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Synthesis and Application of Some 1-[8-Hydroxy-5(or 7)-quinolinyl]-alkylidene-Substituted Heterocycles as Bactericides, Funjicides, and Bioregulator

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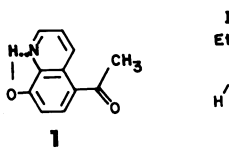
Interaction of 5-acetyl-8-quinolinol, corresponding 1-ethylquinolinium iodides, and 8-hydroxyquinoline-7-carbaldehyde with diethylmalonate under basic condition gave the corresponding of **4—6**. Further reaction of **4—6** with hydrazine, phenyl hydrazine, hydroxylamine, urea, and/or thiourea gave the corresponding 1-[8-hydroxy-5(7)-quinolinyl]alkylidene-substituted heterocyclic derivatives (**7—16**) and corresponding 1-ethylquinolinium iodides (**17—21**). The structure of the synthesized compounds was confirmed by elemental and spectral analysis. The biological activity of 5-substituted 8-quinolinol was tested as microbicidal and bioregulator agents, the results obtained were interpreted according to their structure-activity relationships.

The biological activity of azoles and barbituric acid derivatives is of interest.[1-3] Pharmacological studies showed that some of these compounds possessed hypolipidimic central nervous system depressant[4] and antitumor activities.[5] In this work 5(7)-heteroarylidenemethyl-8-hydroxyquinolines were prepared to evaluate the effect of substitution on the biological activity of 8-quinolinol nucleus as antimicrobial and bioregulator agents. Structure activity relationships has also been studied to detect the preferable structures required for such purposes.

Results and Discussion

The reaction of 5-acetyl-8-quinolinol (**1**), its corresponding 1-ethylquinolinium iodide (**2**), and 8-hydroxyquinoline-7-carbaldehyde (**3**) with diethyl malonate in the presence of sodium ethoxide gave the corresponding ethyl 2-ethoxycarbonyl-3-(8-hydroxy-5-quinolinyl)-2-butenoate (**4**), corresponding 1-ethylquinolinium iodide (**5**), and ethyl 2-ethoxycarbonyl-3-(8-hydroxy-7-quinolinyl)-2-propenoate (**6**) respectively.



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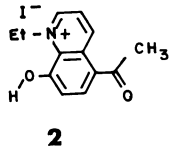

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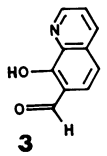

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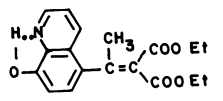

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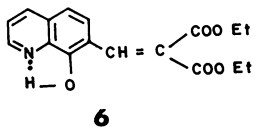

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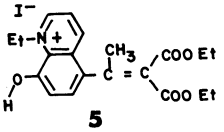
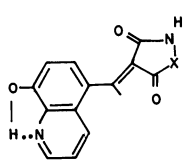
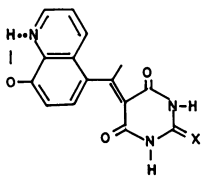


5

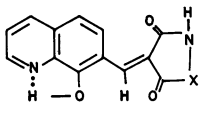
Further reaction of **4—6** with hydrazine hydrate, phenylhydrazine, hydroxylamine hydrochloride, urea, and thiourea gave the corresponding 4-[1-(8-hydroxy-5-quinolinyl)ethylidene]-3,5-pyrazolidinedione (**7**), 4-[1-(8-hydroxy-5-quinolinyl)ethylidene]-1-phenyl-3,5-pyrazolidinedione (**8**), 4-[1-(8-hydroxy-5-quinolinyl)-ethylidene]-3,5-isoxazolidinedione (**9**), 5-[1-(8-hydroxy-5-quinolinyl)ethylidene]barbituric acid (**10**), 5-[1-(8-hydroxy-5-quinolinyl)ethylidene]-2-thiobarbituric acid (**11**); corresponding 1-ethylquinolinium iodides (**17—21**); and 4-[(8-hydroxy-7-quinolinyl)methylene]-3,5-pyrazolidinedione (**12**), 4-[(8-hydroxy-7-quinolinyl)-methylene]-1-phenyl-3,5-pyrazolidinedione (**13**), 4-[(8-hydroxy-7-quinolinyl)methylene]-3,5-isoxazolidinedione (**14**), 5-[(8-hydroxy-7-quinolinyl)methylene]barbituric (**15**) and 2-thiobarbituric acid (**16**). The structures of the synthesized compounds were confirmed by elemental and spectral analysis. The infrared and ultraviolet spectral data are given in Table 3. All of the synthesized compounds 1-[8-hydroxy-5(or 7)-quinolinyl]alkylidene-substituted heterocyclic compounds showed the presence of $\nu_{\text{-NH}}$ group at 3100—3190 cm^{-1} and the lack of $\nu_{\text{-NH}_2}$. The NMR ($CDCl_3$) of compound **11** showed signals at δ 2.7 (3H, CH_3, s), 6.8—7.7 (5H, aromatic, m), and 11.3—11.5 (2H, NH, s).



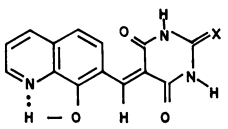
7, X=NH
8, X=N-C_6H_5
9, X=O



10, X=O
11, X=S



12, X=NH
13, X=N-C_6H_5
14, X=O



15, X=O
16, X=—S

The role of hydrogen bonding, 5-acetyl group and ring size of the 5-substituted 8-quinolinol are essential factors on the biological activity of the synthesized

Table 1. Physical and Analytical Data of Compounds **4**—**11**

Compd	Solvent of crystallization	Yield %	Mp(θ_m/°C)	R_f value	Molecular formula	Calcd/Found(%)[f]			
						C	H	N	S
4	Ethanol	78	340	0.34[a]	$C_{18}H_{19}NO_5$	69.90	6.15	4.26	—
						70.12	6.30	4.30	—
5	Ethanol	70	245—247 (decomp)	0.7[b]	$C_{20}H_{24}NO_5I$	49.48	4.95	2.90	—
						49.63	5.10	2.80	—
6	Dioxane	63	258—260	—	$C_{17}H_{17}NO_5$	69.15	5.76	4.44	—
						69.33	5.84	4.51	—
7	Ethanol	63	323—325 (decomp)	0.4[c]	$C_{14}H_{11}N_3O_3$	62.45	4.09	15.61	—
						62.60	4.21	15.57	—
8	Methanol	61	218—220	0.46[c]	$C_{20}H_{15}N_3O_3$	69.56	4.34	12.17	—
						69.80	4.52	12.22	—
9	Ethanol	63	327—329 (decomp)	0.43[c]	$C_{14}H_{10}N_2O_4$	62.22	3.70	10.37	—
						62.48	3.92	10.46	—
10	Ethanol	67	210—212	0.51[c]	$C_{15}H_{11}N_3O_4$	60.60	3.70	14.40	—
						60.83	3.88	13.09	—
11	Ethanol	57	258—260	0.56[c]	$C_{15}H_{11}N_3O_3S$	57.51	3.51	13.42	10.22
						57.83	3.68	13.11	10.30
12	Ethanol	43	288—290	0.38[c]	$C_{13}H_9N_3O_3$	61.18	3.53	16.47	—
						61.32	3.70	16.39	—
13	Ethanol	45	220—222 (decomp)	0.45[c]	$C_{19}H_{13}N_3O_3$	68.88	3.93	12.69	—
						69.05	4.11	12.75	—
14	Ethanol	55	279—280 (decomp)	0.41[c]	$C_{13}H_8N_2O_4$	60.94	3.12	10.94	—
						61.16	3.35	11.02	—
15	Ethanol	46	228—230	0.49[c]	$C_{14}H_9N_3O_4$	59.36	3.18	14.84	—
						59.50	3.22	14.91	—
16	Dioxane	40	330—332 (decomp)	0.53[c]	$C_{14}H_9N_3O_3S$	56.19	3.01	14.05	10.70
						56.24	3.30	14.20	10.61
17	Ethanol	66	328—329 (decomp)	0.63[d]	$C_{16}H_{16}N_3O_3I$	45.17	3.76	9.88	—
						45.35	3.95	9.93	—
18	Ethanol	54	345—347 (decomp)	0.58[d]	$C_{22}H_{20}N_3O_3I$	52.69	3.99	8.38	—
						52.77	4.12	8.45	—
19	Ethanol	54	268—270 (decomp)	0.61[d]	$C_{16}H_{15}N_2O_4I$	45.70	3.52	6.57	—
						45.90	3.70	6.61	—
20	Benzene	62	99—100	0.55[e]	$C_{17}H_{16}N_3O_4I$	45.03	3.53	9.27	—
						44.90	3.28	9.33	—
21	Benzene	47	113	0.66[e]	$C_{17}H_{16}N_3O_3SI$	43.50	3.41	8.96	6.82
						43.78	3.50	9.00	6.91

a) Benzene–ethanol (2:1). b) Benzene–ethanol (1:1). c) Benzene–ethanol (3:1). d) Benzene–ethanol (4:1). e) Toluene–ethanol (2:1). f) All compounds gave satisfactory C, H results.

Table 2. Antifungal and Antibacterial Screening

Compd	Inhibition zones (mm) Fungi						Inhibition zones (mm) bacteria		
	Penicillium notatum 100 ppm	*Aspergillus flavus* 100 ppm	*Stachybotrys atra*				*Bacillus subtilis*	*Micrococcus luteus*	*Serratia sp.*
			100 ppm	50 ppm	25 ppm	12.5 ppm			
1	30	35	71	55	40	35	22	19	23
2	25	22	65	48	35	—	—	—	20
4	20	—	52	45	32	—			
5	20	—	58	—	—	—			
10	20	21	53	—	—	—			
11	—	19	52	—	—	—			
15	20	21	53	—	—	—			
16	—	19	52	—	—	—			
17	25	—	50	—	—	—			
18	30	21	65	50	45	35	20		20
19	—	—	53	—	—	—			
20	22	—	57	46	32	—			
21	20	23	56	50	35	—	—		23

The compounds **3**, **6**—**9**, and **12**—**14** have no effect for all the fungi used. The compounds **3**—**21** have no effect for all the bacteria used (except **18** and **21**).

compounds. Thus 5-acetyl-8-quinolinol (**1**) is quite potent as fungicides especially *Stachybotrys atra* (71 mm inhibition zone at 100 ppm, cf. Table 2). Quaternization of **1** decreases its potency. Substitution of 5-acetyl by a butenoate moiety decreases its potency. 6-Membered barbituric and thiobarbituric heterocycles are more effective as fungicides than 5-membered (azoles) ones. On the other hand the above compounds are less potent as bactericides. The results are given in Table 2. Water-soluble compounds were choosen as bioregulator for *Vicia faba* seeds. Germination as expressed in the seedling height after 14 days versus the concentration with respect to the control was studied. It is clear that some of these compounds e.g. (**2**, **7**, **10**, **11**, **17**) enhance the seedling growth. The results are shown in Fig. 1.

More than one shoot per seedling was observed with percentage of 10% at the concentration of 100 ppm for compounds **1** and **7**; 50 and 1000 ppm for compound **17** and 500 ppm for compounds **10** and **11**. The difference in seedling height and the multishooted per seedling phenomena in the treated seeds led us to the

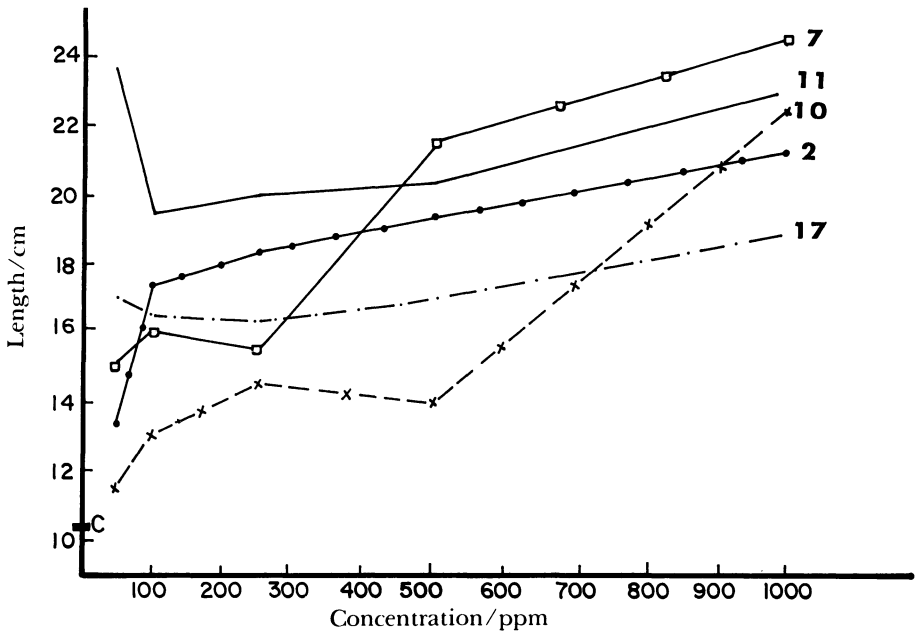
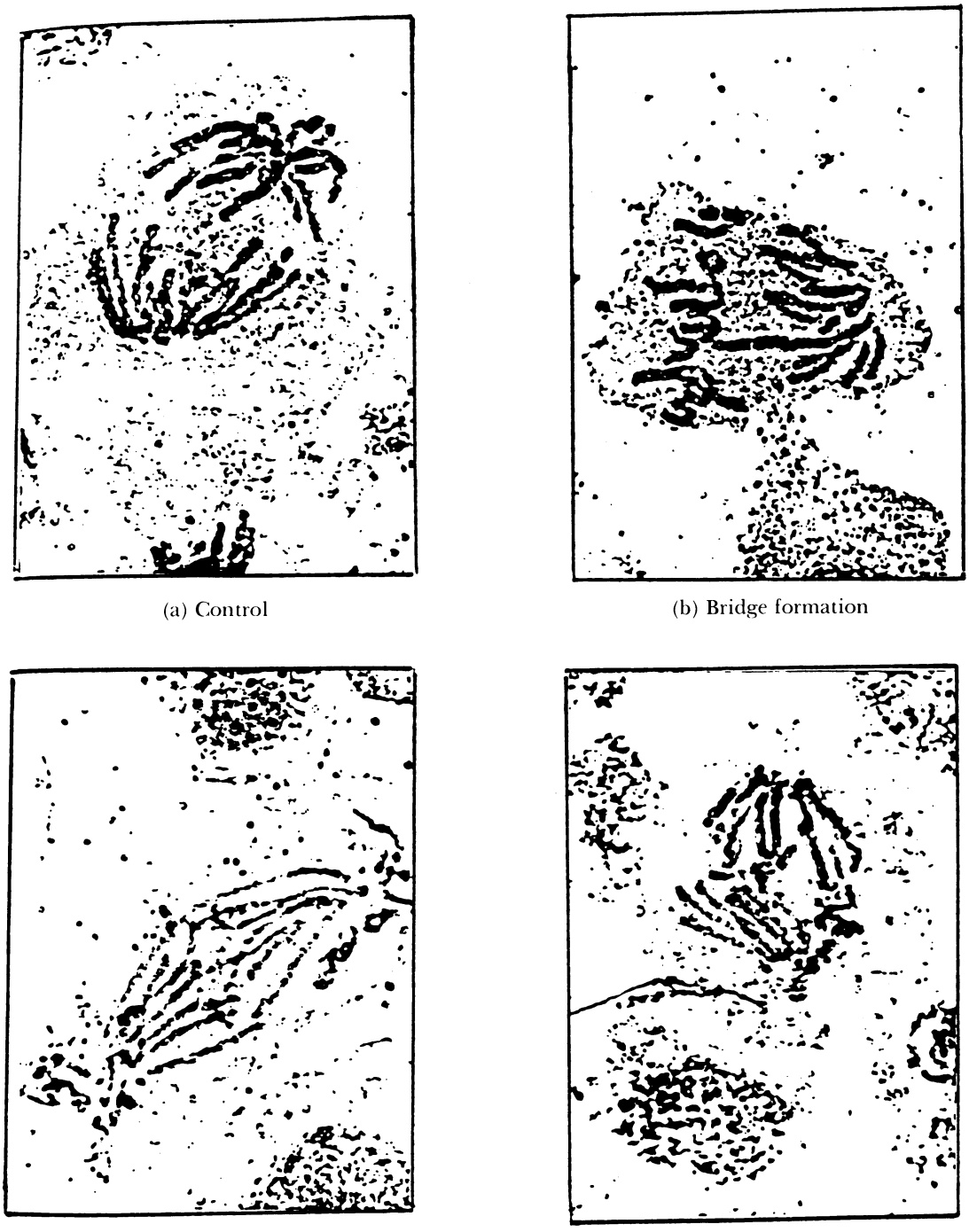


Fig. 1. Germination of *Vicia faba* seeds as expressed in seedling height after 14 days versus the concentration with respect to the control C.

Table 3. IR and UV Spectral Data of Compounds **4**—**21**

Compd	ν_{OH} cm^{-1}	ν_{NH} cm^{-1}	ν_{CO} cm^{-1}	λ_{max} (ε)		
4	3325(s)	—	1725(s)	—	320(5500)	404(2400)
5	3350(s)	—	1630(m), 1730(s)	280 (8700)	305(5800)	392(7000)
6	3345(s)	—	1630(m), 1670(m)		310(4900)	
7	3400	3190(s)	1700(b)	260 (9500)	335(7300)	380(6200)
8	3400(s)	3190(s)	1710(s)	285(15400)	340(7600)	380(5800)
9	3350(s)	3170(s)	1715(s)	260 (9500)	290(6300)	400(2400)
10	3430	3185(s)	1712(s), 1718	280 (6000)	336(7900)	402(3500)
11	3180	3100(s)	1715(s), 1720	285 (7100)	338(9600)	400(1000)
12	3320(b)	3100(b)	1700(m)		314(1900)	
13	3330(b)	3100(b)	1720(m)		312(3600)	
14	3320(b)	3090(s)	1720(m)		313(8200)	
15	3325(b)	3100(m)	1715(s)		310(5900)	
16	3330(b)	3100(m)	1715(s)		320(1000)	
17	3350(s)	3100(m)	1640(m)	—	310(4300)	391(3600)
18	3340(s)	3100(m)	1640(m)	—	306(7200)	394(8100)
19	3335(s)	3100(m)	1650(m)	—	328(5800)	392(3600)
20	3300(s)	3130(m)	1650(s)	—	326(7700)	392(3300)
21	3300(s)	3130(m)	1640(s)	—	328(9400)	390 (800)



(a) Control (b) Bridge formation

(c) More bridge formed (d) Fragment produced

Fig. 2. Chromosomal aberrations of the root-tips of the treated *Vicia faba* seeds as bridge and/or fragments with respect to the control.

cytological examination in the anatelophase. Rootless of the treated seeds showed chromosomal aberation as bridge and/or fragments with respect to the control. This chromosomal aberation is responsible for this behavior of the treated *Vicia faba* seeds (Fig. 2).

Experimental

All melting points are uncorrected. Infrared spectra were determined with a Perkin-Elmer 599 B spectrophotometer using the KBr wafer technique. NMR spectra were carried out in $CDCl_3$ using a Varian EM 390 (90 MHz). UV spectra were recorded in ethanolic solutions using a Cary 219 spectrophoto-meter.

5-Acetyl-[6] and 7-formyl-8-quinolinol[7] were prepared according to literature method reported earlier.

Synthesis of 5-Acetyl-1-ethyl-8-hydroxyquinolinium Iodide (2): A mixture of 10 g (0.054 mol) of 5-acetyl-8-quinolinol[6] (**1**) and 15 ml of ethyl iodide was heated in a sealed tube at 105 °C for 7 h. The product was filtered off, air dried and recrystallized from ethanol to give 19.4 g (82%) of the product

2 in the form of yellowish brown crystals, mp 285—287 °C. Found: N, 4.15%. Calcd for $C_{13}H_{14}NO_2I$: N, 4.08%.

Synthesis of Ethyl 2-Ethoxycarbonyl-3-(8-hydroxy-5-quinolinyl)-2-butenoate (4), Its Ethiodide (5), and Ethyl 2-Ethoxycarbonyl-3-(8-hydroxy-7-quinolinyl)-2-propenoate (6): Diethylmalonate (1.6 g, 0.01 mol) was added to ethanolic sodium ethoxide solution (0.1 g Na in 30 ml absolute ethanol) and the mixture was stirred at room temperature for 1 h. To the resulting sodiomalonate was added an equivalent amount of ethanolic solution from 5-acetyl-8-quinolinol[6] (**1**, 1.9 g in 30 ml), or its ethiodide (**2**, 3.4 g in 50 ml), or 8-hydroxy-7-quinolinecarbaldehyde (**3**, 1.7 g in 30 ml) in one portion. The reaction mixture was heated under reflux for 7 h, cooled and neutralized with acetic acid. The precipitated solid was filtered by suction and air dried. Physical and analytical data are given in Table 1.

Synthesis of 1-[8-Hydroxy-5(or 7)-quinolinyl]alkylidene-Substituted Azolidinediones and Barbituric Acid Derivatives (7—16), and Their Ethiodides (17—21). A mixture of **4**, **5**, or **6** (0.01 mol), hydrazine hydrate, phenylhydrazine, urea, or thiourea (0.01 mol) in ethanolic sodium ethoxide solution (0.1 g Na in 30 ml absolute ethanol) was heated under reflux for 7 h. The reaction mixture was filtered while hot and the filtrate was cooled and neutralized with acetic acid. The precipitated solid was filtered with suction and air dried. Physical and analytical data are given in Table 1.

Biological Activity of Selected New Synthesized Compounds as Antimicrobial and Plant Growth Regulator. The Antimicrobial Activity: The selected new synthesized compounds were dissolved in ethylene glycol (10 mg/100 ml, 100 ppm) and transfered to filter paper disc (15 mm), diffusion plate method.[8] The antifungal activity was determined against *Penicillium notatum, Aspergillus flavus,* and *Stachybotrys atra.* The antibacterial effect of the same compounds was determined against *Bacillus subtilis, Micrococcus luteus,* and *Serratia Sp.*

Bacterial suspension was prepared by adding 10 ml of sterile distilled water to 10 d old culture of the test bacteria grown on a nutrient agar of NA.[9] The culture consisted of beef extract (10 g L^{-1}), peptone (10 g L^{-1}), NaCl (5 g L^{-1}), and agar (10 g L^{-3}) at pH 7.4. One milliliter aliquots of the bacterial suspension were added to NA Petri dishes (one plate/test compound). The excess liquid has removed and filter paper disc (15 mm diameter) containing the test compound was placed on the plate. Plates were then incubated at 37 °C, and the diameter of the inhibition zones were measured after 24 h. These experiments were repeated thrice. The results are given in Table 2.

Spore suspension was prepared by adding 10 ml of sterile distilled water to 10-d-old culture of the test fungus grown on potato-D-glucose-agar (PDA) potatose (peeled and sliced, 200 g dm^{-3}), D-glucose (20 g dm^{-3}), and agar (17 g dm^{-3}) at pH 6.5.[10] One ml aliquots of the spore suspension were added to PDA Petri dishes (plate/test compound). The excess liquid was removed and filtered paper disc containing the tested compound was placed on the plate, then the plate is incubated at 37 °C and the inhibition zones were measured after 3 d. The experiments were carried out in triplicate. The results are given in Table 2.

Biological Effects on the Germination of *Vicia faba* (Variety Giza 2) Seeds: Materials and Methods: Seeds of *Vicia faba* (variety Giza 2) were treated with five concentrations 50, 100, 250, 500, and 1000 ppm of the selected compounds. Fresh solution of the required concentration were prepared using distilled water. A total of 100 seeds were used for each of the five treatments and the control. Seeds were immersed in the solution at room temperature of 25±2 °C for 4 h. Control seeds were treated with distilled water. After treatment, the seeds were washed thoroughly with distilled water to eliminate the solution traces. The seeds of each concentration was germinated on wet germinating papers in the Petri dishes for estimating the germination percentage, seedling height and for cytological studies. After 14 d, germinating and nongerminating seeds were counted and the percentage of germination was determined for each treatment and the number of seeds with more than one shoot were counted for each concentration. The results are shown in Fig. 1.

Cytological Examination: Secondary rootlets of 5—10 mm in length were excised and fixed in a 3:1 ethanol-glacial acetic acid mixture for 12 h and stored in 70% ethanol in a refrigerator. Fixed rootlets were prepared for cytological examination by the acetocarmine Smear technique.[11] For each treatment, preparations from 4 seedling were examined. The chromosomal aberrations were determined in the anaphase stage as bridges and fragments. The experiment was repeated twice and the results are shown in Fig. 2.

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