Journal Pre-proofs

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PII: S0960-894X(20)30098-6
DOI: https://doi.org/10.1016/j.bmcl.2020.127028
Reference: BMCL 127028

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 3 January 2020
Revised Date: 5 February 2020
Accepted Date: 11 February 2020

Please cite this article as: Chen, J., Wei, C., Wu, S., Luo, Y., Wu, R., Hu, D., Song, B., Novel 1,3,4-oxadiazole thioether derivatives containing flexible-chain moiety: Design, synthesis, nematocidal activities, and pesticide–likeness analysis, *Bioorganic & Medicinal Chemistry Letters* (2020), doi: https://doi.org/10.1016/j.bmcl.2020.127028

Novel 1,3,4-oxadiazole thioether derivatives containing flexible-chain moiety: Design, synthesis, nematocidal activities, and pesticide–likeness analysis

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ABSTRACT: Seventy-two novel 1,3,4-oxadiazole thioether derivatives containing different flexible-chain moieties were designed and synthesized. The nematicidal activities of all the title compounds were evaluated, and some compounds showed excellent nematicidal activities against citrus nematodes. The compounds **15**, **16**, **18**, **27**, **41**, **42**, **44**, **53**, and **71** had the mortality to citrus nematodes of 92.5, 93.7, 90.3, 91.5, 92.6, 92.8, 93.5, 91.3, and 91.0% at the concentration of 100 mg/L, which were better than the control agent of avermectin (85.9%). After the test concentration was reduced to 50 mg/L, the nematicidal activities of the compounds **16**, **42**, **44**, **53**, and **71** were still superior to avermectin (65.1%), with the mortality of 72.3, 71.3, 70.6, 71.1, and 73.9%, respectively. The LC_{50} values of the compounds **16**, **42**, **44**, **53**, and **71** were 16.3, 18.8, 20.8, 17.5, and 14.7 mg/L, which were better than the commercial positive control agent of avermectin (24.8 mg/L). Meanwhile, the qualitative and quantitative analysis of the pesticide-likeness shows that compound **71** exhibits the potential insecticide-likeness. This work indicates that novel 1,3,4-oxadiazole thioether derivatives containing flexible-chains deserve further research as potential nematicides to protect citrus crops in the future.

Keywords: 1,3,4-Oxadiazole, Nematicidal activity, Thioether derivatives, Flexible-chain, Pesticide-likeness

The citrus nematodes (*Tylenchulus semipenetrans* Cobb) are an important plant-parasitic nematode with the high degree of specialization and a small range of host plants, which mainly harm to citrus plants.[1,2] There are many obvious manifestations that serve as the warning when the roots of citrus tree were attacked, such as, the yellowing of the leaves, short planting, poor growth, and falling flowers and fruits.[3,4] What is more, the fruit cannot bear and the tree may be die when the trees are seriously endangered by the citrus nematodes, which caused huge losses for the citrus production.[5]

In the past ten years, the application of chemical nematicides has played an extreme important role in the control of nematodes, which greatly reduce the economic losses caused by the nematodes.[6] However, the problems of serious environmental pollution and drug resistance are raised with the long-term reuse of the high toxic nematicides, such as dibromochloropropane, methyl bromide, oxamide, and aldicarb.[7] Meanwhile, many high toxic nematicides are restricted or banned in recent years as people become more aware of human health and environmental protection.[8] Therefore, to meet the requirements of modern agricultural development, many researches were conducted to discover and develop the nematicides with the merits of high-efficiency, low-toxicity, and environmentally friendly.[9]

The five-membered heterocyclic compounds play a very important role in the development of nematicides. For example, the tioxazafen and fluensulfone (**Fig. 1A**) containing the 1,2,4-oxadiazole or thiazole ring have been successfully marketed as new generation nematicides.[10,11] As one of the most important members of the five-membered heterocyclic family, many varieties of derivatives were synthesized based on the 1,3,4-oxadiazole ring, and they have a broad spectrum of the biological activities, such as, nematicidal,[12] antifungal,[13] antibacterial,[14] insecticidal.[15]

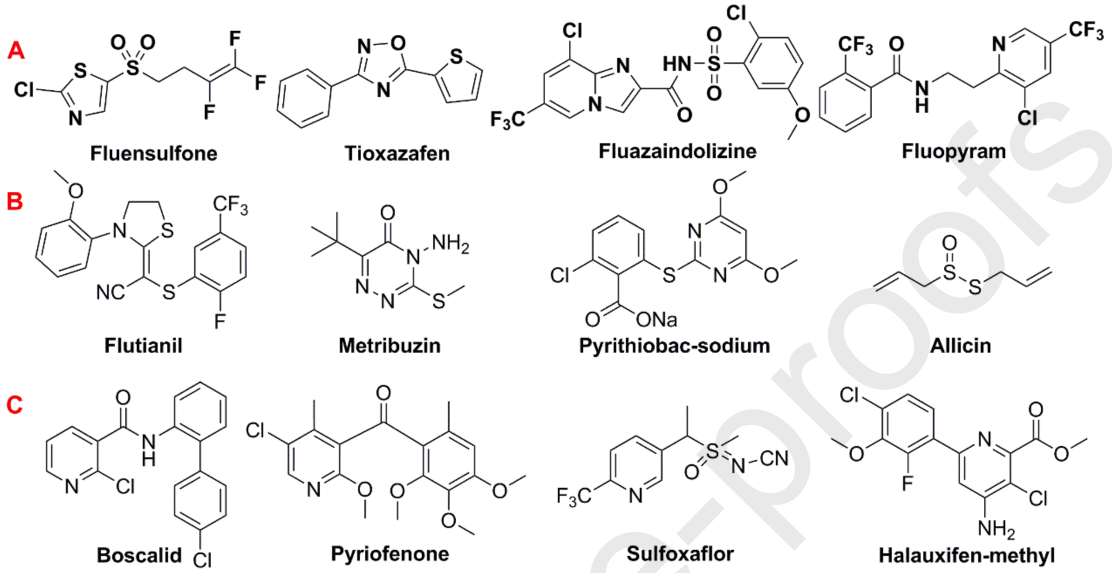


Fig. 1. The structures of the commercial pesticides. (A) The structures of the commercial nematicides. (B) The structures of the commercial pesticides containing thioether groups. (C) The structures of the commercial pesticides containing pyridine groups.

The thioether groups exhibit a broad spectrum of the biological activities, and receive more and more attention from many researchers.[16] The biological activities and the hydrophilicity of the 1,3,4-oxadiazole compounds can be increased by introducing the thioether groups.[17-19] The flutianil, pyrithiobac-sodium, metribuzin, and allicin containing thioether groups (**Fig. 1B**) are the representative commercial pesticides, which play an important role in plant protection.

In our previous research, a series of 1,3,4-oxadiazole thioether derivatives containing the trifluorobutene moiety were designed and synthesized based on the lead compound of fluensulfone, and some compounds showed moderate nematicidal activities against citrus nematodes.[12] Subsequently, a series of 1,3,4-oxadiazole bisthioether derivatives were designed and synthesized through introducing the sulfur atom and methylene group to linked the benzene ring and the 1,3,4-oxadiazole ring, and some compounds show good nematicidal activities against *Caenorhabditis elegans*.[20] In addition, some studies show that biological activity of the pyridine moiety is fully reflected in many pesticides,[21,22] such as boscalid, pyriofenone, sulfoxaflor, and halauxifen-methyl (**Fig. 1C**). In present work, the pyridine ring was used to instead of the benzene ring, and the methylene group connected to the sulfur or oxygen atom was used as the flexible chain to link the pyridine ring and the 1,3,4-oxadiazole ring (**Fig. 2**).

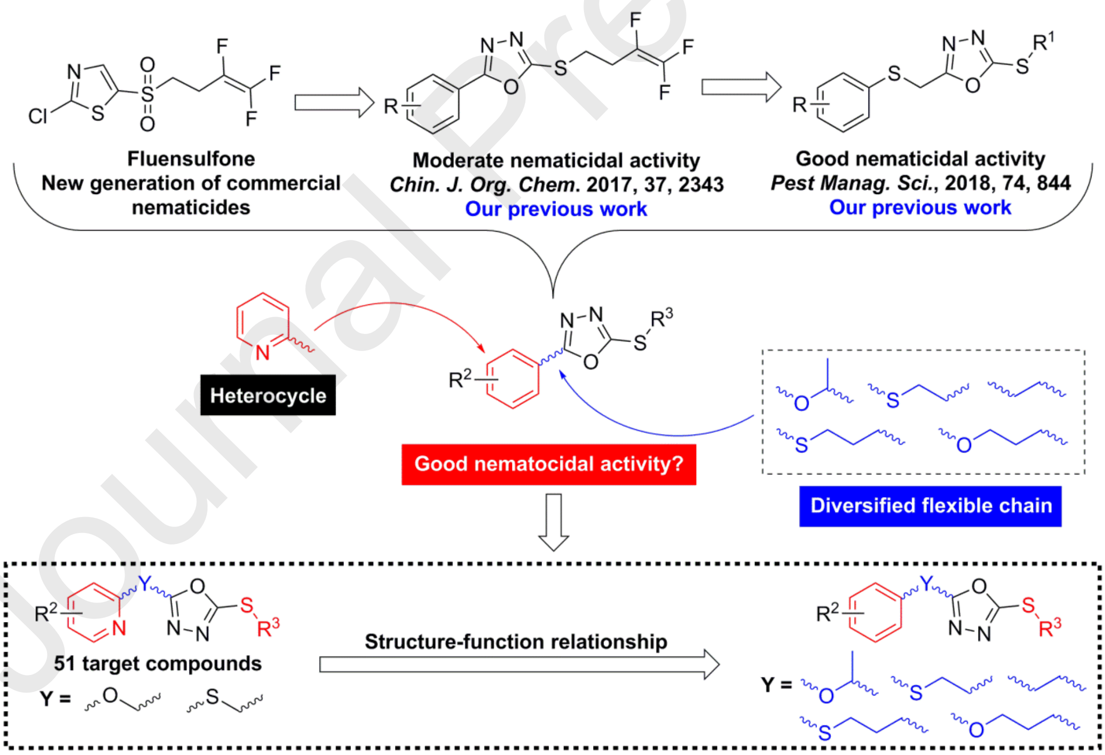


Fig. 2. The design idea of target compounds.

Therefore, the novel 1,3,4-oxadiazole compounds **1–51** containing the different flexible linker were synthesized (Fig. 3 and 4) according to our previously reported method,[12,23] and the structures of all target compounds were characterized by ^{1}H NMR, ^{13}C NMR and HRMS spectra.

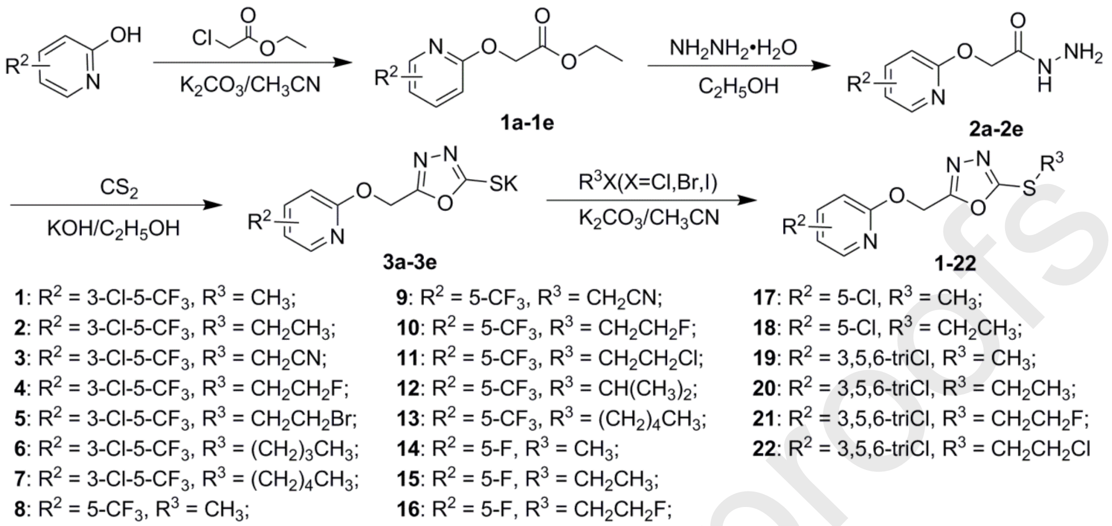


Fig. 3. The synthesis route of target compounds **1-22**.

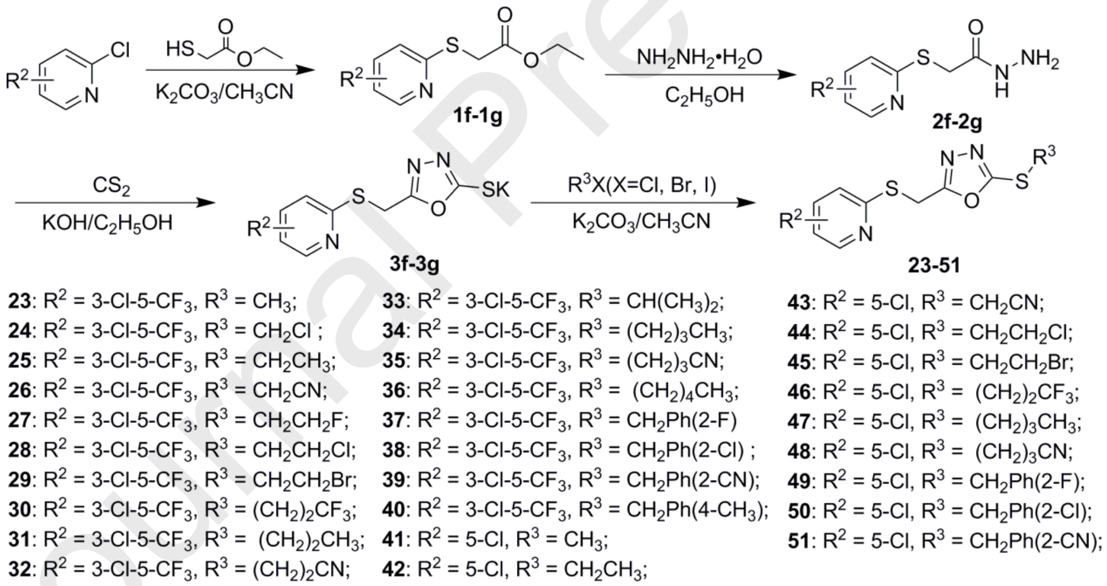


Fig. 4. The synthesis route of target compounds **23-51**.

The nematicidal activities of the target compounds **1–51** were evaluated by reported methods,[12,24] and the commercial nematicide of avermectin was used as the positive control. The nematicidal activities of the compounds **1–51** against citrus nematodes were listed in **Tables 1** and **2**. Some target compounds showed better nematicidal activities compared to positive control agents. For example, The compounds **15**, **16**, **18**, **27**, **41**, **42**, and **44** showed excellent nematicidal activities against citrus nematodes, with the mortality of 92.5, 93.7, 90.3, 91.5, 92.6, 92.8, and 93.5% at the concentration of 100 mg/L, which were better than the control agent of avermectin (85.9%). When the test concentration was reduced to 50 mg/L, some compounds still showed good nematicidal activities against citrus nematodes, which were better than the control agent of avermectin (65.1%). For example, the mortality of the compounds **16**, **42**, and **44** were 72.3, 71.3, and 70.6% against citrus nematodes, respectively.

Table 1. The nematicidal activities of the compounds **1−22** against citrus nematodes.

Compound	R^2	R^3	mortality/%[a]	
			100 mg/L	50 mg/L
1	3-Cl-5-CF_3	CH_3	71.3±1.9	43.0±1.9
2	3-Cl-5-CF_3	CH_2CH_3	71.6±1.9	40.4±2.1
3	3-Cl-5-CF_3	CH_2CN	64.2±2.5	33.1±2.5
4	3-Cl-5-CF_3	CH_2CH_2F	74.0±1.0	48.7±2.1
5	3-Cl-5-CF_3	CH_2CH_2Br	70.4±1.6	39.1±2.8
6	3-Cl-5-CF_3	$(CH_2)_3CH_3$	50.4±1.8	27.6±0.7
7	3-Cl-5-CF_3	$(CH_2)_4CH_3$	43.1±2.0	27.7±1.3
8	5-CF_3	CH_3	59.8±1.9	29.7±1.1
9	5-CF_3	CH_2CN	43.0±2.3	26.2±2.0
10	5-CF_3	CH_2CH_2F	66.2±1.6	40.5±3.0
11	5-CF_3	CH_2CH_2Cl	63.3±1.4	38.9±1.1
12	5-CF_3	$CH(CH_3)_2$	51.3±1.4	31.3±1.6
13	5-CF_3	$(CH_2)_4CH_3$	33.1±2.0	14.6±1.1
14	5-F	CH_3	82.2±2.3	53.4±3.6
15	5-F	CH_2CH_3	92.5±1.0	69.4±1.2

16	5-F	CH_2CH_2F	93.7±1.4	72.3±0.7
17	5-Cl	CH_3	79.9±1.6	57.6±2.4
18	5-Cl	CH_2CH_3	90.3±1.8	65.2±0.6
19	3,5,6-triCl	CH_3	35.9±1.5	15.7±1.5
20	3,5,6-triCl	CH_2CH_3	47.7±3.1	22.3±0.8
21	3,5,6-triCl	CH_2CH_2F	56.5±2.1	32.7±1.3
22	3,5,6-triCl	CH_2CH_2Cl	45.2±2.6	21.0±1.8
Avermectin[b]	-	-	85.9±2.5	65.1±1.6

[a] The average of three tests.
[b] The commercial nematicide avermectin was used as a positive control.

Table 2. The nematicidal activities of the compounds **23−51** against citrus nematodes.

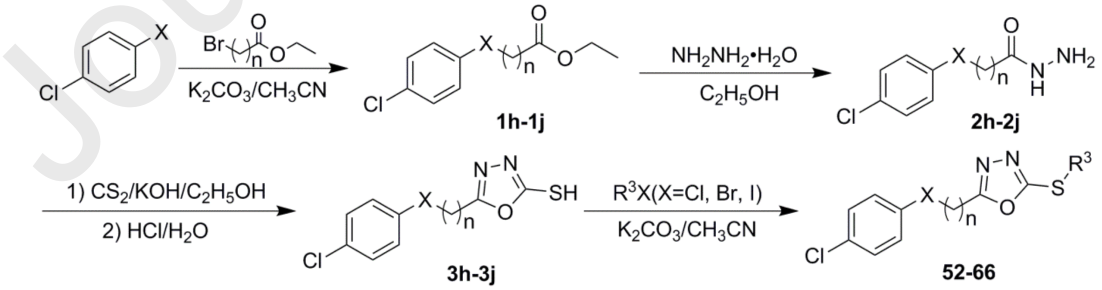
Compound	R^2	R^3	mortality/%[a]	
			100 mg/L	50 mg/L
23	3-Cl-5-CF_3	CH_3	77.9±2.5	46.4±3.8
24	3-Cl-5-CF_3	CH_2Cl	83.7±3.0	54.3±2.8
25	3-Cl-5-CF_3	CH_2CH_3	83.0±2.1	51.0±3.1
26	3-Cl-5-CF_3	CH_2CN	71.4±3.1	29.7±1.7
27	3-Cl-5-CF_3	CH_2CH_2F	91.5±3.6	62.7±3.2
28	3-Cl-5-CF_3	CH_2CH_2Cl	89.1±2.6	60.3±1.4
29	3-Cl-5-CF_3	CH_2CH_2Br	85.0±3.3	50.4±2.9
30	3-Cl-5-CF_3	$(CH_2)_2CF_3$	72.0±2.1	30.7±1.8
31	3-Cl-5-CF_3	$(CH_2)_2CH_3$	58.1±2.0	34.6±2.9
32	3-Cl-5-CF_3	$(CH_2)_2CN$	75.2±3.2	23.1±2.3
33	3-Cl-5-CF_3	$CH(CH_3)_2$	54.4±2.8	36.8±3.0
34	3-Cl-5-CF_3	$(CH_2)_3CH_3$	50.9±2.5	25.9±2.7
35	3-Cl-5-CF_3	$(CH_2)_3CN$	48.6±2.9	17.5±2.6
36	3-Cl-5-CF_3	$(CH_2)_4CH_3$	35.2±3.1	14.9±2.1
37	3-Cl-5-CF_3	CH_2Ph(2-F)	18.8±1.8	6.6±1.8
38	3-Cl-5-CF_3	CH_2Ph(2-Cl)	15.4±1.3	6.4±2.0
39	3-Cl-5-CF_3	CH_2Ph(2-CN)	16.3±2.0	5.8±0.9
40	3-Cl-5-CF_3	$CH_2Ph(2-CH_3)$	36.5±2.8	16.4±2.0

41	5-Cl	CH_3	92.6±2.2	64.2±4.1
42	5-Cl	CH_2CH_3	92.8±2.9	71.3±2.6
43	5-Cl	CH_2CN	75.0±3.3	38.2±3.6
44	5-Cl	CH_2CH_2Cl	93.5±2.8	70.6±2.7
45	5-Cl	CH_2CH_2Br	83.3±2.4	62.6±2.2
46	5-Cl	$(CH_2)_2CF_3$	78.5±2.7	41.3±3.2
47	5-Cl	$(CH_2)_3CH_3$	66.0±5.4	33.0±2.7
48	5-Cl	$(CH_2)_3CN$	42.5±2.9	16.6±2.6
49	5-Cl	CH_2Ph(2-F)	28.2±3.1	11.3±3.0
50	5-Cl	CH_2Ph(2-Cl)	22.6±3.2	10.1±2.3
51	5-Cl	CH_2Ph(2-CN)	26.1±2.4	12.1±1.7
Avermectin[b]	-	-	85.9±2.5	65.1±1.6

[a] The average of three tests.

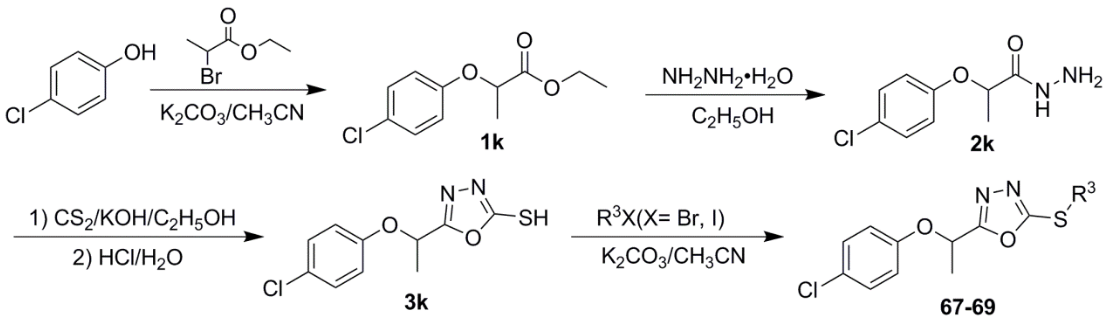
[b] The commercial nematode avermectin was used as a positive control.

The preliminary structure-activity relationship of the compounds **1–51** showed that R^3 is the small alkyl chain or halogen-substituted alkyl chain, the compound has a good nematicidal activity. On the contrary, the large groups, such as benzyl and pentyl, are not conducive to improving the nematicidal activity of the compound. Therefore, the compounds **52–72** were designed and synthesized based on the structure-activity relationship (**Fig. 5, 6** and **7**).



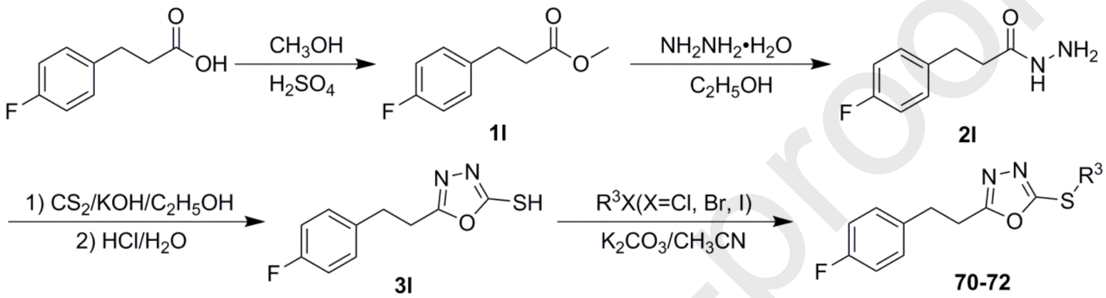
52: R^3 = CH_3, X = S, n = 2;
53: R^3 = CH_2CH_3, X = S , n = 2;
54: R^3 = $(CH_2)_2CH_3$, X = S, n = 2;
55: R^3 = $CH(CH_3)_2$, X = S, n = 2;
56: R^3 = $CH_2CH(CH_3)_2$, X = S, n = 2;
57: R^3 = CH_3, X = S, n = 3;
58: R^3 = CH_2CH_3, X = S, n = 3;
59: R^3 = CH_2CH_2F, X = S, n = 3;
60: R^3 = CH_2CH_2Cl, X = S, n = 3;
61: R^3 = CH_2CH_2Br, X = S, n = 3;
62: R^3 = $(CH_2)_2CH_3$, X = S, n = 3;
63: R^3 = $CH(CH_3)COCH_3$, X = S, n = 3;
64: R^3 = CH_3, X = O, n = 3;
65: R^3 = CH_2CH_3, X = O, n = 3;
66: R^3 = $(CH_2)_2CH_3$, X = O, n = 3;

Fig. 5. The synthesis route of target compounds **52−66**.



67: $R^3 = CH_3$, X = O; **68**: $R^3 = CH_2CH_2F$, X = O; **69**: $R^3 = CH_2CH_2Cl$, X = O;

Fig. 6. The synthesis route of target compounds **67−69**.



70: $R^3 = CH_3$; **71**: $R^3 = CH_2CH_3$; **72**: $R^3 = (CH_2)_2CH_3$

Fig. 7. The synthesis route of target compounds **70−72**.

The nematicidal activities of compounds **52−72** is shown in **Tables 3** and **4**. The compounds **53** and **71** showed excellent nematicidal activities against citrus nematodes, with the mortality of 91.3 and 91.0% at the concentration of 100 mg/L, which were better than the control agent of avermectin (85.9%). When the test concentration was reduced to 50 mg/L, the compounds **53** and **71** still showed good nematicidal activities against citrus nematodes, with the mortality of 71.1 and 73.9%, respectively.

Table 3. The nematicidal activities of the compounds **52−66** against citrus nematodes.

Compound	R^3	X	n	mortality/%[a]	
				100 mg/L	50 mg/L
52	CH_3	S	2	82.6±5.1	67.6±3.5
53	CH_2CH_3	S	2	91.3±1.7	71.1±2.1
54	$(CH_2)_2CH_3$	S	2	84.1±3.3	65.2±5.8

55	$CH(CH_3)_2$	S	2	80.5±3.3	36.1±2.9
56	$CH_2CH(CH_3)_2$	S	2	73.7±3.6	31.6±5.0
57	CH_3	S	3	77.4±4.3	57.1±6.5
58	CH_2CH_3	S	3	83.9±3.3	64.9±7.0
59	CH_2CH_3F	S	3	86.5±4.2	61.3±3.8
60	CH_2CH_3Cl	S	3	85.1±3.8	64.1±3.7
61	CH_2CH_3Br	S	3	82.3±4.3	62.7±2.2
62	$(CH_2)_2CH_3$	S	3	78.1±3.2	35.7±2.8
63	$CH(CH_3)COCH_3$	S	3	63.1±2.7	43.4±3.8
64	CH_3	O	3	79.4±4.8	63.9±3.2
65	CH_2CH_3	O	3	89.6±4.1	68.7±5.8
66	$(CH_2)_2CH_3$	O	3	82.6±5.1	67.6±3.5
Avermectin[b]	-	-	-	85.9±2.5	65.1±1.6

[a] The average of three tests.

[b] The commercial nematicide avermectin was used as a positive control.

Table 4. The nematicidal activities of the compounds **67−72** against citrus nematodes.

Compound	R^3	mortality/%[a]	
		100 mg/L	50 mg/L
67	CH_3	78.0±4.4	57.3±7.1
68	CH_2CH_2F	89.4±2.1	50.7±6.8
69	CH_2CH_2Cl	81.3±4.9	48.2±1.4
70	CH_3	85.0±3.4	68.1±7.1
71	CH_2CH_3	91.0±2.7	73.9±4.7
72	$(CH_2)_2CH_3$	86.4±4.7	68.0±2.6
Avermectin[b]	-	85.9±2.5	65.1±1.6

[a] The average of three tests.

[b] The commercial nematicide avermectin was used as a positive control.

The some LC_{50} values of compounds **1−72** were tested to further evaluate the nematicidal activities (**Table 5**). The compounds **16**, **42**, **44**, **53**, and **71** showed excellent nematicidal activities, with the LC_{50} of 16.3, 18.8, 20.8, 17.5, and 14.7 mg/L, respectively, which were superior to the control agent of avermectin (24.8

mg/L). Meanwhile, the nematicidal activities of the compounds **16** and **71** were also evaluated at different times and concentrations (**Fig. 8**). The nematicidal activities of the compounds **16** and **71** against citrus nematodes were lower than that of the avermectin at 1 and 10 h at the concentration of 100 mg/L, but after 10 h, the nematicidal activities of the compounds **16** and **71** were better than that of the avermectin. At the same time, the nematicidal activities of the compounds **16** and **71** against citrus nematodes were consistently higher than that of avermectin at 48 h at different concentrations.

Table 5. The LC_{50} of some compounds against citrus nematodes.

Compound	LC_{50}/mg/L[a]	Compound	LC_{50}/mg/L[a]
15	23.9±3.9	**44**	20.8±7.4
16	16.3±1.3	**53**	17.5±5.2
42	18.8±3.1	**71**	14.7±2.2
Avermectin[b]	24.8±5.7	-	-

[a] The average of three tests.
[b] The commercial nematicide avermectin was used as a positive control.

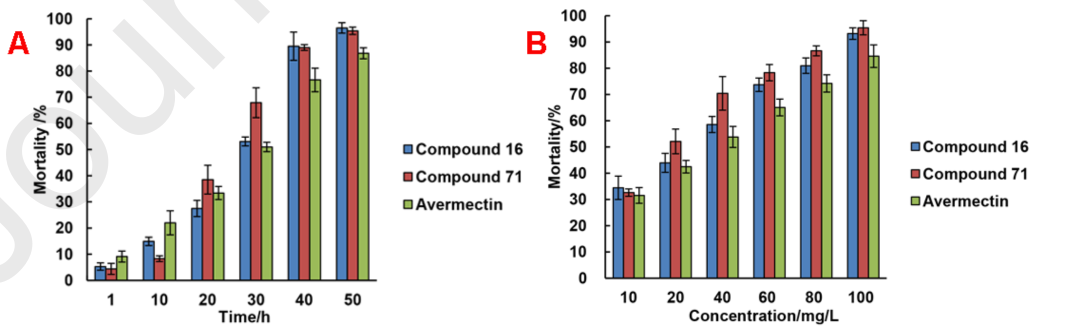


Fig. 8 (A) The changes of the nematicidal activities for the compounds **16** and **17** at different times when the concentration was 100 mg/L. (B) The changes of the nematicidal activities for the compounds **16** and **17** at different concentrations when the time was 48 h.

The overall structure-activity relationship of the compounds **1–72** against citrus nematodes at the concentration of 100 mg/L is as follows: (a) When R^2 = -Cl, and R^3

= $-CH_3$, the nematicidal activities of those compounds decreased gradually with Y = $-SCH_2-$, $-SCH_2CH_2-$, $-OCH_2-$, $-OCH_2CH_2CH_2-$, and $-SCH_2CH_2CH_2-$. Such as the nematicidal activities of the compounds **41** (Y = $-SCH_2-$, R^2 = -Cl, R^3 = $-CH_3$) > **52** (Y = $-SCH_2CH_2-$, R^2 = -Cl, R^3 = $-CH_3$) > **17** (Y = $-OCH_2-$, R^2 = -Cl, R^3 = $-CH_3$) > **64** (Y = $-OCH_2CH_2CH_2-$, R^2 = -Cl, R^3 = $-CH_3$) > **57** (Y = $-SCH_2CH_2CH_2-$, R^2 = -Cl, R^3 = $-CH_3$). (b) When R^2 and Y are unchanged, the nematicidal activities of those compounds with R^3 = $-CH_3$ is less the compounds with R^3 = $-CH_2CH_3$. Such as the nematicidal activities of the compounds **18** (Y = $-OCH_2-$, R^2 = -Cl, R^3 = $-CH_2CH_3$) > **17** (Y = $-OCH_2-$, R^2 = -Cl, R^3 = $-CH_3$). (c) If R^2 and Y have not changed, the nematicidal activities of those compounds can be improved when the R^3 is ethyl, and a H atom on ethyl is substituted by a F atom. such as the nematicidal activities of the compounds **27** (Y = $-SCH_2-$, R^2 = 3-Cl-5-CF_3, R^3 = $-CH_2CH_2F$) > **25** (Y = $-SCH_2-$, R^2 = -3-Cl-5-CF_3, R^3 = $-CH_2CH_3$). In general, changes in the flexible chains (Y = $-SCH_2-$, $-SCH_2CH_2-$, $-OCH_2-$, $-OCH_2CH_2CH_2-$, or $-OCH_2CH_2CH_2-$) have little effect on the nematicidal activities of those compounds. However, the changes of the substituents R^2 and R^3 can significantly affect the nematicidal activities of those compounds. Meanwhile, when the para-position of those compounds are substituted by a F or Cl atom, and R^3 are substituted by a short-chain alkyl chain containing an electronegative atom, those are beneficial to the improvement of the nematicidal activities.

The platform named Insecticide Physicochemical-properties Analysis Database (InsectiPAD) (http://chemyang.ccnu.edu.cn/ccb/database/InsectiPAD/), which covers

495 approved insecticides and over 22,200 related physicochemical properties, was used to evaluate the insecticide-likeness of the compound **71** and positive control avermectin based on previously reported methods.[25,26] The insecticide-likeness qualitative and quantitative analysis of the compound **71** and positive control avermectin were illustrated in **Fig. 9**. The scores of Relative drug likelihood (RDL),[27] Quantitative estimate of insecticide-likeness (QEI),[26] Gaussian scoring function (GAU),[28] for the avermectin (**Fig.9A**) and compound **71** (**Fig.9B**) and were 1.884, 0.112, 1.259, and 1.632, 0.751, 6.027, respectively. The values of molecular weight (MW), log of the octanol−water partition coefficient (ALogP), number of hydrogen bond acceptors (nHBAcc), number of hydrogen bond donors (nHBDon), number of rotatable bonds (nRotB), number of aromatic rings (nAromBond) for the compound **71** were 220-320, 1-3, 2, 0, 4-6, 10-15, respectively, which coincide with Lipinski's Ro5 approach.[29-31]

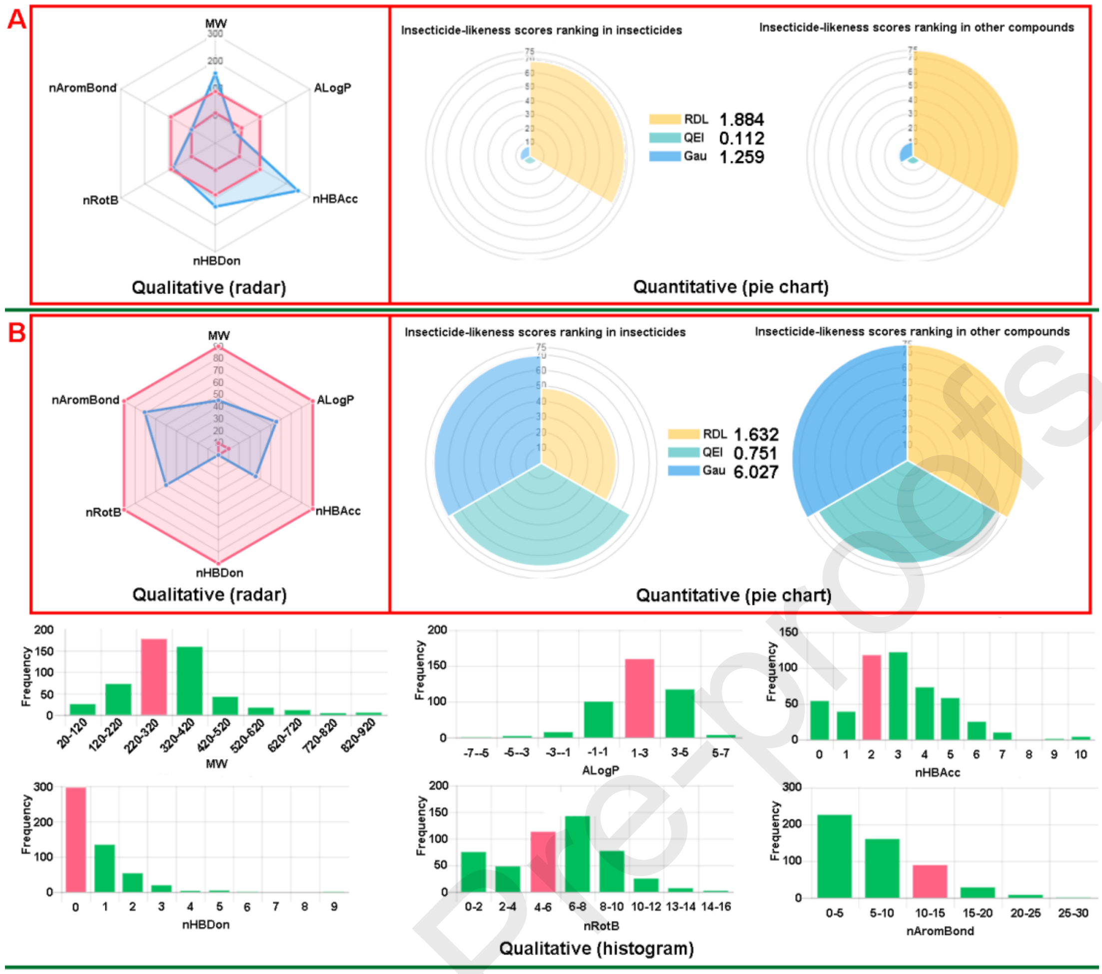


Fig. 9 (A) The insecticide-likeness qualitative and quantitative analysis of the commercial nematicide avermectin. (B) The insecticide-likeness qualitative and quantitative analysis of the compound **71**. RDL, Relative drug likelihood, QEI, Quantitative estimate of insecticide-likeness, GAU, Gaussian scoring function, MW, molecular weight, ALogP, log of the octanol-water partition coefficient, nHBAcc, number of hydrogen bond acceptors, nHBDon, number of hydrogen bond donors, nRotB, number of rotatable bonds, nAromBond, number of aromatic rings.

It can be known from the analysis of insecticide-likeness that the avermectin has lower QEI (0.112) and GAU (1.259), but it has a higher RDL (1.884), which may be caused by the characteristics of the avermectin (large molecular weight, lower AlogP and nAromBond, high nRotB, nHBDon, and nHBAcc). Meanwhile, the compound **71** exhibits potential insecticide-likeness, with the RDL, QEI, and GAU of 1.632, 0.751, 6.027, respectively, which may be determined by the better AlogP, nAromBond, and nRotB.

In summary, seventy-two novel 1,3,4-oxadiazole thioether derivatives containing flexible-chain moieties were designed and synthesized. The results of the nematicidal activity assay showed that compounds **16**, **42**, **44**, **53**, and **71** had the better nematicidal activities against citrus nematodes than the positive control agent of avermectin. The structure-activity relationship of the compounds was analyzed and the compound **71** exhibits the potential insecticide-likeness. This work demonstrates that novel 1,3,4-oxadiazole sulfide derivatives containing flexible chain moieties have the potential to protect citrus trees, and deserve further consideration in future research.

Acknowledgments

The authors are grateful to the National Key Research and Development Program of China (2018YFD0200100) and National Natural Science Foundation of China (No. 21672044) for supporting the project.

Abrreviations

LC_{50}, Median lethal concentration, RDL, Relative drug likelihood, QEI, Quantitative estimate of insecticide-likeness, GAU, Gaussian scoring function, MW, molecular weight, ALogP, log of the octanol-water partition coefficient, nHBAcc, number of hydrogen bond acceptors, nHBDon, number of hydrogen bond donors, nRotB, number of rotatable bonds, nAromBond, number of aromatic rings.

Declaration of interest

The authors declare no competing financial interest.

Supporting information

The Materials and Methods of this article can be found online at https://doi.org/.

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Declaration of interests

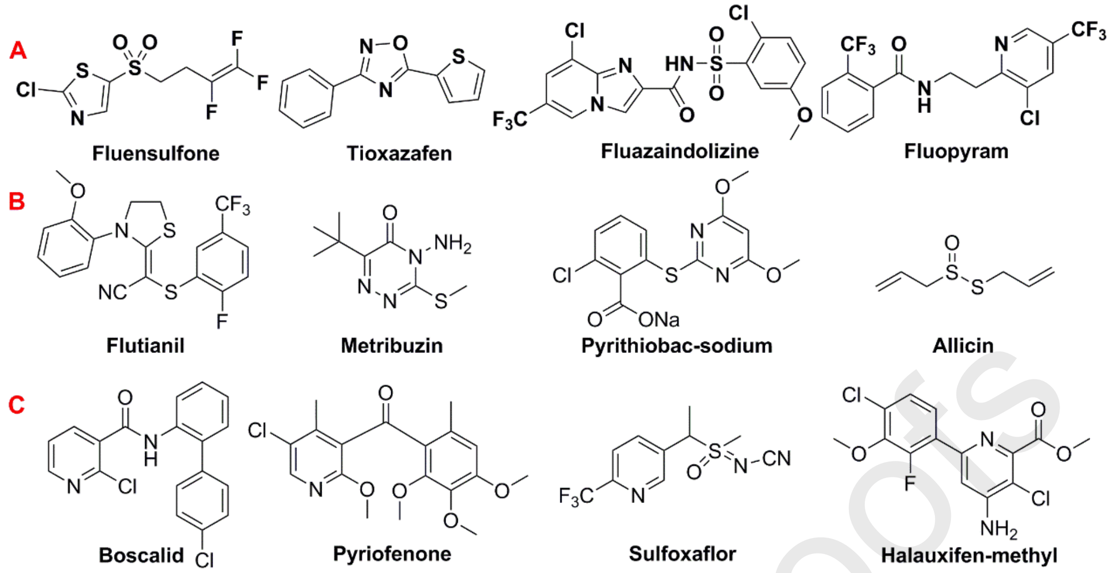
☑ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

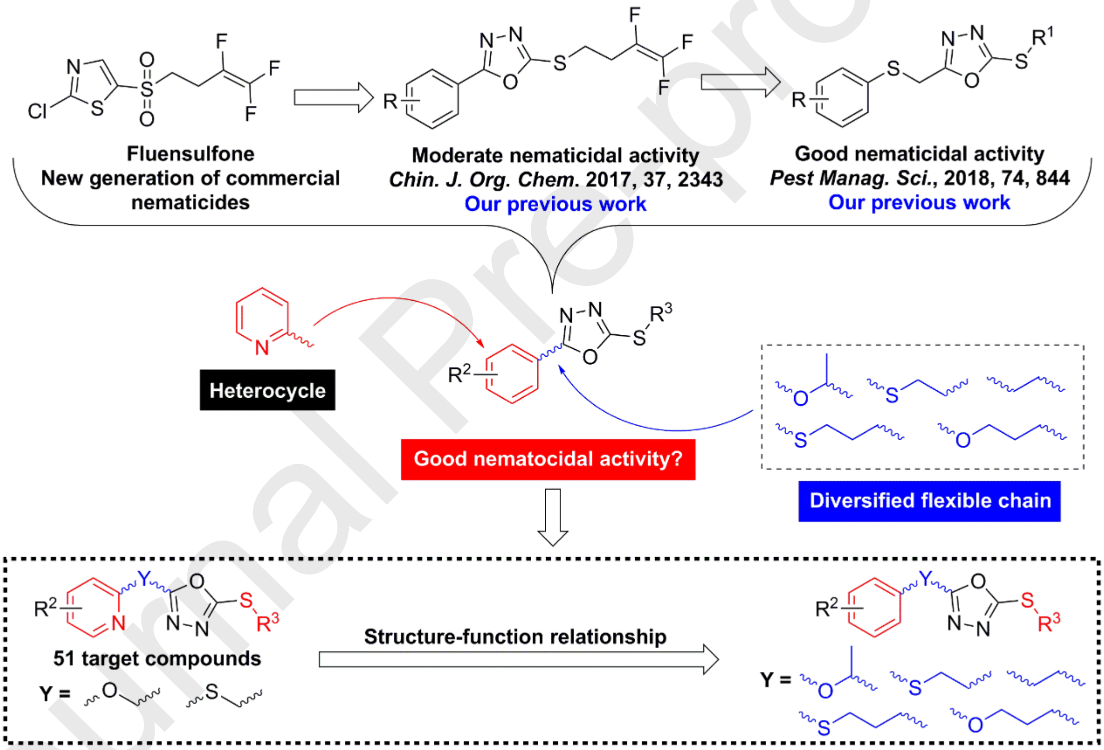
32.

1. Seventy-two 1,3,4-oxadiazole thioether derivatives containing flexible-chain moieties were designed and synthesized.
2. The LC_{50} values of the compounds 16, 42, 44, 53, and 71 were 16.3, 18.8, 20.8, 17.5, and 14.7 mg/L.
3. The structure-activity relationship of the series of the compounds was analyzed.
4. The pesticide-likeness analysis shows that the compound **71** exhibits the potential insecticide-likeness.

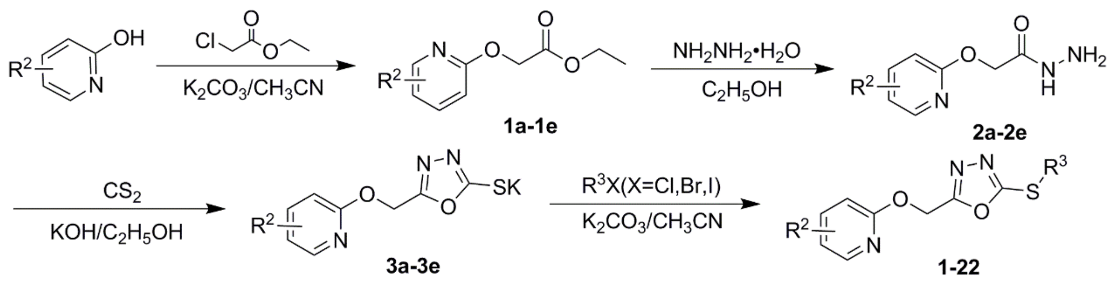
33.


A
Fluensulfone
Tioxazafen
Fluazaindolizine
Fluopyram
B
Flutianil
Metribuzin
Pyrithiobac-sodium
Allicin
C
Boscalid
Pyriofenone
Sulfoxaflor
Halauxifen-methyl

34.

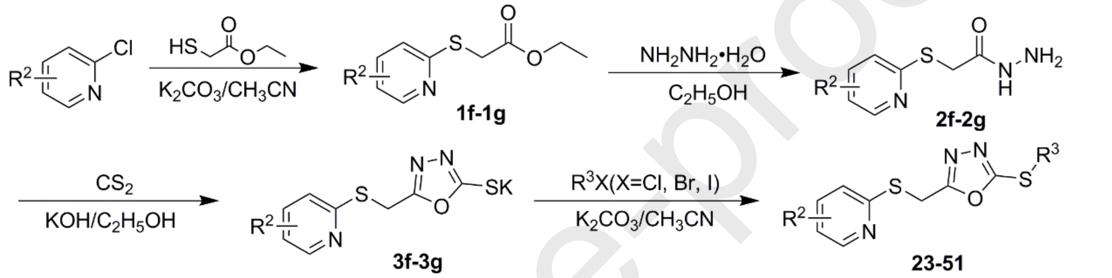

Fluensulfone
New generation of commercial nematicides
Moderate nematicidal activity
Chin. J. Org. Chem. 2017, 37, 2343
Our previous work
Good nematicidal activity
Pest Manag. Sci., 2018, 74, 844
Our previous work
Heterocycle
Good nematocidal activity?
Diversified flexible chain
51 target compounds
Structure-function relationship

35.



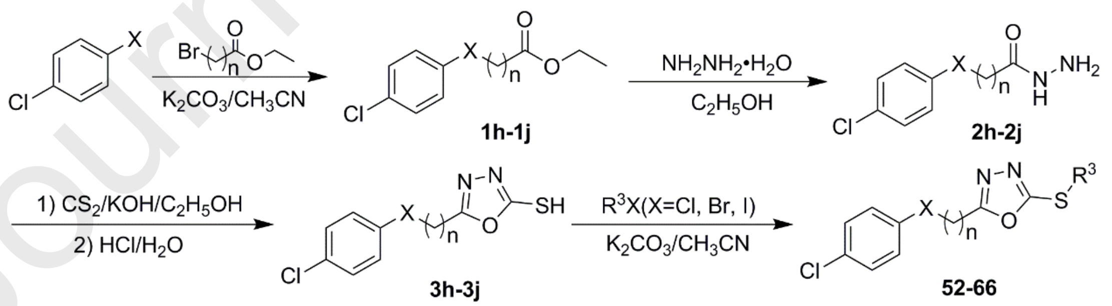
1: R^2 = 3-Cl-5-CF_3, R^3 = CH_3;
2: R^2 = 3-Cl-5-CF_3, R^3 = CH_2CH_3;
3: R^2 = 3-Cl-5-CF_3, R^3 = CH_2CN;
4: R^2 = 3-Cl-5-CF_3, R^3 = CH_2CH_2F;
5: R^2 = 3-Cl-5-CF_3, R^3 = CH_2CH_2Br;
6: R^2 = 3-Cl-5-CF_3, R^3 = $(CH_2)_3CH_3$;
7: R^2 = 3-Cl-5-CF_3, R^3 = $(CH_2)_4CH_3$;
8: R^2 = 5-CF_3, R^3 = CH_3;
9: R^2 = 5-CF_3, R^3 = CH_2CN;
10: R^2 = 5-CF_3, R^3 = CH_2CH_2F;
11: R^2 = 5-CF_3, R^3 = CH_2CH_2Cl;
12: R^2 = 5-CF_3, R^3 = $CH(CH_3)_2$;
13: R^2 = 5-CF_3, R^3 = $(CH_2)_4CH_3$;
14: R^2 = 5-F, R^3 = CH_3;
15: R^2 = 5-F, R^3 = CH_2CH_3;
16: R^2 = 5-F, R^3 = CH_2CH_2F;
17: R^2 = 5-Cl, R^3 = CH_3;
18: R^2 = 5-Cl, R^3 = CH_2CH_3;
19: R^2 = 3,5,6-triCl, R^3 = CH_3;
20: R^2 = 3,5,6-triCl, R^3 = CH_2CH_3;
21: R^2 = 3,5,6-triCl, R^3 = CH_2CH_2F;
22: R^2 = 3,5,6-triCl, R^3 = CH_2CH_2Cl

36.



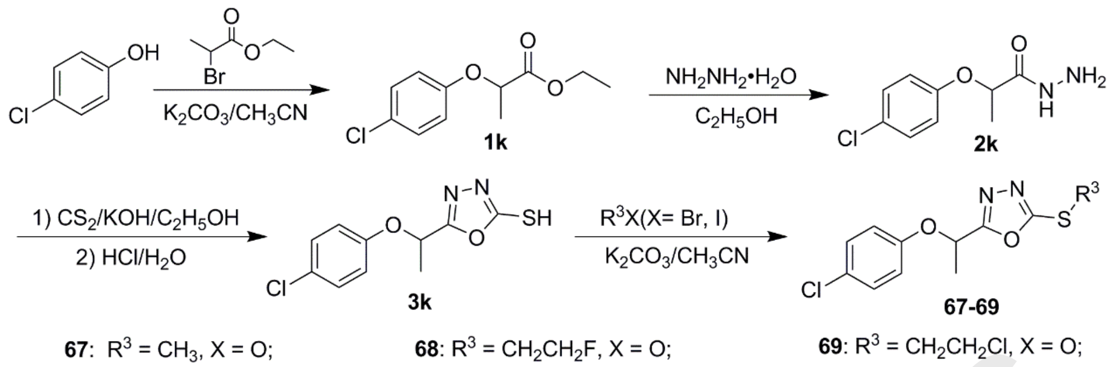
23: R^2 = 3-Cl-5-CF_3, R^3 = CH_3;
24: R^2 = 3-Cl-5-CF_3, R^3 = CH_2Cl ;
25: R^2 = 3-Cl-5-CF_3, R^3 = CH_2CH_3;
26: R^2 = 3-Cl-5-CF_3, R^3 = CH_2CN;
27: R^2 = 3-Cl-5-CF_3, R^3 = CH_2CH_2F;
28: R^2 = 3-Cl-5-CF_3, R^3 = CH_2CH_2Cl;
29: R^2 = 3-Cl-5-CF_3, R^3 = CH_2CH_2Br;
30: R^2 = 3-Cl-5-CF_3, R^3 = $(CH_2)_2CF_3$;
31: R^2 = 3-Cl-5-CF_3, R^3 = $(CH_2)_2CH_3$;
32: R^2 = 3-Cl-5-CF_3, R^3 = $(CH_2)_2CN$;
33: R^2 = 3-Cl-5-CF_3, R^3 = $CH(CH_3)_2$;
34: R^2 = 3-Cl-5-CF_3, R^3 = $(CH_2)_3CH_3$;
35: R^2 = 3-Cl-5-CF_3, R^3 = $(CH_2)_3CN$;
36: R^2 = 3-Cl-5-CF_3, R^3 = $(CH_2)_4CH_3$;
37: R^2 = 3-Cl-5-CF_3, R^3 = CH_2Ph(2-F)
38: R^2 = 3-Cl-5-CF_3, R^3 = CH_2Ph(2-Cl) ;
39: R^2 = 3-Cl-5-CF_3, R^3 = CH_2Ph(2-CN);
40: R^2 = 3-Cl-5-CF_3, R^3 = $CH_2Ph(4\text{-}CH_3)$;
41: R^2 = 5-Cl, R^3 = CH_3;
42: R^2 = 5-Cl, R^3 = CH_2CH_3;
43: R^2 = 5-Cl, R^3 = CH_2CN;
44: R^2 = 5-Cl, R^3 = CH_2CH_2Cl;
45: R^2 = 5-Cl, R^3 = CH_2CH_2Br;
46: R^2 = 5-Cl, R^3 = $(CH_2)_2CF_3$;
47: R^2 = 5-Cl, R^3 = $(CH_2)_3CH_3$;
48: R^2 = 5-Cl, R^3 = $(CH_2)_3CN$;
49: R^2 = 5-Cl, R^3 = CH_2Ph(2-F);
50: R^2 = 5-Cl, R^3 = CH_2Ph(2-Cl);
51: R^2 = 5-Cl, R^3 = CH_2Ph(2-CN);

37.

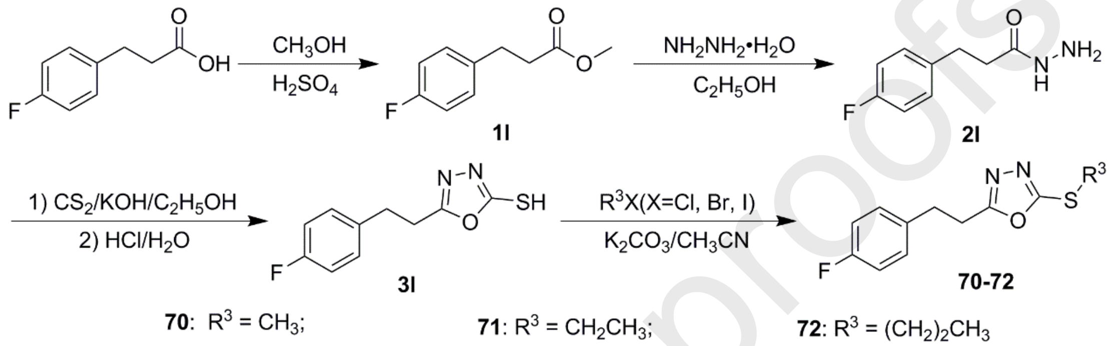


52: R^3 = CH_3, X = S, n = 2;
53: R^3 = CH_2CH_3, X = S , n = 2;
54: R^3 = $(CH_2)_2CH_3$, X = S, n = 2;
55: R^3 = $CH(CH_3)_2$, X = S, n = 2;
56: R^3 = $CH_2CH(CH_3)_2$, X = S, n = 2;
57: R^3 = CH_3, X = S, n = 3;
58: R^3 = CH_2CH_3, X = S, n = 3;
59: R^3 = CH_2CH_2F, X = S, n = 3;
60: R^3 = CH_2CH_2Cl, X = S, n = 3;
61: R^3 = CH_2CH_2Br, X = S, n = 3;
62: R^3 = $(CH_2)_2CH_3$, X = S, n = 3;
63: R^3 = $CH(CH_3)COCH_3$, X = S, n = 3;
64: R^3 = CH_3, X = O, n = 3;
65: R^3 = CH_2CH_3, X = O, n = 3;
66: R^3 = $(CH_2)_2CH_3$, X = O, n = 3;

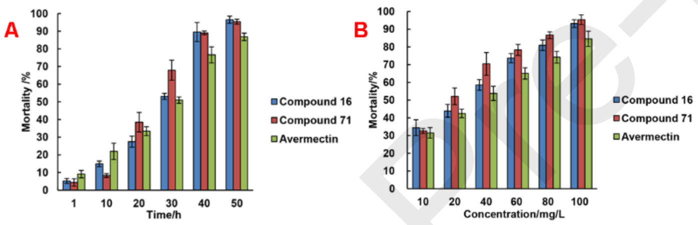
38.


OH
Br
K_2CO_3/CH_3CN
Cl
1k
NH_2NH_2•H_2O
C_2H_5OH
2k
1) $CS_2/KOH/C_2H_5OH$
2) HCl/H_2O
SH
3k
R^3X(X= Br, I)
K_2CO_3/CH_3CN
67-69
67: $R^3 = CH_3$, X = O;
68: $R^3 = CH_2CH_2F$, X = O;
69: $R^3 = CH_2CH_2Cl$, X = O;

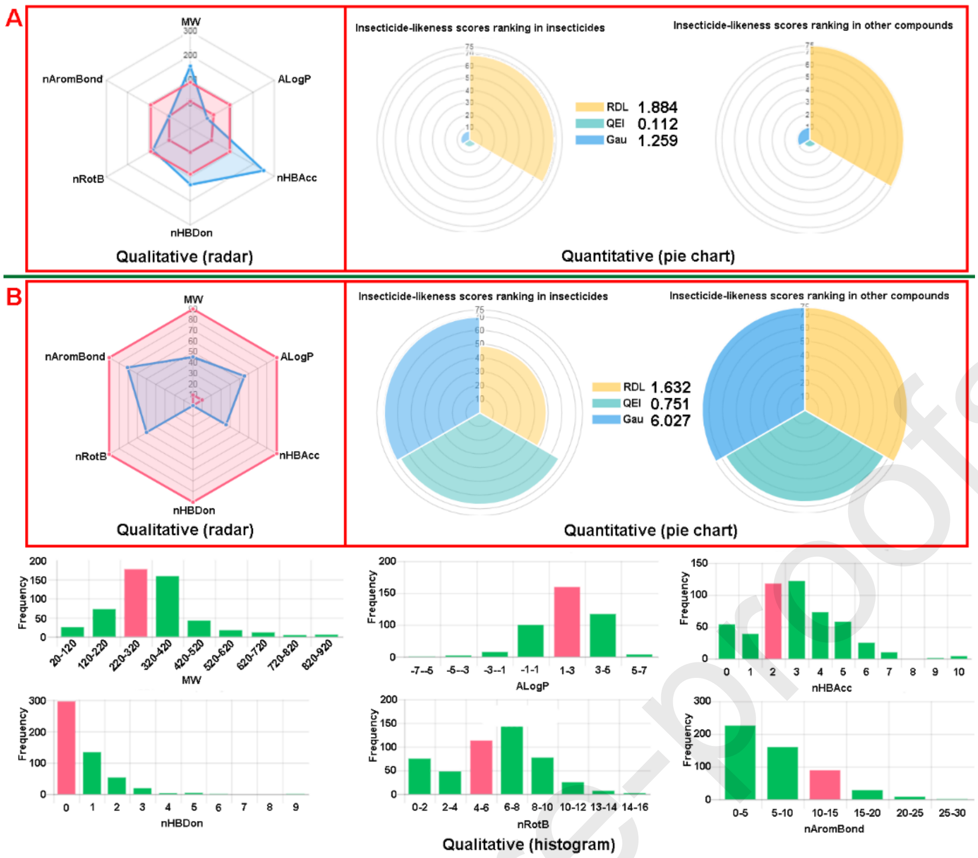
39.


OH
CH_3OH
H_2SO_4
F
1l
NH_2NH_2•H_2O
C_2H_5OH
2l
1) $CS_2/KOH/C_2H_5OH$
2) HCl/H_2O
SH
3l
R^3X(X=Cl, Br, I)
K_2CO_3/CH_3CN
70-72
70: $R^3 = CH_3$;
71: $R^3 = CH_2CH_3$;
72: $R^3 = (CH_2)_2CH_3$

40.


A
B
Mortality/%
Time/h
Concentration/mg/L
Compound 16
Compound 71
Avermectin

41.



42.

Table 1. The nematicidal activities of the compounds **1−22** against citrus nematodes.

Compound	R^2	R^3	mortality/%[a]	
			100 mg/L	50 mg/L
1	3-Cl-5-CF_3	CH_3	71.3±1.9	43.0±1.9
2	3-Cl-5-CF_3	CH_2CH_3	71.6±1.9	40.4±2.1
3	3-Cl-5-CF_3	CH_2CN	64.2±2.5	33.1±2.5
4	3-Cl-5-CF_3	CH_2CH_2F	74.0±1.0	48.7±2.1
5	3-Cl-5-CF_3	CH_2CH_2Br	70.4±1.6	39.1±2.8
6	3-Cl-5-CF_3	$(CH_2)_3CH_3$	50.4±1.8	27.6±0.7
7	3-Cl-5-CF_3	$(CH_2)_4CH_3$	43.1±2.0	27.7±1.3
8	5-CF_3	CH_3	59.8±1.9	29.7±1.1
9	5-CF_3	CH_2CN	43.0±2.3	26.2±2.0
10	5-CF_3	CH_2CH_2F	66.2±1.6	40.5±3.0
11	5-CF_3	CH_2CH_2Cl	63.3±1.4	38.9±1.1
12	5-CF_3	$CH(CH_3)_2$	51.3±1.4	31.3±1.6
13	5-CF_3	$(CH_2)_4CH_3$	33.1±2.0	14.6±1.1

14	5-F	CH_3	82.2±2.3	53.4±3.6
15	5-F	CH_2CH_3	92.5±1.0	69.4±1.2
16	5-F	CH_2CH_2F	93.7±1.4	72.3±0.7
17	5-Cl	CH_3	79.9±1.6	57.6±2.4
18	5-Cl	CH_2CH_3	90.3±1.8	65.2±0.6
19	3,5,6-triCl	CH_3	35.9±1.5	15.7±1.5
20	3,5,6-triCl	CH_2CH_3	47.7±3.1	22.3±0.8
21	3,5,6-triCl	CH_2CH_2F	56.5±2.1	32.7±1.3
22	3,5,6-triCl	CH_2CH_2Cl	45.2±2.6	21.0±1.8
Avermectin[b]	-	-	85.9±2.5	65.1±1.6

[a] The average of three tests.

[b] The commercial nematicide avermectin was used as a positive control.

Table 2. The nematicidal activities of the compounds **23−51** against citrus nematodes.

Compound	R^2	R^3	mortality/%[a]	
			100 mg/L	50 mg/L
23	3-Cl-5-CF_3	CH_3	77.9±2.5	46.4±3.8
24	3-Cl-5-CF_3	CH_2Cl	83.7±3.0	54.3±2.8
25	3-Cl-5-CF_3	CH_2CH_3	83.0±2.1	51.0±3.1
26	3-Cl-5-CF_3	CH_2CN	71.4±3.1	29.7±1.7
27	3-Cl-5-CF_3	CH_2CH_2F	91.5±3.6	62.7±3.2
28	3-Cl-5-CF_3	CH_2CH_2Cl	89.1±2.6	60.3±1.4
29	3-Cl-5-CF_3	CH_2CH_2Br	85.0±3.3	50.4±2.9
30	3-Cl-5-CF_3	$(CH_2)_2CF_3$	72.0±2.1	30.7±1.8
31	3-Cl-5-CF_3	$(CH_2)_2CH_3$	58.1±2.0	34.6±2.9
32	3-Cl-5-CF_3	$(CH_2)_2CN$	75.2±3.2	23.1±2.3
33	3-Cl-5-CF_3	$CH(CH_3)_2$	54.4±2.8	36.8±3.0
34	3-Cl-5-CF_3	$(CH_2)_3CH_3$	50.9±2.5	25.9±2.7
35	3-Cl-5-CF_3	$(CH_2)_3CN$	48.6±2.9	17.5±2.6
36	3-Cl-5-CF_3	$(CH_2)_4CH_3$	35.2±3.1	14.9±2.1

37	3-Cl-5-CF_3	$CH_2Ph(2\text{-}F)$	18.8±1.8	6.6±1.8
38	3-Cl-5-CF_3	$CH_2Ph(2\text{-}Cl)$	15.4±1.3	6.4±2.0
39	3-Cl-5-CF_3	$CH_2Ph(2\text{-}CN)$	16.3±2.0	5.8±0.9
40	3-Cl-5-CF_3	$CH_2Ph(2\text{-}CH_3)$	36.5±2.8	16.4±2.0
41	5-Cl	CH_3	92.6±2.2	64.2±4.1
42	5-Cl	CH_2CH_3	92.8±2.9	71.3±2.6
43	5-Cl	CH_2CN	75.0±3.3	38.2±3.6
44	5-Cl	CH_2CH_2Cl	93.5±2.8	70.6±2.7
45	5-Cl	CH_2CH_2Br	83.3±2.4	62.6±2.2
46	5-Cl	$(CH_2)_2CF_3$	78.5±2.7	41.3±3.2
47	5-Cl	$(CH_2)_3CH_3$	66.0±5.4	33.0±2.7
48	5-Cl	$(CH_2)_3CN$	42.5±2.9	16.6±2.6
49	5-Cl	$CH_2Ph(2\text{-}F)$	28.2±3.1	11.3±3.0
50	5-Cl	$CH_2Ph(2\text{-}Cl)$	22.6±3.2	10.1±2.3
51	5-Cl	$CH_2Ph(2\text{-}CN)$	26.1±2.4	12.1±1.7
Avermectin[b]	-	-	85.9±2.5	65.1±1.6

[a] The average of three tests.

[b] The commercial nematode avermectin was used as a positive control.

Table 3. The nematicidal activities of the compounds **52−66** against citrus nematodes.

Compound	R^3	X	n	mortality/%[a]	
				100 mg/L	50 mg/L
52	CH_3	S	2	82.6±5.1	67.6±3.5
53	CH_2CH_3	S	2	91.3±1.7	71.1±2.1
54	$(CH_2)_2CH_3$	S	2	84.1±3.3	65.2±5.8
55	$CH(CH_3)_2$	S	2	80.5±3.3	36.1±2.9
56	$CH_2CH(CH_3)_2$	S	2	73.7±3.6	31.6±5.0
57	CH_3	S	3	77.4±4.3	57.1±6.5
58	CH_2CH_3	S	3	83.9±3.3	64.9±7.0
59	CH_2CH_3F	S	3	86.5±4.2	61.3±3.8
60	CH_2CH_3Cl	S	3	85.1±3.8	64.1±3.7
61	CH_2CH_3Br	S	3	82.3±4.3	62.7±2.2
62	$(CH_2)_2CH_3$	S	3	78.1±3.2	35.7±2.8
63	$CH(CH_3)COCH_3$	S	3	63.1±2.7	43.4±3.8
64	CH_3	O	3	79.4±4.8	63.9±3.2
65	CH_2CH_3	O	3	89.6±4.1	68.7±5.8

66	$(CH_2)_2CH_3$	O	3	82.6±5.1	67.6±3.5
Avermectin[b]	-	-	-	85.9±2.5	65.1±1.6

[a] The average of three tests.
[b] The commercial nematicide avermectin was used as a positive control.

Table 4. The nematicidal activities of the compounds **67−72** against citrus nematodes.

Compound	R^3	mortality/%[a]	
		100 mg/L	50 mg/L
67	CH_3	78.0±4.4	57.3±7.1
68	CH_2CH_2F	89.4±2.1	50.7±6.8
69	CH_2CH_2Cl	81.3±4.9	48.2±1.4
70	CH_3	85.0±3.4	68.1±7.1
71	CH_2CH_3	91.0±2.7	73.9±4.7
72	$(CH_2)_2CH_3$	86.4±4.7	68.0±2.6
Avermectin[b]	-	85.9±2.5	65.1±1.6

[a] The average of three tests.
[b] The commercial nematicide avermectin was used as a positive control.

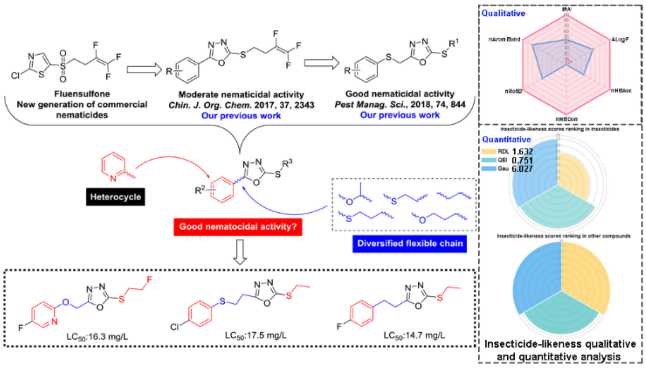
Table 5. The LC_{50} of some compounds against citrus nematodes.

Compound	LC_{50}/mg/L[a]	Compound	LC_{50}/mg/L[a]
15	23.9±3.9	**44**	20.8±7.4
16	16.3±1.3	**53**	17.5±5.2
42	18.8±3.1	**71**	14.7±2.2
Avermectin[b]	24.8±5.7	-	-

[a] The average of three tests.

[b] The commercial nematicide avermectin was used as a positive control.

43.

44. 
Fluensulfone
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Moderate nematicidal activity
Chin. J. Org. Chem. 2017, 37, 2343
Our previous work
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Our previous work
Heterocycle
Good nematocidal activity?
Diversified flexible chain
LC50:16.3 mg/L
LC50:17.5 mg/L
LC50:14.7 mg/L
Qualitative
nArom Bond
ALogP
nRotB
nHBAcc
nHBDon
Quantitative
RDL 1.632
QEI 0.751
Gau 6.027
Insecticide-likeness qualitative and quantitative analysis