Structure-activity and molecular modeling studies of strobilurin-based dual fungicides for the control of rice blast pathogen *Pyricularia oryzae*

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Fungicide resistance in plant pathogens is becoming a serious problem for sustainable crop disease management and requires urgent and innovative solutions. Here, we summarize our research on the design and development of innovative dual strobilurin-based fungicides, and the improvement of lead compounds based on structural investigations and molecular modeling. The first-generation dual molecules containing strobilurin and succinate dehydrogenase pharmacophores showed in some cases good activity against wild-type *Pyricularia oryzae*, but lacked activity against strobilurin-resistant strains. Therefore, structure-activity relationship studies were performed with the aim to improve the activity of novel compounds also against strobilurin-resistant strains. The design of the novel molecules was supported also by molecular modeling. The first three-dimensional model of *P. oryzae* cytochrome *bc1* complex containing azoxystrobin as a ligand was developed. The model was validated with a set of commercially available strobilurins, and it well explains the resistance mechanism of the mutation G143A to strobilurins caused by the sterical hindrance of alanine residue. Moreover, the model explains the activity of metyltetraprole against strobilurin-resistant strains. This research contributes to identification of the key recognition determinants of strobilurin-like compounds in the cytochrome *bc1* active site. A compound with >80% in vitro inhibitory activity against both wild-type and mutant *P. oryzae* was identified and will be further optimized and tested in vivo.