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Research paper

Bioactivity-guided mixed synthesis accelerate the serendipity in lead optimization: Discovery of fungicidal homodrimanyl amides

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This work was dedicated to Prof. Wenjun Wu on the occasion of his retirement from Northwest A&F University.

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ABSTRACT

The bioactivity-guided mixed synthesis was conceived, in which the designed mix-reactions were run in parallel for simultaneous construction of different kinds of analogs. The valuable ones were protruded by biological screening. This tactic will facilitate more rapid incorporation of bioactive candidates into pesticide chemists' repertoire, exemplified by the optimization of less explored homodrimanes as antifungal ingredients. The discovery of **D9** as a potent fungicidal agent can be completed in <2 weeks by one student, with EC_{50} of 3.33 mg/L and 2.45 mg/L against *S. sclerotiorum* and *B. cinerea*, respectively. To confirm the practicability, time-efficiency, and reliability, specific homodrimanes (82 derivatives) were synthesized and elucidated separately and determined for EC_{50} values. The SAR correlated well with the intentionally mixed synthesis and the potential was further confirmed by the in *vivo* bioassay. This methodology will foster more efficient exploration of biologically relevant chemical space of natural products in pesticide discovery, and can also be tailored readily for the lead optimization in medicinal chemistry.

1. Introduction

Improving food production with limited cultivated land represents a significant challenge as the global population is ever increasing and is projected to over 9 billion by 2050 [1]. How to eliminate or cut down the estimated 20–40% global crop losses caused by fungi, insects, and weeds becomes increasingly urgent [2]. With the occurrence of resistance to many currently available agrochemicals, there is a continuing requirement for the development of novel agrochemicals to address the worsening pest control problems. As precious gifts to human beings in the competition with various pests, natural products co-evolved with biological systems for millions of years and can be used directly or served as scaffolds for further optimization through semi-synthesis or derivative synthesis [3]. They can also inspire the development of new agrochemicals with the undiscovered mechanism of action. >60% of all action mechanisms of pesticides can be attributed to natural products or natural products inspired synthetic pesticides [4].

It is undoubted that natural/nature-inspired products play a pivotal role in modern crop protection. Semi-synthesis or derivative synthesis is deemed to be a simple but powerful approach to the discovery of more promising agrochemicals, exemplifying emamectin benzoate and spinetoram [4], and other natural products [5–7]. Due to the simple operability and prevalence of this tactic, etherification, esterification, imidization and amidation etc. have been being carried out for optimization and exploration of structure and activity relationship in many labs, especially for the “tinpot” abs, based on natural products with a hydroxyl, carboxyl, ketone or amine functional groups. A staggering amount of simple analogs or derivatives of natural products were synthesized and elucidated, then biologists have to deal with a series of complicated screening procedures. Though the synthetic procedure was not challenging, the structure elucidation and biological evaluation were tedious and time consuming without cost-efficacy. Moreover, the stream of new targets from genomics and proteomics require

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new chemotypes which are difficult to generate using a pure combinatorial chemistry approach [8]. Biology-oriented or bioactivity-guided synthesis has proven their worth in mapping the chemical space and the discovery of novel and biologically active structures in medicinal chemistry [9,10]. Furlan group introduced a strategy to furnish natural product-like libraries with interesting biomolecular properties through chemically engineered modification or chemical diversification of nature product mixtures (Fig. 1) [11,12]. These tactics underscore the potential for further application in both basic research and drug discovery.

2. Tactic and design

In contrast to the rapidity with which scientific information on the isolation of natural products was published, the *de novo* design of agrochemicals with natural products as starting points and discovery of more promising ones often remain slow. Methods to rapid assess and identify bioactive derivatives are desirable and will facilitate the process of novel pesticide discovery.

With the aim of finding more promising nature-like products for crop protection, we report here a strategy to generate and confirm the bioactive compounds through bioactivity-guided mixed synthesis. Our idea and design are relatively simple, and our approach to modifying the natural product is based on chemical functionalities. An easily accessible and bulky natural product with a specific structure was chosen as a starting point, and functional group based modification with different reagents will be implemented in one pot. A considerable number of compounds will be generated and the changes in the biological properties of the mixture will be hypothesized to occur consequently. The different reaction systems will be categorized by reaction types, and the hypothesis is that the bioactivity is mainly due to the core functionalities or the categories of modification rather than a tiny change in substituents. This approach will accelerate the discovery of molecules of promising biological interest without purification and elucidation of all the synthesized compounds, also featured simple operability, cost-efficacy, and time-efficacy (Fig. 2). Herein, we will take our efforts to explore the potential of homodrimanes as fungicidal ingredients to elaborate this model (Fig. 3).

3. Results and discussion

3.1. Chemistry

3.1.1. Drimane sesquiterpenoids as a model

Generally, if a flexible and a rigid ligand can form the same pattern of hydrogen bonds and hydrophobic interactions with the protein, the rigid ligand will exhibit much stronger binding due to lower entropic losses [13]. Both structure rigidity and chirality are deemed to be well-established factors in drug discovery to enhance the specificity and efficacy. Catering to those essential requirements, natural products and nature-inspired compound libraries have always been regarded as valuable sources for biologically active molecules. With the aim of discovering the green crop protection chemicals, which are not only novel in the mode of action and highly selective to pest species, but also possess favorable environmental and human hazard and risk potentials, our efforts to the design and rapid construction of chiral fungicidal

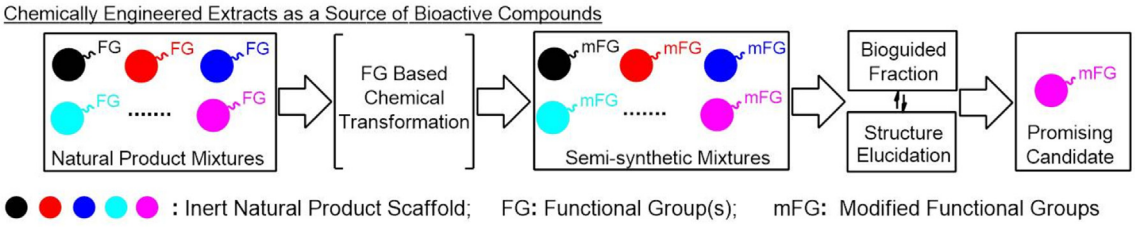

Fig. 1. Chemically engineered extracts as a source of bioactive compounds.

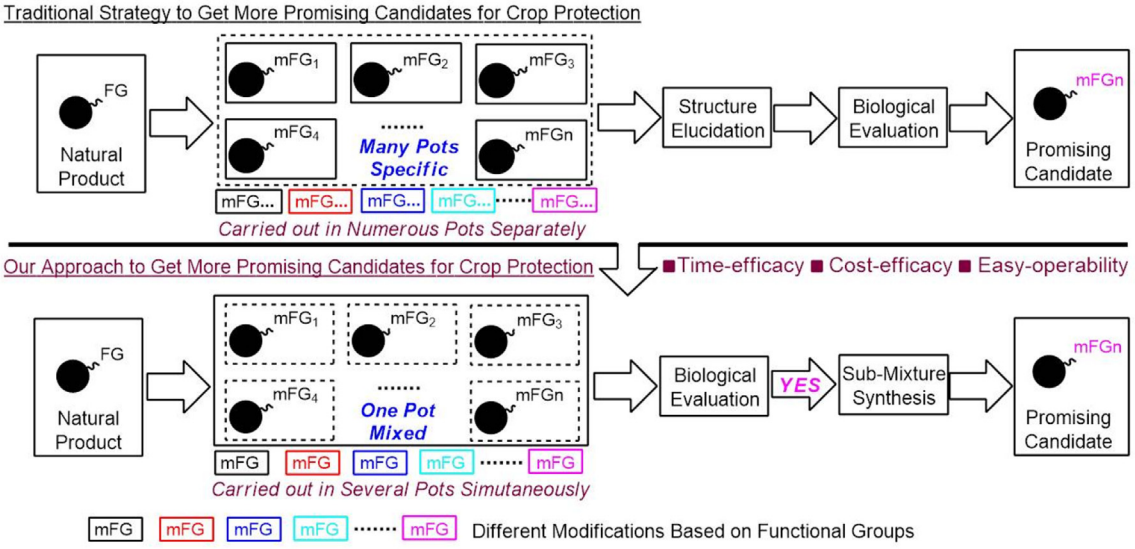

Fig. 2. Our approach to find promising pesticides candidates.