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SYNTHESIS AND BIOLOGICAL ACTIVITY OF CERTAIN 1,3-AND 1,5-DIMETHYL-N-SUBSTITUTED PYRAZOLE CARBOXAMIDES

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ABSTRACT

Positional isomers of dimethyl pyrazole carboxylic acid derivatives were prepared. Some of these compounds showed variable binding capacities towards Cu (II). Zn (II) and Mg (II). The most active chelators Ig and its isomer IIg showed antidotal and antiinflammatory activities higher than D-penicillamine. Both are more active in dose levels much lesser than their median lethal doses (LD50). 5(3)-Methylpyrazole-3(5)-carboxamide showed significant growth inhibition of R.solani. The other derivatives tested displayed growth stimulating activity rather than growth inhibition of the fungus.

INTRODUCTION

Different pyrazole derivatives were rported as enzyme inhibitors[1], anticancer[2], antibacterial[3], antifungal[4], analgesic, antiinflammatory[5a-7] and hypoglycemic agents[8-11].

Chelating ability of pyrazoles with a number of divalent metals have been described[5b,12]. Further coordinative power of pyrazole nucleus can be supplemented by other coordinating groups attached either to 1 or 3 (5) positions[12]. However, a clear relation between the biological activity and the chelating properties can be hardly traced in literature of pyrazoles[13].

In this paper, we report the preparation of some 1-methylpyrazole derivatives with potential chelating functions placed in α-positions to the pyridinic nitrogen I and the pyrrolic one II. N-carbamoyl substituents in I and II were chosen to enhance chelating properties inherent in pyrazole ring.

Metal binding ability, which can be followed by UV spectrophotometry was determined for a wide range of compounds : metal ratios[14]. We also report by a similar method the binding ability of the prepared derivatives of I and II. In addition, antidotal, antiinflammatory and antifungal properties were discussed in relation to the metal binding potentials of I and II.

EXPERIMENTAL

All melting points are uncorrected and were obtained with an electrothermal capillary melting point apparatus. ^{1}H-nmr spectra were obtained in Me_2SO-d_6 using EM-390, 90MHz instrument with TMS as internal standard. IR spectra were recorded on Perkin-Elmer 720 Spectrophotometer in KBr discs. UV apectral measurements were performed with Unicam SP-1750 Spectrophotometer adapted with a Unicam SP-1805 controller and AR 55 linear recorder. Mass spectra were carried out using mass spectrometer Varian MAT SM-1.

Purity of the prepared compounds was checked by TLC silica plates.

5 (3)-Methylpyrazole-3 (5)-Carboxamide III :

Was prepared from ethyl-5 (3)-methylpyrazole-3 (5)-Carboxylate[15] according to the reported procedure[16]. Yield 56%, m.p 157-159°C as reported, IR and ^{1}Hnmr spectral data is given in Table 3.

1,5-Dimethyl-1H-pyrazole-3-carboxylic acid derivatives 1 (Table 1), and 1,3-dimethyl-1H-pyrazole-5-carboxylic acid derivatives II (Table 2).

A general procedure is given for the preparation of the pyrazoles I and II :

A solution of the acid chloride A or B[4] (0.01 mol) in 10 ml dry benzene was added to the amine (0.022 mol) and stirred at room temperature for 30 min. (I a,b; II a,b,i) or Ih (Ic,d,e,f,j; IIc,d,e,f). For the preparation of Ig, i and IIg, the amine (0.015 mol) in pyridine 20 ml was refluxed with the acid chloride for Ih.

The hydrazides Ih and IIh were prepared by stirring under reflux for 2h a mixture of the ester A[17] or B[18] (0.01 mol and hydrazine hydrate (0.75 ml, 0.015 mol) in ethanol 10 ml. IR and ^{1}Hnmr spectral data is given in Table 3.

Synthesis of Copper Chelate IV :

A solution of Ig (0.43 g, 0.002 mol) in methanol was added to copper acetate (0.4 g, 0.002 mol) solution in methanol, stirred for five minutes then the methanol was distilled under vacuum. The olive green residue was filtered, washed with methanol (10 ml) and dried, m.p.230°, yield quantitative.

Anal. $C_7H_9N_5OS$. Cu (II) calcd; C : 30.48%, H : 3.65%, N : 25.39%, found; C : 30.7%; H : 3.40%, N : 24.80%. IR spectral data is given in Table 3.

Screening of the Metal Binding Properties of I(a-j), II (a-i),and III :

a-Solutions of the Compounds :

Accurately weighed amounts of the compounds were dissolved in methanol, then the volume adjusted to 10 ml in a volumetric flask to provide a final dilution of 1 x 10^{-3}M solution.

b-Metal Salt Solutions :

Accurately weighed amounts of copper acetate monohydrate (0.020 g, 0.001 mol), anhydrous magnesium sulfate (0.012 g, 0.001 mol), and zinc acetate (0.018 g, 0.001 mol) were dissolved separately in methanol (50 ml) by gentle heating. Each solution was transferred to a volumetric flask (100 ml) and completed with methanol to provide 1 X 10^{-3}M final dilution.

c-Solutions for Spectral Measurements :

Into volumetric flasks each 5 ml capacity aliquots of the solutions of metal salts and the solutions of the compounds were mixed in ratios indicated in (Table 4) and the volumes were adjusted by methanol.

d-Spectral Scanning :

Solutions of the compounds and those for spectral measurements were scanned in the range of 200-800 nm using methanol and metal salt solutions as blanks respectively.

Evaluation of Antidotal Activity[19] :

Groups of adult albino rats (180-300 g) each consisting of 6 animals at least were used. Animals were anesthetized with urethane (1.6 g/kg i.p.) and their jugular veins were exposed and cannulated for i.v.infusion. In the control groups of animals the threshold lethal dose of $CuSO_4$ (1% solution in normal saline) was determined fifteen minutes following the i.p. injection of 1 ml of 20% ethanol (the solvent used to dissolve the compounds Ig, IIg under investigation). Copper sulfate was infused at a rate of 0.5 ml/ min. until the animals developed cardiac standstill as monitored by electrocardiographic recordings using "Cardiosuny ECG". The mean threshold dose of $CuSO_4$ was determined and calculated in terms of mg/kg. In the other groups of animals each of the test compounds and D-penicillamine were intraperitoneally injected in two dose levels (20 & 30 mg/kg). Fifteen minutes later, the threshold lethal dose of $CuSO_4$ was determined as in control group. The results are given in Table 5.

Evaluation of Antiinflammatory Activity :

Antiinflammatory activity was determined by the trypan blue method[20] in groups of adult albino rats (150-250 g) each of 6 animals. This method depends on the quantitative determination of the effects of the drugs under investigation on the rate of capillary permeability disturbance caused by the intradermal injection of a phlogogenic substance such as histamine.

Each of the test compounds Ig and IIg as well as D-penicillamine were intraperitoneaily injected into the femoral vein in a dose of 20 mg/kg. Fifteen minutes after administration, histamine phosphate (0.02 ml of 1% solution) was injected intradermally. Trypan blue solution was then injected into a femoral vein in

a dose of (2 ml/kg). The time taken for the appearance of the blue colour around the site of histamine injection was determined. Animals of the control group were treated in the same manner after the injection of 1 ml of 20% ethanol. The results are illustrated in Table 6.

Determination of LD_{50}:

Six groups of albino mice (25-30 g), each of 10 animals were injected intraperitoneally, with graduated dose levels of the test compound. Mortality of animals in each group was determined during 24 hours period.

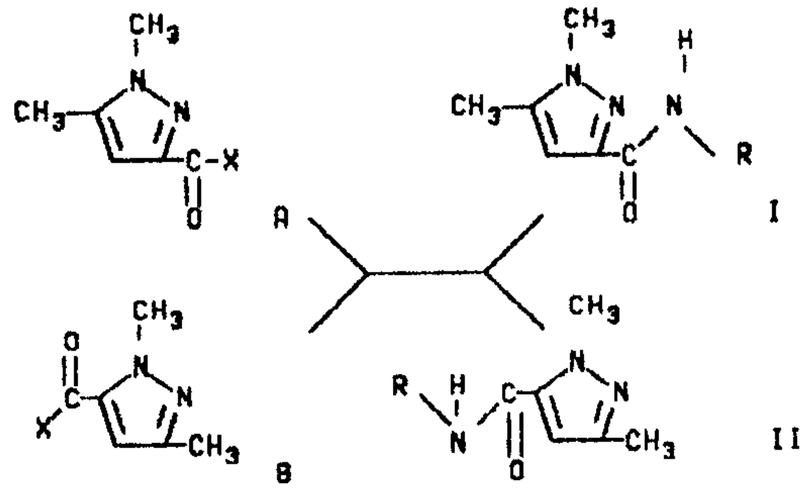
Computation of LD_{50} and its confidence limits were processed according to the method of Litchfield and Wilcoxon[21].

Evaluation of Antifungal Activity :

The compounds tested were incorporated in the potato dextrose agar (PDA) medium at concentration of 100 ppm (w/v) before mounting in petri dishes. Four replicates were used for each treatment and untreated medium were inoculated with equal discs of Rhizoctonia solani (Kukn.) obtained from 4 days old culture. Inoculated plates were incubated at 25°C for 4 days before measuring the radial growth of the fungus (in cm). Results are illustrated in Table 7.

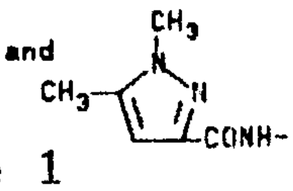
RESULTS AND DISCUSSION

Synthesis of the target compounds I and II was attempted by the route outlined by Scheme 1 starting from the acid chlorides[4] or the ethyl esters[17,18] of the appropriate pyrazole carboxylic acids : Reaction of ethylacetopyruvate with methylhydrazine sulfate yielded the acid A (X=H) in 70% yield, which can be transformed to the acid chloride and the ester (X=Cl, OEt) in routine fashion by the methods previously described.



X = Cl, OEt

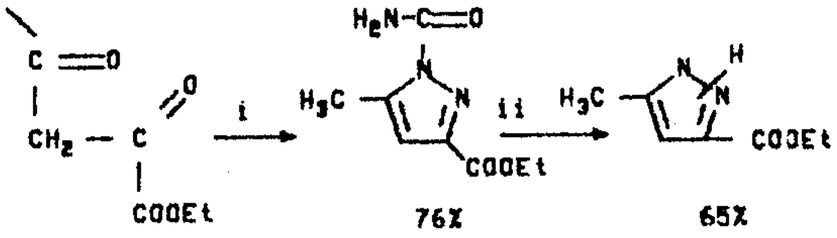
R = H, CH_3, C_2H_5, C_6H_{11}, C_6H_5, $CH_2C_6H_5$, $NHCSNH_2$

NH_2, OH, $NHCONH_2$ and 

Scheme 1

On the other hand, reaction of ethylacetopyruvate with hydrazine hydrate yielded N-nor ester, ethyl-5 (3)-methylpyrazole-3 (5)-carboxylate, in 82% yield. The N-nor ester on methylation by methyl-p-toluenesulfonate in presence of MeONa gave the ester B(X=OEt)[14] in 78% yield. Hydrolysis of the ester and treatment of the free acid with thionyl chloride yielded the acid chloride B(X=Cl).

An alternative approach to N-nor ester was attempted[22] as shown in Scheme 2



Scheme 2

However, this route was not adopted due to the relatively low yield of the N-nor ester compared to the single step reaction with hydrazine hydrate.

The unsubstituted amides[23] Ia, IIa, anilides[4,24] IIE, Ie and hydrazides[6] Ih, IIh are already known, however metal binding ability, antidotal, and antiinflammatory activities have not been reported, for most of them. Resynthesis of these drivatives was undertaken for compilation of the target study. Compound Ia has been reported with markedly lower melting point than that determined in our work. For the oily compounds IIb and IIc, the methods of synthesis and the spectral characterizations served as positive identification of structure. In all instances the ^{1}H-nmr spectra accorded completely with structure (Table 3).

In some cases the desired reaction could not be conveniently effected. For instance the preparation of hydroxamic acid derivative R=OH from B(X=Cl, OEt), could not be fulfilled under any of the handled procedures. Secondly, reaction of A (X=Cl, OEt) with semicarbazide yielded biurea in yields 13-19% together with the acid (A=H). Isolated biurea was identified by elemental microanalysis and m.p. 258°C as reported[25]. Electron impact at 70 eV revealed molecular ion peak M^+118 (4%) and base peak at m/e 75 corresponding to that of semicarbazide (M^+-HNCO).

Metal binding ability of the prepared compounds I-III were tested against Cu (II), Zn and Mg (II). Ratios of compound : metal salts (4:1; 2:1; 1:1; 1:2 and 1:4) were examined to reveal any binding potentials. This was monitored by the appearance of a new maxima at longer wavelength and/or the shift of the absorption maxima of parent compounds[14,26]. The pattern for Cu (II), Zu (II) and Mg (II) bound to pyrazole derivatives was displayed by (Table 4). Compounds omitted from Table 4 are devoid of metal binding capacities at any of the practiced dilutions.

It can be observed that metal binding ability was also affected by type of metal ion. Copper (II) was bound by all compounds in (Table 4) and Mg (II) was bound by Ig and Ij only while Zn (II) occupied an intermediate position between Cu (II) and Mg (II). Isolation of Cu (II) chelate IV was attempted by mixing equimolar ratios of methanolic solutions of Ig and Cu $(OAC)_2$. The isolated compound afforded microanalysis complying with that calculated for the structure of 1:1 metal-compound ratio. Disappearance of C=O band and other bands attributable to vibrations involving interaction between C=S and NH stretchings from the ir spectra of IV (Table 3) proves the involvement of these functions in chelate formation.

Antidotal and Antiinflammatory Activities[23,27] :

Compound Ig, the most potential chelator in the series was screened for antidotal and antiinflammatory activity (Table 5 displays the mean increase in the mean threshold lethal dose of copper sulfate after administration of Ig matched to its isomer IIg. Both compounds showed more potent antidotal activity at 95% confidence level than that displayed by D-penicillamine. D-penicillamine was believed to be a good candidate as reference drug for its dual activity as antidote for copper poisoning and as antiinflammatory

agent. It was noticed that 20 mg/kg dose led to a more pronounced antidotal activity than that observed at higher dose level.

Using the trypan blue method[20], compound Ig and IIg were tested for their antiinflammatory activities in rats. The intraperitoneal administration of each of the test compounds led to marked increase of the time taken by the blue coloured dye to appear. Compound Ig showed more delayed appearance of the colour than IIg which is significantly more active than D-penicillamine (Table 6). The LD_{50} of Ig and IIg were determined according to Litchfield and Wilcoxon method[21]. It was shown that LD_{50} and its 95% confidence levels were 120 (94.5-142.4) mg/kg (i.p.) for Ig and 135 (123.3-147.8) mg/kg (i.p.) for IIg.

The results of pharmacological screening shows that the enhanced antidotal and antiinflammatory activities of Ig and IIg goes parallel with their toxicities.

Antifungal Activity :

The antifungal properties of mono, di and trimethylpyrazole carboxanilides have been investigated by Huppatz et al[4] and it was found that the 1-methyl group is associated with maximum activity. 1,3,5-trimethylpyrazole carboxanilide showed the most potent fungicidal activity in this series against Rhizoctonia solani. It was shown also by the same authors that the activity *in-vitro* and soil is assigned to the dimethylcarboxanilides I_e and II_e. Positions of substituents proved to be important for enhanced activity. Compound II_e revealed more than 30 times the antifungal activity of its isomer I_e.

In our work certain substituents of the isomers I and II were chosen as models screened to clarify two objectives : a) role of metal binding ability of derivatives; b) effect of phenyl group in carboxanilide series of Huppatz et al[4]. We also proved two candidates compound III and the copper complex IV.

Regarding the first objective, it can be observed from Table 7 that there is no relation between radial growth inhibition and metal binding ability of the tested compounds. Compound III exhibited significant inhibition of radial growth while compound II_i showed nonsignificant effect although both have potential metal binding capacities to Cu II and Zn (II). It can be also added that II_e and I_e with reported inhibitory activity, have not shown any metal binding capacities in our work. Other compounds like Ig, h, i and j; IIg exerted growth stimulation and not inhibition.

The role of phenyl group in I_e and II_e was tackled by dual approaches : abolishing the aromaticity by substitution of cyclodexyl group in place of phenyl represented by I_d and II_d, and ubrupting the n-π conjugation in CONHph via insertion of methylene group as in I_f and II_f. Both approaches yielded potent growth stimulants.

It can be observed from our study and that of Huppatz et al[4] that a carboxamide group at C-3 or C-5 is necessary but not sufficient to conserve antifungal activity. However, a phenyl group conjugated with CONH, together with 1-methyl substitution are essential to

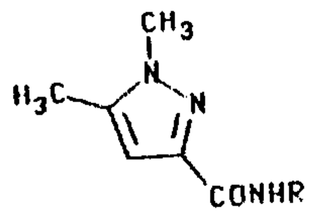
boost growth inhibition as shown by matching III, I_e and II_e.

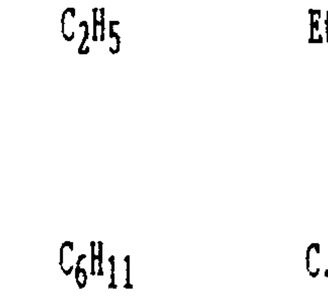
On the other hand, the mild to strong growth stimulation effect showed by most of the compounds screened may be of value in future approaches of molecular design in this series. On the contrary to the reported Cu (II) chelate of pyridine derivatives, compound IV showed insignificant inhibition effect on the growth of R. solani[24]. From other point of view compound IV abolished the growth stimulant action of the noncomplexed I_g.

Acknowledgements :

The authors would like to acknowledge the assistance offered by Department of plant pathology, Assiut University for screening the antifungal activities of the synthesized compounds.

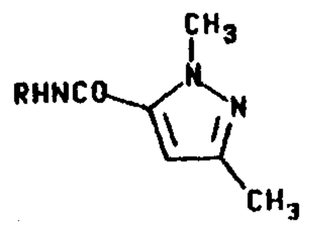
Table 1: 1,5-Dimethyl-1H-pyrazole-3-carboxylic acid derivaties II.



Comp No.	R	Amine used	M.P. (°C) Crystallization solvent	Yield[1] (%)	Molecular formula	Microanalysis (%) Calculated/Found C	H	N	S
Ia[2]	H	Ammonium hydroxide 25%	192-194 water	43	$C_6H_9N_3O$	51.79 51.50	6.52 6.60	30.20 30.60	
Ib	CH_3	Methylamine 25%	82 (Pet. ether 60-80/ ethanol)	43	$C_7H_{11}N_3O$ H_2O	49.11 48.62	7.65 7.16	24.54 24.21	
Ic	C_2H_5	Ethylamine	115-117 (Pet. ether 60-80/ ethanol)	48	$C_8H_{13}N_3O$	57.46 58.10	7.84 7.10	25.13 25.00	
Id	C_6H_{11}	C.Hexylamine	108 (Aqueous ethanol)	40	$C_{12}H_{19}N_3O$	65.13 65.68	8.65 9.04	18.99 19.00	
If	$-CH_2-C_6H_5$	Benzylamine	130 (Aqueous ethanol)	65	$C_{13}H_{15}N_3O$	68.10 67.60	6.59 6.80	18.33 17.70	
Ig	$NHCSNH_2$	Thiosemicarbazide	227-228 (Acetonitril/ethanol) or water	40	$C_7H_{11}N_5OS$	39.42 40.33	5.20 5.37	32.84 33.52	15.03 15.20
Ii	OH	Hydroxylamine	210 (Ethanol)	36	$C_6H_9N_3O_2$	46.45 47.00	5.85 6.30	27.08 26.30	
Ij			242 (Ethanol)	36	$C_{12}H_{16}N_6O_2$	52.16 52.30	5.84 5.78	30.42 30.60	

1- The crude product; 2- Reported m.p. 178°C (23).

Table 2: 1,3-Dimethyl-1H-pyrazole-5-carboxylic acid derivatives II.



Comp No.	R	Amine used	M.P. (°C) Crystallization solvent	Yield[1] (%)	Molecular formula	Microanalysis (%) Calculated/Found C	H	N
IIb	C_6H_{11}	C.hexylamine	139 (Aqueous ethanol)	49	$C_{12}H_{19}N_3O$	65.13 65.10	8.65 7.90	18.90 18.60
IIc	$-CH_2-C_6H_5$	Benzylamine	108-110 (Aqueous ethanol)	39	$C_{13}H_{15}N_3O$	68.10 67.90	6.59 6.80	18.33 18.50
IIe	$NHCSNH_2$	Thiosemicarbazide	229-230	38	$C_7H_{11}N_5OS$	39.42 39.20	5.20 5.00	32.80 33.00
IIh	$NHCONH_2$	Semicarbazide	233-235 (Aqueous ethanol)	25	$C_7H_{11}N_5O_2$ ¼H2O	41.67 41.90	5.62 5.50	34.86 35.00

1- The crude product.

Table 3: Spectral data of the prepared pyrazole derivatives I-IV.

Compd. No.	IR ν (cm^{-1}) C=N, C=O, NH/OH	^{1}H-NMR δ (ppm) $C-CH_3$	$N-CH_3$	C_4-H	CONHR
Ia	1620, 1680, 3350-3300	2.27	3.73	6.33	7.10
Ib	1570, 1650, 3500-3360	2.16	3.96	6.53	7.50
Ic	1558, 1650, 3360	2.23	3.70	6.30	7.83
Id	1525, 1660, 3410	2.27	3.75	6.30	7.40
Ie	1595, 1655, 3290	2.27	3.77	6.47	9.77
If	1550, 1650, 3370	2.27	3.77	6.47	8.53
Ig	1610, 1695, 3420,3320 3260,3200 NHCS(1510,1230,1075, 880)	2.27	3.73	6.47	9.78
Ih	1620. 1670. 3490-3210	2.30	3.78	6.47	9.13
Ii	1560. 1645. 3220-3100	2.30	3.77	6.33	8.73
Ij	1640. 1699. 3480-3310	2.27	3.77	6.40	9.67
IIa	1620. 1685. 3400-3190	2.16	3.96	65.3	7.50
IIb	1565. 1650. 3400-3300	2.20	3.97	6.50	8.20
IIc	1560. 1650. 3400-3300	2.20	3.97	6.51	8.25
IId	1560. 1630. 3280	2.22	3.97	6.58	8.07
IIe	1595. 1650. 3290	2.20	3.97	6.75	10.03
IIf	1570. 1665. 3300-3290	2.13	3.93	6.57	8.78
IIg	1625. 1680. 3340-3300 3160-3130 NHCS (1540. 1250.1080 880)	2.10	3.87	6.57	10.13
IIh	1628. 1660. 3320-3280	2.10	3.90	6.43	9.57
IIi	1620. 1685. 1695.3370 3200	2.17	3.97	6.73	10.07
III	1600. 1670. 3360-3200	2.28	-	6.4	7.25
IV	1595. ----. 3430-3310 (1510)				

Table 4 : Ability of Cu (II), Zn (II) and Mg (II) ions to Bind Various Pyrazole Derivatives in Methanol.

Compd, No.	Ratio	Metal ions					
		Cu (II)		Zn (II)		Mg (II)	
λMax (nm)	(Compd:M)	Δλ max	New λ max	Δλ max	New λ max	Δλ max	New λ max
Ig	4:1	0	316	0	307	0	306
228.246	2:1	0	316	0	302	0	306
	1:1	0	316	0	306	0	306
	1:2	0	316	0	312	0	306
	1:4	0	316	0	312	0	306
		a					
Ih	4:1	8	-	0	-	0	-
224	2:1	8	-	0	-	0	-
234	1:1	8	-	0	-	0	-
	1:2	8	-	0	-	0	-
	1:4	8	-	0	-	12	-
		b a					
Ii	4:1	24;0	-	6;2	-	0	-
194;	2:1	22;2	-	6;2	-	0	-
232	1:1	20;8	-	4;2	-	0	-
	1:2	16;10	-	4;2	-	0	-
	1:4	16;10	-	22;2	-	0	-
Ij	4:1	4	317	4	310	4	-
236	2:1	4	317	4	310	4	-
	1:1	-6;8	327	-6;6	322	0	310
	1:2	-6;8	327	-6;6	327	0	310
	1:4	-6;8	327	-6;6	327	0	310
IIg	4:1	0	290	0	286	0	-
226	2:1	0	294	0	288	0	-
246	1:1	0	310	0	288	0	-
	1:2	0	310	0	296	0	-
	1:4	0	310	0	290	0	-
IIi	4:1	3	286	0	-	0	-
229	2:1	3	286	0	-	-	-
	1:1	15	286	0	290	0	-
	1:2	15	-	0	290	0	-
	1:4	15	-	0	290	0	-
III	4:1	2	320	2	-	0	-
226	2:1	8	320	2	-	0	-
	1:1	8	320	3	-	0	-
	1:2	4	320	0	-	0	-
	1:4	4	320	0	-	0	-

a) Shift of the longer wave length .
b) Shift of the shorter wave length.

Table 5 : Effect of Different dose Levels of Compounds Ig, IIg and D-penicillamine on the mean Threshold Lethal dose.

Compound	Dose mg/kg	Mean threshold lethal dose[1] mg/kg	% change
Control	-	148.10 ± 08.30	0
D-penicillamine	30	240.13 ± 15.00	71.40
	20	233.80 ± 12.70	62.14
Ig	30	315.40 ± 15.80*	112.961
	20	412.96 ± 12.04*	178.801
IIg	30	281.30 ± 22.30	89.94
	20	385.70 ± 13.80*	160.101

I Data represent mean ± S.E. of 6 observations.

* Significant difference from the D.penicillamine $p < 0.05$.

Table 6 : The Antiinflammatory Activity of Compounds Ig. IIg and D-penicillamine at dose Level 20 mg/kg.

Compound	Mean time (sec.)[1]	Change
Control 20% v/v ethanol	80.33 ± 5.00	0
D-penicillamine	130.00 ± 7.20	61.80
Ig	165.30 ±16.20*	105.80
IIg	153.00 ± 4.50	90.50

I Data represent mean ± S.E. of 6 observations.

* Significant difference from the D-Penicillamine at $p < 0.05$.

Table 7 : Effect of Some Pyrazole Derivatives on the Radial Growth of *Rhizoctonia Solani*.

Compound	R	Mean of radial growth (cm)[a]		% change
Control		4.33 (± 0.69)	(1)	0
III		3.43 (± 1.17)	(2)	- 20.80[b]
Ia	H	3.65 (± 0.6)	(1)	- 15.70
IV		3.65 (± 0.54)		- 15.70
IIj	$NHCONH_2$	3.78 (± 0.41)		- 12.70
IId	C_6H_{11}	5.50 (± 0.41)	(3)	+ 27.00[c]
Ii	OH	6.00 (± 0.63)		+ 38.60
IIf	$CH_2C_6H_5$	6.53 (± 0.56)	(4)	+ 50.80
Id	C_6H_{11}	7.58 (± 0.43)	(5)	+ 75.00
Ig	$NHCSNH_2$	7.80 (± 0.77)		+ 80.10
IIg	$NHCSNH_2$	8.03 (± 0.21)		+ 85.50
If	$CH_2C_6H_5$	8.08 (± 1.00)	(6)	+ 86.60
Ih	NH_2	8.35 (± 0.42)		+ 92.80
IIh	NH_2	8.55 (± 0.10)		+ 97.50
Ij	$C_5H_7N_2CONH$	8.88 (± 0.25)		+105.00

a) Means with the same figure are not significantly different according to L.S.D. test at 5% level.

b)(-) Decrease of the % of radial growth than that of control.

c)(+) Increase of the % of radial growth than that of control.

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التشييد والنشاط البيولوجى لبعض كربوكساميدات ار ٣ – و ار ٥ – ن – محتل البيرازول

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اظهرت بعض المتشابهات الوضعية لثنائى ميثيل البيرازول كاربوكساميد درجات مختلفة من فاعليتها لربط الايونات الثنائية لكل من النحاس والزنك والمغنسيوم . حيث وجد ان اكثر هذه المركبات نشاطا لعمل المرتبطات هو المركب Ig وشبيهه IIg حيث اظهر فاعلية كمضادات للسمية والالتهابات اكبر من D – بنسلامين وكلاهما كان مؤثرا عند جرعات بعيدة عن جرعة LD_{50} بينما اظهر المركب الوحيد ٥ (٣) ميثيل بيرازول – ٣(٥) – كاربوكساميد خاصية مضادة لنمو فطر R. solani . نجد ان باقى المركبات اظهرت تأثيرا عكسيا حيث نشط نمو الفطر بصورة واضحة .

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