Current Chemistry Letters 11 (2022) 285–290

Contents lists available at GrowingScience

Current Chemistry Letters

homepage: www.GrowingScience.com

Selective synthesis, characterization, and toxicological activity screening of some furan compounds as pesticidal agents

Omar M. Elhady[a], Erian S. Mansour[b], M. M. Elwassimy[a], Sameh A. Zawam[c*], Ali M. Drar[b] and Shaban A. A. Abdel-Raheem[d]

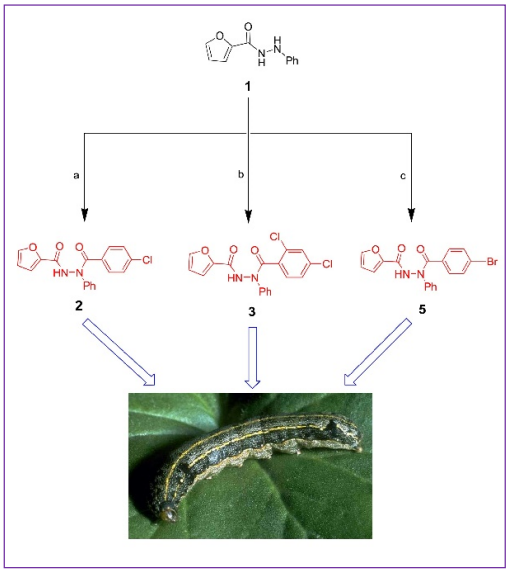
[a]*Chemistry Department, Faculty of Science, Sohag University, Egypt*
[b]*Plant Protection Research Institute, Agriculture Research Center, Dokki, Giza, Egypt*
[c]*Chemistry Department, Faculty of Science, Menoufia University, Egypt*
[d]*Soils, Water, and Environment Research Institute, Agricultural Research Center, Giza, Egypt*

C H R O N I C L E A B S T R A C T

Article history:
Received January24, 2022
Received in revised form
March6, 2022
Accepted March17, 2022
Available online
March17,2022

Keywords:
Chemistry
Toxicity
Cotton
Crop management
Entomology

A series of furan derivatives tebufenozide analogues comprising five compounds **(2**, **3**, **4**, **5**, and **6)**have been designed and synthesized via reaction of *N′*-phenylfuran-2-carbohydrazide **(1)** with different acid chlorides. The structures of the synthesized compounds were identified by elemental analyses and spectroscopic data. The analogues compounds have the active center of tebufenozide (mimic) with change of tertiary butylhydrazine by phenylhydrazine. Studying the effect of this change on the toxicological activity against *Spodoptera littoralis* larvae was performed for three compounds of the synthesized ones. Toxicological activity data showed that compound **(3)** is more active than compounds **(2)** and **(5)**.



Graphical Abstract

* Corresponding author.
E-mail address:samehzwwam87@gmail.com (S. A. Zawam)

doi: 10.5267/j.ccl.2022.3.006

1. Introduction

The importance of synthetic organic compounds, especially furan derivatives, as effective bioactive agents in different fields is well-known. Furan ring, as a critical pharmacophore, is widely present in many active natural products such as toosendanin (a known natural-product insecticidal agents) and limonin.[1-4] So, different compounds derived from furan were used previously as potential insecticidal agents.[5,6] Tebufenozide is considered by a lot of scientists to be the safest, most selective, and most useful insect control agent ever to be discovered.[7] It is a powerful toxicant for controlling both susceptible and field-resistant strains of *S. littoralis.* Tebufenozide compounds have no adverse activity on the predators, *Podisus maculiventris* (Say), *Podisus nigrispinus* (Dallas), and *Orius insidiosus* (Say).[8,9] Tebufenozide binds to the ecdysteroid receptors by initiating the molting process and force insects to molt prematurely which typically results in stoppage of feeding and ultimately in insect death.[10] Other effects of these compounds on insects include increased egg mortality and reduced rates of reproduction.[11] In view of these findings, the current study was planned to synthesize some heterocyclic compounds containing a furan moiety and screening the insecticidal activity against *Spodoptera littoralis* (Boisd.) hoping to find compounds with a good insecticidal activity and being safer toward aquatic life.

2. Results and Discussion

2.1 Chemistry

As following of our project in synthesis and toxicity evaluation of some new tebufenozide (mimic) analogues and the applied fields,[12-21] we prepared here some mimic analogues that are shown in **Fig. 1**. The new tebufenozide (mimic) analogues compounds, namely, *Ń*-phenyl(4-chlorobenzoyl)-furan–2-carbohydrazide **2**, *Ń*-phenyl(2,4-dichlorobenzoyl)-furan-2-carbohydrazide **3**, *Ń*-phenyl(4-aminobenzoyl)-furan– 2-carbohydrazide **4**, *Ń*-phenyl(4-Bromobenzoyl)-furan-2-carbohydrazide **5**, and *Ń*-phenyl(thenoyl)-furan-2-carbohydrazide **6** were synthesized as follow:

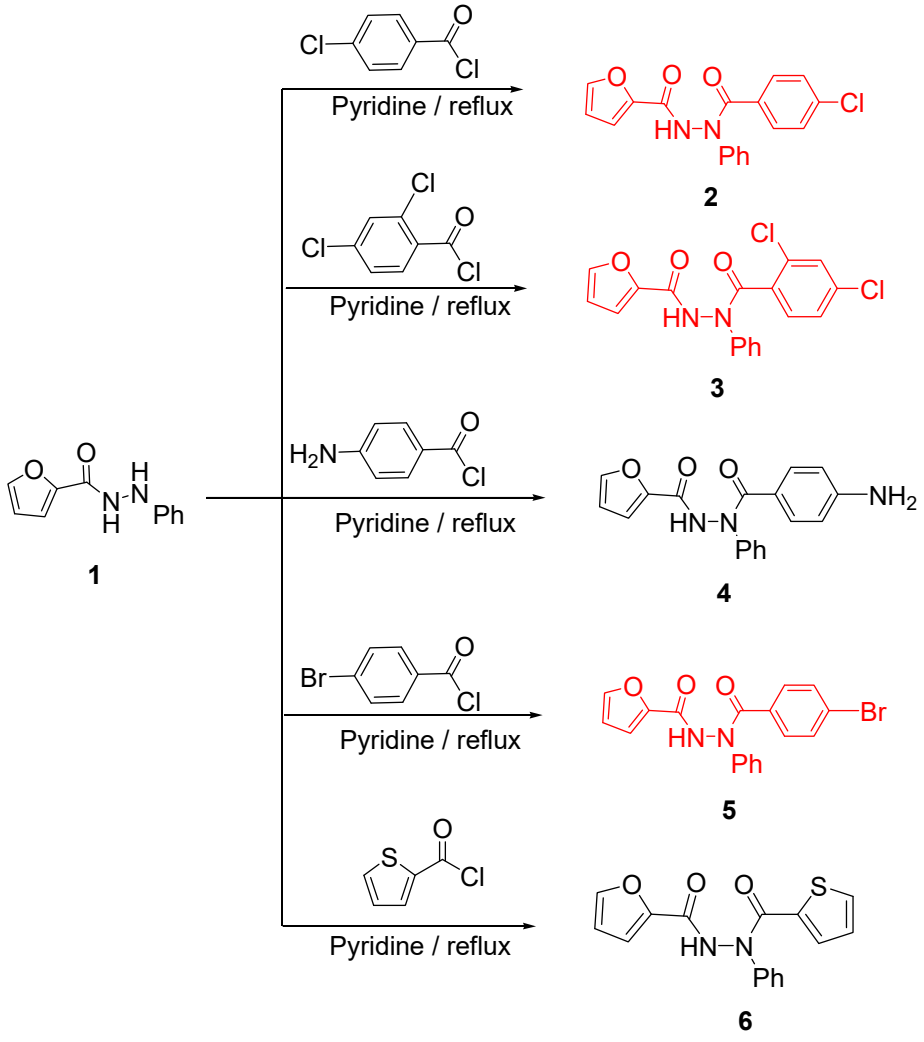


Fig. 1. Synthesis of compounds **2**, **3**, **4**, **5** and **6**

Ń-Phenyl furan-2-carbohydrazide (**1**) reacts with different acid chlorides namely; 4-chlorobenzoyl chloride, 2,4-dichlorobenzoyl chloride, 4-amino benzoyl chloride, 4-bromobenzoyl chloride and thenoyl chloride, by refluxing in pyridine to give: *Ń*-phenyl(4-chlorobenzoyl)-furan–2-carbohydrazide **2**, *Ń*-phenyl(2,4-dichlorobenzoyl)-furan-2-carbohydrazide **3**, *Ń*-phenyl(4-aminobenzoyl)-furan–2-carbohydrazide **4**, *Ń*-phenyl(4-Bromobenzoyl)-furan-2-carbohydrazide **5** and *Ń*-phenyl(thenoyl)-furan-2-carbohydrazide **6**.

The structure of all newly synthesized compounds were elucidated and confirmed on the basis of their elemental analyses and spectroscopic data. The results of elemental analyses were found to be in good agreement with the calculated values. The spectral data of all prepared compounds were in accordance with their proposed structures.

IR spectrum for compound **2** showed absorption bands at 3140 and 1673 cm^{-1} characteristics for (NH) and (C=O) groups respectively. ^{1}HNMR (DMSO-d_6) spectrum for compound **2** showed that NH group at 12.5 ppm, CH aromatic proton signals at 7.97-7.59 ppm. ^{13}CNMR (DMSO-d_6) spectrum of compound **2** showed different signals at 168.4 (C=O), 163.6 (C=O), 151.0 (C-Cl), 149.3 (C-N), 142.5 (C-CO), 140.3 (C-CO), other aromatic C-H carbons at 131.8, 120.9, 120.1, 119.5, 117.2, 116.9, 115.3, 112.4.

2.2 Toxicity test

Toxicity test for the 2nd instar larvae of the cotton leaf worm *S. littoralis* (Boisd.), revealed compound **3** is the most effective compound, giving LC_{50} value (269 ppm.), while compounds **2** and **5** showed the LC_{50} values (397 and 499 ppm), respectively (**Table 1**).

Table 1. Toxicity of compounds **2, 3** and **5** against 2nd instar of *S. littoralis*

Compound	*LC_{25} (ppm)*	*LC_{50} (ppm)*	*Slop*
2	170	397	1.830 +/- 0.711
3	93	269	1.466 +/- 0.717
5	207	499	1.768 +/- 0.696

Toxicity test for the 4th instar larvae of the cotton leaf worm *S. littoralis* (Boisd.), revealed compound **3** is the most effective compound, giving LC_{50} value (496 ppm.), while compounds **2** and **5** showed the LC_{50} values (787 and 660 ppm), respectively (**Table 2**).

Table 2. Toxicity of compounds **2, 3** and **5** against 4th instar of *S. littoralis*

Compound	*LC_{25} (ppm)*	*LC_{50} (ppm)*	*Slop*
2	327	787	1.772 +/- 0.699
3	115	496	1.064 +/- 0.671
5	330	660	2.243 +/- 0.717

3. Conclusion

This work involves the synthesis of five heterocyclic compounds (**2**, **3**,**4**, **5** and **6**) and studying the biological activity as potential insecticides for compounds (**2**, **3**, and **5**) against 2nd and 4th instar of *S. littoralis*. The results showed that the compound **3** is more active than the compounds **2** and **5**. This result is encourageable for further work searching on new insecticidal agents.

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 Tubofenozide (mimic)

4.2 Synthesis of compounds 2, 3, 4, 5 and 6.

4.2.1 General procedures:

Freshly prepared acid chloride (1mol) was added drop wise while stirring to an equimolecular amount of *N′*-Phenylfurancarbohydrazide (1mol) in 20 ml pyridine and refluxed for 8-16 hrs. A solution of hydrazide derivative was poured on ice water acidified by HCl. The resulting precipitate was collected by filtration, washed thoroughly with H_2O and purified by crystallization from methanol.

4.2.2 Ń-phenyl (4-chlorobenzoyl)-furan–2-carbohydrazide (2):

Brown solid (73% yield); mp. 158-160˚C; IR (ν^-, cm^{-1}): 3140.2 (NH), 3045.8 (CH_{arom}), 1673.0 (C=O). ^{1}HNMR (DMSO-d_6), (δ ppm): 12.5 (s, 1H, NH_{exch}), 7.97-7.59 (m, 12H, H_{arom}). ^{13}CNMR (DMSO-d_6), (δ ppm): 168.4 (C=O), 163.6 (C=O), 151.0 (C-Cl), 149.3 (C-N), 142.5 (C-CO), 140.3 (C-CO), other aromatic C-H carbons at 131.8, 120.9, 120.1, 119.5, 117.2, 116.9, 115.3, 112.4. *Anal*. For $C_{18}H_{13}ClN_2O_3$ (340.76): Calcd. /found C: 63.44/63.21, 3.85/3.88, 8.22/8.32.

4.2.3 Ń-phenyl (2, 4 dichlorobenzoyl)-furan-2-carbohydrazide (3):

Brown solid (83% yield); mp. 147-150˚C; IR (ν^-, cm^{-1}): 3209.2 (NH), 3045.8 (CH_{arom}), 1669.7 (C=O). ^{1}HNMR (DMSO-d_6), (δ ppm): 12.4 (s, 1H, NH_{exch}), 7.96-7.68 (m, 11H, H_{arom}). ^{13}CNMR (DMSO-d_6), (δ ppm): 168.4 (C=O), 163.6 (C=O), 153.0 (C-Cl), 152.0 (C-Cl), 149.3 (C-N), 142.5 (C-CO), 140.3 (C-CO), other aromatic C-H carbons at 128.4, 122.7, 120.3, 119.8, 118.9, 118.6, 117.9, 114.2, 112.9. *Anal*. For $C_{18}H_{12}Cl_2N_2O_3$ (375.2): Calcd./found C: 57.62/57.53, 3.22/3.33, 7.47/7.69.

4.2.4 Ń-phenyl (4-aminobenzoyl)-furan– 2-carbohydrazide (4):

Brown solid (80% yield); mp. 130-134˚C; IR (ν^-, cm^{-1}): 3166.2 (NH), 3092.6 (CH_{arom}), 1658.6 (C=O).^{1}HNMR (DMSO-d_6), (δ ppm): 12.6 (s, 1H, NH_{exch}), 7.91-7.43 (m, 12H, H_{arom}),5.6 (s, 2H, NH_{exch}), ^{13}CNMR (DMSO-d_6), (δ ppm): 166.4 (C=O), 163.9 (C=O), 148.1 (C-N), 144.6 (C-NH_2), 142.4 (C-CO), 141.6 (C-CO), other aromatic C-H carbons at 128.7, 123.9, 121.1, 119.2, 118.2, 116.9, 112.4, 112.2. *Anal*. For $C_{18}H_{15}N_3O_3$ (321.33): Calcd./found C: 67.28/67.30, 4.71/4.87, 13.08/13.10.

4.2.5 Ń-phenyl (4-Bromobenzoyl)-furan-2-carbohydrazide (5):

Brown solid (77% yield); mp. 108-112˚C; IR (ν^-, cm^{-1}): 3194.2 (NH), 3086.64 (CH_{arom}), 1655.30 (C=O). ^{1}HNMR (DMSO-d_6), (δ ppm): 11.95 (s, 1H, NH_{exch}), 7.91-7.439 (m, 12H, H_{arom}). ^{13}CNMR (DMSO-d_6), (δ ppm): 168.2 (C=O), 166.9 (C=O), 154.9 (C-Br), 149.3 (C-N), 140.4 (C-CO), 139.6 (C-CO), other aromatic C-H carbons at 130.8, 122.3, 120.5, 118.5, 117.9, 116.9, 112.8, 111.7. *Anal*. For $C_{18}H_{13}BrN_2O_3$ (385.21): Calcd./found C: 56.12/56.25, 3.40/3.36, 7.27/7.33.

4.2.6 Ń-phenyl(thenoyl)-furan-2-carbohydrazide (6):

Brown solid (73% yield); mp. 133-134˚C; IR (ν^-, cm^{-1}): 3140.2 (NH), 3074.40 (CH_{arom}), 1673.15 (C=O). ^{1}HNMR (DMSO-d_6), (δ ppm): 12.51 (s, 1H, NH_{exch}), 7.97-7.59 (m, 12H, H_{arom}). ^{13}CNMR (DMSO-d_6), (δ ppm): 167.3 (C=O), 166.2 (C=O), 149.3 (C-N), 143.9 (C-CO), 142.3 (C-CO), other aromatic C-H carbons at 133.5, 128.6, 124.6, 122.3, 122.1, 119.3, 117.8, 107.9, 105.3. *Anal*. For $C_{16}H_{12}N_2O_3S$ (312.34): Calcd./found C: 61.53/61.55, 3.87/3.72, 8.97/8.89.

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 leaf worm *S. littoralis* (Boisd.) to the Mimic derivatives.

4.3.2 Laboratory bioassay (S. littoralis).

From pretest furan derivatives **2**, **3** and **5** were the highest active compounds, so they chosen for bioassay test. A series of concentrations (acetone) for each compound were prepared as the active ingredients based on ppm by diluting with water. Castor-bean leaves were dipped (Leaf-dipping technique corresponding to that described by Tabashnik)[22] for 30 seconds in each concentration then left to dry for one hour. The 2nd and 4th instars larvae tested 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. The average of mortality percentage was corrected using Abbott's formula.[23] The corrected mortality percentage of each compound was statistically computed according to Finney, (1971).[24] 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. This work ensures the importance of agricultural applications in life.[25-26]

References

1. Liu Y., Zhang S., & Abreu P. J. (**2006**) Heterocyclic terpenes: linear furano-and pyrroloterpenoids. *Nat. Prod. Rep.*, 23 (4) 630-651.
2. Chen W., Isman M. B., & Chiu S. F. (**1995**) Antifeedant and growth inhibitory effects of the limonoid toosendanin and Melia toosendan extracts on the variegated cutworm, Peridromasaucia (Lep., Noctuidae). *J. Appl. Entomol.*, 119 (1-5) 367-370.
3. Shi, Y., Wang, W., Liao, C., & Chiu, S. (1986). Effect of toosendanin on the sensory inputs of chemoreceptors of the armyworm larvae Mythimna separata. *Acta entomol. sin.*, 29 (3) 233-238.
4. Zhao W., Wolfender J. L., Hostettmann K., Xu R., & Qin G. (**1998**) Antifungal alkaloids and limonoid derivatives from Dictamnus dasycarpus. *Phytochemistry*, 47 (1) 7-11.
5. Wise J. C., Kim K., Hoffmann E. J., Vandervoort C., Gökçe A., & Whalon M. E. (**2007**) Novel life stage targets against plum curculio, Conotrachelus nenuphar (Herbst), in apple integrated pest management. *Pest Manag. Sci.*, 63 (8) 737-742.
6. Smagghe G., & Degheele D. (**1994**) Action of a novel nonsteroidal ecdysteroid mimic, tebufenozide (RH-5992), on insects of different orders. *Pest. Sci.*, 42 (2) 85-92.
7. Smagghe G., & Degreele D. (**1995**) Biological activity and receptor-binding of ecdysteroids and the ecdysteroid agonists RH-5849 and RH-5992 in imaginal wing discs of Spodoptera exigua (Lepidoptera: Noctuidae). *Eur. J. Entomol.*, 92 (1) 333-340.
8. Wing K. D. (**1988**) RH 5849, a nonsteroidal ecdysone agonist: effects on a Drosophila cell line. *Science*, 241 (4864) 467-469.
9. Dhadialla T. S., Carlson G. R., & Le D. P. (**1998**) New insecticides with ecdysteroidal and juvenile hormone activity. *Ann. Rev. Entomol.*, 43 (1) 545-569.
10. Teixeira M. G., Alvarenga E. S., Pimentel M. F., & Picanço M. C. (**2015**) Synthesis and insecticidal activity of lactones derived from furan-2 (5H)-one. *J. Braz. Chem. Soc.*, 26 (11) 2279-2289.
11. Isyaku Y., Uzairu A., Uba S., Ibrahim M. T., & Umar A. B. (**2020**) QSAR, molecular docking, and design of novel 4-(N,N-diarylmethyl amines) Furan-2(5H)-one derivatives as insecticides against Aphis craccivora. *Bull. Natl. Res. Cent*., 44 (1) 1-11.
12. Abdel-Raheem Sh. A. A., Kamal El-Dean A. M., Hassanien R., El-Sayed M. E. A., & Abd-Ella A. A. (**2020**) Synthesis and biological activity of 2-((3-Cyano-4,6-distyrylpyridin-2-yl)thio)acetamide and its cyclized form. *Alger. j. biosciences*, 01 (02) 046-050.
13. Bakhite E. A., Abd-Ella A. A., El-Sayed M. E. A., & Abdel-Raheem Sh. A. A. (**2014**) Pyridine derivatives as insecticides. Part 1: Synthesis and toxicity of some pyridine derivatives against Cowpea Aphid, Aphis craccivora Koch (Homoptera: Aphididae). *J. Agric. Food Chem.*, 62 (41) 9982–9986.
14. Bakhite E. A., Abd-Ella A. A., El-Sayed M. E. A., & Abdel-Raheem Sh. A. A. (**2017**) Pyridine derivatives as insecticides. Part 2: Synthesis of some piperidinium and morpholinium cyanopyridinethiolates and their Insecticidal Activity. *J. Saud. Chem. Soc.*, 21 (1) 95–104.
15. Kamal El-Dean A. M., Abd-Ella A. A., Hassanien R., El-Sayed M. E. A., Zaki R. M., & Abdel-Raheem Sh. A. A. (**2019**) Chemical design and toxicity evaluation of new pyrimidothienotetrahydroisoquinolines as potential insecticidal agents. *Toxicol. Rep.*, 6 (2019) 100-104.
16. Kamal El-Dean A. M., Abd-Ella A. A., Hassanien R., El-Sayed M. E. A., & Abdel-Raheem Sh. A. A. (**2019**) Design, Synthesis, Characterization, and Insecticidal Bioefficacy Screening of Some New Pyridine Derivatives. *ACS Omega*, 4 (5) 8406-8412.
17. Abdel-Raheem Sh. A. A., Kamal El-Dean A. M., Zaki R. M., Hassanien R., El-Sayed M. E. A., Sayed M., & Abd-Ella A. A. (**2021**) Synthesis and toxicological studies on distyryl-substituted heterocyclic insecticides. *Eur. Chem. Bull*., 10 (4) 225-229.
18. Abdel-Raheem Sh. A. A., Kamal El-Dean A. M., Hassanien R., El-Sayed M. E. A., & Abd-Ella A. A. (**2021**) Synthesis and characterization of some distyryl-derivatives for agricultural uses. *Eur. Chem. Bull.*, 10 (1) 35-38.
19. Al-Taifi E. A., Abdel-Raheem Sh. A. A., & Bakhite E. A. (**2016**) Some reactions of 3-cyano-4-(*p*-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydroquinoline-2(1*H*)-thione; Synthesis of new tetrahydroquinolines and tetrahydrothieno[2,3-*b*]quinolines. *Assiut University Journal of Chemistry (AUJC)*, 45 (1) 24-32.
20. Tolba M. S., Sayed M., Kamal El-Dean A. M., Hassanien R., Abdel-Raheem Sh. A. A., & Ahmed M. (**2021**) Design, synthesis and antimicrobial screening of some new thienopyrimidines. *Org. Commun.*, 14 (4) 334-345.
21. Khodairy A., Mansour E. S., Elhady O. M., & Drar A. M. (**2021**) Synthesis of Neonicotinoid analogues and study their toxicological aspects on *Spodoptera littoralis* and *Schizaphis graminum*. *Int. J. Pest Manag.*, Accepted Manuscript (DOI: 10.1080/09670874.2021.1943048).
22. Tabashnik B. E., Finson N., & Johnson M. W. (**1991**) Managing Resistance to Bacillus thuringiensis: Lessons from the Diamondback Moth (Lepidoptera: Plutellidae. *J. Econ. Entomol.*, 84 (1) 49-55.
23. Abbott W. S. (**1925**) A method of computing the effectiveness of an insecticide. *J. Econ. Entomol.*, 18 (2) 265-267.

24. Finny D. J. (**1952**) *Probit Analysis: A Statistical Treatment of the Sigmoid Response Curve*, 2nd Ed, Cambridge Univ. Press, Cambridge, U. K.
25. Yassin O. M., Ismail S., Ali M., Khalil F., & Ahmed E. (**2021**) Optimizing Roots and Sugar Yields and Water Use Efficiency of Different Sugar Beet Varieties Grown Under Upper Egypt Conditions Using Deficit Irrigation and Harvesting Dates. *Egypt. J. Soil Sci.*, 61 (3) 367-372.
26. Abdelgali A., Mustafa A. A., Ali S. A. M., Yassin O. M. (**2018**) Irrigation intervals as a guide to surface irrigation scheduling of maize in Upper Egypt. *J. Biol. Chem. Environ. Sci.*, 13 (2) 121-133.