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Modern agrochemical research: a missed opportunity for drug discovery?

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The word 'agrochemical' has often taken on a pejorative character in the public mind. Some of the negative tone might have coloured the perception of the industry by pharma, together with views on the chemical nature of agrochemicals that seem to be based on older pesticides that date back to the 1950s and 1960s. In this review, we try to address some of these concerns, draw out the similarities between agrochemical and pharmaceutical research and highlight opportunities for drug discovery that are offered by pesticide-related compounds, particularly with regard to herbicides and compounds with leadlike physical properties.

The birth of civilization can be traced back to the time when humans first began to cultivate crops – the so-called Neolithic revolution (The archaeology of V. Gordon Childe [1]). This caused a dramatic increase in the number of people that could be supported in a given environment, but it also brought problems that farmers have had to contend with ever since. The devastation to crops wrought by weeds and pests is something we have become blasé about in the urbanized West, where we have become accustomed to a wide variety of cheap, nutritious food. Farmers the world over, however, are on the frontline of the fight against these forces of destruction and some of their most important weapons are agrochemicals, which help to protect against the worst crop losses. We sometimes forget that adequate nutrition and clean water are as important to human health as effective new drugs.

The chemical protection of crops probably began in pre-Roman times with the application of elemental sulphur (the Roman author Homer mentions 'pest-averting sulphur', see Williams and Cooper [2]). Progress for the next few hundred years was unspectacular – burning bitumen, cow dung, tobacco and mercury being some typical examples of protection methods. The era of synthetic pesticides really got going in the 1950s with the introduction of compounds such as dichlorodiphenyltrichloroethane (DDT), the carbamate insecticides and 2,4-dichlorophenoxyacetic acid (2,4 D). Over the past 50 years chemical pest control has moved from indiscriminate biocides to exquisitely potent, selective compounds with many of the features of modern drugs, making marginal agricultural land productive and increasing crop yields enormously. The transformation has been driven by an increased regulatory burden and a need to improve cost and efficacy to produce a competitive edge over older, cheaper products. The agrochemical industry is now a large (US$30 billion annual sales) research-driven business that depends on world-class science to drive it forward. Unfortunately, public perception of the industry does not always reflect this shift [3,4].

Historically, agrochemical and pharmaceutical operations have often been divisions of the same company, and this arrangement allowed knowledge to flow freely between the two. In the past decade many such companies have restructured, separating the two businesses and effectively ending this exchange of ideas. We believe that there are good reasons, for both parties, to look at ways to re-establish some of these links, particularly with regard to chemistry.

Agrochemicals have advanced to the point where it is difficult to tell the difference between a modern pesticide and a drug, representing a kind of convergent evolution brought about by distinct but analogous pressures. We will examine how agrochemical research could help in the development of new medicines and try to dispel some of the prejudices that are often associated with the word pesticide.

Some common (mis)conceptions about agrochemicals

Over the past 100 years agricultural crop protection has changed beyond all recognition. A century ago, the compounds used to help farmers control weeds, insect pests and fungal diseases tended

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to be vicious biocides such as sulphuric acid, creosote and arsenicals. Many people believe that little has changed since those days and that pesticides today are horrid poisons, the use of which should be drastically reduced or even eliminated from modern-day agriculture. We submit that this view is profoundly mistaken.

Toxicity and mode of action

Acute and chronic mammalian toxicity are key issues for pesticide research. Pesticides are applied to fields by human operators who might be exposed to concentrated pesticide formulations and we all eat food that could contain low concentrations of pesticide residues. Toxicity is something that is tested during the research phase of a project, and structures are optimized for low mammalian toxicity.

In fact, modern pesticides are generally much less toxic than most people believe – often less toxic on a gram for gram basis than commonly used medicines. Table 1 illustrates this point using the rat acute oral toxicity data for the top ten best-selling herbicides, fungicides and insecticides (global sales in 2003, Phillips McDougall Agriservice) compared with the best-selling medicines (global sales in 2003; http://www.forbes.com/technology/2004/03/16/cx_mh_0316bestselling.html).

Although acknowledging the short-comings of acute LD_{50} (lethal dose 50) values for summarizing toxicity [5], these data suggest that agrochemicals are not inherently more toxic than drugs, it depends on the specific chemical in question.

The majority of commercial pesticides used today produce their effects by acting at a single molecular target site [6]. All of the 300 plus pesticidal active ingredients introduced to the market since 1980 are believed to act via single, specific modes of action (MOA). Some multi-site fungicides remain commercially significant as part of mixtures, owing to their utility in resistance management programmes. However, these compounds constitute <5% of the total pesticide market and there have been no new product introductions in this class since 1967.

Modern-day pesticides often have nanomolar affinity (or better) for their target site (two examples are the sulphonyl urea herbicides [7] and mesotrione [8]). The equivalent of a dose of pesticide is usually quoted in grams of active ingredient required to achieve the desired level of pest control per hectare (ha) of farmland. A hectare is an area equivalent to ~15 tennis courts. Typical use rates have declined from 1–10 kg/ha to 100–300 g/ha since the 1960s, and the most effective commercial pesticides today are active at 10 g/ha or less. This trend, for ever lower doses based on exquisitely potent and specific interactions with the molecular target site, still continues.

Chemical composition

Anecdotal evidence (e.g. casual conversation with pharmaceutical colleagues at conferences) suggests that there is a perception that agrochemicals tend to be excessively halogenated or contain phosphorous, tin and even heavy metals. We feel that this view is a manifestation of old (pre-1970s) compounds rather than a fair representation of modern agrochemicals. In this regard, the standard reference for the industry (*The Pesticide Manual* [9]) does us no favours – over half the entries in the electronic version refer to compounds that first appeared in CAS (CAS Registry Number® is a registered trademark of the American Chemical Society) before 1970. This age effect is particularly pronounced in the case of phosphorous-containing compounds, which comprise 14% of *The Pesticide Manual* – 90% of them were registered in CAS before 1974, mainly as insecticides. The charge of excessive halogenation also seems to be based on a handful of prominent pesticides from the 1950s and 1960s, such as lindane and DDT. Halogens also occur in pharmaceuticals, although to a slightly lesser extent. For example, 16% of a set of marketed drugs [10] contain more than one halogen, verses 22% for the whole pesticide manual and 12% for a typical agrochemical company collection (Syngenta).

How similar are pharmaceutical and agrochemical research?

The concept of the life-science company (a term often used to describe a company that produced agrochemicals and pharmaceuticals) came to a rather ignominious end during the late 1990s as the major commercial differences between the pharmaceutical and agrochemical industries became apparent [11]. One of the

TABLE 1

Toxicity data (rat acute oral LD_{50} mg/kg) for the best-selling agrochemicals and drugs (sales data from 2003)

Sales rank	Pesticide	Rat acute LD_{50} (mg/kg)	Medicine	Rat acute LD_{50} (mg/kg)	Citation
1	Glyphosate	5000	Atorvastatin	5000	http://www.wisda.de/dossier.php?s_inn=Atorvastatin
2	Imidacloprid	450	Simvastatin	4438	MDL toxicity database 2005.4
3	Acetochlor	2148	Olanzapine	175	http://www.emea.eu.int/humandocs/PDFs/EPAR/Zyprexav/H-287-PtdIns-en.pdf
4	Azoxystrobin	5000	Amlodipine besylate	393	MDL toxicity database 2005.4
5	Paraquat	143	Epoetin alfa	NA	*Protein – no mg/kg toxicity figures available
6	Tebuconazole	2850	Lansoprazole	5000	MDL toxicity database 2005.4
7	Chlorpyrifos	149	Esomeprazole	2210	MDL toxicity database 2005.4
8	Metolachlor	2780	Clopidogrel bisulfate	1914	MDL toxicity database 2005.4
9	2,4-dichlorophenoxyacetic acid (2,4-D)	702	Fluticosone propionate and Salmeterol xinafoate	2000	MDL toxicity database 2005.4 (Fluticosone only)
10	Mancozeb	5000	Sertraline hydrochloride	1460	http://www.inchem.org/documents/pims/pharm/pim177.htm

main arguments for forming such companies in the first place was that both parties could benefit from research synergies. The thinking behind this was driven by some of the salient similarities between the two businesses. Although the synergies could not offset the increase in complexity entailed by running two businesses, the common ground between the two types of research, particularly with regard to chemistry, remains.

Chemistry

The similarities between modern agrochemicals and drugs can be expressed in several ways, but perhaps the most telling is the similarity between the chemists who make them [12,13]. Both buy their reagents from the same suppliers, read comparable literature and perform similar types of reactions. The result is that drugs and agrochemicals tend to be moderately sized organic molecules with a smattering of functional groups to provide specific binding and the right physical properties. Both types of molecule are developed by iterative rounds of synthesis and biological testing using similar notions of SAR to guide the process. Some typical end-results for agrochemicals [9] are shown in Figure 1, and we would submit that these modern products are indistinguishable, at a glance, from many marketed drugs.

The term druglikeness has become well entrenched in the literature [14] and can cover everything from simple physical property ranges to complex analyses of arrays of calculated molecular descriptors. A key issue for us is: how druglike are agrochemicals? The gross similarities are clear from Figure 1, but they extend to a deeper level when one compares the prevalences of various functional groups in the two sets of compounds. A study by Bemis and Murcko [15] produced a list of the twenty most common substituents and sidechains found in the Comprehensive Medicinal Chemistry (CMC) Database (MDL Information Systems, San Leandro, CA, USA). An in-house search for these substituents in *The Pesticide Manual* not only found all twenty but also found that most occurred with similar frequency to the CMC database. Even more-sophisticated approaches to modelling druglikeness have been reported in the literature, typically using complex molecular descriptors (topological [16], fingerprint [17]) and advanced pattern recognition techniques (neural nets [18], recursive partitioning [19]). One common approach used to derive these models is to compare a pair of large collections of molecules, one assumed to be rich in druglike compounds [the CMC or the World Drug Index (WDI), Derwent Information, London, UK], the other presumed to be relatively

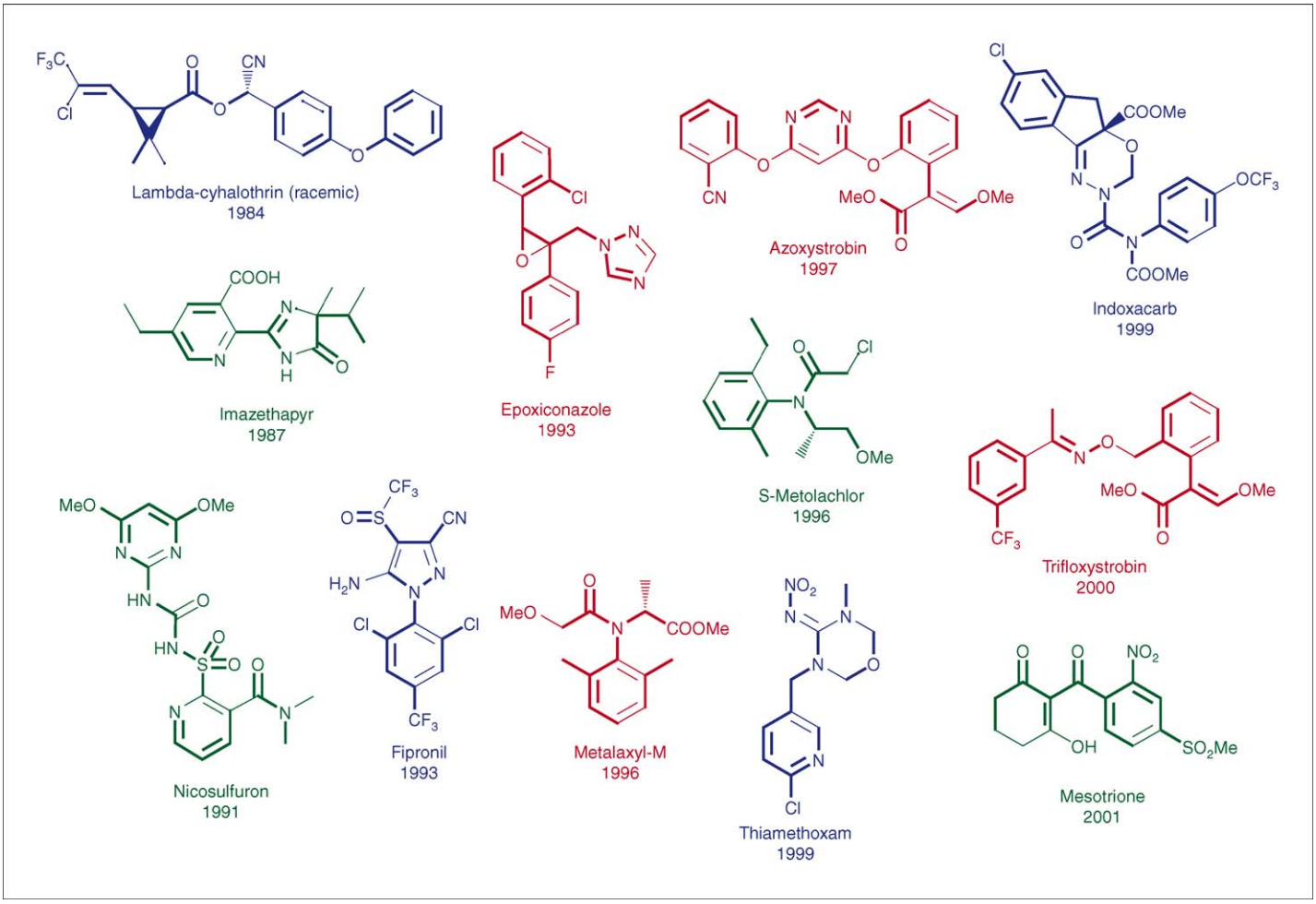

FIGURE 1

A selection of modern, commercially important agrochemicals [9]. Insecticides are coloured blue, fungicides are red and herbicides are green. The products' names and launch-dates are included.

deficient [usually the Available Chemicals Directory (ACD), MDL Information Systems, San Leandro, CA, USA]. A model that produces a large difference in scores between the two sets of molecules should capture some important features of druglikeness. Unfortunately, we do not have access to these proprietary models to assess how well agrochemicals score, but we note that Pfizer appear to use *The Pesticide Manual* as their drug-deficient counter-example database, in preference to ACD [14,20]. Their justification for this is interesting – agrochemicals are acknowledged as bioavailable compounds with specific modes of action, but are deemed not druglike because of their human toxicity (a point we address elsewhere in this article). The implication is that agrochemicals are the most sophisticated available decoy for a druglikeness model, something that we, in the agrochemical industry, might take as a back-handed complement.

The integrity of an agrochemical collection in terms of its sample purity and knowledge of the associated structures is of paramount importance as SAR hypotheses will be constructed from the results of biological tests. Samples are generally single components with known structure and stereochemistry because these factors lend themselves to the most interpretable sets of results. The compounds are purified using various chromatographic techniques and validated by spectroscopy.

Samples in an agrochemical research collection are drawn from a wide variety of sources. Comparisons performed by two major chemical sample supply companies (Chembridge and Chemical Block) show a large degree of overlap between selections made by pharmaceutical customers and their agrochemical counterparts, indicating that the respective definitions of what constitutes a desirable starting point for synthetic projects are largely the same. The spread and age of the samples will reflect the history of the organization's research with diversity as the main theme, but with islands heavily populated with analogues that have resulted from intense exploration of areas of activity. Both industries work with inventories of hundreds of thousands or millions of samples, store solubilized compounds in dimethyl sulfoxide (DMSO), with its attendant problems [21], and are viewed by vendors of large, automated storage, retrieval and dispensing systems as valuable customers, with their need to support HTS campaigns.

Target sites

All known biological processes are based on a relatively limited vocabulary, ultimately reducible to the four bases that form DNA. Plants, animals, bacteria and fungi all conduct the bulk of their life processes through enzymes and receptors made of protein, and interference with these proteins is the main way that bioactive compounds exert their effect. Evolution has also conserved certain types of metabolic and signalling pathways across different phyla, for example G-protein-coupled receptors and the citric acid cycle. Access to these sites in all living things is mediated through systems of active transport, metabolic transformation and passive diffusion through lipid membranes.

In summary, the target-binding sites for drugs and agrochemicals are very similar – enzyme active sites and receptor-binding sites – and the path they must traverse to reach them are comparable. This has ramifications for the physical properties that are favourable for reaching a binding site, which we will discuss in the next section.

TABLE 2

A summary of the physical property limits for drugs (Lipinski) and agrochemicals (Tice)

Property	Lipinski	Tice
Molecular weight	<500	<500
logP octanol	<5	<5
H-bond donors	<5	<3
H-bond acceptors	<10	<12

Bioavailability

The increasing emphasis on high-throughput *in vitro* screening in the pharmaceutical industry has produced a demand for large numbers of distinct chemicals to feed it. In the early years this led to chemical libraries being produced with more of an eye to the numbers of compounds rather than their physical properties. Concerns about this approach were crystallized by Lipinski and coworkers in 1997 [22], where the upward drift in average molecular weight and lipophilicity of screening collections was noted for the first time. The negative impact of this on the oral bioavailability of active compounds led to the Rule of Five, which placed upper limits on acceptable logP, molecular weight and H-bonding parameters for orally available drugs.

Lipinski's approach did not go unnoticed in the agrochemical industry, where first Tice [23] and then Clarke and Delaney [24] performed comparable analyses on pesticidal products. The conclusions reached in these studies were very similar, both to each other and to Lipinski's work. We have included a table comparing the most widely cited agrochemical rules (Tice) with those of Lipinski (Table 2).

There are differences in the optimal properties for the different types of agrochemicals and drugs. Agrochemicals have a lower tolerance for H-bond donors than do drugs. This might be a manifestation of the general need for agrochemicals to resist metabolic attack by the pest species [23,24]. Herbicides present a particular issue from a drug development perspective because they are often acidic (~25% of the herbicides in *The Pesticide Manual*), this being a desirable property for phloem mobility (movement from the leaf to the root of the plant). Anionic compounds are sometimes regarded as problematic from a drug development standpoint because they can have poor protein-binding properties. This view has become more nuanced recently with the caveat that only anions where the polar surface area exceeds 75 $Å^2$ are likely to display poor availability [25], and this puts half the herbicidal acids in *The Pesticide Manual* back in play as reasonable starting points for drugs.

Opportunities

The extant similarities between the molecules produced by the pharmaceutical and agrochemical research processes mean that there are potential opportunities for both industries to exploit each others compound collections usefully. The relative paucity of commercially available molecules, made with an eye to biological activity and bioavailability, makes compound swaps between the two industries potentially attractive.

Novel chemistry

Ultimately, the most convincing evidence for using agrochemicals to help discover drugs are examples where a compound that

started life in the field finds a therapeutic application. A well-known example is fluconazole, which, although derived from Jansen's pharmaceutical work on azoles in the 1960s [26], was actually covered by an agrochemical patent [27] before its clinical use, an indication that areas of chemistry often overlap between the two fields. This also demonstrates an obvious commonality between medicines for humans and crops – fungal diseases. In researching this article, we expected most examples of agrochemicals with medicinal applications to be antifungals, but Table 3 shows a surprisingly diverse set of pharmacological effects. The three main agrochemical indications seem to offer contrasting opportunities for pharmacological effects.

Insecticides

Many insecticidal MOAs are related to interference with nerve signal transduction and there could well be potential here for the treatment of neurological conditions. Two concrete examples are the nicotinic acetylcholine receptor, a potential target for the treatment of Alzheimer's disease [28] and the site of action of the neonicotinoid insecticides [29], and the voltage-gated sodium channel, which is relevant to anaesthesia and the pyrethroid insecticides [30].

Fungicides

Agrochemical fungicides have a clear relevance to human pathogenic fungal infections, but their action on kinases [31] and microtubule formation [32] might also have utility in other areas where treatment involves selective cell death – such as cancer, or as antibacterials.

Herbicides

Herbicides produce the most unexpected results in inherited metabolic disease [33,34], bone loss [35] and cardiovascular function [36]. Many herbicide target sites are chosen on the basis that there is no human equivalent, because this lowers the chances of toxicological problems in development [37]; this is practical owing to the large evolutionary divergence between plants and animals. Most of the pharmaceutical MOAs detailed here are the result of off-target effects from bioavailable molecules, something that is inherently unpredictable but potentially exciting [38].

The ability of the agrochemical industry to perform an *in vivo* test at a very early stage means that the sample weights required for subsequent tests can rapidly escalate as larger, more mature target specimens that are used for experimentation in the screening cascade. It is more efficient to produce reasonably large samples upfront (10–100 mg), in anticipation of more-advanced testing if found to be active. Unfortunately, it is a fact of life that most of the compounds in a typical company collection are inactive. These two facts mean that we retain fairly large samples of compounds for which we have no immediate use. Drug companies are increasingly looking to larger sample sizes as a way of building a stable core collection – one where a compound can be used in multiple *in vitro* tests. An agrochemical company's compound collection provides a clear opportunity to enhance a pharmaceutical collection with large samples of good-quality chemistry.

Leadlike physical properties

We have talked about druglikeness as a concept, but more-recent deliberation in the pharma industry has tended to focus on the concept of leadlikeness [39,40]. The idea, first proposed by Teague *et al.* [41], is that the process of optimizing an *in vitro* hit into a saleable drug has a tendency to drive molecular weight up – this is a consequence of the hunt for increased intrinsic binding, which is most easily achieved by adding bulk to better-fill the binding pocket. Starting from a screen hit that has perfect druglike properties means that, in taking it through to a medicine, one inevitably tends to shift the physical properties away from that very ideal. A leadlike compound tends to be smaller and less lipophilic, allowing headroom for the optimization process.

The development pattern for agrochemicals is, to some extent, the mirror image of this. Here, an *in vivo* screen hit often sheds

TABLE 3

Agrochemical compounds with a pharmaceutical application

Compound	[a]Ag indication	Pharma indication	[b]Cell cidal MOA	Company
Epothilone [48]	F	Anticancer	Y	Ciba
Triazolopyrimidines [49]	F	Anticancer	Y	BASF
Fluconazole [27]	F	Antifungal	Y	ICI
Fenpropidine [50]	F	Antimycotic	Y	BASF
Nitisinone [33,34]	H	Hereditary tyrosinaemia type 1 and alkaptonuria	N	Syngenta
Anisomycin [51]	H	Antibacterial	Y	Nippon Kayaku
Glyphosate [52]	H	Antiparasitic	Y	Monsanto
Bisphosphonates [35]	H	Bone loss	N	Syngenta
Endothelin agonist [36]	H	Cardiovascular	N	BASF
Sulphonylureas [53]	H	Anticancer	Y	Dupont
Nikkomycin [54]	I	Antifungal	Y	Bayer
Staurosporin [55]	I	Anticancer	Y	Ciba
Abamechtin/Ivermechtin [56]	I	Antiparasitic	Y	Ciba
Imizadolines [57]	I	Hypertension	N	Wellcome

[a] The Ag indication refers to whether the compound is a fungicide (F), herbicide (H) or insecticide (I).
[b] The cell cidal MOA refers to whether the compound's pharmaceutical effect is based on cell death.

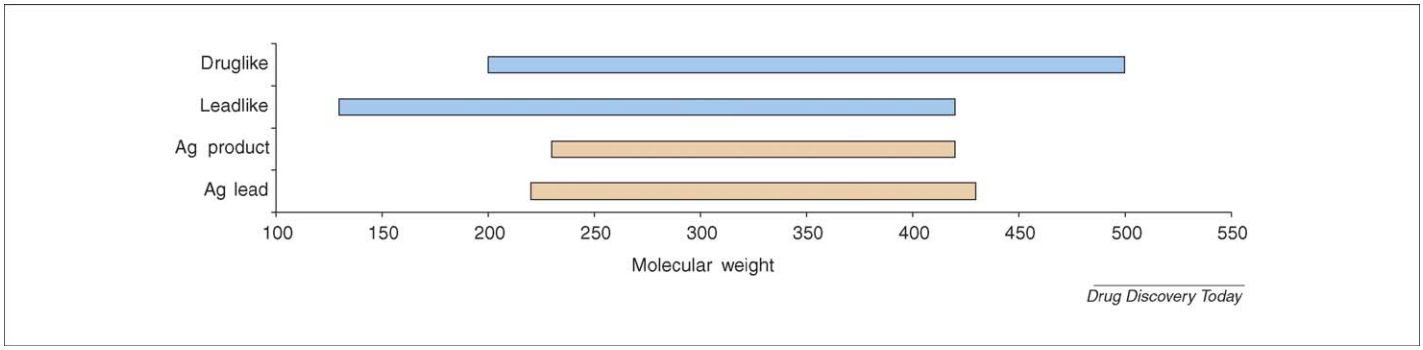

FIGURE 2

Acceptable molecular weight ranges for drugs and agrochemicals. The bars represent the 10th and 90th percentile ranges for leads and products for the two types of molecule. The terms 'druglike' and 'leadlike' refer to the properties of commercial medicines and the molecules that acted as leads for them, respectively. 'Ag product' and 'Ag lead' refer to the collective weight ranges for a wide array of marketed pesticides and Syngenta in-house lead compounds, respectively.

mass during optimization because movement properties are enhanced to get expression of activity in the field. This produces many compounds (particularly herbicides) that fit well with emerging ideas about leadlikeness in pharma. Figure 2 illustrates this point using molecular weight data extracted from the work of Oprea *et al.* [10] (drugs) and Clarke and Delaney [42].

The relatively narrow size limits for agrochemical leads and products overlaps extremely well with the lower end of the druglike range and the upper end of the leadlike range – the best of both worlds?

Conclusions

We have explored some of the prejudices that exist about agrochemicals and made a case for the proposition that agrochemical research has much in common with pharmaceutical research. This leads us to consider why this resource has been underexploited.

The pharmaceutical industry is a true Goliath of the business landscape – most other industries are dwarfed by it, and agrochemicals are no exception. This sheer size can make it harder to look outside for opportunities. Compound swaps have been often stymied by worries over structure disclosure and the effect on sample-handling resource, which is stretched drum-tight by HTS commitments [43]. These obstacles are surmountable, but only if the prize is worth the game. Needless to say, we believe that it is.

One of the frustrations of HTS is how little, really interesting activity exists in diverse chemical space [40,44–46]. Moving away from known series leaves a thin gruel of weak hits with little in the way of SAR to encourage further work. We have found that we get much better results from compounds that have been designed for some sort of bioactivity, particularly when the molecules have a pharmaceutical origin. There is every reason to expect that this observation should apply in the other direction, with agrochemical-like compounds showing interesting pharmacological effects.

The other area where agrochemicals might have something to offer is leadlikeness. Starting from a small, bioavailable compound seems to fit better with the inherent nature of drug optimization – increasing intrinsic binding through increasing size – than trying to improve a drug-sized, weakly active molecule. The early use of *in vivo* testing in agrochemicals tends to push many series towards smaller more-soluble compounds that retain intrinsic binding. The drug and agrochemical discovery processes are somewhat complementary in terms of the kind of lead-compound physical properties they need, which suggests some potential for fruitful crossover between the two.

Agrochemicals have evolved to the point where their chemical structures, physical properties and site-specific binding make them hard to distinguish from commercial drugs. In areas such as antifungals the target sites are identical, and there is also a clear overlap of interest in nerve receptors. The potential for unanticipated side-activity is clearest in herbicides that also tend to have desirable leadlike properties. The '*Silent Spring*' [47] image of pesticides is an anachronism that serves to obscure the pharmaceutical potential lurking within agrochemical collections. An opportunity missed?

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