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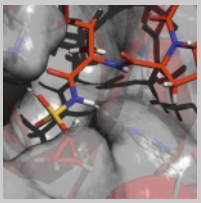

Medicinal Chemistry and Chemical Biology Highlights

Division of Medicinal Chemistry and Chemical Biology
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Where Do Agrochemicals Come From?

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Ensuring a safe and sustainable food production is of paramount importance to feed a growing world population. Farmers face an uphill struggle to protect their crops from insects, weeds and pathogens that compete for these foods especially in face of climate change which accentuates extreme weather events, pest pressure and promotes rapid pest shifts.[1,2] This must be achieved whilst preserving the environment and the health of future generations.

The industry is responding to these challenges by actively evaluating precision agriculture technology in order to reduce overall pesticide use while developing natural product pesticides and new modalities for crop protection such as biologicals, peptides[3] and RNAi-based solutions to provide complementary solutions to synthetic chemical pesticides. Until these concepts establish their role in the marketplace, a new generation of effective, selective and safe small molecules must be designed to comply not only with current regulations but also to anticipate the rapid pace of change in the regulation of synthetic crop protection products around the globe.

At the same time many known chemotypes with a specific mode of action are no longer effective against resistant pests and novel resistance breaking ones must be identified along with one acting on new biological targets. The more complex set of features, in addition to basic pest control, a modern agrochemical must meet results in a higher attrition rate in the discovery process. All these factors result in an urgent need for novel starting point. But how are new leads targeting novel targets discovered?

To understand the inception process of new agrochemicals, we analyzed 20 years (1998–2018 covering 218 structures) of agrochemical research focusing on public agrochemical ISO common names which are the earliest public information on development of novel agrochemicals.[4] Such a long-view enables to de-bias against recent one-off events and to focus on trends. We isolated the new chemotypes from this set and looked into the most likely origins of each these and categorized them in seven categories: 1) 'Chemistry-Driven' where no obvious biological hypothesis was used and chemical novelty was the goal; 2) 'Chemistry-Driven in Known Class', where the new chemotype was invented as part of SAR exploration project within a known chemical class; 3) 'Hit other Mode of Action (MoA)/indication' where a compound made for one project is active in a different indication or mode of action than the lead series; 4) 'Natural Product', where an exact natural product was used; 5) 'Natural Product Analog' where post synthetic modifications were made; 6) 'Natural Product Inspired' where a synthetic analog of a known natural product was the starting point; 7) 'Random Screen' where externally purchased screening compounds were the origin. The result of this analysis is summarized in Fig. 1.

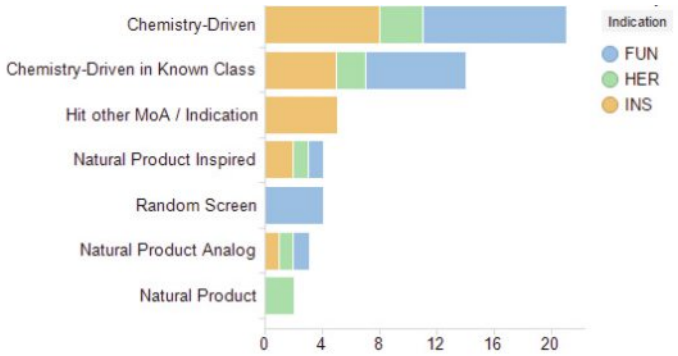

Fig. 1. Categorization of the origin of '1st in class' agrochemicals that have received an ISO common name between 1998 and 2018 (218 total) based on data form the website *http://alanwood.net/*. FUN – Fungicides, HER – Herbicides including safeners and stimulants, INS – Insecticides. The origin of 17% of new agrochemical is unknown or was not determined.

The first interesting finding was that most agrochemicals have their origins in serendipitous chemistry-driven approaches. Interestingly these starting points mostly originate from within industrial labs and are less often from commercial screening collections. Natural products and natural products inspired compounds are the second biggest source of starting points.[5] Surprisingly, to the best of our knowledge no current agrochemicals with an ISO name originate from a hit coming from *in silico* rational design, virtual screening or an '*in vitro* first' screening campaign on a known target.

Why are chemistry-driven strategies around known bioactive areas so successful? The agrochemical screening model primarily relies on an '*in vivo* first' (phenotypic screening) approach where all new compounds are screened against a fixed panel of agronomically relevant pests across indications (disease, insect and weed control). Inactive compounds will rarely be screened again. With this strategy an *in vivo* active compound must at the same time have the right bioavailability properties (ADME) to arrive at the target in sufficient concentration and effect the target sufficiently strongly so that the pest displays observable symptoms (*i.e.* lethality). This is the ultimate fail fast strategy which ensures that lack of efficacy is less of an issue in later stages by circumventing the difficult *in vivo* to *in vitro* translation.

The extreme selection pressure of an *in vivo* first approach favors an exploration strategy that aims to generate novel chemical input in a very favorable ADME space. Unfortunately, ADME understanding on the behavior of small molecules across agronomically relevant plants, insect and fungi species is extremely sparse relative to knowledge for mammals and only rudimentary

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models exist.[6] A pragmatic approach to circumvent this issue is to recycle parts of existing agrochemicals in the hope that the favorable ADME feature will carry through. In the simplest form this means using so-called 'Intermediate Derivatization Methods'.[7] The citation from Sir James Black "The most fruitful basis of the discovery of a new drug is to start with an old drug" is even truer in agrochemistry than in medicinal chemistry.

So, the art of discovering new leads is about skillfully navigating the space between the known bioactive chemical space and completely uncharted space. Creating the new from the old while avoiding reinventing the wheel. Eagleman and Brandt provide a useful framework for human creativity which applies itself very well to chemical space exploration. They propose that all human creativity functions using a combination of three processes bending, breaking, blending ('three Bs').[8] Bending is a makeover of an existing prototype through alteration. Breaking is fragmentation and making something new with the fragments. Blending combines two or more sources in novel ways.

Fig. 2 illustrates a thought experiment on how the marketed agrochemicals Fluopyram and Fluoindoziline could have been discovered using the three Bs framework from the bending of the 'magic pyridine' (so-called because at least 10 active ingredients make use of it).[9] What is striking is that a simple carbon homologation from aminomethyl in Fluopicolide to aminoethyl in Fluopyram leads to a change in mode of biological activity.

Fig. 3 illustrates a similar thought experiment on the three Bs process across several chemical classes, indications and several decades of research. Changing a pyridophtalamide core for a nitrophtalimide one induced a conformational change and a switch from herbicidal activity to a weak insecticidal one ultimately leading to Flubendiamide. Searching for an alternative to a C_3F_7 group in Flubendiamide led to the introduction of an isoxazoline which displayed weak insecticidal activity but a different phenotype. Reversing the amide and reoptimizing the physicochemical properties led to Fluxametamide acting through a novel GABA antagonist mode of action.

Seemingly small structural alterations in the backbone of a bioactive compound can lead to a significant conformational change which in turn can lead to binding to a new target while retaining many of the favorable bioavailability properties of the parent agrochemical. The key for agrochemical discovery is to test all compounds on panels of phenotypic assays beyond the desired indication and keep an eye out for unusual weak hits.

Although chemistry-driven approaches are tried and true methods for discovery, these are not the sole research axes in the agrochemical industry and target-based and *in silico* approaches are being actively pursued. They in fact complement each other by providing new bioactive chemical matter to test on yet unvalidated protein targets.

We suspect these observations hold true in medicinal chemistry where despite the more sophisticated discovery process and techniques, the origin of many novel clinical trial candidates also have their roots in existing drugs.[10] For the same reasons drug repurposing is a very active field of research.[11]

Go out and bend, break and blend your active series to make new discoveries!

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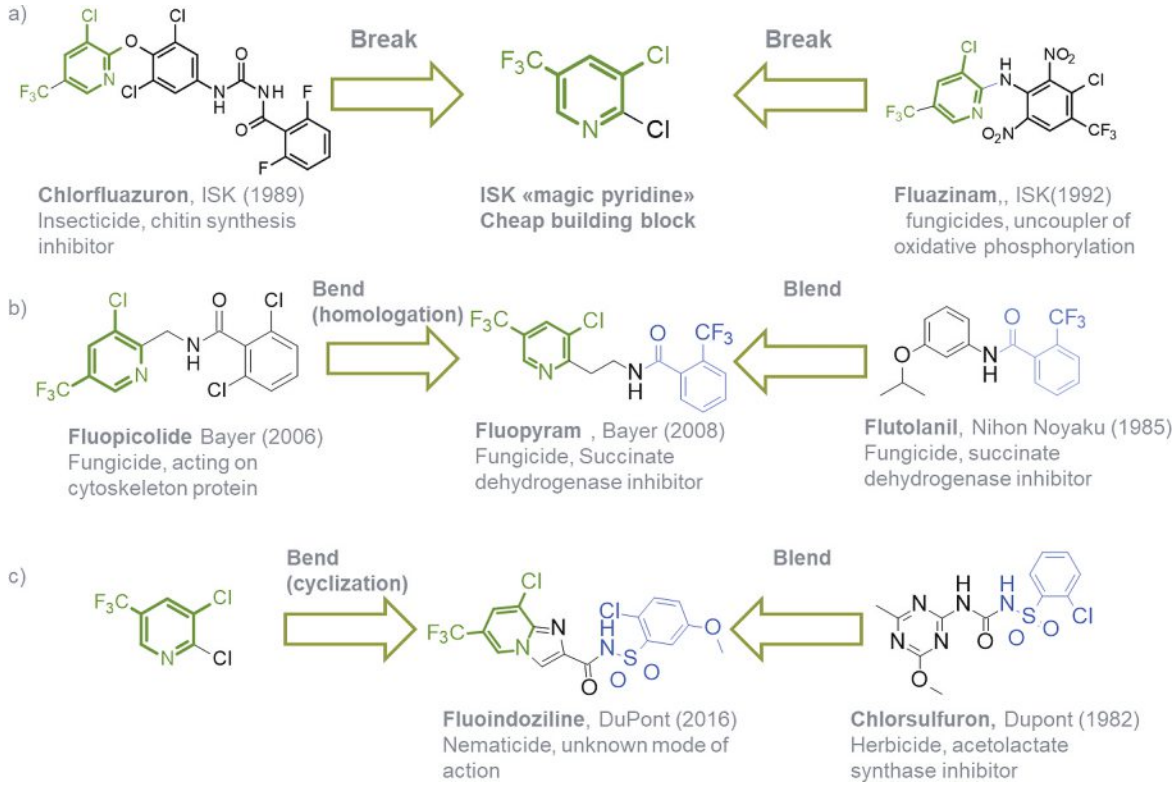

Fig. 2. Illustrative example of the thought experiment on how an agrochemical could have been invented using bending, breaking and blending of existing starting points. a) Breaking, identification of a common heterocycle in two different agrochemicals; b) Bending Fluopicolide and blending in Flutolanil to generate Fluopyram with a different mode of action.

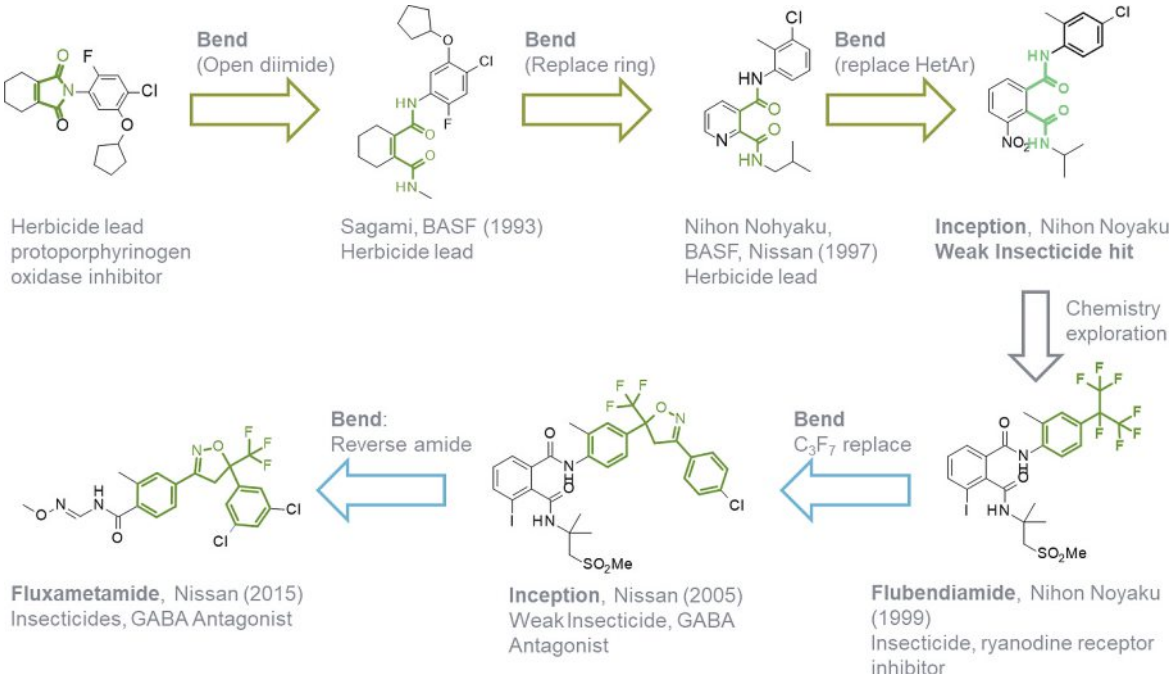

Fig. 3. Illustrative thought experiment of how successive bending processes could have led to the invention of three different chemical classes all acting on different target across plants and insects.

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