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Periodic Research

Antitubercular and Antimicrobial Activity of Chalcone Derivatives Derived from Methylsulfanylbenzaldehyde

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Abstract

Chalcone derivatives have been found to possess wide therapeutic activities. With a view to supplement these valid observations 3-(4-Methylsulfanylphenyl)-1-aryl-propenone derivatives **(a-j)** have been synthesized by the condensation of 4-Methylsulfanyl-benzaldehyde with different substituted-acetophenones. The newly synthesized compounds have been characterized by IR, ^{1}H NMR and mass spectroscopy. The compounds have been screened for their antimicrobial activity at a concentration of 50 µg against various strains of bacteria & fungi, and also tested for antimycobacterial activity at a concentration of 12.5 µg/ml.

Keywords: Antitubercular activity, Antimicrobial activity, Chalcone

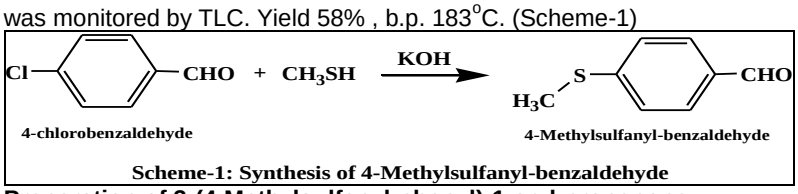
Introduction

Chalcones a biosynthetic product of the shikimate pathway, belonging to flavanoid family are precursors of open chain flavonoids and isoflavonoids, which are abundant in edible plants. Chalcones are also key precursors in the synthesis of many biologically important heterocycles such as benzothiazepine, pyrazolines, 1,4-diketones, and flavones. Thus the synthesis of chalcones has generated vast interest to organic as well as for medicinal chemists. Different chalcone derivatives are found to provide the structure of natural products like hamlock tannin, Cyanomaclurin, Ploretin eriodictyl, homoeriodictyle, Naringenin etc., also found an application as stabilizers, photosensitive materials, polymerization catalyst, fluorescents and whitening agents[1-3]. In the present study biologically active chalcones have been synthesized using 4-Methylsulfanyl-benzaldehyde and characterized.

Experimental

Preparation of 4-Methylsulfanyl-benzaldehyde

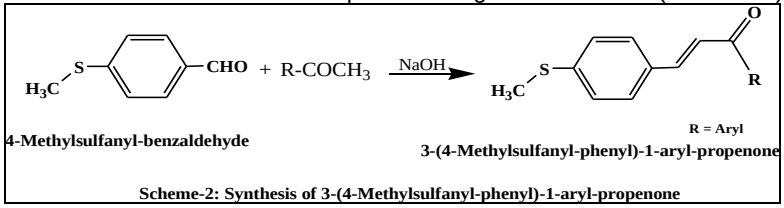
A mixture of 4-chlorobenzaldehyde (5.27 g, 0.375m), excess of CH_3SH (3.6g, 0.75m), 2.5g KOH and ethanol (50 ml) was refluxed in R.B.F. for 3 hrs. During the reflux CH_3SH is bubbled in the mixture was diluted with water and extracted with carbon tetrachloride. The reaction was monitored by TLC. Yield 58% , b.p. 183^{o}C. (Scheme-1)



Scheme-1: Synthesis of 4-Methylsulfanyl-benzaldehyde

Preparation of 3-(4-Methylsulfanyl-phenyl)-1-aryl-propenone

All the Chalcone derivatives **(a-j)** were prepared by following general method. Substituted-acetophenones (0.01 M) in ethanol (95%, 15 ml) was added to the mixture of 4-Methylsulfanylbenzaldehyde (0.01 M) in ethanol (95%, 15ml) and aqueous sodium hydroxide (40%, 3ml). The reaction mixture was stirred at 20-30^{o}C for 24 hrs. The resulting mixture was poured into crushed ice and isolated by acidification and crystallized from ethanol. The details of compounds are given in Table-1. (Scheme-2)



Scheme-2: Synthesis of 3-(4-Methylsulfanyl-phenyl)-1-aryl-propenone

Table-1 Analytical and Physical data of chalcone derivatives

Comp.	R	Molecular formula	M.W.	M.P. °C	Yield %
a	C_6H_{5-}	$C_{16}H_{14}OS$	254	60	70
b	4-Br-C_6H_4	$C_{16}H_{13}OSBr$	333	156	68
c	4-Cl-C_6H_4	$C_{16}H_{13}OSCl$	288	143	61
d	2,4-$(OH)_2$-C_6H_3	$C_{16}H_{14}O_3S$	286	151	65
e	4-OC_2H_5-C_6H_4	$C_{18}H_{18}O_2S$	298	135	68
f	2-OH-C_6H_4	$C_{16}H_{14}O_2S$	270	144	71
g	4-OH-C_6H_4	$C_{18}H_{18}O_2S$	270	124	64
h	4-OCH_3-C_6H_4	$C_{17}H_{16}O_2S$	284	97	62
i	4-CH_3-C_6H_4	$C_{17}H_{16}OS$	268	84	67
j	4-NO_2-C_6H_4	$C_{16}H_{13}NO_3S$	299	156	69

Antimicrobial screening

Antibacterial activity

Antibacterial activity was carried out by cup-plate method. The nutrient Agar-broth prepared by usual method was inoculated aseptically with 0.5 ml of 24 hours old subculture of B. Megaterium, B. Subtillis and E. Coli. in separate conical flask at 40-50°C and mixed well by gentle shaking. About 25 ml of the concentrates of the flask were poured and evenly spread in Petri-dish (13 cm in diameter) and allowed to set for 2 hours. The cups (10 mm in diameter) were formed with the help of borer in agar medium and filled with 0.05 ml (50 µg) solution of sample in DMF. The plates were incubated at 37°C for 24 hours and the control was also maintained with 0.05 ml of sample in DMF (1 mg/ml) in similar manner and zones of inhibition were measured in mm. (Table-3) [4]

Antifungal activity

A. Niger was employed for testing antifungal activity using cup-plate method. The culture was maintained on sabouraud's agar slant. Sterilized medium was inoculated with 72 hours old 0.5ml suspension of different fungal spores in a separate flask. About 25 ml of the inoculated medium was poured and evenly spreaded in a sterilized petri-dish and allowed to set for 24 hours. The cups (10 mm in diameter) were formed by the help of the borer in agar medium and filled with 0.05 ml (50 µg) solution of a sample in DMF by means of sterile 0.1 ml pipette. The plates were incubated at 37°C for 48 hours. After the completion of incubation period the zone of inhibition was measured in mm. (Table-3) [5]

Antitubercular Screening:

The antitubercular evaluation of the compounds was carried out at Tuberculosis Antimicrobial Acquisition Coordinating Facility (TAACF), Southern Research Institute (USA). Primary screening of the compounds were conducted at 12.5 µg/ml against Mycobacterium tuberculosis H37Rv in BACTEC 12B medium using the BACTEC 460 radiometric system. The antimycobacterial activity data were compared with standard drug Rifampin at 0.031 µg/ml concentration which showed 97% inhibition. (Table-4) [6,7]

Results and Discussion

The chalcone derivatives were synthesized and characterized by IR, ^{1}H NMR and Mass spectroscopy. The synthesized compounds were evaluated against Gram positive and Gram negative bacteria and Fungi. The compounds were also evaluated for their Antitubercular activity.

Characterization of chalcones

The IR spectra of compounds show sharp peak between 1650-1655 cm^{-1}, which confirms the presence of (C=O) of ketones. The sharp peak observed between 1590-1597 cm^{-1} indicates presence of (–CH=CH-). A sharp peak between 600-700 cm^{-1} is due to the presence of (-C-S-C str). The important IR frequencies are given in Table-2. The IR spectrum of one of the chalcone is shown in figure-1 [8].

Figure-1: IR spectrum of Chalcone

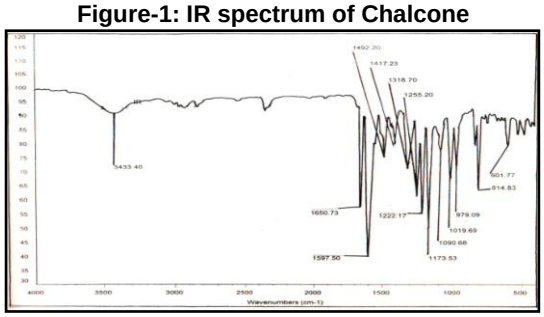
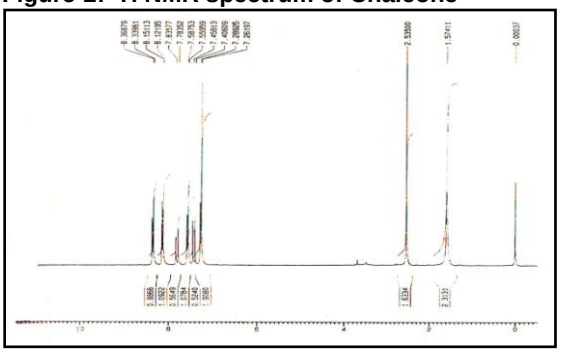


Table-2 Important IR frequencies of chalcone derivates

Type	Vibration mode	Frequency in cm^{-1}	
		Observed	Reported
Alkane	C-H (Asym)	2910	2975-2950
	C-H (Sym)	2880	2880-2860
Aromatic	C-H Str.	3060	3100-3000
	C=C Str.	1489	1473-1453
		1551	1583-1571
		1200	1286-1252
Chalcone Moiety	C=O Str.	1651	1700-1440
	-CH=CH- Str	1588	1644-1618
S-CH_3	C-S-C Str.	691	700-600

The ^{1}H NMR spectra of synthesized compounds show singlet at 2.53 δ ppm of S-CH_3 protons. The multiplets were found between 7.26 to 8.36 δ ppm confirms the aromatic and ethylinic protons. The ^{1}H NMR spectrum of one of the chalcone is given in Figure-2 [8,9].

Figure-2: ^{1}H NMR spectrum of Chalcone



Biological activity

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The antimicrobial and antitubercular activities of chalcones were compared with standard drugs. Some of the compounds show significant activities against microorganism are listed in Table-5. The Biological activity charts are shown in Figure-3 & 4.

Table-3: Antimicrobial activity of chalcone derivatives

Comp	Antibacterial Zone of inhibition in m.m.			Antifungal
	E. Coli	B. subtillis	B. megateriu m	A. Niger
a	20	18	17	21
b	18	17	15	20
c	21	19	20	17
d	23	19	18	19
e	23	17	19	18
f	19	20	17	22
g	22	18	19	17
h	16	17	19	15
i	19	16	18	18
j	21	20	18	16

Table-4: Primary Assay of Antitubercular Activity, TAACF, Southern Research Institute (USA)

Comp.	MTb Strain	MIC	% Inhibition		Comment
a	H37Rv	<12.5	95	+	MIC Rifampin=0.25µg/ml@98% inhibition
b	H37Rv	>12.5	74	-	MIC Rifampin=0.25µg/ml@98% inhibition
c	H37Rv	>12.5	82	-	MIC Rifampin=0.25µg/ml@98% inhibition
d	H37Rv	<12.5	94	+	MIC Rifampin=0.25µg/ml@98% inhibition
e	H37Rv	>12.5	68	-	MIC Rifampin=0.25µg/ml@98% inhibition
f	H37Rv	>12.5	38	-	MIC Rifampin=0.25µg/ml@98% inhibition
g	H37Rv	<12.5	96	+	MIC Rifampin=0.25µg/ml@98% inhibition
h	H37Rv	>12.5	70	-	MIC Rifampin=0.25µg/ml@98% inhibition
i	H37Rv	>12.5	86	-	MIC Rifampin=0.25µg/ml@98% inhibition
j	H37Rv	>12.5	84	-	MIC Rifampin=0.25µg/ml@98% inhibition

Table-5: Biological evaluation of compounds exhibiting the highest activity against microbes investigated

Antibacterial activity			Antifungal activity	Antitubercular activity
Zone of Inhibition in mm				% of Inhibition
E. Coli	B. Subtillis	B. Megateriu m	A. Niger	Tuberculosis H 37 RV
d(23)	f(20)	c(20)	f(22)	g(96)
e(23)	j(20)	e(19)	a(21)	a(95)
g(22)	c(19)	g(19)		
c(21)				
j(21)				
Comparable activity with known standard drugs				
Ampicillin (24)	Ampicillin e (23)	Chloramphenicol (20)	Griseofluvin (20)	Refampin = 0.02 to 0.031 µg/ml 98% inhibition

Figure 3: Antimicrobial Activity Chart

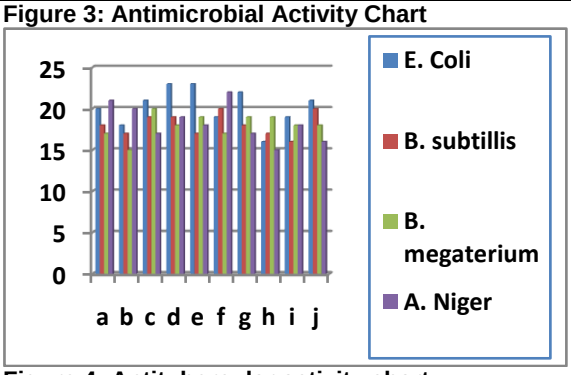
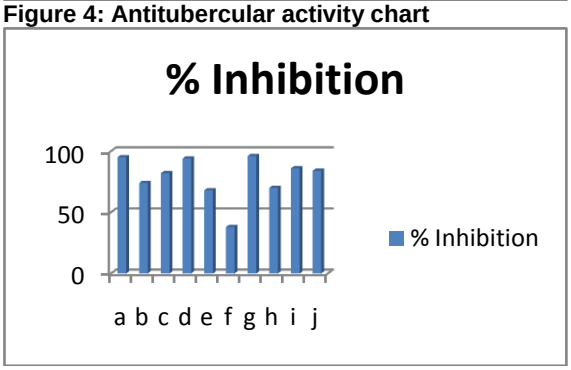


Figure 4: Antitubercular activity chart



Conclusion

The chalcone compounds **a & g** have been found most potent against Tuberculosis H 37 RV. Compound **c, d, e, g and j** show highest activity against E. Coli. The chalcone **C, f, and j** have been found active against B. Subtillis, while compounds **c, e and g** show good inhibition against B. Megaterium. Compounds like **a and f** are also very potent against fungus A. Niger.

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