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Antibacterial activity of 1-(4-methyl sulfonylphenyl)-3-(1-phenyl-3-aryl-*1H*-pyrazol-4-yl)-2- propen-1-ones and it's derivatives

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ABSTRACT

Various chalcone derivatives of 1-(4-methyl sulfonylphenyl)-3-(1,3-diphenyl-1H-pyrazol-4-yl)-2-propen-1-one were synthesized by condensation of 1,3-diphenyl-1H-pyrazole-4-carbaldehyde and 4-methyl sulfonylphenyl acetophenone. Chalcone derivatives were characterized by FT-IR, ^{1}H-NMR, Mass spectral analysis and elemental analysis. All the synthesized compounds have been screened for their antibacterial activities by using cup-plate method.

Keywords: Pyrazole aldehyde, p-Sulfonyl Acetophenone, Antibacterial Activity

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INTRODUCTION

The chemistry of chalcones have generated intensive scientific studies throughout the world, especially interesting are their biological and industrial application. Chalcones are coloured compounds because of the presence of the chromophore, auxochromes. They are known as benzalacetophenones or benzylidine acetophenones.

Here we synthesized different pyrazole aldehyde[**1,2]** by using different acetophenone[3] and phenyl hydrazine[4]. These synthesized pyrazole aldehyde further condensed with acetophenone derivative to give different type of chalcone derivatives[5].

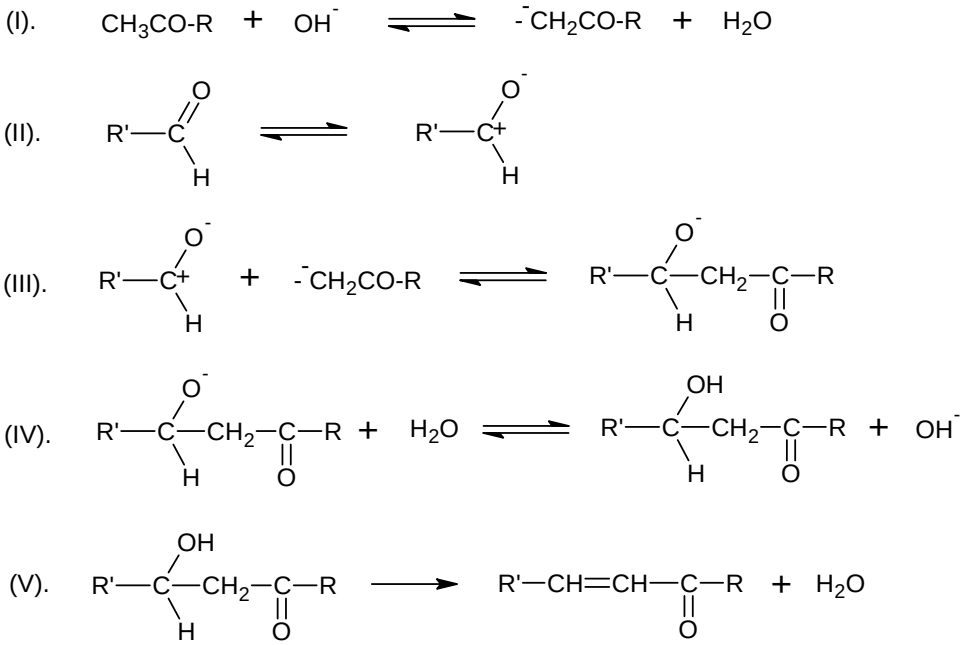
Mechanism
Chalcone formation proceeds through aldol type of condensation and the process is catalyzed by the presence of alkali. Following are the steps of the reaction mechanism.

The intermediate aldol type of products formed readily undergoes dehydration even under mild condition, particularly when R and R' are aryl groups.

Importance of chalcones
In recent years an increasing number of groups have become interested in chalcones and related compounds since they are finding extensive use in several medicinal and industrial fields.

Therapeutic Interest
Chalcones are potential biocides, some naturally occurring antibiotics and aminochalcones probably owe their biological activity to the presence of α,β-unsaturated carbonyl group.

They were found to possess Insecticidal, Antiulcer, Bactericidal[6,7], Fungicidal[6,7], Antiinflammatory[8], Antiviral, Antiallergic, Carboxygenase inhibitor, Antioxident[9], Antitumor, Antimalarial, Anticancer, Antileshmanial, Cardiovascular, Anti-HIV etc. activity



MATERIALS AND METHODS

[A] Synthesis of N-Phenylamino-*α*-methyl-phenyl azomethine

A mixture of phenyl hydrazine (1.08gm, 0.01M) and acetophenone (1.20gm, 0.01M) in absolute ethanol was refluxed in waterbath for 4 hrs. in presence of 1ml glacial acetic acid. Product obtained after cooling was crystallized from absolute ethanol. Yield, 1.8gm (90%), M.P.: 64˚C. ($C_{14}H_{14}N_2$; **Calculated** : C, 80.00; H, 6.66; N, 13.37%; **Found**: C, 79.92; H, 6.64; N, 13.34%).

This typical experimental procedure was followed to prepare other analogs of this series.

[B]Synthesis of 1,3-diphenyl-1H-pyrazole-4-carbaldehyde

N-Phenylamino-α-methyl-phenyl azomethine (0.84gm, 0.004M) was added in a mixture of Vilsmeier-Haack reagent (prepared by dropwise addition of 1.2ml $POCl_3$ in ice cooled 10ml DMF) and refluxed for 6 hrs. The reaction mixture was poured into crushed ice followed by neutralization using sodium bicarbonate. Crude product was isolated and crystallized from methanol. Yield, 2.16gm (87%), M.P. : 125˚C. ($C_{16}H_{12}N_2O$; **Calculated** : C, 77.42; H, 4.84; N, 11.29%; **Found** : C, 77.39; H, 4.80; N, 11.28%).

Exactly similar experimental procedure was followed to prepare other analogs of this series.

[C] Synthesis of 1-(4-methyl sulfonylphenyl)-3-(1,3-diphenyl-1H-pyrazol-4-yl)-2-propen-1-one (l_a)

A mixture of 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde (2.48gm, 0.01M) and 4-methyl sulfonylphenyl acetophenone (1.98gm, 0.01M) was dissolved in 40ml ethanol. To this mixture, 40% aq. NaOH was added till the mixture became basic. The reaction mixture was stirred at room temperature for 48 hr. Then reaction mixture was poured over crushed ice and contents were acidified with concentrated HCl. Product thus obtained was crystallized from ethanol. Yield, 3.76gm (88%), M.P. : 267˚C, R_f : 0.64, ($C_{25}H_{20}N_2O_3S$; **Calculated** : C, 70.07; H, 4.70; N, 6.54%; **Found** : C, 70.04; H, 4.68; N, 6.51%).

The same experimental procedure was utilized to prepare other analogs of this series **(l_{a-h})**. Their physical constant data are given in **Table-I.**

Reaction Scheme

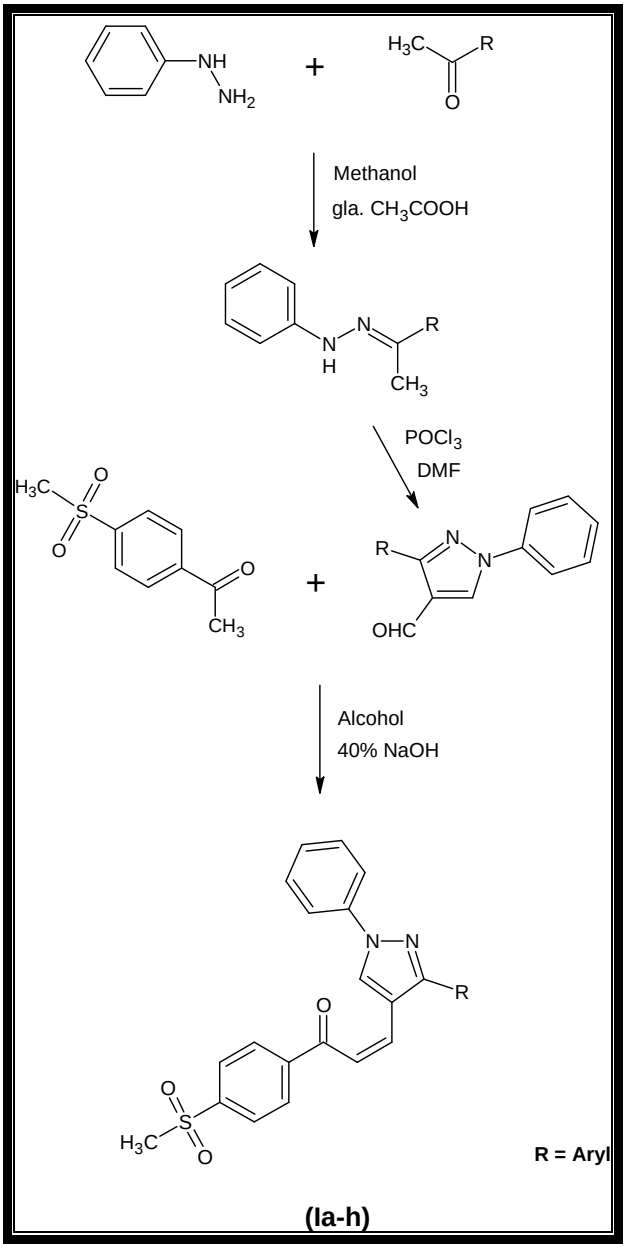


TABLE -I : Physical constants of 1-(4-methyl sulfonylphenyl)-3-(1-phenyl-3-aryl-1h-pyrazol-4-yl)-2- propen-1-ones (I_{a-h})

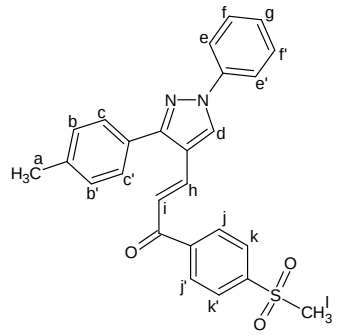
Compd. No.	R	Molecular Formula	%Yield (Final step)	M.P. °C	% of Carbon Found (Calcu.)	% of Hydrogen Found (Calcu.)	% of Nitrogen Found (Calcu.)
Ia	C_6H_5	$C_{25}H_{20}N_2O_3S$	88	267	70.04 (70.07)	4.68 (4.70)	6.51 (6.54)
Ib	4-CH_3-C_6H_4	$C_{26}H_{22}N_2O_3S$	84	252	70.53 (70.57)	4.98 (5.01)	6.30 (6.33)
Ic	4-OCH_3-C_6H_4	$C_{26}H_{22}N_2O_4S$	86	210	68.08 (68.10)	4.81 (4.84)	6.08 (6.11)
Id	4-Cl-C_6H_4	$C_{25}H_{19}N_2O_3ClS$	84	156	64.83 (64.86)	4.11 (4.14)	6.03 (6.05)
Ie	4-Br-C_6H_4	$C_{25}H_{19}N_2O_3BrS$	87	289	59.15 (59.18)	3.74 (3.77)	5.50 (5.52)
If	4-NO_2-C_6H_4	$C_{25}H_{19}N_3O_5S$	82	188	63.37 (63.41)	4.01 (4.04)	8.83 (8.87)
Ig	3-NO_2-C_6H_4	$C_{25}H_{19}N_3O_5S$	82	191	63.38 (63.41)	4.02 (4.04)	8.86 (8.87)
Ih	2,4-Cl-C_6H_3	$C_{25}H_{18}N_2O_3Cl_2S$	85	234	60.35 (60.37)	3.62 (3.65)	5.60 (5.63)

(1) Melting points are measured in open capillaries and are uncorrected
(2) TLC solvent system; Ethyl acetate : Cyclohexane = 8 : 2, TLC taken on Silica gel

SPECTRAL STUDY OF 1-(4-METHYL SULFONYL PHENYL)–3-(1–PHENYL-3-(4-METHYL PHENYL)-1H-PYRAZOL –4-YL)–2-PROPEN–1-ONE (l_b)

Interpretation of IR at a glance:- Aromatic C-H str. 3125.8 cm^{-1}, C=C str. 1504.8 cm^{-1}, C-H i.p. def. 1089.9 cm^{-1}, C-H o.o.p. def. 830.0 cm^{-1}; Chalcone C=O str., 1659.2 cm^{-1}, CH = CH str. 3125.8 cm^{-1} (overl.); Pyrazole moiety, C=N str. 1585.2 cm^{-1}, C-N str. 1213.3 cm^{-1}, -SO_2-CH_3. 1310.5 cm^{-1} (overl.), 1178.4 cm^{-1}

Internal Standard : TMS ; Solvent : $CDCl_3$; Instrument : BRUKER Spectrometer (400 MHz)
Interpretation of ^{1}H NMR at a glance



Signal No.	Signal Position (δ ppm)	No. of Protons	Multiplicity	Inference
1	2.442	3H	singlet	Ar-C$H_{3(a)}$
2	3.096	3H	singlet	Ar-SO_2C$H_{3(l)}$
3	7.261 – 7.350	2H	doublet	C-$H_{(e)}$
4	7.369 – 7.390	1H	triplet	C-$H_{(g)}$
5	7.489 – 7.529	2H	triplet	C-$H_{(f)}$
6	7-577 – 7.597	2H	doublet	C-$H_{(b)}$
7	7.793 – 7.817	1H	doublet	-C$H_{(h)}$=CH-
8	7.913 – 7.952	1H	doublet	-CH=C$H_{(i)}$-
9	8.048 – 8.070	2H	doublet	C-$H_{(j)}$
10	8.091 – 8.112	2H	doublet	C-$H_{(k)}$
11	8.381	1H	singlet	C-$H_{(d)}$

Mass Spectrum : m/z = 442.13

RESULTS AND DISCUSSION

The characterized heterocyclic compounds containing pyrazole ring were subjected for antibacterial screening with gram +ve ; gram –ve bacteria. The results suggested that as far as antibacterial activity is concerned, the synthesized heterocyclic compounds were uneffective at low concentrations unlike standard drugs. At higher concentrations,

antibacterial action was observed. When halogens replaced alkyl or alkoxyl group at 4 aryl position, the activity decreased. Out of nitro phenyl derivatives, nitro group at 3 position has slight higher activity. Dihalogenation in the aromatic ring only slightly increased antibacterial activity. In comparison to phenyl substitution, 4-methyl phenyl and 4-methoxy phenyl substituted derivatives were slightly more effective as antibacterial.

Comparative antimicrobial activity of 1-(4-methyl sulfonylphenyl)-3-(1-phenyl-3-aryl 1h-pyrazol-4-yl)-2-propen-1-ones I_{a-h} (Minimum inhibition Concentration in µg/ml)

Antibacterial activity (Zones of inhibition in mm)															
Compd. No.	R	*S. pyogens* MTCC-442							*S. aureus* MTCC-96						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
Ia	C_6H_5	-	-	10	12	14	16	18	-	-	13	14	16	18	19
Ib	4-CH_3-C_6H_4	-	-	11	13	15	17	18	-	-	13	15	15	16	18
Ic	4-OCH_3-C_6H_4	-	-	12	13	16	17	17	-	-	12	14	18	18	19
Id	4-Cl-C_6H_4	-	-	10	11	14	15	16	-	-	12	13	16	17	18
Ie	4-Br-C_6H_4	-	-	10	12	14	14	16	-	-	13	14	16	17	18
If	4-NO_2-C_6H_4	-	-	11	13	14	15	17	-	-	12	13	15	16	17
Ig	3-NO_2-C_6H_4	-	-	12	14	15	15	17	-	-	12	13	15	17	18
Ih	2,4-Cl-C_6H_3	-	-	10	12	14	14	15	-	-	11	14	16	17	19
Comparative activity of (I_{a-h}) with known chosen standard drugs															
Standard drug		**Antibacterial activity**													
Ampicillin		11	13	14	16	18	19	20	10	12	13	14	16	18	21
Chloramphenicol		10	12	13	19	20	20	22	12	13	14	19	20	21	22
Ciprofloxacin		10	18	19	21	21	22	22	17	18	19	21	22	22	23
Norfloxacin		18	18	19	20	21	21	23	19	20	22	25	26	28	28

N.B. (-) : No Activity

Comparative antimicrobial activity of 1-(4-methyl sulfonylphenyl)-3-(1-phenyl-3-aryl 1h-pyrazol-4-yl)-2-propen-1-ones I_{a-h} (Minimum inhibition Concentration in µg/ml)

Antibacterial activity (Zones of inhibition in mm)															
Compd. No.	R	*E. coli* MTCC-443							*P. areuginosa* MTCC-1688						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
Ia	C_6H_5	-	-	11	13	17	17	18	-	-	12	13	16	18	21
Ib	4-CH_3-C_6H_4	-	-	14	15	16	18	19	-	-	11	12	14	17	20
Ic	4-OCH_3-C_6H_4	-	-	12	13	15	17	18	-	-	11	13	15	19	22
Id	4-Cl-C_6H_4	-	-	13	14	15	17	19	-	-	12	13	14	18	21
Ie	4-Br-C_6H_4	-	-	14	15	17	18	19	-	-	13	13	14	17	20
If	4-NO_2-C_6H_4	-	-	14	15	17	18	19	-	-	13	14	14	17	19
Ig	3-NO_2-C_6H_4	-	-	14	15	17	18	19	-	-	12	13	14	18	20
Ih	2,4-Cl-C_6H_3	-	-	13	14	17	19	20	-	-	12	14	15	19	21
Comparative activity of (I_{a-h}) with known chosen standard drugs															
Standard drug		**Antibacterial activity**													
Ampicillin		14	14	15	16	19	20	22	14	14	15	15	18	20	23
Chloramphenicol		14	15	17	23	23	23	23	14	16	17	18	19	21	22
Ciprofloxacin		20	21	23	28	28	28	28	20	21	23	24	26	27	27
Norfloxacin		22	23	25	26	27	29	29	18	19	19	21	23	23	25

N.B. (-) : No Activity

CONCLUSION

Eight pyrazole derivatives were synthesized and characterized for their possible structure. Spectra and chemical analyses supported the expected structural formula. These compounds were subjected to antibacterial screening. Overall, the antibacterial activities were less compared to the standard drugs. However, there are certain points which indicate that proper structure modification may lead to increased antibacterial activity.

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