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Marine Natural Products as Prototype Agrochemical Agents

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In the interest of identifying new leads that could serve as prototype agrochemical agents, 18 structurally diverse marine-derived compounds were examined for insecticidal, herbicidal, and fungicidal activities. Several new classes of compounds have been shown to be insecticidal, herbicidal, and fungicidal, which suggests that marine natural products represent an intriguing source for the discovery of new agrochemical agents.

KEYWORDS: Agrochemicals; insecticides; herbicides; fungicides; marine natural products

INTRODUCTION

Insects, weeds, and phytopathogenic fungi cause great damage to agriculture, home, and garden. Where insect pests, weeds, and disease are not systematically controlled, an estimated 40% of a typical crop is lost preharvest and an additional 20% is lost postharvest (*1*). Much of the increase in agricultural productivity over the past half century has been due to the control of these pests with synthetic chemical pesticides (*2*). Crop protection chemicals continue to be the major tools for protecting food and fiber crops from damaging pests. In 1997, world pesticide sales amounted to nearly $37 billion, of which 31% was for insecticides, 46% for herbicides, and 16% for fungicides (*3*). User expenditures for pesticides in the United States totaled $11.9 billion, of which $6.8 billion was spent for insecticides, $3.6 billion for herbicides, and nearly $800 million for fungicides (*3*).

Synthetic pesticides have successfully controlled a number of agricultural pests; however, there is a need to search for alternative chemistries. One serious problem has been the development of resistance to current pesticides. From 1984 to 1990, documented insect and mite resistance to pesticides increased by 13% (*4*). Furthermore, contamination of food, soil, water, and air by pesticides has become a major concern for the U.S. public (*5*). Accordingly, there is increasing social legislative pressure to replace or reduce the use of synthetic chemical pesticides because of their toxicological and environmental risks (*1*). To address environmental concerns, new agrochemicals developed from natural products may be perceived as more environmentally acceptable than those presently used (*5*, *6*). The investigation of terrestrial organisms has yielded many of the pesticides on the market today, including the frequently used pesticide ivermectin (**1**; **Figure 1**), the selective hydrogenation products of avermectin B1 islolated from *Streptomyces avermitilis* MA-4680 (NRRL 8165) (*7*, *8*). In contrast, the plants, animals, and microorganisms of the marine environment, with their wide range of chemical and bioactive diversity, are still largely an unexplored resource for new agrochemical agents (*9*).

Compared to the search for new pharmaceutical compounds, little effort has been devoted to the exploration of agrochemical compounds from marine natural products. Nereistoxin (**2**) and its analogues thiocyclam (**3**), bensultap (**4**), and cartap (**5**) are probably the ocean's only major agrochemical agents being used as insecticides in some parts of the world (*10*).

Marine Natural Products as Insecticides, Herbicides, and Fungicides: An Update. In our previous paper (*11*), the insecticidal compounds of marine origin and their activities were reviewed. In addition to developments summarized in our earlier paper, a new sesquiterpene, hydroxycolorenone (**6**), was isolated from the soft coral *Nephithea chabrolii*, which showed strong

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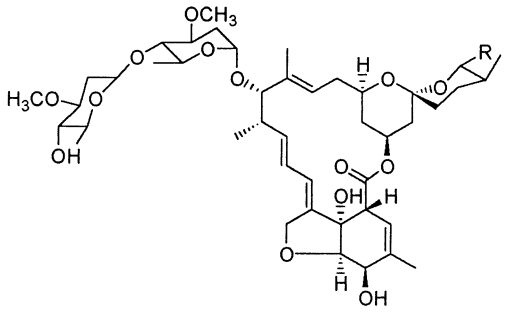
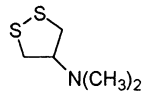
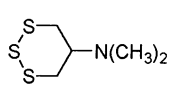


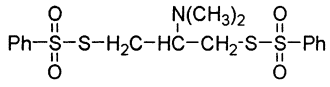
Ivermectin (**1**)
mixture of R=$CH(CH_3)_2$ and $CH(CH_3)CH_2CH_3$



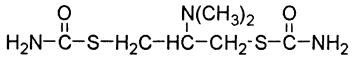
Nereistoxin (**2**)



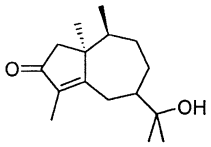
Thiocyclam (**3**)



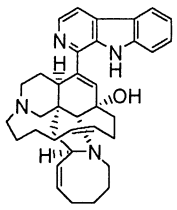
bensultap (**4**)



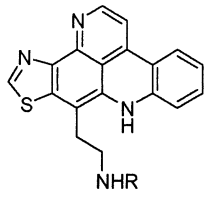
cartap (**5**)



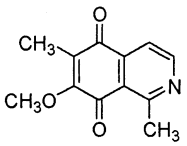
hydroxycolorenone (**6**)



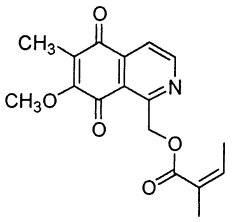
manzamine A (**7**)



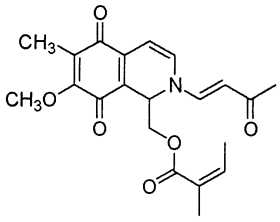
kuanoniamine C (**8**): R=COC_2H_5
kuanoniamine D (**9**): R=$COCH_3$
N-deacetylkuanoniamine D (**10**): R=H



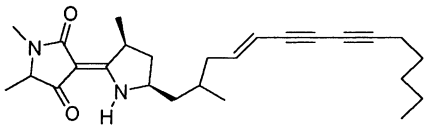
(**11**)



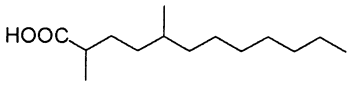
renierone (**12**)



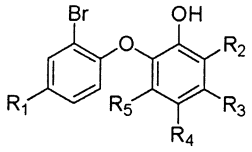
N-(3-oxo-1-butenyl)
renierone (**13**)



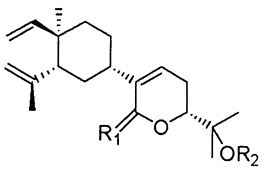
fischerellin A (**14**)



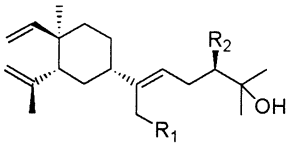
2,5-dimethyldodecanoic acid (**15**)



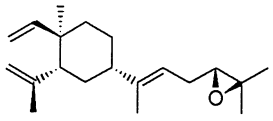
(**16**): R_1=H R_2=R_3=R_4=R_5=Br
(**17**): R_1=R_2=H R_3=R_4=R_5=Br
(**18**): R_1=R_4=H R_2=R_3=R_5=Br
(**19**): R_1=R_3=H R_2=R_4=R_5=Br
(**20**): R_1=R_2=R_3=R_4=R_5=Br
(**21**): R_1=R_2=R_4=Br R_3=R_5=H



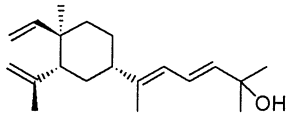
(**22**): R_1=H_2 R_2=H
(**23**): R_1=H_2 R_2=Ac
(**24**): R_1=O R_2=H



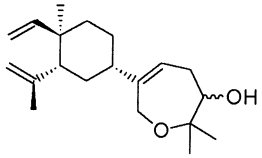
(**25**): R_1=OAc R_2=OH
(**26**): R_1=R_2=OAc
(**27**): R_1=H R_2=OH
(**28**): R_1=H R_2=OAc



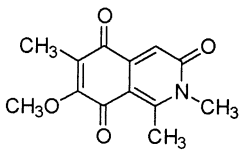
(**29**)



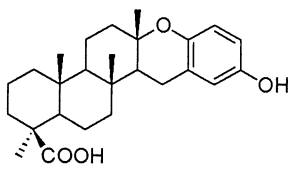
(**30**)



(**31**)



mimosamycin (**32**)



strongylophorine-3 (**33**)

Figure 1. Structures of reviewed active compounds.

insecticidal activity with an EC_{50} 35 μM and an LC_{50} 1.8 mM against neonate larvae of the polyphagous pest insect *Spodoptera littoralis* (*12*). The marine-derived β-carboline alkaloid manzamine A (**7**) was reported to exhibit insecticidal activity toward neonate larvae of the polyphagous pest insect *S. littoralis* with an ED_{50} of 63 μM (*13*). Pyridoacridine alkaloids are characterized by an 11*H*-pyrido[4,3,2-*mn*]acridine moiety. Kuanoniamin C (**8**), kuanoniamine D (**9**), and *N*-deacetylkuanoniamine D (**10**) are pyridoacridine alkaloids reported from the Micronesian tunicates and sponges of the genera *Stelleta* and *Oceanapia*. Kuanoniamine C (**8**) and kuanoniamine D (**9**) exhibited insecticidal activity against *S. littoralis* with LC_{50} values of 0.42 and 0.16 mM, respectively, whereas *N*-deacetylkuanoniamine D (**10**) was marginally active and inhibited the growth of the larvae with an ED_{50} of 0.44 mM (*14*). The isoquinoline alkaloids isolated from the Philippine sponge of the genus *Xestospongia* also exhibited insecticidal activity (*15*). 1,6-Dimethyl-7-methoxy-5,8-dihydroisoquinoline-5,8-dione (**11**) showed insecticidal activity with an EC_{50} of 0.16 mM and an LC_{50} 2.4 mM against *S. littoralis*. Renierone (**12**) and *N*-(3-oxo-1-butenyl) renierone (**13**) exhibited weak insecticidal activity against *S. littoralis*.

Herbicides. To date, research focused on the isolation of herbicidal leads from marine origin has resulted in the report of just two compounds. Fischerellin A (**14**), isolated from the cyanobacteria *Fischerella muscicola*, demonstrated herbicidal activity against *Lemna minor* at 50 μM (60% PS-II inhibition, 44% growth inhibition), and at 100 μM the photosystem of this plant was almost totally blocked (98% PS-II inhibition, 74% growth inhibition) (*16*). 2,5-Dimethyldodecanoic acid (**15**) strongly inhibited the growth of *L. minor* (*17*) with a growth inhibition of 58% at 2.2 μM and 91% at 22 μM at pH 5. This inhibition is pH dependent, and at low pH, the inhibition is highest. Methylation of this fatty acid decreased the activity.

Fungicides. Polybrominated diphenyl ethers (**16**−**21**) are a class of phytopathogenic fungicides isolated from the sponge *Dysidea herbacea* Keller (*18*), in which a mixture of 3,5,6-tribromo-2-(2′-bromophenoxy)phenol (**18**) and 3,4,6-tribromo-2-(2′-bromophenoxy)phenol (**19**) (3:2) represents the best activity at 25 nmol, inducing an inhibition zone of 8 mm against the phytopathogenic fungus *Cladosporium cucumerinum*. 3,4,5,6-Tetrabromo-2-(2′-bromophenoxy)phenol (**16**) also showed significant activity against *C. cucumerinum* followed by 3,4,5-tribromo-2-(2′-bromophenoxy)phenol (**17**), then 3,4,5,6-tetrabromo-2-(2′,4′-dibromophenoxy)phenol (**20**), and finally 4,6-dibromo-2-(2′,4′-dibromophenoxy)phenol (**21**), which showed the weakest activity. Edrada (*19*) reported 10 lobane diterpenes (**22**−**31**) from the Philippine soft coral *Lobophytum pauciflorum*, all of which showed activity against the phytopathogenic fungus *C. cucumerinum*. The labatrienetriol congeners (**25** and **26**) were most active, followed by the oxepin congener (**26**) and then the labatrienediol congeners (**27** and **28**) and the oxinine congeners (**22**−**24**), whereas the epoxide congener (**29**) and the diene congener (**30**) showed the weakest activity. Mimosamycin (**32**) is another isoquinoline quinone isolated from a sponge of the genus *Xestospongia* (*15*). Unlike its analogues, it is not active against insects, but it is active against the phytopathogenic fungus *C. cucumerinum* with an inhibition zone of 15 mm at 30 mM. Strongylophorine-3 (**33**) is both insecticidal and fungicidal (*20*). It induced inhibition zones of 15 and 10 mm at 0.80 and 0.10 μmol, respectively, against *C. cucumerinum*. Fischerellin A (**14**) also showed fungicidal activity against several agronomically important microorganisms that could severely affect a wide range of crop plants. It exhibits a 100% growth inhibition of the brown rust on beans (*Uromyces appendiculatus*) at 0.61 μM, whereas 100% inhibition of the powdery mildew on barley (*Erysiphe graminis*) required a concentration of 2.4 mM. Fischerellin A (**14**) exhibited 80% inhibition of downy mildew (late blight, *Phytophthora infestans* on tomato) and rice blast (*Pyricularia oryzae*) at 2.4 mM. Less activity (30% growth inhibition at 2.4 mM) was observed against brown rot (blossom blight, *Monilinia fructigena*) and stem break (*Pseudocercosporella herpotrichoide*) grown on agar (*16*).

MATERIALS AND METHODS

Marine-Derived Compounds. Eighteen structurally diverse compounds from our marine-derived compound library were assayed including manzamine A (**7**), *ent*-8-hydroxymanzamine A (**34**), *ent*-manzamine F (**35**), (+)-aeroplysinin-1 (**36**), latrunculin B (**37**), jaspamide (**38**), kahalalide F (**39**), halichondramide (**40**), muqubilin (**41**), heteronemin (**42**), deacetylheteronemin (**43**), sceptrin (**44**), monobromosceptrin (**45**), sigmosceptrellin A (**46**), uranidine (**47**), 10-isothiocyanato-4-amorphene (**48**), 9β-hydroxysarcophine (**49**), and 7α,8β-dihydroxydeepoxysarcophine (**50**) (**Figure 2**). The structure determination of each compound was based on the analysis of NMR and mass spectral data, authenticated by comparison of those data with the literature. The manzamine alkaloids were first isolated from the Okinawan sponge genus *Haliclona* (*21*). Several Indonesian sponges have been identified as a rich source of manzamine alkaloids. The yield of *ent*-8-hydroxymanzamine F (**34**) was shown to be 1.24% (*22*), and the yield of manzamine A from the same sponge can reach as much as 5%. (+)-Aeroplysinin-1 (**36**) was first isolated from *Aplysina aerophoba* (*23*). This compound was reisolated from a Jamaican sponge *Aplysina* sp. Latrunculin B (**37**) is a macrolide toxin isolated from the Red Sea sponge *Latrunculia magnifica* (*24*). Jaspamide (**38**), a highly modified cyclic depsipeptide, was first identified from a sponge of the genus *Jaspis* (*25*). Kahalalide F (**39**), which is in clinical trials for the treatment of prostate cancer, was isolated from a Hawaiian mollusk *Elysia rufescens* and its diet, *Bryopsis* sp. (*26*). The absolute stereochemistry of kahalalide F was completely assigned in 2001 through a total synthesis (*27*). Halichondramide (**40**) was a 25-membered macrolide, which accommodates an unusual system of three contiguous oxazole rings in the macrocyclic ring (*28*). The keto−triol formyl enamine moiety of halichondramide was synthesized in 1992 (*29*). Muqubilin (**41**) was identified from a sponge of the genus *Prianos* (*30*), and its absolute configuration was determined in 1985 (*31*). The muqubilin tested in these experiments was isolated from the Red Sea sponge *Diacarnus erythraeanus* (*32*). Heteronemin (**42**) was first reported from the sponge *Heteronema erecta* (*33*). Deacetylheteronemin (**43**) is a semisynthetic compound generated through the hydrolysis of the acetate ester. Sceptrin (**44**) and monobromosceptrin (**45**) were isolated from a Caribbean sponge *Agelas conifera* (*34*). Sigmosceptrellin A (**46**) and 10-isothiocyanato-4-amorphene (**48**) were first isolated from the sponge *Sigmosceptrella laevis* (*35*) and a *Halichondria* sponge (*36*), respectively, and reisolated as part of Dr. Dunbar's dissertation research (*37*). Uranidine (**47**) is the yellow zoochrome first reported from the sponge *Verongia aerophoba* (*38*). 9β-Hydroxysarcophine (**49**) and 7α,8β-dihydroxydeepoxysarcophine (**50**) were biotransformation products generated from the natural product sarcophine (*39*).

Insecticidal Assay. Candidate compounds were tested against three economically important insect pest species in feeding bioassays. The insect species used in bioassay were the western corn rootworm (WCR), *Diabrotica virgifera virgifera* (LeConte) (Coleoptera: Chrysomelidae); the tobacco budworm (TBW), *Heliothis virescens* (Fabr.) (Lepidoptera: Noctuidae), and the western tarnished plant bug (WTPB), *Lygus hesperus* (Knight) (Heteroptera: Miridae) (*40*).

Assay Procedure. Purified samples (1 mg) were dissolved in 50 μL of DMSO or acetone and were diluted to 1 mg/mL with either 1% DMSO or 50% acetone. Only one dilution per sample was used (100 ppm). For WCR and TBW bioassays, microtiter plates with 96 wells were prepared with a synthetic insect diet (BioServ Co., Frenchtown, NJ) at a concentration of 200 μL per well), and 20 μL of the 1 mg/mL sample solution was pipetted onto the top of each of 16 wells for each insect (*41, 42*). For WTPB bioassays, the dilutions were as described

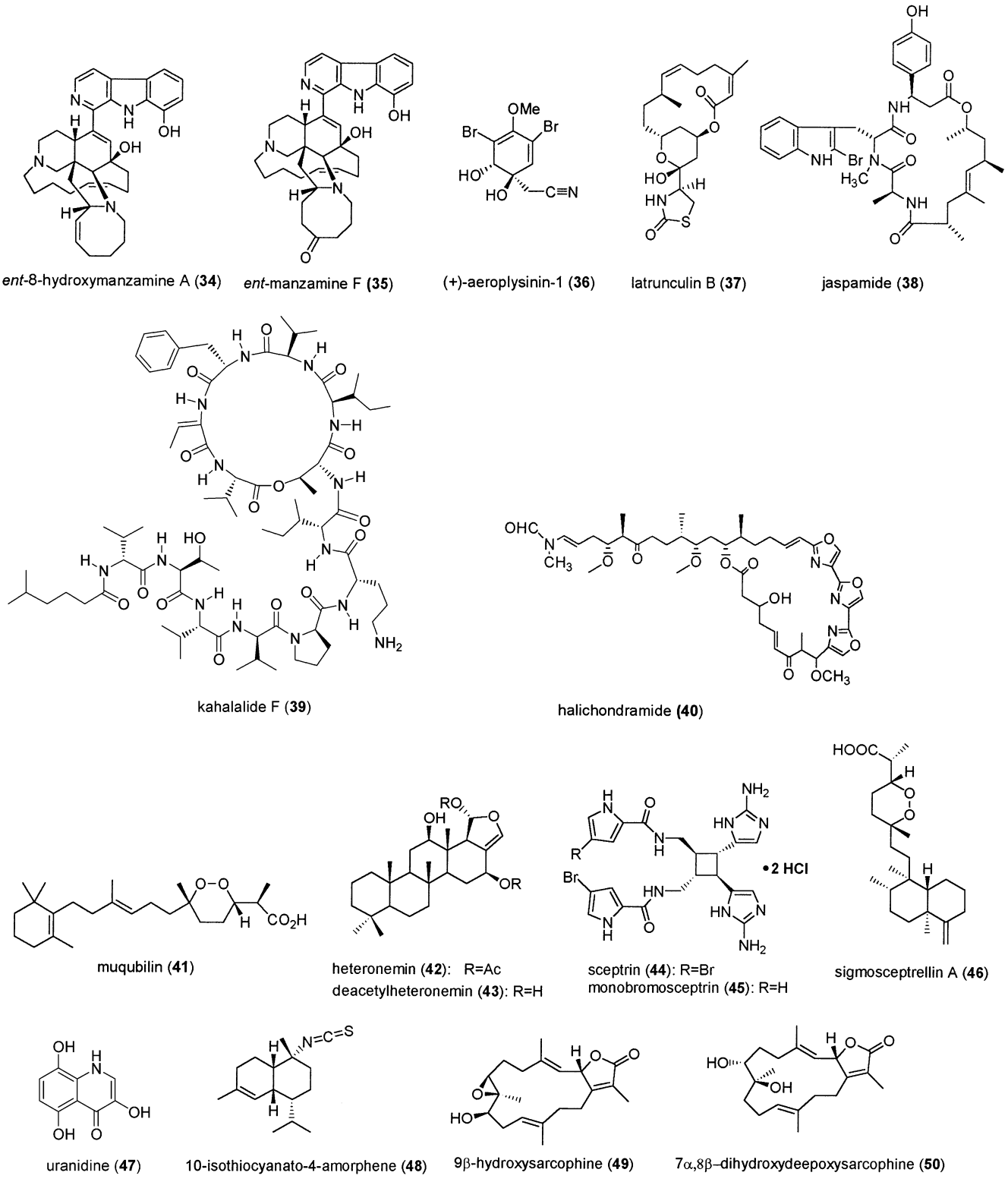


Figure 2. Structures of tested compounds.

above for WCR and TBW but the samples were fed to WTPB using a Mylar-based sachet system (*43*). Negative controls of 6% DMSO and 51% acetone were similarly added to diet wells. Plates were allowed to surface-dry under a hood. After drying, four to six insect eggs (12−24 h from hatching) were pipetted into each well in 25 μL of 0.2% agar. The plates were again allowed to surface-dry, then were covered with a layer of Mylar film, and sealed with a tacking iron. An insect pin was used to create an aeration hole in the Mylar over each well. Plates were incubated at 26 °C for 6 days, at which time the plates were evaluated; wells with survivors were counted, and a qualitative assessment of survivor size was made.

Herbicidal Assay. General herbicidal activity was determined by utilizing two plant species, *Agrostis stolonifera* (creeping bentgrass) and *Nicotiana tabacum* (tobacco). The selection of these two species allows for the determination of narrow- or broad-spectrum type of activity.

Assay Procedure. Test solutions were provided at 1 mg/mL in 100% DMSO. Samples were diluted with DI-H_2O to provide a test concentra-

Table 1. Insecticidal Activity of the Tested Marine-Derived Compounds in Diet Overlay Feeding Assays

compound	concn of overlay, mM	% mortality: western corn rootworm	% mortality: western tarnish plant bug	stunting severity 1–3: tobacco budworm
manzamine A (**7**)	6	100	75	2
ent-8-hydroxymanzamine A (**34**)	2	100	25	1
ent-manzamine F (**35**)	3	100	0	1

Table 2. Herbicidal Activity of the Tested Marine-Derived Compounds

compound	concn (μM)	creeping bent grass (*A. stolonifera*)	tobacco (*N. tabacum*)
latrunculin B (**37**)	6.4	3	3[a]
jaspamide (**38**)	6.4	3	3
kahalalide F (**39**)	6.4	1	3
halichondramide (**40**)	6.4	2	3
muqubilin (**41**)	6.4	0	2

[a] 0–3 rating for herbicidal effect.

tion of 500 g/ha per treatment. A 96-well microtiter plate was filled with a micronutrient-enriched synthetic growth medium prior to assay initiation. Duplicate plates (one per species) for each set of treatments were made by placing diluted test solutions on top of the growth medium and allowing them to absorb for at least 1 h. Measured amounts of *A. stolonifera* and *N. tabacum* seeds were then applied to each well in the treated plate, covered with a lid, and placed into a growth environment (18−20 °C, 75% humidity, 12 h photoperiod) for 7−9 days. Visual observations such as size, color, and morphology of the shoot and root growth were then recorded.

Fungicidal Assay. Fungicidal activities were determined using five phytopathogenic fungi, *Stagonospora nodorum* (wheat glume blotch), *Fusarium culmorum* (head scab), *Phytophthora infestans* (potato late blight), *Pyricularia grisei* (rice blast), and *Puccinia recondita* (brown rust of wheat).

Assay Media. S. nodorum was maintained on yeast malt extract agar and assayed in Czapek Dox broth with 0.1% agar. *F. culmorum* was maintained in carboxymethylcellulose medium and assayed in Czapek Dox broth with 0.1% agar. *Ph. infestans* was maintained on V8 medium and assayed in rye seed medium with 0.1% agar. *Py. grisei* was maintained on rice polish agar and assayed in potato dextrose broth with 0.1% agar. *Pu. recondita* was assayed on "rust medium" containing 1.3 g/L NH_4SO_4, 0.5 g/L KH_2PO_4, 0.25 g/L $MgSO_4$, 0.125 g/L KCl, 0.65 g/L alanine, 0.15 g/L arginine, 0.6 g/L glycine, 0.22 g/L leucine, 0.27 g/L lysine, 0.63 g/L methionine, 0.98 g/L ornithine, 0.87 g/L proline, 0.3 g/L glutamine, 0.13 g/L phenylalanine, 0.13 g/L threonine, and 30 g/L sucrose in 1% agar.

Assay Procedure. Inoculum was harvested and prepared concurrent with assay plate preparation. Assay media, except *P. recondite* medium, contain 0.1% agar to maintain an even suspension of spores. For *S. nodorum*, *Ph. infestans*, and *Py. grisei*, 10 mL of sterile water was pipetted onto the surface of culture plates covered with radial growth of each pathogen. The surface of each was scraped with a rubber policeman or sterile loop and washed with 10 mL of sterile water; the resulting liquor was decanted through two layers of sterile cheesecloth. *F. culmorum* spores were generated in liquid medium with agitation, aeration, and a 16 h photoperiod. Inoculum densities were adjusted with media. *P. recondita* was maintained on wheat plants in a growth chamber. Spores were harvested by agitation of infected sporulating leaves, spore collection on foil, and transfer of spores to glass vials stored at room temperature in a desiccator for up to 2 weeks.

Sample mother plates were prepared for all pure compounds ~24 h prior to the initiation of assays at a sample concentration of 100 ppm in 10% DMSO. Reference plates, which contain reference standards for low growth (50 ppm of Epoxicoazole, 50 ppm of Amistar, and 50 ppm of Cyprodinil formulated in 10% DMSO, $n = 16$ wells) and high growth (10% DMSO, $n = 16$ wells) were used. A 10 μL sample was dispensed from the mother plate into its respective assay plate on the morning of the assay. Ninety microliters of inoculated medium was pipetted into each assay plate well. All plates were covered and incubated until the reference standards had an OD of 0.25−0.30 at 595 nm measured at 595 nm on a Bio-Rad model 3550 plate reader. The incubation times were 3 days for *S. nodorum* and *F. culmorum*, 6 days for *Ph. infestans* and *Py. grisei*, and 1 day for *Pu. recondita*. Percent inhibition was calculated relative to the OD values of the high and low reference standards. Those wells with measured ODs near that of the average low control wells had calculated percent inhibitions near 100%. Rust plates (*P. recondite*) were manually evaluated for spore germination and germ tube growth using an inverted microscope.

RESULTS AND DISCUSSION

Insecticidal Activity. The insecticidal activities of 26 marine-derived compounds were reported in our last paper (*11*). An additional 11 compounds were tested for insecticidal activity in this experiment (**Table 1**). Three manzamine alkaloids, manzamine A (**7**), *ent*-8-hydroxymanzamine A (**34**), and *ent*-hydroxymanzamine F (**35**), showed substantial insecticidal activity against western corn rootworm at concentrations of 6, 2, and 3 mM, respectively. Manzamine A (**7**) also caused >75% mortality to the test insect western tarnished plant bug, which suggests that the manzamine alkaloids represent a class of insecticidal structures that are worthy of further investigations. No significant activity was observed for the remaining assayed compounds **36**, **43**−**45**, and **47**−**50**.

Herbicidal Activity. Eighteen marine-derived compounds were tested for herbicidal activity (**Table 2**) at a concentration of 6.4 μM. The macrolides latrunculin B (**37**), halichondramide (**40**), and modified peptide jaspamide (**38**) have herbicidal activity against both of the tested plant species *A. stolonifera* and *N. tabacum*. The polypeptide kahalalide F (**39**) exhibited herbicidal activity against *N. tabacum*. Muqubilin (**41**) showed

Table 3. Fungicidal Activity of the Tested Marine-Derived Compounds against Phytopathogelic Fungi[a]

compound	*F. culmorum*	*S. nodorum*	*Ph. infestans*	*Py. grisei*	*Pu. recondita*
manzamine A (**7**)	1	66	77	38	0
ent-8-hydroxymanzamine A (**34**)	0	92	41	22	0
ent-manzamine F (**35**)	31	79	80	19	0
(+)-aeroplysinin-1 (**36**)	2	0	68	7	0
latrunculin B (**37**)	101	103	91	59	67
jaspamide (**38**)	7	102	95	50	67
kahalalide F (**39**)	12	99	25	57	100
halichondramide (**40**)	102	106	104	58	67
heteronemin (**41**)	1	57	25	99	100
deacetylheteronemin (**42**)	18	85	16	91	100
sceptrin (**44**)	8	36	72	13	0

[a] Growth inhibition (%) at 10 ppm.

moderate activity against *N. tabacum*. These results indicate that some macrolide and peptide metabolites are inhibitory against photoautotrophs. Little research has been carried out on these metabolites, although a study of the herbicidal activity of related structurally less sophisticated compounds would be important in the development of new environmentally friendly herbicides. The other compounds, including **7**, **34**−**36**, and **42**−**50,** were not active at the concentration of 6.4 μM.

Fungicidal Activity. The fungicidal activity of these compounds (**Table 3**) at a concentration of 10 ppm was found to be as follows: three alkaloids, manzamine A (**7**), *ent*-8-hydroxymanzamine A (**34**), and *ent*-manzamine F (**35**), showed >65% inhibition to both *S. nodorum* and *Ph. infestans* except for *ent*-8-hydroxymanzamine A (**34**) to *Ph. infestans*. The polypeptide kahalalide F (**39**), sesterterpene heteronemin (**42**), and deacetylheteronemin (**43**) showed 100% inhibition to *Pu. recondite* and >55% inhibition to *S. nodorum* and *Py. grisei*. The macrolides latrunculin B (**37**) and halichondramide (**40)** showed >50% inhibition of five tested fungi, and the modified peptide jaspamide (**38**) had >50% inhibition of four tested fungi excluding *F. culmorum*. The bromopyrrole alkaloid sceptrin (**44**) and (+)-aeroplysinin-1 (**36**) also showed >65% inhibition of *P. infestans*. The macrolide, polypeptide, and alkaloid derivatives showed potent fungicidal activity, indicating that these structures may inhibit special metabolic pathways of fungi, and are interesting candidates for further investigation of new fungicidal agents against phytopathogenic fungi. Compounds **41** and **45**−**50** did not show significant antifungal activity in this evaluation.

Conclusion. A number of marine natural products from different structural classes have shown insecticidal, herbicidal, and fungicidal activities. The manzamine-derived alkaloids are a particularly intriguing class of insecticidal and fungicidal compounds. The limiting factor in the development of the manzamine alkaloids will clearly be sourcing this structurally complex class of compounds. In addition, manzamine A and 8-hydroxymanzamine A showed extraordinary activity against malaria *Plasmodium berghei* in mice (*44*) and are currently under preclinical investigation for development of a new class of antimalarial drugs. *ent*-Manzamine F (**35**) demonstrated insecticidal and fungicidal activities but did not impart herbicidal or antimalarial activities. This increases the possibility of using manzamine F as a pesticide, because it is a potential byproduct of producing manzamine A and 8-hydroxymanzamine A for their antimalarial properties. Both macrolide and polypeptide marine natural products showed promising results as photoautotroph inhibitors, and both of these classes are also candidates for further investigation.

The marine environment, with its chemical diversity, clearly holds an enormous potential to provide leads for the development of agrochemical agents. This may be especially true for insecticides because insects are almost exclusively terrestrial or freshwater animals (*45*). Accordingly, there would have been little resistance selection among insects to any insecticidal agents biosynthesized in the marine environment. The vast majority of marine-derived structural classes have not yet been examined for their insecticidal, herbicidal, and fungicidal activities, and further studies could clearly lead to more promising agrochemical agents with fewer environmental risks and less pesticide resistance.

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