Design, synthesis and screening of herbicidal activity of new protoporphyrinogen oxidase-inhibitors (PPO) overcoming resistance issues.

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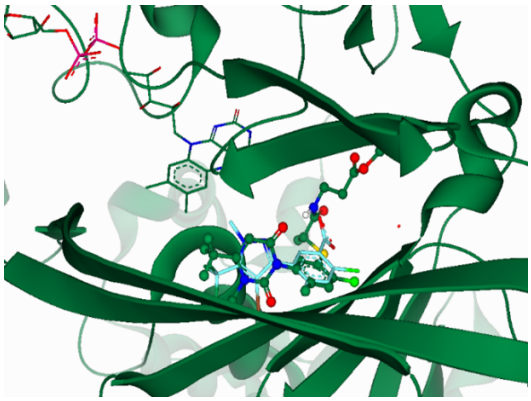
Whilst there are several methods to control weeds, which continuously plague farmers around the globe, theapplication of small molecular compounds is still the most effective technology to date. Plants can evolve to become resistantto PPO-inhibitors, a class of herbicides in commercial use since the 1960s. It is therefore essential to continuously develop newherbicides based on this mode-of-action with enhanced intrinsic activity, an improved resistance profile and favourable phys-icochemical properties. Based on an Amaranthus PPO crystal structure and subsequent modelling studies, halogen-substitutedpyrazoles have been investigated as isosteres of uracil-based PPO-inhibitors. By combining structural features from the commercial PPO-inhibitors tiafenacil and pyraflufen-ethyl and by investigat-ing receptor-binding properties, we identified new promising pyrazole-based lead structures showing strong activityin vitroandin vivoagainst economically important weeds of the *Amaranthus* genus: *A. retroflexus*, and resistant *A. palmeri* and *A. tuberculatus.* The present work covers a series of novel PPO-inhibiting compounds that contain a pyrazole ring and asubstituted thioacetic acid sidechain attached to the core phenyl group. These compounds show good receptorfit in line withexcellent herbicidal activity against weeds that plague corn and rice crops with low application rates. This, in combination withpromising selectivity in corn, have the potential to mitigate and affect weeds that have become resistant to some of the currentmarket standards. Remarkably, some of the novel PPO-inhibitors outlined herein show efficacies against economically impor-tant weeds that were superior to recently commercialized and structurally related tiafenacil.



Superposition of the wild-type *Amaranthus* structure with tiafenacil (dark green) and the targeted molecule **15a.**

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[2] Mattison, R. Beffa, G. Bojack, B. Bollenbach-Wahl, C. Dörnbrack, N. Dorn, J. Freigang, E. Gatzweiler, R. Getachew, C. Hartfiel, I. Heinemann, H. Helmke, S. Hohmann, H. Jakobi, G. Lange, P. Lümmen, R. Mattison, L. Willms, J. Frackenpohl, *Pest. Man. Sci,* **2023,** *79*, 10.1002/ps.7425.