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DESIGN, SYNTHESIS OF NOVEL SCHIFF BASES AS POTENTIAL INSECTICIDAL AGENTS AGAINST *SPODOPTERA FRUGIPERDA* (LEPIDOPTERA: NOCTUIDAE)

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ABSTRACT. In the present work, novel series of Schiff base **2-7** were synthesized *via* treatment of *p*-tosyloxy benzaldehyde with some indole and quinoxaline derivatives in ethanol under reflux. All product structures were verified using elemental analysis and spectroscopic investigations, including ^{13}C NMR, ^{1}H NMR, and IR. Our research was conducted on the insecticidal activity, and biological effects of the recently synthesized Schiff bases on *S. frugiperda*. The results showed that compound **5** was the most active insecticide, nearly surpassing methomyl as a reference, with LC_{50} values of 46.35 mg/L for second-instar larvae and 97.37 mg/L for fourth-instar larvae. This research opened up new avenues for the search for a novel class of insecticide.

KEY WORDS: Schiff bases, *Spodoptera frugiperda*, Insecticidal activity, Biological aspects, Toxicity

INTRODUCTION

Across the world, damaging insect pests in agriculture result in significant losses in agricultural yield and productivity each year [1-3]. Crop yield and growth are constantly in jeopardy due to pest activity, particularly that of animals. The Food and Agriculture Organization (FAO) has released growing estimates of actual and projected losses, which are regularly reported [4, 5], despite several interventions and advancements in crop protection. Pest resistance to pesticides has grown over time, affecting crop development and yield, and is one of the main causes [6]. *Spodoptera frugiperda* (Order: Lepidoptera, Family: Noctuidae) has been one of the most significant and hazardous pests affecting of many major field crops, ornamental plants, vegetables, and weeds in Egypt and many other countries for the past few decades [6, 7]. Because it seriously harms these host plants, it negatively impacts both the amount and quality of agricultural output, which in turn affects these nations' national economies and widens the global food gap [8, 9]. In an effort to control this pest, agricultural pesticides were used excessively and more frequently than necessary. This resulted in the development of pest resistance and the long-term persistence of pesticide residues, which has negative effects on humans and beneficial non-target organisms as parasites, predators, pollutes the environment and upsets the natural balance [10].

Moreover, Shiff bases play an important role in the field of organic chemistry [11-15] due to the simplicity of preparing, diverse chemical structures, and, in addition to their biological and medical applications such as anticancer and antibacterial, immobilization of enzymes, antimicrobial, antiviral, ant tubercular and anticancer activity, antimicrobial, antiviral, ant tubercular and anticancer activity, in addition to in synthesis of metal complexes and in agricultural applications [16-18].

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For these reasons, we had to develop some Shiff base derivatives that are less hazardous to mammals and safer for the environment, without developing cross-resistance to other insecticides, and that may have insecticidal efficacy against *S. frugiperda* in laboratory settings.

EXPERIMENTAL

All commercially available reagents were purchased from Merck, Aldrich and Fluka, and were used without further purification. All reactions were monitored by thin layer chromatography (TLC) using precoated plates of silica gel G/UV-254 of 0.25 mm thickness (Merck 60F254) using UV light (254 nm/365 nm) for visualization. Melting points were detected with a Kofler melting points apparatus and uncorrected. Infrared spectra were recorded with a FT-IR-ALPHBROKER-Platinum-ATR spectrometer, and are given as cm^{-1} using the attenuated total reflection (ATR) method. ^{1}H NMR and ^{13}C NMR spectra for all compounds were recorded in DMSO-*d6* on a Bruker Bio Spin AG spectrometer at 400 MHz and 100 MHz, respectively. Elemental analyses were obtained on a Perkin-Elmer CHN-analyzer model.

Laboratory bioassay

An instar of *S. frugiperda* larvae was taken at the agricultural research station Shandweel in Sohag, Egypt. Five concentrations of target synthesized compounds, namely 200, 100, 50, 25 and 12.5 mg/L, were prepared as emulsions in DMF for each drug in this research. A surfactant of 0.1% Triton X-100 was employed. Immediately following preparation, the emulsions were used. We immersed fresh castor bean leaves in the prepared concentrations of each investigated component for 10 seconds to test for larvicidal achievement [17-22]. Before the larvae could reach the treated leaves, they were allowed to dry in the shade. When the 48 hours were over, the larvae were switched to untreated leaves to continue feeding [23-27]. For every concentration, three replicates with ten larvae each were employed, along with the control. The same methodology was used to conduct control (check) tests without the tested substance. Larval mortality numbers were computed for a period of seven days following the exposure period [28-33]. After mortality was adjusted using Abbott's formula, probit analysis was performed [34]. To find the most effective chemical, the LC_{50} of the tested compounds were obtained by statistically analyzing the toxicity lines (ldp-lines) created on log concentration probit paper using Finney's approach [32]. Additionally, the solar equation was used to compare the tested compounds with the most effective chemical in order to evaluate the efficacy of the investigated substances. A new multiple range test (MRT) developed by Duncan has been used to statistically analyze the biological traits of a laboratory strain of *S. frugiperda* larvae in their fourth instar [35].

General procedure for synthesis of Schiff bases

A mixture of 4-tosyloxybenzaldehyde (**1**) (2 mmol, 0.55 g) with some indole derivatives (2 mmol) namely; *1H*-indole-2,3-dione 3-hydrazone; 1-methyl-*1H*-indole-2,3-dione 3-hydrazone; 5-chloro-1-methyl-*1H*-indole-2,3-dione-3-hydrazone4-methyl-3-oxo-3,4-dihydroquinoxaline-2-arbohydrazide; 3-oxo-3,4-dihydroquinoxaline-2-carbohydrazide or [1,3]thiazolo[3,2-a]benz imidazole-3(*2H*)-one hydrazone were refluxed in ethanol for 5 h. After the reaction finished (TLC), the reaction mixture was left at room temperature and the formed solid product was filtered off, washed with small amounts of ethanol, dried, and crystallized from ethanol.

*4-{(2-Oxo-1,2-dihydro-3H-indol-3-ylidene)hydrazono]methyl}phenyl 4-methylbenzenesulfonate (**2**)*. Yield, 86%; m.p. 179 °C; IR: 3167 (NH), 3090 (CH_{arom}), 1668 (C=O); ^{1}H NMR: δ 10.91 (s, 1H, NH), 8.59 (s,1H, =CH), 8.01-6.90 (m, 12H, CH_{arom}), 2.47 (s, 3H, CH_3); ^{13}C NMR: δ 193.08,

165.17, 159.46, 151.53, 150.52, 146.82, 145.10, 134.42, 132.99, 131.46, 131.00, 128.58, 123.10, 118.05, 116.57, 110.62, 110.51, 21.57; anal. calcd. for $C_{22}H_{17}N_3O_4S$ (419.45): C (63.00%), H (4.09%), N (10.02%), S (7.64%). Found: C (63.13%), H (4.14%), N (10.05%), S (7.59%).

*4-{(1-Methyl-2-oxo-1,2-dihydro-3H-indol-3-ylidene)hydrazono]methyl}phenyl 4-methylbenzene sulfonate (**3**)*. Yield, 87%; m.p. 140 °C; IR: 3198 (NH), 3097 (CH_{arom}), 1662 (C=O); ^{1}H NMR: δ 8.31 (s,1H, =CH), 7.78-7.05 (m, 12H, CH_{arom}), 3.21 (s, 1H, N-CH_3), 2.42 (s,3H, CH_3); ^{13}C NMR: δ 186.25 (C=O);, 156.24, 152.16, 152.03, 146.13, 140.54, 139.16, 135.81, 130.20, 127.00, 125.36, 29.14, 21.56; anal. calcd. for $C_{23}H_{19}N_3O_4S_2$ (433.47): C (63.73%), H (4.42%), N (9.69%), S (7.40%). Found: C (63.79%), H (4.36%), N (9.74%), S (7.37%).

*4-{(5-Chloro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)hydrazono]methyl}phenyl 4-methyl benzenesulfonate (**4**)*. Yield, 80%; m.p. >300 °C; IR: 3145 (NH), 3098 (CH_{arom}), 1664 (C=O); ^{1}H NMR: δ 11.09 (s, 1H, NH), 8.64 (s,1H, =CH), 7.89-6.94 (m, 11H, CH_{arom}), 2.43 (s, 1H, CH_3); ^{13}C NMR: δ 187.46 (C=O), 163.46, 156.81, 150.09, 149.08, 145.56, 144.15, 142.10, 140.00, 136.73, 134.67, 130.15, 129.58, 127.56, 125.34, 123.28, 120.37, 21.42; anal. calcd. for $C_{22}H_{16}ClN_3O_4S$ (453.89): C (58.21%) H (3.55%) Cl (7.81%) N (9.26%), S (7.06%). Found: C (58.32%) H (3.49%), Cl (7.76%) N (9.31%), S (7.12%).

*4-{(5-Chloro-1-methyl-2-oxo-1,2-dihydro-3H-indol-3-ylidene)hydrazono]methyl}phenyl 4-methylbenzenesulfonate (**5**)*. Yield, 83%; m.p. 150 °C; IR: 3190 (NH), 3087 (CH_{arom}), 1676 (C=O); ^{1}H NMR: δ 8.63 (s,1H, =CH), 8.30-7.11 (m, 11H, CH_{arom}), 3.19 (s, 1H, N-CH_3), 2.43 (s, 3H, CH_3); ^{13}C NMR: δ 188.90 (C=O), 164.14, 157.09, 151.00, 148.89, 146.35, 145.13, 143.68, 141.47, 138.26, 135.78, 133.57, 130.57, 129.16, 124.37, 123.95, 121.37, 29.85, 21.50; anal. calcd. for $C_{23}H_{18}ClN_3O_4S$ (467.92): C (59.04%), H (3.88%), Cl (7.58%), N (8.98%), S (6.85%). Found: C (C (59.11%), H (3.93%), Cl (7.52%), N (9.00%), S (6.92%).

*4-[{[(3-Oxo-3,4-dihydroquinoxalin-2-yl)carbonyl]hydrazono}methyl]phenyl 4-methylbenzen esulfonate (**6**)*. Yield, 81%; m.p. 290 °C; IR: 3176 (NH), 3061 (CH_{arom}), 1658 (C=O); ^{1}H NMR: δ 12.39 (s, 1H, NH), 12.21 (s, 1H, NH), 8.34 (s, 1H, =CH), 8.02-6.99 (m, 12H, CH_{arom}), 2.43-2.38 (d, 1H, CH_3); ^{13}C NMR: δ 191.45 (C=O), 169.82(C=O), 159.43, 155.72, 150.06, 149.36, 146.79, 142.80, 140.99, 138.76, 135.96, 134.90, 133.58, 131.05, 130.46, 128.95, 125.06, 123.83, 21.90 anal. calcd. for $C_{23}H_{18}N_4O_5S$ (462.47): C (59.73%), H (3.92%), N (12.11%), S (6.93%). Found: C (59.73%), H (3.92%), N (12.11%), S (6.93%).

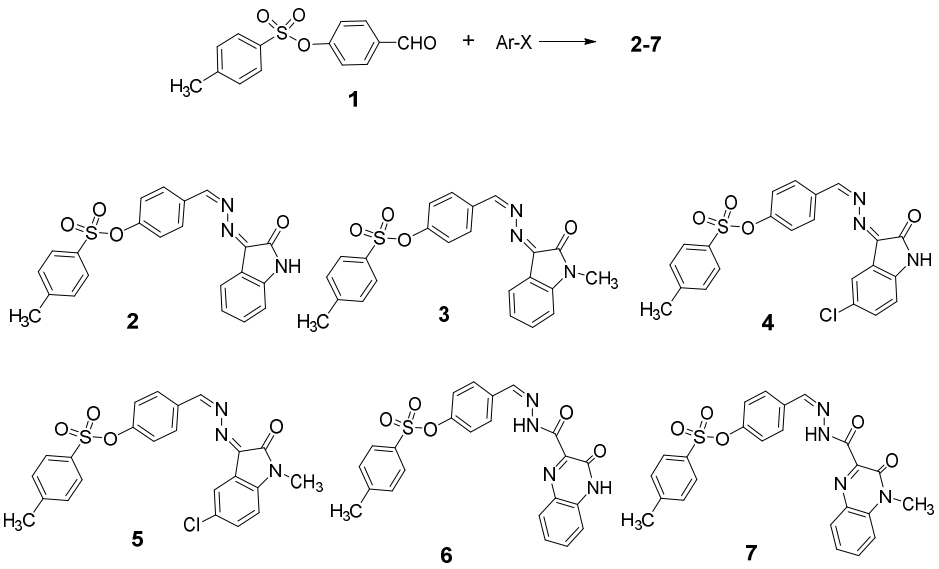
*4-[{[(1-Methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)carbonyl]hydrazono}methyl]phenyl 4-methyl benzenesulfonate (**7**)*. Yield, 83%; m.p. 195 °C; IR: 3190 (NH), 3087 (CH_{arom}), 1676 (C=O); ^{1}H NMR: δ 12.22 (s, 1H, NH), 8.32 (s,1H, =CH), 8.02-6.97 (m, 12H, CH_{arom}), 3.41 (s, 1H, N-CH_3), 2.43 (s,3H, CH_3); ^{13}C NMR: δ 190.99, 167.22, 160.48, 150.30, 148.10, 144.15, 134.20, 133.84, 133.51, 132.98, 132.04, 131.63, 130.76, 130.70, 130.09, 129.41, 128.69, 128.58, 124.72, 124.50, 123.00, 115.63, 29.42, 21.61; anal. calcd. for $C_{24}H_{20}N_4O_5S$ (476.50): C (60.49%), H (4.23%), N (11.76%), S (6.73%). Found: C (60.62%), H (4.18%), N (11.67%), S (6.82%).

RESULTS AND DISCUSSION

Chemistry

Our synthesis begin with treatment of 4-tosyloxybenzaldehyde (**1)** with some indole derivatives namely; 3-hydrazino-1,3-dihydro-*2H*-indol-2-one; 3-hydrazino-1-methyl-1,3-dihydro-*2H*-indol-2-one; 5-chloro-3-hydrazino-1,3-dihydro-2*H*-indol-2-one; 5-chloro-3-hydrazino-1-methyl-1,3-dihydro-2*H*-indol-2-one or quinoxalines such as 3-oxo-3,4-dihydroquinoxaline-2-carbohydrazide

and 4-methyl-3-oxo-3,4-dihydroquinoxaline-2-carbohydrazide in ethanol under reflux to afford the crossponding Shiff bases **2-7**. (Scheme 1).



Scheme 1. Synthesis of Schiff bases **2-7**.

The structure of all products was confirmed on the basis of IR, ^{1}H-NMR, ^{13}C NMR, and elemental analyses. Their IR spectra showed the absence of NH_2 and aldehydic C=O group absorption bands and the appearance of new band due to NH in the region 3345 - 3217 cm^{-1} and the carbonyl groups of indole ring appearance in the region 1640-1668 cm^{-1}. ^{1}H NMR spectra showed, in addition to the expected aromatic protons signals, new singlet signals at δ 10.91, 11.09, 12.39 ppm and δ 12.22 ppm due to NH groups in compounds **2**,**4**,**6** and **7**, respectively. Moreover, the N=CH groups in compounds **3**-**7** showed new band in the region δ 8.64-8.31 ppm. Furthermore, the N-CH_3 groups in compounds **3**, **5** and **7** appear at δ 3.21, 3.19 and δ 3.41 ppm respectively, and the CH_3-tosyl groups in the range δ 2.47-2.38 ppm. Their ^{13}C NMR spectra showed the appearance of new signals in the region δ 191.45- 169.82 ppm due to C=O groups; the N-CH_3 groups in compounds **3**, **5** and **7** showed new siginals from 29.85 ppm to δ 29.14 ppm. respectively, in addition to the CH_3 groups in regions δ 21.90 - 21.50 ppm., The elemental analyses of compounds provided the structure of the new compounds (cf. experimental).

Insecticidal activity

The toxicity tested results for *S. frugiperda* (Order: Lepidoptera, Family: Noctuidae) are indicated in Table 1, which showed the insecticidal efficacy of sex innovatively tested compounds against the second instar larvae of the laboratory strain of the polyphagous pest, *S. frugiperda*, at different concentrations. The represented data showed that the mortality percentages directly increase with the increasing concentrations and days post-treatment. As a result, the compounds **2-7** against the treated larvae of *S. frugiperda* were 73.02%, 66.67%, 53.34%, 87.33, 46.67, and 36.67%, respectively, compared with methomyl as a reference insecticide, in which the mortality

percentage was 97.33%. Based on the LC_{50} value, all of the substances that were investigated showed strong harmful effects after seven days. Compounds **5** and **2** show the best results out of all of them, with 73.02 and 87.33, respectively.

Table 1. Mortality% of the 2nd instar larvae of *S. frugiperda* after treatment by the newly synthesized compounds **2-7** compared with a reference insecticide methomyl, after 7 days of treatment.

Compound	% after days post treatment				
	Conc.	1 day	3 days	5 days	7 days
Methomyl	12.5	9.33	11.67	19.00	25.33
	25	27.67	32.10	40.67	52.61
	50	68.67	74.67	85.33	91.23
	100	80.00	82.33	91.00	96.67
	200	86.00	89.62	92.32	97.33
2	12.5	3.32	11.02	15.67	19.00
	25	6.67	13.32	21.00	31.00
	50	23.34	34.34	42.34	51.24
	100	33.20	42.20	55.24	66.24
	200	34.36	45.35	59.67	73.02
3	12.5	2.20	4.34	9.00	18.67
	25	3.26	6.67	15.65	28.82
	50	16.67	26.67	36.67	46.67
	100	23.34	36.67	46.67	60.00
	200	26.67	45.54	56.67	66.67
4	12.5	0	2.36	6.67	10.00
	25	2.36	3.34	13.34	23.34
	50	13.34	23.34	36.67	43.34
	100	16.67	26.67	40.00	50.00
	200	23.34	33.34	43.34	53.34
5	12.5	6.33	9.67	11.00	15.33
	25	19.67	22.10	25.67	29.61
	50	33.67	44.67	49.33	52.23
	100	52.00	59.33	63.00	66.67
	200	76.00	79.62	82.32	87.33
6	12.5	0	0	0	3.34
	25	0	0	3.34	13.34
	50	3.34	6.67	10.00	25.00
	100	6.67	16.67	26.67	36.67
	200	13.34	23.34	36.67	46.67
7	12.5	0	0	0	0
	25	0	0	0	6.67
	50	0	3.34	13.34	23.34
	100	6.67	13.34	20.00	33.34
	200	3.34	13.34	23.34	36.67

Toxicological studies

The purpose of the laboratory bioassay investigation was to determine the insecticidal efficiency of freshly synthesized chemicals intended for sex targets against a sensitive lab strain of the highly phytophagous pest *S. frugiperda's* second and fourth larval instars. The results of the bio evaluation showed that all of the target synthesized tested compounds exhibited strong to moderate insecticidal activity after seven days of treatment. For second-instar larvae, the LC_{50} values ranged from 46.35 to 313.1 mg/L, and for fourth-instar larvae, from 97.37 to 1588.3 mg/L.

As a result, after seven days of treatment, the ten target-tested compounds demonstrated insecticidal activity for the second and fourth instars of *S. frugiperda* larvae. The newly synthesized compounds' harmful effects for *S. frugiperda* were evaluated in order to determine the toxicological applicability of these compounds as insecticidal agents. Consequently, Table 1 and Figure 1 were used to determine the LC_{50} values. The newly created substances underwent screening to determine their insecticidal bio efficacy, as indicated below: Following a 7-day period, the target chemicals **2**, **3**, **4**, **5**, **6**, and **7** tested against larvae in their second instar showed the following LC_{50} values: 60.84, 97.37, 186.4, 46.35, 313.1, and 128.1 mg/L. After seven days, the target compounds Shiff base were tested against larvae in their second instar and showed the following LC_{50} values: 102.2, 798.3, 965.1, 97.37, 1588.3, and 745.9 mg/L. The results show that compound **6** was more nearly in activity than the reference insecticide methomyl, in which LC_{50} of **6** was 46.35 mg/L and LC_{50} of methomyl was 26.63 mg/L.

Table 1. The insecticidal efficacy for recently synthesized Shiff base was recorded after 7 days of the behavior of the products as toxicity toward a sensitive laboratory strain of the 2nd and 4th larval instar of *S. frugiperda.*

	2nd instar larvae				4th instar larvae			
Comps.	LC_{50} (mg/L)	slope	x^2	Toxic ratio	LC_{50} (mg/L)	slope	x^2	Toxic ratio
2	60.84	0.225±0.820	0.231	43.70	102.2	0.239±0.095	0.589	71.77
3	97.37	0.229±0.081	0.174	27.31	798.3	3.418±0.953	0.663	9.10
4	186.4	1.365±0.388	0.186	14.20	965.1	2.083±1.077	0.036	7.10
5	46.35	1.295±0.392	0.699	57.40	97.37	0.229±0.083	0.652	75.53
6	313.1	1.815±1.014	0.053	8.50	1588.3	3.436±1.182	0.892	4.60
7	128.1	1.297±0.097	0.016	20.71	745.9	3.176±1.184	0.365	9.80
Methomyl	26.63	0.246±0.080	0.252	100	73.35	0.460±0.085	0.231	100

Notes: Toxicity Ratio is calculated as methomyl's LC_{50} value for baseline toxicity / the compounds' LC_{50} value $\chi 100$.

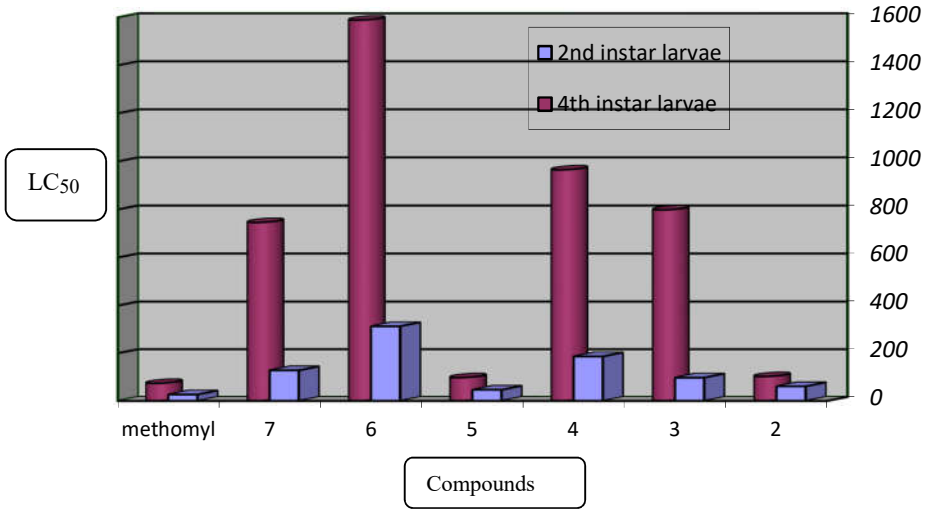


Figure 1. Insecticidal activity of Shiff bases **2-7** against the 2nd and 4th instar larvae of *S. frugiperda* after treatment.

Biological studies

We have tested the synthetic target components **2-7** on a number of biological traits of *S. frugiperda*. Recently molted fourth instar *S. frugiperda* larvae were fed caster bean leaves treated with LC_{25} concentrations of the most lethal sulphonate derivatives of the species for 8 days before being switched to untreated leaves until pupation, in an attempt to gain a better understanding of the biology of the species. The findings are displayed in Tables 3 after a summary of the significant biological elements that were investigated.

Table 3. The very toxic, freshly synthesized compounds **2**, **3**, **4**, **5**, **7** at their LC_{25} values had an impact on the biological traits of a laboratory strain of fourth-instar *S. frugiperda* larvae.

Tested comp.	Larval duration Days ± SE	Pupal duration Days ± SE	Weight [mg] ± SE	Normal pupae %±SE	Deformed pupae %±SE	Adult emergence %±SE
5	$18.26^{a} \pm 0.20$	$10.53^{d} \pm 0.20$	$240.11^{d} \pm 0.21$	$32.43^{e} \pm 0.52$	$17.12^{a} \pm 0.33$	$71.44^{c} \pm 0.51$
2	$16.25^{b} \pm 0.20$	$10.52^{d} \pm 0.20$	$252.22^{c} \pm 0.19$	$70.42^{d} \pm 0.41$	$14.94^{b} \pm 0.32$	$66.11^{c} \pm 0.86$
3	$12.19^{c} \pm 0.01$	$15.01^{c} \pm 0.01$	$273.52^{b} \pm 0.17$	$82.22^{c} \pm 0.5$	$6.91^{c} \pm 0.30$	$69.22^{b} \pm 0.57$
4	$10.85^{d} \pm 0.20$	$15.12^{c} \pm 0.20$	$278.23^{b} \pm 0.14$	$90.01^{a} \pm 0.80$	$4.81^{d} \pm 0.20$	$82.25^{b} \pm 0.38$
7	$8.20^{e} \pm 0.20$	$17.72^{b} \pm 0.20$	$298.20^{a} \pm 0.11$	$95.62^{a} \pm 0.25$	$3.92^{d} \pm 0.17$	$83.54^{a} \pm 0.61$
Control	$8.05^{e} \pm 0.20$	$19.11^{a} \pm 0.20$	$298.20^{a} \pm 0.15$	$95.12^{a} \pm 0.25$	$3.84^{d} \pm 0.17$	$92.73^{a} \pm 0.62$
LSD=0.05	0.71	0.71	0.71	1.02	0.82	1.20

According to Duncan's check, letters indicate significant changes across treatments (SE = standard error). The data presented in Table 3 indicates that every examined chemical significantly lengthened the larval duration, which was, according to control in (8.05 days), **5** (18.26 days), **2** (16.25 days), **3** (12.19 days), **4** (10.85 days) and **7** (8.05 days). On the other hand, the examined components shortened the pupal time, tabulating as **5** (10.53 days) and **2** (10.52 days), with results that differed greatly from one another. The effects of **3, 4** and **7** were different from those of the larvae that were not treated (17.1 days), tabulating at 15.12, 17.72, and 19.11 days, respectively.

The tabulated results displayed in Table 2 indicate that the pupal weight trended in the same manner. In comparison to the control pupal weight of 298.20 mg, the examined components all considerably reduced pupal weight, with **6** being the most effective, recording (240.11 mg). **2**, **3**, **4**, and **7** followed at 252.22, 273.52, 278.23, and 298.20, respectively.

Compounds **5, 2, 3, 4,** and **7** were the most effective in producing the latent effects, percentages of malformed pupae, healthy pupae, and adult emergence, as indicated by Table 3's results. These factors were (42.43, 17.12, 71.44 %), (70.42, 17.94, 66.11 %), (82.22, 6.91, 69.22 %), (90.01, 4.81, 82.25 %), (95.62, 3.92, 83.54 %), and control moiety (95.12, 3.84, and 92.73%).

CONCLUSION

New series of Schiff base were synthesized *via* treatment of *p*-tosyloxybenzaldehyde with some indole, quinoxaline or thiazolo[3,2-a]benzimidazole derivatives. These products were characterized by spectral techniques such as IR, ^{1}H NMR and ^{13}C NMR spectra and elemental analysis. The newly synthesized Schiff base were assessed against *S. frugiperda*. It has been found that compound **5** has an LC_{50} of 46.35 mg/L for second-instar larvae and an LC_{50} of 97.37 mg/L for fourth instar larvae, which indicated the most active and closely outperforming methomyl as a reference insecticide in terms of activity.

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