doi:10.2533/chimia.2021.772 Chimia 75 (2021) 772–779

Use of Renewable Resources Towards the Sustainable Production of Crop Protection Agents

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Abstract: Today, the production of food accounts for roughly one quarter of anthropogenic greenhouse gas emissions. Since the 1970s, thanks to substantial research and development, the overall yield output in farm fields has increased by *ca.* 60%, while the net use of crop protection agents per square meter of farm field has been reduced by more than 90%. The development of modern crop protection agents remains an important need as new pests, diseases and weeds continue to affect crops. The vast majority of these effective solutions are manufactured using raw materials that ultimately come from fossil resources. In this article, we are touring within the agrochemical landscape to provide the reader with an overview of concrete examples on how in this industrial field, renewable and sustainable raw materials have been used to produce active ingredients. We are also discussing the opportunities for future development as well as some of the challenges and needs that are emerging.

Keywords: Agrochemicals · Crop protection · Renewable feedstocks · Sustainability

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1. Introduction

One of the most important challenges that the fine chemicals and life science industry is currently facing is sustainable development; that is, how to produce organic molecules that meet the needs of the present society without compromising the ability of future generations to meet theirs. Over the past two centuries this production has almost exclusively relied on fossil resources and the rapidly increasing population with higher living standards has resulted in a constantly growing demand for these chemicals, contributing ultimately to raising carbon dioxide level in the atmosphere and to the global climate change challenge. To reverse this trend and because the fossil resources will sooner or later be depleted, the sustainable production of fine carbon-based chemicals must be improved, and renewable resources must increasingly become the preferred source of raw materials.

In 2004, a group of experts compiled an exhaustive summary of so-called platform molecules which originate from renewable resources, typically from cellulose, hemicellulose and lignin.[1–4] A large number of journal resources and books[5] are available to provide the interested reader with exhaustive insights in available raw materials from renewable feedstocks.

It is important to define the terms sustainable and renewable resources. Indeed, exploitation of a renewable resource is only

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sustainable if it is harvested at a pace slower or equal to its rate of regeneration.[6] Several definitions of renewable resources can be found. These are resources able to naturally regenerate themselves over a human time scale (as opposed to fossil fuels which regenerate over millions of years). The Renewable Carbon Initiative[7] alternatively defines renewable resources as carbon sources taken from either the biosphere, the atmosphere or the technosphere – but not from the geosphere.

Green and sustainable chemistry considers the full life cycle of a product. Both upstream, *i.e.* where the raw material is coming from and how it is produced, as well as downstream stages, *i.e.* product usage, its end-use and its disposal, are critical elements to be included in any sustainability assessment.[8]

Another important criterion to consider is the competitive use of such resources vs other uses, such as food or feed purposes in particular. As much as possible, valorizing streams considered as waste today – *i.e.* upcycling – should be favored. In this special issue, the reader will surely discover fantastic stories where companies and academic groups followed such an approach.

A number of initiatives have been started by governmental agencies promoting the use of renewable feedstocks as an alternative to fossil fuels in order to make significant progress towards a carbon neutral industry by 2050.[9] Funding for research in this area is well incentivized by these agencies and it is reasonable to expect that the observed growth in this area over the last 10 years will continue. Recently, a survey[10] estimated that the worldwide production of biobased products was projected to grow from approximately $203.3 billion in 2015 to $400 billion by 2020 and $487 billion by 2024.

It is conceptually attractive to prepare crop protective agents from building blocks which themselves were previously harvested from plant or biomass-derived renewable resources. In this article, we will be reviewing some of the initiatives and concrete applications which took place in the agrochemical sector towards such approaches.

1.1 *Index for Renewable Sources*

As mentioned above, the sustainability of a new active ingredient must be evaluated *via* a full life cycle analysis, considering how it is prepared, its benefits to the user, its use and environmental impact and its end-of-life/disposal. In practice, the design of new active ingredients will rely on finding the best possible compromise between key factors such as targeted biological effect, innocuous impact on non-target organisms, non-persistence in the environment and affordability (this latter factor incorporates the sustainable manufacturing of the ingredient). The steep evolution of new regulations for registration of active ingredients within the last 20 years has raised the bar significantly to satisfy each of these criteria. This is a challenging but exciting task which fuels innovation and continuous improvement mindset which chemists in the crop protection industry must meet today (Fig. 1).

In this article, we will see, through concrete examples, how incorporating renewable feedstocks in the design of biologically active compounds can be expected to bring advantages while also posing key challenges.

Prior to outlining a selection of examples of crop protection active ingredients, it is important to define the metric which we use herein to evaluate the degree of incorporation of renewable feedstocks. The term *Renewable Carbon Index* (RCI)[11] was originally developed by Evonik. This index is obtained by dividing the number of carbons derived from renewable sources by the total number of carbons. Such an index has been used by a range of companies to evaluate the 'renewability' performance of their ingredients.[12] Jimenez-Gonzales *et al.* and later Elroy *et al.* also proposed the use of renewable intensity (RI) which reports the weight in kg of renewable ingredients used per kg of product.[13,14] Throughout this article we will be using as a metric the *Renewable Atom Index* (RAI) which accounts for the proportion of atoms found in the active ingredient which come from renewable resources.

2. Complex Natural Products as Raw Materials for Crop Protection Products

Natural products have been a tremendous source of inspiration for crop protection chemists[15-17] and can be exploited in several ways. First, they can act as an original source of inspiration for the development of purely synthetic solutions (synthetic mimics). The pyrethroid insecticides represent the first historical example of such a successful approach. For centuries, *Chrysanthemum coccineum* and *Chrysanthemum cineraria folium* flowers were used in houses to control insects.[18] In the 1970s, chemists identified[19] that this activity was mainly due to a secondary metabolite produced by the plant named pyrethrum, which showed outstanding insecticidal properties but limited stability and duration of effect and is still in use today.[20] This led in the years thereafter to the development of many synthetic pyrethroid analogues with improved properties. Strobilurin fungicides and neonicotinoid insecticides are synthetic molecules, which similarly found the origins of their design from natural product resources.[21,22] According to an analysis of the IRAC (Insecticide Resistance Action Committee),

Fig. 1. Key criterias to fulfill when designing modern agrochemicals.

synthetic molecules deriving directly or indirectly from natural products represent about 37% of the total economic value of the insecticide market.[23,24]

Second, natural products can enable the discovery of new target sites of action for subsequent target-based discovery efforts. Such cases are of very high value for resistance management which require constant discovery of active ingredients with novel modes of action to overcome the reduced sensitivity of pests to marketed products over time.

Finally, natural products can also be used as crop protection agents without further transformation or act as platform molecules which after a few synthetic modifications lead to successful crop protection agents. In both these cases, a substantial portion of the active ingredient originates straight from renewable resources. Below we illustrate several examples of such cases.

Natural chemotypes also enable the exploration of biologically active chemical space complementary to purely synthetic means and they are uniquely able to access challenging ligandable sites. These include not only catalytic sites within enzymes, but also protein–protein interfaces, post translational modification sites and other types of regulatory or functional domains across the proteome.[25,26]

Over the past years registration of crop protection chemicals has become more and more restrictive,[27] in particular in the European Union. Today, a modern active ingredient needs to fulfill a much wider range of criteria than in the past (Fig. 1), and natural products can offer several opportunities towards this. In particular, by virtue of their often-complex molecular architecture, they can show a very high target specificity and consequently a low toxicity towards non-target organisms. They also generally show a shorter persistence in soil,[17] which can be a true advantage for differential *in vivo* metabolism and limiting exposure in non-target organisms. Finally, in some cases, their efficacy is higher than for conventional synthetic molecules. All these aspects are making natural products attractive sources of effective crop protection solutions with potential for higher regulatory and public acceptance.

2.1 *Mectins*

Abamectin, discovered in 1978 in Japan (**1**, Scheme 1), is a naturally occurring mixture of avermectins B_1 and B_1b which was introduced onto the veterinary market by Merck Sharp & Dohme under the name Agvet in 1997.[28] Abamectin acts *via* the γ-aminobutyric acid (GABA)/glutamate-gated chloride channels, which results in the disruption of nerve impulses and paralysis of the targeted insects.[28,29] It is particularly effective against a large number of mite and lepidopteran pest insect species. These 16-membered macrocyclic lactones are produced by fermentation of *Streptomyces avermitilis*. Abamectin and mectin analogues are important not only in crop protection but also as veterinary anthelmintics. Their discovery led to the Nobel prize in Physiology and Medicine in 2015 jointly awarded to Satoshi Omura and William Campbell. Abamectin has a RAI of 100%.

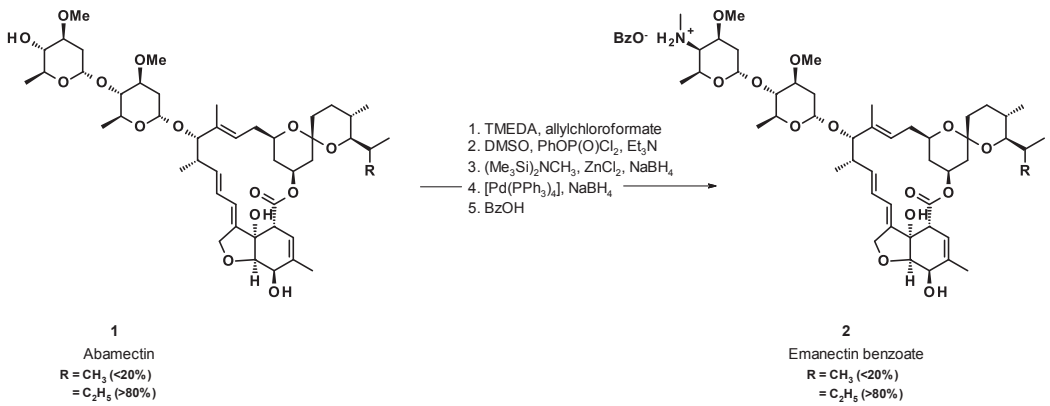
Emamectin benzoate (**2**, Scheme 1) is a semi-synthetic analog of Abamectin which was introduced to the market by Novartis (now Syngenta Crop Protection) in 1997. Emamectin benzoate is prepared from Abamectin by a selective protection of the most reactive allylic hydroxyl group at C_5 as an O-allyloxycarbonyl derivative, followed by the C4'' hydroxyl group oxidation to the ketone. Subsequently a reductive amination and deprotection gives **2**. This key transformation causes a 10-fold increase in activity[30] and a shift in the spectrum of pests controlled, as Emamectin benzoate shows greatly improved activity against a broad spectrum of lepidoptera.[31,32] Emamectin benzoate has as a RAI of 85%.

Illustrating the above-described benefits of natural products as active ingredients, the efficacy of Emamectin benzoate is outstanding with application rates as low as 10–30 g/ha.[17] Schematically, this represents roughly the equivalent of one teaspoon of the active ingredient to protect the area of a soccer pitch. As a comparison, use rates of crop protection agents in the 1960s were rather in the order or 1.0–2.0 kg/ha, and in 2000s in the range of 75–100 g/ha on average.[34]

2.2 *Spinosyns*

Spinosad is one member of the spinosyn class of natural products and is very effective against a broad range of chewing pests (caterpillars, leaf miners, thrips, flies, drywood termites, and some beetles)[33,35] which was introduced by Dow (now Corteva™ Agriscience) in 1997.[33] Spinosad is used in both organic and conventional farming, in particular in cotton fields, fruits and vegetables crops. These complex natural products act as nicotinic acetylcholine receptor agonists and are fatal to the targeted insects through ingestion or contact. Spinosad is produced by fermentation of the actinomycete *Saccharopolyspora spinosa* (RAI = 100%) and isolated as a mixture (85:15) of spinosyn A and spinosyn D (**3** and **4**, Scheme 2).

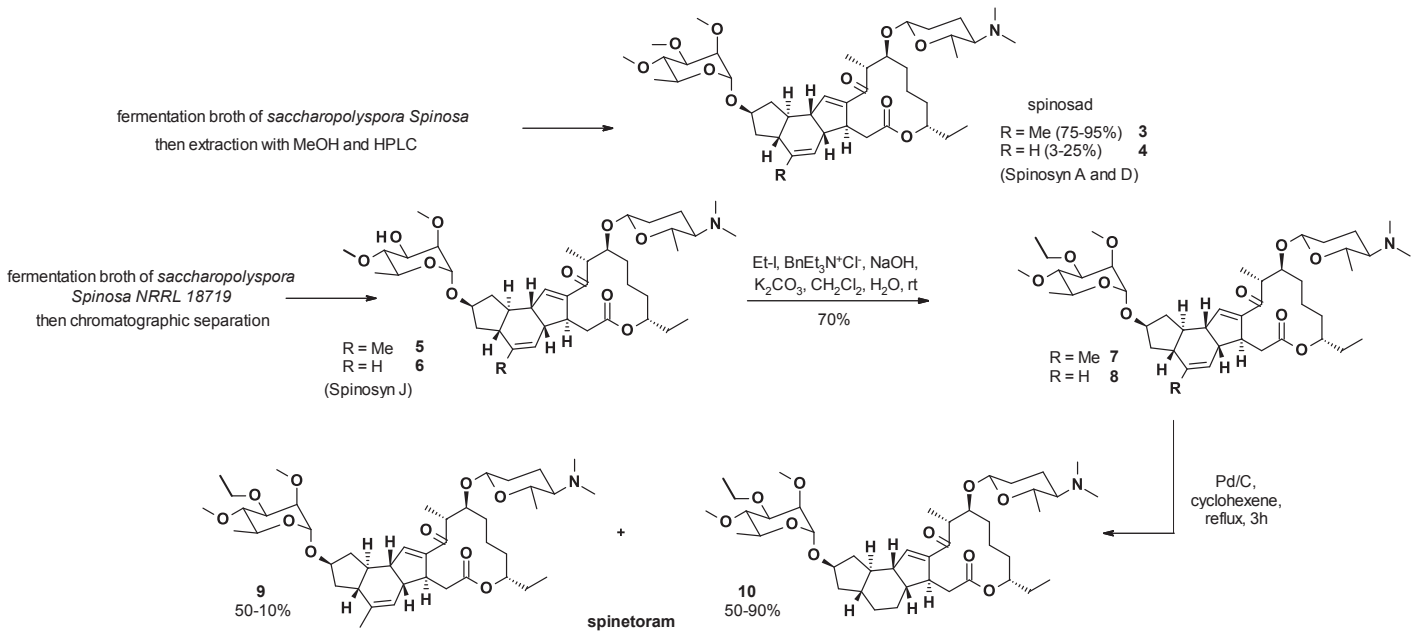
The physicochemical properties of spinosad (at pH = 7: log P = 4.0, *i.e.* relatively non polar and water solubility = 235 mg/L)[35] grant these isomers unfavorable properties for systemic activity (*i.e.* the ability for the active substance to move into and then through the plant sap, namely *via* translaminar movement and phloem/xylem transport). Substantial efforts devoted to derivatizing the spinosyn architecture were undertaken and it was found that modification of the D-forosamine and tri-O-methyl-L-rhamnose portions led to improved properties. Treatment of spinosyn J with an ethylating agent selectively alkylated the 3'-rhamnose position. The obtained mixture was then selectively hydrogenated at the 5,6 double bond position to provide a mixture of two compounds (**9** and **10**, Scheme 2) which showed greater potency, faster speed of action and extended duration of activity in comparison to spi-



1
Abamectin
R = CH_3 (<20%)
= C_2H_5 (>80%)

2
Emanectin benzoate
R = CH_3 (<20%)
= C_2H_5 (>80%)

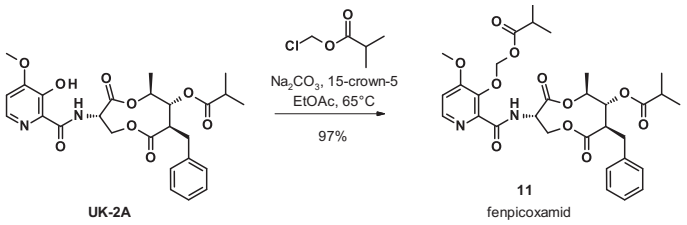
Scheme 1. Abamectin and Emamectin benzoate.



Scheme 2. Spinosyns.

nosad. These synthetic changes led to the marketing of spinetoram (RAI = 96%) which was introduced in 2007.

Spinosad confirmed expectations from natural products regarding safety and environmental aspects (*vide infra*). Chronic toxicity tests in mammals showed that Spinosad has no carcinogenic, teratogenic, mutagenic, or neurotoxic effects and is therefore considered innocuous for human health.[36] After delivering their biological activity, both spinetoram and spinosad are rapidly degraded to inactive materials in the presence of either natural or artificial light.[37–39] Both spinosad and spinetoram were awarded the EPA Green Chemistry award challenge in 1999 and 2008 respectively.[40]



Scheme 3. UK-2A and fenpicoxamid.

2.3 *UK-2A, Fenpicoxamid*

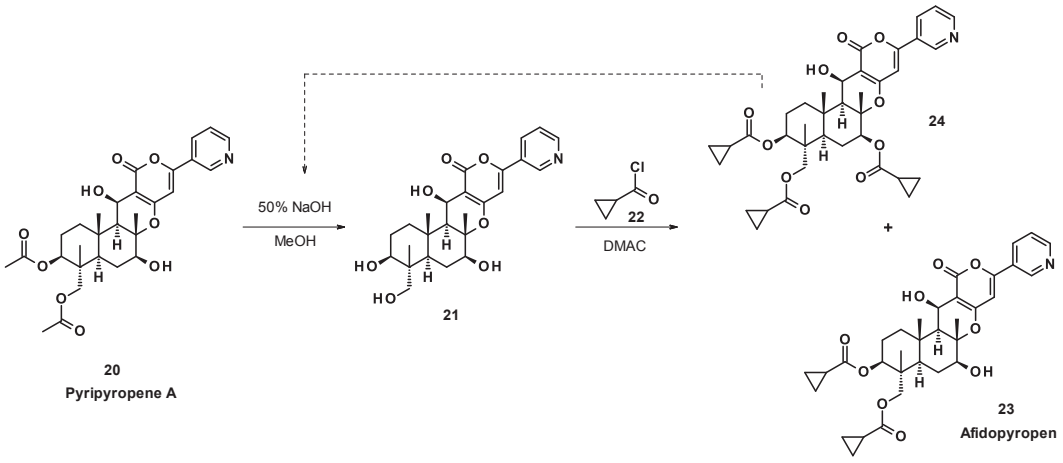
Dow AgroSciences LLC (now Corteva™ Agriscience) in collaboration with Meiji Seika Pharma Co. Ltd discovered the semi-synthetic active ingredient Fenpicoxamid (Inatreq™ active) which is highly effective for controlling pathogens in cereals and other crops.[41,42] It is readily prepared from the natural product UK-2A (Scheme 3), which is isolated from the fermentation broth of *Streptomyces sp.* 571-02.[43,44] Its molecular target is the Qi ubiquinone binding site of the mitochondrial complex III of the target fungi, different to the Qo binding site of strobilurins hence exhibiting no cross-resistance to these widely used fungicides. UK-2A exhibits a unique picolinamide moiety which contributes to its selectivity to the fungal Qi molecular target in contrast to the related antimycin antibiotic which is highly toxic to mammals and fish. UK-2A has a strong antifungal activity but is too unstable photolitically and is readily degraded – before it has time to deliver its biological effect – when exposed to air and light which are typical conditions occurring during foliar application on plant leaves. For example, when UK-2A is deposited as a thin film on a leaf, after 24 h less than 10% of the compound is still present.[42]

Improved stability (photostability in particular) was achieved by capping of the free hydroxyl group present on the picolinamide ring. The alkylation of UK-2A with chloromethyl isobutyrate led to the invention of fenpicoxamid (**11**, Scheme 3). Fenpicoxamid has a RAI of 82% and was introduced on the market in 2020 primarily for use in cereals in Europe. In comparison to UK-2A, in the same photostability test mentioned above, the newly prepared analog **11** was recovered in 100% yield after 24 h of exposure to the same conditions. As UK-2A, fenpicoxamid efficiently controls the fungus *Zymoseptoria tritici* which is essential for protecting important crops such as wheat. Unsurprisingly, fenpicoxamid acts as a pro-fungicide which is converted *in vivo* to natural product UK-2A, the active principle accounting for the biological activity. This example, similar to emamectin benzoate and spinetoram, nicely demonstrates how chemists are capable, with slight modifications, to use natural resources to their advantage. The synthetic modification appended to UK-2A (and therefore not 100% RAI) increases the fungal activity by a factor of roughly 1000 in comparison to the parent natural product.[42]

2.4 *Afidopyropen*

Afidopyropen is a semi-synthetic insecticide (RAI = 77%) with systemic efficacy for controlling sucking pests such as aphids (**23**, Scheme 4). It is currently being developed towards commercial introduction by BASF, Meiji Seika Pharma and the Kitasato institute.[46,47] The synthesis of Afidopyropen starts from the natural product pyripyropene, which is obtained by fungal fermentation process of *Penicillium coprobium*.[51] Pyripyropene A (**20**) has a tetracyclic core, appended with a pyridine ring and flanked with eight stereocenters. After fermentation, the natural product is further converted to Afidopyropen *via* a series of steps, namely, a saponification and a selective acylation of two of the four alcohols of **21** with cyclopropyl acid chloride **22** (Scheme 4). The latter step's selectivity is moderate only, but overacylated compound **24** can be recycled back into the first saponification step of the process further enhancing the overall efficiency.[47,48] Afidopyropen shares the same symptomology as commercial synthetic insecticides Pymetrozine and

Scheme 4. Afidopyropen.

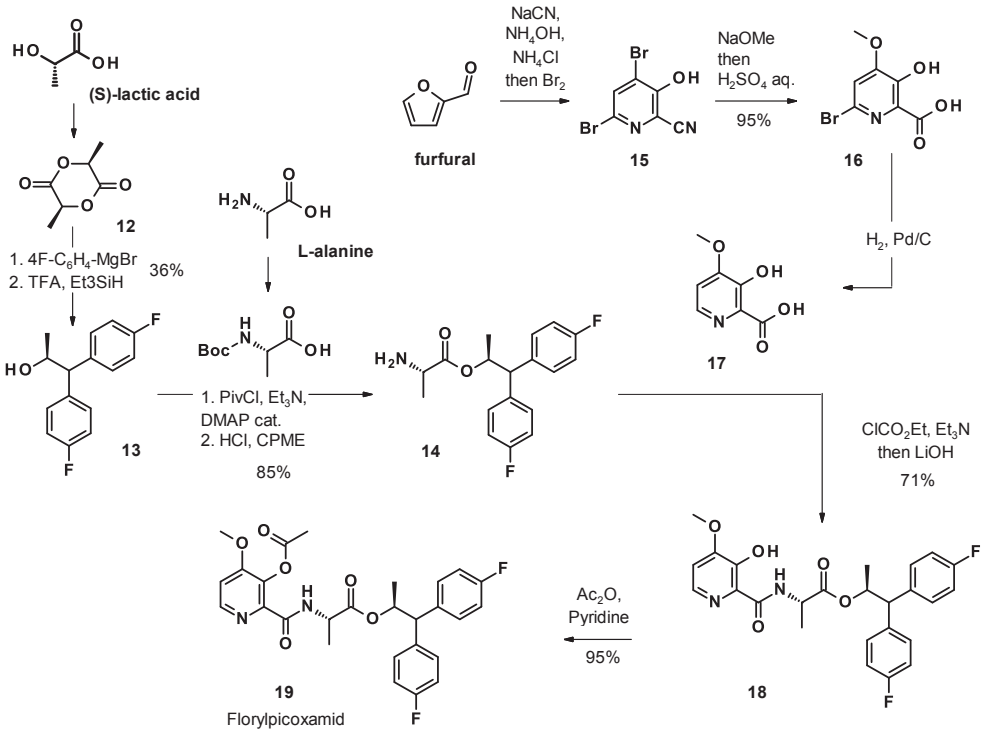


Flonicamid and causes uncoordinated locomotion and cessation of feeding in targeted insects.[49] It does so by interacting as a modulator of insect's vanilloid-type transient receptor potential (TRPV) chordotonal channels (new IRAC group 9).[50] This innovative new active ingredient is more potent than pymetrozine and no known cross-resistance to other commercial insecticides has been observed.

3. Platform Molecules as Raw Materials for Crop Protection Agents: Florylpicoxamid

The deconstruction of UK-2A's macrocycle gave birth to another crop protection product, florylpicoxamide (Adavelt™ active) (**19**, Scheme 5).[51] This novel active ingredient has a broader spectrum of action *vs* fenpicoxamid and enables, for example, good control of powdery mildew pathogens.[41,51] Other substantial benefits include rapid plant uptake, systemicity (*i.e.* the ingredient translocates throughout the plant for its protection) and curative activity (*i.e.* it stops the dissemination of the pathogen once the plant has been infected). Florylpicoxamid is not prepared from a natural product starting material, but scientists from Corteva™ Agrisicence have made outstanding use of renewable resources as starting materials.[52–54] Furfural is derived from lignocellulosic biomass and is a raw material that mostly comes from agricultural waste. Reacting furfural with sodium cyanide in the presence of an ammonium source gives a transient Strecker intermediate which, when treated with Br_2, provides the tetrasubstituted pyridine **15**. Further sequential treatment of **15** with sodium methoxide and aqueous sulfuric acid gives **16** which is finally converted to **17** by deletion of the C_2-Br atom *via* hydrogenolysis. Chiral alcohol **13** is efficiently assembled from (*S*)-lactic acid which is readily available from renewable carbohydrates sources. Finally, the third raw material L-alanine is industrially produced from the decarboxylation from L-aspartic acid using immobilized *Pseudomonas dacunhae* cells[55,56] (by the enzyme aspartate 4-decarboxylase) (L-alanine may also be produced synthetically from acetaldehyde and hydrogen cyanide). Overall, 42% of the atoms present in florylpicoxamid are likely to originate from renewable resources.

Scheme 5. Florylpicoxamid.



Florylpicoxamid shares a few similarities with fenpicoxamid. It is also a pro-fungicide and converts *in vivo* to the deacetylated intermediate **18** which acts as the active principle. The mode of action of florylpicoxamid and fenpicoxamid are identical and both agents provide control of pathogens know to be resistant to other classes of fungicides (for example strobilurins).[51] The first sales of florylpicoxamid are expected for the Asia Pacific region in 2023.[47]

4. Amino Acids as Raw Materials for Crop Protection Agents: Peptide SPEAR-T® and Nanobody Evoca®

Another highly attractive class of renewable building blocks for the generation of crop protection agents is represented by naturally occurring amino acids.[57] Peptides and proteins produced by fermentation in recombinant organisms could constitute a truly carbon-neutral solution to protect crops. Key opportunities include a very favorable environmental impact profile since ultimately benign amino acid metabolites are generated. Additionally, these metabolites could also serve as nutrients for the plant[58] they initially aimed at protecting from aggressors.

In 2019, the US-based biotech Vestaron Corporation brought to the American market the first spider toxin-based bioinsecticide, GS-omega/kappa HXTX-Hv1a, which was trade named as SPEAR®.[60] This peptide was found in the venom of the Blue Mountains funnel-web spider and acts as a positive allosteric modulator of the insect nicotinic acetylcholine receptor at a site different from spinosyns and neonicotinoids,[59] hence exhibiting no cross-resistance to these classes. It is manufactured by recombinant yeast fermentation, taking sugar derived from corn as its primary energy input (RAI = 100%). Quite notably, SPEAR® demonstrates no effect on mammalian nor on non-target invertebrate ion channels and it consequently shows no sign of toxicity against humans, beneficial insects such as bees[61] or other environmental targets such as aquatic organisms. Another unique feature of the product, thanks to its proteinaceous nature, is that it can be applied in the field up to the very same day of harvest (zero-day pre-harvest interval). SPEAR® received the 2020 EPA Green Chemistry Challenge award.[62]

Another biotech company based in Belgium, Biotalys (previously Agrosavfe), recently entered the submission process for registration in the US and EU of the first nanobody-based biofungicide, Evoca®, to control powdery mildews and *Botrytis cinerea* in fruits and vegetable crops.[63] This small protein active ingredient was discovered from libraries of antibody fragments generated by immunization of camelids with fungal antigens.[64] While Vestaron harvested a bioactive peptide directly from Nature resulting from millions of years of Darwinian competitive evolution between spiders and their prey, the Biotalys discovery platform was able to mimic and accelerate such evolutionary processes in the laboratory towards the targeted control of specific fungal diseases with small camelid antibodies.

Taken together these two recent examples of innovative products and approaches illustrate the innovation potential of peptide and protein-based active ingredients to deliver renewable crop protection solution to control insect pests and plant diseases exploiting natural evolutionary mechanisms.

5. Perspectives

As demonstrated by the abovementioned examples, a mindset shift towards the use of raw materials not coming from fossil resources is already underway in the crop protection industry. It is clear that reducing the current high dependence on oil-derived resources will contribute to reducing the CO_2 footprint of manufacturing such compounds. However, as of today only very few crop protection agents are prepared by using renewable resources. Therefore, even more ambitious endeavors must be supported to meet the stringent environmental and regulatory requirements of the future, empowered by emerging technologies.

In this context new modalities pioneered by pharmaceutical research[65] represent an opportunity to further apply green chemistry principles in agrochemical discovery. RNA interference (RNAi) technology has been recently recognized as a promising approach to control insect pests[66] through ingestion of sprayable double-stranded RNA fragments (dsRNAi). Inspired by natural mechanisms such as defense against viruses, the dsRNAi induces, after cellular uptake in the insect gut, the specific association with a targeted mRNA through sequence complementarity leading to the mistranslation of the corresponding essential protein eventually leading to the death of the insect. Through this process the dsRNAi is highly selective to the target pest protein, which it has been designed to control. It can be produced in recombinant cells and turn them into benign nucleic acid metabolites in the field overall representing a highly attractive renewable pest control tool. Bifunctional protein degraders such as PROTACs have also recently emerged as a novel drug modality,[67] triggering an enormous interest in the pharmaceutical field and has witnessed recent investment in the crop protection area as well,[68] anticipating the benefit of its unique pharmacology. Interestingly the first known E3 ubiquitin ligase ligands are natural phytohormones such as auxin, gibberellin or abscisic acid,[69] therefore one can conceive plant PROTACs as a promising platform to generate neo-function to these natural products leading to renewable plant physiology modulators through protein degradation. Finally, it is worth considering that natural products also represent a rich source of electrophilic reactivity, which often correlates with their antimicrobial activity.[70] Understanding the protein targets of electrophilic natural products and deconvoluting their complex polypharmacology is essential to fully leverage their potential. Modern chemoproteomic techniques will facilitate accurate target annotation, abrogating the potential risks associated with developing electrophilic natural products as modern crop protection agents with low environmental impact.[71]

Embedding raw materials coming from sustainable and renewable resources is a key principle (#7) from the 12 Green and Sustainable principles formulated by J. Warner and P. Anastas in 1998.[53,72] At Syngenta, we have and are continuing to rethink agrochemical innovation, guided by the 12 Green Chemistry Principles. We are actively pursuing a science-based approach to the sustainable design of new ingredients.[73] Onboarding renewable feedstocks into the design of active ingredients is increasingly appearing as demonstrated by the synthesis of thiametoxam analogs from the available natural product Nootkatone.[74] Such an aim is a clear objective on our strategic agenda and we are intensifying our efforts in this direction. A key observation is that retrofitting an established process to a given active ingredient towards more sustainable raw materials is often possible but arguably an area where chances of success are not high. A more promising approach is to follow the '*benign by design*' principle and embed such raw materials as early as possible in discovery programs. In addition to a direct reduction of the carbon footprint, such starting materials may offer additional advantages: a) they often lead to a chemical space less explored (for example when using terpenes as starting materials); b) active ingredients embedding such motifs in their architecture may be metabolized back to these basic molecules or benign metabolites and therefore provide improved environmental end-of-life profiles (Design for degradation, Green chemistry principle #10).[72]

From an industrial point of view, we rely on the support from academic innovators and their ability: i) to discover new renewable platform molecules and b) to discover efficient, selective and complementary methods to functionalize such starting materials derived from renewable resources. To incentivize research in the area of green and sustainable chemistry, including the use of renewable feedstocks as a key pillar, Syngenta, together with the Swiss

Chemical Society as hosting institution, created in 2020 an award aiming at recognizing outstanding contributions from academic investigators.[75] Not least, we rely as well on the help from common chemical suppliers to support the availability of the newly developed 'green' building blocks to render as low as possible the barrier to adoption.

6. Conclusion

Since the 1970s, chemists have continuously improved the state-of-the-art of crop protection agents. Natural products have served since many years as a primary source of innovation for the design of agrochemicals and continue to do so. They can themselves be used as such, in which case they come 100% from renewable resources. Chemists have also demonstrated their ability to enhance what Nature provides by modifying natural products and designing highly efficient semi-synthetic crop protection agents.

Efforts to prepare new crop protection agents from renewable resources, for example originating from lignin biomass, from terpenic derivatives or from fermentation processes are starting to become visible. More examples will surely be reported within the next few years. There are still a lot of challenging and exciting targets to be met in the field. For example, as of today, very few herbicidal active ingredients derived from natural and renewable resources have entered the market. Although several natural products have shown promising profiles, such as hydantocidin[76] or the recently reported aspterric acid,[77] chemists have not yet succeeded to turn them into useful products for crop growers.

Received: July 5, 2021

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