

Synthesis and Biological Evaluation of Some Tri- and Tetra-Substituted Pyrazoles and Isoxazoles

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A series of tri and tetra-substituted pyrazoles and isoxazoles were synthesized by the reaction between 3-acetylflavone (**IIa-f**) and hydrazine hydrate, phenylhydrazine and hydroxylamine hydrochloride respectively. The new compounds were screened for their antibacterial activity.

Key Words: Substituted pyrazoles, Isoxazoles, Biological evaluation.

There is a considerable interest in the chemotherapeutic activity of pyrazole and isoxazole derivatives. This includes analgesic¹, antibacterial² anti-inflammatory³ and hypoglycemic⁴ activities. Flavones have been extensively used to synthesize pyrazoles. Keeping these facts in view, some tri- and tetra-substituted pyrazoles and isoxazoles have been synthesized and screened against gram positive (*S. aureus*) and gram negative (*P. aeruginosa*) pathogens.

IR spectra (KBr) were recorded on Perkin-Elmer 577 spectrophotometer. PMR spectra were recorded on Perkin-Elmer R-32 and Varian XL-100, a high NMR spectrometer. m.p. were determined in open glass capillaries and are uncorrected. The purity of samples was checked by TLC on silica gel-G plates.

3-Acetylflavone (**IIa-f**) the starting material were prepared by oxidative cyclization of 1-(2-hydroxyphenyl)-2-arylidene-3-methyl-1,3-propanediones (**Ia-f**). IR (cm⁻¹): 1730 v(C=O), 1680 v(cyclic C=O), 1620 v(CH=CH); PMR in δ (ppm) 2.48 (s, 3H, ArCH₃), 3.81 (s, 3H, COCH₃), 7.4–7.6 (m, 5H, Ar—H), 7.8–7.9 (m, 3H, Ar—H) (**IIa**).

Synthesis of 5-(2-hydroxyphenyl)-4-acetyl-3-phenylpyrazoles (**IIIa-f**):

A mixture of 3-acetylflavones (**IIa-f**) (0.01 mol) and hydrazinehydrate (0.02 mol) in ethanol (20 mL) or acetic acid (20 mL) was separately refluxed for 1 h. After cooling the reaction mixture was diluted with water. The solid product thus separated was crystallized from 50% ethanol; yield 50–60%.

IR (cm⁻¹): 3160 v(—OH), 3030 v(NH), 1610 v(C=O), 1580 v(C=N), PMR in δ (ppm) 1.8 (s, 3H, ArCH₃), 2.15 (s, 3H, COCH₃), 6.2 (s, 1H, NH), 6.7–7.5 (m, 8H, Ar—H) (**IIIa**).

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Synthesis of 5-(2-hydroxyphenyl)-4-acetyl-1,3-diarylpyrazoles (IVa-f)

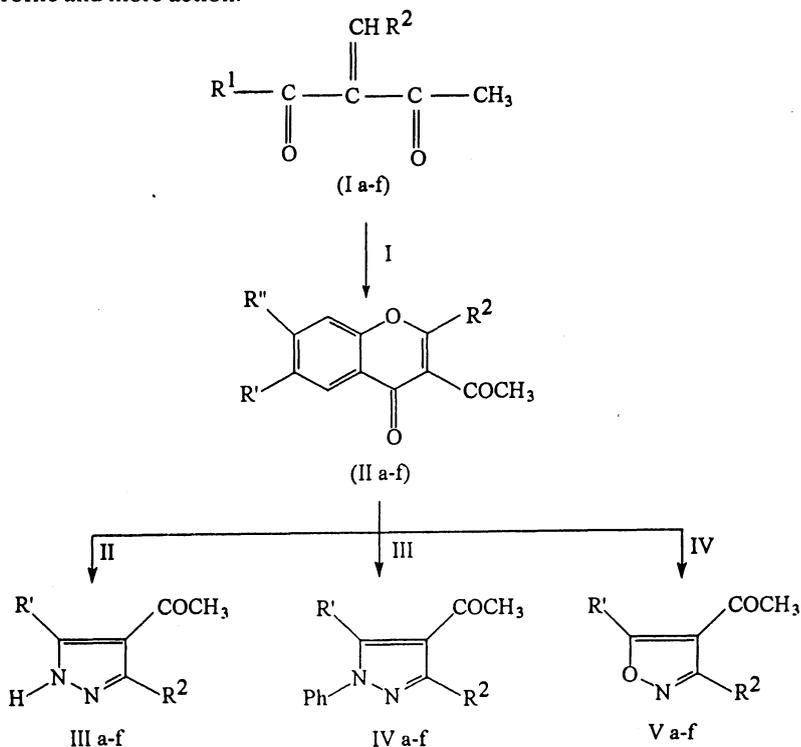
A mixture 3-acetylflavones (**IIa-f**) (0.01 mol) and phenylhydrazine (0.02 mol) in methanol (3.0 mL) or phenylhydrazine hydrochloride (0.02 mol) in pyridine (20 mL) was refluxed separately for 3 h. The reaction mixture was diluted to get compound (**IVa-f**), with 60–65% yield. IR (cm^{-1}): 3160 $\nu(\text{OH})$, 1610 $\nu(\text{C}=\text{O})$, 1585 $\nu(\text{C}=\text{N})$, PMR in δ (ppm) 2.15 (s, 3H, ArCH_3), 2.35 (s, 3H, COCH_3), 6.8–7.9 (m, 3H, Ar-H) (**IVa**).

Synthesis of 5-(2-hydroxyphenyl)-4-acetyl-3-arylisoxazoles (Va-f)

A suspension of 3-acetylflavones (**IIa-f**) (0.01 mol) and hydroxylamine hydrochloride (0.02 mol in 2 mL water) in methanol (20 mL) or pyridine (20 mL) was refluxed separately for 2 h. After cooling the reaction mixture was diluted with water. The crude product thus obtained was crystallized in ethanol to get compound (**Va-f**), with 60–70% yield. IR (cm^{-1}): 3100 $\nu(\text{OH})$, 1660 $\nu(\text{C}=\text{O})$, 1530 $\nu(\text{C}=\text{N})$, PMR in δ (ppm) 2.25 (s, 3H, ArCH_3), 2.26 (s, 3H, COCH_3), 6.45–7.42 (m, 8H, Ar-H) (**Va**).

Antibacterial activity

The activity assay was carried out by using disc diffusion method by measuring the zones of inhibition in mm. All the compounds were screened *in vitro* and their antibacterial activity against *P. aeruginosa* and *S. aureus* was determined (Table-1). Result shows that compounds **IV** and **V** exhibited significant antibacterial profile and more action.

**Scheme-1**

		Compd.	R ₁	R ₂
I.	I ₂ /DMSO	a	4-CH ₃ C ₆ H ₃ OH	Phenyl
II.	N ₂ H ₄ ·H ₂ O/EtOH	b	4-CH ₃ C ₆ H ₃ OH	C ₆ H ₅ OCH ₃
III.	NH ₂ OH·HCl/MeOH	c	-C ₆ H ₄ OH	Phenyl
IV.	PhNHNH ₂ /EtOH	d	-C ₆ H ₄ OH	C ₆ H ₅ OCH ₃
	PhNHNH ₂ ·HCl/C ₅ H ₅ N	e	-3-CH ₃ C ₆ H ₃ OH	Phenyl
		f	-3-CH ₃ C ₆ H ₃ OH	C ₆ H ₅ OCH ₃

TABLE-1
PHYSICAL DATA & ANTIBACTERIAL ACTIVITY OF SYNTHESIZED COMPOUNDS
(Zone of inhibition measured in mm)

S.No.	Compound	m.p. (°C)	<i>S. aureus</i>	<i>C. aeruginosa</i>
1.	IIIa	196	4	4
2.	IIIb	175	4	5
3.	IIIc	238	4	4
4.	III d	265	4	5
5.	III e	180	4	3
6.	III f	190	6	5
7.	IVa	140	10	11
8.	IVb	205	11	12
9.	IVc	190	10	11
10.	IVd	105	10	10
11.	IVe	185	11	12
12.	IVf	185	10	10
13.	Va	172	11	10
14.	Vb	110	12	11
15.	Vc	190	11	12
16.	Vd	137	12	13
17.	Ve	215	12	11
18.	Vf	225	11	12

REFERENCES

1. M.I. Younes, H.H. Abbas and S.A.M. Metwally, *Pharmazie*, **46**, 98 (1991).
2. D.A. Nuhlich, M. Capdepuy and G. Devalx, *Eur. J. Chem.*, **25**, 285 (1990).
3. H.V. Patel and P.S. Fernandes, *J. Indian Chem. Soc.*, **67**, 321 (1990).
4. R. Soliman, H.M. Faidallah and S.K. El-Sadany, *J. Pharm. Sci.*, **76**, 626 (1987).

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