Synthesis and anti-Aphid Aphis gossypii (Glover) activity of some new quinoline derivatives

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Síntesis y actividad contra el pulgón Aphis gossypii Glover de algunos nuevos derivados de quinolina

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Recibido: 18 de mayo de 2010; aceptado: 23 de julio de 2010

RESUMEN

Se prepara una serie de derivados de quinolina por reacción de 2-(m- y p-acetilanilino)quinolinas **6a-b** con aldehídos en condiciones de Claisen-Schmidt seguida de ciclación con fenilhidrazina y hidroxilamina. La reacción de **6a y 6b** con hidrazina, semicarbazida, tiosemicarbazida y cianoacetilhidrazida, seguida de reacciones de condensación, rinde diversos derivados de quinolina. Se evalúa la actividad contra el pulgón Aphis gossypii, que daña las cosechas de algodón en Egipto. El compuesto **12** muestra un valor de LC50 de 19429E-10 ppm, siendo por tanto mucho más activo que Marshal (Carbosulfan), uno de los insecticidas de amplio espectro extensamente empleados en este campo.

Palabras clave: Insecticidas, Pulgón Aphis gossypii, Quinolina, Pirazol, Tiosemicarbazida.

SUMMARY

A series of quinoline derivatives have been elaborated from reaction of 2-(*m*- and *p*-acetylanilino)-quinolines **6a-b** with aldehydes under Claisen-Schmidt conditions followed by cyclization with phenyl hydrazine and hydroxylamine. Reaction of **6a** and **6b** with hydrazine, semicarbazide and thiosemicarbazide, cyanoacetylhydrazide and subsequent some condensation reactions led to diverse quinoline derivatives. Anti aphid *Aphis gossypii* that harm cotton crop in Egypt was screened. Compound **12** showed an LC_{50} value of 19429E-10 ppm which is very more active than Marshal (Carbosulfan), one of the broad spectrum insecticides widely used in this field.

Key words: Insecticides, Aphid *Aphis gossypii*, Quinoline, Pyrazole, Thiosemicarbazide.

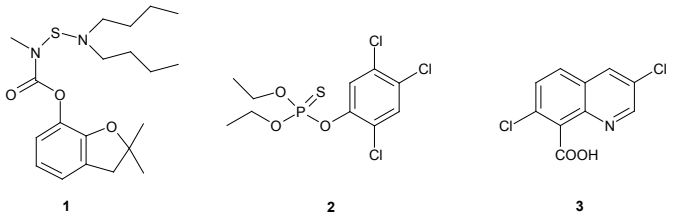
RESUM

Es prepara una sèrie de derivats de quinolina per reacció de 2-(m- i p-acetilanilino)quinolines 6a-b amb aldehids en condicions de Claisen-Schmidt seguida de ciclització amb fenilhidrazina i hidroxilamina. La reacció de 6a i 6b amb hidrazina, semicarbazida, tiosemicarbazida i cianoacetilhidrazida, seguida de reaccions de condensació, rendeix diversos derivats de quinolina. S'avalua l'activitat contra el pugó Aphis gossypii, que danya les collites de cotó a Egipte. El compost 12 mostra un valor de LC50 de 19429E-10 ppm, essent per tant molt més actiu que Marshal (Carbosulfan), un dels insecticides d'ampli espectre extensament emprats en aquest camp.

Mots clau: Insecticides, Pugó Aphis gossypii, Quinolina, Pirazole, Tiosemicarbazida.

INTRODUCTION

Cotton aphid, *Aphis gossypii* Glover (Homoptera: Aphididae), is a piercing-sucking insect that harm cotton, *Gossypium barbadense* L., crop worldwide.[1] Damage occurs as a result of direct feeding and excretion of honeydew rich in monosaccharides and many free amino acids resulting in associated pathogenic fungal growth and viruses transmission causing more than 50 cotton plant diseases.[2] Biological control[3] through natural enemies including predators (bugs and spiders),[4] parasitoids (*Aphidus gifuensis*)[5], pathogens such as the entomopathogenic fungus *Neozygites fresenii* and are well known.[6-7] Relay intercropping[5] of agricultural co-systems as mutualistic plant protection and use of transgenic cotton species were valuable in protection of the crop.[8] Ecological effects represented in O_3[9] on aphid infestation as well as use of remote sensing for detection of plant damage were investigated.[10] Chemical control, on the other hand, has gained great interest due to the widespread cultivation of cotton worldwide to satisfy the global requirements.



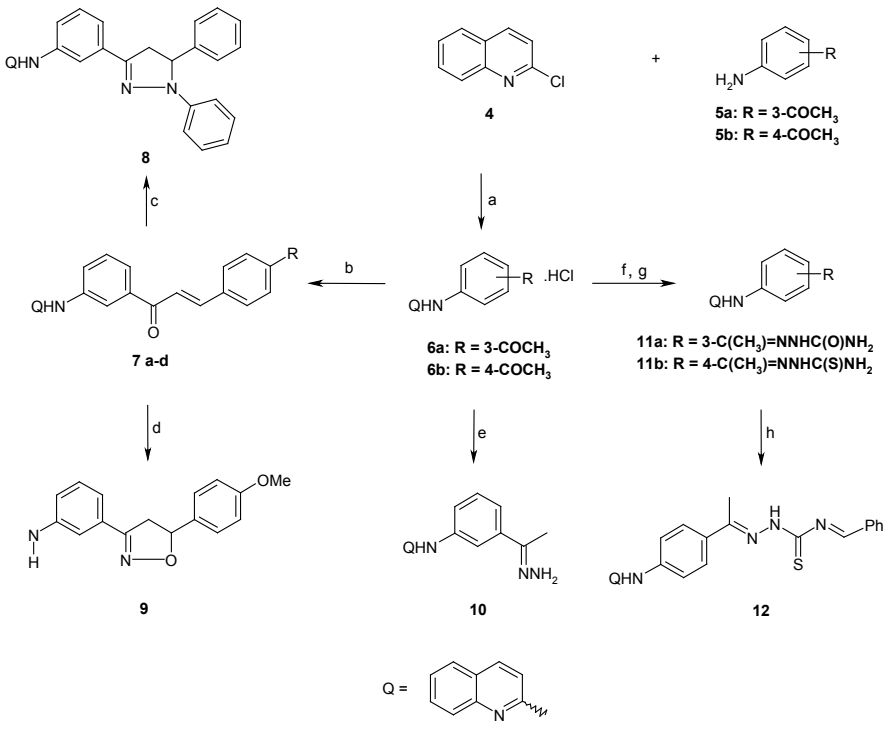
Scheme 1

Despite the diversity of these insecticides,[11-13] *A. gossypii* could continuously evolve insecticidal resistance and insecticides on their own have singularly failed to control this pest[14] and application of wide-spectrum insecticides have devastated natural enemies, thus, contributing to aphid outbreaks.[1] A study done in Egypt on ten insecticides of the carbamates and organophosphates families tested against adult stages of the pest collected from eight Egyptian governorates showed that Marshal **1** and Dursban **2** were the most toxic insecticides.[15] Although, quinoline derivatives are of diverse biological activities,[16] only little, to the best of our knowledge, are of agro-applications. For instance, Quinclorac **6** is used as herpicide, [17] **Scheme I**. This prompted us to synthesize a set of quinolines modified with various functionalities encountered in several pesticides to assess their contribution as anti-aphid candidates for future protection of cotton cultivation.

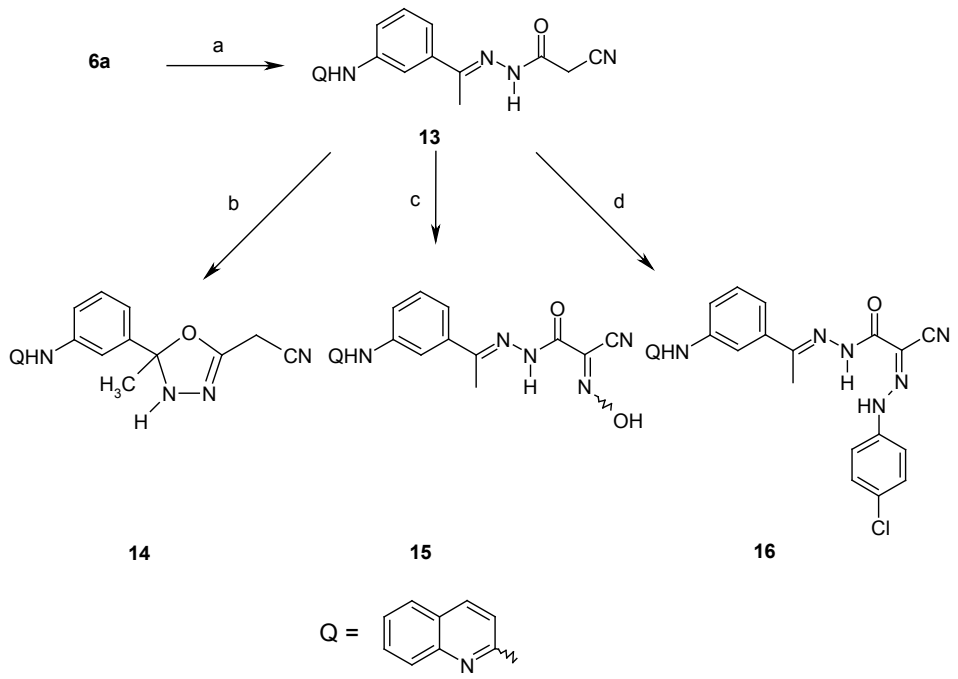
RESULTS AND DISCUSSION

Chemistry

To our endeavor, substrates **6a** and **6b**[18] were obtained by nucleophilic substitution of 2-chloroquinoline **4** with the appropriate acetylaniline derivative **5a-b** in refluxing EtOH containing drops of HCl. The acetyl moieties in these derivatives are active enough to carry diverse functionalizations that might lead to new insecticide candidates. The first group that we thought about was the chalcone derivatives **7a-d** and some of their derived heterocycles **8-9**, **Scheme II**, were prepared. Compounds **7a-d** were obtained in 60-75% yields *via* condensation of **6a** with the appropriate aldehyde under Claisen-Schmidt condensation conditions with modified NaOH proportion into 2.5 equivalents as the substrate is a hydrochloride form. ^{1}H NMR spectra of **7a-d** showed a doublet for one of the two olefinic protons at δ



Scheme II. *Reagents & conditions: (a) EtOH, HCl, rfx., 70% for* **6a***; (b) PhCHO, NaOH, EtOH,* **7a** *(65%), p-MeOC$_6$H$_4$CHO, NaOH, EtOH* **7b** *(70%), p-ClC$_6$H$_4$CHO, NaOH, EtOH* **7c** *(60%), m-HOC$_6$H$_4$CHO, NaOH, EtOH* **7d** *(75%); (c)* **7a***, PhNHNH$_2$, EtOH, rfx., 60%; (d)* **7b***, NH$_2$OH.HCl, NaOH, EtOH, rfx., 70%; (e) N$_2$H$_4$. H$_2$O, H$_2$SO$_4$, 80%; (f)* **6a***, Semicarbazide, EtOH, rfx., 65%; (g)* **6b***, Thiosemicarbazide, EtOH, rfx., 60%; (h)* **11b***, BzH, EtOH, rfx., 65%.*



Scheme III. *Reagents & conditions: (a) EtOH, rfx., 75%; (b) Et_3N, Dioxane, rfx., 60%; (c) $NaNO_2$, HCl, 0 ºC, 70%; (6) p-ClC_6H_4N=NCl, NaOAc, 0 ºC, 65%.*

6.94-6.99 ppm (*J* 8.4-9.0 Hz), while, the second one was overlapping, as do the imine proton, with the aromatic protons in the range δ 7.26-8.43 ppm. The methoxy protons of **7b** were observed as singlet at 3.86 ppm and the molecular ion peak of **7c** was observed as the base peak at *m/z* 385. Pyrazole **8** was obtained in 60% yield *via* Michael-addition of phenyl hydrazine to **6a** in refluxing EtOH, **Scheme II**. The methylene protons of the pyrazole moeity, H-$4_{Pyrazole}$, were diastereotopic. They appeared as a pair of doublet-of-doublets at δ 3.17 and 3.87 ppm with common germinal coupling constant, J_{gem}, of 15.8 Hz. The pyrazole proton H-5 was observed consequently as doublet-of-doublet at higher shift, δ 5.31 ppm, with two different *J* values of 6.4 and 7.8 Hz. Isoxazole **9**, **Scheme II**, was obtained in 70% yield by treatment of **7b** with hydroxylamine hydrochloride. The H-4 methylene protons of the isoxazole moiety were diastereotopic as do the in the pyrazole ring in the ^{1}H NMR spectrum with the exception of overlapping of one of these protons with the methoxy protons giving a multiplet at δ 3.69-3.88 ppm. H-5 was observed, as expected, at higher shift, δ 5.71 ppm, compared with **8**, δ 5.31 ppm, due to the electronegativity difference between oxygen and nitrogen. The molecular ion peak for **9**, *m/z* 395, was observed at intensity of 52%.

The second class of derivatives that we thought about their synthesis is the carbazides, their derivatives and analogues as some semicarbazides and thiosemicarbazides are commercially available insecticides. Therefore, the acetyl moieties of **6a-b** are quite suitable to graft quinoline with these active motif and related groups. Thus, condensation of **6a** with excess of excess of hydrazine hydrate in refluxing EtOH containing a drop of conc. H_2SO_4 afforded hydrazone **10**, **Scheme II**, in 80% yield. ^{1}H NMR revealed a singlet at δ 2.37 ppm for the methyl group protons, a multiplet for the aromatic protons at δ 6.93-8.53 ppm and a D_2O exchangeable proton singlet at δ 9.54 corresponding to the hydrazone moiety NH_2-group. Semicarbazone **11a**, **Scheme II**, was obtained in 65% yield by refluxing **6a** with semicarbazide in EtOH. IR-spectrum showed stretching bands for the groups NH at 3314-3427, NH_2 at 3185, C=O at 1678 and C=N at 1571 cm^{-1}. MS revealed a molecular ion peak at *m/z* 319 with intensity of 66% while ^{1}H NMR showed D_2O exchangeable broad singlets at δ 6.60 ppm for the NH_2 group, 9.59 and 11.20 ppm for the two NH groups. Thiosemicarbazone **11b**, **Scheme II**, was obtained analogously from **6b** and thiosemicarbazide in 70% yield. IR-spectrum revealed stretching bands at 3261-3423 for the NH group, 3062 for the NH_2 group and 1660 cm^{-1} for the C=N group. Molecular ion peak of *m/z* 335 was observed at intensity of 1%. Condensation of **11b** with benzaldehyde in refluxing EtOH afforded Schiff-like-base **12**, **Scheme II**, in 65% yield. MS showed the molecular ion peak *m/z* 423 at intensity of 0.1%, whereas, the characteristic aldimine proton signal was observed satisfactorily in the ^{1}H NMR spectrum as singlet at δ 10.20 ppm.

Condensation of **6a** with cyanoacetohydrazide was studied, **Scheme II**, the reaction was conducted in refluxing EtOH affording the active methylene containing derivative **13** in 75% yield. The molecular ion peak, *m/z* 342 was observed at intensity of 2%. ^{1}H NMR spectrum showed the amide proton was observed as two singlets at δ 11.17 and 11.01 ppm due to tautomerism, while, the protons of the active methylene moiety were observed as singlet at δ 4.29 ppm. Treatment of **13** with Et_3N in refluxing dioxane afforded oxadiazole **14** in favour of a pyrazolone. This was deduced based of the persistence of the active methylene protons signal in ^{1}H NMR spectrum and change in melting point of **13**.

Finally, Condensation of **13** with nitrous acid prepared *in situ* at 0 ºC afforded oxime **15** in 70% yield, **Scheme III**. The two NH proton signals, ^{1}H NMR spectrum, were observed at δ 9.70 and δ 8.69 ppm while oxime-OH was observed at δ 3.36 ppm. Azo-dye derivative **16** was obtained by coupling of **13** with benzene diazonium chloride at 0

ºC in 65% yield. Disappearance of the active methylene protons signal, ^{1}H NMR spectrum, was decisive for this coupling. [19-21]

Toxicological studies

Table 1. *Toxicity index of compounds* **6-16** *against Aphis gossypii (Glover).*

Compd.*1	LC_{25}	LC_{50}	LC_{90}	Slope	Tox. Index(%)*2
12	35694E-17	19429E-10	12220E+3	0.1±0.058	100
10	81034E-11	0.0008	326.702	0.227±0.063	0.243
11a	73380E-16	0.0019	17259E+9	0.08±0.055	0.102
8	53930E-14	0.0022	78512E+5	0.102±0.056	0.088
14	52740E-19	0.013	44387E+17	0.054±0.054	0.015
7d	0.013	0.831	2373.394	0.371±0.062	0.0002
15	0.0004	0.993	33390E+2	0.196±0.056	0.0002
16	0.0034	1.663	21055E+1	0.251±0.058	0.0001
13	0.017	7.655	87934E+1	0.253±0.058	0.000025
Marshal	6.807	184.734	97840.292	0.470±0.091	0.000001
11b	13.041	268.236	83887.89	0.514±0.091	72432E-11
7a	791.667	1445.496	4537.717	2.580±1.015	13441E-11
7b	321.521	1540.632	30246.865	0.991±0.246	12611E-11
6b	0.057	4652.192	99768E+8	0.137±0.058	41763E-12
6a	8.104	5086.203	10524E+5	0.214±0.068	38199E-12
9	13.0	43300E+1	16969E+10	0.149±0.063	44871E-14
7c	445.962	63730E+1	62976E+7	0.214±0.076	30486E-14

**1 Compounds are arranged according to decrease in their toxicities relative to the active compound 12 taking Marshal as reference.*
**2 Toxicity index = (LC_{50} of the tested compound/ LC_{50} of the most active compound) x 100.*

Toxocological assay of compounds **6-16**, **Table 1** and **Fig. 1**, revealed that the thiosemicarbazide Shiff base derivative **12** is the most toxic one this quinoline series with LC_{50} value of 19429×10^{-10} ppm which is very more toxic than Marshal. Come next to this derivative and with nearby range of toxicity the hydrazone **10**, semicarbazide **11a** then the pyrazole **8**. These derivatives are more toxic than Marshal but very less toxic than **12**. The cyanoacetylhydrazone series, **Schemes III**, where found to be the whole series that was more toxic than Marshal and oxadiazole **14** was the most toxic one and followed **8** directly and separated from the rest of the series with the hydroxylated chalcone like derivative **7d**. This chalcone derivative was the only active derivative among other chalcones compared with the reference insecticide. This result adds an impact to the intriguing biological activity[22] of chalcones which is attributed, most of the case, to the affinity of its enone-system to free sulfohydryl groups in proteins[23] which might targeted some insect's proteins elaborating this insecticidal activity. Follows **7d** in toxicity were oxime **15** then the azo-dye derivative **16** and finally cyanoacetylhydrazone **13** which was still more toxic than Marshal. Although, **12** showed the highest anti-aphid activity, its thiosemicarbazide precursor **11b** was less toxic than the reference insecticide and so did the rest of chalcones **7a-c** and oxazoline **9**.
In general, treatment of the cotton aphids, *Aphis gossypii* (Glover) with these quinoline derivatives, in comparison with the recommended insecticide, Marshal (Carbosulfan) 25% WP gave two groups (Table 1 and Fig. 4), the first group is more toxic than Marshal, these are compounds **12**, **10**, **11a**, **8**, **14**, **7a**, **15**, **16** and **13**, and a second group which is less toxic than Marshal, these are compounds **11b**, **7a**, **7b**, **6b**, **6a**, **9** and **7c** .
These results, thus, reflects the impact of these derivatives as new insecticide candidates for cotton cultivation which were in good accordance with our hypothesis.

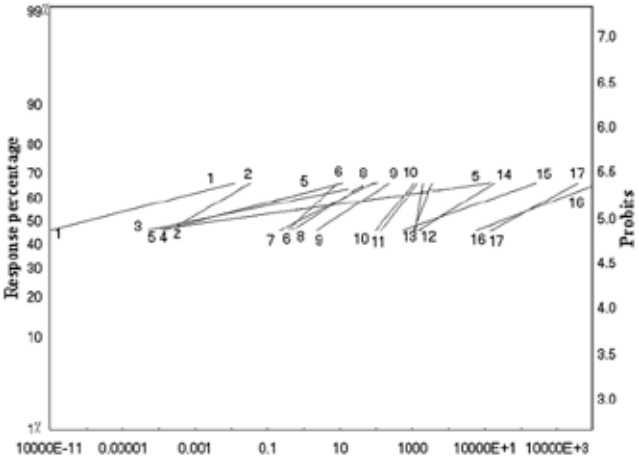


Fig. 4*: Log concentration probit lines of susceptibility of the cotton aphids, Aphis gossypii (Glover) to compounds* **6-16***. Number indications are: 1 (***12***), 2 (***10***), 3 (***11a***), 4 (***8***), 5 (***14***), 6 (***7d***), 7 (***15***), 8 (***16***), 9 (***13***), 10 (***Marshal***), 11 (***11b***), 12 (***7a***), 13 (***7b***), 4 (***6b***), 15 (***6a***), 16 (***9***), 17 (***7c***).*

EXPERIMENTAL

Chemistry
General, Melting points were determined on Gallenkamp apparatus and are uncorrected. Elemental analyses were performed on Flash EA1112 in ThermoFischer Center, Milan, Italy. NMR spectra were recorded on AC200 Brucker instruments of the technical university in Vienna and varian Mercury VX-300 instrument at Cairo University. IR-spectra were recorded using JASCO FT IR-460 plus spectrometer while the mass spectra were recorded on GCMS-QP 1000Ex Shimadzu spectrometers in the microanalysis unit at Cairo University. Insecticidal activity was done in the plant protection research Institute, Agricultural Research Center, Mansoura branch, Egypt.
1-[3-(quinolin-2-ylamino)phenyl]ethanone (6a):
A mixture of 2-cholorquinoline **4** (16.3 g, 99.0 mmol) and 3-aminoacetophenone **5a** (14.8 g, 109.0 mmol) and 5 drops of HCl in EtOH (30 ml) was heated under reflux for 8 hours then left to reach ambient temperature. The precipitate formed was filtered and recrystallized from benzene to afford **6a** (11.0 g, 70%) as reddish crystals, m.p. 127 ºC $C_{17}H_{14}N_2O$ (262)
General procedure for synthesis of 7a-d.
A mixture of **6a** (2.98 g , 0.01 mol), the appropriate aromatic aldehyde (0.01 mol) and NaOH (1.0 g, 25.0 mmol) in EtOH 10 ml was refluxed in a water-bath for 4 h then left to reach ambient tempreture. The precipitate formed was filtered and recrystallized from EtOH to afford **7a-d**.
3-Phenyl-1-[3-(quinolin-2-ylamino)phenyl]prop-2-en-1-one (7a): Obtained as yellow crystals in 65% yield; m.p.

176 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.34 (s, 1H, NH), 8.04-7.26 (m, 16H, Ar, -C*H*=CH-), 6.99 (d, 1H, *J* 9.0 Hz, -CH=C*H*-). $C_{24}H_{18}N_2O$ (350).

3-(4-Methoxyphenyl)-1-[3-(quinolin-2-ylamino)phenyl] prop-2-en-1-one (7b): Obtained as yellow crystals in 70% yield; m.p. 166 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.33 (s, 1H, NH), 8.01-6.98 (m, 16H, Ar, -C*H*=CH-), 6.95 (d, 1H, *J* 8.8 Hz, -CH=C*H*-), 3.86 (s, 3H, OMe). $C_{25}H_{20}N_2O_2$ (380).

3-(4-Chlorophenyl)-1-[3-(quinolin-2-ylamino)phenyl] prop-2-en-1-one (7c): obtained as yellow crystals in 60% yield; m.p. 171ºC; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.43 (s, 1H, NH), 7.97-7.26 (m, 15H, Ar, -C*H*=CH-), 6.94 (d, 1H, *J* 8.8 Hz, -CH=C*H*-); EI-MS: *m/z* (%), 385 (M^+, 100), 261 (91), 219 (35). $C_{24}H_{17}ClN_2O$ (384)

3-(3-Hydroxyphenyl)-1-[3-(quinolin-2-ylamino)phenyl] prop-2-en-1-one (7d): Obtained as colorless crystals in 75% yield; m.p. 184 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.31(s, 1H, NH), 8.00-7.26 (m,15 H, Ar, -C*H*=CH-), 6.95 (d, 1H, *J* 8.4 Hz, -CH=C*H*-), 2.65 (s , 1H, OH). $C_{24}H_{18}N_2O_2$ (366).

3-[3-(Quinolin-2-ylamino)phenyl]-4,5-dihydro-1,5-diphenylpyrazole (8):

A mixture of **7a** (1.75 g, 5.0 mmol) and phenylhydrazine (0.5 ml, 5.0 mmol) in EtOH (10 ml) was heated under reflux for 6 h then left to reach ambient temperature. The precipitate formed was filtered and recrystallized form MeOH to afford **8** (1.09 g, 60%) as colorless crystals; m.p.163 ºC. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.06-6.80 (m, 21H, 2 Ph, 2 Ar, NH), 5.31 (dd, $J_{4,5}$ 6.4, $J_{4`,5}$ 7.8 Hz, H-5$_{pyr}$), 3.87 (t, 1H, $J_{gem}$ 15.8 Hz, $J_{4,5}$ 6.4 Hz, H-4$_{pyr}$), 3.17 (dd, 1H, $J_{gem}$ 15.8, $J_{4`,5}$ 7.8 Hz, 1 H, H-4`$_{pyr}$). $C_{30}H_{24}N_4$ (440.2).

3-[3-(Quinolin-2-ylamino)phenyl]-4,5-dihydro-5-(4-methoxyphenyl)isoxazole (9): A mixture of **7b** (1.9 g, 5.0 mmol), hydroxylamine hydrocholoride (0.34 g 5.0 mmol) and NaOH (0.01 mol) in EtOH (15 ml) was heated under reflux for 7 h then left to reach ambient temperature. The precipitate formed was filtered and recrystillized from MeOH to afford **9** (1.3 g, 70 %) as colorless crystals; m.p. 146 ˚C. IR (KBr): υ (cm^{-1}): 3378 (NH$_{str}$), 1607 (C=N$_{str}$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.02 (s, 1H, NH), 7.83-6.89 (m, 14H, Ar), 5.71 (dd, 1H, $J_{4,5}$ 11.0, $J_{4`,5}$ 9.0 Hz, H-5$_{isoxaz}$), 3.88-3.69 (m, 4H, H-4$_{isoxaz}$, OMe), 3.36 (dd, 1H, $J_{4`,5}$ 9.0, J_{gem} 16.8 Hz, H-4`$_{isoxaz}$); EI-MS: *m/z* (%): 395 (M^+, 52.6), 260 (73.2), 219 (47.4), 128 (71.1), 77(100). $C_{25}H_{21}N_3O_2$ (395.1).

1-[3-(quinolin-2-ylamino)phenyl]ethan-1-one hydrazone (10): A mixture of **6a** (2.98 g, 0.0l mol), hydrazine hydrate (3.4 g, 0.05 mol) and H_2SO_4 (0.01 ml) in EtOH (15 ml) was stirred at rt for 2h. The precipitate formed was filtered and recrystallized from EtOh to afford **10** (2.38 g, 80%) as colorless crystals; m.p. 178 ºC. 1H NMR (500 MHz, DMSO-*d6*): δ 9.54 (s, 1H, NH), 8.53-6.93 (m, 12 H, Ar), 3.21 (br.s, 2H, NH_2), 2.37 (s, 3H, CH_3). $C_{17}H_{16}N_4$ (276.1).

1-[3-(quinolin-2-ylamino)phenyl]ethan-1-one semicarbazone (11a):

A mixture of **6a** (2.98 g, 0.0l mol), semicarbazide (1.11 g, 0.01 mol) and sodium acetate (0.01 mol) in EtOH (15 ml) was heated under reflux 2 h with stirring then left to reach ambient temperature. The precipitate formed was filtered and recrystallized from MeOH to afford **11a** (0.72 g , 65 %) as colorless crystalls; m.p. 218 ˚C). IR (KBr): υ (cm^{-1}): 3427-3314 (NH$_{str}$), 3185 (NH$_{2str}$), 1678 (C=O$_{str}$), 1571 (C=N$_{str}$); ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.49 (s, 1H, NHCO-), 8.44-7.32 (m, 11H, NH, Ar), 3.78 (br.s, 2H, NH_2), 2.25 (s, 3H, CH_3); EI-MS: *m/z* (%): 319 (M^+, 66.7), 234 (66.7). $C_{18}H_{17}N_5O$ (319).

1-[4-(quinolin-2-ylamino)phenyl]ethan-1-one thiosemicarbazone (11b): A mixture of **6b** (2.98 g, 0.0l mol) and thiosemcarbazide (0.91 g, 0.01 mol) in EtOH (20 ml) containing H_2SO_4 (0.01 ml) was stirred at ambient temperature for 3 h. The precipitate formed was filtered and recrystallized from EtOH to afford **11b** (2.0 g, 70 %) as yellow crystals; m.p. 219 ˚C. IR (KBr): υ (cm^{-1}): 3261-3423 (NH$_{str}$), 3062 (NH$_{2str}$), 1605 (C=N$_{str}$), EI-MS: *m/z* (%): 335 (M^+, 1.0). $C_{18}H_{17}N_5S$ (335).

1-[4-(quinolin-2-ylamino)phenyl]ethan-1-one N-[phenylmethylene]semicarbazone (12): A mixture of **11b** (3.35 g, 0.0l mol) and benzaldehyde (1.06 g, 0.01 mol) in EtOH (10 ml) was heated under reflux for 3 h then left at ambient temperature overnight. The precipitate formed was filtered and recrystallized from aqueous EtOH to afford **12** (2.17 g, 65 %) as colorless crystals; m.p. 181 ˚C. 1H NMR (200 MHz, DMSO-*d6*): δ 10.20 (s, 1H, -N=CH-), 8.23-8.02 (2s, 2 H, 2 NH), 7.87-7.43 (m, 15H, Ar), 2.46 (s, 3H, CH_3); EI-MS: *m/z* (%): 423 (M+, 0.1), 261 (100), 219 (23), 128 (77.24). $C_{25}H_{21}N_5S$ (423).

2-cyano-N'-{1-[3-(quinolin-2-ylamino)phenyl]ethylidene}acetohydrazide (13): A mixture of **6a** (2.987 g, 0.0l mole) and cynoacetohydrazide (0.99 g, 0.01 mole) in dry EtOH (30 ml) containing H_2SO_4 (0.01 ml) was stirred for 2 h at ambient temperature. The precipitate formed was filtered off and recrystallized from MeOH to afford **13** (2.24 g, 75 %) as reddish crystals; m.p. 224 ˚C**.** ^{1}H NMR (200 MHz, DMSO-d_6): δ 11.17 (s, 1 H, NHCO-), 11.0 (s, 1H, NH), 8.44-7.34 (m, 10H, Ar), 4.29 (s, 2H,- CH_2), 2.39 (s, 3H, CH_3); EI-MS: *m/z* (%): 342.5 M^+, 2), 303 (3.31), 261 (100), 219 (10.05), 128 (1.98); $C_{20}H_{17}N_5O$ (343).

2-Cyanomethyl-5-[3-(quinolin-2-ylamino)phenyl]-5-methyl-1,3,5-oxadiazol-3,4(2*H*) (14): A mixture of **13** (3.43 g, 0.0l mole) and Et_3N (5 ml) in dioxin (20 ml) was heated under reflux for 4 h then allowed to reach ambient temperature. The precipitate formed was filtered and recrystallized from MeOH to afford **14** (2.09 g, 60%) as colorless crystals; m.p. 230 ˚C. IR (KBr): υ (cm^{-1}): 3343-3450 (NH*str*), 2264 (CN$_{str}$), 1683 (C=O$_{str}$), 1543 (C=N$_{str}$); ^{1}H NMR (200 MHz, DMSO-d_6): δ 11.11 (s, 1 H, N-H), 9.55 (s, 1H, N-H), 8.56-7.08 (m, 10H, Ar), 4.33 (s, 1H , -CH_2-), 2.35 (s, 3H, CH_3). EI-MS: *m/z* (%): 343 (M^+, 25.8). $C_{20}H_{17}N_5O$ (343).

2-Cyano-2-(hydroxyimino)-N'-{1-[3-(quinolin-2-ylamino)phenyl]ethylidene}acetohydrazide (15): A solution of **13** (3.43 g , 0.01 mole) in dioxin (10 ml) containing HCl (5 ml) was treated with a solution of $NaNO_2$ (0.7 g) in H_2O (5ml) at 0 ºC with stirring. The precipitate formed was recrystallized from EtOH to afford **15** (2.4 g, 70%) as colorless crystals; m.p.174 ˚C. IR (KBr): υ (cm^{-1}): 3363 (NH$_{str}$), 1672 (C=O$_{str}$), 1538 (C=N$_{str}$); ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.70 (s, 1H, N-NH-), 8.69 (s, 1H, NH), 8.10-7.08 (m, 10H, Ar), 3.36 (s, 1H, OH), 2.51 (s, 3H, CH_3). $C_{20}H_{16}N_6O_2$ (372).

2-cyano-2-(4-chlorophenyldiazeneyl)-N›-{1-[3-(quinolin-2-ylamino)phenyl]ethylidene}acetohydrzide (16): A mixture of **13** (3.43g, 0.01 mol), NaOAc (3g, 0.3 mol) in dioxane (20 ml) was stirred at 0 ºC then treated with *p*-chlorobenzene diazzonium chloride (0.01 mol).The precipitate formed was recrystallized from EtOH to afford **16** (2.22 g , 65%) as colorless crystals; m.p.170 ˚C. IR (KBr): υ (cm^{-1}): 3366-3230 (NH$_{str}$), 2215 (CN$_{str}$), 1690 (C=O$_{str}$), 1599 (C=N$_{str}$); ^{1}H NMR (500 MHz, DMSO-*d6*): δ 12.72, 12.06, 10.48, 9.64 (4s, 3H, 3 N-H *D_2O exchangeable*), 8.53-7.01 (m, 15 H, Ar), 2.34(s, 3H, CH_3). $C_{26}H_{20}ClN_7O$ (481).

TOXICOLOGICAL STUDIES

Samples of cotton leaves infested with cotton aphid, *Aphis gossypii* Glover (Homoptera : Aphididae) were collected form cotton fields of Dakahlia Governorate, Egypt, in June, 2008 and transferred into the laboratory. Slide dip technique adopted by Thistlewood *et al.*[24] was applied to evaluate the efficiency of the tested modified heterocyclic compounds, in addition to the recommended insecticide, Marshal (Carbosulfan) 25 % WP against aphids . A piece of double –faced scotch tape was pressed tightly to the surface of a glass slide, using a moist brush. At least six concentrations for each compound were used. Three replicates with 10 apterous adults (1-2 days old) each were made for each concentration. The aphids were stuck to the tape on their backs so that their legs and antennae were free. Slides with aphids were dipped into a beaker containing compound solutions which mixed with Triton X at a concentration of 0.3 %, so that the aphids were immersed for 10 seconds to ensure complete wetting. Control aphids were similarly dipped in water with Triton X at concentration of 0.3 %. When withdrawn, slides were touched down, on edge, on absorbent paper towelling and then allowed to dry at room temperature. The treated slides were then placed into a glass slide holding chamber to conserve the moisture. Mortality counts were tallied after 24 hours of treatment. Aphids responding to touch with brush were considered alive. Mortality data were corrected according to Abbott formula[25] and the corrected mortality percentage of each compound was statistically computed according to Finney.[26] From which the corresponding concentration probit lines (LC-p lines) were estimated in addition to determination of 25, 50 and 90% mortalities, as well as slope values of tested compounds were also estimated. In addition, the efficiency of different compounds was measured by comparing the tested compound with the most effective compound by using the following equation Toxicity index = LC_{50} of the most effective compound / LC_{50} of the tested compound x 100, Sun *et al.*[27]

CONCLUSION

Condensation reactions of 2-acetylanilinoquinolines were good leads for new quinoline derivatives grafted with several functionalities frequently encountered in commercial pesticides. Some of these derivatives were more toxic than Marshal as one of the best anti-aphid pesticide in the market. These results put quinoline derivatives of these series as leads for developing new potential pesticides.

AKNOWLEDGEMENTS

The Authors are so grateful for Suez Canal University, the National Research Center and Plant Protection Research Institute, Agricultural Research Center, Mansoura branch for financial support.

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