

Insecticidal Evaluation and Structure-Activity Relationship Study of Some Synthesized Urea and Thiourea Derivatives Against *Spodoptera littoralis* (Boisd.)

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Abstract: Because utilizing insecticides can cause some serious issues, finding safe options for these chemicals has become decisive. So, in order to create novel Hexaflumuron analogues as insect growth regulators that could be screened & tested against *Spodoptera littoralis* (Boisd), urea and thiourea derivatives that were projected to be toxicologically active were synthesized in pure form. An equimolecular amount of 4-nitroaniline was added with stirring to phenyl isocyanate and phenyl isothiocyanate in dry 1,4-dioxane. By using spectroscopic and elemental investigations, the structure of synthesized substances was determined. Target compounds **3a** and **3b** had moderate insecticidal toxicity; their LC₅₀ values for the second larval instar were determined to be 147.26 and 316.01 mg/L, respectively, whereas the LC₅₀ value for the reference insecticide, hexaflumuron, was 17.01 mg/L. Finally, this work further demonstrates the anti-proliferation of *S. littoralis* and discusses how to discover novel target compounds that may one day be employed as effective insecticidal agents.

Keywords: Urea, Thiourea, Insecticides, *Spodoptera littoralis*, Hexaflumuron.

1. Introduction

The moth species *S. littoralis* contacts & belonging to the Noctuidae field & is extensively allocated throughout Africa, Mediterranean Europe, & the Middle East [1, 2]. The cotton leaf worm is well distinguished to cause noteworthy financial losses for numerous countries [3]. *S. littoralis* is a polyphagous moth that feeds on more than 100 species of highly valuable plants, including cotton, potatoes, maize and vegetables. It is extremely harmful [4, 5]. In recent years, the sulfur and nitrogen-containing chemicals urea and thioureas have shown to be crucial components in therapeutic research [6, 7]. benzoylthioureas, diarylsulphonylureas, benzoylureas and *N*-nitrosoureas are only a few examples of the urea and thiourea derivatives that have a variety of anti-leukemia & anti-solid tumor properties [8]. The derivatives of thiourea & urea are well-known key elements in synthetic and medical chemistry [9]. These compounds' biologically and chemically active

substances, which are utilized as therapeutic & pharmaceutical qualities, have a wide range of structural forms in common [10-12]. The superior efficacy of acylurea and acylthiourea components as insecticides and plant growth regulator intermediates is well recognized [13, 14]. In the agrochemical business, heterogeneous nitrogen and sulphur are also crucial in the production of effective chemicals like insecticides and herbicides [15]. Additionally, the intrinsic N-O or N-S bonds found in some molecules have a beneficial effect on plant metabolism and uptake [16, 17]. In keeping with this, we would like to design and characterize fresh urea and thiourea analogues that have been found to be insecticidal against *S. littoralis* instar larvae.

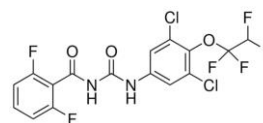


Fig. (1): Chemical structure of hexaflumuron.

2. Materials and methods

A Fisher-John mechanical approach was used to estimate MP for all created target compounds.

2.1. Instrumentations and chemicals:

Sigma-Aldrich supplied the chemicals and solvents used in this report. Utilizing the KBr technique, the ^1H and ^{13}C -NMR spectra of the produced compounds were recorded on a Bruker Advance 400 MHz spectrometer. a mention the insecticide Hexaflumuron was purchased from Sigma-Aldrich. The target synthesized compounds that were synthesized and Hexaflumuron's insecticidal efficacy when evaluated on *S. littoralis* instar larvae.

2.2. Bioassay Screening

Standard leaf dip bioassay methods [18-25] were used to evaluate the insecticidal bio-effectiveness of all produced urea and thiourea, derivatives. The target substances' test results were noted, and the concentrations needed to kill 50% (LC_{50}) of *S. littoralis* larvae were calculated. In this study, 0.1% Tween-80 was utilized as a surfactant together with 5 concentrations of urea and thiourea derivatives. Castor bean leaf discs (9 cm in diameter) were dipped in the concentration under test for 10 seconds, dried, and then fed to second and fourth larvae, which were roughly the same size & housed in glass jars (5 lb). Each treatment was carried out three times with ten larvae each. The control discs didn't move to the untreated one until they were immersed in water and treated with tween-80. Castor bean is what the larvae eat for 48 hours. Then moved to an untreated one. For all designed components, the humanity was computed at 72 hours, 22 2 c, & 60 5% relative humidity. The Abbott recipe reduced the mortality [27]. By using probit analysis, the mortality relapsed line was quantitatively decomposed [28]. Sun equations were used to establish the harmfulness index [29].

2.3. Breeding larvae insect

The agricultural research centre farm Sohag branch received the *S. littoralis* insects to assess the activity of the produced compounds and the Hexaflumuron reference insecticide on the

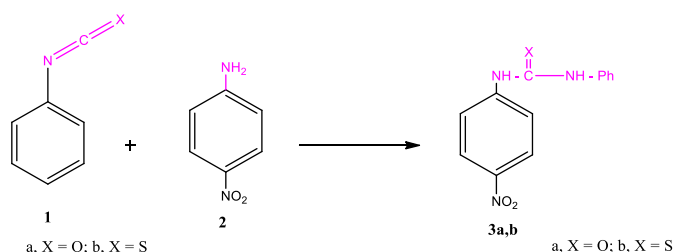
S. littoralis insects throughout the 2023 growing season.

3. Results and Discussion

Herein, target products, namely, 1-(4-nitrophenyl)-3-phenylurea 3a & 1-(4-nitrophenyl)-3-phenylthiourea 3b were productively designed, the obtained yield is 68–90% through the following steps.

3.1. Synthesis of aryl phenylurea derivatives

An equimolecular amount of 4-nitroaniline 2 was added dropwise with stirring to an equimolecular amount of phenyl isocyanate and phenyl isothiocyanate 1 dry 1,4-dioxane and refluxed for 5 hours to give 3a and 3b in 70–89% yield (Scheme 1).



Scheme 1: Designing components 3a, b.

3.2. General method for designing components 3a and 3b.

An equimolecular amount of 4-nitroaniline was added drop wise with stirring to an equimolecular amount of phenyl isothiocyanate or phenyl isocyanate in dry dioxin and refluxed for 5 hours to give 3a and 4b. The impetuous was collected & washed thoroughly with H_2O & crystallization from methyl alcohol/dichloromethane mixture (2:3).

1-(4-nitrophenyl)-3-phenylurea (3a)

Brown powder (75% yield), mp. 160-162 $^{\circ}\text{C}$; IR (ν , cm^{-1}): 3295 (HN-), 3079 (CH_{arom}), 1690 ($\text{O}=\text{C}$), 1565.44 ($\text{C}=\text{C}$). ^1H -NMR ($\text{DMSO}-d_6$), (δ ppm): 9.36 (s, 1H, NH_{exch}), 8.584 (s, 1H, NH_{exch}), 8.62-7.01 (m, 9H, H_{arom}). ^{13}C -NMR: 152.39, 146.81, 141.51, 139.46, 129.24, 126.74, 122.25, 118.78, 112.87. *Anal.* for $\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}_3$ (257.2): Calcd./found C: 60.70/60.62, H: 4.31/4.33 & N:16.33/16.54%.

1-(4-nitrophenyl)-3-phenylthiourea (3b)

Yellow solid (80% yield); mp. 128-130°C; IR (ν , cm^{-1}): 3333 (HN), 3109 (CH_{arom}), 1628 (C=O), 1580 (C=C). $^1\text{H-NMR}$ ($\text{DMSO-}d_6$), (δ ppm): 10.73 (s, 1H, NH_{exch}), 6.63 (s, 1H, NH_{exch}), 8.24-7.37 (m, 9H, H_{arom}). $^{13}\text{C-NMR}$: 156.07, 146.05, 143.39, 136.26, 126.76, 124.81, 124.25, 122.58, 112.90. *Anal.* for $\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}_2\text{S}$ (273.3). Calcd. / found C:57.13/57.15, H: 4.06/4.09 and N: 15.37/15.52%.

3.3. Toxicological effectiveness test for 2nd larvae

Results of compound **3a** and **3b** were tested against 2nd larvae insect. As revealed in Table 1 the bioefficacy results of tested compounds demonstrate from high to low toxicological effectiveness against the 2nd larvae for example LC_{50} value of components **3a** & **3b** were 147.26, and 316.01 mg/L respectively, in which Hexaflumuron stander insecticide value was 17.01mg/L.

3.4. Toxicological effectiveness checked for adults 4th larvae

Results of compound **3a** and **3b** were tested against 2nd larvae insect. As shown in Table 1 the bioefficacy results of tested components demonstrate from excellent to low toxicological effectiveness against the 4th larvae for example LC_{50} value of components **3a** & **3b** were 1232.8 and 1428.1 mg/L respectively, in which Hexaflumuron stander insecticide value was 103.12mg/L.

3.5. Structure-action relationship (SAR)

Regarding of the toxicity value in Table 1 & Figure 1 the

structure-action relationship was established. The compounds **3a** and **3b** were active against 2nd and 4th larvae insect. The high activity of these compounds may be due to the occurrence of nitrophenyl in its structure. The presence of nitrophenyl & phenylgroupin, which is considered as an electron-withdrawing group increases effectiveness than the other urea and/or thiourea synthesized derivatives compared to the commercial Hexaflumuron insecticide.

4. Conclusion

Novel Hexaflumuron analogues have been synthesized as insect growth regulators that could be screened and checked against *Spodoptera littoralis* (Boisd). Urea and thiourea derivatives that were projected to be toxicologically active were synthesized in pure form. An equimolecular amount of *p*-nitroaniline was added with stirring to phenyl isocyanate and phenyl isothiocyanate. By using spectroscopic and elemental investigations, the structure of synthesized substances was determined. Target compounds 1-(4-nitrophenyl)-3-phenylurea (**3a**) and 1-(4-nitrophenyl)-3-phenylthiourea (**3b**) had moderate insecticidal toxicity; their LC_{50} values for the second larval instar were determined to be 147.26 and 316.01 mg/L, respectively, whereas the LC_{50} value for the reference insecticide, hexaflumuron, was 17.01 mg/L. Finally, this work further demonstrates the anti-proliferation of *S. littoralis* and discusses how to discover novel target compounds that may one day be employed as effective insecticidal agents.

Table 1: Insecticidal effectiveness of components **3a**, **3b** and Hexaflumuron as reference insecticide against for the 2nd and 4th larvae instar of *S. littoralis* after 72 hours of treatment.

2 nd instar larvae				4 th instar larvae		
Comp.	LC_{50} (mg/L)	Slope	Toxic ratio ^a	LC_{50} (mg/L)	slope	Toxic ratio ^a
Hexaflumuron	17.01	0.246±0.0791	1	103.12	0.234 ± 0.083	1
3a	147.26	0.302±0.098	0.115	1232.8	0.420±0.938	0.083
3b	316.01	1.25±1.21	0.053	1428.1	0.438±0.810	0.065

[*] Notes: Toxicity Ratio is estimated as Hexaflumuron's LC_{50} value for baseline toxicity / the components' LC_{50} value

CRedit authorship contribution statement:

Conceptualization: Ahmed M. M. El-Saghier, and Antar A. Abdllhamid.; **Methodology:** Mohamed A. Gad, Nabila A. Ahmed and Antar A. Abdllhamid. **Software:** Mohamed A. Gad, Safwat A. Aref and Nabila A. Ahmed. **Validation:** Ahmed M. M. El-Saghier, Mohamed A. Gad and Nabila A. Ahmed. **Formal analysis:** Ahmed M. M. El-Saghier, Mohamed A. Gad, Nabila A. Ahmed and Antar A. Abdllhamid. **Investigation:** Ahmed M. M. El-Saghier, Mohamed A. Gad, and Antar A. Abdllhamid. **Resources:** Ahmed M. M. El-Saghier, Mohamed A. Gad, Safwat A. Aref and Nabila A. Ahmed. **Data curation:** Ahmed M. M. El-Saghier, Mohamed A. Gad, Nabila A. Ahmed and Antar A. Abdllhamid. **Writing—original draft preparation:** Mohamed A. Gad and Antar A. Abdllhamid. **Writing—review and editing:** Ahmed M. M. El-Saghier, Mohamed A. Gad, and Antar A. Abdllhamid. **Visualization:** Ahmed M. M. El-Saghier, Mohamed A. Gad, Safwat A. Aref, and Nabila A. Ahmed. **Supervision:** Ahmed M. M. El-Saghier, Mohamed A. Gad, Safwat A. Aref, and Antar A. Abdllhamid. **Project administration:** Ahmed M. M. El-Saghier, Mohamed A. Gad, and Antar A. Abdllhamid. **Funding acquisition:** Ahmed M. M. El-Saghier, Mohamed A. Gad, Safwat A. Aref and Nabila A. A. Ahmed. **All authors have read and agreed to the published version of the manuscript.**

Data availability statement

The data used to support the findings of this study are available from the corresponding author upon request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests.

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