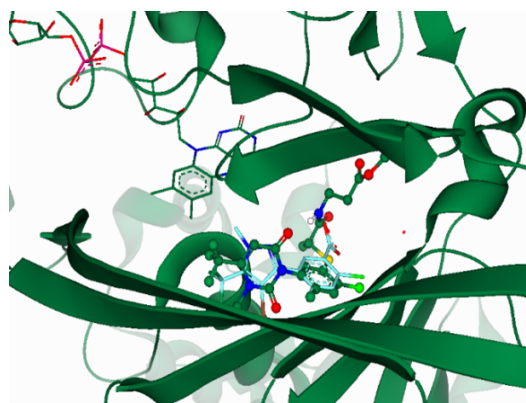


Design, synthesis and screening of herbicidal activity of new protoporphyrinogen oxidase-inhibitors (PPO) overcoming resistance issues.

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Whilst there are several methods to control weeds, which continuously plague farmers around the globe, the application of small molecular compounds is still the most effective technology to date. Plants can evolve to become resistant to PPO-inhibitors, a class of herbicides in commercial use since the 1960s. It is therefore essential to continuously develop new herbicides based on this mode-of-action with enhanced intrinsic activity, an improved resistance profile and favourable physicochemical properties. Based on an *Amaranthus* PPO crystal structure and subsequent modelling studies, halogen-substituted pyrazoles 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 investigating receptor-binding properties, we identified new promising pyrazole-based lead structures showing strong activity in vitro and in vivo against 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 a substituted thioacetic acid sidechain attached to the core phenyl group. These compounds show good receptor fit in line with excellent herbicidal activity against weeds that plague corn and rice crops with low application rates. This, in combination with promising selectivity in corn, have the potential to mitigate and affect weeds that have become resistant to some of the current market standards. Remarkably, some of the novel PPO-inhibitors outlined herein show efficacies against economically important 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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