Available Online at ESci Journals
International Journal of Entomological Research
ISSN: 2310-3906 (Online), 2310-5119 (Print)
http://www.escijournals.net/IJER

EVALUATION OF NEW, TRIAZOLOISOQUINOLINE AND PYRAZOLOPYRIDAZINE COMPOUNDS AGAINST THE DESERT LOCUST *SCHISTOCERCA GREGARIA* (ORTHOPTERA: ACRIDIIDAE)

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A B S T R A C T

The present study deals with the bioactivities of 3-Acetyl[1,2,4]triazolo[3,4-*a*]isoquinoline was used to prepare a novel enaminone 5. Reactions of 5 with hydrazonoyl halides 6 gave triazoloisoquinolines 10 with a carbonylpyrazole as a side chain. Hydrazinolysis of 10 gave the pyrazolopyridazines 12. Bioactivity of these compounds was applied on 4th nymphal instar of the desert locust *Schistocerca gregaria*. Results clearly showed that the compound 12b was the most effective against 4th nymphal instars, while the compound 12a has the lowest effect. Meanwhile the chemical compounds, 10b and 10a were intermediate bioactive. In order of toxicity the lethal concentration was 0.31, 0.37, 0.46, and 0.57 of the chemical compounds 12b, 10b, 10a and 12a respectively. On the other hand some deformation of the treated nymphs was observed by the effect of different chemical compounds due to molting inhibition for the next stages.

Keywords: [1,2,4]Triazolo[3,4-*a*]isoquinolines, Enaminones, Hydrazinolysis, Hydrazonoyl Chlorides, Cycloaddition Reactions. Bioactivities study, desert locust, *Schistocerca gregaria*.

INTRODUCTION

Researchers have studied quite number of new biologically active chemicals used against pests. This is because of claims of reported resistance to traditional chemicals as well as negative effects on non-target organisms (Mulla and Su,1999). The mode of action of different novel chemicals groups were investigated against many pests as well as bacteria and other microorganisms. Many chemicals and drugs possessed modified pharmacological and toxicological properties when administered in the form of complexes. (Sorenson, 1976 and Ruiz, *et al*., 1995). Desert locust, *Schistocerca gregaria* are among the most important plant hoppers (Uvarov, 1966). The novel chemical compounds pyrazolo- and tryazolo- chemical derivatives.pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrami-dine derivatives have been detected as both potent of biological and receptors antagonists (Lerner, 1989; Luisa Savini, *et al.,* 2001; Straub *et al*., 2002; Wiley-Liss, 2001). On the other hand triazolo derivatives have been detected as bioactive compounds in vivo for their anti-inflammatory and analgesic activities (Reprod Fertil, 1989; Luisa Savini, *et al.,* 2001 and Bioorg, 2002).

Fused isoquinoline derivatives comprise a very interesting class of compounds due to their significant pharmacological and biological activities (Tiwaria, *et al*., 2006; Solecka, *et al*., 2009; Bentley, 2003 and Fülöp *et al.,* 1990).

These compounds obtained from the synthesis of triazoloisoquinoline compound 4 *via* reaction of 3,4-dihydro-6,7-diethoxyisoquinoline 3 with hydrazonoyl chloride 1 in chloroform in the presence of triethylamine or in pyridine as catalyst and solvent (Awad *et al.,* 2001; Hassaneen *et al*., 2006-07; and Hassaneen, *et al*., 2009) which was found to be useful precursor for the synthesis of enaminone 5. The latter compound 5 was used to prepare conjugates of triazoloisoquinolines with carbonylpyrazoles 10 and

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pyrazolopyridazines 12.

As a part for our going Research on metabolic studies aimed at developingsimple andeffecient synthesis of polyfunctional heteroaromatic compounds that have bioactivity against the 4th instar nymph of the plant hoppers, *Schistocerca gregaria*.

MATERIALS AND METHODS

Desert locusts culture: *Shistocerca greagaria* (Forskal) were reared at the rearing facility in the Department of Entomology, Faculty of Science, Cairo University as described by (Hunter-Jones, 1966). The gregarious colony was reared under crowded conditions in a 12hrs. light: 12hrs. dark regime at a temperature of 29±2°Cand a relative humidity of 60-70%. Locust feed on clover *Medicago sativa* provided fresh daily throughout the study period.

Experimental treatment: Fourth instars of *Sch. gregaria* were feed on clover that were treated with the chemical compounds (Triazoloisoquinoline and Pyrazolopyridazine) at the following concentrations of 0.25, 0.5, and 0.75 (mg/ml) using dimethyl sulfoxide as solvent. Nymphal mortalities were estimated and the LC50 values were calculated.

Bioassay and statistical calculation: Nymphal mortalities were estimated according to Abbot (1925) and the LC50 values were calculated using probit analysis (Finney, 1971). Data was analyzed by the Student's *t*- distribution and refined by Bessel correction (Moroney, 1956).

Spectrophotmeteric analysis: The IR spectra were recorded as KBr pellets using an FTIR Bruker-Vector 22 spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and [D_6] DMSO as solvents at 300 MHz on a Varian Gemini NMR spectrometer using TMS as internal standard. Chemical shifts are reported in δ units (ppm). Mass spectra were measured on a Shimadzu GMMS-QP-1000 EX mass spectrometer at 70 eV.(E)-1-(8,9-Diethoxy-1-phenyl-1,5,6,10b-tetrahydro[1,2,4]triazolo[3,4-a]isoquinolin-3-yl)-3 dimethylaminopropenone (5). A mixture of 1-(8,9-diethoxy-1-phenyl-1,5,6,10b-tetrahydro-[1,2,4]triazolo[3,4-*a*]isoquinolin-3-yl)ethanone 4 (1.895g, 5 mmol) and dimethylformamide-dimethylacetal (DMF-DMA) (3mL) was refluxed for 4 h. The solid that precipitated was collected and crystallized from ethanol.

Synthesis of pyrazolyl triazoloisoquinoline derivatives (***10a-b***)**:** To a solution of hydrazonoyl halides 6 (5 mmole) and (E)-1-(8,9-diethoxy-1-phenyl-1,5,6,10b-tetrahydro[1,2,4]triazolo[3,4-*a*]-isoquinolin-3-yl)-3-dimethylaminopropenone 5 (2.17 g, 5 mmol) in chloroform (60 mL) was added triethylamine (0.7 ml, 5 mmol) at room temperature. The reaction mixture was refluxed for 4 h. The solvent was evaporated and the residue treated with ethanol. The solid that formed was collected and crystallized from ethanol. The compounds are listed as follows:

1-[4-(8,9-Diethoxy-1-phenyl-1,5,6,10b-tetrahydro[1,2,4] triazolo[3,4-a]isoquinoline-3-carbonyl)-1-phenyl-1H-pyrazol-3-yl]ethanone (10a).

(3-Benzoyl-1-phenyl-1H-pyrazol-4-yl)-(8,9-diethoxy-1-phenyl-1,5,6,10b-tetrahydro[1,2,4]-triazolo[3,4-a]isoquinolin-3-yl)methanone (10b).

Synthesis of pyrazolo[3,4-d]pyridazin derivatives (***12a-b***)**:** The *pyrazolyl triazoloisoquinoline derivatives* **10** (5 mmol) in ethanol (30 mL) and hydrazine hydrate 99 % (0.7 mL, 10 mmol) was refluxed for 4 h, during which the corresponding pyrazolopyrdazine 12 was precipitated. The solid was collected washed with water and crystallized from dimethylformamide. The compounds prepared are listed as follows:

8,9-Diethoxy-3-(7-methyl-2-phenyl-2H-pyrazolo[3,4-d] pyridazin-4-yl)-1-phenyl-1,5,6,10b-tetrahydro[1,2,4] triazolo[3,4-a]isoquinoline (12a).

3-(2,7-Diphenyl-2H-pyrazolo[3,4-d]pyridazin-4-yl)-8,9-diethoxy-1-phenyl-1,5,6,10b-tetrahydro-[1,2,4]triazolo [3,4-a]isoquinoline (12b).

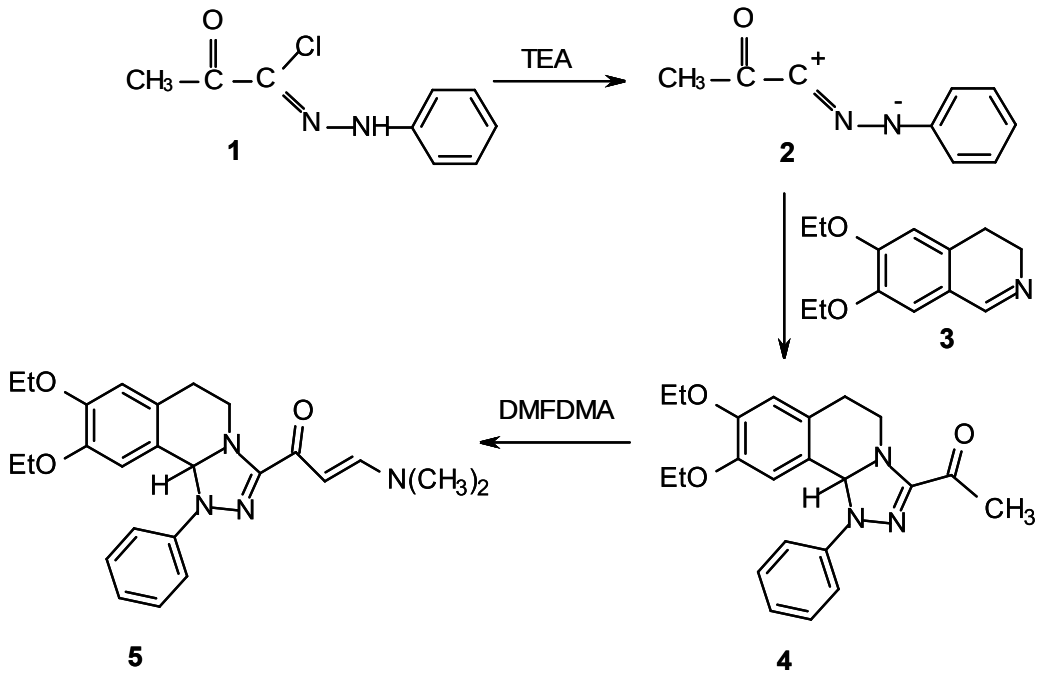
RESULTS AND DISCUSSION

The starting material, 3,4-dihydro-6,7-diethoxyisoquinoline (3), was prepared according to the procedure of Bischler and Napieralsky (1893).

The value of the coupling constant is compatible with the (*E*)-configuration [Dawood, 2005] depicted in Scheme 1.

Reaction of enaminone 5 with hydrazonoyl halides 6 in refluxing chloroform in the presence of triethylamine gave, in each case, one isolable product as evidenced by TLC analysis (Scheme 2). The proposed mechanism leading to the formation of the latter products starts with regioselective 1,3-dipolar cycloaddition of nitrilimines 7 to the carbon-carbon double bond of the enaminone 5 to afford the cycloadducts 8 which afforded the pyrazole derivatives 10 *via* elimination of dimethylamine and the other isomer 11 was discarded (Scheme 2). In addition, the structures of compounds 10 were confirmed by their reactions with hydrazine

hydrate. Thus, refluxing of 10 with hydrazine hydrate in ethanol afforded the pyrazolo[3,4-*d*]pyridazine derivatives 12 (Scheme 3). The structures of the products, indicated by their preparative route and elemental analyses, were further supported by their spectral properties. For example, the IR spectra revealed the absence of carbonyl bands. The ^{1}H NMR spectrum of 12a yielded a signal for the pyridazine methyl group at δ = 3.01 ppm; the acetyl methyl signal in 10a occurred at δ = 2.63 ppm [Shawali,1977].

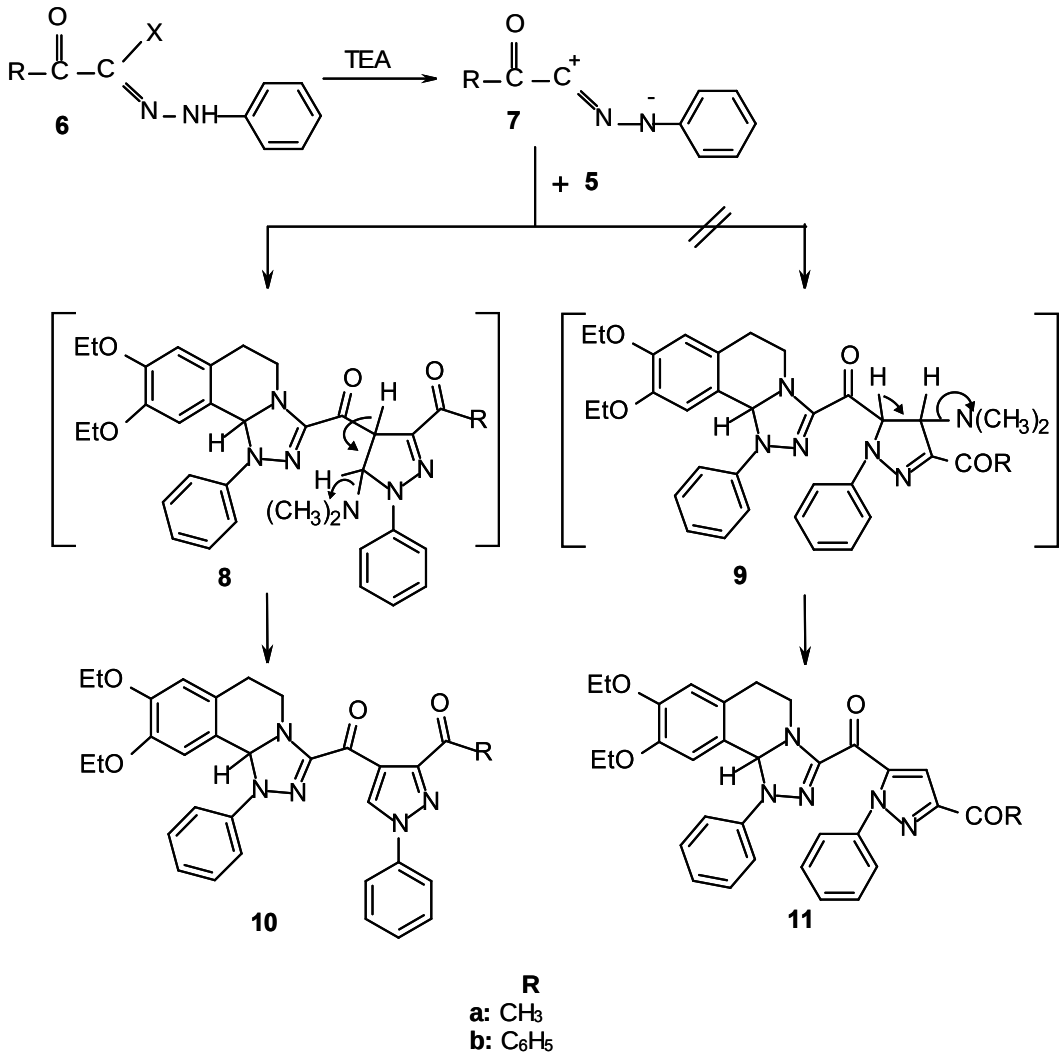


Scheme 1. Synthesis of enaminone 5 compound.

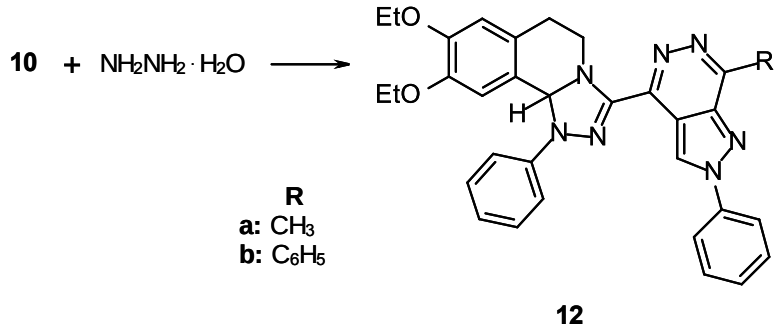
Potential effect of the novel triazoloisoquinoline and pyrazolopyridazine on the 4th nymphal instars of the desert locust *Schistocerca gregaria*: The novel chemical compounds, 10a, 12a, 10b and 12b caused some biological effects against the desert locust *S. gregaria*. Percent of nymphal mortalities of these compounds increased gradually upon increasing concentrations (Table 1).

Table (1): Potential effect of some novel chemicals on desert locust, Schistocerca gregaria.

Chemical compounds	Concentration mg/ml	%Nymphal mortality			%Selective mortality
		24hrs	48hrs	72hrs	
10a	0.25	8.0	7.0	15	30
	0.5	9.0	11	28	48
	0.75	12	19	36	67
12a	0.25	6.0	7.0	7.0	20
	0.5	10	12	14	36
	0.75	15	17	26	58
10b	0.25	11	13	16	40
	0.5	13	17	25	55
	0.75	21	24	40	85
12b	0.25	15	12	23	50
	0.5	19	26	30	75
	0.75	22	26	47	95



Scheme 2. Synthesis of pyrazoles 10 compound.



Scheme 3. Synthesis of pyrazolopyridazines 12 compound.

Highest lethal effect was 95% after feeding the nymph on the treated clover with the highest concentration, 0.75mg/ml of the compound 12b. While the lowest lethal effect was 20% when the nymphs were feed on clover treated with 0.25mg/ml of the chemical compound 12a. Chemical compound 10b were bioactive against nymphal instars than the compounds 10a. This could happen due position attachment of the active nitrogen groups Scheme (2). The insecticidal compositions of imidazo (1,2b) Pyridazinyl esters was

reported as potent for pest control (Perron, *et al*., 1976). Also Straub *et al*. (2002) mention that, pyrazolopyridine compound was metabolite oxidized inside animal bodies. On the other hand, pyrazolopyrdine and pyridine derivatives act as anti-inflammatory against macrophage growth (Hamdy and Gamal-Eldeen, 2009). The biological activity of pyrazolo[4, 3-e]1, 2,4-triazolo[1, 5-c]pyrimidine characterize as antagonists for adenosine receptor (Barrldi *et al*., 2001).

High-affinity radioligand antagonist for this receptor subtype, designated as [^{3}H]MRE3008F20,(Barrldi *et al*., 2001). Also adenosine regulates many physio-pathological functions by interaction with four different G-protein-coupled receptors. Furthermore pyrazolopyridine affected as stimulators of soluble guanylate cyclase enzyme which oxidised at their 5-pyrimidinyl-cyclopropyl and morpholino residue (Bioorg, 2002).

On the other hand, it was observed that the different chemical compounds had many deformation effects due to inhibit the molting processes and disturbance the hormonal system of the different instars of *Sh. gregaria*. Most of deformations was, crawled wings and nymphal adult intermediate stages.

In order of toxicity LC_{50}'s were 0.46, 0.57, 0.37 and 0.31mg/ml of the compounds 10a, 12a, 10b and 12b respectively (Table 2).

Table (2): Toxicological effect of novel chemicals against 4th nymphal instars of *Schi. gregaria*.

Chemical compounds	Lethal effect(LC50)
10a	0.46
12a	0.57
10b	0.37
12b	0.31

Pyrazolidine-3,5-diones possessed herbicidal effect against many of the insects orders. Also, the insecticidal compositions of imidazo(1,2b) Pyridazinyl esters is useful for insect control (Perronnet *et al*., 1976). In Series of 1,2,4-triazolo[4,3-*a*]quinoline derivatives was anti-inflammatory and analgesic activities for some animals (Luisa Savini, *et al*., 2001, and Bartek *et al*., 2004).

The obtained results concluded that alive insect adults from the treated nymphs were unfertile and there is no eggs laid, due to antifertility effect of triazoloisoquinoline derivatives. Furthermore New pyridone, thioxopyridine, pyrazolopyridine and pyridine derivatives are inflammatory mediators in stimulated RAW 264.7 murine macrophage (Hamdy NA, and Gamal-Eldeen, 2009). Also the other hand patel *et al*. (1988) discussed the bioactivity of pyrazolopyridine derivatives is a potent anticonvulsant.

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