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Current Status of Pesticide Chemistry Research and Development and Perspective on the Future

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ABSTRUCT

The global agrochemical market has recently fluctuated by about US$ 30,000 million. Despite the fact that overall sales have not significantly increased over the past ten years, all pesticide categories' chemistry has undergone significant changes. The creation of new structural prototypes has made it possible for new products to replace some outdated insecticides. Lead chemicals for novel insecticides have continued to be produced using classical synthetic chemistry and natural ingredients. Computer-assisted pesticide formulation in three dimensions is now achievable because to the bimolecular identification of numerous pest control drugs' mechanisms of action at the receptor and enzyme levels. Environmental factors must be considered both throughout the manufacturing process and at the end-product level (green chemistry). In addition to biological and biotechnological tools, chemicals used in food and fiber production, disease vector control, and potentially new markets (such as bio renewable it will be essential to improving the wellbeing of the growing world population (for industrial raw materials and energy sources).

INTRODUCTION

Pesticides are a general word for natural, synthetic, and semi-synthetic crop protection chemicals and disease control chemicals. Over the past century, pesticides have been essential to modern agriculture and the management of disease vectors that impact both humans and animals. Agrow (2006) reports that the market for pest management agrochemicals reached US$33.6 billion in 2005, a 45% increase from sales in the 1990s. Pesticide exports increased by more than twofold between 1990 and 2005, reaching a value of almost US$16 billion, as reported by FAOSTAT (2006), demonstrating the consequences of globalization and commerce. However, given the significant chemical alterations that have occurred in this field, which is constantly evolving, these numbers do not accurately reflect them.

Recent studies (Crop Life, 2005; Phillips McDougall, 2005) have shown that the significant Companies that use agrochemicals typically spend 7.5% of their annual revenue on developing new enhancing the effectiveness and security of their current crop protection products. Typically, it takes 8 to 9 years and $200 million to develop a new product from conception to first sales. 53 million are employed for research on toxicology and environmental destiny, 67 million for biological studies, and 80 million for chemistry-related studies. The exploration and development of novel pesticides with an emphasis on specific components will be the main topic of the ensuing chemically focused overview.

Need for New Compounds

The following new diseases and pests, especially invasive species, require innovative control strategies:
Resistance to currently used control agents;

1. Enhancements to current products or replacement with new chemicals that are more ecologically benign and less destructive to non-target animals; and
2. Brand-new pests and ailments.
3. Monetary rewards.

Resistance is one of these challenging factors in the development of new pesticides. The risk of acquiring resistance to a particular therapeutic type increases with sustained reliance on a given class of drugs in a field. Other classes that employ the same action method but have different structural properties may also resist it. Although many of these examples are based on laboratory discoveries, field performance issues have frequently been documented. Resistance to at least one pesticide active ingredient has been found in over 540 insect species, over 300 weed biotypes, and about 350 plant pathogen isolates (IRAC, 2005; Heap, 2006; HRAC, 2005). The adoption of novel chemicals, ideally with a distinct mode of action, is one of the potential ways to reduce the risk of its creation. As a result, crop security has come to rely heavily on resistance management.

Ways to Find New Bioactive Compounds

According to a recent estimate, some 100,000 compounds must be studied before a new pest control treatment may be sold. These novel materials might be obtained by:

Screening of naturally occurring products; serendipity, computer-assisted molecule design using the three-dimensional (3D) structure of the target site, screening of randomly generated synthetic compounds, such as in-house or purchased chemical libraries, enzyme inhibitor design based on essential biological reaction processes, and so on. The analogue design employs structural alterations of substances derived from nature or made by other businesses.

Some of the Above Points Will Be Covered In the Paragraphs That Follow

Insecticides are made from natural substances. Natural products are good sources of structural diversity and specific chemical scaffolds that have proven to be able to bind to target proteins because of their ecological role. Several pesticides are derived from plants, microbes, or animals, despite the fact that most of the present pest control chemicals are synthetic compounds (Ovary, 2002, 2003). These resources are often renewable, and classical breeding or genetic engineering might result in strains that biosynthesize compounds that were formerly generated in low yields that were not commercially feasible. Aside from using synthetic precursors (like analogues of amino acids) that are later incorporated, directed biosynthesis also uses synthetic starting materials.

Enzymes can introduce innovative and complicated structures into the finished molecule that would be difficult to create by the synthesis of chemicals. Systematic analysis of microbial or plant extracts will occasionally find distinct bioactive chemicals.

A few pesticides are semi-synthetic compounds created by appropriately synthetically altering natural materials. It is anticipated that there will be an More of these semi-synthetic derivatives with extremely complex structures and improved effectiveness against pests resistant to the original natural substance are being produced. Here are a few representative cases of naturally occurring substances with various structural make up's and their synthetic equivalents.

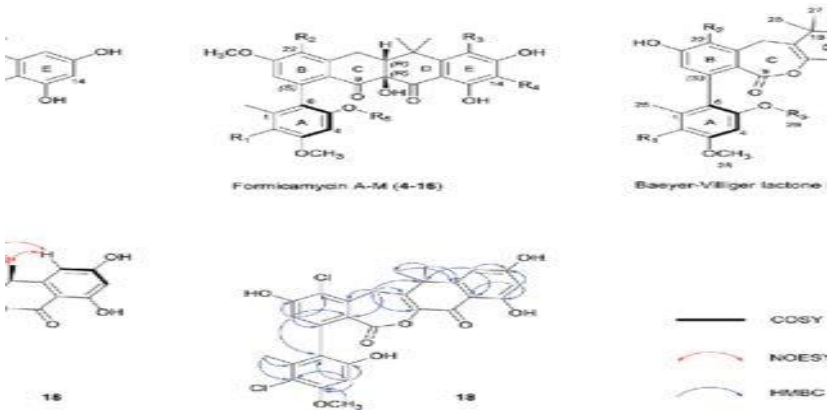

Figure 1 shows the structural variety of a few natural products and other relevant pest control products. For eprinomectin and XDE-175, only the main portion of the manufactured substance is displayed.

A natural product for agricultural usage should be: a) effective against target species; b) safe and selective; c) standardised in terms of content and formulation; and d) easily available. As If any of these conditions are not met, proper synthetic changes or analogue design can lead to marketable pest control agents, as was the case with the unstable natural strobilurins that served as models for a wide variety of synthetic fungicides (such as azoxystrobin, Figure 1). Eprinomectin is one of the parasiticide avermectin's semi-synthetic derivatives. Fermentation, which created complex core structures enabling semi-synthetic changes, recently enabled the creation of a second-generation version of the microbial pesticide spinosad, XDE-175 (Figure 1) (AGROW, 2006b; Sparks et al., 2001). It is projected that the industrial manufacture of structurally complex substances would increasingly rely on the genetic engineering of difficult biosynthetic pathways into manageable host (micro) organisms.

Synthetics screening for discovery The discovery of pesticides has historically relied heavily on synthetic chemistry. Numerous modern pesticides can be linked to research projects that were started solely on chemical grounds, usually about academically exciting structures. Systematic bioassays of novel synthetic compounds can revive curiosity about a long-forgotten mode of action. As a result, the discovery of imidacloprid revived interest in research on the nicotinic acetylcholine receptor, and neonicotinoids, such dinotefuran in Figure 1, appeared within 15 years. Controlled about 15% of the pesticide market. Ryania, a naturally occurring insecticide, attacks the ryanodine receptor. is a recently rediscovered insecticide site of action. Other insecticides with novel modes of action will undoubtedly be made possible

by the recent discovery of rynaxypyr, a new anthranilic acid diamide derivative, and flubendiamide, a novel phthalic acid diamide with a physically comparable structure (Figure 1) (Nauen, 2006).

This established field of study is nevertheless worthwhile to continue since it has the potential to yield novel structures.

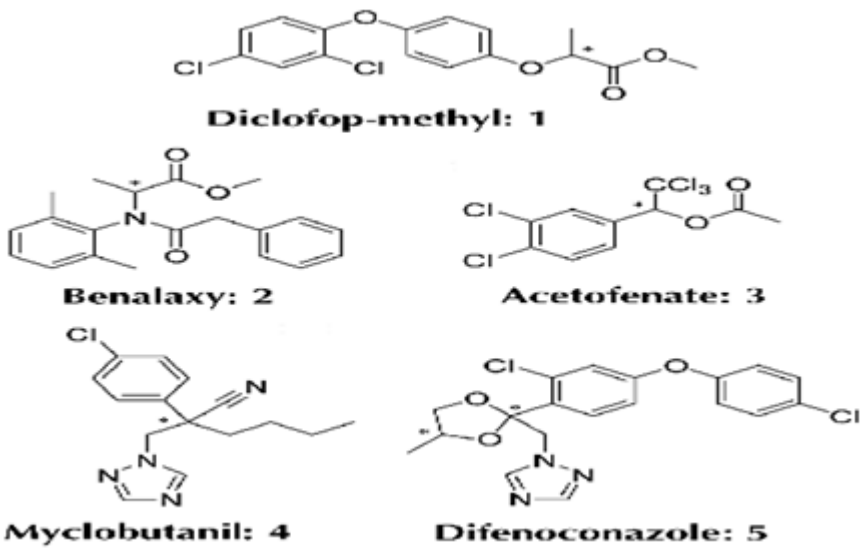

Figure 2 shows the chemical composition of a few pesticides with new architectures. The chiral centre is indicated by an asterisk (*).

Chemistry in combination. A procedure known as combinatorial synthesis uses a sequence of molecular building blocks to quickly prepare vast sets (libraries) of structurally related molecules. This method produces surrounding core structures; there are tens of thousands of analogues, either in solid or solution. phases, generally within days. While early efforts focused more on quantity to create thousands of closely related substances, frequently as undifferentiated mixtures, today's efforts emphasize quality and diversity. While reports on combinatorial chemistry in pesticide research are still rare, it has significantly impacted Pharmaceutical sector lead compound generation and optimisation (Kleschik et al., 2003). The combinatorial strategy's initial practical application was the discovery of a pyrazole A library of 8000 amides and esters contained the carboxamide (Figure 2), which has herbicidal activity at 100 g/ha (Parlow and Normansell, 1996). Recently, sets of 5–50 member libraries of acylamino ketone ecdysteroid receptor agonists produced numerous compounds with strong in vitro activity as analogues of dibenzoyl hydrazine insecticides (Garcia et al., 2005). Several fungicidal chemicals were produced by a comprehensive, whole-organism pesticide screen of different heterocycles (Martnez-Teipel et al., 2005). The physicochemical characteristics required for effective absorption and translocation were incorporated into the development of these heterocycles.

Using high throughput screening, Screening with a high throughput is an automated, miniaturized process that quickly and concurrently examines many substances for biological reactions that can be easily measured. Pesticide research, as opposed to pharmaceutical research, where screening is often done not on the target species, i.e., humans, but rather on animal models/or in vitro systems, provides the cost and risk-saving advantage of testing candidate compounds directly on target species in vivo. This lessens problems brought on by erratic absorption and metabolism, which are essentially absent in vitro assays.

Structure-based design and molecular simulation over the past ten years, the 3D structures of Target enzymes or receptors with small molecule ligands have enabled the computer-aided design of bioactive compounds (Walter, 2002). Only a few complexes involving relevant proteins and pesticide ligands have been studied in 3D (Table 1). Often produced using X-ray crystallography, these structures enable an atomic-level analysis of legend–target interactions and the discovery of new binding sites. A crucial benefit of 3D structural data is that it enables rapid in silico screening of millions of molecules (virtual compound libraries). If the target site structure is known, it is also possible to study in silico how selective and non-selective drugs bind differently. By comparing the X-ray structures of the 4-hydroxyphenylpyruvate dioxygenases completing the structurally related hydroxy pyrazolyl ketones in the plants (Arabidopsis thaliana) and the rats (Yang et al., 2004), the structural basis for the selectivity of these herbicides was found. Recent investigations on the binding mode of the cytochrome P450 inhibitor triazole fungicide ketoconazole utilised the crystal structure of fluconazole connected to bacterial lanosterol 14-demethylase (Ito et al., 2004). The most recent advancements in the realm of insect

Table 1. Representative examples of the currently known X-ray crystal structures of pesticidal compounds in complex with their target biopolymer

Target site	Complexed ligand	PDB Code[1]
	Insecticidal	
acetylcholinesterase[2]	trifluoroacetophenone derivative	1AMN
ecdysone receptor	ponasterone A, bisacylhydrazine	1R20
juvenile hormone esterase	trifluoromethyl ketone derivative	2FJ0
nicotinic acetylcholine receptor[3]	nicotine	1UW6
	Herbicidal	
acetoxyhydroxyacid synthase	chlorsulfuron	1YHZ
	imazaquin	1Z8N
adenylosuccinate synthetase	hydantocidin 5'-monophosphate	1SOO[4]
acetyl-CoA carboxylase carboxyltransferase	diclofop	1UYR
EPSP synthase[5]	glyphosate	1G6S
fatty acid synthetase, type II	triclosan	1D7O
4-hydroxyphenylpyruvate dioxygenase	hydroxypyrazolyl ketone	1TFZ
imidazoleglycerol phosphate dehydratase	2-hydroxy-3-(1,2,4- triazolyl)-propylphosphonate	2F1D
	Fungicidal, bactericidal	
CYP450 14α-sterol demethylase	ketoconazole[6]	1JIP
	pyroquilon	1G0O
trihydroxynaphthalene reductase	azoxystrobin	1SQB
	famoxadone	1L0L

Proteo Data Bank accession number [1]Both http://www.pdbj.org and http://www.rcsb.org include the X-ray structure and extra details for the chosen complex.
[2] From the California Torpedo electric ray.
[3] From Lymnaea stagnalis, a snail.
Escherichia coli, number. [4]The uncompleted A. thaliana enzyme's PDB code X-ray structure is 1DJ2.
[5]Escherichia coli, number
[6] Antifungal drugs structurally similar to agricultural azole fungicides

The X-ray structure of the ecdysone receptor has been elucidated, allowing for the computer-assisted development of novel receptor agonists (Nakagawa, 2005). The 3D structure of the acetylcholine-binding protein complexion nicotine allowed for the deduction of imidacloprid's selectivity and resistance (Matsuda et al., 2005).

Chirality's Role in the Action, Toxicity, and Environmental Biotransformation of Pesticides

Regarding numbers, at least one chiral molecule with at least one asymmetric carbon atom makes for around twenty-four percent of all pest management products mentioned in The Pesticide Manual (Tomlin, 2003). Even though only one of the stereoisomers is frequently responsible for the desired biological activity, many commercially available products—often for economic reasons—are mixtures of isomers made through chemical synthesis. The toxicological characteristics of stereoisomers of a given substance might vary, as can how those stereoisomers degrade in the environment (2002); Garrison (2006); Hegeman and Laane (2006). Only as a counterweight can the biologically inert isomer be used. But in the worst case, the inactive isomer slowly degrades and might harm non-target species. Thus, there is an increasing need to market stereoisomerically enriched goods, particularly if research shows that the unwanted, target-inactive isomer poses health or environmental risks. In some circumstances, proprietary considerations also drive the creation of a chiral form of a well-known racemic active component.

Green Chemistry

Creating a secure manufacturing procedure that can produce the substance in the needed quantity and at the highest quality must come after identifying a good pesticide. According to Phillips McDougall (2005), the expenses of process development and accompanying analytical approaches may be comparable to those spent on discovery. Since pest control products are applied to large areas, environmental factors like selective toxicity and degradation studies have always been necessary to register the active ingredient and the formulation. There are no such statutory standards for manufacturing operations, which may contain harmful or polluting chemicals and solvents. The chemical industry

should To prevent and reduce pollution because of health and environmental concerns, creatively develop and produce materials using green chemistry principles (Anastas and Kirchhoff, 2002; US EPA, 2006). The production of the active pesticide ingredient and the creation of environmentally friendly formulation types will both see an increase in the usage of green chemistry principles in the pesticide industry.

Many of the above ideas had already dominated pesticide chemistry before the term "green chemistry" was first used in the early 1990s. Ten to fifteen years previously, new kinds of selective pest control chemicals had been created and implemented in pest management. For instance, pyrethroids and juvenoids began to replace several organophosphate and carbamate insecticides due to research conducted in the 1970s; Sulfonylureas showed in weed control when employed at application rates typically below 100 g/ha. Pest control products commercialized since the 1980s typically have substantially lower application rates and non-target toxicity than those developed earlier. Technological advancements, market changes, and harsher laws once more fuel research and development.

Chemical Pest Control Combined with Other Crop Protection Methods

According to According to James (2005), the value of the global market for transgenic crops in 2005 was $5.25 billion USD, or around 15% of all global pesticide sales. Crop biotechnology is putting more and more restrictions on the market for conventional pesticides, especially for synthetic insecticides that are being replaced by techniques based on Bt-producing plant varieties. The situation needs to be more evident for the herbicide industry, where characteristics that are herbicide-tolerant do necessitate the use of the specific herbicide. It seems unlikely that new herbicide-resistant types will be created, even though transgenic crops that are already herbicide-tolerant will continue to be widely adopted worldwide (Devine, 2005). This is remarkably accurate for crops used in the food and feed industry. The development of genetically modified crop varieties, however, could result from the rising demand for renewable, such as plants grown for producing fuel or polymers. This could necessitate using new, environmentally friendly, and economically viable herbicides and other pest control agents in these cultivations.

Chemical insect control methods supplement the so-called area-wide integrated pest management control measures. For instance, the first population suppression caused by pesticides usually occurs before the widespread release of sterile insects in remote locations (Dyck et al., 2005).

CONCLUSIONS

Using biochemistry, metabolic engineering, and genomics in conjunction with conventional and automated chemical synthesis opens up exciting prospects for utilizing the diversity of (bio) chemical compounds in the search for new crop protection agents. Such studies and research ought to be conducted while the market for pesticides is not substantially expanding. Nevertheless, safer pest control agents will continue to replace many dangerous ones new chemical and biochemical industrial synthesis techniques will also emerge. As a result of quickly evolving technologies on the one hand and changing market demand on the other, the agrochemical industry will continue to innovate in order to provide customers with cost-effective and secure crop protection and disease vector control agents. Over the past 40 years, many cutting-edge chemical prototypes have been created. The rate of introduction of novel active ingredients has remained relatively the same despite industry consolidations (Phillips and McDougall, 2003). By discovering and perfecting wholly new structural prototypes or by creating analogise of natural goods, chemistry has played a significant part in these breakthroughs.

Ironically, the public is not aware of the significant advancements in pesticide research. Even though chemical pest control agents, particularly those of synthetic origin, have been among the most thoroughly studied and thus among the most "transparent" substances, the pervasive "chemophobia" calls into question their mere necessity. Saying that the use of chemicals in agriculture is over would be incorrect in light of recent developments in our understanding of the selective mode of action of many pesticides at the molecular level and the opportunities provided by structure-based approaches to compound creation. The current barriers to developing novel chemical pest control agents are not scientific but economic, political, and social. One might concur with Gro Harlem Brundtland's recent assertion that "Politics that disregard science and knowledge will not stand the test of time" (Brundtland, 1997). Brundtland is now the director-general of the WHO. The best accessible scientific data is the only basis for wise political judgments. In the areas of resource management and environmental preservation, this is particularly true.

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