ISSN 1068-1620, Russian Journal of Bioorganic Chemistry, 2014, Vol. 40, No. 2, pp. 214–227. © Pleiades Publishing, Ltd., 2014.

Synthesis, Insecticidal, and Fungicidal Screening of Some New Quinoline Derivatives[1]

M. R. E. Aly[a, b, 2], M. M. Ibrahim[a, c], A. M. Okael[d], and Y. A. M. H. Gherbawy[e, f]

[a] *Chemistry Department, Faculty of Science, Taif University, Alhawyah-Taif, 888 Kingdom of Saudi Arabia*

[b] *Chemistry Department, Faculty of Applied Science, Port Said University, Port Said, 42522 Egypt*

[c] *Chemistry Department, Faculty of Science, Kafr El Sheikh University, Kafr El-Sheikh, 33516 Egypt*

[d] *Plant Protection Research Institute, ARC, Dokki, Cairo, Egypt*

[e] *Biology Department, Faculty of Science, Taif University, Alhawyah-Taif, KSA*

[f] *Botany Department, Faculty of Science, South Valley University, Qena, Egypt*

Received August 13, 2013; in final form, October 7, 2013

Abstract—This paper describes the synthesis of a series of quinolines graphted with hydrazones, pyrazoles, pyridazine, phthalazine, triazepinone, semicarbazide, and thiomorpholide moieties and four metal complexes. These derivatives were screened against *Fusarium oxysporum* and the red palm weevil (RPW) *Rhynchophorus ferrugineus* Oliver (coleopteran: Curculionidae) as palm pathogens. Only chlorinated quinolines were active against these organisms with hydrazones being good fungicides, while those modified with pyrazoles and pyrazines showed moderate insecticidal activity. A unique trihydroxylated hydrazone was active against both organisms, while another hydrazone, the most potent fungicide in this series, exhibited insecticidal activity only upon complexation with Zn^{2+} ions.

Keywords: quinoline, hydrazones, fungicidal, insecticidal, red palm weevil

DOI: 10.1134/S1068162014020022

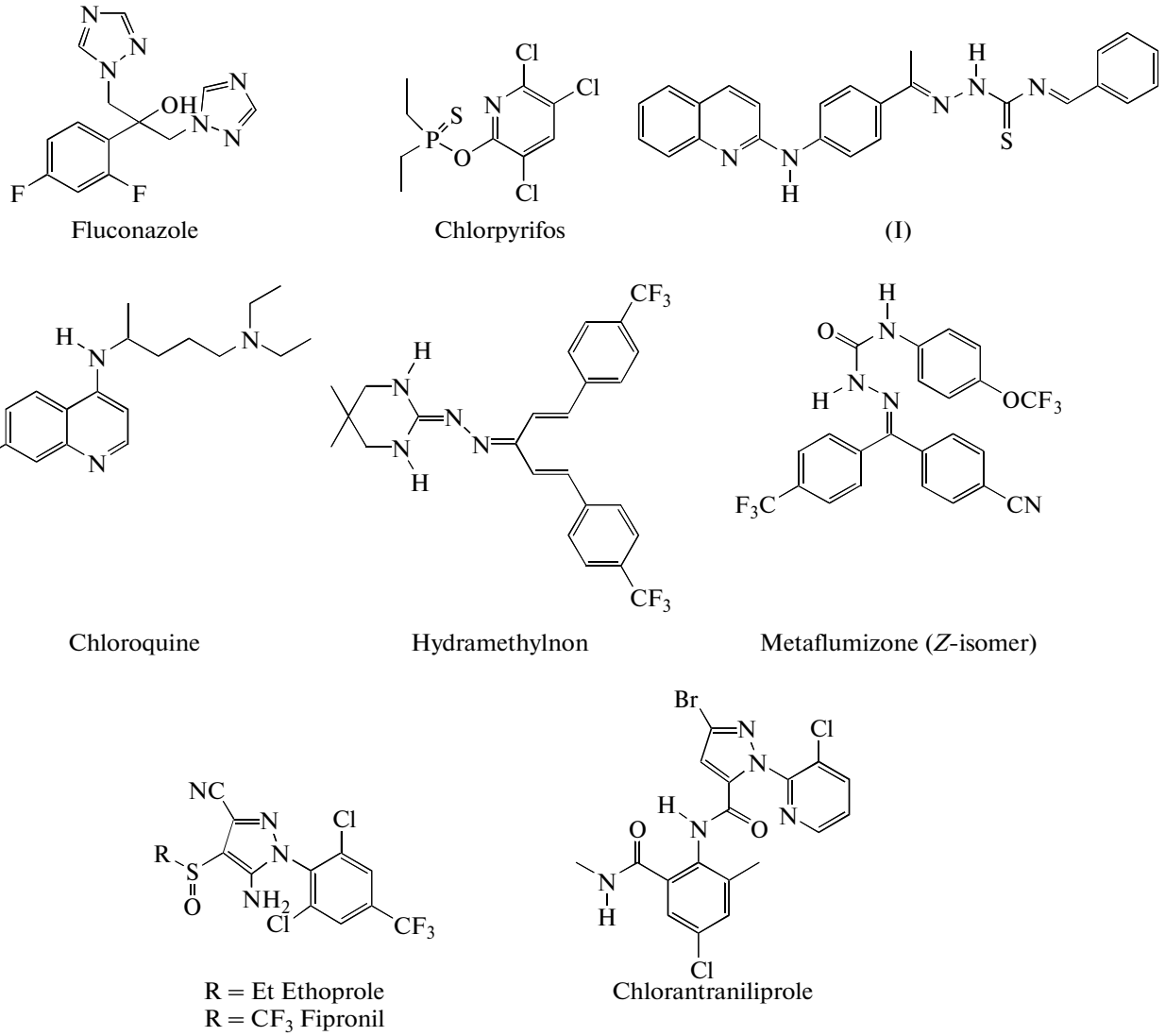
INTRODUCTION

Date crop damage arising from attack of date palms *Phoenix dactylifera* (Palmae) by the destructive red palm weevil (RPW) *Rhynchophorus ferrugineus* (Olivier) [1] and fungal infection with *Fusarium oxysporum* [2] is a growing problem worldwide. Other palm species of economic significances are also harmed by RPW, particularly in Southern Asia. The larval stage of RPW feeds within the trunk, which frequently reduces the crop and finally kills the tree [3, 4]. While *F. oxysporum* is treated with ordinary fungicides, for instance, fluconazole [5], management control of RPW is more complicated due to the concealed nature of the larvae [1]. Chlorpyrifos 48% EC (Brand Name: Chlorozan), an organophosphate pesticide, is a common pesticide involved in RPW control [6]. These pesticides, however, increase the production cost and cause environmental hazards, which restricts its utility, and continuous use of the eco-tolerant grades lead to the development of resistant pests [7]. Therefore, alternatives are under investigation, including biocontrol based on nematodes, viruses, and bacteria; integrated pest management (IPM) with pheromones and pesticides; and finally, application of biotechnology through gene transduction to produce pest resisting palm generations [8]. However, the progress in these tactics is not sufficient yet to control these infections and chemical interference is still of great demand. Therefore, in continuation of our ongoing program to suggest solutions to local agricultural problems in the Middle East and worldwide as well based on synthetic quinolines, we extended this project to the date crop problem. In a previous work [9], a structurally diverse quinoline series were prepared, of which compound (**I**) (Scheme 1) was quite effective against *Aphids gossipy* (Glover) that harms the Egyptian cotton crop. This derivative was contracted to be intensively investigated in fields by Syngenta Agro S. A. E.

In the present work, special emphasis was given to chloroquinolines having basic graphts at position-4. This type of quinolines has special interest as chloroquine was evolved as one of the breakthroughs in antimalarial therapy [10]. Pharmacological potential of the same category was also reported in anticancer research [11, 12]. In pesticide research, the hydrazone moiety is a highly efficient pharmacophore [7] that is widely used in pesticide design. Hydramethylnon [13] and metaflumizone [14] are commercial examples of this class of pesticides (Scheme 1).

[1] The article is published in the original.

[2] Corresponding author: phone: +966 56 26 94 753; e-mail: mrea34@hotmail.com.



Scheme 1. Structure of selected fungicides and pesticides.

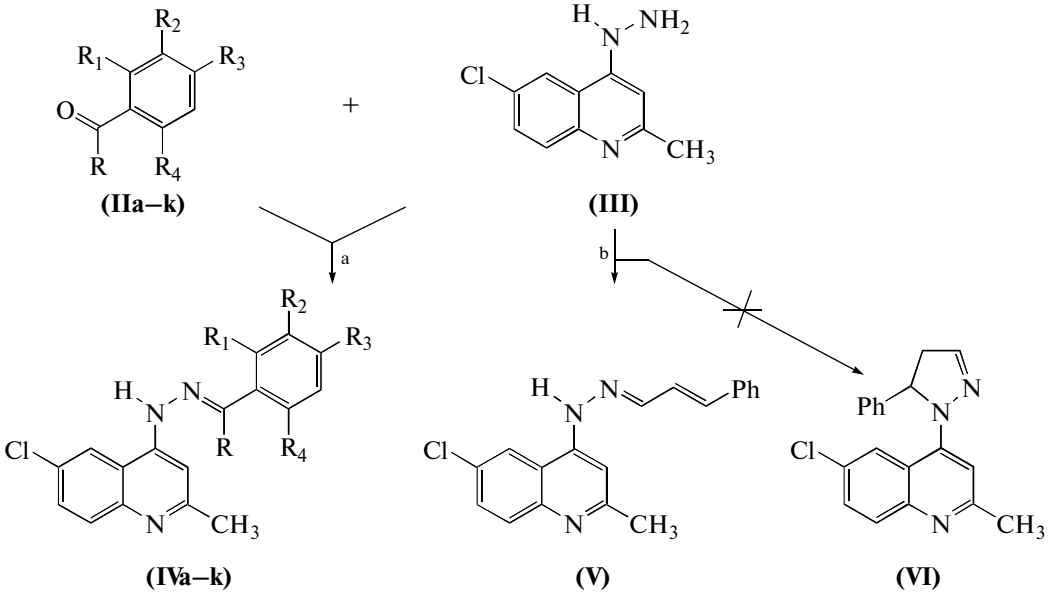
On the other hand, phenyl pyrazoles are important class of pesticides including *N*-aryl pyrazoles, for instance, ethiprole and fipronil, that effectively control pests on corn and soya bean [15]. *N*-Heteroarylpyrazoles, particularly those containing a chloropyridyl moiety, such as chlorantraniliprole, are common larvicides [16]. These two classes of pesticides prompted us to choose the quinoline derivative 6-chloro-4-hydraqzino-2-methylquinoline [17, 18] as readily accessible and reliable scaffold to develop a series of hydrazones, as well as isosteric analogues of *N*-chloropyridylpyrazoles, to be tested against both RPW and *F. oxysporum* on the way to find an integrated solution for palm infections. Another acetylanilinoquinoline derivative was chosen to get a set of thiomorpholide and semicarbazide architectures for the same objective. It is to be mentioned that beside the wide application of quinolines in biological, industrial, and material science researches [19], quinoline-based agrochemicals are known for hydroxyquinolines only and devoted for herbicidal applications [20].

RESULTS AND DISCUSSION

Chemistry

Substrate (**III**) [17, 18] was condensed with 1.1 equivalents of the relevant carbonyl compounds (**IIa–k**) and cinnamaldehyde in refluxing EtOH (Scheme 2 and Table 1). Generally, crystalline pure hydrazones (**IVa–k**) and (**V**) were obtained in good yields. All compounds showed a recognizable molecular ion peak corresponding to the exact mass of each derivative. ^{1}H NMR spectra recorded in DMSO-d_6 showed broad singlet for the NH-proton at about δ 11.0 ppm due to H-bonding while the imine proton was observed at about δ 8.5 ppm if not overlapped with aromatic protons. The quinolyl-2-methyl protons could not be seen due to overlap with DMSO protons

at about δ 2.5 ppm. However, its carbon could be seen in the ^{13}C NMR as in the case of (**IVb**) at about δ 23 ppm. In the IR spectra, all compounds showed bands at about 1616 and 1637 cm^{-1} corresponding to the C=N stretching and N–H deformation vibrations, respectively. The N–H stretching band was weak at about 3200 cm^{-1} and this band in the IR spectrum, as well as its signal at δ 11.0 ppm in the ^1H NMR in the case of cinnamaldehyde suggested structure (**V**) rather than the Michael condensation product (**VI**) in this case.

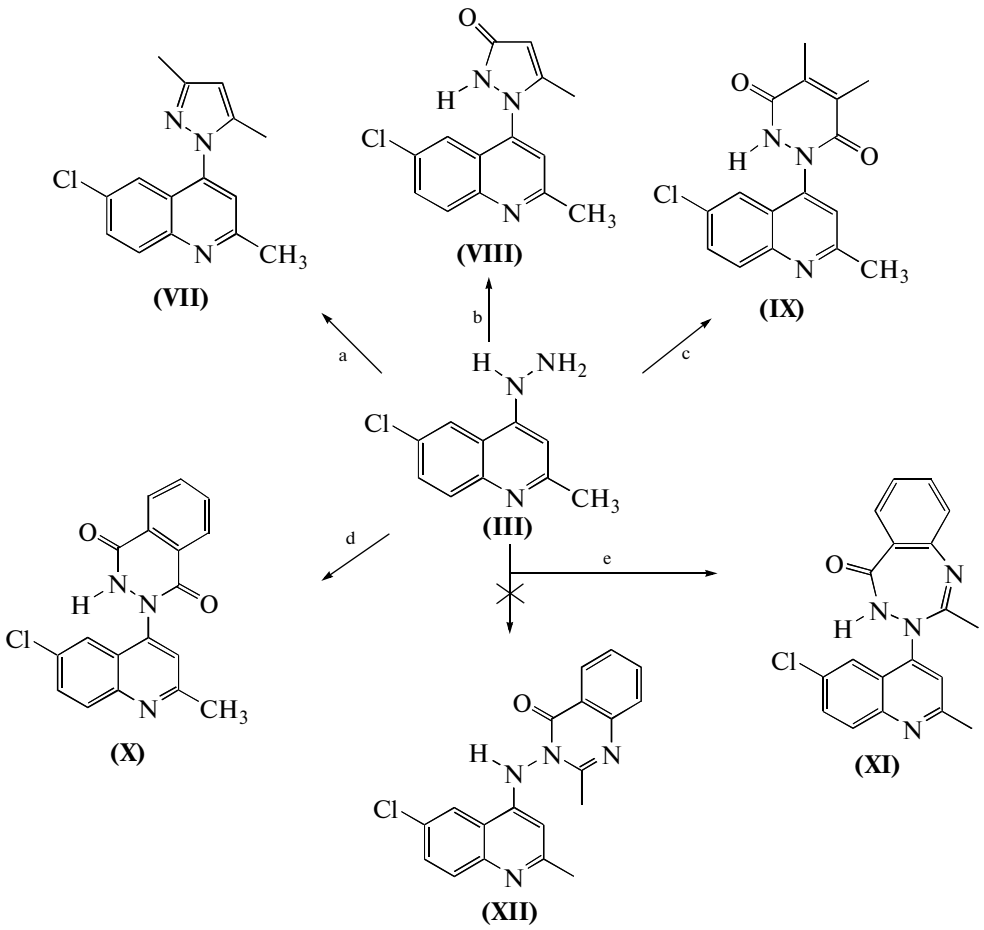


Scheme 2. Reagents and conditions: (a) EtOH, rfx; (b) Cinnamaldehyde, EtOH, rfx.

Compound (**III**) was cyclocondensed with some 1,3-dielectophiles like acetyl acetone and ethylacetoacetate in refluxing EtOH giving rise to the pyrazole derivatives (**VII**) and (**VIII**) in good yields (Scheme 3).

Table 1. Structure and some physical data of compounds (**IVa–k**) and (**V**)

Entry	R	R^1	R^2	R^3	R^4	Yield, %	mp, °C
(IVa)	H	H	H	H	H	82	239
(IVb)	H	H	H	OMe	H	80	230–2
(IVc)	H	H	H	NO_2	H	80	267
(IVd)	H	H	H	Cl	H	65	243–5
(IVe)	H	OH	H	H	H	72	260
(IVf)	H	H	H	OH	H	67	230–4
(IVg)	H	H	H	CH_3	H	81	256–8
(IVh)	H	H	OH	OMe	H	81	242
(IVi)	CH_3	H	H	OH	H	60	282
(IVj)	CH_3	OH	H	H	OH	77	253–5
(IVk)	CH_3	OH	OH	OH	H	56	270–2
(V)	–	–	–	–	–	56	240



Scheme 3. Reagents and conditions: (a) acetylacetone, EtOH, rfx (93%); (b) ethylacetoacetate, EtOH, rfx (51%); (c) dimethylmaleic anhydride, EtOH, rfx (71%); (d) phthalic anhydride, EtOH, rfx (86%); (e) 2-methylbenzoxazolin-4-one, AcOH, rfx (74%).

In the IR of pyrazole (**VII**), all bands of the hydrazine group disappeared and smooth ^{1}H and ^{13}C NMR spectra were obtained. Pyrazolone (**VIII**) is probable to be available in solution, mostly, in the enol form due to the weakness of the C=O signal in the ^{13}C spectrum at 173 ppm and the presence of a broad phenolic proton at 12 ppm in the ^{1}H NMR spectrum, while the NH signal was not observed. However, in solid state, as shown in the IR spectrum, the compound is mainly available in the keto form where a strong C=O absorption band and very weak N–H stretching bands were observed. The ^{13}C NMR spectrum was much complicated, as 15 signals were observed for the 12 aromatic carbons, presumably, due to existence of rotamers.

Reaction of (**III**) with 3,4-dimethylmaleic anhydride, phthalic anhydride, and 2-methylbenzoxazine is believed to proceed via cyclocondensation affording pyridazin-4-one (**IX**), phthalazine-1,4-dione (**X**), and triazipeneone (**XI**), respectively (Scheme 3). These newly formed ring structures at C-4 of the quinoline ring exist in two forms as seen from the ^{1}H NMR (Figs. 1–3) due to iminol-keto tautomerism. In all keto forms, $\delta_{NH} \approx 9.5$ ppm; H–3 of the quinoline ring is more deshielded, $\delta_{H\text{-}3} \approx 6.5$ ppm, compared with the iminol forms, $\delta_{OH} \approx 11.4$ ppm, where $\delta_{H\text{-}3} \approx 5.8$ ppm.

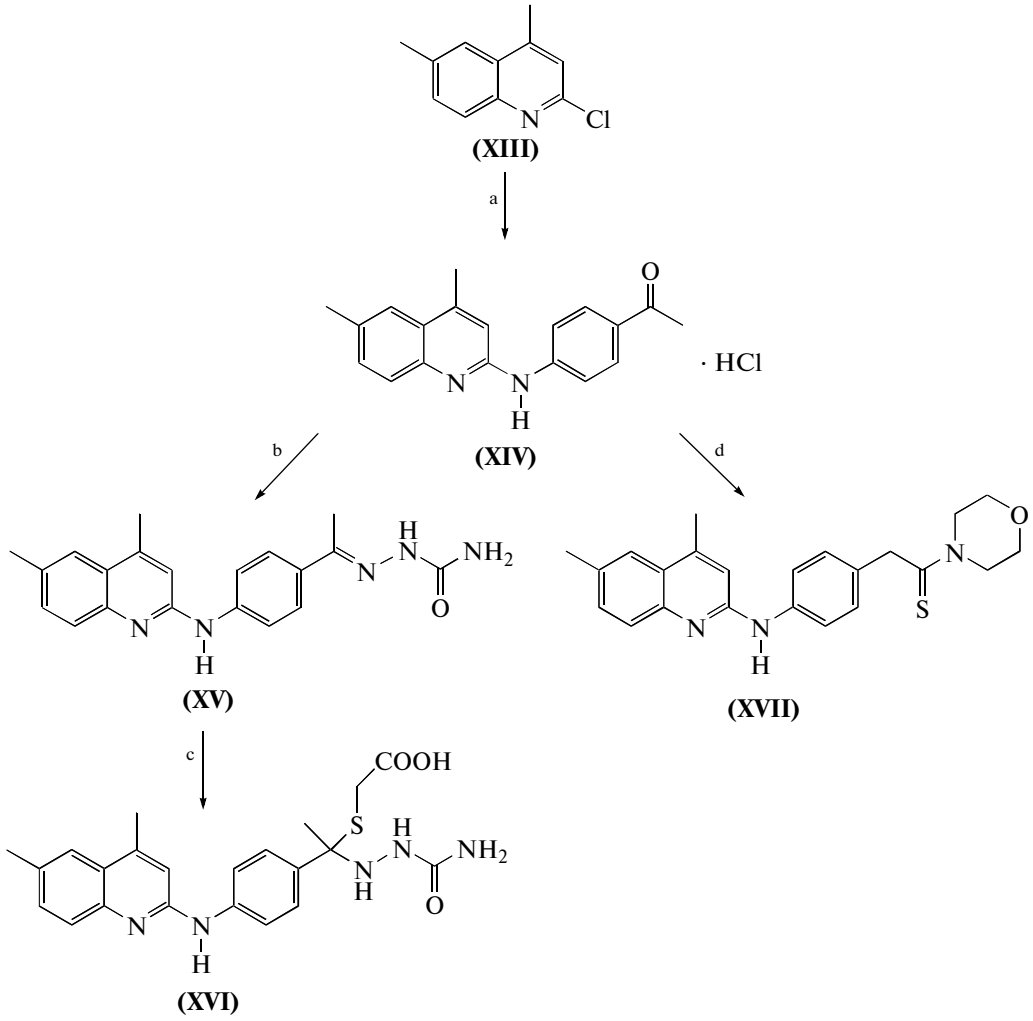
This is interpreted by adaption of the keto-form of a perpendicular orientation at C-4 to avoid steric hindrance between the N–H and C_5–H bonds. In this case, there is no resonance between the out-of-plane nitrogen atom lone-pair of electrons and the π-cloud of the quinoline ring. Thus, the H-3 become deshielded compared with the iminol-form which is free of hindrance between the prementiond bonds and the whole molecule is planar and lone-pair interaction with the π-cloud shields the H-3 atom and comes into resonance at higher field.

Further, in compounds (**IX**) and (**X**), H-3 atom in the iminol form shown in (Figs. 1 and 2), the most

favored configuration as calculated by HyperChem program, is subjected to magnetic anisotropic shielding by the carbonyl group. Acquisition of the ^{1}H NMR at 50°C simplified the spectrum and the keto-form was the uniquely existing form.

Acquisition of the ^{1}H NMR of (**XI**) (Fig. 3), at 50°C coincides with that taken at ambient temperature. This is quite important as it precludes the possibility of nucleophilic substitution and formation of (**XII**). If (**XII**) was formed, the two D_2O-labile signals at low field might be correlated to partial intramolecular H-bonding. If this is so, the H-bond was to break down at 50°C and only one signal was to be seen.

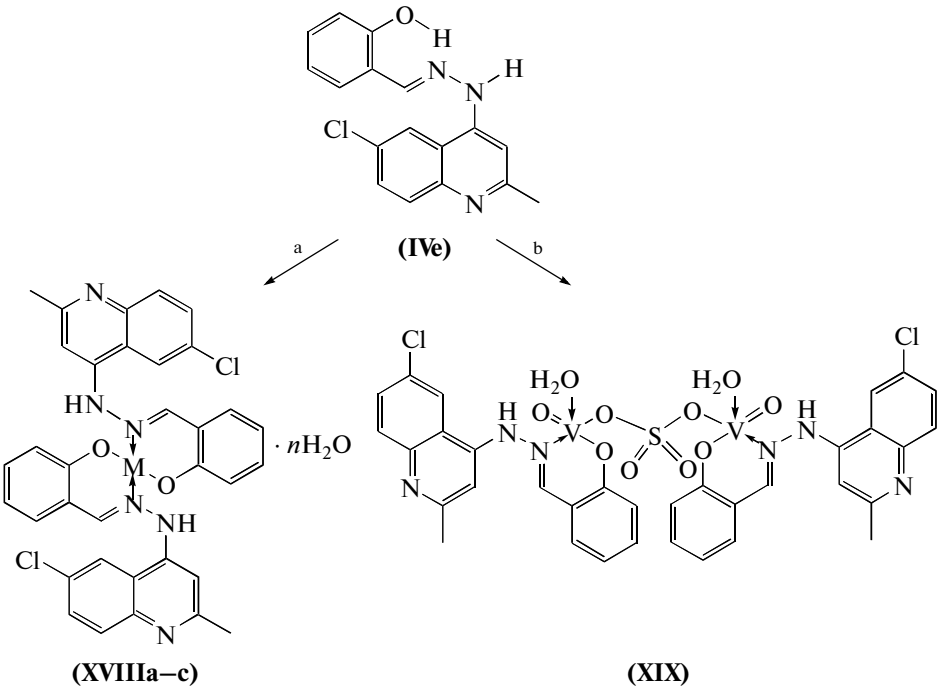
To have non halogenated quinoline models for comparison reason, compounds (**XVI**) and (**XVII**) were prepared from (**XIII**). Thus, nucleophilic substitution of chloroquinoline (**XIII**) [21] with *p*-aminoacetophenone in EtOH containing drops of HCl afforded (**XIV**) in high yield, it was then incoroporated in two different reactions. In the first one, it was condensed with semicarbazide hydrochloride in refluxing EtOH containing K_2CO_3, which was followed by treatment with mercaptoacetic acid in refluxing EtOH. The thiol group was just added to the intermediate semicarbazide (**XV**) without cyclyzation between the carboxyl group and the polar head of the semicarbazide moiety affording (**XVI**) (Scheme 4). MS showed a weak molecular ion peak at m/z 439 and the ^{1}H NMR was in good accordance with the formula, however the carboxyl proton was not observed, probably it was too broad to be seen. In the IR spectrum, however, all characteristic bands of the carboxyl, as well as amide groups, could be clearly seen, in particular, the O–H stretching at 2699 cm^{-1} and C=O stretching at 1705 cm^{-1} as good evidence for the existence of the carboxyl moiety.



Scheme 4. Reagents and conditions: (a) *p*-aminoacetophenone, EtOH, HCl, rfx (98%); (b) semicarbazide, HCl, K_2CO_3, EtOH, rfx (80%); (c) mercaptoacetic acid, EtOH, rfx (96%); (d) S, morpholine, rfx (81%).

In the second modification of (**XIV**), it was incorporated in Willigrodet's reaction with sulfur in refluxing morpholine giving rise to thiomorpholide (**XVII**) in good yield (Scheme 4). MS was in good agreement with suggested formula and the molecular ion peak was observed at *m/z* 391. In the ^{1}H NMR spectrum, the four methylene entities of the morpholine moiety were clearly seen as four triplets with the $-OCH_2-$ protons more deshielded than the two $-NCH_2-$ entities. The $-C(=S)CH_2-$ group was observed as singlet at 4.33 ppm, while, the C=S ^{13}C NMR signal was observed at 199.31 ppm. The C=S IR band was observed as strong band along with the C–N stretching band in the range 1027–1107 cm^{-1}, while the N–H band was observed at 3294 cm^{-1}, despite it was not seen in the ^{1}H NMR spectrum.

To augment the potential of biological activity, metal (II) complexes (**XVIIIa–c**) and (**XIX**) were prepared by treating a methanolic solution of nitrate salts of Zn^{2+}, Cu^{2+}, and Ni^{2+} with two equivalents of the bidentate salicylhydrazone ligand (**IVe**), a Schiff-like base, in the presence of NaOH. Vanadyl complex (**XIX**) was prepared similarly under equimolar conditions using $VOSO_4 \cdot 2H_2O$ (Scheme 5). All the complexes are colored, non-hygroscopic, and thermally stable solids indicating the strength of metal-ligand binding. The complexes are insoluble in water but soluble in common organic solvents such as EtOH, DMF, and DMSO. Electrical conductivity measurements of the obtained complexes in EtOH recorded Λ_M values of 3–5 Ω^{-1} cm^2 mol^{-1} indicating that they are neutral and non-electrolytes [22]; elemental analyses were in agreement with the suggested hydrated forms drawn in (Scheme 5 and Table 2).



Scheme 5. Reagents and conditions: (a) MNO_2 (0.5 eq), NaOH, MeOH, [M = Zn, *n* = 2.5 for (**XVIIIa**); M = Cu, *n* = 3.0 for (**XVIIIb**); M = Ni, *n* = 3.0 for (**XVIIIc**)]; (b) $VOSO_4 \cdot H_2O$, NaOH, MeOH.

Thermal analysis of (**XVIIIa**) as a representative example was studied using the TG–DTG technique. The thermogram showed an endothermic event at 343 K accompanied by a mass loss of 6.87% (Calcd. 6.14%), assigned for removal of 2.5 water molecules of crystallization. The dehydration step is followed by one decomposition process with a strong endothermic event at 573 K due to decomposition of two mols of the ligand, forming two mols of ZnO and ZnC_2 as a final solid.

In the electronic spectra of complexes (**XVIIIa–c**) and (**XIX**) and their parent ligand (**IVe**), three very similar absorptions in the 300–450 nm region with maxima around 220, 365–400, and 440 nm were observed, therefore, they are most likely to be due to transitions involving orbitals of the ligand only.

In the IR spectra, a very strong and sharp band located at 1578 cm^{-1} was assigned to the (C=N) stretching vibration of the hydrazone moiety. This band is shifted 27–60 cm^{-1} to lower wave number indi-

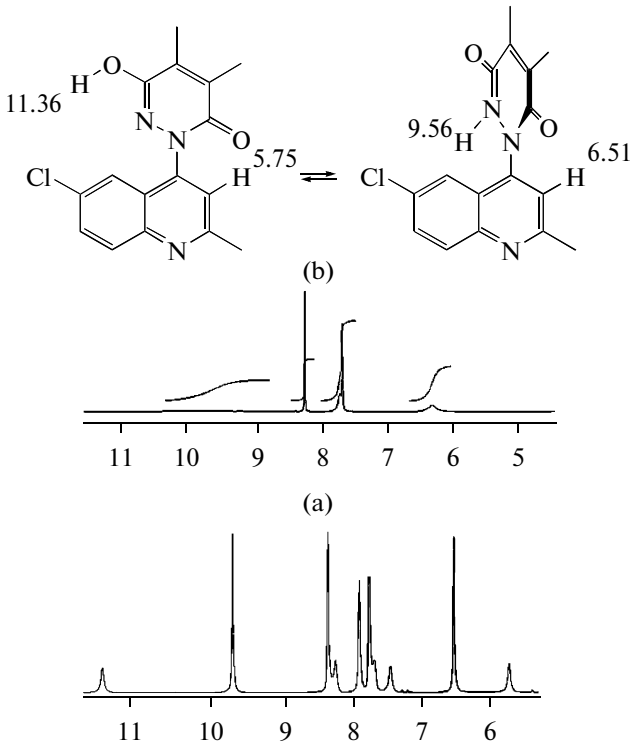


Fig. 1. (a) ^{1}H NMR of (**IX**) (600 MHz, DMSO, rt); (b) ^{1}H NMR of (**IX**) (50°C).

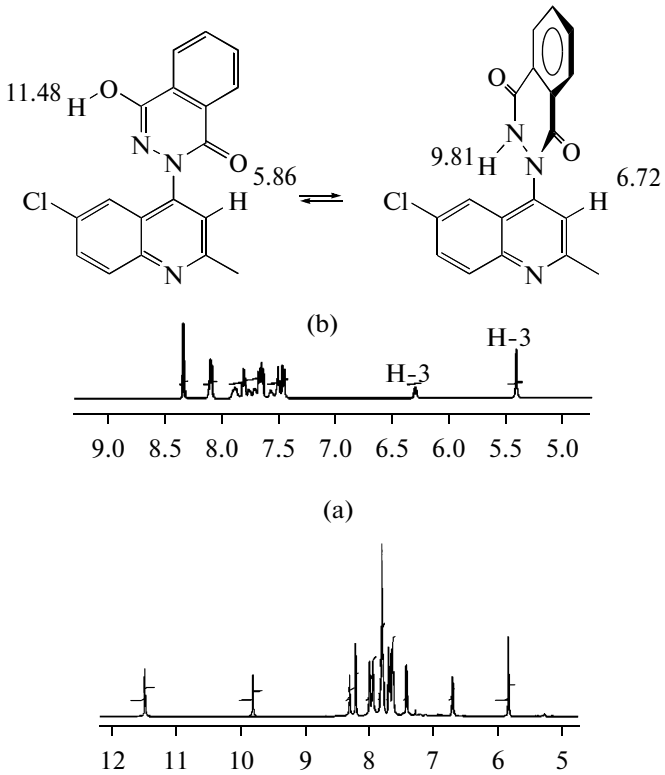


Fig. 2. (a) ^{1}H NMR of (**X**) (600 MHz, DMSO); (b) ^{1}H NMR of (**X**) (600 MHz, DMSO/D_2O).

cating the coordinate bond formation, and this shift can be explained by donation of electrons from nitrogen to the empty *d* orbital of the metal ion [23, 24].

Raman spectrum of the ligand (**IVe**) also showed an intense band at 1606 cm^{-1}, characteristic for C=N moiety. This band shows a slight shift in zinc(II) complex (**XVIIIa**) which also indicates the coordination of this group to the zinc(II) ion.

The presence of N–H broad band at 3282 cm^{-1} in the ligand and at 3241–3291 cm^{-1}, in the complexes indicate that in each complex the N–H functionality exists and is not deprotonated. In addition, the ligand's broad band centered at 3412 cm^{-1}, due to the O–H of the phenol, is probably involved in intramolecular hydrogen bonding [25], particularly, it disappeared due to complexation. Shift of the C–O stretching of phenol to higher wave number, 1365–1398 cm^{-1}, confirms that metal ions are bound to the phenolic oxygen. The strong bands observed at 1655–1533 cm^{-1} and 1093–1005 cm^{-1} are tentatively assigned [26, 27] to asymmetric and symmetric stretching of (C=C) and (C=N) of quinoline ring breathing and deformations respectively. These bands remain practically unchanged after complexation suggesting the non-involvement of quinolinic-nitrogen in complex formation. The oxidovanadium(IV) complex (**XIV**) showed a strong band in the region 943–884 cm^{-1}, which has been assigned to (V=O) with a monomeric square pyramidal coordination geometry [26–28]. The bands observed in the region of 477–523 cm^{-1} were also assigned to (V–N) stretching, while, the band at 433 cm^{-1} is attributed to (V–O) vibration [31]. A relatively medium broad absorption band with maximum at 3409–3444 cm^{-1} in all complexes is probably due to the adsorbed water molecule [27]. The Raman spectral bands, in the ligand are practically unchanged in these complexes, however some new bands with medium-to-weak intensities appeared in the region of 253 and 177 cm^{-1} in the complexes under study, which are assigned to (M–O) and (M–N) vibrational modes [25, 27]. These bands do not occur in the same position for all of the complexes, due to variation of the metal ions.

BIOLOGY

Insecticidal Activity

Only chloroquinolines modified with basic 5-membered and 6-membered rings showed insecticidal activity against the eggs of RPW, with phthalazine (**X**) being the most active one, but still far away from chlorazan, which gives maximum activity (93.3% mortality) at 0.004 M concentration, which is five-fold less concentrated than the test concentration of the synthesized samples (Table 3).

The study showed the importance of the chlorine atom for insecticidal activities, as compounds (**XVI**)

Table 2. Analytical and physical data of metal complexes (**XVIIIa–c**) and (**XIX**)

Compound	Empirical formula	Yield, %	Color	Melting point	Molar cond., Ω^{-1} cm^2 mol^{-1}	Chemical analysis found (calc.), %			
						C	H	N	M
L = **IVe**	$C_{17}H_{14}ClN_3O$ (311.76)		Yellow						
$[Zn(L)_2] \cdot 2.5H_2O$ **(XVIIIa)**	$C_{34}H_{33}Cl_2N_6O_{4.5}Zn$ (733.95)	79	Yellow	>300	3.24	54.82 (55.63)	4.65 (4.53)	11.20 (11.45)	8.78 (8.90)
$[Cu(L)_2] \cdot 3H_2O$ **(XVIIIb)**	$C_{34}H_{34}Cl_2N_6O_5Cu$ (741.13)	83	Brown	>300	3.34	55.82 (55.10)	3.82 (4.62)	11.97 (11.34)	8.69 (8.57)
$[Ni(L)_2] \cdot 3H_2O$ **(XVIIIc)**	$C_{34}H_{28}Cl_2N_6O_2$ (736.30)	81	Yellowish brown	>300	3.12	54.50 (55.46)	4.36 (4.65)	18.80 (11.41)	7.84 (7.97)
$[VO(L)(H_2O)]_2$-(SO_4) **(XIX)**	$C_{34}H_{30}Cl_2N_6O_{10}SV_2$ (887.50)	77	Yellow	>300	4.41	46.85 (46.01)	3.41 (3.72)	10.40 (9.47)	11.69 (12.48)

and (**XVII**) were inactive. Interestingly, polyhydroxyhydrazone (**IVk**) was the unique derivative that showed fungicidal and insecticidal activities which might be an axis for developing a complete solution for palm protection. Nevertheless, (**IVe**) was inactive, only its zinc complex (**XVIIIa**) could show the same activity as (**X**). Phthalazine (**X**) and the zinc complex (**XVIIIa**) showed the highest toxicities among the synthesized compounds (25% of the control), they have the lowest slope value of 1.5 (22% of the control). Consequently, the test organism individuals have the least homogeneity in their sensitivity and/or resistance to these derivatives compared with, for instance, pyrazole (**VII**), which is less toxic (20% of the control) but has the highest slope value of 3.4 (50% of the control).

Fungicidal Activity

Screening of the newly synthesized quinoline derivatives at unique concentration of 0.02 M in DMSO revealed activity for nearly all the hydrazones. Fluconazole was used as internal standard, i.e. positive control, under the same conditions and DMSO was used as negative control (Table 4).

Inspection of the inhibition zones showed that hydrazone (**IVe**) with *ortho* OH-group, which is efficient metal ion chelator, and its analogue (**IVi**) are the most active derivatives giving reason for these derivatives to be investigated more for potential application as fungicides for palm protection. Other derivatives, including *p* electron withdrawing (**IVc**) or even donating groups (**IVg**), gave activity comparable to fluconazole, therefore, they are also promising for further investigation as candidates for palm protection. None of the heterocyclic graphted quinolines, nonhalogenated derivatives, or metal complexes could show any fungicidal activity.

EXPERIMENTAL

Chemistry

Melting points were determined on Gallenkamp apparatus and are uncorrected. Flash chromatography was carried out on silica gel (Baker, 30–60 μm). TLC monitoring tests were carried out using plastic sheets precoated with silica gel 60 F_{245} (layer thickness 0.2 mm) purchased from Merck. Spots were visualized by their fluorescence under UV-lamp (λ 245 and 366 nm) or staining with iodine vapour. NMR spectra were recorded on an AC200 Brucker instrument of the Technical University in Vienna, a Varian Mercury VX-300 instrument at Cairo University, and Bruker 600 MHz spectrometer, Central laboratory, King Abd El Aziz,

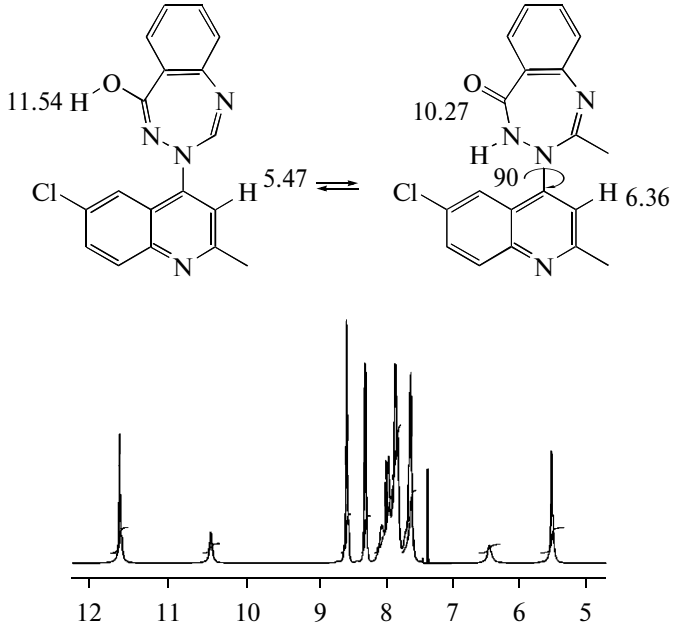


Fig. 3. ^{1}H NMR of (**XI**) (600 MHz, DMSO).

Table 3. Toxicity results of active derivatives against red palm weevil (RPW) *Rhynchophorus ferrugineus* Oliver

Compd.	LC_{25}	LC_{50}	LC_{90}	Slope	Toxicity index (%)
(IVk)	0.420 0.387 0.455	0.726 0.657 0.822	2.047 1.641 2.762	2.846 ± 0.231	13.085
(VII)	0.294 0.272 0.316	0.460 0.428 0.499	1.075 0.921 1.318	3.476 ± 0.264	20.652
(IX)	0.371 0.342 0.399	0.599 0.551 0.664	1.489 1.235 1.921	3.241 ± 0.268	15.860
(X)	0.137 – –	0.373 – –	2.505 – –	1.549 ± 0.123	25.469
(XI)	0.357 0.331 0.383	0.565 0.527 1.018	1.351 1.168 1.628	3.386 ± 0.229	16.814
(XVIIIa)	0.137 – –	0.373 – –	2.505 – –	1.549 ± 0.123	25.469
Chlorozan	0.076 – –	0.095 – –	0.145 – –	6.987 ± 0.401	100.000

Jeddah, Saudi Arabia. IR spectra were recorded using a JASCO FT IR-460 plus spectrometer while the mass spectra were recorded on a GCMS-QP 1000Ex Shimadzu spectrometers in the microanalysis unit at Cairo University and ATR-Alpha FT-IR Spectrophotometer from 400 to 4000 cm^{-1}. Raman spectra were obtained as powders in glass capillaries on a Nicolet FT Raman 950 spectrophotometer. The spectra were recorded at room temperature with a germanium detector maintained at liquid nitrogen temperature and using 1064 nm radiation generated by Nd-YAG laser with a resolution of 2 cm^{-1}. The conductivity measurements were carried out using Equiptronics digital conductivity meter model JENWAY 4070 at room temperature for 1×10^{-3} mol L^{-1} solutions. All UV-Vis measurements were recorded by Perkin-Elmer Lambda 25 UV/Vis double-beam spectrophotometer. Thermal analyses of the complexes were recorded on a Netzsch STA 449F3 with system interface device in nitrogen. The temperature scale of the instrument was calibrated with high-purity calcium oxalate. The operational range of the instrument was from ambient to 1200°C. Pure sample (5 mg) was used for dynamic TG scans at 10°C min^{-1}. Insecticidal activities were evaluated at the Insect Research Institute, Cairo Egypt, while the fungicidal activities were estimated at the Biology Department, Taif University, Taif, Saudi Arabia.

Table 4. Fungicidal (*F. oxysporum*) activities

Entry	Fungicidal activity	
	inhibition zone diameter, mm*	MIC, mM
(IVa)	14	1.48
(IVb)	15	1.40
(IVc)	17	0.88
(IVd)	14	1.48
(IVe)	24	0.77
(IVf)	15	1.48
(IVg)	17	0.89
(IVh)	12	1.48
(IVi)	20	0.84
(IVj)	12	1.80
(IVk)	16	1.10
(V)	15	1.40
Fluconazole**	32	0.45

* Measurements at 0.02 M (200 μL).

** Reference fungicide.

*General Procedure for the Synthesis of Hydrazones (**IVa–k** and **V**)*

A mixture of compound **(III)** (1 mmol) and the appropriate carbonyl derivative **(IIa–k)** or cinnamaldehyde (1.1 mmol) in EtOH (5 mL) was refluxed on a boiling water bath for 2 h and then left to reach ambient temperature. The crystalline product that separated was filtered at the pump, washed thoroughly with Et_2O–petroleum ether (1 : 1) mixture, and dried well to afford analytically pure product.

(*E*)-4-(2-Benzylidenehydrazinyl)-6-chloro-2-methylquinoline (IVa). Yellow crystals; IR (ν_{max}, cm^{-1}): 1574 ($C{=}N_{str}$), 1650 ($N{-}H_{def}$), 3203 ($N{-}H_{str}$). Found, %: C 69.06, H 4.73, N 13.6. $C_{17}H_{14}ClN_3$ (295.77). Calcd., %: C 69.04; H 4.77; N 14.21. ^{1}H NMR (200 MHz, DMSO-d_6): δ 11.10 (1 H, bs, NH), 7.10–8.35 (10 H, m, 9 Ar, –CH=N–), 2.49 (3 H, s, CH_3). ^{13}C NMR (50 MHz, DMSO): δ 160.26 ($C{=}N_{quinoline}$), 134.84, 129.48, 129.28, 128.74, 127.98,

126.63, 120.78 (15C), 24.80 (CH_3). EI-MS *m/z* (%): 295 (M, 21), 192 (37), 176 (11), 122 (30), 105 (49), 77 (65), 51 (100).

(*E*)-6-Chloro-4-(2-methoxybenzylidene)hydrazinyl)-2-methylquinoline (IVb). Yellow crystals; IR (ν_{max}, cm^{-1}): 1583 (C=N_{str}), 3206 (N–H_{str}). Found, %: C 66.24, H 4.93, N 12.94. $C_{18}H_{16}ClN_3O$ (325.80). Calcd., %: C 66.36, H 4.95, N 12.90. ^{1}H NMR (200 MHz, DMSO-d_6): δ 10.98 (1 H, br. s, NH), 6.95–8.45 (9 H, m, Ar, –CH=N–), 3.79 (3 H, s, –OMe), 2.56 (3 H, s, CH_3); ^{13}C NMR (50 MHz, DMSO-d_6): δ 160.26 (C=$N_{quinoline}$), 146.21, 142.91, 130.41, 129.34, 128.14, 127.33, 120.53, 114.23, 101.02 (15C, Ar), 55.20 (–OMe), 23.20 (CH_3). EI-MS *m/z* (%): 325 (M, 100), 217 (15), 192 (66), 164 (40), 134 (44), 107 (27), 77 (78).

(*E*)-6-Chloro-2-methyl-4-(2-(4-nitrobenzylidene) hydrazinyl)quinoline (IVc). Brown crystals; IR (ν_{max}, cm^{-1}): 1329 ($NO_{2sym\ str}$), 1565 ($NO_{2asym\ str}$), 1584 (C=N_{str}), 3194 (N–H_{str}). Found, %: C 59.21, H 3.83, N 16.21. $C_{17}H_{13}ClN_4O_2$ (340.77). Calcd., %: C 59.92, H 3.85, N 16.44. ^{1}H NMR (200 MHz, DMSO-d_6): δ 11.40 (1 H, bs, NH), 7.28–8.45 (9 H, m, Ar–H, –CH=N–), 2.56 (3 H, s, CH_3). EI-MS *m/z* (%): 340 (M, 92), 310 (10), 218 (14), 191 (57), 164 (100), 123 (33), 99 (28), 76 (62).

(*E*)-6-Chloro-4-(2-(4-chlorobenzylidene)hydrazinyl)-2-methylquinoline (IVd). Yellow crystals; IR (ν_{max}, cm^{-1}): 1586 (C=N_{str}), 1643 (N–H_{def}), 3195 (N–H_{str}). Found, %: C 61.23, H 3.85, N 12.56. $C_{17}H_{13}Cl_2N_3$ (330.21). Calcd., %: C 61.83, H 3.97, N 12.73. ^{1}H NMR (200 MHz, DMSO-d_6): δ 11.20 (1 H, br. s, NH), 7.20–8.70 (9 H, m, Ar, –N=CH–), 2.50 (3 H, s, CH_3). ^{13}C NMR (50 MHz, DMSO-d_6): δ 158.83 (C=$N_{quinoline}$), 133.82, 133.57, 129.53, 128.76, 128.20, 128.02, 120.85, 101.01 (15C, Ar), 24.23 (CH_3). EI-MS *m/z* (%): 330.0 (M, 28.6), 3.29 (43), 239 (10), 218 (350, 192(53), 164 (55), 137 (39), 111 (59), 89 (100).

(*E*)-2-((2-(6-chloro-2-methylquinolin-4-yl)hydrazono)methyl)phenol (IVe). Yellow crystals; IR (ν_{max}, cm^{-1}): 1600 (C=N_{str}), 1641 (N–H_{def}), 2921 (–C=N–··· H–O–), 3152 (N–H_{str}). Found, %: C 61.57, H 5.00, N 12.51. $C_{17}H_{14}ClN_3O$. H_2O (329.81). Calcd., %: C 61.90, H 4.88, N 12.70. ^{1}H NMR (200 MHz, DMSO-d_6): δ 10.91 (1 H, bs, NH), 10.10 (1 H, br.s, OH), 8.09–8.52 (2 H, m, H-$8_{quinoline}$, –CH=N–), 7.23–7.61 (3 H, m, Ar), 6.59–6.92 (3 H, m, Ar), 7.12 (1 H, m, Ar), 2.45 (3 H, s, CH_3). ^{13}C NMR (50 MHz, DMSO-d_6): δ 160.66 (C=$N_{quinoline}$), 136.35, 130.56, 129.11, 122.21, 119.40, 117.15, 115.94, (15C, Ar, CH=N), 23.15 (CH_3). EI-MS *m/z* (%): 311 (M, 30), 294 (21), 240 (17), 209 (18), 192 (100), 164 (64), 143 (37), 123 (49), 93 (78), 65 (90).

(*E*)-4-((2-(6-Chloro-2-methylquinolin-4-yl)hydrazono)methyl)phenol (IVf). Yellow crystals; IR (ν_{max}, cm^{-1}): 1588 (C=N_{str}), 3469 (O–H_{str}). Found, %: C 63.81, H 4.64, N 12.82.65 (80). $C_{17}H_{14}ClN_3O$. 0.5 H_2O (320.80). Calcd., %: C 63.64; H 4.72; N 13.10. (^{1}H NMR, DMSO-d_6): δ 10.75 (1 H, br.s, NH), 9.79 (1 H, br.s, OH), 8.10 (2 H, m, H-8, CH=N), 6.95 (1 H, s, H-$3_{quinoline}$), 6.63–7.39 (4 H, m, H-$7_{quinoline}$, H-$5_{quinoline}$, H-3_{phenol}, H-5_{phenol}), 6.61 (2 H, d, *J* 7.1 Hz, H-2_{phenol}, H-6_{phenol}), 2.45 (3 H, s, CH_3). ^{13}C NMR (50 MHz, DMSO-d_6): δ 158.83 (C=$N_{quinoline}$), 115.64, 120.78, 125.86, 127.82, 128.36, 129.39 (15C, Ar, CH=N), 23.10 (CH_3). EI-MS *m/z* (%): 311 (M, 100), 218 (21), 192 (54), 164 (46), 128 927), 93 (55).

(*E*)-6-Chloro-2-methyl-4-(2-(4-methylbenzylidene) hydrazinyl)quinoline (IVg). Cream-colored plates; IR (ν_{max}, cm^{-1}): 1585 (C=N_{str}), 3138 (N–H_{str}). Found, %: C 69.72, H 5.01, N 13.59. $C_{18}H_{16}ClN_3$ (309.81). Calcd., %: C 69.79; H 5.21; N 13.56. ^{1}H NMR (600 MHz, DMSO-d_6): δ 10.90 (1 H, br.s, N$H_{D_2Oexchangeable}$), 8.28–8.34 (2 H, m, H-$8_{quinoline}$, –N=CH–), 7.73 (1 H, d, *J* 8.4 Hz, H-$7_{quinoline}$), 7.62 (2 H, d, *J* 7.2 Hz, H-$2_{toluene}$, H-$6_{toluene}$), 7.52 (1 H, d, *J* 7.8 Hz, H-$5_{quinoline}$), 7.25 (1 H, s, H-$3_{quinoline}$), 7.20 (2 H, d, *J* 7.2 Hz, H-$3_{toluene}$, H-$5_{toluene}$), 2.54 (3 H, s, $CH_{3\ quinoline}$), 2.33 (3 H, s, $CH_{3toluene}$). EI-MS *m/z* (%): 309 (M, 100), 294 (2.03), 281 (2.25), 274 (4.43), 256 (4.17), 246 (2.24), 232 (2.17), 218 (24).

(*E*)-5-((2-(6-Chloro-2-methylquinolin-4-yl)hydrazono)methyl)-2-methoxyphenol (IVh). Faint brown crystals; IR (ν_{max}, cm^{-1}): 1586 (C=N_{str}), 3266 (N–H_{str}), 3451 (O–H_{str}). Found, %: C 62.95, H 4.36, N 11.86. $C_{18}H_{16}ClN_3O_2$ (341.79). Calcd., %: C 63.25, H 4.72, N 12.29. ^{1}H NMR (600 MHz, DMSO-d_6): δ 10.89 (1 H, s, $NH_{D_2Oexchangeable}$), 9.50 (1 H, s, $OH_{D_2Oexchangeable}$), 8.26–8.39 (2 H, m, H-$8_{quinoline}$, –N=CH–), 7.61 (1 H, s, Ar), 7.75 (1 H, s, Ar), 7.37 (1 H, s, Ar), 7.26 (1 H, s, H-$3_{quinoline}$) 6.83, 7.15 (2 H, 2d, *J* 7.8 Hz), 3.82 (3 H, s, –OCH_3), 2.49 (3 H, s, $CH_{3quinoline}$). EI-MS *m/z* (%): 341 (M, 100), 325 (2), 311 (2), 298 (3), 291 (1), 270 (1).

(*E*)-4-(1-(2-(6-Chloro-2-methylquinolin-4-yl)hydrazono)ethyl)phenol (IVi). Yellow crystals; IR (ν_{max}, cm^{-1}): 1592 (C=N_{str}), 1643 (N–H_{def}), 3402 (O–H_{str}). Found, %: C 64.42, H 5.08, N 12.61. $C_{18}H_{16}ClN_3O$. 0.5 H_2O (334.83). Calcd., %: C 64.56, H 5.12, N 12.55%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.71 (1 H, s, NH), 9.52 (1 H, br. s, OH), 6.78–8.23 (8 H, m, Ar), 2.41, 2.47 (6 H, 2s, 2 CH_3). EI-MS *m/z* (%): 325 (M, 63), 248 (10), 218 914), 192 (39), 164 (18), 134 (100), 91 921), 63 (60).

(*E*)-2-(1-(2-(6-Chloro-2-methylquinolin-4-yl)hydrazono)ethyl)benzene-2,6-diol (IVj). Yellow powder;

IR-KBr (ν_{max}, cm^{-1}): 1616 (C=N_{str}), 1636 (N–H_{def}), 3227 (N–H_{str}), 3553–3410 (O–H_{str}). Found, %: C 62.65, H 4.75, N 12.10. $C_{18}H_{16}ClN_3O_2$. 0.25 H_2O (346.32). Calcd., %: C 62.42, H 4.72, N 12.10. ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.80–12.20 (3 H, 3 br.s, 2 OH, NH), 6.32–8.28 (7 H, m, Ar), 2.29–2.47 (6 H, 2s, 2 CH_3). ^{13}C NMR (50 MHz, DMSO-d_6): δ 155.55 (C=$N_{quinoline}$), 130.14, 127.73, 127.24, 107.52, 106.88 (15C, Ar, CH=N), 23.74 ($CH_{3quinoline}$), 18.21 (CH_3). EI-MS *m/z* (%): 341 (M, 50), 324 (28), 192 9100), 166 (21), 150 (82), 102 (53), 77 (50).

(*E*)-4-(1-(2-(6-Chloro-2-methylquinolin-4-yl)hydrazono)ethyl)benzene-2,3,4-triol (IVk). Brown powder; IR-KBr (ν_{max}, cm^{-1}): 1615 (C=N_{str}), 1637 (N–H_{def}), 3232 (N–H_{str}), 3562–3411 (3 OH_{str}). Found, %: C 57.58, H 4.60, N 11.20. $C_{18}H_{16}ClN_3O_3$. H_2O (375.84). Calcd., %: C 57.51, H 4.83, N 11.20. ^{1}H NMR (200 MHz, DMSO-d_6): δ 6.15-8.26 (6 H, m, Ar), 2.27–2.45 (6 H, 2s, 2 CH_3). ^{13}C NMR (50 MHz, DMSO-d_6): δ 152.62, 152.05 (2 C=N), 132.59, 132.14, 129.11, 127.41, 123.03, 120.73, 118.64, 112.99, 112.50, 107.60, 98.64 (14 C_{Ar}), 26.22, 18.19 (2 CH_3). EI-MS *m/z* (%): 357 (M, 31), 340 (16), 192 (100), 164 (21), 140 (13), 123 (15), 99 (25), 79 (16), 63 (46).

6-Chloro-2-methyl-4-((E)-2-((E)-3-phenylallyli-dene)hydrazinyl)quinoline (V). Yellow crystals; IR (ν_{max}, cm^{-1}): 1586 (C=N_{str}), 1626 (N–H_{def}), 3152 (N–H_{str}). Found, %: C 70.28, H 4.96, N 12.46. $C_{19}H_{16}ClN_3$ (321.80). Calcd., %: C 70.91, H 5.01, N 13.06. ^{1}H NMR (600 MHz, DMSO-d_6): δ 10.95 (1 H, s, NH), 8.35 (1 H, s, Ar), 8.17 (1 H, d, *J* 9.6 Hz), 7.75 (1 H, d, *J* 9.0 Hz), 7.57 (3 H, m, Ar), 7.36 (2 H, t, *J* 7.2, 7.8 Hz), 7.28 (1 H, t, *J* 7.2 Hz), 7.16 (1 H, s, Ar), 7.06 (1 H, dd, *J* 9.0, 9.6 Hz), 6.95 (1 H, d, *J* 16.2, Olefinic), 2.52 (3 H, s, CH_3). ^{13}C NMR (150 MHz, DMSO-d_6): δ_C 159.32 (C=N), 146.76, 145.88, 145.30, 136.59, 136.16, 130.39, 129.29, 128.71, 128.34, 128.23, 126.73, 125.69, 120.52, 116.40, 101.30 (17C), 25.16 (CH_3). EI-MS *m/z* (%): 321 (M, 82.5), 293 (5), 279 (2.7), 257 (3.7), 244 (15), 230 (4).

6-Chloro-4-(3,5-dimethyl-1*H*-pyrazol-1-yl)-2-methylquinoline (VII). A mixture of (**III**) (0.24 g, 1.1 mmol) and acetylacetone (3 mL) was heated under reflux for 3 h, then coevaporated with toluene in vacuo and the residue was purified by flash chromatography (toluene–ethylacetate, 8.5 : 1.5) to afford (**VII**) as colorless sun-shape crystals (0.29 g, 93%). R_f 0.12 (toluene–ethylacetate, 8.5 : 1.5); mp 120°C. IR (ν_{max}, cm^{-1}): 876 (C–Cl_{str}), 1611 (C=N_{str}). Found, %: C 66.58, H 5.06, N 15.79. $C_{15}H_{14}ClN_3$ (271.74). Calcd., %: C 66.30, H 5.19, N 15.46. ^{1}H NMR (600 MHz, DMSO): δ 8.04 (1 H, d, *J* 9.0 Hz, H-$8_{quinoline}$), 7.80 (1 H, dd, *J* 2.4, 9.0 Hz, H-$7_{quinoline}$), 7.59 (1 H, d, *J* 1.8 Hz, H-$5_{quinoline}$), 7.56 (1 H, s, H-$4_{pyrazole}$), 6.23 (1 H, s, H-$3_{quinoline}$), 2.71, 2.24, 2.17 (9 H, 3s, 3 CH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ 159.57, 150.53, 147.69, 143.30, 141.12, 132.78, 131.15, 130.50, 124.20, 122.57, 120.46, 116.42, 107.08 (12 C_{ar}), 25.33 ($CH_{3quinoline}$), 13.64, 11.75 ($2CH_{3\,pyrazole}$). EI-MS *m/z* (%): 271 (M, 11), 270 (28), 250 (100), 229 (63), 225 (63).

1-(6-Chloro-2-methylquinolin-2-yl)-5-methyl-1*H*-pyrazol-3(2*H*)-one (VIII). A mixture of (**III**) (0.24 g, 1.1 mmol) and ethylacetoacetate (3 mL) was heated under reflux for 3 h, then left to reach ambient temperature. The precipitate was filtered and recrystallized from EtOH or MeOH/AcOH to afford (**VIII**) (0.2 g, 64%) as fine colorless crystals. R_f 0.3 (toluene–acetone, 7 : 3); mp 253°C. IR (ν_{max}, cm^{-1}): 829 (C–Cl_{str}), 1549 (*Amide II*), 1615–1599 (*Amide I*), 1747 (C=O_{str}), 3101 (N–H_{str}). Found, %: C 61.11, H 4.03%. $C_{14}H_{12}ClN_3O$ (273.72). Calcd., %: C 61.43, H 4.42. ^{1}H NMR (600 MHz, DMSO): δ 11.99 (1 H, br. s, O–H), 8.05 (1 H, d, *J* 9.0 Hz, H-$8_{quinoline}$), 8.04 (1 H, d, *J* 2.4 Hz, H-$5_{quinoline}$), 7.84 (1 H, dd, *J* 9.0, 2.4 Hz, H-$7_{quinoline}$), 7.75 (1 H, s, H-$4_{pyrazole}$), 6.00 (1 H, s, H-$3_{quinoline}$), 2.73 (3 H, s, $CH_{3quinoline}$), 2.00 (3 H, s, $CH_{3pyrazole}$). ^{13}C NMR (150 MHz, DMSO): δ 159.45, 159.15, 153.47, 151.56, 147.77, 145.98, 138.86, 132.55, 131.12, 130.59, 122.63, 122.04, 118.41, 105.91, 102.00 (12 C_{Ar}), 25.31 ($CH_{3quinoline}$), 19.80, 14.83 ($CH_{3pyrazole}$). EI-MS *m/z* (%): 275 (M + 2, 1.5), 274 (M + 1, 4), 273 (M, 0.7), 261 (11), 241 (24), 217 (40), 77 (100).

1-(6-Chloro-2-methylquinolin-4-yl)-4,5-dimethyl-1,2-dihydropyridazine-3,6-dione (IX). A mixture of (**III**) (0.3 g, 1.4 mmol) and dimethylamaleic anhydride (0.2 g, 1.6 mmol) in EtOH (5 mL) was heated under reflux for 4 h and then left to reach ambient temperature. The fine crystals formed upon cooling were collected, washed with little MeOH, then Et_2O, and dried well, and might be recrystallized from EtOH, if necessary, to afford (**IX**) (0.32 g, 71%) as fine crystals. R_f 0.46 (toluene–MeOH, 4 : 1); mp 252–254°C (Dec.). IR (ν_{max}, cm^{-1}): 835 (C–Cl_{str}), 1570–1595 (C=C_{str}, C=N_{str}), 1716 (C=O_{str}), 3563 (O–H_{str}). Found, %: C 58.62, H 4.68, N 12.72. $C_{16}H_{14}ClN_3O_2$. 0.5 H_2O (324.79). Calcd., %: C 59.16, H 4.66, N 12.94. ^{1}H NMR (600 MHz, DMSO): δ 11.36 (0.3 H, br. s, O–$H_{D_2Oexchangeable}$), 9.56 (0.7 H, br. s, N–$H_{D_2Oexchangeable}$), 8.25 (0.7 H, s, H_{arom}), 8.15 (0.3 H, s, Ar), 7.82 (0.7 H, s, Ar), 7.69 (0.7 H, s, Ar), 7.58 (0.3 H, s, Ar), 7.39 (0.3 H, s, Ar), 6.51 (0.7 H, s, H-$3_{quinoline\text{-}Keto}$), 5.75 (0.3 H, s, H-$3_{quinoline\text{-}Iminol}$), 2.35 (3 H, s, $CH_{3quioline}$), 1.93, 1.90 (6 H, 2s, 2 CH_3). EI-MS *m/z* (%): 315 (M, 24), 307 (23), 298 (23), 280 (46), 261 (49), 260 (49), 243 (64), 99 (100).

2-(6-Chloro-2-methylquinoline-4-yl)-2,3-dihydrophthalazine-1,4-dione (X). A mixture of (**III**) (0.3 g, 1.4 mmol) and phthalic anhydride (0.23 g, 1.5 mmol)

in EtOH (6 mL) was heated under reflux for 6 h and then allowed reaching ambient temperature. The precipitate was filtered and purified by flash chromatography (toluene–ethyl acetate, 1 : 1) to afford (**X**) as fine yellow solid (0.15 g, 31%). R_f 0.18 (toluene–ethyl acetate, 1 : 1); mp 294°C. Found, %: C 60.55, H 3.60, N 11.30. $C_{18}H_{12}ClN_3O_2 \cdot H_2O$ (355.78). Calcd., %: C 60.76, H 3.97, N 11.81. ^{1}H NMR (600 MHz, DMSO): δ 11.48 (0.6 H, s, $O-H_{D_2O exchangeable}$), 9.81 (0.4 H, s, $N-H_{D_2O exchangeable}$), 8.33 (0.4 H, s, Ar), 8.23 (0.6 H, s, Ar), 8.02 (0.4 H, s, Ar), 7.97 (0.6 H, s, Ar), 7.82, 7.72, 7.66 (4.4 H, 3m, Ar), 7.43 (0.6 H, d, *J* 8.4 Hz, Ar), 6.72 (0.4 H, s, $H\text{-}3_{quinoline\text{-}Keto}$), 5.86 (0.6 H, s, $H\text{-}3_{quinoline\text{-}Iminol}$), 2.41 (3 H, s, CH_3). EI-MS *m/z* (%): 239 (M + 2, 45), 338 (M+1, 26), 337 (M, 100), 322 (2), 310 (2.6), 292 (6.5), 279 (2).

3-(6-Chloro-2-methylquinolin-4-yl)-2-methyl-3*H*-benzo[*e*][1,2,4]triazepin-5(4*H*)-one (XI). A mixture of (**III**) (0.5 g, 2.4 mmol) and 2-methylbenzoxazolin-4-one (0.5 g, 3.1 mmol) in AcOH (2 mL) was heated under reflux for 6 h and then allowed reaching ambient temperature. The reaction mixture was coevaporated with toluene azeotrope in vacuo and the residue was recrystallized from EtOH/AcOH to afford (**XI**) (0.62 g, 74%) as colorless fine crystals. R_f 0.13 (toluene–MeOH, 4 : 1); mp 324–325°C. IR (ν_{max}, cm^{-1}): 1561–1603 (C=N, *Amide II*), 1634–1649 (*Amide I*), 3148 ($N-H_{str}$). Found, %: C 64.73, H 3.95, N 15.60. $C_{19}H_{15}ClN_4O$ (350.80). Calcd., %: C 65.05, H 4.31, N 15.97. ^{1}H NMR (600 MHz, DMSO): δ 11.56 (0.75 H, s, $O-H_{D_2O exchangeable}$), 10.29 (0.25 H, s, $N-H_{D_2O exchangeable}$), 8.38 (0.25 H, s, Ar), 8.34 (0.75 H, s, Ar), 8.12 (0.25 H, d, *J* 7.2 Hz, Ar), 8.08 (0.75 H, d, *J* 7.8 Hz, Ar), 7.88 (0.25 H, t, *J* 8.4, 9.6 Hz, Ar), 7.77 (0.75 H, t, *J* 7.8, 7.2 Hz, Ar), 7.72 (0.25 H, d, *J* 7.2 Hz, Ar), 7.67 (1 H, d, *J* 9.0 Hz, Ar), 7.63 (0.75 H, d, *J* 8.4 Hz, Ar), 7.55 (0.25 H, t, *J* 7.2 Hz, Ar), 7.45 (1.75 H, m, Ar), 6.36 (0.25 H, s, $H\text{-}3_{quinoline\text{-}keto}$), 5.47 (0.75 H, s, $H\text{-}3_{quinoline\text{-}Iminol}$), 2.40 (3 H, s, $CH_{3quinoline}$), 2.18 (3 H, s, $CH_{3triazepinone}$). ^{13}C NMR (150 MHz, DMSO): δ 159.65 (C=O), 157.39 ($C=N_{quinoline}$), 154.89, 147.69, 146.85, 137.05, 133.52, 131.42, 127.58, 126.63, 126.25, 125.71, 123.36, 121.07, 119.77, 96.26 (17C), 21.52 ($CH_{3quinoline}$), 19.42 ($CH_{3triazepinone}$). EI-MS *m/z* (%): 352.1 (M + 2, 42.37), 351.15 (M + 1, 24.81), 350.10 (M, 100), 335.10 (41.73), 333.15 (32.31), 308.20 (17.66).

2-[1-(2-Carbamoylhydrazinyl)-1-(4-(4,6-dimethylquinolin-2-ylamino)phenyl)ethylthio]acetic acid (XVI). A mixture of (**XIV**) (0.51 g, 1.5 mmol) and semicarbazide hydrochloride (0.2 g, 1.8 mmol) and K_2CO_3 (0.5 g, 3.6 mmol) in EtOH (4 mL) was heated under reflux with stirring for 5 h and then allowed reaching ambient temperature. The precipitate was filtered, then stirred with warm H_2O, filtered, washed with water, then a little EtOH, and dried well to afford (**XV**) (0.43 g, 80%) as creamy crude. R_f 0.48 (toluene–ethyl acetate-*iso*-PrOH, 4 : 3 : 3), mp 206–208°C. IR (ν_{max}, cm^{-1}): 1578–1607 ($C=N_{str}$, *Amide II*), 1694 (*Amide I*), 3200 ($N-H_{str}$), 3428, 3469 (NH_{2str}).

A mixture of (**XV**) (0.2 g, 0.6 mmol) and mercaptoacetic acid (0.25 mL, 3.6 mmol) in EtOH was heated under reflux with stirring for 5h and then allowed reaching ambient temperature. The precipitate formed was filtered at the pump and recrystallized from EtOH affording (**XVI**) (0.24 g, 96%) as fine lemon yellow crystals. R_f 0.18 (toluene–ethyl acetate–*iso*-PrOH, 6 : 2 : 1), mp 153–154°C. IR (ν_{max}, cm^{-1}): 1370, 1392 ($C-N_{str}$, $C-O_{str}$), 1569, 1612 (*Amide II*), 1661 (*Amide I*), 1705 ($C=O_{acid}$), 2699 ($O-H_{str}$), 3218–3281 ($N-H_{str}$), 3448–3800 (NH_{2str}). $C_{22}H_{25}N_5O_3S$ (439.58). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.41 (s, 1 H, $N-H_{Aniline}$), 9.22 (1 H, s, $N_1-H_{Semicarb.}$), 7.91 (2 H, d, *J* 8.4 Hz, Ar), 7.72 (2 H, m, *J* 8.4 Hz, Ar), 7.67 (1 H, d, *J* 8.4 Hz, Ar), 7.59 (1 H, s, $H\text{-}5_{Quinoline}$), 7.41 (1 H, d, *J* 8.4 Hz, Ar), 6.87 (1 H, s, $H\text{-}3_{Quinoline}$), 6.48 (br.s, 3 H, NH_2, $N_{3Semicarb.}-H$), 3.65 (2 H, s, CH_2), 2.53 (3 H, s, $C_{4quinol.}-CH_3$), 2.43 (3 H, s, $C_{6quinol.}-CH_3$), 2.16 (3 H, s, CH_3). EI-MS *m/z* (%): 439.55 (M^+, 0.08), 438.55 (0.08), 409.4 (0.1), 389.15 (0.13), 80.0 (100).

2-[4-(4,6-Dimethylquinolin-2-ylamino)phenyl]-1-morpholinoethanethione (XVII). A mixture of (**XIV**) (0.24 g, 0.8 mmol), sulfur (0.2 g, 6.2 mmol), and morpholine (3 mL) was heated under reflux with stirring for 10 h and then allowed to stand at ambient temperature overnight. The crystals were filtered and washed thoroughly with cold EtOH and dried well affording (**XVII**) (0.16 g, 50%) as fine faint yellow crystals. The combined mother liquor was evaporated in vacuo and the residue was purified by flash chromatography (toluene–ethyl acetate, 4 : 1) affording another 0.1 g raising the total yield to 81%. R_f 0.16 (toluene–ethyl acetate, 4 : 1); mp 254–256°C. IR (ν_{max}, cm^{-1}): 1027, 1107 ($C=S_{str}$, $C-N_{str}$), 1602 ($C=N_{str}$), 1636 ($N-H_{def}$), 3294 ($N-H_{str}$). Found, %: C 70.19, H 6.30, N 10.51. $C_{23}H_{25}N_3OS$ (391.57). Calcd., %: C 70.56, H 6.44, N 10.73. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.70 (1 H, d, *J* 9.0 Hz, Ar), 7.58 (1 H, s, $H\text{-}5_{quin.}$), 7.54 (2 H, d, *J* 8.4 Hz, Ar), 7.43 (1 H, dd, *J* 8.4, 1.2 Hz, Ar), 7.29 (2 H, d, *J* 8.4 Hz, Ar), 6.78 (1 H, s, $H\text{-}3_{quin.}$), 4.37, 3.76 (4 H, 2t, J_{gem} 9.6, J_{vic} 4.8 Hz, $-OCH_2$), 4.33 [2 H, s, $-CH_2C(=S)-$], 3.67, 3.46 (4 H, 2t, J_{gem} 9.6, J_{vic} 4.8 Hz, 2 $-NCH_2-$), 2.58 (3 H, s, $C_{4quin.}-CH_3$), 2.49 (3 H, s, $C_{6quin.}-CH_3$); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.31 (C=S), 131.11, 130.65, 128.22, 123.67, 123.2, 118.35, 113.75 (Ar), 65.88, 65.74 (2 $O-CH_2$), 50.69, 49.90 (2 $N-CH_2$) 48.73 ($-CS-CH_2$) 21.10 (C_6-CH_3), 18.49 (C_4-CH_3). EI-MS *m/z* (%): 391.1 (M^+, 0.02), 390.2 (0.02), 389.1 (0.03), 260.6 (99.98), 259.6 (88.9), 202.1 (100).

General procedure for the synthesis of metal complexes (XVIIIa–c) and (XIX). Ligand (**IVe**) (0.374 g, 1.2 mmol) dissolved in dry MeOH (10 mL) containing NaOH (48 mg, 1.2 mmol) was treated with the nitrate salt of Zn^{2+}, Cu^{2+}, or Ni^{2+} (0.6 mmol) or $VO \cdot SO_4 \cdot 2H_2O$ (1.2 mmol) and the mixture was stirred at 65°C for 2–3 h. The resulting solid was filtered off, washed with cold dry MeOH, then dried at 100°C. The analytical and physical data of the obtained metal complexes are given in (Table 2).

BIOLOGY

Insecticidal Screening

Cocoons and adults of RPW were collected from infected palm trees; adults which were collected directly from the field and those emerged from the cocoons were put, each 3 pairs of males and females, in a Petri dish (15 × 1.5 cm) with 3 pieces (10 × 1 cm) of sugar cane as an oviposition site and adult food; this was repeated 30 times. The sugar cane pieces were desiccated after two days and existing eggs were collected carefully with a small brush; each 10 eggs were put in a Petri dish (15 × 1.5 cm) lined with filter paper and a piece (1.5 × 0.5 cm) of sugar cane. Thirty eggs were used in 3 replicates for each treatment. A volume of 0.1 mL from each test compound (0.02 M in EtOH) was dropped on the 10 eggs in each dish and incubated at 25°C. EtOH was used as negative control, while chlorozan in H_2O was used as positive control and its recorded activity (Table 3) represents the same volume of 0.1 mL of 0.004 M stock as field recommended dose. The Petri dishes were examined daily and the hatched eggs and the number of larvae which succeeded to bore in the sugar cane were recorded. For lethal dose, slope, and toxicity estimation, the stock solution of each compound was diluted twice to have three concentrations of 0.02, 0.01, and 0.005 M and each concentration was tested exactly under the same conditions described above. Mortality data were corrected according to the Abbott formula [32] and the corrected mortality percentage of each compound was statistically computed according to Finney et al. [33], from which the corresponding concentration probit lines (LC-p lines) were estimated in addition to determination of 25, 50, and 90% mortalities. 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) × 100, Sun et al. [34].

Fungicidal Screening

The fungicidal activities of the synthesized compounds, 0.02 M in DMSO, were measured against *F. oxysporum* through poisoned food technique described by Borum and Sinclair [35] on potato dextrose agar (PDA) medium. A volume of 1.0 mL of *Fusarium oxysporum* spore suspension was poured in Petri dish and 20 mL PDA medium was poured and left till solidification. Using sterile cork porer, pores in the middle of each plate were made. An aliquot of 200 μL of each test compound were pipette in each pore. The plates were incubated at 27°C for 5 days. The effective compound showed inhibition zone around the pores. The diameter of the inhibition zones was measured. Fluconazole, 0.02 M, was used as positive control and DMSO as negative control.

For determination of the minimal inhibitory concentration (MIC), dilutions incorporated in molten Sabouraud agar were homogenized and poured into 90-mm Petri dishes. The fungus *F. oxysporum* was picked from purified culture in the form of a 5–mm agar disc and inoculated in the center of each Petri plate. Four replicate plates were inoculated for each tested chemical concentration. The dishes were incubated at 25°C receiving fluorescent light with 12 h cycling. Mean colony diameter was measured after 3, 5, and 7 days of inoculation.

CONCLUSIONS

A series of hydrazones, dipolar cyclocondensation and nucleophilic substitution products arising from 6–chloro-4-hydrazinoquinaldine (**III**), two nonhalogenated quinoline derivatives, including semicarbazides and thiomorpholides, as well as metal complexes, were prepared and tested as insecticides and fungicides. Hydrazones were active against *Fusarium oxysporum*, while the cyclocondensation products, besides the zinc complex, were active against the red palm weevil, with the polyhydroxylated hydrazone (**IVk**) being active against both organisms. Nonhalogenated derivatives were inactive against both organisms. Thus, derivative (**III**) might be a good lead for potential fungicides and insecticides development by further investigations.

ACKNOWLEDGMENTS

The financial support of Port Said University and Taif University (project no. 1–432–1309) and the statistical analysis of insecticide activities done by Prof. Ahmad Abd El Mageed are gratefully acknowledged.

REFERENCES

1. Murphy, S.T. and Briscoe, B.R., *Biocontrol News and Information*, 1999, vol. 20, no. 1, pp. 35N–46N.
2. Saremi, H., Okhovvat, S.M., and Ashrafi, S.J., *Commun. Agric. Appl. Biol. Sci.*, 2007, vol. 72, no. 4, pp. 831–837.
3. Ferry, M. and Gomez, S., *Palms*, 2002, vol. 46, no. 4, pp. 172–178.

4. Monzer, M.A. and Hesham, A.S., *Egypt. Acad. J. Biolog. Sci.*, 2009, vol. 2, no. 1, pp. 47–53.
5. Longley, N., Muzoora, C., Taseera, K., Mwesigye, J., Rwebembera, J., Chakera, A., Wall, E., Andia, I., Jaffar, S., and Harrison, T.S., *Clinical Infectious Diseases,* 2008, vol. 47, no. 12, pp. 1556–1561.
6. Muller, F., *Agrochemicals: Composition, Production, Toxicity, Applications*, Toronto: Wiley-VCH, 2000.
7. Wu, J., Song, B.A., Hu, D.Y., Yue, M., and Yang, S., *Pest Manag. Sci.*, 2012, vol. 68, pp. 801–810.
8. Al Jabr, A., and Abo-El-Saad, M., *Am. J. Environ. Sci.*, 2008, vol. 4, no. 6, pp. 595–601.
9. Aly, M.R.E., Abd El-Mageed, A.E.M., El-Kafafy, A.M.A., and Nawwar, G.A., *J. Plant Prot. Res.*, 2011, vol. 51, no. 2, pp. 114–120.
10. Krafts, K., Hempelmann, E., and Skorska-Stania, A., *Parasitol. Res.*, 2012, no. 1, pp. 1–6.
11. Boschelli, D.H. and Wu, B., Ye. F., Durutlic, H., Golas, J. M., Lucas, J., and Boschelli, F., *Bioorg. Med. Chem.*, 2008, vol. 16, pp. 405–412.
12. Zhang, H.Z., Claassen, G., Crogran-Grundly, C., Tseng, B., Drewe, J., and Cai, S.X., *Bioorg. Med. Chem.,* 2008, vol. 16, pp. 222–231.
13. Hollingshaus, J.G., *Pestic. Biochem. Physiol.*, 1987, vol. 27, pp. 61–70.
14. Klein, C.D. and Oloumi, H., in *Proceedings of the 5th International Conference on Urban Pests*, Lee, C.Y., and Robinson, W.H., Eds., Perniagan Ph`ng, P&Y Design Network, Malaysia, 2005, p. 101.
15. Dai, H., Yu, H.-B., Liu, J.-B., Li, Y.-Q., Qin, X., Zhang, X., Qin, Z.-F., Wang, T.-T., and Fang, J.-X., *Arkivoc*, 2009, vol. II, pp. 126–142.
16. Dong, W.-L., Xu, J.-Y., Xiong, L.-X., and Li, Z.-M., *Molecules*, 2012, vol. 17, pp. 10414–10428.
17. Savini, L., Chiasserini, L., Gaeta, A., and Pellerano, C., *Bioorg. Med. Chem.*, 2002, vol. 10, pp. 2193–2198.
18. Hasanen, J.A., Ibrahim, E.I., Orabi, A.S., Youssef, M.F., and Oriental, J., *Chem.*, 2007, vol. 23, pp. 27–33.
19. Lubenets, V.I., Stadnitskaya, N.E., and Novikov, V.P., *Russ. J. Org. Chem.*, 2000, vol. 36, no. 6, pp. 851–853.
20. Chi-Hoon, L., Ju-Hyun, J., Sang-Guei, L., and Hoi-Seon, L., *J. Korean Soc. Appl. Biol. Chem.*, 2010, vol. 53, no. 4, pp. 464–469.
21. Aly, M.R.E., El Shahed, F.A., Soliman, H.A., Ibrahim, E.I., Ibrahim, Z.S., and El-Shazly, S.A.M., *Russ. J. Bioorg. Chem.*, 2012, vol. 38, no. 4, pp. 428–434.
22. Girolami, G.S., Rauchfuss, T.B., and Angelici, R.J., *Synthesis and Technique in Inorganic Chemistry*, 3rd ed., Sausalito: University Science Books, 1999.
23. Chiswell, B., Crawford, J.P., and O'reilly, E.J., *Inorg. Chim. Acta*, 1980, vol. 40, pp. 223–228.
24. Maurya, M.R., Antony, D.C., Gopinathan, S., Puranik, V.G., Tavale, S.S., Gopinathan, C., and Maurya, R.C., *Bull. Chem. Soc. Jpn.*, 1995, vol. 68, pp. 2847–2852.
25. Silverstein, R.M., Bassler, G.C., and Morrill, T.C., *Spectroscopic Identification of Organic Compounds,* 5th ed., New York, NY, USA: John Wiley and Sons, 1991.
26. Mishra, A.P. and Pandey, L.R., *Indian J. Chem. A*, 2005, vol. 44, pp. 1800–1805.
27. Nakamoto, K., *Infrared and Raman Spectra of Inorganic and Coordination Compounds, Part A and Part B*, New York, NY, USA: John Wiley and Sons, 1998.
28. Selbin, J., *Chem. Rev.*, 1965, vol. 65, pp. 153–175.
29. Maurya, R.C. and Rajput, S., *J. Mol. Str.*, 2006, vol. 794, pp. 24–34.
30. Ibrahim, M.M., Mersal, G.A.M., El-Shazly, S.A., and Ramadan, A.M., *Int. J. Electrochem. Sci.*, 2012, vol. 7, pp. 7526–7546.
31. Aranha, P.E., Do Santo, M.P., Romera, S., and Dockal, E. R., *Polyhedron*, 2007, vol. 26, pp. 1373–1382.
32. Abbott, W.S., *J. Econ. Entomol.*, 1925, vol. 18, no. 2, pp. 265–267.
33. Finney, D.J., *Probit Analysis. A Statistical Treatment of the Sigmoid Response Curve*, 7th ed., Cambridge, England: Cambridge Univ. Press, 1971.
34. Sun, Y.P., *J. Econ. Entomol.*, 1950, vol. 43, no. 1, pp. 45–60.
35. Broum, D.F. and Sinclair, J.B., *Phytopath.*, 1968, vol. 58, pp. 976–980.