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NEW PYRAZOLINES, ISOXAZOLINES AND SULPHIDES FROM 4;7-DIMETHOXY-5-ACETYL-6-HYDROXY-BENZOFURAN (KHELLINONE) AND THEIR ANTI-MICROBIAL ACTIVITIES

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Treatment of khellinone (I) with some aromatic aldehydes afforded the corresponding chalcones (II). The reaction of chalcones II with phenyl hydrazine in acetic acid led to the formation of phenylpyrazolines (III), the reaction of II with hydrazine hydrate in alcohol gave the pyrazoline derivatives (IV), whereas, the same reaction in acetic acid afforded the corresponding N-acetyl pyrazoline derivatives (V). Similarly the condensation of II with hydroxyl amine hydrochloride afforded isoxazolines (VI). The reaction of II with thiophenol in presence of piperidine led to the formation of the corresponding sulphides (VII). The antimicrobial properties of the new derivatives were studied.

Key words: Khellinone, Chalcones, Phenyl pyrazoline.

Introduction

It has been reported that the pyrazolines show a broad spectrum biological activity [1]. Some pyrazoline derivatives used as bacteriostatic, fungicidal, bacteriocidal, psychopharmacological and anticancer [2-6]. Also the biological activity of isoxazoline series proved to be antituberculosis antibiotic [7,8], prompted these authors to senthesize some new pyrazoline, isoxazoline and sulphide derivatives containing the well known biologically active khellinon [9].

Results and Discussion

Khellinone (I) condensed with some aromatic aldehydes namely, benzaldehyde, anisaldehyde, 2-chlorobenzaldehyde, 4-chloro- benzaldehyde, 4-N, N-dimethyl aminobenzaldehyde and thiophene aldehyde, in ethanolic potassium hydroxide yielded the corresponding cinnamoyl derivatives (IIa - f).

The action of hydrazines on II were studied. It was found that IIa-f react with one equivalent phenyl hydrazine in boiling acetic acid leading to the formation of the corresponding phenylpyrazolinyl derivatives (IIIa-f).

The reaction of II with hydrazine hydrate in ethyl alcohol gave pyrazolinyl derivatives (IVa-f), whereas compounds II reacting with hydrazine hydrate in boiling acetic acid afforded the N-acetylpyrazolinyl derivatives (Va-f).

The infrared spectra of the pyrazolinyl derivatives [10] are characterized by a band in the region of 1580-1640 cm^{-1} for (C=N-) and a well defined absorption bands at 1700 cm^{-1} and 3440 cm^{-1} due to (C=0) and (OH), respectively.

The ^1H NMR spectra of pyrazolinyl derivatives [10] showed signals at δ = 13.1, 4.2 and 1.8 ppm attributed to OH, OCH_3 and CH_2 protons respectively.

The reaction of compounds II with hydroxyl amine hydrochloride in ethyl alcohol-water, followed by few drops of 50% potassium hydroxide afforded the corresponding isoxazolinyl derivatives (VIa-f).

The infrared spectra of isoxazolinyl derivatives [10] are characterized by a band in the region of 3300 - 3500 cm^{-1} due to (OH) and a well defined absorption bands at 1635 cm^{-1} and at 2600 cm^{-1} due to (C=N-) and (-CH_2), respectively.

The ^1H NMR spectra of the isoxazolinyl derivatives [10] showed signals at δ= 4.5-4.7, 1.8 ppm attributed to (OH, OCH_3) and CH_2 protons respectively.

The reaction of compounds II with thiophenol in presence of pepridine as catalyst led to the formation of the β-keto-sulphides (VIIa-f).

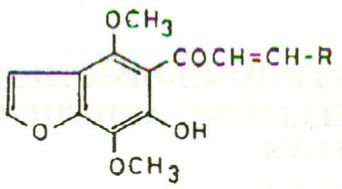
The infrared spectra of the β-keto-sulphides [11] are characterized by a band in the region of 1655 - 1690 cm^{-1} for due to (C=0), it does not have any OH absorption band indicating that the hydroxyl hydrogen in a tautomerism with the carbonyl at position 2.

Experimental

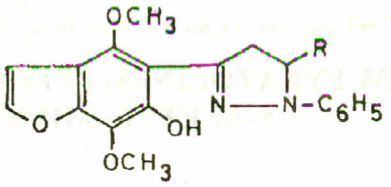
M.P's are uncorrected. The ^1H NMR spectra were run in $CDCl_3$ and TMS as reference on a 60 MHz Varian A60 spectrometer. IR spectra were recorded on Zeiss IMR 16 (W.G.). The prepared compounds were analysed for C, H and N, the microanalytical data are in full agreement with the suggested structures. Khellinone (I) and chalcones (II) were prepared according to (13, 14).

General procedure for preparation of phenyl pyrazolinyl derivatives (IIIa-f). Chalcone (0.01 mole) was dissolved in glacial acetic acid (10 ml) and refluxed with phenyl hydrazine (0.01 mole) for 5-10 hr. The reaction mixture was cooled and poured onto water. The deposited crystals were filtered off and crystallised from ethyl alcohol.

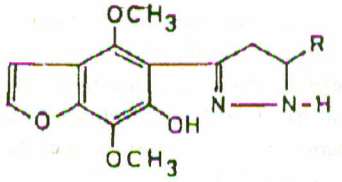
General procedure for preparation of pyrazolinyl derivatives (IVa-f). Chalcone (0.01 mole) was dissolved in ethyl alcohol (10 ml) and refluxed with hydrazine hydrate (0.01 mole) for 10 hr. The reaction mixture was diluted with water and the solid formed was filtered off and crystallised from ethyl alcohol.



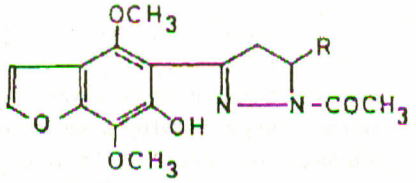
II



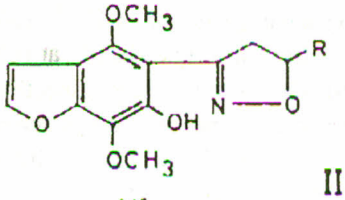
III



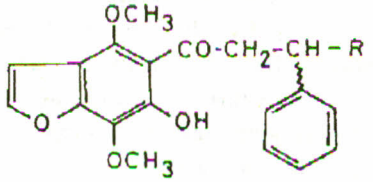
IV



V



VI



VII

II-VII a, R = C_6H_5

b, R = $C_6H_4OCH_3$-p

c, R = C_6H_4Cl-o

d, R = C_6H_4Cl-p

e, R = $C_6H_4N(CH_3)_2$-p

f, R = 

General procedure for preparation of N-acetyl pyrazolinyl derivatives (Va-f). Chalcone (0.01 mole) was dissolved in acetic acid (10 ml) and refluxed with hydrazine hydrate (0.01 mole) for 12 hr. The reaction mixture was poured onto water. The solid formed was filtered off and crystallised from ethanol.

General procedure for preparation of isoxazolinyl derivatives (VIa-f). Chalcone (0.01 mole) was dissolved in ethanol (10 ml), a mixture of hydroxylamine hydrochloride (0.015 mole) in ethanol (8 ml) and water (2 ml), followed by few drops of 50% potassium hydroxide was added. The reaction mixture was refluxed for 9 hr. The solid formed was filtered off and crystallised from ethanol.

General procedure for preparation of β-sulphides (VIIa-f). Chalcone (0.01 mole) was dissolved in benzene (10 ml), then thiophenol (0.015 mole), followed by few drops of piperidine was added. The reaction mixture was heated gently with stirring for 6 hr. The stirring was continued overnight. Glacial acetic acid was added dropwise until pH 5-6. The solvent was evaporated under reduced pressure. The deposited material was filtered off and crystallised from ethanol.

The physical data for the prepared compounds are listed in Table 1.

TABLE 1. PHYSICAL DATA FOR THE PREPARED COMPOUNDS.

Compound	M.P. °C	Yield %	Mol. Formula	Analysis Calcd/Found C%	H%	N%
IIc	163	83	$C_{19}H_{15}O_5Cl$	63.59	4.18	
				63.21	4.63	
IId	149	90	$C_{19}H_{15}O_5Cl$	63.59	4.18	
				63.50	4.62	
IIe	125	90	$C_{21}H_{21}NO_5$	68.66	5.72	3.81
				68.11	5.50	3.68
IIf	120	86	$C_{17}H_{14}O_5S$	61.82	4.24	
				61.62	4.41	
IIIa	190	82	$C_{25}H_{22}N_2O_4$	72.46	5.31	6.76
				72.31	5.57	6.51
IIIb	172	75	$C_{26}H_{24}N_2O_5$	70.27	5.41	6.31
				70.59	5.62	6.70

(Table 1, continue...)

(Table 1, continue...)

IIIc	183	76	$C_{25}H_{21}N_2O_4Cl$	66.89	4.68	6.26
				67.02	5.02	6.22
IIId	229	70	$C_{25}H_{21}N_2O_4Cl$	66.89	4.68	6.26
				66.51	5.07	6.19
IIIe	119	60	$C_{27}H_{27}N_3O_4$	70.90	5.91	9.19
				70.63	5.47	9.52
IIIf	156	92	$C_{23}H_{20}N_2O_4S$	65.71	4.76	6.67
				65.24	5.06	6.16
IVa	126	84	$C_{19}H_{18}N_2O_4$	67.46	5.33	8.28
				67.62	5.39	8.83
IVb	132	80	$C_{20}H_{20}N_2O_4$	68.18	5.68	7.59
				68.37	5.66	7.97
IVc	160	90	$C_{19}H_{17}N_2O_4Cl$	61.21	4.56	7.52
				61.72	4.05	6.96
IVd	209	84	$C_{19}H_{17}N_2O_4Cl$	61.21	4.56	7.52
				61.53	4.08	7.25
IVe	176	82	$C_{21}H_{23}N_3O_4$	66.14	6.04	11.02
				66.71	5.97	11.53
IVf	125	87	$C_{17}H_{16}N_2O_4S$	59.30	4.65	8.14
				59.27	4.98	8.57
Va	164	82	$C_{21}H_{20}N_2O_5$	66.38	5.26	7.37
				66.44	5.60	8.05
Vb	123	85	$C_{22}H_{22}N_2O_6$	64.39	5.37	6.83
				64.38	5.23	6.38
Vc	179	85	$C_{21}H_{19}N_2O_5Cl$	60.79	4.58	6.75
				60.69	5.08	6.68
Vd	168	85	$C_{21}H_{19}N_2O_5Cl$	60.79	4.58	6.75
				60.80	4.52	6.27
Ve	171	68	$C_{23}H_{25}N_3O_5$	65.25	5.91	9.93
				65.69	6.24	9.53
Vf	150	88	$C_{19}H_{18}N_2O_5S$	59.07	4.66	7.25
				59.46	4.96	7.89
VIa	131	62	$C_{19}H_{17}NO_5$	67.26	4.05	4.51
				67.32	4.07	4.72
VIb	102	75	$C_{20}H_{19}NO_6$	65.04	5.15	3.79
				65.34	5.28	3.70
VIc	147	64	$C_{19}H_{16}NO_5Cl$	61.04	4.28	3.75
				61.54	4.38	3.95
VId	137	87	$C_{19}H_{16}NO_5Cl$	61.04	4.28	3.75
				61.31	4.58	3.71
VIe	150	67	$C_{21}H_{22}N_2O_3$	65.97	5.76	7.33
				65.87	5.95	7.64
VIf	129	62	$C_{17}H_{15}NO_5S$	59.13	4.35	4.06
				59.42	3.85	4.08
VIIa	126	63	$C_{25}H_{22}O_5S$	69.12	5.07	
				69.51	5.39	
VIIb	110	80	$C_{26}H_{24}O_6S$	67.24	5.17	
				67.64	5.45	
VIIc	163	88	$C_{25}H_{21}O_5ClS$	64.03	4.48	
				64.32	4.30	
VIId	208	60	$C_{25}H_{21}O_5ClS$	64.03	4.48	
				64.62	4.56	
VIIe	139	70	$C_{27}H_{27}O_5NS$	67.92	5.66	2.94
				68.07	5.13	2.60
VIIf	115	64	$C_{23}H_{20}O_5S_2$	72.73	4.55	
				72.49	4.60	

Biological activity test. The activity of the compounds were tested by the disk diffusion method [12]. Whattman No;1 filter paper disks were sterilized by autoclaving for 1 hr at 140°. The sterile disks were impregnated with the different new compounds (100 µg/disk). Agar plates were surface inoculated uniformly from fresh broth culture of *Bacillus subtilis, Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli, Proteus mirabilis, Citrobacter freundii, Klebsella pneumonia and Saccharomyces.* The impregnated disks were placed on the medium suitably spaced apart and the plates were incubated 24 hours at 28°.

The sensitivity of micro-organisms to the compounds is identified in the following manners:

+++ = Highly sensitive (inhibition zone 12-12 mm).,
++ = Fairly sensitive (inhibition zone 9-12 mm),
+ = Slightly sensitive (inhibition zone 6-9 mm).

The code number of the micro-organisms tested:

1. *Bacillus subtilis*
2. *Pseudomonas aeruginosa*
3. *Staphylococcus aureus*
4. *Escherichia coli*
5. *Proteus mirabilis*
6. *Citrobacter freundii*
7. *Klebsellapneumonia*
8. *Saccharomyces*

The results of the biological activity are shown in Table 2.

TABLE 2. THE PREPARED COMPOUNDS AGAINST MICRO-ORGANISMS

Compound	Micro-organisms							
No.	1	2	3	4	5	6	7	8
IIa	-	-	-	-	-	-	-	-
IIb	-	-	-	-	-	-	-	-
IIc	-	-	-	-	-	-	-	-
IId	-	-	-	+	-	-	+	-
IIe	-	-	-	+	+	-	-	+
IIf	-	-	-	-	-	-	-	-
IIIa	-	-	-	+++	-	-	-	++
IIIb	-	+++	-	-	-	-	-	-
III	+++	-	-	-	-	-	-	-
IIId	-	-	-	-	-	-	-	-
IIIe	-	-	-	-	-	-	++	-
IIIf	-	-	-	-	-	-	-	-
IVa	-	-	-	-	-	-	-	-
IVb	-	-	+	++	-	-	-	-
IVc	-	++	-	-	-	-	-	-
IVd	+	-	-	-	-	-	-	-
IVe	+	+	+	-	-	-	-	-
IVf	-	-	-	-	-	-	-	-
Va	-	-	-	-	-	-	-	-
Vb	-	-	-	-	-	-	-	-
Vc	-	-	-	-	-	-	-	-
Vd	-	-	-	-	+	-	-	-
Ve	+	+	+	-	-	-	-	-
Vf	-	-	-	-	-	-	-	-

(Table 2, continue...)

(Table 1, continue...)

VIa	+	-	-	+	-	-	-	-
VIb	-	+	-	-	-	+	-	-
VIc	-	-	-	-	+	-	+	-
VId	++	-	+	-	-	-	-	-
VIe	-	-	+	-	-	+	-	-
VIf	-	-	-	-	-	-	-	-
VIIa	-	++	-	-	-	-	-	-
VIIb	-	+	+	-	+	-	-	-
VIIc	-	++	+	-	++	-	-	+
VIId	-	++	++	-	++	-	-	-
VIIe	-	-	-	-	-	-	-	-
VIIf	-	+	+	-	+	-	-	-

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