Structure Revision of Four Acylphloroglucinols Isolated from the Leaves of *Syzygium polyanthum*

Anthony R. Carroll [1,2]

[1] Eskitis Institute, Griffith University, Gold Coast, Queensland, Australia

[2] Centre for Clean Environment and Energy, Griffith University, Gold Coast, Queensland, Australia

Abstract

The structures of four 1-acyl-2,3,5-trihydroxybenzene derivatives (**1**–**4**) that inhibit the enzyme protein tyrosine phosphatase 1B, previously reported from the leaves of *Syzygium polyanthum*, have been revised based upon reinterpretation of NMR spectroscopic data. The corrected structures are all 1-acylphloroglucinol derivatives (**5**–**8**).

Key words

Syzygium polyanthum · Myrtaceae · phloroglucinol · NMR chemical shift analysis

Supporting information available online at http://www.thieme-connect.de/products

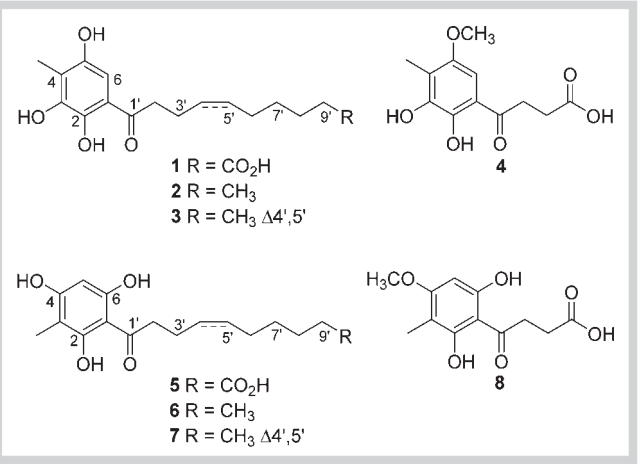

Fig. 1 Chemical structures of published (**1**–**4**) and corrected (**5**–**8**) acylphloroglucinol structures.

The plant family Myrtaceae is a major source of phloroglucinol natural products with potent and varied biological activities [1]. *Syzygium* is a diverse genus within the family and contains over 1000 rainforest shrub and tree species that occur mainly in South East Asia and Australasia [2]. The importance of this genus is borne out by the many species that are used as foods, medicines, and timber, with for example, the spice trade from the 17th century being based upon the exploitation of spices such as cloves, the intensely aromatic flower buds of *Syzygium aromaticum* (L.) Merr. & L.M. Perry, harvested from plants growing on a select few islands of the Indonesian archipelago, to be sold in markets in Europe [3]. Surprisingly only a relatively few papers have reported on the non-volatile chemicals present in *Syzygium* species but acylphloroglucinol compounds predominate, with over 20 compounds from this class being reported [1,4–6]. It was therefore surprising when Saifudin et al. reported in 2012 that the leaves of *Syzygium polyanthum* (Wight) Walp. collected in Indonesia contain four compounds with an unusual 1-acyl-2,3,5-trihydroxy-4-methylphenyl substitution pattern [7]. Three of these compounds showed micromolar inhibition of the enzyme PTP1B that has been implicated with diabetes [7]. Further investigation of the literature revealed that another study on the same species, published at about the same time by Har et al., reported compounds containing the more typical acylphloroglucinol structure class and interestingly, these compounds had similar length acyl side chains to those reported by Saifudin et al. [5,7]. An additional paper also reported long chain acylphloroglucinol derivatives from *Syzygium levinei* (Merr.) Merr., although these compounds lacked an aromatic methyl group [6]. These conflicting reports suggested that one of the group of authors may have incorrectly assigned their structures, and since the compounds reported by Saifudin et al. do not fit the expected polyketide biogenetic pathway typical of acylphenols, their structure assignments were most likely incorrect. This concern was further reinforced when the ^{13}C NMR data for the compounds reported by Saifudin et al. were compared to those reported for other acylphloroglucinols since the aromatic carbon chemical shifts were almost identical to those reported in other papers [4–6]. Reanalysis of the spectroscopic data reported by Saifudin et al. indicates that the structures of **1**–**4** should be revised to **5**–**8** (**Fig. 1**) with all four compounds containing a phloroglucinol moiety rather than a 2,3,5-trihydroxybenzene moiety.

Saifudin et al. rely exclusively on the presence of a key HMBC correlation between the aromatic proton, H-6 and the acyl carbonyl carbon, C-1′ to conclude that the aromatic proton, H-1 is *ortho* to the acyl side chain in the four compounds isolated [7]. Using this premise the rest of their proposed structures were constructed through the logical analysis of the remaining HMBC correlations. However $^{4}J_{CH}$ correlations from H-3 or H-5 of an aromatic moiety to the benzylic carbonyl carbon attached at C-1 have been reported for acylphloroglucinols [8]. These correlations tend to be much weaker than the typical aromatic $^{3}J_{CH}$ and $^{2}J_{CH}$ correlations and so correlation intensity can be a useful tool to assign longer range couplings. The 2,4,6-trihydroxy substitution pattern of acylphloroglucinols results in the aromatic carbons present in these molecules having very characteristic carbon chemical shifts, with three downfield oxygenated carbons resonating at ~160–165 ppm and three upfield aromatic carbons, each *ortho* to two oxygenated carbons, resonating at ~95–110 ppm [8]. In comparison the oxygenated aromatic carbons in 1,2-dihydroxyphenyl compounds typically resonate between 145–150 ppm, while protonated aromatic carbons which are *ortho* to only one oxygenated carbon resonate between ~110–117 ppm and quaternary aromatic carbons *ortho* to only one oxygenated carbon resonate between 115–120 ppm [9]. Therefore the ^{13}C NMR data for the 2,3,5 trioxygenated phenyl structures proposed by Saifudin et al. should have two of the oxygenated aromatic carbons resonating between ~145–150 and the third between ~160–165, the protonated and one of the quaternary aromatic carbons resonating between 110–120 ppm and the remaining aromatic carbon resonating at approximately 100 ppm. However, in all four compounds three downfield aromatic carbons were observed between δ_C 160.3 and 165.4 and three upfield aromatic

carbons were observed between δ_C 90.9 and 105.6. This provided conclusive evidence to assign phloroglucinol structures (**5**–**8**) to the four compounds. HMBC correlations corroborated these revised structure assignments. In compound **5** for example, key HMBC correlations were observed between 3-CH_3 and C-2, C-3, and C-4 and between H-5 and C-1, C-3, and C-4 however no correlation was reportedly observed to C-6 from H-5. This is unsurprising for a phloroglucinol structure since this correlation would be for a $^2J_{CH}$ coupling which can be quite small, but it is highly irregular in the 2,3,5-trihydroxyphenyl structure since this correlation would be between H-6 and C-2, a $^3J_{CH}$ coupling, which are usually between 8–10 Hz in aromatic systems [9]. Comparsion of the published ^{13}C NMR data reported for carbons associated with the 3-methyl-1-acylphloroglucinol moiety in three related compounds were in close agreement to those observed in **5**–**8** (see **Table 3 S**, Supporting Information). The corrected NMR data for compounds **5**–**8** are presented in **Tables 1 S** and **2 S** in the Supporting Information.

The structures of compounds **5**–**8** have not been reported previously in the literature, however the methyl ester of **5**, anthuminoate has been reported as a constituent from the leaves of *S. polyanthum* by Har et al. [5]. The ^{13}C NMR data reported for anthuminoate was also in close agreement with that obtained for **5**. The aromatic oxygenation and methylation pattern present in the amended structures for the *S. polyanthum* derivatives **5**–**8** are typical for plants from the Myrtaceae as this family is a major source of phloroglucinol derivatives [1]. The corrected structures therefore provide useful evidence that can be used for chemotaxomic purposes. This paper highlights a salient point, that relying solely on potentially ambiguous 2D correlations to assign compound structures without due regard for chemical shift considerations can lead to erroneous conclusions.

Supporting information

Corrected NMR assignments in two tables (**Table 1 S** and **2 S**) and ^{13}C NMR data for related 3-methyl-acylphloroglucinols (**Table 3 S**) are available as Supporting Information.

Conflict of Interest

The author declares no conflict of interest.

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received August 29, 2015
revised December 2, 2015
accepted December 18, 2015

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DOI http://dx.doi.org/10.1055/s-0035-1568260
Published online February 5, 2016
Planta Med Lett 2016; 3: e8–e9

ISSN 2199-157X

Correspondence
Prof. Anthony Carroll
Eskitis Institute
Griffith University
Gold Coast Q4222
Queensland
Australia
Phone: + 61 7 55 52 91 87
Fax: + 61 7 55 52 77 85
a.carroll@griffith.edu.au