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On the structures of the penduflorines from *Tabernaemontana penduliflora*

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ABSTRACT

The structures of the recently published monoterpene indole alkaloids penduflorines A and B (**1a** and **1b**), isolated from *Tabernaemontana penduliflora* (Apocynaceae), have been revised. Rather than an inseparable mixture of two compounds, they appear to be the known alkaloid vobasine (**2**). Although we could not comprehensively revise the structures of penduflorines C-E due to lacking spectral data, since their structural elucidations were based on that of **1a** and **1b**, their structures should also be treated with caution.

The Apocynaceae is a predominantly tropical and subtropical family containing ca. 1850 species across 163 genera [1]. Known colloquially as the "Dogbane" family due to its toxic effects upon ingestion by animals, it is an unusually prominent producer of a variety of alkaloids with potent biological activities. The most famed of these are the monoterpene indole alkaloids (MIAs), a class including the clinically used hypertension drug reserpine (isolated from *Rauvolfia serpentina*), the vertebrate poison strychnine (*Strychnos ignatia*) and the anti-cancer MIA dimers vincristine and vinblastine (*Catharanthus roseus*) [2]. The immense historical importance of this plant family and a certain abundance of still undiscovered alkaloids drive research into its chemical constituents to this day [3].

Recently, several new MIAs were described from *Tabernaemontana penduliflora* (Apocynaceae) [4]. Closer examination of their structures (particularly those of penduflorines A and B (**1a** and **1b**), reportedly obtained as an inseparable 1:1 mixture) revealed inconsistencies between their reported NMR data and their proposed structures (Fig. 1). The most notable of these is the presence of an aldehyde in both structures with no corresponding peak in the ^{1}H NMR spectrum (Fig. S1, Supporting Information). There is also no crosspeak in the HSQC spectrum, nor associated $^1J_{CH}$ coupling in the HMBC spectrum (Fig. S2, Supporting Information). Further, if **1a**/**1b** were isolated in a 1:1 ratio, one would expect the integrals of the methyl groups at *N*-4 in **1a**/**1b** to be half the intensity of most other peaks. Examination of the provided ^{1}H NMR (Fig. S1, Supporting Information) data shows that both methyl groups at *N*-4 in **1a**/**1b** (δ_H 2.59 in **1a**, 2.64 in **1b**) occur in a 1:1:1 ratio with, for example, H_3–18. If these were unseparable isomers, these should be in a 1:1:2 ratio, since the resonance associated with H_3–18 is identical in both compounds. Furthermore, the methyl group at *N*-4 in **1b** (δ_C 50.4, δ_H 2.64) does not show the expected two- and three-bond HMBC correlations to C-3/C-5/C-21, only showing a single four-bond correlation to a carboxylate group at C-5 (δ_C 171.3). The methyl group at *N*-4 in **1a** (δ_C 42.3, δ_H 2.59) is similarly problematic, only displaying two HMBC correlations to C-5/C-21, while the expected three-bond correlation to C-3 is absent (Fig. S2, Supporting Information). As described recently by Burns and Reynolds [5], two- and three-bond HMBC correlations from methyl protons are extremely reliable, and failure to observe them is a strong indication that a proposed structure is incorrect. These irregularities led to a closer examination of the 2D NMR data provided for **1a**/**1b**. The conclusion was reached that this is most likely the known compound vobasine (**2**) (Fig. 1). One hallmark of this

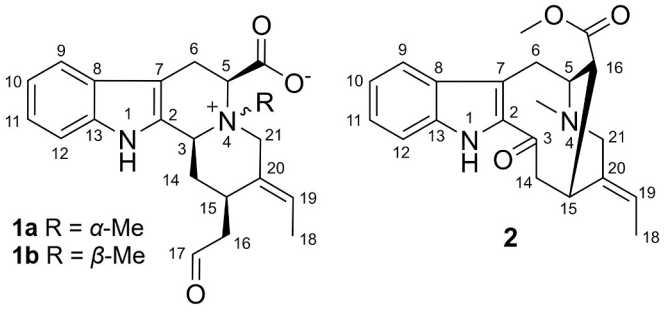

Fig. 1. Reported structures of penduflorines A and B (**1a and 1b**) and the structure of vobasine (**2**).

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Table 1
Comparison of ^{13}C NMR chemical shifts for **1a**/**1b** and **2** ($CDCl_3$). Carbon numbering refers to structure **2**.

position	**1a**/**1b**[a]	**2**[b]
2	134.2	134.1
3	190.3	190.1
5	57.3	57.2
6	20.5	20.3
7	120.4	120.4
8	128.5	128.5
9	120.9[c]	120.8
10	120.4	120.4
11	126.7	126.7
12	112.0	111.7
13	136.6	136.3
14	43.1	43.0
15	30.5	30.4
16	46.5	46.6
18	12.4	12.3
19	121.0[c]	120.8
20	135.9	135.8
21	51.8	51.8
$CO_2\underline{\boldsymbol{CH_3}}$	50.4	50.3
$\underline{\boldsymbol{CO_2}}CH_3$	171.3	171.2
N_4-CH_3	42.3	42.3

[a] 100 MHz. Observed from ^{13}C NMR spectrum reported by Bitombo et al. (2021) [4].
[b] 75 MHz. Reported by Pereira et al. (2008) [7]. Similar data is also reported by Ahond et al. (1976) [8].
[c] Signals interchangeable.

MIA skeleton is the characteristic highly shielded ^1H NMR chemical shift (δ_H 2.64) of the methoxy group due to the anisotropic effect of the indole ring [6], and we believe that this unusually shielded methoxy group led to its erroneous assignment as an *N*-methyl. Comparison of the author-provided ^{13}C NMR spectrum of **1a**/**1b** [4] with previously published data of **2** [7,8] showed a perfect match between the data (Table 1; Fig. S3, Supporting Information). Both **1a**/**1b** and **2** also have identical molecular formulae. Unfortunately, we are unable to offer revised structures of penduflorines C-E (which are proposed to have the same structural backbone as **1a**/**1b**) due to lacking spectral data. However, since the structural elucidations of these compounds were based on that of **1a**/**1b**, their proposed structures should be treated with caution.

Credit author statement

Validation of structure revision and writing of paper: Mehdi A. Beniddir, Ulf Göransson, and Luke P. Robertson.

Declaration of Competing Interest

There are no conflicts to declare.

Data availability

All data used is already freely available on the internet from the papers referenced.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fitote.2023.105506.

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