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Biotransformations at Syngenta: A Focused Perspective on Metabolites and Natural Products

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Abstract: In this article we present our perspective on how biotransformations can contribute to key sustainability challenges faced by the agrochemical industry. We focus on two key areas where biotransformations have enabled research breakthroughs, the preparative synthesis of metabolite standards and natural products. Increasingly stringent regulatory requirements have rendered early metabolite identification and production an expanding activity to progress an active ingredient to the market. We present a collaborative project on unspecific peroxygenases for selective oxidation of pyrethroid-related compounds, illustrating future directions in research for the production of metabolites. Natural products provide an opportunity to explore a vast chemical space and to have an improved sustainability profile. Nevertheless, their fermentation at large scale and low cost is still challenging, and we present strategies aiming at increasing the fermentation titre and batch purity.

Keywords: Crop protection · Metabolites · Natural products

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1. Introduction

Farmers around the world are facing the adverse effects of global warming whilst needing to produce more food under unprecedented climate conditions. Climate stressors such as drought and high temperature variations are becoming more frequent and have a negative impact on crop yields. The agricultural industry needs to meet farmers' needs while adapting to an increasingly stringent regulatory environment. Policies that must be adhered to include the European Union's Green Deal, India's Zero Budget Natural Farming policy, and organic farming incentives in the

United States. These policies require farmers to re-evaluate the crop protection toolbox available to them. Public and food chain pressure towards products with low or no residues creates an additional challenge both for farmers and for the agrochemical industry, who need to incorporate this consideration early in the active ingredient design. As a result, the parameters considered when designing an agrochemical have evolved (Fig. 1a). Product safety, which incorporates both human and environmental safety, always occupies a central place. New modes of action are always sought to tackle evolution of pest resistance and population shifts. If a broad spectrum is always desirable, it is not considered a major criterion, and answering farmers and consumers specific needs with a tailored solution has become more important. Finally, the rising costs of energy and a challenging global economic situation means the cost of active ingredients is a key factor when buying a crop protection agent. In this context, sustainability is at the heart of our activities within the agrochemical industry.

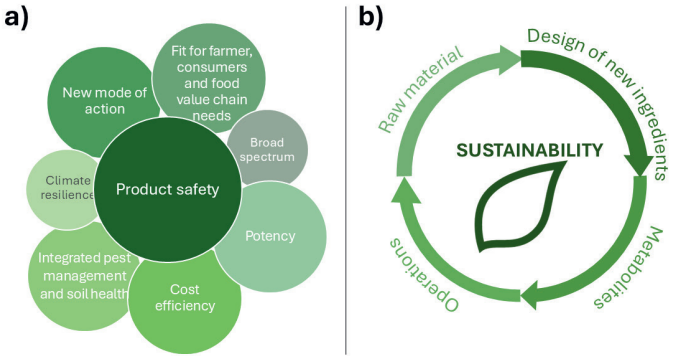


Fig. 1. a) Parameters being considered when designing a new crop protection agent. The size of the circle represents the relative importance of the criteria; b) Sustainability parameters that biotransformations can contribute to.

Our approach to sustainability encompasses several key aspects, depicted in Fig. 1b:

- *Sustainability in raw material sourcing*: the use of renewable resources as starting materials contributes to significantly reduce the carbon footprint associated with the production of the active ingredients.
- *Sustainability in the design of new ingredients*: achieving higher crop yields and higher selectivity in controlling the target species contributes to lower application rates, thus less residues in the environment.[1]
- Providing crop protection solutions that degrade to benign metabolites that can contribute to maintaining a healthy soil and a sustainable environment.
- *Sustainability in operations*: our ambitious goal is to reduce emissions of our own operations and energy purchases by 38% by 2030 (starting from the 2022 baseline). This can be achieved by reducing energy consumption as well as water and waste intensity in the production sites among other options.[2]

In this article we would like to focus on two topics that represent the focus of our research on biotransformations: the preparation of metabolite standards and the use of fermentation to access natural products of agrochemical interest. They illustrate several aspects of our sustainability strategy.

2. Biotransformations for Metabolite Identification and Production

2.1 *Metabolites of Agrochemicals*

Agrochemicals are applied in the environment and subjected to varied degradation pathways, resulting in a wide range of metabolites. As well as assessing the metabolism of our compounds in pest and crop species, we also have to consider a wide range of other organisms. These include algae, mammals, birds, fish, non-target insects and soil microorganisms (bacteria and fungi). All of these organisms can utilise different metabolic pathways to degrade crop protection agents. To assess the environmental fate of active ingredients, identification and profiling of metabolites is essential and required for market registration. The design of active ingredients requires a balanced holistic profile. By enhancing the potency and selectivity of a molecule lower application rates can be achieved. Ensuring that the active ingredient has been designed to allow the production of benign downstream metabolites is another core goal of crop protection research. A balance needs to be found as certain aqueous, photo- and metabolic stabilities are also required to enable the active ingredient to act on the target organism over a sufficient period of time to avoid the requirement for multiple applications during a season. The complex holistic profile that an active agrochemical ingredient needs to achieve is depicted in Fig. 1b, where the main parameters considered during design are shown. In order to meet all these requirements, the new compounds typically exhibit increased structural complexity. In particular, there is now a preference for single enantiomers over racemates in the case of a chiral molecule.[3]

The commercialisation of crop protection agents requires compliance with standards set by regulatory agencies. In the European Union, the standard maximum residue level (MRL, highest level of agrochemical residue that is legally tolerated on a food product when applied correctly) is 0.01 mg/kg[4] and the precautionary groundwater quality standard is 0.1 µg/L.[5] These values are general guidelines, which can be adjusted when data on the safety profiles of the residues are provided at registration. This has shifted the identification and preliminary profiling of metabolites to an earlier stage of the research process, when several candidates are still being evaluated.

In humans and mammals in general, primary metabolism is often mediated through the use of oxidative enzymes, primarily through cytochromes P450 (P450s),[6,7] and glucuronidation.[8] In other kingdoms and organisms, different enzymes can predominate and lead to different metabolites being formed. For instance, fungi may use enzymes like laccases or peroxidases to carry out oxidation. Insects possess a larger and more diverse set of P450s, also involved in insecticide resistance.[9,10] Plants also use hundreds of P450s for xenobiotic metabolism,[11,12] as well as many more glycosyltransferases than mammals for sugar conjugation.[13] Malonyltransferases and peroxidases are not reported to play a significant role in human xenobiotic metabolism, but are heavily implicated in plant metabolism.[14,15] The soil microbiome is a complex environment with a great capacity to adapt and degrade xenobiotics it is exposed to. Abiotic processes also contribute to the environmental degradation of agrochemicals. The combined effects of these different metabolism pathways are difficult to predict and go beyond the more thoroughly studied mechanisms in human metabolism.[16]

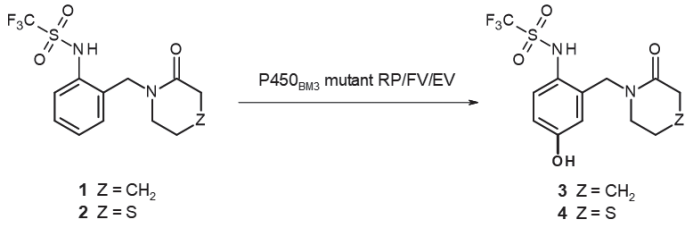
Generation of putative metabolites can be achieved through accessing a wide toolbox. Microbial or fungal strains, known to have a broad xenobiotic scope, can be screened. Lysates of wild types or mutant enzymes for oxidative metabolism are also routinely used, as well as other classes of enzymes such as hydrolases. Finally animal S9 fractions and sludges can be considered. As the goal is to generate many potential metabolites, enzymes that have a wide substrate scope are preferred. In general, biocatalysts that have the active ingredient as a substrate are preferred as it avoids the design of a new synthetic route to access the metabolite of interest.[17] P450s are challenging to express, which can negatively affect their scalability and cost compared to other enzyme classes such as hydrolases. Nevertheless, recombinantly expressed human and bacterial P450s kits

are available and provide a screening solution for generating oxidized molecules.

Often sufficient structural information about a putative metabolite can be acquired with milligram or even sub-milligram amounts of material. Once a standard is matched to a formed metabolite, scale up may be required for profiling of the metabolite. Scale up on the kilogram scale may be necessary if dietary animal studies are needed for toxicological profiling. Ideally, the method used to produce the standard can be scaled up for metabolite production. Unfortunately, this is rarely feasible at the kilogram scale within reasonable timelines and resource constraints. Typically, scaling up a P450 oxidation to the kilogram sale may entail several rounds of evolution to improve the robustness of the P450 based system. Significant time and cost investment are necessary, as expensive cofactors such as NAD(P)H or reductases are necessary.[18]

In a collaboration with the groups of Prof. Wong and Prof. Robertson at Oxford University, we explored the use of P450 BM3 mutants to oxidize two aniline-containing herbicides, **1** and **2** (Scheme 1).[19] *Para* hydroxylation of the triflated aniline occurred to form aminophenols **3** and **4**, accompanied by side-reactions, such as sulfoxide formation in the case of substrate **2**. The hydroxylated products could be used as metabolite standards. Such reactions, conducted on a low milligram scale, would require extensive investigations to be scaled up in order to improve the selectivity for the desired hydroxylation as well as the titer and reaction conditions.

Other methods can then be explored, such as P450 mimics, electrochemistry, or photochemistry. This challenge has driven our interest in investigating alternative enzyme classes to P450s that could be more readily scaled up.



Scheme 1. Hydroxylation of herbicides **1** and **2** by a P450 BM3 variant.[19]

2.2 *Unspecific Peroxygenases for Formation of Metabolites Relevant to Pyrethroids.*

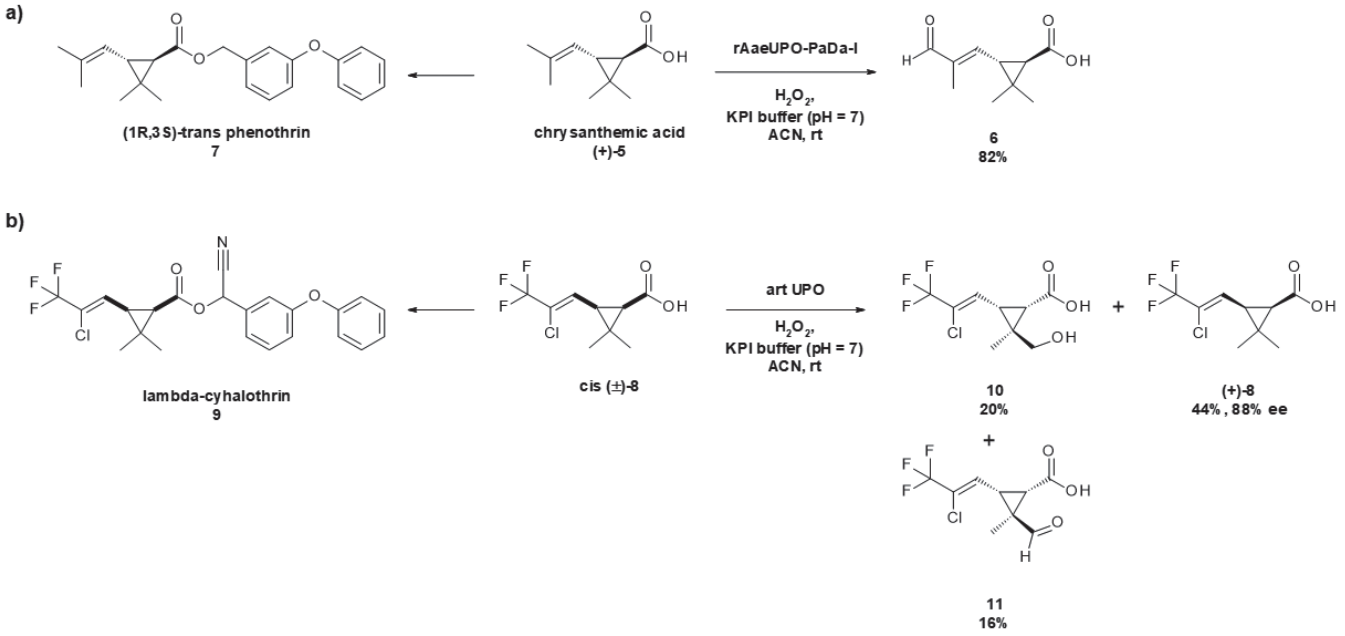
Unspecific peroxygenases (UPOs) are secreted fungal heme oxgenases, which can carry out a variety of oxidative reactions, such as aromatic and aliphatic hydroxylations and oxidations, alkene epoxidations as well as halogenations and sulfoxidations.[20–22] They rely on hydrogen peroxide as the oxidant to form the catalytically active iron oxo species and as final electron acceptor. UPOs are not concerned by O_2 uncoupling, a major issue when using P450s.

Two families of UPOs have been characterized so far, based on their sequence: family I UPOs have shorter sequences and molecular weights than family II UPOs. These two families differ not only by their structure but also by their substrate scopes, as the substrate access channels are lined with different amino acids, offering a different topology and size.

While their potential as biocatalysts has emerged in recent years, they also suffer some drawbacks.[23] Achieving high expression levels is still challenging, heterologous expression is usually done in yeasts (for instance *Saccharomyces cerevisiae* or *Pichia pastoris*) to enable protein glycosylation. Currently this has hindered approaches towards directed evolution programs, although there has been promising recent progress.[24–26] Enzyme inactivation by an excess of hydrogen peroxide and over oxidation of the products can also occur.

In order to explore their applicability towards agrochemically relevant substrates we entered into a collaboration with the groups of Prof. Grogan and Prof. Unsworth at York University. We explored the application of unspecific peroxygenases (UPOs) for the selective oxidation of a chrysanthemic acid inspired fragment, a key building block in the synthesis of commercial pyrethroids (Scheme 2), as well as for the oxidation of small terpenes as potential sustainable building blocks.[27] Pyrethroids, potent insecticides that modulate voltage-gated sodium channels of axons in insects nervous systems and are used on a variety of pests and crops, were selected as their metabolism has been studied: after hydrolysis of the ester, oxidation of the acid moiety can occur, especially on the different methyl groups.[28,29]

First, chrysanthemic acid **(+)-5** was oxidized with rAaeUPO-PaDa-I-H, an unspecific peroxygenase variant from Agrocybe aegerita, a member of the longer family II UPOs (Scheme 2a).



Scheme 2. Biotransformation of chrysanthemic acid and an analogue using UPOs. Adapted from ref. [27]. a) Oxidation of chrysanthemic acid with rAaeUPO-PaDa-I-H, a member of the longer family II UPOs; b) oxidation of a chrysanthemic acid analog using 'artUPO', a member of family I short UPOs.[30,31]

The reaction was carried out on a several milligrams scale, leading to the selective formation of aldehyde **6** in very good yield. Chrysanthemic acid is the acid moiety of (1*R*,3*S*)-*trans*-phenothrin **7**, used to control fleas and ticks.

Racemate *cis* **(±)-8**, a chrysanthemic acid analogue, was subjected to biotransformation using 'artUPO', which was developed in Prof. Grogan's group and is homologous to a member of family I short UPOs, *Marasmius rotula* UPO (MroUPO) (Scheme 2b).[30,31] Acid **(±)-8** can be further esterified to produce lambda-cyhalothrin **9**, mostly used to control lepidopterans on crops such as cereals or cotton. Interestingly, a kinetic resolution was observed, as only one enantiomer was oxidized to alcohol **10** and aldehyde **11**, leaving the **(+)-8** enantiomer unreacted. The transformation was also diastereoselective, with only one of the geminal methyl groups being oxidized.

These examples showcase the potential of UPOs for selective oxidations of agrochemically relevant compounds, opening new avenues for metabolite preparation.

3. Fermentation to Access Natural Products

Syngenta has a long-standing interest in the use of natural products and their production through fermentation could fulfil a key part of the sustainability strategy. They are a validated source of inspiration for new agrochemicals, leading over the years to the development of blockbusters such as pyrethroids, strobilurins, semisynthetic spinosyns and mectins or mesotrione.[32] They also represent a largely untapped chemical space and offer an opportunity to discover new modes of action. Even if it is rare to find a natural product that has the activity and properties required for application in the field on commercially relevant pests and crops, natural products provide a complementary approach to synthetic small molecule agrochemicals.[33] Nevertheless, once identified and their mode of action elucidated, their chemical complexity can lead to very high potency and specificity. They may be prone to faster environmental degradation owing to inherent metabolic liabilities. A few chemical modifications are sometimes required to improve the physicochemical properties of the ingredients, for instance by capping a free amine or an alcohol, or to broaden the pest spectrum. Bringing a natural product to the market represents a different challenge compared to small molecules. Since extensive structural diversification is out of scope, most of the effort in research consists of finding a suitable fermentation method to produce material for testing with the required quality.

One natural product family that has been widely used for agrochemicals is the 'mectins', a class of glycosylated 16-membered macrolactones.[34] The avermectins are produced by the soil actinomycete Streptomyces avermitilis, while the milbemycins were isolated initially from *Streptomyces hygroscopicus subsp. Aureolacrimosus*. The structure of the avermectins is depicted in Fig. 2a. Among the different congeners, abamectin, a mixture of avermectin B1a and B1b, is used as such in crop protection, under the commercial names of Avicta® and Vertimec® for instance. It activates the glutamate-gated chloride channels found in insects and mites' nerve and muscle cells. One remarkable feature of abamectin as an insecticide is the low rate of application. Control of key pests can be achieved with less than 50 grams per hectare, and its rapid degradation by soil microorganisms leads to a very low residue level on crops.[35] A synthetic modification was introduced by Novartis and allowed tuning of the activity profile of abamectins to control the lepidopterans unaffected by abamectin. The alcohol at the C4'' position of the disaccharide moiety was substituted by a methylamine through a 4-step sequence. It is now marketed by Syngenta under the brand name Proclaim®.

These natural products and derivatives rely on fermentation for industrial production in an economically viable way. The process development, accomplished at Merck, focused on increasing the titer of the overall avermectins produced, as well as the ratio

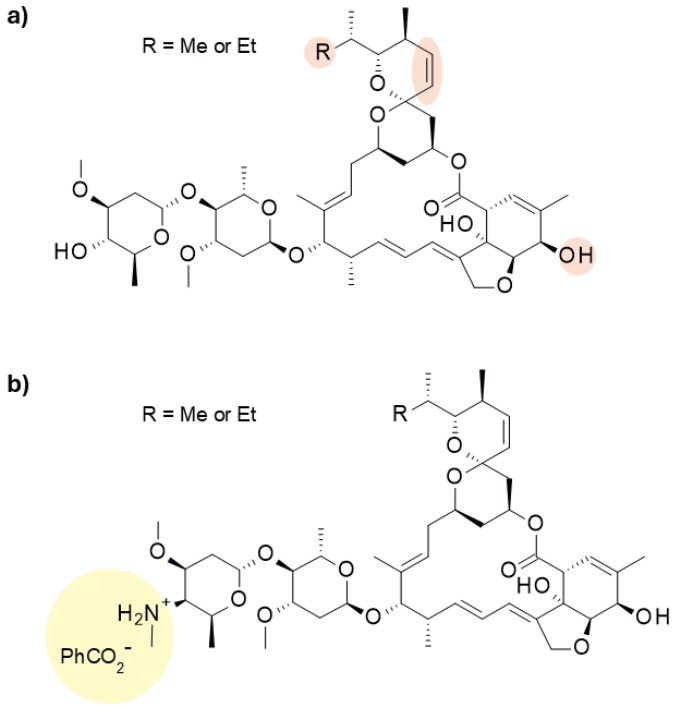


Fig. 2. a) Structure of abamectin, a mixture of avermectin B1a (R = ethyl) and B1b (R = methyl). The areas in orange represent the areas where structural diversity occur among the different avermectins; b) structure of emamectin benzoate. The moiety highlighted in yellow represents the derivatization point compared to avermectin B1.

of the desired avermectin B1a and B1b in comparison to the other avermectins.[36] The fermentation occurs from the original strain *Streptomyces avermitilis*. Strain mutagenesis, seed and production media development provided initial improvements. The scale up development phase focused on oxygen transfer, rendered difficult by the viscosity created by the mycelia. Downstream extraction was accomplished by acidification of the broth and extraction with a solvent such as toluene at high temperature. Initially, a purification step to separate abamectin from the other fermentation products, lipids and other avermectins, was required. After a few more processing steps, crystallization afforded the active ingredient as a mixture of two components.

Since the development of abamectin and emamectin benzoate, many advances have been accomplished in the domains of synthetic biology and metabolic engineering for natural product fermentation.[37,38] Producing an agrochemical requires high production volumes at a low cost, so extensive development of the production process is necessary before market introduction. Several strategies are being explored to improve the production of natural products:[39]

- Optimization of media and physicochemical parameters in the fermentation process.
- Genetic strain optimization: downregulation or deletion of biosynthetic gene clusters leading to formation of undesired by-products, or deletion of genes to reduce pathways that may be competing for precursors or intermediates. Removing of non-essential pathways can allow the energetic resources to be directed towards the natural product formation.
- Up-regulation of positive regulator genes, exchange of native promoters and deletion of negative regulators.
- Diversification of hosts for heterologous expression of the biosynthetic gene cluster.
- Downstream processing: an efficient process to extract the natural product while removing any other unwanted components from the broth, for instance some lipids or other natural product analogues. To meet the typical scale and cost of an

agrochemical, column chromatography is not conceivable, and crystallization, precipitation or spray drying methods are preferred.

Some of the differences between agrochemical and pharmaceutical natural production are the scale, usually higher for a crop protection agent, the target cost, much lower for an agrochemical product, and the fact agrochemicals do not need to be produced under GMP conditions. Many challenges and techniques are otherwise identical. The improvement and learnings done on fermentation of natural products can also be applied more generally to the fermentation of other biologicals, such as biocontrols, biostimulants, or nutrient use efficiency products.

4. Conclusions

Biotransformations have the potential to impact all of our sustainability objectives. As highlighted in this perspective, metabolite production and identification are critical activities for our industry and biocatalyzed approaches have proved to be an excellent synthetic enabler. Identifying scalable oxidative enzymes with a broad scope is of particular interest. We are actively exploring the use of biocatalysts across our pipeline both within research and development. Scaling biocatalytic processes is well aligned to agrochemical specific commercial and sustainability drivers. Using biotransformation in early research could enable the usage of renewable feedstocks as starting materials. In addition, accessing bulk quantities of these feedstocks could allow access to differentiated building blocks to help explore the chemical space at an earlier stage in research. Ultimately, this would lead to more options for farmers who need to produce food in agreement with more stringent sustainability policies.

Finally, using biotransformations for the synthesis of natural products is an ongoing effort that is part of our broader strategy to be leading the innovation on biologicals. The recently announced acquisition of the collection of natural products and genetic strains for agricultural use from Novartis by Syngenta will expand our capabilities and reflects our commitment to sustainability.[40]

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