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ORIGINAL RESEARCH ARTICLE

Qualitative structure-activity relationships of aryl isoprenoid derivatives as biorational juvenoids — reweighing

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Abstract

Juvenoids are juvenile hormone (JH) mimetics, with specific structural features and defined molecular size that disrupt the target insect development. Juvenoid activity (= JH-type activity) of various isoprenoid-based derivatives as insecticidal candidates of the insect growth disruptors (IGDs) type were rated against the house fly, *Musca domestica* L. The epoxidized decenyl and nonenyl phenyl ether derivatives have more active compounds than those of both parent alkoxidized or olefinic structures. The highest juvenoid potency was shown by 3,4-methylenedioxyphenyl ethers of 8,9-epoxy-5,9-dimethy1-3,8-decadiene. Qualitative structure-activity relationships are offered to relate the chemical structure criteria to observed juvenoid-related activity. Differences in activity among the reported isoprenoid-based derivatives were qualitatively rationalized. This study advances understanding of the structural qualifications and activity determinants of isoprenoid juvenoids, which is important for the development of new filth flies eco-friendly insecticides.

Keywords Juvenoids · Juvenile hormone mimics · Isoprenoids · Structure-activity correlation · Filth flies

Introduction

The house fly, *Musca domestica* Linnaeus (Insecta: Diptera: Muscidae), is a synanthropic cosmopolitan medical and veterinary insect pest. This fly causes severe annoyance to humans and livestock and feeds on foodstuffs and wastes where they can acquire and disseminate bacterial, fungal, parasitic, protozoal, and viral disease agents (Khamesipour et al. 2018; Balaraman et al. 2021). House flies are capable of mechanically transmitting agents causing amoebic and bacillary dysentery, cholera, conjunctivitis, coronavirus disease 2019 (COVID-19), mucormycosis, poliomyelitis, salmonellosis, shigellosis, tuberculosis, typhoid, and viral gastroenteritis among others. The house fly is also implicated in the spread of antimicrobial resistance (Onwugamba et al. 2018). It has shown a remarkable ability to rapidly evolve resistance against insecticides (Liu and Yue 2000). Such adverse problems/losses could be cut largely by implementing effective control tactics, including developing and/or reconsidering benign insecticides against this serious pest, in specific those which disrupt development like the JH mimics.

Juvenile hormones (JHs) are structurally-related acyclic sesquiterpenes derived from the 15-carbon precursor farnesyl diphosphate *via* the mevalonate biosynthetic pathway. JHs are secreted by the insect *corpora allata* to regulate a complex set of physiological and developmental processes, including metamorphosis, through interaction with ecdysteroids (molting hormones) (Goodman and Cusson 2012; Picard et al. 2021). The presence of JH in the hemolymph at low nanomolar levels maintains the *status quo*, the larval stage and later stages, and can prevent metamorphosis. When JH levels sharply decrease to picomolar levels with concomitant spikes in levels of ecdysteroids, development of

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pupal and adult stages is allowed (Kamita et al. 2011; Sláma 2015; Kamruzzaman et al. 2020). JHs are isoprenoids (terpenoids) that exists in six major forms (JH 0, JH I, JH II, JH III, 4-methyl-JH I, and JH III bisepoxide [JHB-3]); all have an α, β-unsaturated methyl ester at one end of the molecule and an epoxide at the other (Morgan 2010; Kamita et al. 2011). JH III is the most widely distributed JH homologue (Noriega 2014; Sláma 2015). Identification of the functions of JH in insects gave impetus for the exploration and development of synthetic juvenoids, compounds that show biological activity similar to that of natural JHs.

Insect growth disruptors (IGDs) are a diverse class of synthetic compounds that mimic the structure and/or the action of JHs to disrupt insect development, thus they represent advanced biorational insecticides (Dhadialla et al. 2009; Pener and Dhadialla 2012). They are particularly suited as larvicides for the control of noxious insects for their low persistence and environmental impacts. Juvenoids are natural or synthetic JH analogues (JHAs) that selectively inhibit metamorphosis by mimicking natural JHs and block larva-to-pupa-to-adult or nymph-to-adult molt and replace it by isometric growth, causing hyperjuvenilism (Kamita et al. 2011; Pener and Dhadialla 2012; Sláma 2015). In addition to developmental retardation, juvenoids applications can cause malformation and disturbance in gametogenesis and organ formation (Kikukawa et al. 1989; King and Bennett 1989). In some species resistance has been reported (Hollingworth and Dong 2008; Abbas and Hafez 2021). Several biologically active juvenoids differ in their chemical structure from the sesquiterpenoid JHs (Jindra and Bittova 2020). Hence, better knowledge of their structural qualifications as IGDs is critical for using these compounds as insecticides. The remarkable variation in chemical structures of juvenoid IGDs (JHAs), heterogeneity of the target species and/or the developmental stage(s), and lack of a standard bioassay (mostly extrapolation from the bioassays to *in vivo* activities is a troublesome issue) make structure-activity-relationships (SARs) challenging (Liszeková et al. 2009; Ramaseshadri et al. 2012; Sláma 2015). Therefore, SAR studies are best restricted to a certain group of JHAs and to a definite insect species, or a closely related group of insects (Lv et al. 2016; Bassal et al. 2018).

Juvenoids have specific structural features and defined molecular size (Pener and Dhadialla 2012; Qu et al. 2015, 2018). Their physicochemical properties include low polarity, lipophilicity, and volatility. Nearly 4,000 synthetic juvenoids have been developed and tested on hundreds of insect species as potential insecticides (Sláma 2015). They can be structurally divided into (i) terpenoids (= isoprenoids) [or 'hybrid' terpenoids] (simply with an aliphatic chain, like methoprene) and (ii) nonterpenoids (having an aromatic or alicyclic component; more or less phenoxy compounds, like pyriproxyfen) (Pener and Dhadialla 2012). Terpenoid (isoprenoids) juvenoids have been used against larvae of both cyclorrhaphous flies and mosquitoes (Henrick 2007; Harshman et al. 2010). Phenoxy juvenoids are ovicidal and cause infertility and morphogenetic defects in some insects (King and Bennett 1989; Ortego and Bowers 1995; Boina et al. 2010). Nonetheless, JHAs have not been as frequently utilized as less specific and occasionally lethal insecticides (*e.g.,* neonicotinoids, organophosphates, pyrethroids, *etc.*) (Liszeková et al. 2009). Therefore, continuing studies on synthetic JHAs may provide novel potent compounds. The aryl isoprenoid juvenoids (containing phenoxy or other cyclic groups in addition to isoprenoid-related molecule) group have continued to attract interest (Schwartz et al. 1974; McGovern et al. 1980; Liszeková et al. 2009).

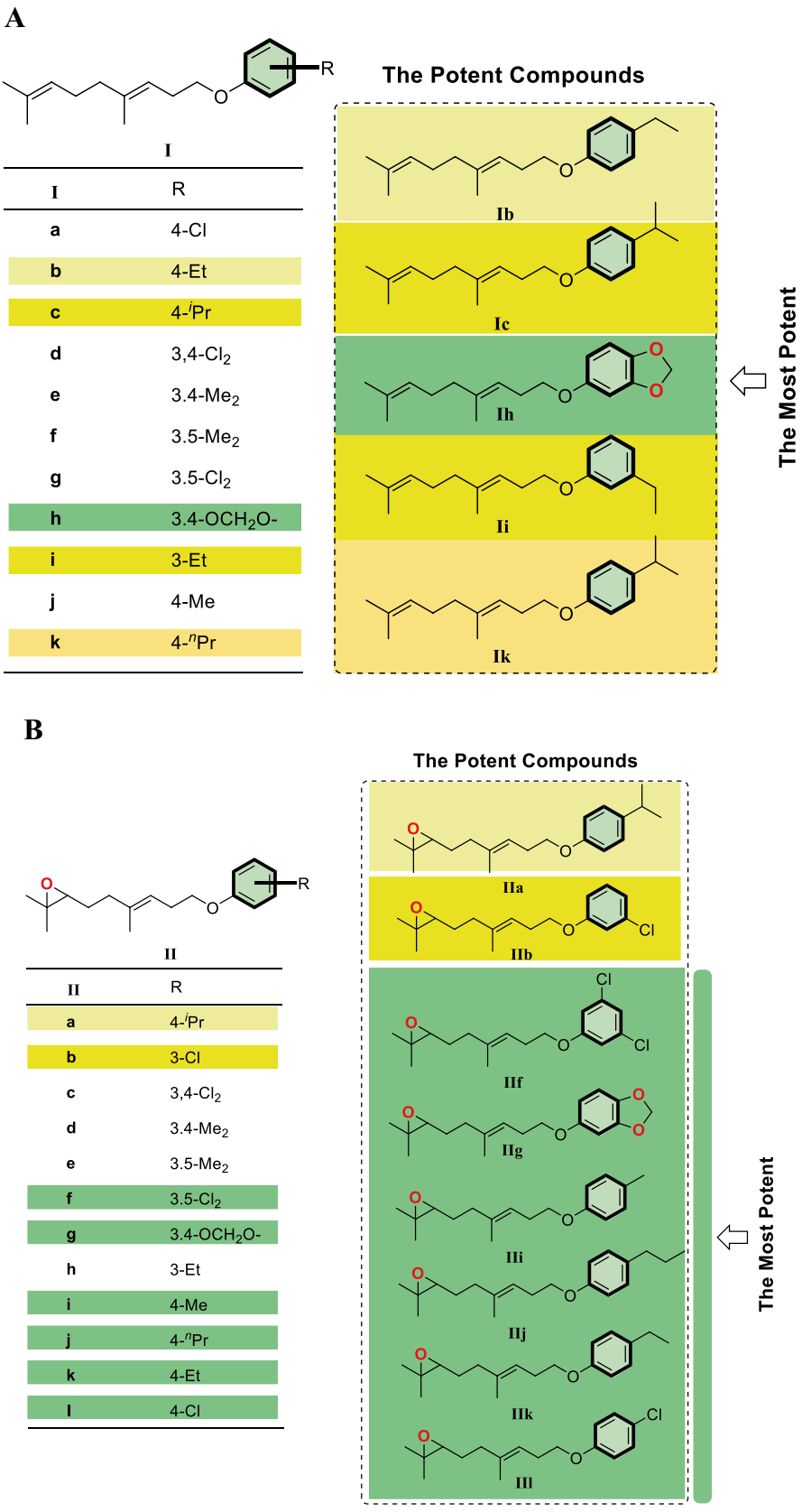
The activity of hybrid isoprenoid aromatic derivatives and closely related compounds against *M. domestica* was of interest because of their target specificity and their high chemical stability. Qualitative modeling/ assessment methods relating chemical structure to biological activity, called structure-activity relationship analyses or SAR, are applied to the characterization of chemical toxicity. Hence, recognition of which structural features correlate with chemical and biological reactivity of the reported isoprenoid-based derivatives was basically undertaken/aimed. The behavior of insecticidal isoprenoids derivatives, and their oxygenated nonenes and decenes analogues bearing a wide range of aryl substituents against the house fly is reported herein.

Material and methods

House flies, *M. domestica*, were maintained as a colony in cages (50 x 50 x 50 cm) at conditions of 25 ± 2 °C, ambient (40–60%) relative humidity (RH), and 12L:12D photoperiod. Larvae were fed a standard rearing medium consisted of a mixture of 10 g yeast powder, 10 full-cream milk powder, and 2 g agar in 100 ml H_2O (Grosscurt and Tipker 1980), and adults were fed a mixture of milk powder and granulated sucrose (1:1 ratio) and given water *ad libitum*. Each breeding cycle constituted a period of ca. 3 weeks. The 3rd instar *M. domestica* was used in all experiments.

All the tested isoprenoid-based derivatives (Table S1) used in this study were originally synthesized by the procedure described previously (McGovern et al. 1980). These 83 isoprenoid derivatives of 4 nonenyl and 6 decenyl type-structures, 95 % purity, have different types of substituents placed at different sites of the molecule (Fig. 1) and were evaluated as IGDs of the JH type against the prepupae of *M. domestica.* The chemical structures and the schematic molecular models were made with ChemDraw® v. 16.0 (PerkinElmer Inc., MA, U.S.A.), using IUPAC nomenclature.

The juvenoid-like activity of the various isoprenoid-based derivatives were assayed according to the protocol



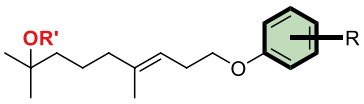
I	R
a	4-Cl
b	4-Et
c	4-^{i}Pr
d	3,4-Cl_2
e	3.4-Me_2
f	3.5-Me_2
g	3.5-Cl_2
h	3.4-OCH_2O-
i	3-Et
j	4-Me
k	4-^{n}Pr

II	R
a	4-^{i}Pr
b	3-Cl
c	3,4-Cl_2
d	3.4-Me_2
e	3.5-Me_2
f	3.5-Cl_2
g	3.4-OCH_2O-
h	3-Et
i	4-Me
j	4-^{n}Pr
k	4-Et
l	4-Cl

Fig. 1 **A**-**J**: Derivatization and detailed structural classification with the potency of the isoprenoid derivatives

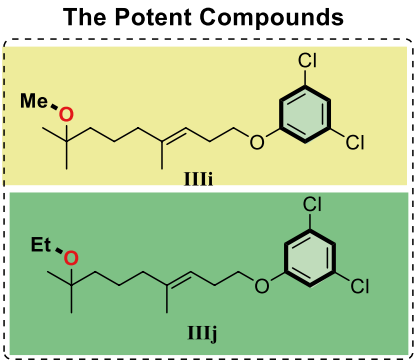
Fig. 1 (continued)

C



III

III	R	R'
a	4-Cl	Et
b	4-^{i}Pr	Me
c	4-^{i}Pr	Et
d	3,4-Cl_2	Me
e	3,4-Cl_2	Et
f	3.4-Me_2	Me
g	3.4-Me_2	Et
h	3.5-Me_2	Me
i	3.5-Cl_2	Me
j	3.5-Cl_2	Et



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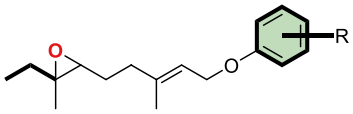
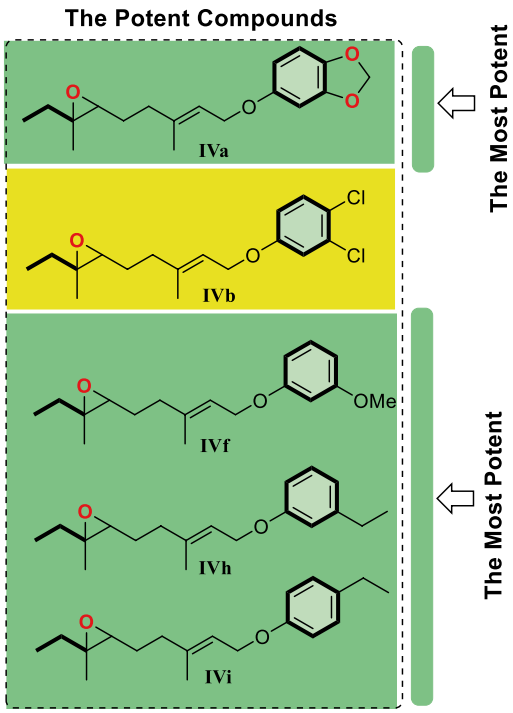


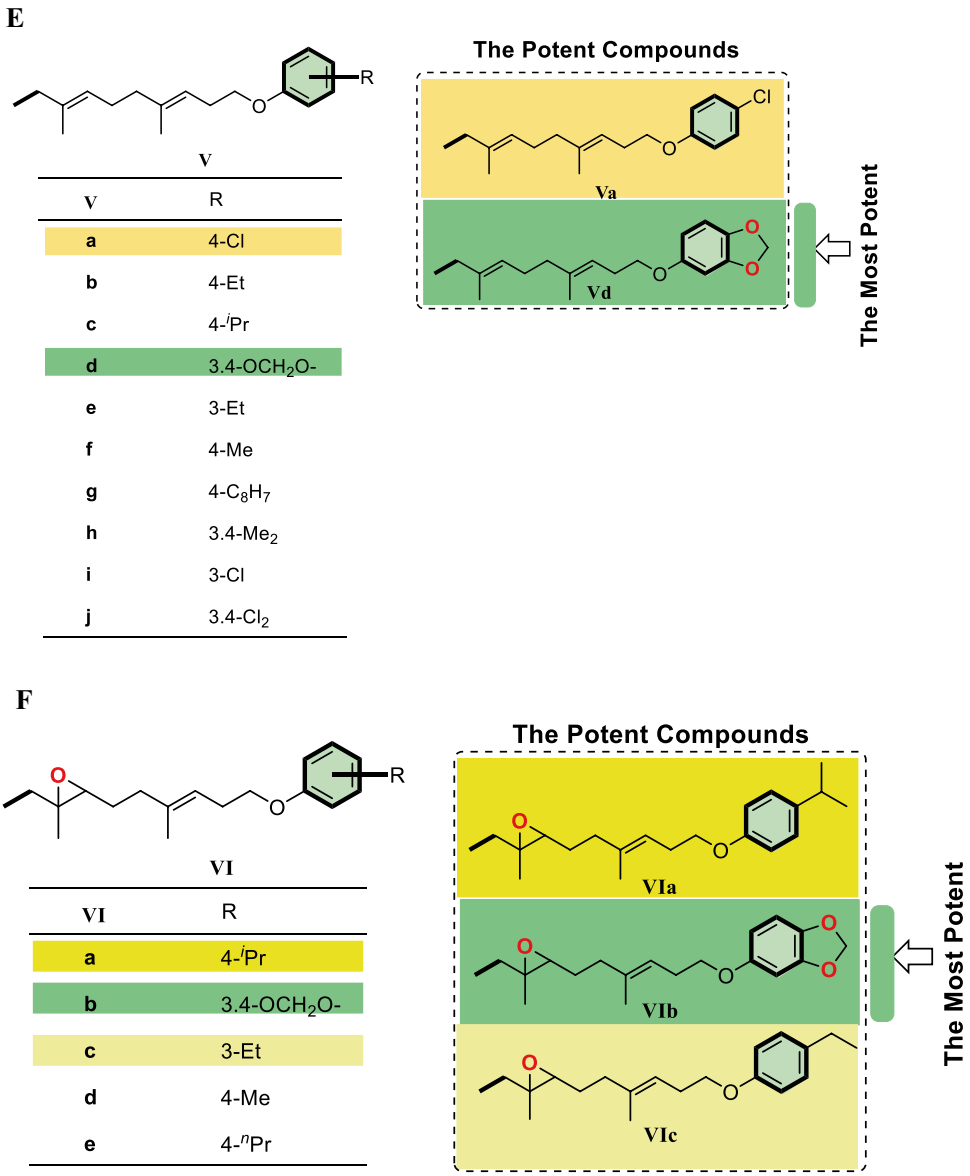
IV

IV	R
a	3.4-OCH_2O-
b	3,4-Cl_2
c	4-Me
d	4-^{i}Pr
e	4-NO_2
f	3-MeO
g	3-NO_2
h	3-Et
i	4-Et



of Chang et al. (1972). Briefly, three different doses of 10^3, 10^2, and 10 ppm of each compound, prepared in acetone, were topically applied, individually, to the abdominal tergum of the fully mature 3rd instar *M. domestica*. Triplicate replicates, each with 25 individuals, were tested. With each run, an acetone-treated group was used as control. The treated and control specimens were held at 27 ± 2 °C (12L:12D, 40–60% RH) until adult emergence. The activity rating system was calculated as the percentage of total failures in pupation, or emergence of adults in relation to controls, known as the "*morphogenetic efficiency*" = (Number of malformed insects / Total number of insects

Fig. 1 (continued)



V	R
a	4-Cl
b	4-Et
c	4-^{i}Pr
d	3.4-OCH_2O-
e	3-Et
f	4-Me
g	4-C_8H_7
h	3.4-Me_2
i	3-Cl
j	3.4-Cl_2

VI	R
a	4-^{i}Pr
b	3.4-OCH_2O-
c	3-Et
d	4-Me
e	4-^{n}Pr

succeeded to metamorph) X 100, originally developed by Varjas and Sehnal (1973). This index indicates the number of morphologically affected insects that survive until the first ecdysis after treatment in proportion to the total number of surviving insects (healthy or malformed) (Varjas and Sehnal 1973).

Statistical analyses were conducted using the IBM SPSS Statistics Version 22 (IBM Corp. Armonk, NY, USA). A one-way analysis of variance (ANOVA) and a Student's t-test were calculated to explore whether there were differences in activity rating between compounds within the same dose and between the same compound at different doses; ANOVAs were followed by the Bonferroni-Holm method for multiple comparisons among compounds. Significant differences were accepted at $p < 0.05$.

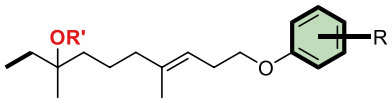
Results and discussion

The general (parent) structures of nonenyl and decenyl phenyl ethers used in the present study belong to 10 basic isoprenoid structure I-X as shown in Fig. 1A-J (at the top of each subfigure). The structural specifications of these compounds are shown also in Fig. 1A-J, with the type of substituted group(s), while chemical structures of the potent compounds are given at the right side of Fig. 1A-J. IUPAC names of all compounds are given in Table S1. The activity rating data are presented in Fig. 2. The general structural correlation between tested compounds is presented in Fig. 3.

Three different doses of each compound—(10^3, 10^2, and 10 ppm, representing the high, the medium, and the low dose, respectively)—were used to assess the activity

Fig. 1 (continued)

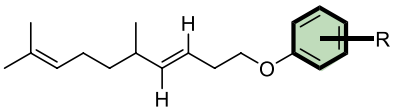
G



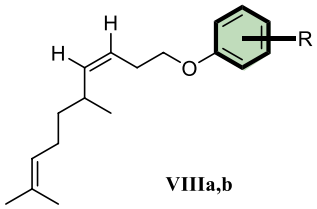
VII

VII	R	R'
a	4-Cl	Et
b	4-^{i}Pr	Me
c	4-^{i}Pr	Et
d	4-Cl	Me
e	3-Cl	Me

H

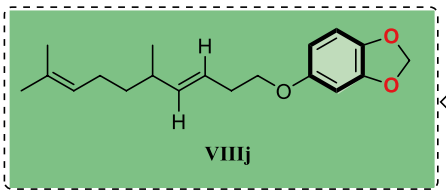


VIIIc-j



VIIIa,b

VIII	R
a	4-Cl
b	4-Et
c	4-^{i}Pr
d	3-Et
e	4-Et
f	4-Ph
g	3.4-Me_2
h	3-Cl
i	4-Me
j	3.4-OCH_2O-

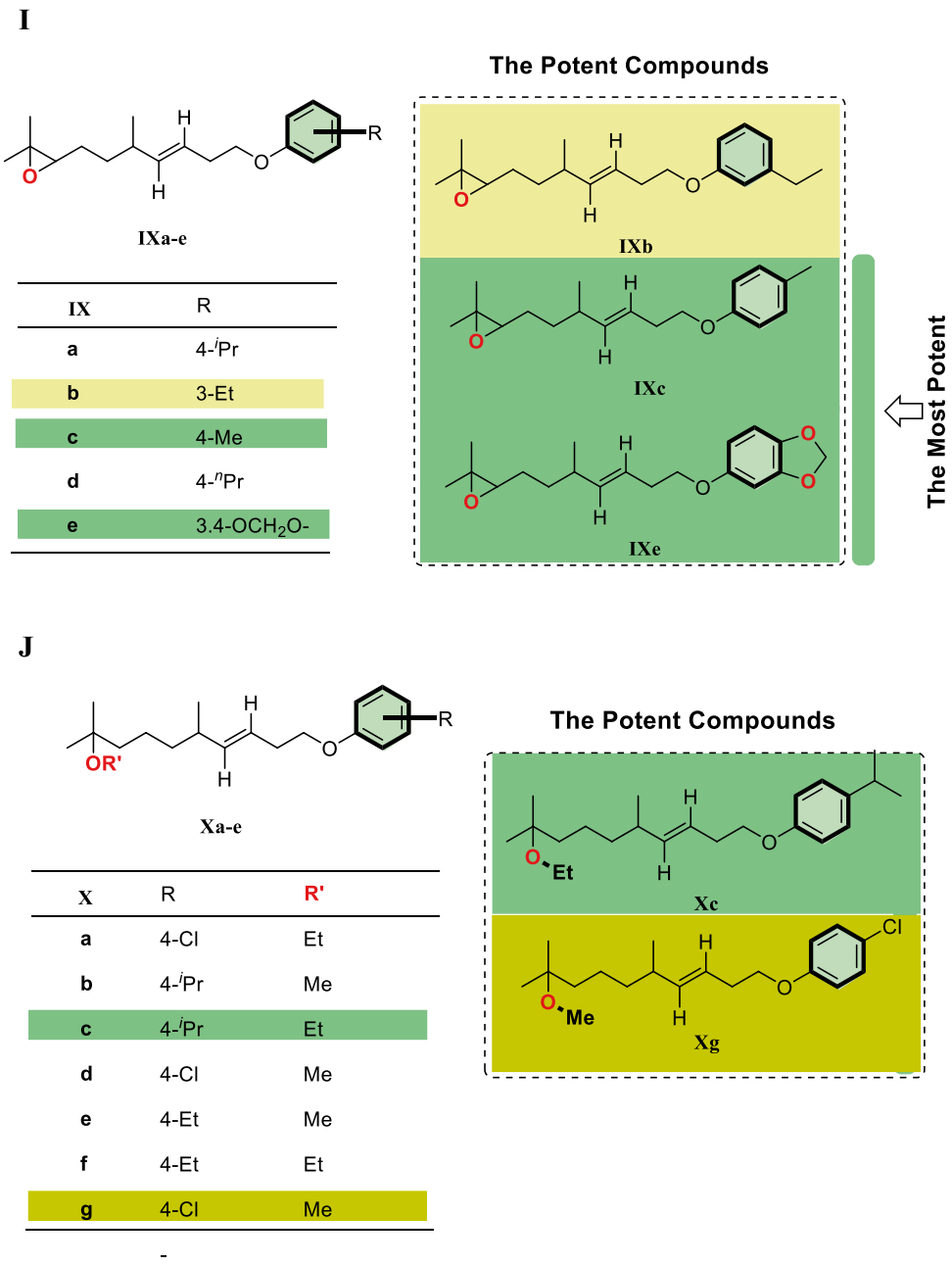


VIIIj

The Most Potent

rating against the third instar *M. domestica*. Few derivatives exhibited moderate juvenoid activity in *M. domestica* (Fig. 2). Significant differences were reported for the activity rating scores of the IGDs tested at high ($F = 21.057$, $df = 30$, $p < 0.001$) and medium ($F = 13.630$, $df = 13$, $p < 0.001$) doses. However, other compounds did not show activity at the low dose except the VIIIj compound, which showed 37.3% activity against *M. domestica* larvae. The activity rating of this compound varied significantly with respect to dose ($F = 6.067$, $df = 2$, $p = 0.036$). In general, the activity of the compounds ranged from 8.0 to 50.6% at the high dose and from 9.3 to 49.3% at the medium dose. The most active IGDs are ranked according to their activity rating scores at the high dose as follows: IIk, 50.6 ± 2.3% = IIIj > Ih, 49.3 ± 4.6% = IIg = IIi = IIl = IVa = IVf = Vd = VIb = VIIIj = IXe. At the medium dose, the active IGDs are ranked as follows: VIIIj, 49.3 ± 4.6% > Xc, 46.6 ± 16.1% >Ih, 34.6 ± 4.6% > IXe, 33.3 ± 4.6% > Vd, 29.3 ± 4.6% > VIb, 28.0 ± 4% > IIl, 20.0 ± 4% IIi > 18.6 ± 2.3% > IVa, 16.0 ± 4%. Furthermore, for IGDs that showed activity at both doses, activity differed significantly for each compound between high and medium doses ($t = 2.910$–21.920, $p = 0.0001$–0.044). However, the compound Xc did not show a significant difference in activity between the two doses ($t = 0.120$, $p = 0.911$) (Fig. 2).

Fig. 1 (continued)



IX	R
a	4-^{i}Pr
b	3-Et
c	4-Me
d	4-^{n}Pr
e	3.4-OCH_2O-

X	R	R'
a	4-Cl	Et
b	4-^{i}Pr	Me
c	4-^{i}Pr	Et
d	4-Cl	Me
e	4-Et	Me
f	4-Et	Et
g	4-Cl	Me

-

Many structural features of the isoprene unit (the main building block of isoprenoids [=terpenoids]) are expected to affect activity, including positioning of alkyl branching groups, derivatization of the terminal olefinic bond, geometry of internal olefinic bonds, and length of the hydrocarbon backbone. Methoxylation or ethoxylation of nonadienyl derivatives suppressed the activity at the three dose levels regardless of the identity and position of the monosubstituent at the aromatic moiety. Except the ethoxylated derivative with 3,5-dichlorophenyl substituent which showed a relatively high activity against larval *M. domestica*. Other disubstituents showed low or no activity. The methoxylated derivative with the 3,5-dichlorophenyl substituent showed very weak activity. In case of alkoxylated decadienyl derivatives (with the same double bond position) none of the compounds showed and activity. However, moving the methoxy moiety near the terminal of the aliphatic chain was effective in case of 3,4-(methylenedioxy)phenylether even at lower dose (10 ppm), to attain relatively high activity. Likewise, in case of 4-chlorophenyl ether, a good activity has been obtained.

The epoxides analogues showed an interesting activity against larval *M. domestica*. Epoxidation of the nonadienyl derivatives of the isoprenoid-based derivatives showed excellent activity regardless of the electronic nature of the substituents and their numbers. In general, para-substituted aromatic substituents (4-postion in aromatic moiety) showed

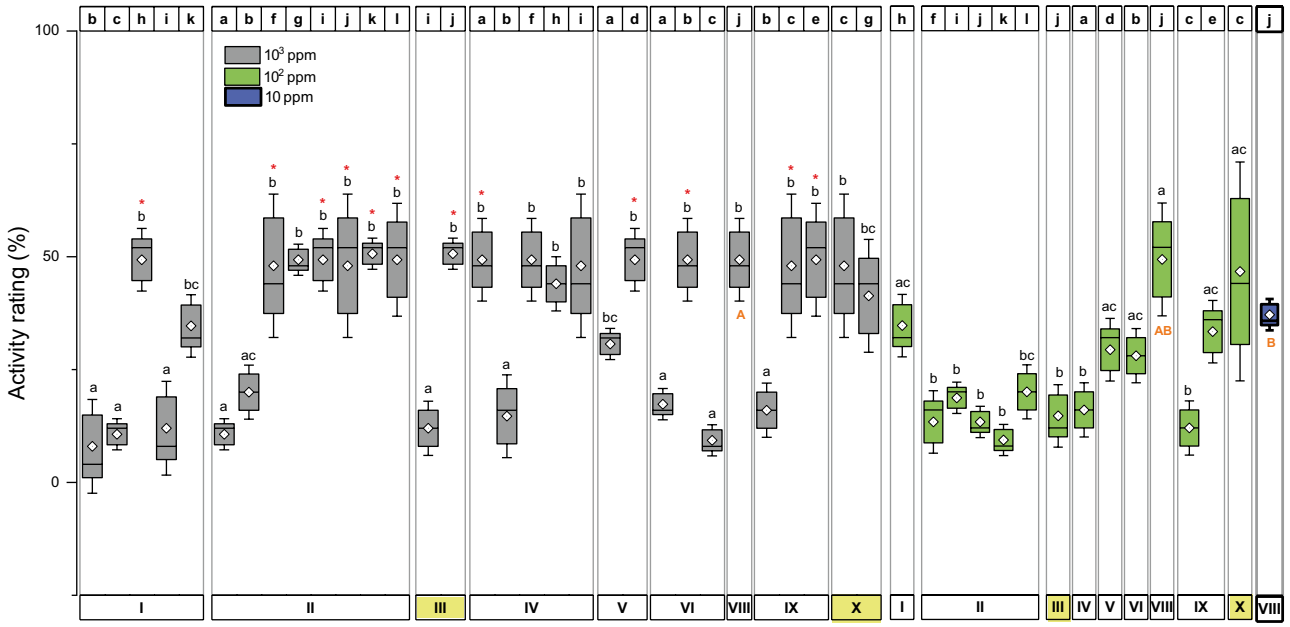


Fig. 2 Activity rating scores—*morphogenetic efficiency*—of the tested phenoxy nonenes and decenes isoprenoid-based ethers, IGDs, applied topically against fully mature 3rd instar *Musca domestica*. The highlighted compounds (III & X) have both R and R1 substituted groups, while all the other compounds have only one substitution (R). Data are presented as mean ± SD in ppm. Boxes followed by different lowercase letters denote significant differences in activity rating among different compounds of the same dose (10^3 or 10^2 ppm), whereas boxes with different uppercase letters below indicate significant differences in activity rating of the same compound between different doses (10^3, 10^2 and 10 ppm) (analysis of variance [ANOVA]; Bonferroni-Holm test; $p < 0.05$). The asterisk '*' indicates that activity rating of the same compound is significantly different between the two doses 10^3 and 10^2 ppm (Student's t-test, $p < 0.05$)

more activity than in the meta-position of the aryl moiety (3-postion). Interestingly, the branching in the alkyl chain (n-propyl to isopropyl group) caused a marked decrease in activity. The addition of heteroatoms (oxygen atom) to the hydrocarbon chain in form of oxirane ring results in an overall increase in potency, which may be related to the change in lipophilicity regardless the electronic identity or the number of the substituent at the aromatic moiety.

Epoxidation of the decadienyl derivatives did not change activity profile of the compounds in the V structural group, and only 3,4-(methylenedioxy)phenyl ether showed excellent activity rather than other substituents. Separation of the oxirane ring and the double bond in 3-position in case of decenyl derivatives as in IX by one methylene group than the nonenyl derivatives II resulted in a decrease in the activity of most substituents except the 3,4-(methylenedioxy) and 4-methyl derivatives.

The 3,4-(methylenedioxy)phenyl compounds are of special interest, because they are closely related to the reported epoxygeranyl 3,4-(methylenedioxy)phenyl ether which has considerable activities as JHAs (Bowers 1969; Redfern et al. 1971; Bassal et al. 2018). Methylendioxyphenyl compounds in all the related derivatives (open chain, epoxides or alkoxylated) showed excellent activity against the housefly *M. domestica*. Chang et al. (1972) reported that JHAs containing methylenedioxyphenyl derivatives, topically applied to the 5th instar *Bombyx mori* have marked inhibitory effect on larval-pupal metamorphosis. They further used these derivatives to obtain quality silkworm cocoons in a high yield per unit rearing time and per unit amount of feedstuff (*i.e.*, these methylenedioxyphenyl derivatives aided formation of giant cocoons).

Correlation between the structural features of the targeted isoprenoid-based derivatives and their juvenoid-related activity can be summarized as illustrated in Fig. 3. Overall, the cyclization of the carbon chain (epoxidized forms), diminished the biological activity, as evidenced for a number of the tested juvenoids, (For explanations see Patel et al. (1984), Niwa et al. (1988), and Zabza and Wawrzeńczyk (1994) for effect of sterical stiffness parameters of cyclic systems on the biological activity of juvenoids. Also, literature-reported variations of activity from species to species arise due to the presence of the double bonds in the carbon skeleton that hinders the free rotation around the molecule axis which leads to restricted conformations at some specific positions in the juvenoid structure that may be required to fit the biological receptor, and consequently diminish the biological activity of juvenoids (Sláma 2013; Dhadialla et al. 1998). It is worth emphasizing that the biologically active synthetic juvenoids does not resemble JH shape at the time when it binds to the biological receptors.

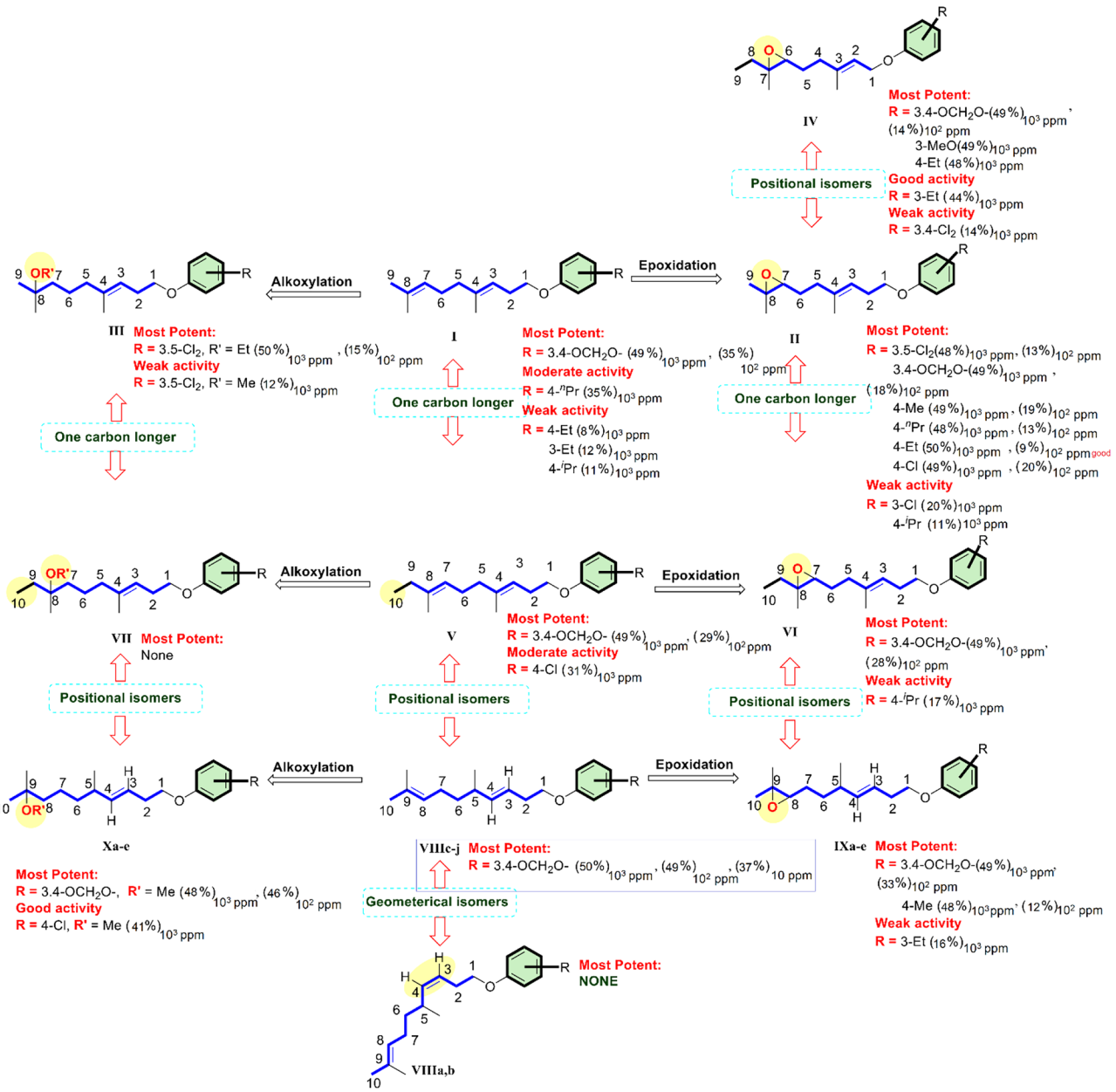


Fig. 3 Structural correlation between isoprenoid derivatives and juvenoid-related activity

Conclusions

Considering all above information, we conclude that (1) several examined aromatic terpenoid ethers possess a high degree of morphogenetic activity against the house fly *Musca domestica* L. (2) The parent alkoxidized or olefinic structures do not contain as many active compounds as the epoxidized decenyl and nonenyl phenyl ether derivatives. (3) The most active compounds were the 3,4-methylenedioxyphenyl ethers of 8,9-epoxy-5,9-dimethy1-3,8-decadiene. (4) A significant increase in JH-like activity resulted from the appropriate derivatization of synthetic juvenoids of the aryl-type isoprenoids. (5) The results suggest that chemistry can be 'custom-made' to feasibly direct juvenoid activity against different insects and/or life stages to suit specific insect control practices.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s42690-023-01025-3.

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Data availability All data related to this study are present in the paper and the supplementary material.

Declarations

Conflict of interest No potential conflict of interest was reported by the authors.

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