Pergamon

Tetrahedron 58 (2002) 1631–1646

TETRAHEDRON

Tetrahedron report number 599

Allelochemicals as leads for new herbicides and agrochemicals

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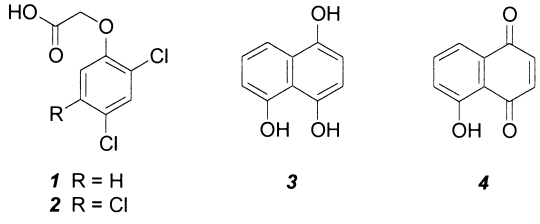
Received 29 October 2001

Contents

1. Introduction and history of allelopathy

Maximizing the world's agricultural efficiency depends largely on controlling a variety of diseases and pests—especially weeds. Weeds, simply defined as plants growing in an undesired location, compete with crops for resources, lower crop yields, and can contaminate the crop with their seeds thereby perpetuating the problem into subsequent growing seasons. Nearly 7000 weed species have been identified but far fewer, perhaps two or three hundred, are particularly troubling to the world's farmers.[1,2] Interference from these weeds, however, diminishes crop yields to such an extent that farmers in the US spent $6 billion on herbicides in 1998, nearly 70% of total agrochemical sales.[3] The herbicide industry was built on the success of 2,4-D (**1**) and 2,4,5-T (**2**) (Fig. 1) and weed control research over the last 50 years has been focused almost exclusively on synthetic herbicides.[4] The development of genetically engineered herbicide resistant crops has further expanded the use of herbicides. Widespread use of synthetic herbicides has resulted in herbicide-resistant weeds, and public concerns over the impact synthetic herbicides have on human health and the environment are increasing.[2,4] These concerns are shifting attention to alternative weed control technologies based on natural products.[5,6]



1 R = H
2 R = Cl
3
4

Figure 1.

Allelopathy is most commonly defined as any direct or indirect effect (stimulatory or inhibitory) by one plant,

Keywords: allelochemicals; herbicides; allelopathy.
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PII: S0040-4020(02)00052-2

including microorganisms, on another through production of chemical compounds released into the environment.[7–9] Allelochemicals can be released into the environment by a variety of mechanisms: volatilization from leaves, exudation from roots, and leaching from leaves and plant litter on the ground by precipitation.[6] Although the term *allelopathy* was first used in 1937,[10] the chemical interaction between plants has been known for thousands of years. Theophrastus noted the effects of chick pea on other plants in ca. 300 B.C., and Pliny noted the harmful effects of several plants on cropland ca. 1 A.D. Pliny may also have been the first to record the allelopathic effects of the walnut tree.[8] The walnut (*Juglans nigra* and *J. regia*) is perhaps the best known allelopathic plant, causing many crops and other plants near it to wither and die. The leaves, roots, and fruit hulls of the plant produce hydroquinone **3**, which is oxidized in the environment to juglone (**4**), the compound responsible for the toxic effects on other plants (Fig. 1).[11]

For many years, allelopathy research was conducted mainly by botanists and focused on allelopathic cover crops, intercropping, and application of crude plant extracts to study the effects on crop yields and weed suppression under field conditions.[9,12] While this work continues, there has been a recent expansion in research aimed at determining which specific natural products are responsible for allelopathic effects.[13] Current allelopathy research is interdisciplinary and requires the contribution of organic chemists, biologists, soil scientists and ecologists to make significant progress.[9] Mallik also attributes the recent resurgence in the field to improved methods and technology for isolation and structure determination of allelochemicals and an improvement in experimental designs.[14]

Allelochemicals that suppress or eliminate competing plant species near the source plant have received special attention due to the agricultural potential of these compounds as selective natural herbicides.[15–17] Allelochemicals that stimulate germination and growth of other plants are also an important area of study.[18] For example, the parasitic weeds of the *Striga* (witchweed), *Orobanche* and *Alectra* families may be controlled by application of an agent to stimulate germination of witchweed seeds in the absence of a host plant, so-called suicide germination (see Section 5.4).[19,20]

Even when allelochemicals are tentatively identified, it is exceedingly difficult to prove their role in plant–plant interactions. This is due in large part to the challenge of demonstrating that interactions between plants are not simply due to competition for resources.[9,21–23] A protocol to prove allelopathy, based on Koch's postulates for identifying disease causing agents, has been suggested and includes the following steps: (i) demonstrate interference, describe symptoms, and quantitate the effect using suitable controls; (ii) isolate, identify and characterize the chemical agent assisted by bioassays; (iii) reproduce the interference by introducing the agent (natural or synthetic) to the biological system at naturally occurring concentrations; (iv) quantify the amount of allelochemical released from the source plant and absorbed by the target plant.[21,24] Points (iii) and (iv) are particularly difficult to achieve. Allelochemicals are introduced into the environment with a vast number of other secondary metabolites as mixtures, and it is likely that synergistic effects enhance the observed activities.[9] Measurement of the amount of an allelochemical released and absorbed is likewise complicated by interactions of the compound with soils of different types, and degradation or modification of the plant compound by microorganisms.

The protocol for proof of allelopathy is made even more difficult because often only minute quantities of the active compound can be isolated from the natural source. Thus, a synthetic source of the implicated allelochemical is essential for comprehensive study of the agent's mode of action and to establish a basic structure–activity profile for the observed activity.[21] Indeed, the agricultural potential and the synthetic challenges found in allelopathic natural products are now beginning to attract the attention of synthetic organic chemists (see Sections 5 and 6).

Some have taken issue with the proof of allelopathy protocol as outlined above as being unreasonable for complicated plant-based systems with so many variables,[25] but others take the position that it is a useful guide for a more rigorous approach to experimental design.[21] A similar but less quantitative set of requirements for demonstrating an allelopathic interaction has been put forth by Inderjit and Weston: (i) an ecological component—demonstration that the interference exists in nature; (ii) a chemical component—isolation, identification and characterization of allelochemicals involved; (iii) a physiological component—identification of the interference mechanism at the biochemical, physiological, cellular, and molecular level.[26]

2. Assays for allelopathy

Strategies for allelochemical discovery are analogous to those for the discovery of lead compounds in the pharmaceutical industry and involve the screening of crude extracts and purified compounds for biological activity. These initial bioassays must be quick, economical, and relevant to the system in question.[27] The latter criterion, with respect to the selection of assay species and ecological factors, is often given only superficial consideration.[26] Care must also be taken in the methods used to obtain the plant extracts for use in allelopathy bioassays. Practices such as grinding plant material, using organic solvents to extract plant material directly, and autoclaving assay media have been seriously questioned.[28] Initial aqueous extraction of plant material is preferred by some researchers who assert that allelopathic interference is most likely due to water-soluble compounds introduced into the environment. This may not be strictly necessary, however, since allelochemicals can also be introduced via volatilization, exudation, and from the decay of plant matter.

Laboratory bioassays are useful in establishing the allelopathic potential of a compound or plant extract, but should ultimately be followed with greenhouse or field studies to see if the observations are reproduced in the natural environment.[28] The most widely used biological assays for allelochemicals are seed germination and seedling growth studies.

In the simplest form of these assays, seeds of the selected plant species are placed on filter paper or agar in a petri dish or small tissue culture wells and treated with a solution of the suspected allelochemical at varying concentrations.[29] It has been shown that the number and size of the seeds and the volume of the solution used are important variables in this process.[30] Germination rate and seedling growth (root and shoot lengths) is then monitored versus control samples. Most of the bioassays used have been discussed in earlier reviews,[31,32] and the strengths and weakness of various bioassays discussed,[28,33] but some recent studies warrant further comment.

The most important consideration in choosing or developing a bioassay for allelopathic study is selection of the target species. For example, *Lemna* sp. (duckweed) is often used for plant–plant interactions in aquatic environments,[34] while barnyardgrass, gooseweed, and ducksalad are more relevant for study of allelopathy in rice.[35,36] Both mono- and dicotyledons should be used in assays to determine potential selectivity of the agent.[35]

Initial screening can be done in 24- or 96-well plates and initial dose-response curves for concentrations ranging from 10^{-4} to 10^{-9} M can be determined with as little as a milligram of material.[35] When a transfer solvent is needed for compounds with sparing solubilities in water, acetone and DMSO have been used successfully. Testing non-polar materials like essential oils present more of a problem, but this has been overcome by using a non-polar organic solvent to transfer the compound to the assay wells, followed by evaporation of the organic solvent prior to adding assay media. This method, of course, makes measuring the amount of material available to the plant more uncertain.[35] A new screening bioassay, the equal-compartment-agar-method (ECAM), was recently used to evaluate 92 strains of wheat for allelopathic activity that would inhibit root growth in annual ryegrass.[37]

Macías recently published a large study aimed at standardizing allelopathy bioassays through determining appropriate standard target species (STS).[38] Commercially available crop seeds were employed to eliminate some of the uncertainty involved with using the genetically more diverse weed seeds. Furthermore, weed seeds often give poor germination rates.[35] The pH and application volume of the test solutions were studied, put pH was found to have no effect in these tests.[38] A hierarchy of nine STS was suggested for cases of limited sample availability. The sensitivity of the STS was determined using mixtures of commercial herbicides and a formulation of terbutryn+ triasulfuron (the commercial herbicide Logran®) was used as an internal phytotoxicity standard to validate the responses measured for test compounds.[38] The STS approach to allelopathy bioassays and the use of standard herbicides of known activity controls will make it easier for researchers across the globe to validate their methods and compare and reproduce their results.

3. Modes of action of allelochemicals

While the commonly used bioassays are useful for measuring activity of allelochemicals when they reach the target plant, there is no one established method for studying the mode of action of these natural herbicides.[39,40] Careful analysis of the allelochemical's structure, including the use of structure–activity databases, may offer clues as to its mode of action. In some cases, observations made during dose-response experiments using whole organisms may narrow the possibilities of the site of action, but it is easy to overinterpret such studies.[35] When root growth is inhibited by an allelochemical, the mitotic index can be measured using onion root to study the agent's effect on root cell division. Measurement of chlorophyll concentrations and fluorescence can be used to assess alterations in photosynthetic efficiency of the treated plant. The photosynthetic process can also be probed using carbon dioxide exchange. Conductivity measurements can be used to identify allelochemicals that disrupt cell membranes, and this method can also be used to determine whether the mode of action is light dependent.[35]

Of the hundreds of identified allelochemicals, modes of action have been determined for only a few.[40] Many allelochemicals operate by mechanisms not possessed by synthetic herbicides, making natural products a promising source of new leads to herbicides.[5] Some of these mechanisms include amino acid synthesis (glutamine synthetase, aspartate aminotransferase, ornithine carbamoyl transferase, β-cystathionase), pigment synthesis (ALA synthetase), plasma membrane functions (H^+-Atase, NADH oxidase), photosynthesis (CF1 ATPase), lipid synthesis (Acetyl-CoA transcyclase, 3-oxoacyl-ACP synthase, ceramide synthase), and nucleic acid synthesis (RNA polymerase, adenylosuccinate synthase, AMP deaminase, isoleucyl-*t*-RNA synthase).[5]

4. Commercial herbicides based on natural products

Herbicides and agrochemicals based on natural products are attractive for a variety of reasons. Most biologically active natural products are at least partially water-soluble and, as a result of natural selection, more likely to exhibit some bioactivity at low concentrations. Natural products are frequently considered to be environmentally benign, but many plant and microbial compounds are potent mammalian toxins.[27] As discussed in Section 3, many allelochemicals exert their influence through mechanisms not possessed by commercial herbicides, making them ideal lead compounds for new herbicide discovery.[5] Unfortunately, the complex structures of most secondary metabolites, usually containing several stereocenters, complicate structural characterization and make the feasibility of economical, large-scale synthesis of the compound questionable. Structural simplification of the lead compound often results in significantly lower biological activity.[27] These issues, of course, are the same ones encountered in the pharmaceutical industry, but the pesticide industry has shown only modest interest in the natural product-based discovery approach to herbicides. Most of the effort that has been expended concerns natural products obtained from microbial sources rather than higher plants.[5]

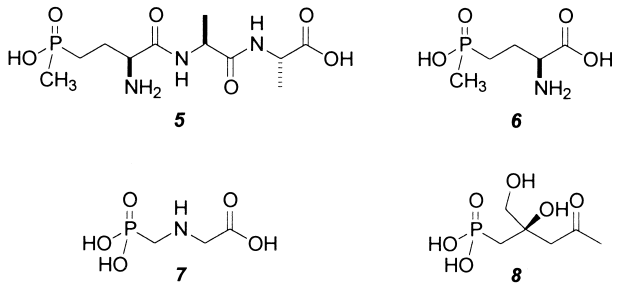


Figure 2.

4.1. Organophosphorous compounds

Two herbicides based on natural products isolated from bacteria have been commercialized to date: bialaphos (**5**) and phosphonthricin (**6**) (Fig. 2). The ammonium salt of synthetic racemic **6** is glufosinate, marketed under a variety of trade names. Bialaphos (also known as phosphonthricyl-alanyl alanine) (**5**) was originally isolated from different *Streptomyces* strains by two independent groups and is currently marketed in Japan under the name Herbiace®. Bialaphos (**5**) is a pro-herbicide and is converted in the plant to the active agent **6**.[41] Phosphonothricin (**6**) exerts its effects through the inhibition of glutamine synthetase and the chemistry of **5** and **6** has previously been reviewed.[42] Although not a natural product, the widely used herbicide glyphosate (**7**)[43] bears a striking structural resemblance to **5** and **6**. Another phosphonate natural product, phosphonothrixin (**8**), was recently isolated from *Saccharothrix* sp. ST-888 and exhibits phytotoxic activity against a variety of plants.[44,45] A synthesis of racemic **8** was reported concurrent with its structure proof,[46] and has been followed by syntheses of both enantiomers of **8** in optically pure form proving the configuration of the natural material to be *S*.[47] Additional study of its herbicidal activity has recently appeared.[48] Based on the success of the organophosphorous herbicides **5**–**7**, phosphonothrixin is an important lead for further development.

4.2. Triketones

Leptospermone (**9**) is a major component in the essential oil of the plant *Leptospermum scoparium* found in Australia and New Zealand (Fig. 3).[49,50] The triketone herbicides, including sulcotrione (**10**) and mesotrione (**11**),[51] are post-emergent broadleaf herbicides based on the leptospermone structure template that inhibit *p*-hydroxyphenylpyruvate dioxygenase (HPPD).[52–54] The herbicidal activity of these compounds correlates well with their acidity, accounting for the electron withdrawing substituents on the benzoyl moiety of these compounds.[55] Structure–activity relationships (SAR) for the dione portion of the triketones have also been reported.[56] The vinylogous acid functional group of the triketones has been altered to form a number of derivatives for use as proherbicides.[56]

4.3. Cinmethylin

The monoterpene ether 1,8-cineole (**12**) is a major component of the essential oils of a number of plant species, and was one of the first compounds implicated as an allelochemical (Fig. 4).[57] Compound **12** and its isomer 1,4-cineole (**13**) are potent phytotoxins, but their high volatility presents a problem for herbicide applications. Cinmethylin (**14**), a benzyloxy derivative of **13**, was developed as a herbicide to control annual grasses.[58] This strategy has prompted further research on benzyl ether derivatives of monoterpenes.[59,60] Cinmethylin (**14**) interrupts mitosis in treated plants,[61] and recent experiments involving asparagine synthetase demonstrated that **13** is in fact a proherbicide that requires cleavage of the benzyl group producing the active agent **15**.[62]

5. Selected allelochemicals

Compounds from numerous structural classes have been implicated in allelopathic interactions.[63,64] The remainder of this Report will concentrate on allelochemicals of selected structural classes, their activity, and in some cases their synthesis. The major focus is on compounds isolated in the last 15 years. Allelochemicals isolated from sunflower (*Helianthus* sp.) are given special attention (Section 6) due to the extensive research and large number of publications in this area during the period of interest.

5.1. Benzoquinones

Sorgoleone (**16**) and its hydroquinone form **19** are

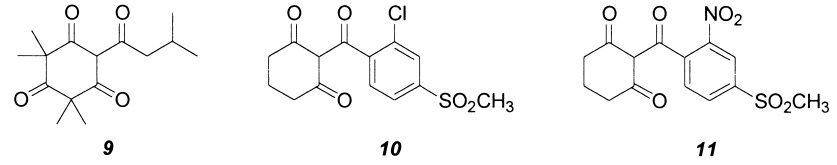


Figure 3.

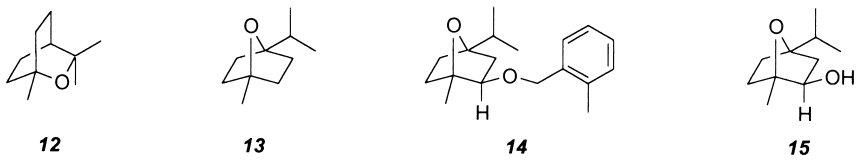


Figure 4.

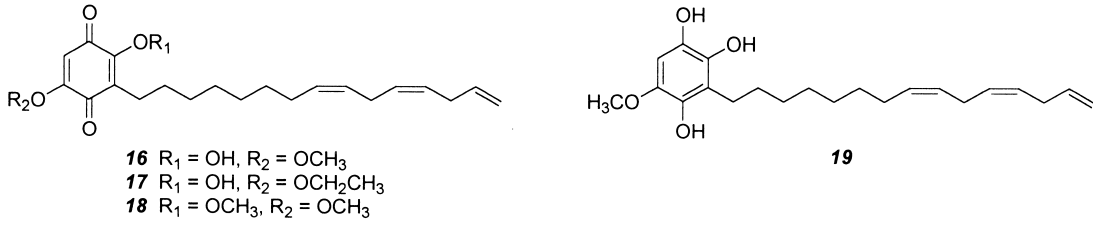


Figure 5.

allelochemicals exuded from the roots of sorghum (Fig. 5).[65,66] Compound **19** was the first natural host germination stimulant for the parasitic weed *Striga asiatica* (witchweed) to be isolated and characterized and has been the subject of a total synthesis.[67] Sorgoleone is highly phytotoxic and inhibits chlorophyll formation[68] and photosynthetic oxygen evolution.[69]

More recent studies have shown that sorgoleone (**16**) inhibits electron transport in photosystem II (PS II) and can displace the commercial herbicide atrazine from the Q_B binding site on the D_1 protein of PSII.[70–73] Ethoxysorgoleone (**17**), also isolated from *Sorghum bicolor*, and synthetic analogues like **18** inhibit PS II electron transport as well.[74]

5.2. Coumarins and flavonoids

Coumarins and flavonoids are ubiquitous in plants, and several have been implicated in allelopathic interactions.[63,64,75,76] Coumarin (**19**) and its derivatives such as scopoletin (**20**) are known inhibitors of seed germination and growth of various plants,[63] and **19** blocked mitosis in *Allium cepia* (onion) (Fig. 6).[77] Coumarin (**19**) and the furanocoumarin psoralen (**21**) are components of *Ruta graveolens* (Rue), a medicinal plant with allelopathic properties.[78] Psoralen (**21**) can inhibit lettuce seed germination of at a concentration of 1 ppb.[64]

Recent studies of the South American shrub *Pilocarpus goudotianus* yielded a number of furano- and pyranocoumarins (**22**–**29**) (Fig. 7).[79,80] These compounds were tested along with selected synthetic coumarins in a lettuce germination bioassay. Significant activity was not observed below 10^{-4} M, thus making compounds **22**, **23**, and **25** most likely responsible for the allelopathic activity of *P. goudotianus* due to their higher natural concentrations in the plant.[80]

The allelopathic activity of compounds isolated from *Melilotus messanensis* (sweet clover) has been the subject of several investigations.[81] Several flavonoids and a coumarin isolated from sweet clover were recently subjected to bioassay, but their observed activities were low, suggesting that triterpenes and saponins are responsible for the activity of sweet clover (see Section 5.3).[81]

5.3. Terpenoids

Tens of thousands of isoprenoid compounds are known and hundreds more are reported in the literature each year. Therefore, it is not surprising that these secondary metabolites have been examined for their allelopathic potential. This topic has been the subject of past reviews.[57,82,83]

Messagenic acids A–I (**30**–**38**) are a family of nine lupane triterpenes isolated from sweet clover along with the oleanane triterpenes melilotigenins B–D (**40**–**42**) (Fig. 8).[84,85] Messagenic acids D, F, and G (**33**, **35**, **36**) were prepared via semi-synthesis from the more plentiful betulinic acid (**39**) in order to supplement the minute amounts of the natural material available. These compounds

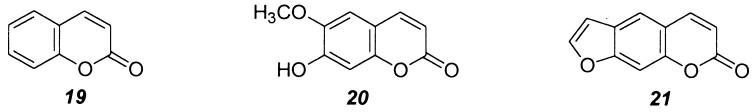


Figure 6.

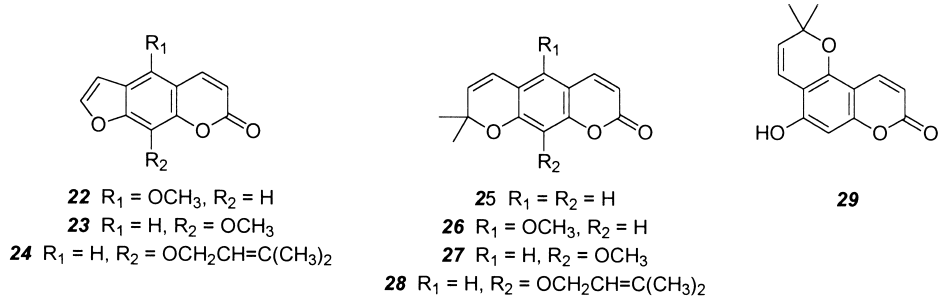
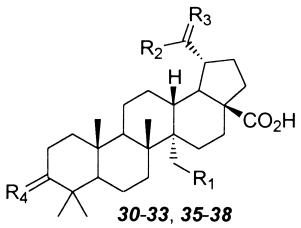
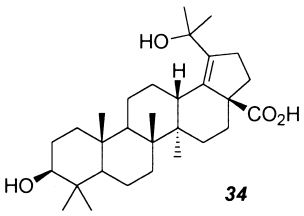


Figure 7.



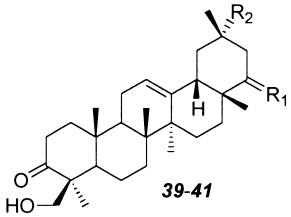
30-33, 35-38

compound	R_1	R_2	R_3	R_4
30	*Z*-4'-hydroxycinnamate	CH_3	CH_2	β-OH, α-H
31	*E*-4'-hydroxycinnamate	CH_3	CH_2	β-OH, α-H
32	H	CH_3	CHO, H	β-OH, α-H
33	H	CH_2OH	CH_2	β-OH, α-H
35	H	CHO	CH_2	β-OH, α-H
36	H	CH_2OH	CH_2	O
37	H	CH_2OH	O	O
38	H	CH_2OH	O	β-OH, α-H
39	H	CH_3	CH_2	β-OH, α-H



34

compound	R_1	R_2
40	O	CH_3
41	β-OH, α-H	CH_3
42	O	CO_2H



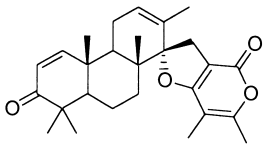
39-41

Figure 8.

were assayed for seed germination and growth activity using both mono- and dicotyledons. The compounds tested showed insignificant effects on lettuce but inhibited the seed germination of *Hordeum vulgare* (barley) and stimulated seed germination of *Allium cepa* (onion).[85]

Breviones A–E (**43**–**47**) (Fig. 9) are novel diterpenoid derivatives with a polyketide moiety attached through a spiro ring junction. The breviones were isolated from *Penicillium Brevicompactum* Dierckx, and their structures were elucidated through a combination of spectroscopic and chemical methods.[86,87] A mechanism for their biogenesis has been proposed.[87] Breviones C and E (**44** and **46**) were the most active compounds in a etiolated wheat coleoptile assay, inhibiting growth of the wheat shoots 80 and 100%, respectively, at 10^{-4} M. Breviones A and B (**43** and **44**) were less active (40% growth inhibition at 10^{-3} M), but brevione D (**45**) was not assayed due to lack of material.

Germacranolides and guaianolides have drawn particular attention among the many classes of sesquiterpenoid lactones that have been studied for allelopathic properties.[57,88] The role of the α-methylene lactone moiety and the effect of molecular conformations for a number of



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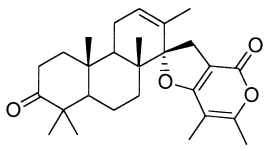

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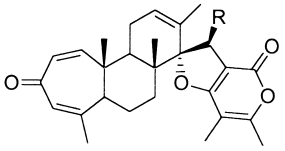

45 R = H
46 R = OH

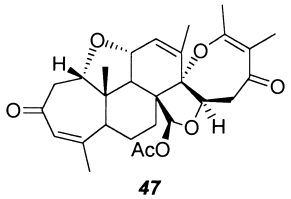

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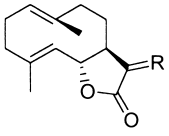
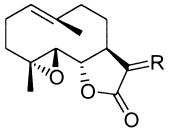
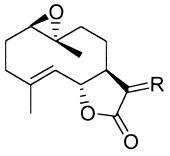
Figure 9.



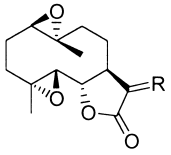
48 R = CH_2
52 R = α-CH_3, β-H



49 R = CH_2
53 R = α-CH_3, β-H



50 R = CH_2
54 R = α-CH_3, β-H



51 R = CH_2
55 R = α-CH_3, β-H

Figure 10.

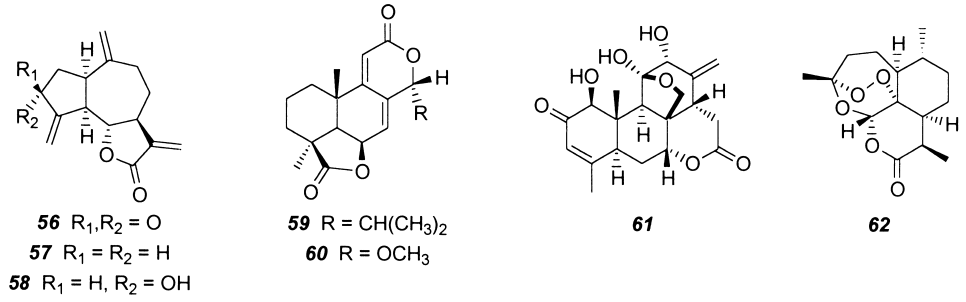


Figure 11.

natural and synthetic sesquiterpene lactones of this type has been examined.[89] More recently Macías continued these investigations, testing the natural germacranolides costunolide (**48**) and parthenolide (**49**) and synthetic derivatives **50**–**55** for phytotoxicity on a number of mono- and dicotyledons (Fig. 10).[90] Costunolide (**48**) and derivatives **50**, **52**, and **54** also stimulate germination of parasitic witchweed species.[20]

Dehydroazulanin C (**56**) (Fig. 11) has been isolated from a number of plant species, and is one of the many guaianolides studied for allelopathic potential.[91,92] Dehydroazulanin C (**56**) is unique, however, in having a dual mechanism. The α-methylene lactone moiety is responsible for germination and growth inhibition similar to other guaianolides, but the second Michael acceptor, the cyclopentenone group, is responsible for rapid leakage of the plasma membrane.[91] Dehydroazulanin C (**56**) was prepared via semi-synthesis from dehydrocostuslactone (**57**) via *iso*zaluzanin (**58**).[92] Other guaianolide derivatives have been prepared by manipulation of **57** and studied with Macías' STS assay to construct a SAR.[93] This SAR study showed that the lactone group was necessary for activity, but did not have to be unsaturated. Furthermore, a second α,β-unsaturated carbonyl enhanced activity if the molecular conformation rendered it sterically accessible. It was also concluded that the presence of additional hydroxyl groups lowered activity when polarity reached a level sufficient to inhibit membrane transport.[93]

Nagalactone F (**59**), LL-Z1271a (**60**) and a variety of related podolactones were recently synthesized and evaluated in Macías' STS bioassay (Fig. 11).[94,95] Compound **60** had a better activity profile than the internal standard in these studies, the commercial herbicide Logran®, at 10^{-4} and 10^{-5} M.[94]

Ailanthone (**61**) (Fig. 11) is a quassinoid lactone from *Ailanthus altissima* (Tree-of-Heaven) and was recently shown to be the major phytoxin of this allelopathic plant. Ailanthone is a post-emergence herbicide, but is rapidly degraded in the field, losing its effect after several days.[96]

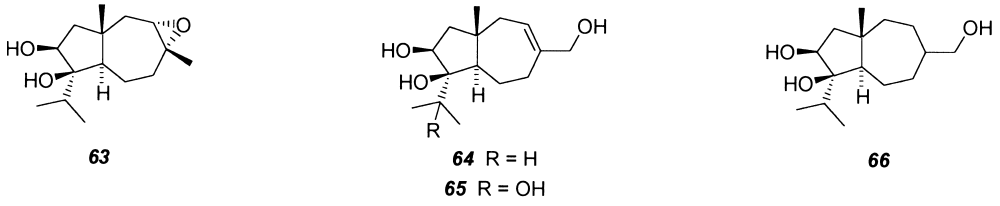


Figure 12.

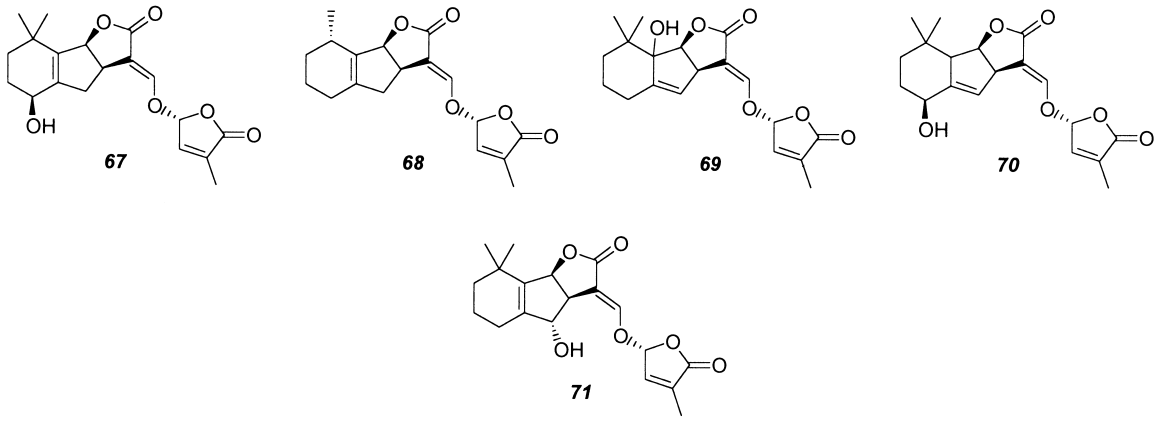


Figure 13.

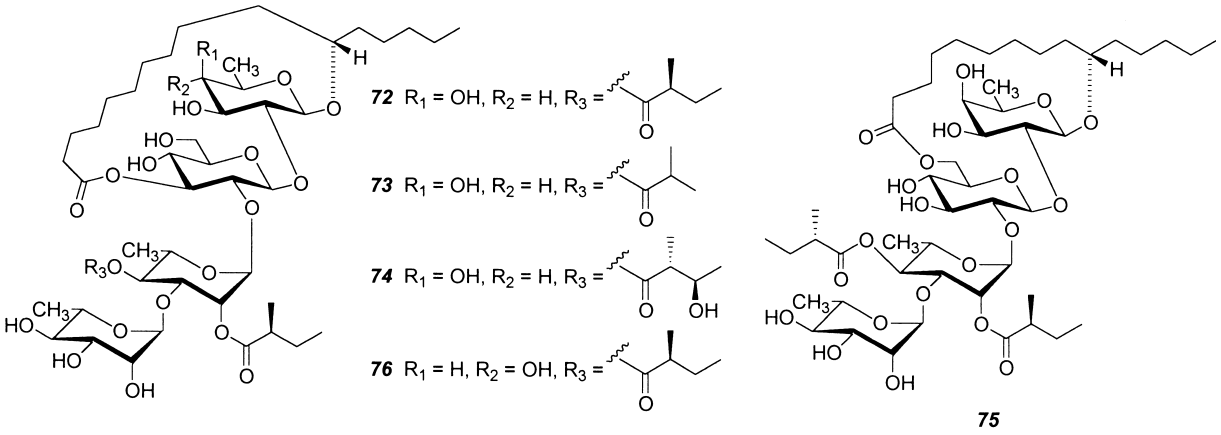


Figure 14.

Artemisinin (**62**) (Fig. 11) is known to most organic chemists as a promising anti-malaria agent,[97–99] but this endoperoxide-containing lactone is also a selective phytotoxin.[100] There is no correlation between herbicidal activity and activity against *Plasmodium* parasites, however.[101] A series of synthetic artemisinin analogues was evaluated for herbicidal activity. The artemisinin analogues increased oxygen uptake and decreased chlorophyll content in treated plants.[101] No membrane disruption was found, however, and complementation experiments suggested that the phytotoxic effect of **62** and the synthetic analogues was not due to inhibition of porphyrin biosynthesis, amino acid synthesis, or nucleic acid synthesis. Thus the mode of action of **62** is still not clear.[102]

Trichocaranes A–D (**63**–**66**) (Fig. 12) are carotane sesquiterpenes recently isolated from the fungus *Trichoderma virens*.[103] Trichocarane D (**66**) was inactive in the etiolated wheat coleoptile assay, but trichocaranes A and B (**63** and **64**) inhibited growth 40% at 10^{-4} M and trichocarane C (**65**) inhibited growth 86% at 10^{-3} M.[103]

5.4. Strigolactones

Parasitic weeds of the *Striga* (witchweeds), *Orobanche*, and *Alectra* families affect a number of important cereal and legume crops, causing dramatic reduction in yield and in severe cases complete destruction of the crop. The problem is especially severe in Africa and is becoming more prevalent.[19,20] The seeds of these parasites only germinate in the presence of chemical stimulants exuded from other plants. Typically the host plant is the source of seed germination stimulant, but the first such germination stimulant to be characterized, strigol (**67**) (Fig. 13), was in fact isolated from a non-host plant.[104] The first seed germination stimulant isolated from a *Striga* host (*S. bicolor*) was the hydroquinone form of sorgoleone (**19**) (Fig. 5).[65,66] Structurally related witchweed seed germination stimulants sorgolactone and alectrol were isolated from sorghum and *Vigna unguiculata* (cowpea) respectively, and assigned structures **68** and **69** (Fig. 13).[105,106] Both of these compounds were obtained in minute quantities and the structures were assigned based on spectral data correlated with data from strigol (**67**), whose structure had been confirmed by X-ray analysis.[104,107] Ororbanchol, a germination stimulant for *Orobanche minor* (clover broomrape) was isolated from its host, *Trifolium pratense* (red clover), and assigned structure **70**.[108] These compounds are commonly referred to as strigolactones and are active at concentrations below 10^{-11} M.[19] Recently a series of semi-synthetic lactones of various sesquiterpenoid families were tested as *Orobanche cumana* germination stimulants.[109]

The strigolactones have also stimulated the interest of synthetic organic chemists with intriguing results. Strigol (**67**) has been synthesized in racemic[110] and optically pure form.[111,112] Zwanenburg concluded that the stereoisomer shown in Fig. 13 is identical to natural strigolactone after synthesizing all eight stereoisomers of **68**.[113] Mori's group disputes this conclusion, however.[114] Mori's group has disproven the originally proposed structures of alectrol,[115] and orobanchol.[116] Based on extensive synthetic effort, Mori's group has concluded that orobanchol is actually **71**.[112,116] Illustrated by the case of the strigolactones, one can clearly see the importance of the synthetic chemist to allelopathic research.

5.5. Miscellaneous

A cover crop of the allelopathic plant *Ipomoea tricolor* (morning glory) is used in some areas of tropical Mexico to eliminate weeds prior to planting the next sugar cane crop.[117,118] Bioassay-guided analysis of *I. tricolor* extract yielded a mixture of phytotoxic resin glycosides, the

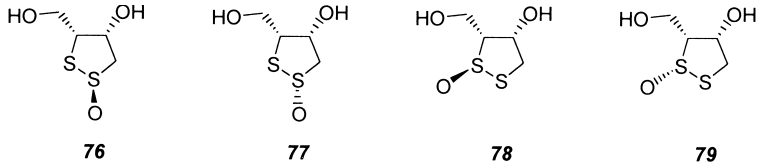


Figure 15.

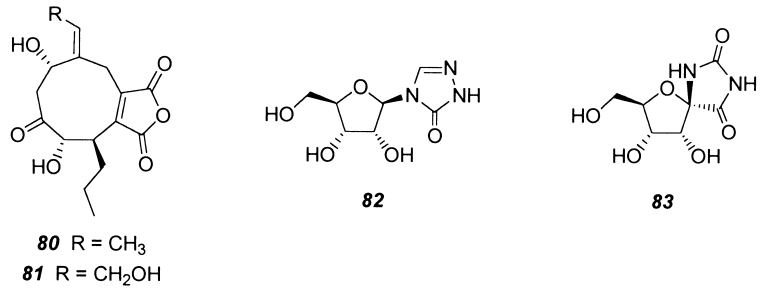


Figure 16.

major component (63%) of which is tricolorin A (**72**) (Fig. 14). This novel macrolactone oligosaccharide has antibiotic and antitumor activity in addition to being a potent plant growth inhibitor.[119] The minor components of the mixture, tricolorins B–E (**73**–**76**) (Fig. 14), were identified by detailed NMR analysis,[120] but studies on the inhibition of H^+-ATPase by the glycoside mixture indicated that tricolorin A (**72**) was the active component.[121] A study that combined petri dish bioassays with greenhouse experiments suggested that the weed suppressive activity of *I. tricolor* may involve both leaching of allelochemicals from the living plant by rain and release of allelochemicals from decaying plant matter.[118] More recent studies indicate that tricolorin A (**72**) uncouples photophosphorylation in spinach chloroplasts and inhibits electron transport in photosystem II, and that the macrolactone is a structural requirement for this activity.[122] The challenge presented by the novel macrolactone structure of the tricolorins has attracted the attention of synthetic chemists.[123–126]

The annual weed *Sphenoclea zeylanica*, known as phak pot in Thailand and gooseweed in the US, is a serious problem in rice paddies, due to its rapid growth and herbicide tolerance.[127] A family of 1,2-dithiolane-1-oxides (**76**–**79**) (Fig. 15) was isolated from gooseweed and their structures confirmed through synthesis from glucose.[128] Cyclic thiosulfinates **76**–**79** all inhibit root growth in rice and germination in lettuce at millimolar concentrations.[128]

Several natural products have recently been isolated from microorganisms that have herbicidal activity worthy of consideration. Cornexistin (**80**)[129] and hydroxycornexistin (**81**)[130] are nonadrides isolated from the fungus *Paecilomyces variotii* (Fig. 16). Both compounds have high post-emergence activity against a variety of broadleaf weeds, but do not harm *Zea mays* (corn).

Triazolone **82** (Fig. 16) was recently isolated from *Actinomadura* fermentation broth and exhibited broad-spectrum herbicidal activity. Further investigation demonstrated that it has the same biochemical target, adenylsuccinate synthetase, as the natural product herbicide, hydantocidin (**83**).[131]

Finally, herboxidiene (**84**) (Fig. 17) is a novel polyketide isolated from *Streptomyces chromofuscus* A7847, which is active against several important weed species.[132] Early synthetic work indicated that the epoxide and the C-18 hydroxyl are important for activity.[133] The absolute configuration of herboxidiene was confirmed through chemical degradation correlated with synthetic intermediates,[134] and **84** has been the subject of synthetic efforts by the Banwell[135–139] and Kocienski groups.[140,141] The complex structure of **84** makes it a challenging lead for herbicide development, but structurally simplified analogs incorporating an aromatic ring in place of the diene, have resulted in at least one active compound (**85**).[142] Furthermore, herboxidiene (**84**) up-regulates gene expression of low density lipoprotein (LDL) receptors[143] and has antitumor activity,[144] making **84** and structural analogs attractive leads for further development.

6. Allelochemicals from sunflower

Few plants have been studied as much in recent years for their allelopathic potential as the sunflower, *Helianthus annuus*. Sunflowers are an important crop in many parts of the world, and dozens of hybrid varieties are known, 26 in the Andalusia region of Spain, for example.[2,145] Leather conducted some of the first studies on this species, and showed that sunflower extracts inhibited germination of growth of a variety of weed species.[146,147] *H. annuus* has activity against such troublesome weeds as morning glory, velvetleaf, pigweed, jimson weed, wild mustard, and others.[6,21,146] Subsequent research has included examination of the effects sunflower growth stage has on the allelopathic effects,[148,149] and examination of other sunflower species.[150,151]

6.1. Heliannuols

The heliannuols (**86**–**96**) (Fig. 18), are a promising group of phenolic allelochemicals isolated from *H. annuus*. The phenolic functional group has long been associated with allelopathic activity.[152,153] Heliannuol A (**86**) was isolated

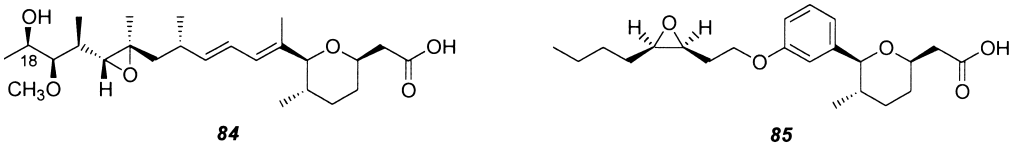


Figure 17.

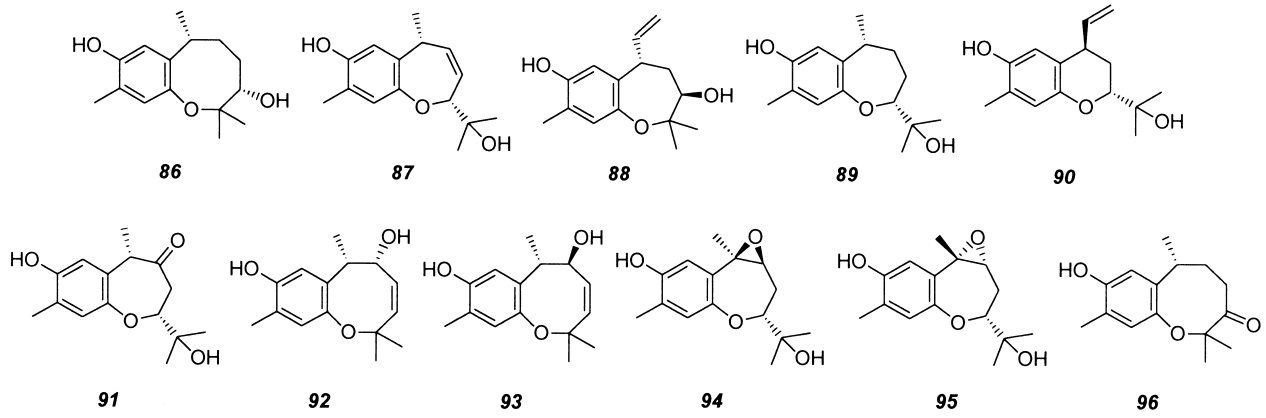


Figure 18.

from an aqueous extract of *H. annuus* L. var. SH-222 and has a novel sesquiterpenoid skeleton consisting of an eight-membered cyclic ether fused to a benzene ring.[154] Heliannuols B, C and D (**87**–**89**) were isolated shortly thereafter, all containing a seven-membered benzofused cyclic ether.[155] Heliannuol E (**90**) has a vinyl substituent like that in **88**, and is the only heliannuol that contains a six-membered benzofused ether.[156] Heliannuols F–K (**91**–**96**) have more highly oxidized benzofused ether rings, but are present in minute quantities—extraction of 6 kg of fresh sunflower leaves yielded only 1–2 mg each of **91**–**96**.[157]

The relative stereostructures of heliannuols A and D (**86** and **89**) were confirmed by X-ray analysis and chemical correlation.[154,155] The absolute configuration of heliannuol A (**86**) was established by ^{1}H NMR analysis of the diastereomeric Mosher ester derivatives.[158] Absolute stereochemical assignments for the remaining heliannuols, with the exception of heliannuol C, were then made by correlation to their proposed biogeneses.[158]

The proposed biosynthesis of the heliannuols involves a cyclization of an aromatic bisabolene epoxide derived from curcuquinone or curcuhydroquinone.[154,155] The biosynthesis of heliannuols C and E (**88** and **90**) cannot be easily explained by the above hypothesis, but a rearrangement via a cyclopropyl phenonium ion has been suggested and evaluated by semiempirical calculations.[155]

Heliespirone A (**97**) (Fig. 19), a novel allelopathic quinone spiroether, was also isolated from *H. annuus* and likely arises from a bisabolene precursor as well.[159] Bisabolene quinones such as glandulones A–C (**98**–**100**) (Fig. 19) have previously been isolated from the noncapitate glandular trichomes of *H. annuus*.[160] The recent isolation of helianane (**101**) (Fig. 19) from an Indonesian sponge shows that the medium-ring ether structural motif of the heliannuols is not limited to the plant kingdom, and sheds additional light on the biogenesis of these compounds.[161]

The activities of the heliannuols against a variety of STS[38] have been studied. In general, the heliannuols inhibit dicotyledon plants and stimulate monocotyledons. Heliannuols A and D (**86** and **89**) appear to be the most active members of the family with effective concentrations as low as 10^{-9} M, followed closely in activity by heliannuols I and K (**94** and **96**). In fact, comparison of selected heliannuols to several commercial herbicides showed that they have better activity profiles with respect to effective concentration.[162,163]

In addition to their value as natural herbicide models, the heliannuols are challenging targets for the synthetic chemist. A total synthesis of heliannuol A (**86**) appeared shortly after its discovery.[164] The first synthesis of (±)-**86** and the recently reported synthesis of (±)-helianane (**101**)[165] both installed the *tert*-alkyl aryl ether moiety prior to closing the eight-membered ether through C–C bond formation. An intramolecular Julia coupling was used in the case of **86**[164] and a ring-closing metathesis (RCM) reaction was used to prepare **101**.[165]

More recent synthetic work on the heliannuols has focused on forming the benzofused ether moiety via C–O bond formation using biomimetic phenol epoxide cyclizations. (±)-Heliannuol D (**89**) was synthesized via cyclization of a phenol epoxide under basic conditions.[166] An enantioselective synthesis of (+)-**86** and (−)-**89** (the unnatural enantiomers) was recently reported that involved enzymatic resolution of a 2-aryl-1,3-propanediol intermediate prior to cyclic ether formation.[167] A similar chemoenzymatic strategy, this time utilizing a 3-aryl-1,5-pentanediol intermediate, resulted in the total synthesis of natural (−)-heliannuol E (**90**).[168]

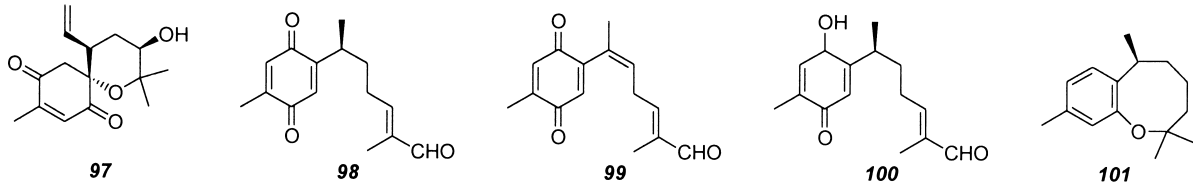


Figure 19.

6.2. Sunflower terpenoids

Sesquiterpene lactones are common constituents of *Helianthus* species.[169] Annuolides A–G (**102**–**108**) (Fig. 20) are a family of guaianolides isolated from sunflower cultivars that exhibit allelopathic activity.[170,171] Bioassay data indicated that the α-methylene lactone was not strictly required for inhibiting lettuce seed germination but the compounds with the α-methylene moiety were active at lower concentrations.[170] Derivatization of the hydroxyl group closest to the methylene lactone as in annuolides F and G (**107** and **108**, respectively) reduced activity.[171]

Helianthus cultivars have also yielded some interesting bisnorsesquiterpenes such as annuionones A–D (**109**–**112**) and helinorbisabone (**113**) (Fig. 21). Macías recently isolated **109**–**113** from hybrid sunflowers, but the stereochemistry of **111** and **113** was not determined.[172,173] Annuionone D (**112**) was synthesized prior to its isolation as a natural product, which assisted in determining the absolute configuration of the annuionones.[174] Helinorbisabone (**113**) has an activity profile similar to heliannuols A and D (**86** and **89**) and was identified as a reasonable candidate for herbicide development.[172] Sundiversifolide (**114**) (Fig. 21) was recently isolated from the exudate of germinating *H. annuus* seeds and its structure determined by analysis of one and two dimensional NMR spectra including NOE studies to establish relative stereochemistry.[175] Bioassays showed that 30 ppm of **114** inhibited shoot and root growth of cat's eyes seedlings 50%.

6.3. Sunflower flavonoids

The sunflower has also yielded chalcones and flavonoids in the search for allelochemicals. Chalcones kulkulkanin B (**115**) and heliannone A (**116**) were isolated along with flavonoids tambulin (**117**), and heliannones B and C (**118** and **119**) from both *H. annuus* cultivars VYP and cv. Peredovick (Fig. 22).[176,177] Bioassays indicated **115**–**119** mainly affected shoot growth of *Lycopersicon esculentum* (tomato) and *H. vulgare* (barley) seedlings, but the chalcones **115** and **116** affected germination as well.[176] The simple structures and straightforward synthesis of these flavonoids[178] make them attractive leads for further study as potential agrochemicals.

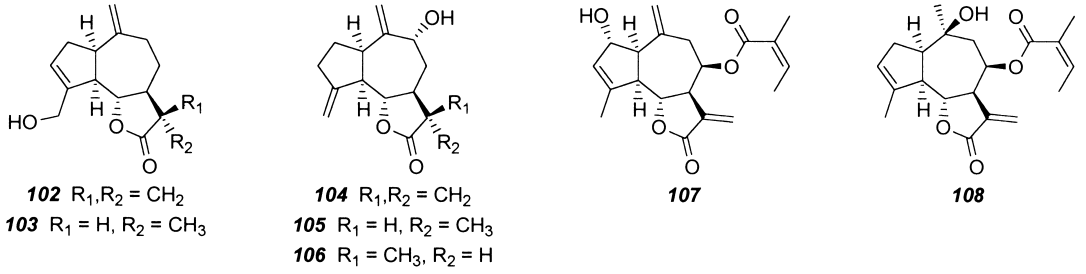


Figure 20.

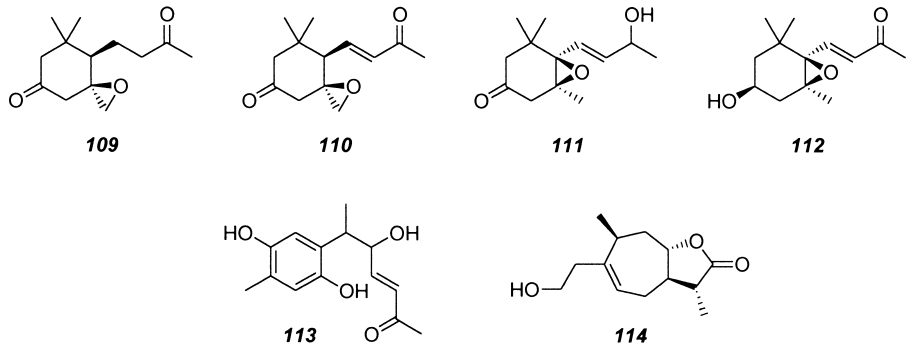


Figure 21.

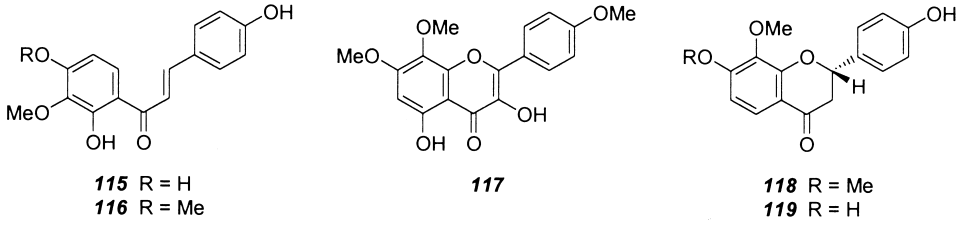


Figure 22.

7. Conclusions

The field of allelopathy has developed significantly since the times of the ancient Greeks, and now requires an interdisciplinary effort of botanists, organic chemists, and molecular biologists to take advantage of the clues found in nature for the development of future herbicides. Researchers involved in natural product isolation can further the cause by including assays for plant growth inhibition in the standard array of screening methods. Finally, synthetic organic chemists can play a unique role in the process by taking aim at the diverse array of allelopathic natural product structures and producing sufficient quantities of the allelochemicals and simplified analogues for more detailed biological testing to determine efficacy, structure–activity relationships, and mode of action.

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Biographical sketch

James Vyvyan was raised in rural southeastern Wisconsin and spent many hours laboring on his grandparents farm, where he learned first hand about the constant battle against weeds to improve crop yields. Science of all types fascinated him as a boy and after high school, Vyvyan enrolled at the University of Wisconcin-Eau Claire to study chemistry. There he conducted research with Professor Leo A. Ochrymowycz preparing tetrathiocrown ethers to study the redox behavior of soft transition metal ions. The years in the research lab and the classroom at UWEC opened Vyvyan's eyes to the beauty of organic synthesis. Graduating *summa cum laude* from UW-Eau Claire in 1991, Vyvyan began graduate school at the University of Minnesota and quickly joined the research group of Professor Thomas R. Hoye. Vyvyan's thesis research involved application of Fischer carbene cyclopropanation reactions to the synthesis of natural product skeletons and he earned his PhD in 1995. Having set his sights on an academic career at a predominantly undergraduate institution, Vyvyan accepted a Camille and Henry Dreyfus Scholar/Fellow position with Professor Stephen K. Taylor at Hope College. At Hope, Vyvyan taught one course each term and mentored undergraduates in the research lab. His research with Taylor involved the use of enzymes and whole cell systems in organic synthesis and the synthesis of lactones via reaction of epoxides with aluminum enolates. In 1997, Vyvyan accepted a position on the chemistry faculty of Western Washington University. His current research efforts are supported by a National Science Foundation CAREER grant and include the total synthesis of the heliannuols and related allelochemicals.