

Cite this: *RSC Chem. Biol.*, 2025, 6, 1727Received 12th August 2025,
Accepted 18th September 2025

DOI: 10.1039/d5cb00208g

rsc.li/rsc-chembio

Sweet dicamba: a carbohydrate pro-herbicide strategy

Karen J. Deane,^{id}^a Joel Haywood,^{id}^b Michael D. Wallace,^{id}^a Kalia Bernath-Levin,^{id}^a Mark T. Waters,^{id}^a Joshua S. Mylne,^{id}^{*b} and Keith A. Stubbs^{id}^{*ac}

Dicamba, although a potent and useful herbicide in weed management, is notorious for its off-target movement due to volatility. Here, we describe carbohydrate esters of dicamba as an unexplored pro-herbicide approach that addresses the volatility of dicamba, while maintaining its herbicidal qualities. Varying the carbohydrate and dicamba attachment point led to changes in potency and hydrolysis, potentially allowing for reactivity tuning of molecules for future weed management practices.

Herbicides play a critical role in modern agriculture. Since the first use of synthetic herbicides in the 1940s, they have helped to meet the growing food demand by providing the necessary weed control to keep these lands useful for crop production.¹ One synthetic herbicide, dicamba (3,6-dichloro-2-methoxybenzoic acid, Fig. 1), has been used for over 50 years and is well known for its ability to control weed growth. The recent introduction of a dicamba-tolerance trait² has made it a first line compound for weed control along with glyphosate.³ Dicamba is a synthetic auxin-type herbicide and, despite its utility and potency, suffers from off-target drift (volatility) issues. These issues have been compounded by an increase in use driven by the introduction of dicamba-tolerant crops,⁴ leading to restrictions on its use.⁵

To address the problems with drift, formulations of dicamba have evolved over time, utilising various salts of the benzoic acid, including dimethylamine, diglycolamine or more recently, *N,N*-bis-(3-aminopropyl)methylamine (BAPMA),⁴ although issues with injury to sensitive broadleaf crops persist,⁶ driving ongoing research into formulation approaches.^{7,8} One method that has had limited investigation^{9,10} and no commercial use has been the development of pro-herbicides of dicamba.

Pro-herbicides ('masked' forms of herbicides that require transformation to become herbicidally active¹¹) of volatile carboxylic acid herbicides have been commercially successful (e.g. 2,4-D ethylhexyl ester¹²) but not in the case of dicamba. Taking advantage of the carboxylic acid residue to couple volatility-reducing groups to decrease drift but also retain potency in a pro-herbicide type approach would be advantageous.¹⁰

Consideration of a potential dicamba pro-herbicide strategy led us to carbohydrate esters. Carbohydrates are environmentally benign molecules that are rich in polar atoms that can enhance aqueous solubility and reduce volatility through increased intermolecular hydrogen bonding, and can be functionalised at different positions of the carbohydrate which may tune hydrolysis rates to release the active ingredient (dicamba). Carbohydrate-herbicide adducts are known as metabolites of carboxylic acid-bearing herbicides such as the synthetic auxin 2,4-D,¹³ with these conjugates readily converted back to the active herbicide.¹⁴ With this in mind, we synthesised a range of dicamba-carbohydrate esters, and evaluated their herbicidal efficacy against the model dicot, *Arabidopsis thaliana*.

Our initial targets were esters linking β -glucose and dicamba, and we synthesised the dicamba β -glucoside **1** and 6-*O*-dicamba- β -glucose **2** (Fig. 1, see SI for synthetic procedures) with both compounds prepared as anomeric mixtures (NMR analysis). Herbicidal activity was then evaluated with comparison to dicamba, against the model dicot *A. thaliana* at a range of concentrations (125 μ M–2 mM) of each compound, with treatment occurring either pre- or post-emergence (Fig. 2).

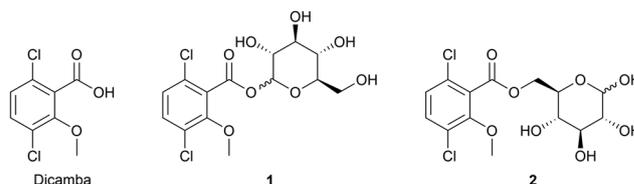


Fig. 1 Dicamba and dicamba-glucose conjugates **1** and **2**.

^a School of Molecular Sciences, University of Western Australia, Crawley, WA 6009, Australia. E-mail: keith.stubbs@uwa.edu.au

^b Centre for Crop and Disease Management, Curtin University, Bentley, WA 6102, Australia. E-mail: josh.mylne@curtin.edu.au

^c ARC Training Centre for Next-Gen Technologies in Biomedical Analysis, School of Molecular Sciences, The University of Western Australia, Crawley, WA 6009, Australia



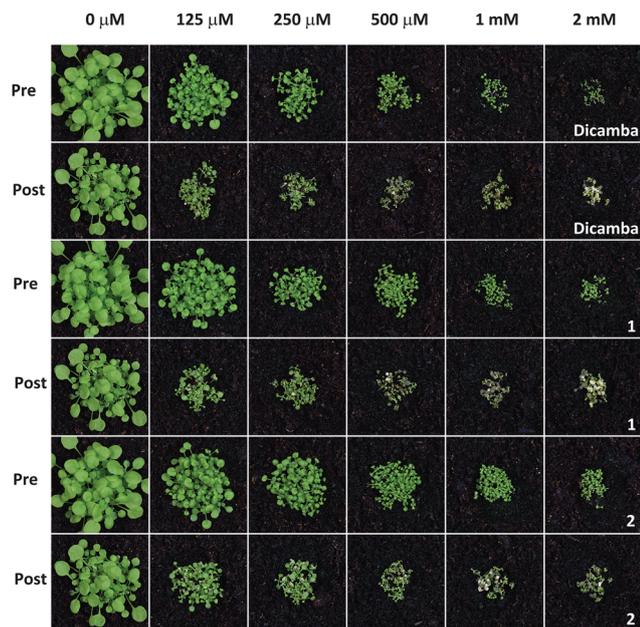


Fig. 2 Pre- and post-emergent herbicidal activity of dicamba and dicamba-glucose conjugates **1** and **2**. Herbicidal activity was assessed on soil-grown *A. thaliana* with post-emergence treatments performed three and six days after germination, assessed on day 16.

Dicamba showed growth inhibition over the concentration ranges tested, with pre-emergent inhibition weak at 125 μM and strong at 1 mM and post-emergent inhibition moderate at 125 μM and strong at 500 μM whereas both **1** and **2** showed similar potency to dicamba.

Ester linkages are known to be susceptible to hydrolysis in aqueous solutions. For **1** and **2**, hydrolysis leads to dicamba and glucose; if this happens too rapidly upon aqueous dilution, the pro-herbicide strategy is negated, although ester bond cleavage and release of dicamba *in planta* is expected to be required for activity. To test inherent aqueous stability, solutions of **1** and **2** in water were analysed by HPLC over 28 days (Table 1 and SI), with the conversion measured as the amount of dicamba as a percentage of all peaks. Conversion of **1** into dicamba was rapid, yielding 45% conversion to dicamba after

Table 1 HPLC determination of dicamba formation in water for compounds **1–10** (expressed as integration of dicamba as a percentage of all peaks at 220 nm). Dicamba was not detected at $t = 0$

Compound	% Dicamba		
	1 day	7 days	28 days
1	45.4	69.3	91.7
2	0.1	0.1	0.5
3	1.0	3.5	13.5
4	1.0	3.3	7.8
5	0.8	2.5	5.7
6	0.1	0.4	2.0
7	3.6	9.9	20.7
8	3.1	11.5	20.1
9	1.1	1.1	2.8
10	1.0	2.8	14.2

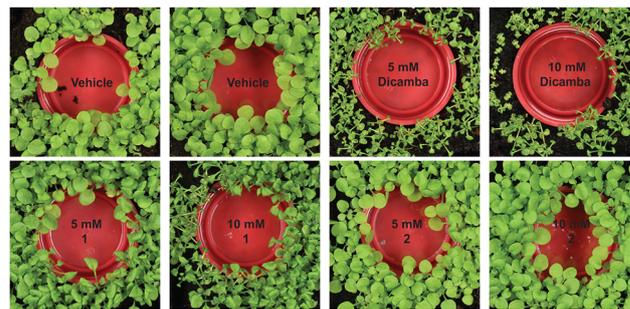


Fig. 3 Drift assay of dicamba and conjugates **1** and **2**, prepared by raising seedlings of wild type *A. thaliana* around a reservoir. After germination, dicamba, **1**, or **2** (5 or 10 mM in vehicle: 0.85 mL water with 0.02% Brushwet surfactant) was added to the reservoir. Leaf curling from treatments was assessed on day 14.

24 hours, while only trace (<1%) dicamba was found for **2** after 28 days. The increased rate of cleavage of **1** is consistent with known trends of reactivity at the anomeric position of carbohydrates.¹⁵ Given the demonstrated stability of **2** in aqueous solution, it implies that the molecule is taken up into the plant intact, with cleavage *in planta* to give dicamba, while for **1**, dicamba may be released prior to uptake.

Next, **1** and **2** were compared against dicamba to assess their propensity to drift and thereby damage plants from volatility. For this, dicamba, **1** and **2** were placed in reservoirs at 5 and 10 mM, and the growth of *A. thaliana* surrounding the reservoir monitored (Fig. 3). Dicamba, as expected, caused 'burn' of the surrounding plants at both concentrations; a reduced effect was also seen for **1**, presumably because of breakdown of **1** into

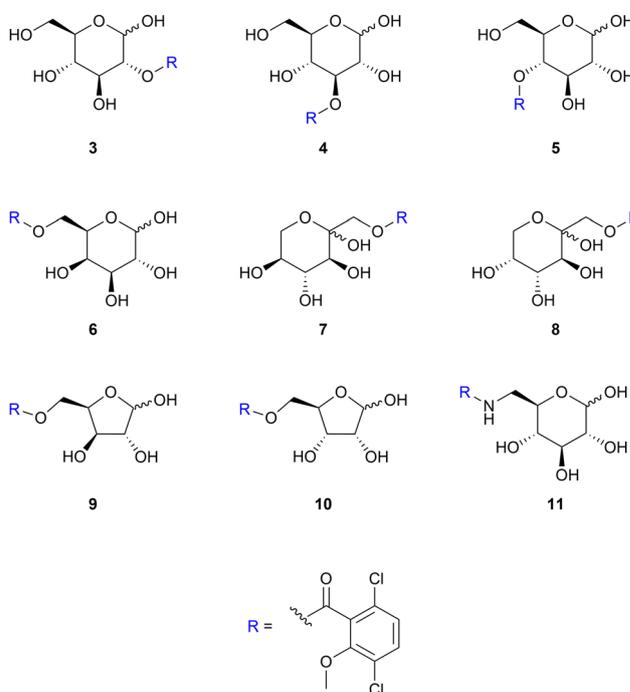


Fig. 4 Dicamba-carbohydrate conjugates **3–11**.



dicamba in line with the HPLC analysis. Compound **2** did not cause any visible disruption to plant growth.

To increase the scope of carbohydrate esters as potential 'pro-dicambas', additional dicamba-carbohydrate esters were synthesised varying both the carbohydrate used, and the linking position (Fig. 4). The 2-, 3- and 4-*O*-substituted *D*-glucose derivatives (**3**, **4** and **5** respectively), as well as the primary alcohol esters of *D*-galactose, *L*-sorbose, *D*-fructose, *D*-xylose and *D*-ribose (**6**, **7**, **8**, **9** and **10** respectively) were prepared (see SI for synthetic procedures). Additionally, the amide analogue **11** (*cf.* ester **2**) was prepared to explore the necessity for a hydrolysable linker.

Herbicidal efficacy against *A. thaliana* (Fig. 5) revealed that the aldohexose-conjugates **2–6** possessed stronger activity

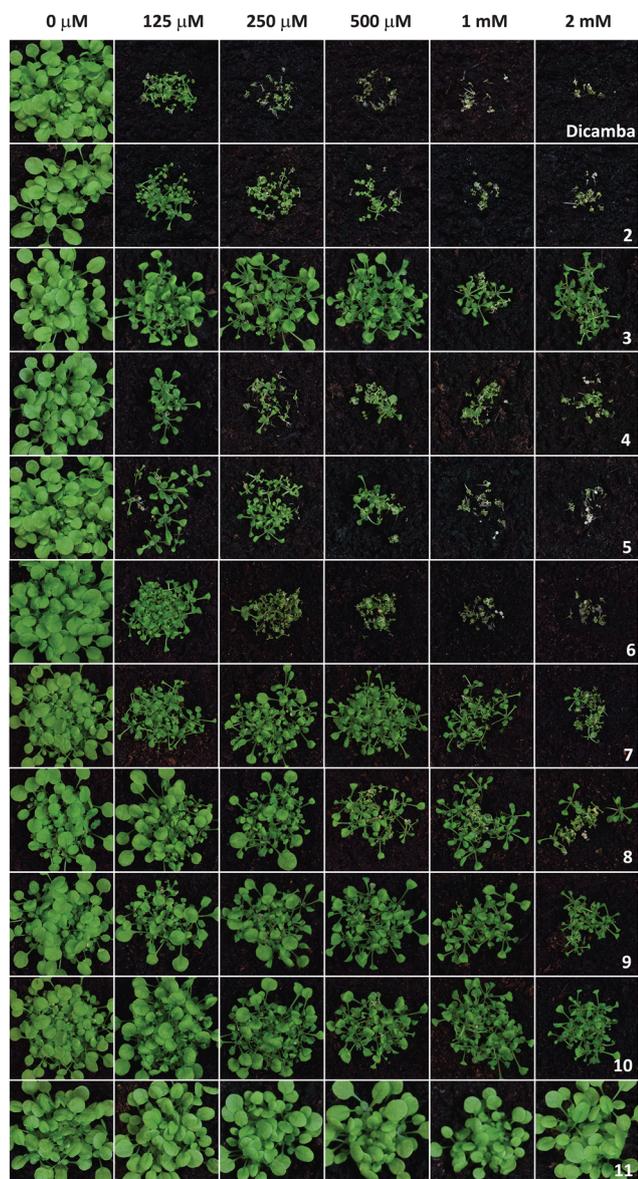


Fig. 5 Post-emergent herbicidal activity of dicamba and dicamba-glucose conjugates **2** and **4–11**. Herbicidal activity was assessed on soil-grown *A. thaliana* with post-emergence treatments performed three and six days after germination, assessed on day 16.

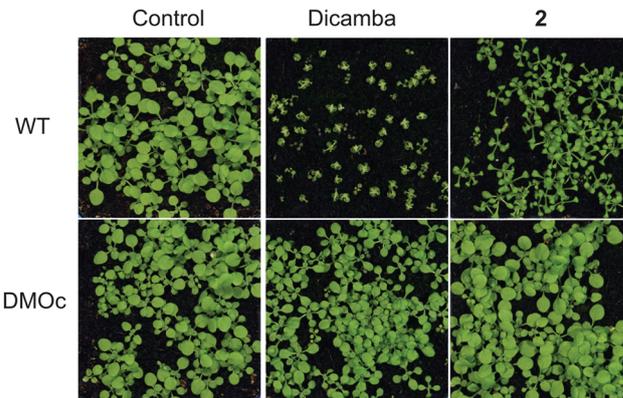


Fig. 6 The dicamba-glucose conjugate **2** is compatible with the dicamba tolerance trait. Wild type *A. thaliana* (WT) or a homozygous, dicamba-tolerant transgenic line (DMOC) were sprayed with dicamba or **2** (500 μ M).

relative to the ketohexoses **7** and **8** and aldopentoses **9** and **10**. The position of substitution also affected activity, with compounds **2**, **4** and **5** (6-, 3-, and 4-substitution of *D*-glucose) appearing similar in herbicidal efficacy, while **3** (2-substitution of *D*-glucose) was less efficacious. Amide **11** was inactive even at the highest concentration tested (2 mM), indicating that release of dicamba is required for herbicidal efficacy.

To investigate the differences between the herbicidal activity associated with the various monosaccharides and how this activity may be impacted by the speed of their cleavage to release dicamba, analysis of the breakdown of the esters in water was again measured by HPLC (Table 1). The relative hydrolysis rates of the glucose isomers **1–5** were found to be $1 \gg 3 > 4 > 5 > 2$, with **2** remaining both the most stable and the most active isomer, while the other aldohexoses were more stable than aldopentoses and ketohexoses.

To confirm that **2** is compatible with the dicamba tolerance trait, a transgenic line of *A. thaliana*, modified with a synthetic dicamba monooxygenase from *Stenotrophomonas maltophilia*,^{2,10} was prepared. Spraying the transgenic line at 500 μ M with dicamba or **2** presented no growth symptoms, while both compounds were herbicidal to wild-type (Fig. 6).

Conclusions

Dicamba use is still widespread, despite continued issues with off-target impacts. In this work, we have described the development of carbohydrate pro-dicamba esters, leading to the discovery of the glucose derivative **2**, that is herbicidally active, non-volatile, stable in aqueous solution and compatible with dicamba-tolerance technology. Taken in conjunction with the previously described 2-dimethylaminoethanol dicamba ester with similar properties,¹⁰ pro-dicamba esters that incorporate polar functional groups are promising formulations, supporting the resurgence of dicamba by overcoming the problems associated with off-target movement due to volatility. More broadly, the carbohydrate ester pro-herbicide strategy may be also applicable to other volatile carboxylic acid herbicides (*e.g.* synthetic auxins including 2,4-D).



Conflicts of interest

K. A. S. and K. J. D. are inventors on a patent application that details these dicamba derivatives (WO/2023/092188). This work was funded in-part by DemAgTech Pty Ltd.

Data availability

The data supporting this article have been included as part of the supplementary information(SI). Supplementary information is available. See DOI: <https://doi.org/10.1039/d5cb00208g>.

Acknowledgements

The authors acknowledge the facilities, and the scientific and technical assistance of the Centre for Microscopy, Characterisation & Analysis, The University of Western Australia, a facility funded by the University, State and Commonwealth Governments.

References

- 1 D. Murphy, *Plants, Biotechnology and Agriculture*, 2011, ch. 9, pp. 194–219, DOI: [10.1079/9781845939137.0194](https://doi.org/10.1079/9781845939137.0194).
- 2 M. R. Behrens, N. Mutlu, S. Chakraborty, R. Dumitru, W. Z. Jiang, B. J. LaVallee, P. L. Herman, T. E. Clemente and D. P. Weeks, *Science*, 2007, **316**, 1185–1188.
- 3 S. R. Padgett, K. H. Kolacz, X. Delannay, D. B. Re, B. J. LaVallee, C. N. Tinius, W. K. Rhodes, Y. I. Otero, G. F. Barry, D. A. Eichholtz, V. M. Peschke, D. L. Nida, N. B. Taylor and G. M. Kishore, *Crop Sci.*, 1995, **35**, 1451–1461.
- 4 T. J. Centner, *Environ. Challenges*, 2022, **6**, 100422.
- 5 United States Environmental Protection Agency, <https://www.epa.gov/pesticides/epa-announces-proposed-decision-approve-registration-new-uses-dicamba-outlines-new>, (accessed July 2025).
- 6 T. C. Mueller and L. E. Steckel, *Weed Technol.*, 2019, **33**, 541–546.
- 7 J. Pernak, D. K. Kaczmarek, T. Rzemieniecki, M. Niemczak, Ł. Chrzanowski and T. Praczyk, *J. Agric. Food Chem.*, 2020, **68**, 4588–4594.
- 8 C. Wu, Y. Xiao, N. Wang, X. Huang, T. Wang, L. Zhou and H. Hao, *J. Controlled Release*, 2024, **375**, 178–192.
- 9 A. Syguda, M. Wojcieszak, K. Materna, M. Woźniak-Karczewska, A. Parus, Ł. Ławniczak and Ł. Chrzanowski, *ACS Sustainable Chem. Eng.*, 2020, **8**, 14584–14594.
- 10 J. Haywood, K. J. Breese, M. Jordi Muria-Gonzalez, K. Bernath-Levin, M. Waters, K. A. Stubbs and J. S. Mylne, *Chem. – Eur. J.*, 2025, **31**, e202404282.
- 11 P. Jeschke, *Pest Manage. Sci.*, 2016, **72**, 210–225.
- 12 J. M. Charles, T. R. Hanley, Jr., R. D. Wilson, B. van Ravenzwaay and J. S. Bus, *Toxicol. Sci.*, 2001, **60**, 121–131.
- 13 D. E. Goggin, G. L. Nealon, G. R. Cawthray, A. Scaffidi, M. J. Howard, S. B. Powles and G. R. Flematti, *J. Agric. Food Chem.*, 2018, **66**, 13378–13385.
- 14 K. Kreuz, R. Tommasini and E. Martinoia, *Plant Physiol.*, 1996, **111**, 349–353.
- 15 M. Mikamo, *Carbohydr. Res.*, 1989, **191**, 150–153.

