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Insect Antifeedant Potential of Xanthohumol, Isoxanthohumol, and Their Derivatives

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ABSTRACT: Xanthohumol (**14**) and isoxanthohumol (**6**) derived from hop (*Humulus lupulus* L., Cannabaceae) and selected chalcone and chromene derivatives, obtained by chemical synthesis, were studied for antifeedant activity against the peach-potato aphid (*Myzus persicae* [Sulz.]). The study used also commercially available 4-chromanone (**1**), flavanone (**4**), naringenin (**5**), chromone (**7**), flavone (**8**), 7-aminoflavone (**9**), *trans*-chalcone (**10**), and 4-methoxychalcone (**12**). For chromone derivatives it was observed that the presence of a phenyl substituent at C-2 in the chromone (**7**) skeleton increased the insect antifeedant activity, and this activity was observed for a longer time. Also, the introduction of an amino group at C-7 of flavone (**8**) considerably increased the insect antifeedant activity, which was observed for the whole test time. Among the compounds examined, the strongest deterrents were isoxanthohumol (**6**), 7-methoxy-2,2-dimethylchroman-4-one (**3**), 7-aminoflavone (**9**), and 4-ethyl-4′-methoxychalcone (**13**).

KEYWORDS: *antifeedants, chalcones, isoxanthohumol, xanthohumol, M. persicae (Sulz.)*

INTRODUCTION

Phenolic compounds are widely distributed in plants, where they play roles of natural coloring agents, antioxidants, insecticides, and fungicides.[1] Most flavonoids contain a 2-phenylchromane skeleton. The group of flavonoids comprises also chalcones. 2′-Hydroxychalcones and their dihydro derivatives without the heterocyclic C-ring play an essential role in the biosynthesis of all classes of flavonoid compounds.[2−4] Common hop *Humulus lupulus* L. (Cannabaceae) contains over 1000 various chemical substances.[5] Flavonoids found in hop (*H. lupulus* L.) are under careful investigation, due to their pro-health properties.[6−9]

Xanthohumol (**14**), the most important chalcone found in hop cones at about 1%, has many valuable biological properties. Apart from a strong antioxidant activity, it demonstrated antiviral[10] and antimicrobial and anti-inflammatory[11] properties. Additionally, it was confirmed that xanthohumol (**14**) inhibits in vitro new blood vessel formation in the carcinogenesis process and has antiproliferative activity against different cancer cell lines, such as human breast cancer (MCF-6, MCF-7, T47-D), human colon cancer (HT-29), human ovarian carcinoma (A-2780), and prostate cancer.[12−16]

There are several literature papers concerning the other two hop flavonoids of great interest, isoxanthohumol (**6**) and 8-prenylnaringenin, the content of which in hop cones is from 10 to 100 times lower than of xanthohumol.[17] Their metabolism in microbial cells and mammals was also studied.[18−20] A very promising tool for medical diagnostics may be haptens containing a hop flavonoid skeleton, which can be employed for the production of monoclonal antibodies.[21] Due to the fact that the only natural source of hop flavonoids and phenolic acids in the human diet is beer,[22,23] recently there have been research efforts to achieve chemical and biological standardization of the hop extract to maintain constant composition of hop-based preparations, potential therapeutic agents.[24] There are also studies on the chemical synthesis of the precursors of natural flavonoids, chalcones, and other flavonoid derivatives, so as to find how different structure modifications affect their pharmacological activity (cytotoxic, anti-inflammatory, anticancer, antimalarial, and antifeedant (feeding deterrent)).[25−27]

Because of the health risks from the widespread use of pesticides and artificial fertilizers, there has been an increasing interest in alternative, safer, and more environmentally friendly plant protection agents. As an alternative to toxic pesticides and for environmental reasons, the compounds with pesticidal activity that are naturally found in plants are more often used nowadays in agriculture.[28] Not only do these substances destroy unwanted microflora and other pests, they are also safe for humans and the environment, which is the most important issue. Being natural compounds they are fully biodegradable; moreover, they are active toward a specific group of insects. Therefore, they are considered environmentally friendly. They may act on the taste receptors of insects and cause them to stop feeding on plants, which leads to starvation and death, eventually.

Because of the small amount of bioactive compounds in plant material, the extraction and use of natural compounds for insect control on a wide scale is costly. For this reason, there is a strong demand for synthetic behavior-modifying chemicals that are simple to obtain in the laboratory. At the same time, certain modifications of natural compound molecules may increase the potency of their deterrent activity.[29−32] In the present work we were interested in whether the incorporation of the prenyl, methyl, hydroxyl, phenyl, and amino groups would affect the

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biological activity. Altogether, three natural compounds, xanthohumol (**14**), isoxanthohumol (**6**), and naringenin (**5**), and 11 synthetic derivatives with various structural modifications were examined for aphid-deterrent activity.

Usually, antifeedants are natural compounds with a lactone ring,[29−31] but they may also belong to terpenes[32,33] or phenolic compounds.[34] Many plants have strong repellent properties, and for this reason they have been used for a long time to repel the wheat weevil, the major pest of stored cereal grains. This group of plants includes field mint (*Mentha arvensis*), common yarrow (*Achillea millefolium*), and several other common plant species.[35] Obtained by extraction, preparations of lavender (*Lavandula luisieri*) and rough cocklebur (*Xanthium sibiricum*) demonstrated insecticidal activity, among others, against the peach-potato aphid (*Myzus persicae*).[36,37] Tropical plants are a very rich source of antifeedants. Among them, Indian neem (*Azadirachta indica*) is one of the best known, because it contains the strongest of known feeding repellents, azadirachtin. Nawrot et al. in 2013 proved the strong deterrent activity of ionic liquids toward wheat weevil beetles (*Sitophilus granarius* L.), confused flour beetle larvae (*Tribolium confusum* Duv.), and khapra beetle larvae (*Trogoderma granarium* Ev.).[38] This activity was equal to or stronger than that of azadirachtin. There is increasing application of microbial agents, so-called bioinsecticides, that contain live bacterial cultures, mostly of the genus *Bacillus* (*Bacillus thuringiensis*).[39] Another large group of biopreparations that inhibit plant pest development is based on viruses and nematodes.[40] Apart from interacting with insect chemoreceptors of taste, preparations of antifeeding activity may inhibit the fertility of insects, prolong their larval development, or inhibit the transmission of some viruses.[41,42]

According to literature data, biological methods constitute only a small fraction of plant protection management. One reason is that there have been no effective biological methods of crop protection developed, especially concerning control of diseases and pests of cereals and plants of the families Fabaceae and Brassicaceae, which are essential for the production of organic food.[43] Gökçe et al. in 2011 proved antifeedant activity of the extract from hop cones (*H. lupulus*) against the Colorado potato beetle (*Leptinotarsa decemlineata*).[44]

In our previously published study, we found that one of the hop extracts examined significantly deterred *M. persicae* settling on treated leaves, and the effect was relatively stable and lasted at least 24 h.[45] However, aphid probing and phloem sap consumption were not impeded. Therefore, we hypothesized that the extract contained a component that could reach sieve elements using the symplastic or apoplastic pathway and produce a delayed, postingestional metabolic detrrent effect without evoking the rejection behavior based on gustatory stimuli. Consequently, we decided that there was a need for a more detailed study to find which components of the hop extract were responsible for the deterrent activity. Exogenously applied hop chemicals, α- and β-hop acids and colupulone, had an antifeedant effect on the grain aphid (*Sitobion avenae*) and bird cherry-oat aphid *Rhopalosiphum padi*.[46] However, to the best of our knowledge, there is no information about the deterrent activity of hop flavonoids toward plant pests, especially aphids. There is also no study on the antifeedant activity of chalcone (**10**) and its structural analogues toward the peach-potato aphid (*M. persicae*).

The aim of our research was to evaluate the deterrent activity of natural flavonoid compounds found in hop (*H. lupulus*): xanthohumol (**14**) and isoxanthohumol (**6**). The settling behavior of the peach-potato aphid (*M. persicae* [Sulz.]) was evaluated. We investigated also the effect of structural modifications of these flavonoid molecules on aphid behavior. We selected compounds of diverse chemical structures, belonging to three flavonoid groups, compounds with 4-chromanone (**1**), chromone (**7**), or *trans*-chalcone (**10**) skeletons.

MATERIALS AND METHODS

Reagents. Chemical reagents were purchased from Sigma-Aldrich, Merck, Chempur, and Alfa Aesar. For the study we used commercially available 4-chromanone (**1**) (Sigma-Aldrich), flavanone (**4**) (Alfa Aesar), naringenin (**5**), chromone (**7**) (Sigma-Aldrich), flavone (**8**) (Sigma-Aldrich), 7-aminoflavone (**9**) (Sigma-Aldrich), *trans*-chalcone (**10**) (Sigma-Aldrich), and 4-methoxychalcone (**12**) (Sigma-Aldrich).

General Procedures. The structures of products obtained were determined by spectroscopic methods (^{1}H NMR, ^{13}C NMR, IR, and HR ESI-MS). The purity of compounds **2**, **3**, **11**, and **13** was established by gas chromatography (GC) using an HP-5 capillary column, whereas, for compounds **6** and **14**, high-performance liquid chromatography (HPLC) was employed, with the help of the reversed-phase C-18 column as described perviously.[19] For the biological tests we used the compounds with the purity >95%.

Synthesis of Compounds. 7-Hydroxy-2,2-dimethylchroman-4-one (**2**) was obtained in the reaction of 1,3-dihydroxybenzene with dimethylacrylic acid (DMAA) in the presence of zinc chloride in phosphorus oxychloride, followed by isomerization of the intermediate product according to a modified method of Alizadeh et al.[47] (80% of isolated yield). The spectroscopic data were consistent with those reported in the literature.[47,48] In the next step the purified product (**2**) was subjected to the Williamson ether synthesis with methyl iodide to give 7-methoxy-2,2-dimethylchroman-4-one (**3**), the spectroscopic data of which matched those reported by An et al.[49] The synthesis of 4-hydroxychalcone (**11**) and 4-ethyl-4′-methoxychalcone (**13**) was carried out according to the literature method[50] under strongly basic conditions (KOH), using methanol as a solvent. Xanthohumol (**14**) was isolated using the earlier described method[51] from spent hops, the residue of supercritical carbon dioxide hop extraction, which was delivered by the Supercritical Extraction Department of the New Chemical Syntheses Institute in Puławy, Poland. The second prenylated hop flavonoid, isoxanthohumol (**6**), was obtained by the alkaline isomerization of xanthohumol (**14**) according to the method of Wilhelm and Wessjohann.[52]

Cultures of Aphids and Plants. Aphids (*M. persicae*) and plants (Chinese cabbage *Brassica pekinensis*) were reared in the laboratory at 20 °C, 65% realtive humidity, and a 16/8 h light/dark photoperiod. All experiments were carried out under the same conditions.

Aphid Settling. This bioassay allows aphid host preferences to be studied under seminatural conditions. In this bioassay, aphids are given free choice between control and treated leaves. The standard leaf-dip method[53] was applied for the evaluation of activities of xanthohumol (**14**), isoxanthohumol (**6**), and their derivatives. The compounds studied were applied by immersing a leaf in 0.1% ethanolic solution of a given compound for 30 s. Control leaves of similar size were immersed in 70% ethanol, which was used as a solvent for the tested compounds. Treated and control leaves were placed in a Petri dish and allowed to air-dry for 1 h before being offered to the insects. Next, aphids were placed in the dish along the line that divided the area into two halves so that aphids could choose between treated (on half of a Petri dish) and control leaves (on the other half of the dish). Aphids that settled, that is, they did not move and the position of their antennae indicated feeding, on each leaf were counted at 1, 2, and 24 h intervals after access to the leaf (8 replicates, 20 viviparous apterous females/replicate). Aphids that were moving or out of any of the leaves were not counted.

The data were analyzed using one-way ANOVA (Statistica 6.1. package). If aphids showed a clear preference for the leaves treated with the tested compound ($P < 0.05$), the compound was described as having **attractant** properties. If aphids settled mainly on the control

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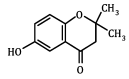
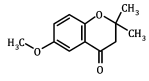
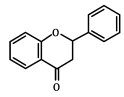
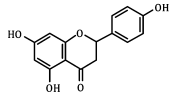
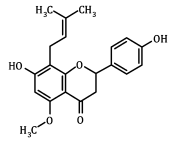
Table 1. Deterrent Activity of Selected Derivatives of 4-Chromanone (1) to the Peach-Potato Aphid *M. persicae* (Sulz.)[a]

Compound number	Chemical structure		Time from the start of the experiment [h]		
			1	2	24
(1)		T	1.3 ± 0.4	0.9 ± 0.4	0.9 ± 0.5
		C	3.9 ±0.7	4.5 ± 0.9	3.0 ± 1.3
		p	**0.0050**	**0.0022**	0.1392
		DI	0.51	0.67	0.55
(2)		T	2.3 ± 0.6	1.9 ± 0.5	4.3 ±1.3
		C	2.5 ±0.5	3.0 ± 0.8	4.8 ± 0.8
		p	0.7356	0.2748	0.7428
		DI	0.05	0.23	0.06
(3)		T	5.6 ± 0.4	5.0 ± 0.7	3,0 ± 1,0
		C	8.0 ± 1.0	6.6 ± 0.9	9.9 ± 1.8
		p	**0.0403**	0.1678	**0,0047**
		DI	0.17	0.14	0.53
(4)		T	7.5 ± 1.4	7.9 ± 1.2	7.6 ± 1.8
		C	4.6 ± 1.3	4.0 ± 1.2	3.8 ± 1.1
		p	0.1597	0.0383	0.0922
		DI	0.24	0.33	0.34
(5)		T	4.6 ± 1.5	4.1 ± 1.2	4.8 ± 0.9
		C	5.3 ± 1.1	5,3 ± 1.3	5.9 ± 1.4
		p	0.7501	0.5474	0.4979
		DI	0.06	0.12	0.11
(6)		T	4.5 ± 1.3	2.6 ± 0.8	3.1 ± 0.8
		C	6.3 ± 1.5	6.4 ± 1.8	12.4 ± 1.4
		p	0.3853	0.0768	**0.0000**
		DI	0.16	0.42	0.60

[a]Numbers for T, test, and C, control, represent mean number of aphids settled on test or control leaves (choice test); *p*, significance level (ANOVA); significant differences (Student's *t* test, $p < 0.05$) between number of aphids settled on either half of the Petri dish are in bold; DI, indices of deterrence.

half of the Petri dish ($p < 0.05$), the compound tested in the respective choice test was labeled a **deterrent**. From the data thus obtained the indices of deterrence (DI) were calculated (DI_1, DI_2, and DI_{24} corresponding with 1, 2, and 24 h after exposure monitoring, respectively):

$$DI = (C - T/C + T)$$

C is the number of aphids settled on control leaves, and *T* is the number of aphids settled on the leaves treated with the tested compound. The value of DI ranged between 1 (ideal deterrent) and −1 (ideal attractant).

RESULTS AND DISCUSSION

Aphid Settling. On the basis of the bioassay, we found that the natural hop flavanone, isoxanthohumol (**6**), has deterrent properties toward the peach-potato aphid. In comparison, xanthohumol (**14**) did not demonstrate such an activity. In contrast, xanthohumol (**14**) was a weak attractant. However, strong deterrent properties of isoxanthohumol (**6**) were expressed with a delay, that is, at least 2 h after treatment ($DI_{24} = 0.6$, $p = 0.0000$) (Tables 1 and 3).

The compounds with strongly polar groups in the aromatic ring, such as hydroxyl ones, were inactive, as opposed to their methoxy derivatives with a 4-chromanone skeleton (**2** and **3**) and to chalcones (**11** and **12**).

Comparing the activity of ketones (**7**) and (**1**), we observed that hydrogenation of the C_2−C_3 double bond in compound **7** resulted in a switch from attractant to deterrent activity. However, the effect on aphid behavior was of various potencies

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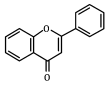
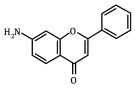
Table 2. Deterrent Activity of Selected Derivatives of Chromone (7) to the Peach-Potato Aphid *M. persicae* (Sulz.)[a]

Compound number	Chemical structure		Time from the start of the experiment [h]		
			1	2	24
(7)		T	7.4 ± 1.3	4.9 ± 1.0	4.1 ± 1.3
		C	3.1 ± 0.7	4.0 ± 1.1	4.0 ± 1.9
		p	**0.0147**	0.5544	0.9573
		DI	-0.40	-0.10	-0.02
(8)		T	3.4 ± 1.0	3.5 ± 1.1	3.1 ± 0.6
		C	9.3 ± 0.9	7.9 ± 0.9	7.1 ± 1.9
		p	**0.0006**	**0.0090**	0.0609
		DI	0.47	0.38	0.39
(9)		T	1.5 ± 0.5	2.4 ± 1.0	2.3 ± 0.8
		C	8.6 ± 1.3	9.0 ± 1.2	6.9 ± 1.5
		p	**0.0002**	**0.0008**	**0.0167**
		DI	0.70	0.58	0.51

[a]Numbers for T, test, and C, control, represent mean number of aphids settled on test or control leaves (choice test); *p*, significance level (ANOVA); significant differences (Student's *t* test, $p < 0.05$) between number of aphids settled on either half of the Petri dish are in bold; DI, indices of deterrence.

and durabilities. For 4-chromanone (**1**), strong deterrent activity was noted until the second hour of the experiment, whereas chromone (**7**) proved to be a weak attractant to the peach-potato aphid. The opposite situation was observed for the derivatives with a phenyl substituent at C-2, where flavone (**8**) ($DI_1 = 0.5$, $p = 0.0006$) was more active than flavanone (**4**), which proved to be inactive: the relative index of deterrence was within the range from $DI_1 = 0.2$ ($p = 0.1597$) to $DI_2 = DI_{24} = 0.3$ ($p = 0.0383$ and $p = 0.0922$, respectively (Tables 1 and 2).

In the case of the derivatives with a chromone system, the presence of a phenyl group at C-2 resulted in an increase in the deterrent activity; during the initial 2 h after treatment later on, the deterrent effect ceased (flavone (**8**): $DI_1 = 0.5$, $p = 0.0006$; $DI_2 = 0.4$, $p = 0.0090$; $DI_{24} = 0.4$, $p = 0.0609$). The introduction of an amine group at C-7 in the flavanone led to a considerable increase of the antifeedant activity, which was observed during the whole time of the experiment. The relative coefficient of deterrence values from DI = 0.7 after 1 h ($p = 0.0002$) to DI = 0.5 after 24 h ($p = 0.0167$) determined for compound **9** proved its high deterrent properties (Table 2).

It was observed that in the case of chalcone derivatives, the compound that caused the strongest reduction of aphid settling on treated leaves was 4-methoxychalcone (**12**). It was proved by the values of the relative coefficient of deterrence ($DI_1 = 0.5$, $p = 0.0086$; $DI_2 = 0.5$, $p = 0.0386$). However, the effect of 4-methoxychalcone (**12**) on inhibition of aphid settling was short-lived. 4′-Methoxy-4-ethylchalcone (**13**) proved to be also an active deterrent, which additionally reduced aphid settling during the whole experiment time (Table 3). The relative index of deterrence value (DI) was within the range from $DI_1 = 0.25$ to $DI_{24} = 0.30$ at $p < 0.05$. The deterrent activity at 2 h after application was also observed for *trans*-chalcone (**10**) ($DI_2 = 0.3$, $p = 0.0406$; $DI_{24} = 0.4$, $p = 0.0216$) (Table 3).

Differences in the durability of deterrent effects of compounds examined in the present study, for example, isoxanthohumol (**6**), and changes in their activity over time may be caused by changing conditions of their action. Presumably, it may be related to altered concentration of a tested substance in the phloem juice and changes in the pH, arising from metabolic transformations in a plant.[45] Additionally, aphids may decompose some substances with the help of their saliva enzymes. The important factors may be also aphid endogenous enzymes and symbiotic microbes, which can perform detoxification of tested compounds.[54] Xanthohumol (**14**), the most important hop prenylated chalcone, in the in vitro study was transformed into isoxanthohumol (**6**) and 8-prenylnaringenin.[55] Biotransformations of isoxanthohumol (**6**) using human liver cells[56] and fungi[57] led to the product of *O*-demethylation, 8-prenylnaringenin, which is the strongest phytoestrogen known so far. An aphid attack may induce synthesis of some organic compounds in *B. pekinensis* as a defense response to feeding. In response to the oxidative stress caused by aphids, a plant may activate a very efficient production of certain enzymes (for example, antioxidative ones, such as superoxide dismutase or catalase), hormones, and signaling molecules, which are part of plant defense against invading insect herbivores (e.g., H_2O_2 and NO).[58] These may also cause transformations of tested compounds into their derivatives.[59]

Structure–Activity Aspects. The current state of the art in antifeedant activity of flavonoid compounds relates to plant extracts, pure compounds, products of their metabolism, and also their synthetic analogues.[60,61] Russel et al.[62] came to the conclusion that the lack of substituents in ring C of flavanone as well as the lack of 3-oxo groups (−OH, $-OCH_3$) at C-3 led to an increase in antifeeding activity of the compounds toward larvae of *Ctenopsteustis obliquana*, which feed on avocado leaf

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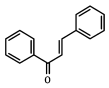
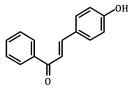
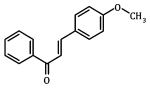
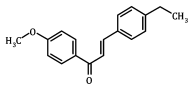
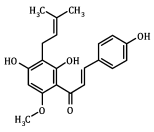
Table 3. Deterrent Activity of Selected Derivatives of Chalcone (10) to the Peach-Potato Aphid *M. persicae* (Sulz.)[a]

Compound number	Chemical structure		Time from the start of the experiment [h]		
			1	2	24
(10)		T	2.0 ± 0.5	2.5 ± 0.6	2.6 ± 0.8
		C	4.1 ± 0.9	4.5 ± 0.7	6.1 ± 1.1
		p	0.05348	**0.0406**	**0.0216**
		DI	0.35	0.29	0.40
(11)		T	4.6 ± 1.1	4.9 ± 1.3	3.9 ± 1.3
		K	4.3 ± 0.9	4.8 ± 0.8	5.6 ± 1.7
		p	0.7977	0.9338	0.4344
		DI	-0.04	-0.13	0.18
(12)		T	2.5 ± 0.6	1.9 ± 0.4	1.9 ± 0.7
		C	7.5 ± 1.5	5.3 ± 1.4	4.9 ± 1.9
		p	**0.0086**	**0.0386**	0.1691
		DI	0.50	0.47	0.44
(13)		T	4.3 ± 0.8	4.3 ± 0.6	3.9 ± 0.7
		C	7.1 ± 1.0	7.9 ± 0.8	7.3 ± 1.3
		p	**0.0345**	**0.0028**	**0.0413**
		DI	0.25	0.30	0.30
(14)		T	4.4 ± 1.6	4.0 ± 1.5	4.8 ± 1.1
		C	7.9 ± 1.6	8.4 ± 1.7	8.8 ± 2.0
		p	0.1519	0.0715	0.0990
		DI	0.29	0.35	0.30

[a]Numbers for T, test and C, control, represent mean number of aphids settled on test or control leaves (choice test); *p*, significance level (ANOVA); significant differences (Student's *t* test, $p < 0.05$) between number of aphids settled on either half of the Petri dish are in bold; DI, indices of deterrence.

shoots and young fruitlets. It is an advantage for antifeedant activity to have an ether linkage such as a pyran moiety in the chemical structure. Among the prenyl flavanones isolated from *Tephrosia apollinea* L., the most active antifeedants proved to be compounds with a dihydrofuran ring.[63] According to the literature, good antifeeding activity was also observed for compounds with a naphthalene substituent[64] and chalcones with electron acceptor groups in ring A.[65,66]

The objective of our work was to obtain hop flavonoid compounds and their derivatives of diverse relatively simple chemical structures and to evaluate their antifeedant activity. For the biological tests we have chosen two major prenylated hop flavonoids, xanthohumol (**14**) and isoxanthohumol (**6**), and an isoxanthohumol derivative without the prenyl and methyl groups, naringenin (**5**), a flavonoid that is commonly found in citrus fruits. As model compounds for this study, flavone and flavanone derivatives were used without the phenyl substituent, containing either a chromone or 4-chromanone skeleton obtained by chemical synthesis and also flavones and flavanones, which are structural analogues of natural phytoestrogens and their derivatives. To the group of compounds described in the earlier works[67,68] and also for comparison, we decided to expand our group of tested substrates by adding a flavone derivative with an amino group at C-7 in ring A. The antifeedant activity of synthetic aminoflavones toward plant pests, especially aphids, has not been investigated, so far. We expected that comparing the results of antifeedant activity of chromones, chromanones, and the selected flavanones and chalcones, which are precursors of flavonoids, would allow us to determine which structural elements of the compounds are necessary for subsequent reduced aphid settling.

The antifeedant activity of hop compounds, selected synthetic chalcone derivatives, and chromones against the peach-potato aphid (*M. persicae* [Sulz.]) was evaluated. Synthetic pesticides, which are used against agricultural pests, are highly toxic to humans and the environment. However, these natural compounds were regarded as one of the plant's defensive systems against phytophagous insects along with the peach potato plant surface. Our results showed that deterrent properties changed depending on their structure, cyclic or not. Isoxanthohumol (**6**), obtained by cyclization of xanthohumol (**14**), had strong deterrent activity against the peach-potato aphid, whereas its derivative, xanthohumol (**14**), was inactive. As we have already mentioned, the presence of a 2′-OH group

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in chalcones facilitates their cyclization to their isomeric forms, flavones. The second major difference likely to affect the activity is the existence in compound **14** of a strong intramolecular hydrogen bond between the carbonyl group and the hydroxyl group. On the ^{1}H NMR spectrum it is evidenced by the presence of a signal at δ 14.7 for the proton of the 2′-OH group involved in a strong intramolecular hydrogen bond.[18] The carbonyl group of isoxanthohumol (**6**) for obvious reasons is not involved in such binding. According to the literature, the observed differences in activity may also arise from inhibition of the activity of the enzymes involved in the detoxification of xenobiotics, for example, cytochrome P450 enzymes.[69] The compounds selected for the study showed various degrees of feeding detterent activity. In our study, flavanones, chromanones, and chalcones having hydroxyl groups did not show any insect antifeedant activity. The most inactive was a 4-hydroxychalcone (**11**), which was an attractant. An additional substituent of a hydroxyl group at the *para* position in ring B of a chalcone decreased the antifeedant activity, compared to the unsubstituted chalcone (**10**). The structure−activity analysis led to the conclusion that acylation of the hydroxyl group in ring B of chalcone **11** results in an increase of the antifeedant activity, compared to the molecule with the free OH group. The presence of hydroxyl groups in the molecule of naringenin (**5**) had a considerable influence on the antifeedant activity, compared to the unsubstituted flavanone (**4**), which was only weakly active. As in the case of other biological activity, moderate deterrent properties of polyphenolic compounds, including naringenin (**5**), stem from the presence of the reactive hydroxyl groups, which facilitate binding to enzyme active sites as well as formation of hydrogen bonding with enzyme system in aphids. These result in a change of their metabolism. Flavonoids **4**, **8**, and **9**, especially, have no hydroxy substituent on the A-ring. Recent research confirming the antifeedant activity of naringenin (**5**) and its derivatives indicates that generalizations concerning the structure−activity relationships of the mentioned compounds cannot be applied to a wide range of pests[34,70,71] because the above-mentioned compounds stimulated feeding behavior of the insects, whereas another was the best feeding deterrent. As describe in the literature, cleavage of the ether linkage of the pyran ring of flavanoids[67] and the hydrogenation of the α,β-unsaturated bond in chalcones decrease the antifeedant activity.[72] Ohmura et al. reported that a dihydrochalcone, phloretin, has the same structure as naringenin, except for the absence of the pyran ring, and showed less antifeedant activity against the subterranean termite *Coptotermes formosanus* than naringenin (**5**). As was reported by Morimoto et al.,[67] although the decrease in the activity and the number of hydroxyl groups were correlated, it was attributable to the penetrability toward the receptor in the insect taste-sensitive organ. The substitution of the flavonoid ring system with the prenyl unit and a $-OCH_3$ group increases the lipophilicity and confers to the molecule a strong affinity for biological membranes, which play an important role in biomolecule transport, distribution, action, and selectivity. The hop compounds intercalate into the lipid bilayer, influencing its glycerol backbone region, hydrocarbon chain region, and, to a lesser extent, polar headgroup region. The calculation of log *P* values identified xanthohumol (4.38 ± 0.78) as a more lipophilic molecule compared to isoxanthohumol (3.82 ± 0.86).[73] However, looking at the structures of our tested compounds it is difficult to predict whether their interactions with the lipid membrane will exert any impact on the antifeedant activity. Our results indicate that the prenyl group, and flavanones, rather than the flavonols and chalcones, might make predominant contributions to antifeedant inhibition. Therefore, prenylated flavonoids possessing lipophilic moieties may be potent candidates for antifeedants. Our results suggested that the antifeedant activity required not only the important 2-position substituent but also the substituent pattern on the A-ring and the hydrogenation of the C_2-C_3 double bond of these insect antifeedants, flavonoids and chromones. Similar results were reported by Morimoto et al.[67] In our study the introduction of an additional amino group at C-7 to flavone (**9**) caused an increase in antifeedant activity against the peach-potato aphid. This is a first report about the feeding deterrent activity of aminoflavones in the literature. Significant correlations were found between biological activity and molecular size of the derivatives with a chromone system. The presence of a phenyl group at C-2 of chromone (**7**) and the introduction of an amino group at C-7 in the flavone (**8**) resulted in an increase in the deterrent activity, which was observed during the longer time. The relationship between physicochemical properties and insect antifeedant activity of compounds has been reported by Morimoto et al.[74]

Among several pest control strategies (comprising mechanical, agrotechnical, and chemical methods), biological methods of crop protection that employ compounds of plant origin (including flavonoids) are best accepted in organic food production. Therefore, this biological method of plant protection should be recommended, which is confirmed by the results of laboratory tests.

In the next step of the research an optimization of the chemical structure of these compounds is needed. This will involve computational methods such as QSAR models that relate experimentally measured biological activities of compounds to their molecular structure.[67] Natural plant compounds, such as hop flavonoids, may be applied as models or substrates for the synthesis of highly specific substances that inhibit feeding of pests.

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Notes

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REFERENCES

(1) Ogah, O.; Watkins, C. S.; Ulbi, B. E.; Oraguzie, N. C. Phenolic compounds in Rosaceae fruits and nut crops. *J. Agric. Food Chem.* **2014**, *62*, 9369−9386.

(2) Shahidi, F.; Naczk, M. Phenolic in cereals, fruit and vegetables: occurence, extraction and analysis. *J. Pharm. Biomed. Anal.* **2006**, *41*, 1523−1542.

(3) Ceylan, M.; Karaman; Gezegen, I. H.; Gürdere, M. B.; Dingil, A. Screening of biological activities of series of chalcone derivatives against human pathogenic microorganisms. *Chem. Biodiversity* **2010**, *7*, 400−408.

(4) Shin, S. Y.; Lee, Y. H. 3-Hydroxyflavanone induced apoptosis in HeLa cells. *Han'guk Eungyong Sangmyong Hwahakhoeji* **2013**, *56*, 113−116.

(5) Dresel, M.; Dunkel, A.; Hofmann, T. Sensomics analysis of key bitter compounds in the hard resin of hops (*Humulus lupulus* L.) and

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J. Agric. Food Chem. 2015, 63, 6749−6756

their contribution to the bitter profile of pilsner-type beer. *J. Agric. Food Chem.* **2015**, *63*, 3402−3418.
(6) Gorjanović, S.; Pastor, F. T.; Vasić, R.; Novaković, M.; Simonović, M.; Milić, S.; Sužnjević, D. Electrochemical versus spectrophotometric assessment of antioxidant activity of hop (*Humulus lupulus* L.) products and individual compounds. *J. Agric. Food Chem.* **2013**, *61*, 9089−9096.
(7) Potaniec, B.; Grabarczyk, M.; Stompor, M.; Szumny, A.; Zieliński, P.; Żołnierczyk, A.; Anioł, M. Antioxidant activity and spectroscopic data of isoxanthohomol oxime and related compounds. *Spectrochim. Acta, Part A* **2014**, *118*, 716−723.
(8) Liu, M.; Yin, H.; Liu, G.; Dong, J.; Qian, Z.; Miao, J. Xanthohumol, a prenylated chalcone from beer hops, acts as an α-glucosidase inhibitor in vitro. *J. Agric. Food Chem.* **2014**, *62*, 5548−5554.
(9) Yu, L.; Zhang, F.; Hu, Z.; Ding, H.; Tang, H.; Ma, H.; Ma, Z.; Zhao, X. Novel prenylated bichalcone and chalcone from *Humulus lupulus* and their quinine reductase induction activities. *Fitoterapia* **2014**, *93*, 115−120.
(10) Wang, Q.; Ding, Z.; Liu, J.; Zheng, Y. Xanthohumol, a novel anti-HIV-1 agent purified from hops *Humulus lupulus*. *Antiviral Res.* **2004**, *64*, 189−194.
(11) Cho, Y.-C.; You, S.-K.; Kim, H. J.; Cho, C.-W.; Lee, I.-S.; Kang, B. Y. Xanthohumol inhibits IL-12 production and reduces chronic allergic contact dermatitis. *Int. Immunopharmacol.* **2010**, *10*, 556−561.
(12) Miranda, C. L.; Stevens, J. F.; Helmrich, A.; Henderson, M. C.; Rodriguez, R. J.; Yang, Y.-H.; Deinzer, M. L.; Barnes, D. W.; Buhler, D. R. Antiproliferative and cytotoxic effects of prenylated flavonoids from hops (*Humulus lupulus*) in human cancer cell lines. *Food Chem. Toxicol.* **1999**, *37*, 271−285.
(13) Gerhauser, C.; Alt, A.; Heiss, E.; Gamal-Eldeen, A.; Klimo, K.; Knauft, J.; Neumann, I.; Scherf, H.-R.; Frank, N.; Bartsch, H.; Becker, H. Cancer chemopreventive activity of xanthohumol, a natural product derived from hop. *Mol. Cancer Ther.* **2002**, *1*, 959−969.
(14) Vanhoecke, B.; Derycke, L.; Marck, V. V.; Depypere, H.; Keukeleire, D. D.; Bracke, M. Antiinvasive effect of xanthohumol, a prenylated chalcone present in hops (*Humulus lupulus* L.) and beer. *Int. J. Cancer* **2005**, *117*, 889−895.
(15) Monteiro, R.; Faria, A.; Azevedo, I.; Calhau, C. Modulation of breast cancer cell survival by aromatase inhibiting hop (*Humulus lupulus* L.) flavonoids. *J. Steroid Biochem. Mol. Biol.* **2007**, *105*, 124−130.
(16) Ho, Y.-C.; Liu, C.-H.; Chen, C.-N.; Duan, K.-J.; Lin, M.-T. Inhibitory effects of xanthohumol from hops (*Humulus lupulus* L.) on human hepatocellular carcinoma cell lines. *Phytother. Res.* **2008**, *22*, 1465−1468.
(17) Stevens, J. F.; Taylor, A. W.; Nickerson, G. B.; Ivancic, M.; Henning, J.; Haunold, A.; Deinzer, M. L. Prenylflavonoid variation in *Humulus lupulus*: distribution and taxonomic significance of xanthogalenol and 4′-*O*-methylxanthohumol. *Phytochemistry* **2000**, *53*, 759−775.
(18) Stompor, M.; Potaniec, B.; Szumny, A.; Zieliński, P.; Żołnierczyk, A.; Anioł, M. Microbiological reduction of xanthohumol and 4-methoxychalcone. *Przem. Chem.* **2013**, *92*, 574−578.
(19) Stompor, M.; Potaniec, B.; Szumny, A.; Zieliński, P.; Żołnierczyk, A.; Anioł, M. Microbial synthesis of dihydrochalcones using *Rhodococcus* and *Gordonia* species. *J. Mol. Catal. B: Enzym.* **2013**, *97*, 283−288.
(20) Bartmańska, A.; Tronina, T.; Popłoński, J.; Huszcza, E. Biotransformation of prenylated hop flavonoids for drug discovery and production. *Curr. Drug Metab.* **2013**, *14*, 1083−1097.
(21) Wyns, C.; Derycke, L.; Soenen, B.; Bolca, S.; Deforce, D.; Bracke, M.; Heyerick, A. Production of monoclonal antibodies against hop-derived (*Humulus lupulus* L.) prenylflavonoids and the development of immunoassays. *Talanta* **2011**, *85*, 197−205.
(22) Mitić, S. S.; Paunović, D. D.; Pavlović, A. N.; Tošić, S. B.; Stojković, M. B.; Mitić, M. N. Phenolic profiles and total antioxidant capacity of marketed beers in Serbia. *Int. J. Food Prop.* **2014**, *17*, 908−922.
(23) Toboła, D.; Stompor, M.; Błażewicz, J.; Anioł, M. Xanthohumol content in Polish beers. *Przem. Chem.* **2014**, *93*, 1447−1450.
(24) Krause, E.; Yuan, Y.; Hajirahimkhan, A.; Dong, H.; Dietz, B. M.; Nikolic, D.; Pauli, G. F.; Bolton, J. L.; Breemen, B. B. Biological and chemical standardization of a hop (*Humulus lupulus*) botanical dietary supplement. *Biomed. Chromatogr.* **2014**, *28*, 729−734.
(25) Anioł, M.; Świderska, A.; Stompor, M.; Żołnierczyk, A. K. Antiproliferative activity and synthesis of 8-prenylnaringenin derivatives by demethylation of 7-*O*- and 4′-*O*-substituted isoxanthohumols. *Med. Chem. Res.* **2012**, *21*, 4230−4238.
(26) Abbas, A.; Naseer, M. M.; Hasan, A.; Hadda, T. B. Synthesis and cytotoxicity studies of 4-alkoxychalcones as new antitumor agents. *J. Mater. Environ. Sci.* **2014**, *5*, 281−292.
(27) Batagin-Neto, A.; Lavarda, F. C. The correlation between electronic structure and antimalarial activity of alkoxylated and hydroxylated chalcones. *Med. Chem. Res.* **2014**, *23*, 580−586.
(28) Nawrot, J.; Dams, I.; Wawrzeńczyk, C. Feeding detergent activity of terpenoid lactones with *p*-menthane system against stored product pest. *J. Stored Prod. Res.* **2009**, *45*, 221−225.
(29) Grudniewska, A.; Dancewicz, K.; Białońska, A.; Ciunik, Z.; Gabryś, B.; Wawrzeńczyk, C. Synthesis of piperitone-derived halogenated lactones and their effect on aphid probing, feeding, and settling behavior. *RSC Adv.* **2011**, *1*, 498−510.
(30) Dancewicz, K.; Gabryś, B.; Dams, I.; Wawrzeńczyk, C. Enantiospecific effect of pulegone and pulegone−derived lactones on settling and feeding of *Myzus persicae* (Sulz.). *J. Chem. Ecol.* **2008**, *34*, 530−538.
(31) Grudniewska, A.; Dancewicz, K.; Białońska, A.; Wawrzeńczyk, C.; Gabryś, B. Piperitone-derived saturated lactones: synthesis and aphid behavior-modifying activity. *J. Agric. Food Chem.* **2013**, *61*, 3364−3372.
(32) Gabryś, B.; Dancewicz, K.; Gliszczyńska, A.; Kordan, B.; Wawrzeńczyk, C. Systemic deterrence of aphid probing and feeding by β-damascone analogues. *J. Pest Sci.* **2014**, DOI: 10.1007/s10340-014-0635-x.
(33) Dancewicz, K.; Gliszczyńska, A.; Wróblewska, A.; Wawrzeńczyk, C.; Gabryś, B. Deterrent activity of (+)-nootkatone and its derivatives towards the peach potato aphid (*Myzus persicae* Sulzer). *Prog. Plant Prot.* **2012**, *52*, 221−225.
(34) Goławska, S.; Sprawka, I.; Łukasik, I.; Goławski, A. Are naringenin and quercetin useful chemicals in pest-management strategies? *J. Pest Sci.* **2014**, *87*, 173−180.
(35) Akhtar, Y.; Pages, E.; Stevens, A.; Bradbury, R.; da Camara, C. A. G.; Isman, M. B. Effect of chemical complexity of essential oils on feeding deterrence in larvae of the cabbage looper. *Physiol. Entomol.* **2012**, *37*, 81−91.
(36) Zhou, Q.; Wei, M. C.; Ou, X. M.; Zhong, Y. H.; Wang, W. X. Antifeedant and deterrent effect of active fractions in *Xanthium sibiricum* leaf against insect pests and its chemical component. *J. Plant Res. Environ.* **2009**, *18*, 74−79.
(37) Julio, L. F.; Martin, L.; Muñoz, R.; Mainar, A. M.; Urieta, J. S.; Sanz, J.; Burillo, J.; González-Coloma, A. Comparative chemistry and insect antifeedant effects of conventional (Clevenger and Soxhlet) and supercritical extracts (CO_2) of two *Lavandula luisieri* populations. *Ind. Crops Prod.* **2014**, *58*, 25−30.
(38) Nawrot, J.; Klejdysz, T. Ionic liquids as feeding deterrents for stored product pests. *Przem. Chem.* **2013**, *92*, 1643−1645.
(39) Palma, L.; Muñoz, D.; Berry, C.; Murillo, J.; Caballero, P. Draft genome sequences of two *Bacillus thuringiensis* strains and characterization of a putative 41.9-kDa insecticidal toxin. *Toxins* **2014**, *6*, 1490−1504.
(40) Jóźwicka, K.; Donskow-Łysoniewska, K.; Doligalska, M. *Caenorhabditis elegans* nematode − convenient for the study anthelmintic activity in plant saponins. *Med. Wet.* **2011**, *67*, 829−834.
(41) Fraizer, J. L.; Chyb, S. Use of feeding inhibitors in insect control. In *Regulatory Mechanisms of Insect Feeding*; de Boer, G., Chapman, R. F., Eds.; Chapman and Hall: New York, 1995.
(42) Halder, J.; Srivastava, C.; Dhingra, S.; Dureja, P. Effect of essential oils on feeding, survival, growth and development of third

DOI: 10.1021/acs.jafc.5b02025
J. Agric. Food Chem. 2015, 63, 6749−6756

instar larvae of *Helicoverpa armigera* Hubner. *Natl. Acad. Sci. Lett.* **2012**, *35*, 271−276.
(43) Ahmad, S.; Khan, I. A.; Hussain, Z.; Shah, S. I. A.; Ahmad, M. Comparison of a biopesticide with some synthetic pesticides against aphid in rapeseed crop. *Sarhad J. Agric.* **2007**, *23*, 1117−1120.
(44) Gökçe, A.; Isaacs, R.; Whalon, M. E. Dose−response relationship for the antifeedant effects of *Humulus lupulus* extracts against larvae and adults of the Colorado potato beetle. *Pest Manage. Sci.* **2012**, *68*, 476−481.
(45) Dancewicz, K.; Wiśniewska, E.; Lagiera, M.; Anioł, M.; Gabryś, B. Effect of spent hop extracts on the probing and setting behaviour of *Myzus persicae* (Sulzer, 1776), Aphids and other hemipterous insects. *Hemipterol. Sect. Polish Entomol. Soc.* **2011**, *17*, 121−127.
(46) Powell, G.; Hardie, J.; Pickett, J. A. Laboratory evaluation of antifeedant compounds for inhibiting settling by cereal aphids. *Entomol. Exp. Appl.* **1997**, *84*, 189−193.
(47) Alizadeh, B. H.; Foroumadi, A.; Shafiee, A. New synthetic route towards 2,2-dimethylchromene and synthesis of substituted 7-(dimethylpropargyl) chromene. *J. Heterocycl. Chem.* **2008**, *45*, 909−912.
(48) Garazd, Y. L.; Garazd, M. M.; Khilya, V. P. Modified coumarins. 13. Synthesis of cyclopentane-annelated pyranocoumarins. *Chem. Nat. Compd.* **2004**, *40*, 427−433.
(49) An, H.; Eum, S.-J.; Koh, M.; Lee, S. K.; Park, S. B. Diversity-oriented synthesis of privileged benzopyranyl heterocycles from *s-cis*-enones. *J. Org. Chem.* **2008**, *73*, 1752−1761.
(50) Tran, T.-D.; Park, H.; Kim, H. P.; Ecker, G. F.; Thai, K.-M. Inhibitory activity of prostaglandin E_2 production by the syntetic 2′-hydroxychalcone analogues: synthesis and SAR study. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1650−1653.
(51) Anioł, M.; Szymańska, K.; Żołnierczyk, A. K. An effecient synthesis of the phytoestrogen 8-prenylnaringenin from isoxanthohumol with magnesium iodide etherate. *Tetrahedron* **2008**, *64*, 9544−9547.
(52) Wilhelm, H.; Wessjohann, L. A. An efficient synthesis of the phytoestrogen 8-prenylnaringenin from xanthohumol by a novel demethylation process. *Tetrahedron* **2006**, *62*, 6961−6966.
(53) Cuthbertson, A. G. S.; Blackburn, L. F.; Northing, P.; Luo, W.; Cannon, R. J. C.; Walters, K. F. A. Leaf dipping as an environmental screening measure to test chemical efficacy against *Bemisia tabaci* on poinsettia plants. *Int. J. Environ. Sci. Technol.* **2009**, *6*, 347−352.
(54) Hanske, L.; Loh, G.; Szczęsny, S.; Blaut, M.; Braune, A. Recovery and metabolism of xanthohumol in germ-free and human microbiota-associated rats. *Mol. Nutr. Food Res.* **2010**, *54*, 1405−1413.
(55) Yilmazer, M.; Stevens, J. F.; Deinzer, M. L.; Buhler, D. R. In vitro biotransformation of xanthohumol, a flavonoid from hops (*Humulus lupulus*), by rat liver microsomes. *Drug. Metab. Dispos.* **2001**, *29*, 223−231.
(56) Guo, J.; Nicolic, D.; Chadwic, L. R.; Guido, F. P.; Van Breemen, R. B. Identification of human hepatic cytochrome P450 enzymes involved in the metabolism of 8-prenylnaringenin and isoxanthohumol from hops (*Humulus lupulus* L.). *Drug. Metab. Dispos.* **2006**, *34*, 1152−1159.
(57) Fu, M.-L.; Wang, W.; Chen, F.; Dong, Y.-C.; Liu, X.-J.; Ni, H.; Chen, Q.-H. Production of 8-prenylnaringenin from isoxanthohumol through biotransformation by fungi cells. *J. Agric. Food Chem.* **2011**, *59*, 7419−7426.
(58) Mai, V. C.; Drzewiecka, K.; Jeleń, H.; Narożna, D.; Rucińska-Sobkowiak, R.; Kęsy, J.; Floryszak-Wieczorek, J.; Gabryś, B.; Morkunas, I. Differential induction of *Pisum sativum* defense signaling molecules in response to pea aphid infestation. *Plant Sci.* **2014**, *221−222*, 1−12.
(59) Dietz, B. M.; Hagos, G. K.; Eskra, J. N.; Wijewickrama, G. T.; Anderson, J. R.; Nikolic, D.; Guo, J.; Wright, B.; Chem, S.-N.; Pauli, G. F.; Breemen, R. B.; Bolton, J. L. Differential regulation of detoxification enzymes in hepatic and mammary tissue by hops (*Humulus lupulus*) in vitro and in vivo. *Mol. Nutr. Food Res.* **2013**, *57*, 1055−1066.
(60) Thoison, O.; Sevenet, T.; Niemeyer, H. M.; Russell, G. B. Insect antifeedant compounds from *Nothofagus dombeyi* and *N. pumilio*. *Phytochemistry* **2004**, *65*, 2173−2176.
(61) Napal, G. N. D.; Defago, M. T.; Valladares, G. R.; Palacios, S. M. Response of *Epilachna paenulata* to two flavonoids, pinocembrin and quercetin, in a comparative study. *J. Chem. Ecol.* **2010**, *36*, 898−904.
(62) Russel, G. B.; Bowers, W. S.; Keesing, V.; Niemeyer, H. M.; Sevenet, T.; Vasanthaverini, S.; Wratten, S. D. Patterns of bioactivity and herbivory on *Nothofagus* species from Chile and New Zealand. *J. Chem. Ecol.* **2000**, *26*, 41−56.
(63) Nenaah, G. E. Toxic and antifeedant activities of prenylated flavonoids isolated from *Tephrosia apollinea* L. against three major coleopteran pests of stored grains with reference to their structure-activity relationship. *Nat. Prod. Res.* **2014**, *28*, 2245−2252.
(64) Nalwar, Y. S.; Sayyed, M. A.; Mokle, S. S.; Zanwar, P. R.; Vibhute, Y. B. Synthesis and insect antifeedant activity of some new chalcones against *Phenacoccus solanopsis*. *World J. Chem.* **2009**, *4*, 123−126.
(65) Kumar, R.; Sharma, P.; Shard, A.; Tewary, D. K.; Nadda, G.; Sinha, A. K. Chalcones as promising pesticidal agents against diamondback moth (*Plutella xylostella*): microwave-assisted synthesis and structure−activity relationship. *Med. Chem. Res.* **2012**, *21*, 922−931.
(66) Sundararajan, R.; Arulkumaran, R.; Kamalakkannan, D.; Suresh, R.; Joseph, S. J.; Ranganathan, K.; Sakthinathan, S. P.; Vanangamudi, G.; Vijayakumar, S.; Thirunarayanan, G. Insect antifeedant potent halogen substituted phenyl chalcones. *Int. Lett. Chem., Phys. Astron.* **2014**, *1*, 67−73.
(67) Morimoto, M.; Kumeda, S.; Komai, K. Insect antifeedant flavonoids from *Gnaphalium affine* D. Don. *J. Agric. Food Chem.* **2000**, *48*, 1888−1891.
(68) Morimoto, M.; Tanimoto, K.; Nakano, S.; Ozaki, T.; Nakano, A.; Komai, K. Insect antifeedant activity of flavones and chromones against *Spodoptera litura*. *J. Agric. Food Chem.* **2003**, *51*, 389−393.
(69) Yuan, Y.; Qiu, X.; Nikolić, D.; Chen, S.-N.; Huang, K.; Li, G.; Pauli, G. F.; van Breemen, R. B. Inhibition of human cytochrome P450 enzymes by hops (*Humulus lupulus*) and hop prenylphenols. *Eur. J. Pharm. Sci.* **2014**, *53*, 55−61.
(70) Goławska, S.; Łukasik, I. Antifeedant activity of luteolin and genistein against the pea aphid *Acyrthosiphon pisum*. *J. Pest Sci.* **2012**, *85*, 443−450.
(71) Fulcher, A. F.; Ranney, T. G.; Burton, J. D.; Walgenbach, J. F.; Danehower, D. A. Role of foliar phenolics in host plant resistance of *Malus* taxa to adult Japanese beetles. *HortScience* **1998**, *33*, 862−865.
(72) Ohmura, W.; Doi, S.; Aoyama, M.; Ohara, S. Antifeedant activity of flavonoids and related compounds against the subterranean termite *Coptotermes formosanus* Shiraki. *J. Wood Sci.* **2000**, *46*, 149−153.
(73) Wesołowska, O.; Gąsiorowska, J.; Petrus, J.; Czarnik-Matusewicz, B.; Michalak, K. Interaction of prenylated chalcones and flavanones from common hop with phosphatidylcholine model membranes. *Biochim. Biophys. Acta, Biomembr.* **2014**, *1838*, 173−184.
(74) Morimoto, M.; Fukumoto, H.; Nozoe, T.; Hagiwara, A.; Komai, K. Synthesis and insect antifeedant activity of aurones against *Spodoptera litura* larvae. *J. Agric. Food Chem.* **2007**, *55*, 700−705.

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