{4,11}$]tridecane-2,12-dione skeleton of compound **6** (Hu and Sim, 2000). Compound **4** is the only polyprenylated benzophenone derivative with the central bicyclo[3.3.1]nonane-2,4,9-trione core produced from intermediate V. Epoxidation of the prenyl group at C-3 produces intermediate X, followed by intramolecular cyclization between 4-OH and C-18 or C-19. Intramolecular cyclization between 2-OH and C-19 produces the six-membered ring of compounds **4** (Fig. 2) (Tian et al., 2016; Xiao et al., 2007).

Compound **3** was first isolated from *Hypericum sampsonii* and named it as sampsonione L (Hu and Sim, 2000). Two years later, Matsuhisa et al. (2002) reported the isolation of compounds **1**–**3** for the first time from *Hypericum scabrum* and named them as hyperibones A, B and G. However, the authors of the later study failed to mention that compound **3** was previously isolated from *Hypericum sampsonii* and, therefore, their claim about the novelty of compound **3** was not correct. Curiously, the same mistake was done by Xiao et al. (2007) that incorrectly reported the isolation of compound **1** and **2** as novel compounds. Weng et al. (2003) have reported the isolation of a new type C polycyclic polyprenylated acylphloroglucinol (garcinielliptone I) from *Garcinia subelliptica*, but the assignment of type C skeleton is controversial and proved to be incorrect (Yang et al., 2017). It seems, however, that garcinielliptone I corresponds to hyperibone B. Compound **1** and **2** have also been isolated from *Clusia minor* (Mangas Marín et al., 2008). Compound **1** has also been isolated from Brazilian propolis type 6, whereas compound **5** was first isolated from Cuban propolis (Rubio et al., 1999a). Compound **4** has only been isolated from *Hypericum sampsonii* and named as Hypersampsone T (Tian et al., 2016). Compound **6** was first isolated from *Hypericum sampsonii* and named as sampsonione B (Hu and Sim, 1998, 2000), but this compound has also been isolated from *Clusia obdeltifolia* (Cruz and Teixeira, 2004) and *Garcinia multiflora* (Cheng et al., 2018).

Polyisoprenylated benzophenones have been identified in flowers, fruits, stems, branches and leaves of *Clusia* species. In *Clusia burle*

-marxii, these compounds were only isolated from the stem hexane extract. Benzophenone derivatives from *Clusia* species were organized into groups according to their structural similarity. Benzophenones derivatives with the bicyclo[3.3.1]nonane-2,4,9-trione core are the most representative group, along with simple 2,4,6-trihydroxybenzophenone derivatives. Compounds 1–6 are classified as type-A PPBS and compound 6 show an unusual adamantyl skeleton of ring. Type-A PPBS comprise a highly sophisticated class of compounds widely distributed amongst *Clusi a* and *Hypericum* species (Anholeti et al., 2015; Wu et al., 2014; Yang et al., 2018). An important characteristic of benzophenones in *Clusia* species is the presence of isoprene units, varying from two to five isoprene units, with tetraprenylated benzophenone derivatives being the most representative for the genus. There has been some degree of controversy amongst taxonomists to the exclusion of the Hypericoideae subfamily from the Clusiaceae family, with subsequent establishment of the Hypericaceae or St. John's wort family. The phylogeny of Malpighiales order demonstrate a close evolutionary relationship amongst Clusiaceae and Hypericaceae families within the Clusioids clade (Wurdack and Davis, 2009). Compounds 1, 2, and 6 are reported for the first time in *Clusia burle-marxii*, whereas compounds 3, 4 and 5 are reported for the first time in the Clusiaceae family. Moreover, polyprenylated benzophenone derivatives with the bicyclo[3.3.1] nonane-2,4,9-trione core have been isolated from several genera of the Clusiaceae family, such as *Garcinia* (Ali et al., 2000), *Platonia* (Júnior et al., 2013), *Symphonia* (Marti et al., 2010), and *Moronobea* (Marti et al., 2009). The occurrence of high degree of prenylation and low oxidation indexes is characteristics to *Clusia* species and according to Anholeti et al. (2015) it provides further confirmation that Clusiaceae is a family in transition, justifying its change in the taxonomic position in recent years. The distribution and occurrence of these polyprenylated benzophenone derivatives in Clusiaceae species suggest that these compounds could be used as powerful chemotaxonomics markers for the Clusiaceae family, and perhaps for the clusioids clade of the Malpighiales order.

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CRediT authorship contribution statement

Caline G. Ferraz: and. **Maria do C.C. Silva:** Data acquisition, and analysis. **David A.S.G. Pereira:** Data acquisition, and analysis. **Brenno V.V. Caldas:** Data acquisition, and analysis. **Rafael Mattos:** Data acquisition, and analysis. **Vivian V.G. Oliveira:** Data acquisition, and analysis. **Eberson M.J. Andrade:** Data acquisition, and analysis. **Ana C. F. Soares:** and. **Franceli da Silva:** Data acquisition, and analysis, Funding acquisition. **Frederico G. Cruz:** and. **Paulo R. Ribeiro:** Conceptualization, Data acquisition and analysis, Funding acquisition, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bse.2020.104218.

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