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Synthesis and characterization of some new tebufenozide analogues and study their toxicological effect against Spodoptera littoralis (Boisd.)

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A B S T R A C T

Many of mimic analogues synthesized before depending on the change in the structure of aromatic rings. In this work, the carbonyl group in the structure of compounds **1**-**4** converted to thiocarbonyl group, and then studying the toxicological activity due to chemical change in the active center of mimic analogues was performed for compounds *N*-*tert*-butyl-2,4-dichloro-*N*'-(2,4-dichlorobenzoyl)benzohydrazide (**2**) and *N*-tert-butyl-2,4-dichloro-*N'*-[(2,4-dichlorophenyl)carbonothioyl]benzenecarbothiohydrazide (**6**). The toxicological study was done by using 2nd and 4th instar larvae of the cotton leaf worm, *Spodoptera littoralis (Boisd.)*. Five concentration levels (600, 300, 150, 75 and 37.5 ppm) of compounds (**2**) and (**6**) were applied on the fresh plant food to the newly grown (2nd and 4th) instar larvae.

1. Introduction

In Egypt among all cotton pests, the cotton leaf worm, *Spodoptera littoralis* (Boisd.), is the most important. It is extremely polyphagousand always appropriate to inflict excessive damage when it occurs in masses during certain years, commonly referred to as "cotton worm monsoons.[1] Tebufenozide (**Fig. 1**) is registered for control of Lepidoptera insects, which mimic ecdysone and force insects to molt prematurely which typically results in stoppage of feeding and ultimately in insect death.[2]

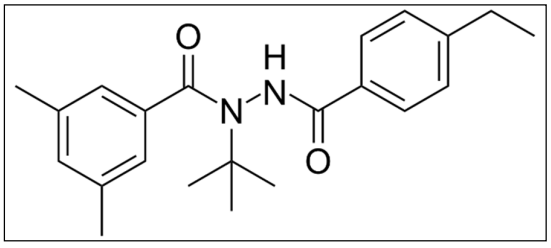

Fig. 1. Structure of tebufenozide

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Tebufenozide is used to protect pomes fruit, canola, rice, almonds, sweet potato, cranberries, sugarcane, walnuts, pecan/pistachio nuts, cotton, turnips, mint, blueberries, forest/ornamental trees, pastures, rangelands, row crops, vegetables and vines.[3,4] Tebufenozide is considered by many to be the safest, most selective, and most useful insect control agent ever to be discovered.[4] At present, analogues of tebufenozide such as methoxifenozide (RH-2485), halofenozide (RH-0345), and chromafenozide (ANS-118) have already been brought into agrochemical market.[5,6] Many of tebufenozide analogues synthesized due to their insecticidal activity.[7]

2. Results and Discussion

2.1 Chemistry

As following of our project in synthesis and toxicity evaluation of some new mimic analogues, here we prepared some mimic analogues that are shown in **Fig. 2**. The mimic analogues compounds, namely, *N-tert*-butyl-4-chloro-*N*'-[(4-chlorophenyl)carbonothioyl]benzenecarbothiohydrazide **5**, *N-tert*-butyl-2,4-dichloro-*N*'-[(2,4-dichlorophenyl)carbonothioyl]benzenecarbothiohydrazide **6**, *N-tert*-butyl-*N*'-(furan-2-ylcarbonothioyl)furan-2-carbothiohydrazide **7** and *N-tert*-butyl-*N*'-(thiophen-2-ylcarbonothioyl)thiophene-2-carbothiohydrazide **8** were synthesized as follow:

Compounds **1**, **2**, **3** and **4** were obtained according to the reported method.[7]

Compounds **1**, **2**, **3** and **4** reacted with phosphourspentasulphide to give the corresponding thio-derivatives **5**, **6**, **7**, and **8**.

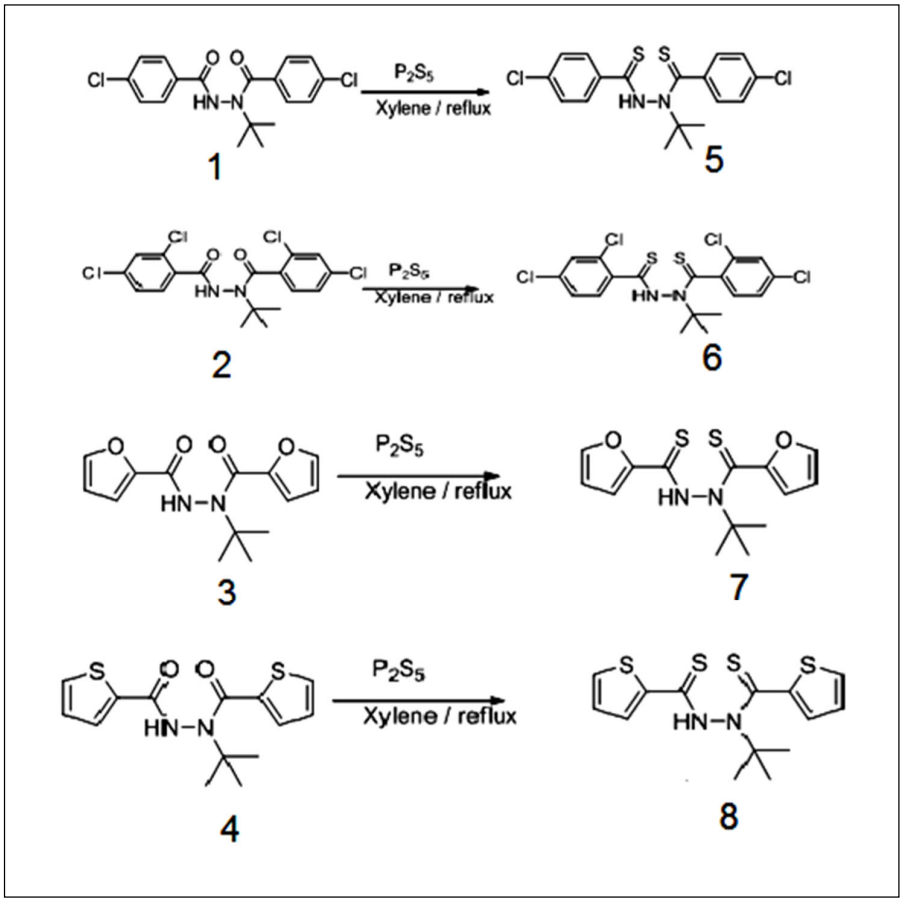

Fig. 2. Synthesis of compounds **5**, **6, 7** and **8**

2.2 Toxicity test

Toxicity test for the 2nd instar larva of the cotton leafworm *S. littoralis* (Boisd.) as shown in **Table 1** that revealed compound (**2**) is the most effective IGRs giving LC_{50}Value 294.70 ppm. Compound (**6**) showed the LC_{50} value of 464.20 ppm. In relation to the efficiency of the tested IGRs against 4th instar larvae of the laboratory strain, compound (**2**) was the most effective IGR giving LC_{50} value of 143.70 ppm, compound (**6**) showed the LC_{50} values of 411.60.

From **Tables 1,2** we can say that change of carbonyl group to a thiocarbonyl group reduced the activity of its imitative analogues, this obtained when compare compound **6** (LC_{50} = 464.20) with compound **2** (LC_{50} = 294.70) in case of 2nd instar and in 4th instar compound **6** (LC_{50} = 411.60) with compound **2** (LC_{50}= 143.70).

Table 1. Indicate toxicity of compounds **2** and **6** against 2nd instar of *Spodoptera littoralis* (Boisd.).

Compd	LC_{25} (ppm)	LC_{50} (ppm)	Slop
2	89.76	294.70	1.3014 +/- 0.3335
6	83.31	464.20	0.9042 +/- 0.3202

Table 2. Indicate toxicity of compounds **2** and **6** against 4th instar of *Spodoptera littoralis* (Boisd.).

Compd	LC_{25} (ppm)	LC_{50} (ppm)	Slop
2	87.19	143.70	3.1089 +/- 0.4997
6	81.46	411.60	0.9588 +/- 0.3209

Table 3. Indicate total activity of compound **2** on different stages of *Spodoptera littoralis* (Boisd.), show percentage of dead larvae, percentage of dead pupae and percentage of malformed.

	2nd				4th			
Conc. (ppm)	Dead larvae %	Dead pupae %	Malformed%	Total activity %	Dead larvae %	Dead pupae %	Malformed %	Total activity %
600	70	5	10	85	96.67	-	-	96.67
300	43.33	20	15	78.33	93.33	-	-	93.33
150	30.33	10	15	65.33	40	30	10	80
75	26.66	15	6.66	48.33	20	45	10	75
37.5	6.66	13.32	26.64	46.62	33.33	40	5	78.33
Control	3.33	5		8.33	3.33			3.33

Data presented in **Table 3**, showed that compound (**2**) the highest percentage of dead larvae at 2nd instar larvae occurred at concentration (600) ppm was (70%), followed by 43.33, 30.33, 26.66 and 6.66 at 300, 150, 75 and 37.5 ppm, opposite to 3.33% in control. And the highest percentage of dead pupae occurred at concentration (300) ppm was (20%), followed by 15, 13.32, 10 and 5 at 75, 37.5, 150 and 600 ppm, opposite to 5% in control. And the highest percentage of malformed occurring at concentration (37.5) ppm was 26.64 %, followed by 15, 15, 10 and 6.66 % at 300, 150, 600and 75 ppm, opposite to zero % malformed in control. And the highest total activity (dead larvae + dead pupae + malformed) of compound **2** is occurred at concentration (600) ppm was 85%, followed by 78.33, 65.33, 48.33 and 46.62 % at 300, 150, 75 and 37.5 ppm, opposite to 8.33 % total activity in control.

Data presented in **Table 3**, showed that compound (**2**) the highest percentage of dead larvae at 4thin star larvae occurred at concentration (600) ppm was (96.67%), followed by 93.33, 40, 33.33 and 20 at 300, 150, 37.5 and 75 ppm, opposite to 3.33% in control. And the highest percentage of dead pupae occurring at concentration (75) ppm was (45%), followed by 40, 30 at 37.5 and 150 ppm, and zero % at (600, 300) ppm, opposite to zero% in control. And the highest percentage of malformed occurring at concentration (150 and 75) ppm was 10%, followed by 5 % at 37.5 ppm, and zero% malformed at (600, 300) ppm, opposite to zero % malformed in control. And the highest total activity (dead larvae + dead pupae + malformed) of compound **2** is occurred at concentration (600) ppm was 96.67% , followed by 93.33, 80, 78.33 and 75 % at 300, 150, 37.5 and 150 ppm, opposite to 3.33 % total activity in control.

Data presented in **Table 4**, showed that compound (**6**) the highest percentage of dead larvae at 2nd instar larvae occurred at concentration (300) ppm was (50%), followed by 35, 30, 25 and 15 at 600, 150, 75 and 37.5 ppm, opposite to 3.33% in control. And the highest percentage of dead pupae occurred at concentration (150) ppm was (45%), followed by 20, 20, 15 and 15 at 600, 300, 75 and 37.5 ppm, opposite to 5% in control. And the highest percentage of malformed occurring at concentration (600) ppm was 25%, followed by 16, 15, 5 and zero % at 37.5, 75, 300 and 150 ppm, opposite to zero % malformed in control. And the highest total activity (dead larvae + dead pupae + malformed) of compound **6** is occurred at concentration (600) ppm was 80% , followed by 75, 75, 65 and 46 % at 300, 150, 75 and 37.5 ppm, opposite to 8.33 % total activity in control.

Data presented in **Table 4**, showed that compound (**6**) the highest percentage of dead larvae at 4thin star larvae occurred at concentration (600) ppm was (50%), followed by 45, 45, 25 and 10 at 300, 150, 75 and 37.5 ppm, opposite to 3.33% in control. And the highest percentage of dead pupae occurring at concentration (300) ppm was (35%), followed by 25, 20, 13 and 5 at 600, 75, 37.5 and 150 ppm, opposite to zero % in control. And the highest percentage of malformed occurring at concentration (600) ppm was 20%, followed by 15 and 10 % at 37.5, 150 ppm, and zero malformed at (300, 150) ppm, opposite to zero% malformed in control. And the highest total activity (dead larvae + dead pupae + malformed) of compound **6** is occurred at concentration (600) ppm was 95% , followed by 80, 60, 45 and 38 % at 300, 150, 75 and 37.5 ppm, opposite to 3.33 % total activity in control.

Table 4. Indicate total activity of compound **6** on different stages of *Spodoptera littoralis* (Boisd.), show percentage of dead larvae, percentage of dead pupae and percentage of malformed.

Conc.	2nd				4th			
	Dead larvae %	Dead pupae %	Malformed%	Total activity %	Dead larvae %	Dead pupae %	Malformed %	Total activity %
600	35	20	25	80	50	25	20	95
300	50	20	5	75	45	35	-	80
150	30	45	-	75	45	5	10	60
75	25	15	15	55	25	20	-	45
37.5	15	15	16	46	10	13	15	38
Control	3.33	5		8.33	3.33			3.33

3. Conclusion

Some of the mimic analogues compounds were synthesized via reaction of compounds **1-4** with phosphourspentasulphide. Then, toxicity of compounds **2** and **6** against 2nd and 4th instar of *Spodoptera littoralis* (Boisd.) was estimated and demonstrated that compound **2** is higher in activity than compound **6**. These results are hopeful and valuable for additional work on the improvement of new promising insecticidal agents and other potential pesticides.

4. Experimental

4.1 Materials and methods

Melting points are uncorrected and were determined by Kofeler melting point apparatus. IR (cm^{-1}) spectra were listed (KBr disc) on a Shimadzu DR-8001 spectrophotometer. ^{1}HNMR and ^{13}CNMR (DMSO-d_6) spectra were listed at 400 and 100 MHz on a Varian Gemini NMR spectrometer, the chemical shift is expressed in δ value (ppm) using TMS as an internal reference. Elemental analyses were carried out on a Perkin-Elmer 240°C Micro analyzer.

The present work was conducted to prepare new derivatives of mimic

4.2 Synthesis of compounds 5, 6, 7 and 8

4.2.1 Genera; procedures

To a suspension of selected Compounds **1, 2, 3**, and **4** in xylene (20 ml), phosphoruspentasulfide (1.1g, 5mmol,) was added. The mixture was refluxed for 5 hr and filtrated. The filtrate was evaporated, the residue was treated with acetone / hexane mixture, the solid precipitate, was filtrated.

4.2.2 N-tert-butyl-4-chloro-N'-[(4-chlorophenyl)carbonothioyl]benzenecarbothiohydrazide (5)

Yellow solid (60%, yield); mp. 167-169˚C; IR (ν^{-}, cm^{-1}): 3020.61 (CH_{arom}), 2961.20(CH_{aliph}). ^{1}H NMR (DMSO-d_6), (δppm): 8.20-7.28 (m, 8H, H_{arom}+1H NH), 1.25(s, 9H, CH_3). ^{13}C NMR: 200.30 (**C**=S), 199.12 (**C**=S), 153.0 (**C**-Cl), 152.0 (**C**-Cl), 142.5 (**C**-CS), 140.3 (**C**-CS), other aromatic C-H carbon at 137.97, 133.52, 133.08, 128.77, 121.69, other aliphatic carbon at 61.4(**C-3**CH_3), 2۵٫۶(CH_3). *Anal*. for $C_{18}H_{18}Cl_2N_2S_2$ (397.38): Calcd. / found C: 54.40/54.82, H 4.57/4.36, N 8.64/8.96.

4.2.3 N-tert-butyl-2,4-dichloro-N'-[(2,4-dichlorophenyl)carbonothioyl]benzenecarbothiohydrazide (6)

White solid (82%, yield); mp. 172-174˚C; IR (ν^{-}, cm^{-1}): 3018.60 (CH_{arom}), 2991.21 (CH_{aliph}). ^{1}H NMR (DMSO-d_6), (δ ppm): 8.2-7.28 (m, 6H, H_{arom}+1H NH), 1.25(s, 9H, CH_3). ^{13}C NMR: 201.00 (**C**=S), 199.02 (**C**=S), 153.0 (**C**-Cl), 152.0 (**C**-Cl), 142.5 (**C**-CS), 140.3 (**C**-CS), other aromatic C-H carbon at 134.90, 133.10, 133.01, 130.51, 121.01, 118.95, other aliphatic carbon at 61.4(**C-3**CH_3), 2۵٫۶(CH_3). *Anal*. for $C_{18}H_{16}Cl_4N_2S_2$ (466.23):Calcd. /found C: 46.37/46.70, H 3.46/3.59, N 6.10/6.42.

4.2.4 N-tert-butyl-N'-(furan-2-ylcarbonothioyl)furan-2-carbothiohydrazide (7)

Pale yellow solid (64%, yield); mp. 270˚C; IR (ν^{-}, cm^{-1}): 3022.61 (CH_{arom}), 2930.02(CH_{aliph}). ^{1}H NMR (DMSO-d_6), (δ ppm): 7.96-6.49 (m, 6H, H_{arom}+ 1H NH), 1.5(s, 9H, CH_3). ^{13}C NMR: 202.23 (**C**=S), 199.14 (**C**=S), 132.20 (**C**-CS), 132.01 (**C**-CS), other aromatic C-H carbon at 131.02, 130.02, 128.46, 127.25, other aliphatic carbon at 61.4(**C-3**CH_3), 2۵٫۶(CH_3). *Anal*. for $C_{14}H_{16}N_2O_2S_2$ (308.41): Calcd. / found C: 54.52/54.97, H: 5.23/5.01, N: 9.08/8.75.

4.2.5 N-tert-butyl-N'-(thiophen-2-ylcarbonothioyl)thiophene-2-carbothiohydrazide (8)

Yellow solid (71%, yield); mp. 96-100˚C; IR (ν^{-}, cm^{-1}): 3018.60 (CH_{arom}), 2945.42(CH_{aliph}). ^{1}H NMR (DMSO-d_6), (δ ppm): 7.96-7.68 (m, 6H, H_{arom}+1H NH), 1.25(s, 9H, CH_3). ^{13}C NMR: 201.12 (**C**=S), 199.87 (**C**=S), 142.51 (**C**-CS), 140.34 (**C**-CS), other aromatic C-H carbon at 133.03, 131.54, 128.02, 127.63, other aliphatic carbon at 61.4 (**C-3**CH_3), 2۵٫۶(CH_3). *Anal*. for $C_{14}H_{16}N_2S_4$ (340.55): Calcd. / found C: 49.38/49.72, H: 4.74/4.51, N: 8.23/8.55.

4.3 Biological tests

4.3.1 Toxicological studies

The present work was conducted to study the susceptibility in laboratory of 2nd and 4th instars larvae of the cotton leafworm *S. littoralis* (Boisd.) to the Mimic derivatives.

4.3.2 Tested insect growth regulators

The pre-test of synthesized compounds, show that compound (**2**) is the most effective compound against *Spodoptera littoralis* (Boisd.) more than other compounds (**1**, **3** and **4**), so it chosen for test it toxicological activity with compound (**6**), to study the change of carbonyl group to thio group and effect of this change on toxicological activity of compound. The two compounds were compared with the control (acetone + water).

4.3.3 Cotton leaf worm strains

Laboratory strain of the cotton leaf worm S. *littoralis* (Boisd.) was obtained from Assiut Agricultural College as a susceptible strain to carry out the present investigation.

Laboratory bioassay: a series of concentrations (acetone) for each IGR were prepared as the active ingredients (**2** and **6**) based on ppm by diluting with water. Castor-bean leaves were dipped for 30 seconds in each concentration then left to dry for one hour. The 2nd and 4th instars larvae of each tested strain were confined with treated leaves in glass jars covered with muslin for 24 hrs. . Treated leaves were then removed and fresh untreated leaves provided. Three replicates (each of 20 larvae) were tested for each concentration. Daily inspection was carried out for all treatments and mortality percentages were recorded after treatment. The average of mortality percentage was corrected using Abbott's formula.[8] The corrected mortality percentage of each compound was statistically computed according to Finney (1971).[9] From which the corresponding concentration probit lines (ld-p lines) were estimated in addition to determine 50 and 90% mortalities, slope values of tested compounds were also estimated. All these findings presented in this paper confirm the reported importance of organic compounds in different biological fields.[10-25]

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