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Synthesis and insecticidal activity of the fluorinated galegine analogues

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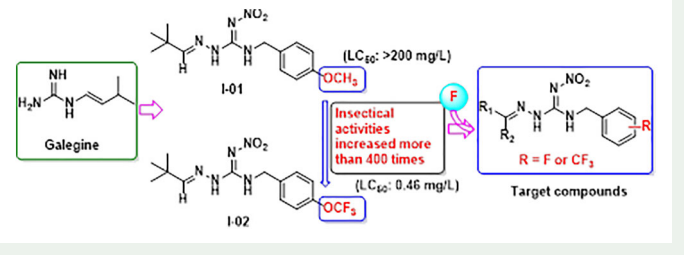
ABSTRACT

The introduction of fluorine atom can increase the biological activities of the target compounds remarkably. To find more safe and efficient insecticides, natural product galegine as lead compound, a series of novel fluorinated galegine analogues were designed and synthesized. The bioassay results indicate that all the target compounds have moderate to high insecticidal activities against *Hyalopterus pruni* Geoffroy and *Aphis gossypii* Glover, in particular, compounds IIa-05, IId-02 and IIe-03 show the best insecticidal activities against *Hyalopterus pruni* with the mortality of 100%, 100% and 96.6%, respectively. And compounds IIa-02, IId-02, IId-04, IIc-01, IIc-02 and IId-01 show 0.6-7 times insecticidal activities against *Aphis gossypii* as Imidacloprid with their LC_{50} values are 0.28 mg/L, 0.38 mg/L, 0.33 mg/L, 0.09 mg/L, 0.03 mg/L and 0.12 mg/L, respectively The analysis of structure-activity relationship indicates that the compounds with difluoro-substituted benzene ring have more potent insecticidal activities than the single fluoro-substituted compounds.



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Galegine; fluorine atom; insecticidal activity; aphids; synthesis

1. Introduction

In our previous study (Wu et al. 2019), a series of hydrocarbylidene nitrohydrazinecarboximidamides **I** (Figure 1) were synthesized with the natural product galegine

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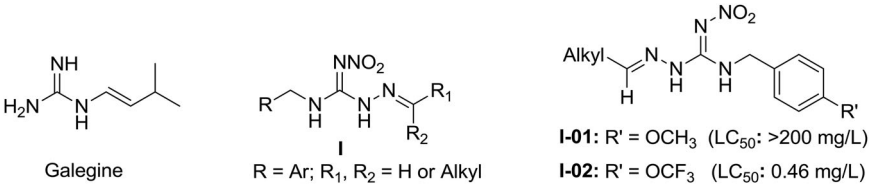


Figure 1. The structures of galegine and hydrocarbylidene nitrohydrazinecarboximidamides **I**, and LC_{50} (mg/L) of the **compoundI-01 and compoundI-02**.

(Figure 1) as scaffold and most coumpounds showed excellent insecticidal activities against *Aphis gossypii* Glover. It is noteworthy that the insecticidal activities of the compound **I-02** (Figure 1, LC_{50}: 0.46 mg/L), which obtained from substituting CH_3O of the compound **I-01** (Figure 1, LC_{50}: $>$ 200 mg/L) with CF_3O, increased more than 400 times.

As we well know, fluorine atom has special physicochemical property, and is widely applied in molecular design as a bioisostere of hydrogen atom (Purser et al. 2008; Kirk 2008; Jeschke 2004). The introduction of fluorine atom can improve the solubility, stability, permeability and other molecular biological properties of molecules that often can increase the biological activities of the target compounds remarkably (Kirk 2006). The fluorine atom can also change the molecular conformation to enhance the biological properties of the compound, such as the ability to bind to target receptors and enzymes, the ability to transport in organisms, and the rate of metabolism. (Theodoridis 2006; Smart 2001; Hagmann 2008). To find more efficient insecticides, we designed and synthesized 26 new compounds (**II**) (Figure 2) by the introduction of fluorine atom. The leaf dip method was used to determine the insecticidal activity of all compounds against aphids, calculated the Log Kow value of the target compounds by the ALOGPS 2.1 program and the structure-activity relationship was discussed.

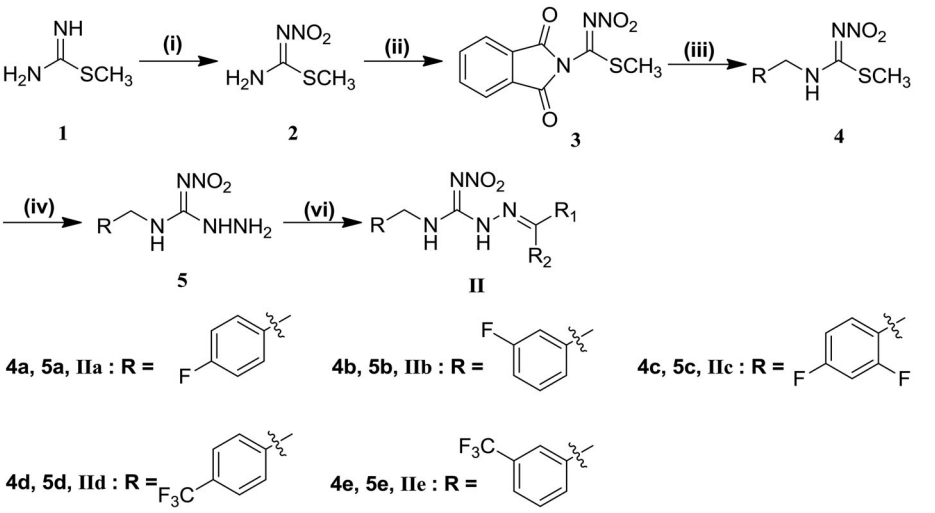
2. Results and discussion

2.1. Chemistry

The synthetic route of the target compounds was achieved in Figure 2. Treatment of 2-methyl-2-thiopseudourea sulfate with nitric acid and sulfuric acid at $-10\,^{\circ}C$ for 1 hour afforded intermediate **2**, which reacted with phthaloyl dichloride and pyridine at $0\,^{\circ}C$ gave intermediate **3**. Subjecting intermediate **3** to the corresponding fluorinated benzylamines at 0–5 $^{\circ}C$ led to compounds **4a~4e** which were reacted with hydrazine hydrate under reflux for 1 hour afforded the intermediate **5a~5e**. Then, the target compound IIa-01∼IIf-04 was synthesized by the reaction of compound **5** with aldehydes and ketones using glacial acetic acid as catalyst (Xu et al. 2017). Their structures were confirmed by 1H-NMR, high resolution mass spectrum (HR-MS). (Analysis data of all the synthesized compounds are available in Supplementary Information).

2.2. Insecticidal activity

First, all the target compounds were screened for their insecticidal activities against *Hyalopterus pruni* Geoffroy at 200 mg/L (Zhang et al. 2015), and the results are shown



IIa-01: R_1= *n*-Pr, R_2= H	**IIb-02**: R_1= *t*-Bu, R_2= H	**IId-03**: R_1= *i*-Pr, R_2= H
IIa-02: R_1= *i*-Pr, R_2= H	**IIb-03**: R_1= *n*-C_6H_{13}, R_2= H	**IId-04**: R_1= *t*-Bu, R_2= H
IIa-03: R_1= *n*-Bu, R_2= H	**IIc-01**: R_1= CH_3, R_2= CH_3	**IId-05**: R_1= *n*-C_6H_{13}, R_2= H
IIa-04: R_1= *i*-Bu, R_2= H	**IIc-02**: R_1= *n*-Pr, R_2= H	**IIe-01**: R_1= CH_3, R_2= CH_3
IIa-05: R_1= *t*-Bu, R_2= H	**IIc-03**: R_1= *i*-Pr, R_2= H	**IIe-02**: R_1= *n*-Pr, R_2= H
IIa-06: R_1= *n*-C_6H_{13}, R_2= H	**IIc-04**: R_1= *n*-Bu, R_2= H	**IIe-03**: R_1= *i*-Pr, R_2= H
IIa-07: R_1= C_6H_5, R_2= H	**IIc-05**: R_1= *i*-Bu, R_2= H	**IIe-04**: R_1= *t*-Bu, R_2= H
IIa-08: R_1= *n*-$C_{10}H_{21}$, R_2= H	**IId-01**: R_1= CH_3, R_2= CH_3	**IIe-05**: R_1= *n*-C_6H_{13}, R_2= H
IIb-01: R_1= *i*-Pr, R_2= H	**IId-02**: R_1= *n*-Pr, R_2= H	

Figure 2. Synthetic route of target compounds and the structures of fluorinated galegine analogues.

in Table 1. The results indicate that all the target compounds have moderate to high insecticidal activities against *H.pruni* at the concentration of 200 mg/L, but lower than Guadipyr. In particular, compounds IIa-05, IId-02 and IIe-03 show the best insecticidal activities against *H.pruni* with the mortality of 100%, 100% and 96.6%, respectively, that equal to insecticidal activities of guadipyr at the concentration of 12.5 mg/L. As fluorine atom can improve the lip solubility of the compounds, we calculated the Log Kow value of the target compounds by the ALOGPS 2.1 program, and find that the Log Kow of the target compounds with the high insecticidal activities most ranged in 2.90–3.50.

In previous studies, we found that compound **II** showed remarkable insecticidal activities against *A. gossypii* (Xu et al. 2017). So, *A. gossypii* was selected as the target for further evaluation, and the results are listed in Table 2. All the compounds exhibited excellent insecticidal activities against *A. gossypii* at the concentration of 200 mg/

Table 1. Insecticidal activity of compounds II against third-instar nymphs of *Hyalopterus pruni* Geoffroy at the concentration of 200 mg/L.

Compd.	Log K_{ow}	DN/TN	CM (%)	Compd.	Log K_{ow}	DN/TN	CM (%)
CK	–	0/68	0	IIc-02	3.00	13/22	59.1
Guadipyr[a]	2.95	76/78	97.4	IIc-03	2.60	42/74	56.8
IIa-01	2.96	28/52	53.9	IIc-04	3.04	100/118	84.8
IIa-02	2.59	42/114	36.8	IIc-05	3.25	75/95	79.0
IIa-03	3.27	32/93	34.4	IId-01	2.75	21/29	72.4
IIa-04	3.13	30/40	75.0	IId-02	3.44	45/45	100
IIa-05	3.02	26/26	100	IId-03	2.92	30/53	56.6
IIa-06	3.81	15/33	45.5	IId-04	3.02	43/76	56.6
IIa-07	3.11	10/44	22.7	IId-05	4.19	15/27	55.6
IIa-08	5.03	27/133	20.3	IIe-01	2.73	46/56	82.1
IIb-01	2.60	23/35	65.7	IIe-02	3.49	31/49	63.3
IIb-02	3.05	16/19	84.2	IIe-03	2.97	57/59	96.6
IIb-03	3.88	81/108	75.0	IIe-04	3.18	22/26	84.6
IIc-01	2.31	37/45	82.2	IIe-05	4.20	25/69	36.2

CK(dimethylformamide and Triton X-100 mixed solution without compounds);
aGuadipyr was used at 12.5 mg/L; DN(Death number), TN (Total worm number), CM (Corrected mortality)

Table 2. LC50 (mg/L) of the compounds II against *Aphis gossypii* Glover.

Compd.	LC_{50}(mg/L)	95%FL	Compd.	LC_{50}(mg/L)	95%FL
Imidacloprid	0.21	0.14-0.27	IIc-03	0.68	0.11-1.26
IIa-01	0.62	0.23-1.08	IIc-04	1.14	0.22-2.20
IIa-02	0.28	0.05-0.69	IIc-05	1.12	0.56-1.68
IIa-03	4.70	0.24-10.72	IId-01	0.12	0.04-0.25
IIa-04	1.04	0.10-2.48	IId-02	0.38	0.01-0.89
IIa-05	19.59	13.56-25.55	IId-03	0.75	0.25-1.26
IIa-06	2.53	1.72-3.54	IId-04	0.33	0.004-0.79
IIa-07	25.95	11.44-40.00	IId-05	1.65	0.51-3.62
IIa-08	1.01	0.52-1.59	IIe-01	0.61	0.24-1.18
IIb-01	0.49	0.001-1.48	IIe-02	0.80	0.001-2.18
IIb-02	3.09	1.31-5.78	IIe-03	0.86	0.47-7.04
IIb-03	1.56	0.79-2.41	IIe-04	0.48	0.13-0.89
IIc-01	0.09	0.001-0.50	IIe-05	3.01	1.91-4.36
IIc-02	0.03	0.001-0.15			

L, particularly, compounds IIa-02, IId-04 and IId-02 showed the same insecticidal activities as Imidacloprid with the LC_{50} values of 0.28 mg/L, 0.38 mg/L and 0.33 mg/L, respectively. Compounds IIc-01, IIc-02and IId-01 indicated the best insecticidal activities with the LC_{50} values of 0.09 mg/L, 0.03 mg/L and 0.12 mg/L, respectively, higher than Imidacloprid (LC_{50}: 0.21 mg/L). The structure-activity relationship of the target compounds reveal that when the fluorine atom substituted the hydrogen atom on benzene ring of R, the insecticidal activities display *p*-F > *m-F* and difluoro-substituted > single fluoro-substituted. As R is the same group, the compound with R_1 and R_2 being the minor group, such as H, CH_3, *i*-Pr and *n*-Pr,.have the better insecticidal activity against *A. gossypii*.

3. Conclusion

In summary, a series of novel hydrocarbylidene nitrohydrazinecarboximidamides containing fluorine atom were designed and synthesized, and their insecticidal activities against *A. gossypii* and *H. pruni* were detected. The results show that most compounds have moderate to high insecticidal activities against *H.pruni* at the concentration of

200 mg/L, the Log K_{ow} of the target compounds play an important role in insecticidal activities, the optimum value ranged in 2.90–3.50. And all the compounds exhibit excellent insecticidal activities against *A.gossypii*, in particular, compounds IIa-02, IId-02, IId-04, IIc-01, IIc-02 and IId-01 show 0.6 − 7 times insecticidal activities as Imidacloprid. The analysis of structure-activity relationship indicates that the compounds with difluoro-substituted benzene ring have more potent insecticidal activities than the single fluoro-substituted compounds.

Disclosure statement

No potential conflict of interest was reported by the authors.

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