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Synthesis and Biological Screening of 1-{3-[4'-(Dibenzo [B, F] [1, 4] Thiazepin-11"-Yl) Amino] Phenyl}-5-Aryl-1h-Pyrazol-1-Yl-Ethanones

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Abstract: ***Acetyl pyrazoline derivatives procuring shows better therapeutic activity looking at their versatile therapeutic importance and with an aim to getting to synthesize some new pyrazolines. The synthesis of 1-{3-[4'-(diabenzo[b, f][1,4] thiazepin-11"-yl)amino]phenyl}-5-aryl-1-H-pyrazol-1-yl-ethanone have been synthesis by the cyclo condensation of chalcones(5a-5j)with hydrazine hydrate and glacial acetic acid. The constitution of the products has been characterized by elemental analyses IR, ^{1}H NMR and Mass spectral study. The products were screened for their antimicrobial activity against Gram +ve bacteria Gram negative bacteria and fungi at 50 µg concentration by cup-plate method.***
Keywords: Pyrazolines, Anti-microbial activity

I. INTRODUCTION

Pyrazolines containing five membered heterocycles, pyrazolines possess good therapeutic activities. which have been studied extensively for their industrial applications. Pyrazolines gave Anticonvalsant[1-2], Fungicidal[3], Herbicidal[4], Insecticidal[5], Analgesic[6-7], etc activities.

II. MATERIALS AND METHODS

All the melting points are determined in open capillary tubes and are uncorrected. IR spectra recorded on SHIMADZU-FT-IR-8400 Spectrophotometer; 4000-400 cm^{-}(KBr disc). 1H NMR spectra were recorded on a BRUKER spectrometer (400MHz) instrument using TMS as an internal standard. Mass spectra were recorded on Waters QDA spectrophotometer. All the compounds gave satisfactory elemental analyses.

III. EXPERIMENTAL

A. Step-I:Preparation of 4'-Acetylphenyl(dibenzo[b,f][1,4]thiazepines-11-yl]amine

A mixture of 11-chlorodibenzo[b,f][1,4] thiazepine (2.45g, 0.01M) 4-amino acetophenone (1.35g,0.01M)in methanol (25ml) and pyridine (2 ml) was refluxed on an oil bath at 130ºC at 8 hrs. The content was cooled and poured into crushed ice-filtered and washed with water. The isolated product was crystallized from ethanol yield 87.32%, M.P:195^{0}C (Found: C:73.20; H:4.60; N:8.11; $C_{21}H_{16}N_2OS$required C: 73.25; H: 4.65; N:8.13%).

B. Step-II: Synthesis of 1"-[4'-(dibenzo[b,f][1,4]thiazepines-11-yl)aminophenyl]-3"-(3"',4"'-dimethoxy phenyl)-2-ene-1"-one

A Mixture of (4-acetyl phenyl[b,f][1,4] thiazepine-11-yl)amine (3.44g,0.01M) 3,4-dimethoxy benzaldehyde (1.66g,0.01M), ethanol(15 ml), 20% NaOH till the solution vigorously stirring at basic medium at 24 hrs. The contents were poured into crushed ice, acidified filtered and crystallized from ethanol. yield 72.32% M.P.208^{0}C, (Found:C:73.00; H:4.71; N:5.60; $C_{30}H_{24}N_2O_3S$ required: C:73.17; H:4.91; N:5.69%)IR (KBr) cm^{-1}:2966 (C-H Str.(asym) ; 2851 (C-H Str. (sym) ; 1456 (C-H def bending) ; 3047 (C-H str)1485 (C=C Ring skeleton) ; 1257 (C-H i.p.def) ; 763 (C-H o.o.p) ; 1338 (C-N Str.) ; 3321 (N-H Str.) ;1658 (C=O Str.) ; 1232 (C-O-C Str.). ^{1}H NMR(ppm) : 3.82 (6H (s),Ar–OCH_3);6.97-7.59(15H (m)Ar-H);7.73-7.75 (1H (d)=CH); 8.23-8.73 (1H (d) =CH); 9.62 (1H (s) –NH); Mass (m/z): 492,440,369,205,77

C. Step-III: Synthesis of 1-{3-[4'-(diabenzo[b,f][1,4]thiazepin-11"-yl)amino]phenyl}-5-(3"',4"'-dimethoxy phenyl)-1-H-pyrazol-1-yl-ethanone.(5a-5j)

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A mixture of 1"-[4'-(dibenzo[b, f][1,4]thiazepin-11-yl)-amino phenyl]-3"-(3"',4"'-dimethoxy phenyl)-2-ene-1"-one (4.92.g,0.01 M); hydrazine hydrate (1.0ml), glacial acetic acid (2.0ml) and ethanol (20 ml) was refluxed for 10 hrs. The reaction mixture is poured into crushed ice. Filtered, washed with hot water and crystalized from dioxane yield: 79.65 % M.P. 215^{0}C (Found: C: 69.91, H: 4.95, N: 10.04, $C_{32}H_{28}N_4O_3S$, Required: C: 70.05; H: 5.14: N: 10.21%)IR (KBr) cm^{-1}: 2991 (C-H Str. asym) ; 2943 (C-H Str. sym) ; 1458 (C-H def bending) ; 3064 (C-H str.Ar)1537 (C=C Ring skeleton) ; 1338 (C-N Str.) ; 3321 (N-H Str.) ; 1681 (>C=O Str) ;1624 (C=N Str.) ;1257 (C-O-C Str.) ; 2835 (C-S-C Str.) ;^{1}H NMR (ppm): 2.04(2H (d) –CH_2); 2.20 (3H (s) CH_3) 3.84(6H (s) Ar-O-CH_3) ; 4.81 (1H (t) –CH) ; 6.95-8.73(15H (m)Ar-H) ;9.62 (1H (s) –NH) ; Mass (m/z): 549, 493, 247,201,158,77,64. Similarly other compounds (5a-5j) have been synthesized.

D. Reaction Scheme

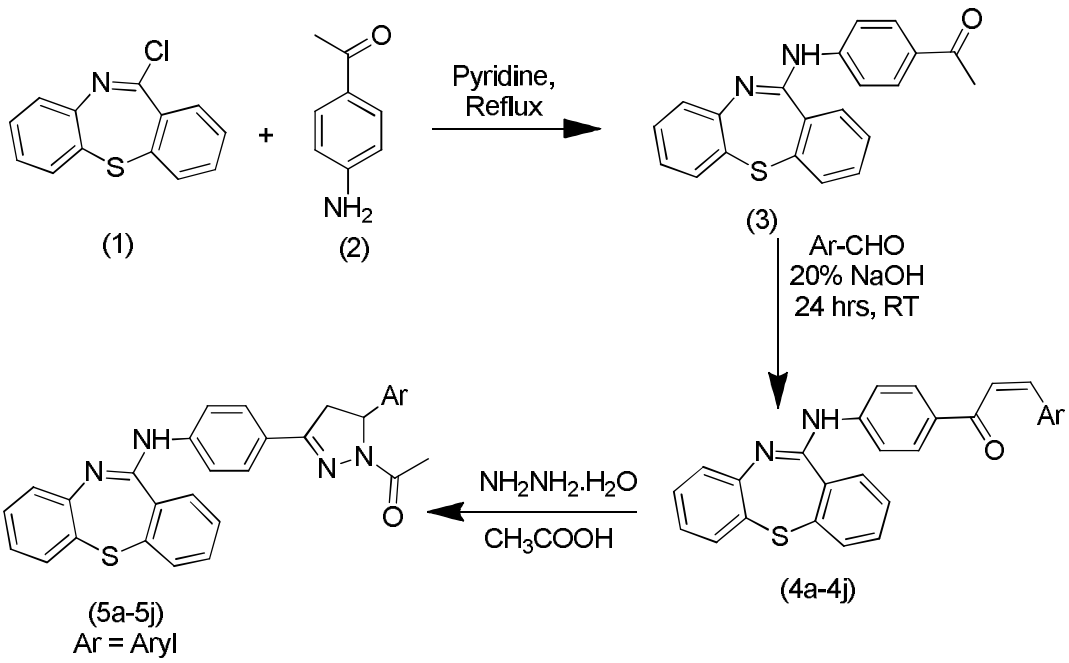


Table : I Physical Constants of the compounds (5a-5j)

Sr. No.	Ar	Molecular Formula	M.P. ^{o}C	Yield	%of Nitrogen	
					Calcd.	Found
5a	C_6H_5-	$C_{30}H_{24}N_4OS$	168	71.25	11.47	11.35
5b	4-CH_3-C_6H_4-	$C_{31}H_{26}N_4OS$	175	83.15	11.15	11.03
5c	2-OCH_3-C_6H_4-	$C_{31}H_{26}N_4O_2S$	183	81.13	10.80	10.73
5d	4-OCH_3-C_6H_4-	$C_{31}H_{26}N_4O_2S$	207	81.80	10.80	10.75
5e	3,4-$(OCH_3)_2$-C_6H_3-	$C_{32}H_{28}N_4O_3S$	215	79.65	10.21	10.04
5f	3,4,5-$(OCH_3)_3$-C_6H_2-	$C_{33}H_{23}N_4O_4S$	232	75.67	9.68	9.57
5g	2-NO_2-C_6H_4-	$C_{30}H_{23}N_5O_3S$	175	73.75	13.12	13.04
5h	3-NO_2-C_6H_4-	$C_{30}H_{23}N_5O_3S$	187	81.55	13.12	13.06
5i	4-NO_2-C_6H_4-	$C_{30}H_{23}N_5O_3S$	132	89.35	13.12	13.01

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5j	4-NH_2-C_6H_4-	$C_{30}H_{25}N_5OS$	162	61.44	13.91	13.83

E. Antibacterial Activity: [8]

The products were screened for their antibacterial activity. The nutrientagarbroth prepared by the usual method, was inoculated specially with 0.5 ml for 24 hours, old subscture of *B. megateriumS. aureus, Escherichia coli, staphimarium*, in separate conical flasks at 40-50^{o}C and mixed well by gentle shaking. About 25ml of the contents of the flask were poured and evenly spread in a petridish(13 cm in diameter) and allowed to set for 2 hrs. The cups (10 mm in diameter) were formed by the help of borer in anagar medium and filled with 0.1 ml (1.0mg/ml) solution of sample in dimethyl formamide. The plates were incubated at 37^{o}C for 24 hrs and the control was also maintained with 0.1 ml of DMF in similar manner and the zone of inhibition of the bacterial growth are measured in mm diameter and are recorded in Table No. II.

F. Antifungal Activity: [9]

Aspergill usniger was employed for testing fungicidal activity using cup-plate method the cultures were maintained on subouraud' sagar slants. Purified compounds were used for testing the fungicidal activity, sterilized subouraud's agar medium was inoculated with 72 hours old 0.5 ml suspension of fungal spores in a sterilized separate flask. About 25 ml of the inoculated medium was evenly spreader in a Petridish and allowed to set for 2 hrs. The cups(10 mm in a diameter) were punched in Petridish and loaded with 0.1 ml (1.0 mg/ml) of solution of a sample in dimethyl formamide The plate was incubated at room temperature 37^{o}C for 48hrs.After the completion of incubation period the zone of inhibition or growth in the form of diameter in mm was measured. Along the test solution in each Petridish one cup was filled up with solvent acts as control. The zones of inhibition are recorded in Table No. II

Table :II

Anti-microbial activityof 1-{3-[4'-(diabenzo[b,f][1,4]thiazepin-11"-yl)amino] phenyl}-5-aryl-1-H-pyrazol-1-yl-ethanone. (5a-5j)

Sr.No.	Ar	Antibacterial activity Zone of inhibition in m.m.				Antifungal activity Zone of inhibition in m.m.
		B. megaterium	S. aureus	S.taphimarium	E.coli	A.niger
5a	C_6H_5-	15	21	20	14	21
5b	4-CH_3-C_6H_4-	23	22	18	13	20
5c	2-OCH_3-C_6H_4-	20	14	13	14	14
5d	4-OCH_3-C_6H_4-	23	15	14	23	15
5e	3,4-$(OCH_3)_2$-C_6H_3-	17	17	21	14	17
5f	3,4,5-$(OCH_3)_3$-C_6H_2-	18	18	23	16	18
5g	2-NO_2-C_6H_4-	19	19	23	21	14
5h	3-NO_2-C_6H_4-	18	18	18	14	20
5i	4-NO_2-C_6H_4-	19	23	14	23	16
5j	4-NH_2-C_6H_4-	13	20	21	13	21

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IV. RESULTS AND DISCUSSION

Compounds (5a-5j) were screened for their in vitro antibacterial activity using cup-plate agar diffusion method at a concentration of 50 µg/ml using Gram positive bacterial strains such as B. megateriumand S. aureus Gram negative bacterial strain such as Escherichia coli and S.taphimarium and fungi A. niger. The compounds activity compare with Known antibiotics like ampicillin, Chloramphenicol, norfloxacin, and Griseo fulvin. comparable antimicrobial activity represented in Table - III

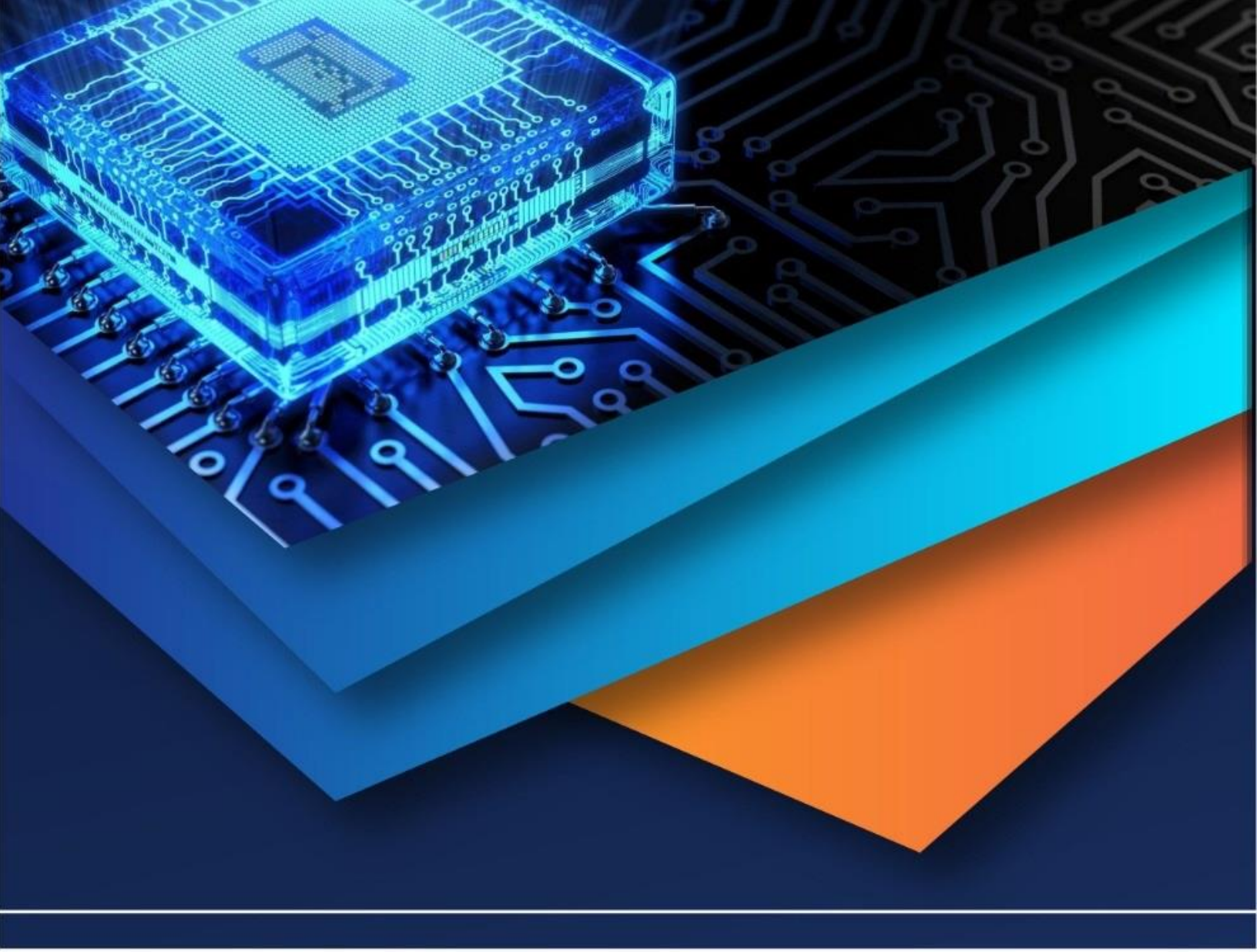
Table : III Comparable antimicrobial activity of compounds (5a-5j) with known standard drugs

	Antibacterial activity Zone of inhibition in m.m.				Antifungal activity Zone of inhibition in m.m.
	B. megaterium Ar	S. aureus Ar	S.taphimarium Ar	E.coli Ar	A.niger Ar
	4-CH_3-C_6H_4-23	C_6H_4 - 21	4-OCH_3-C_6H_4-14	4-OCH_3-C_6H_4-23	C_6H_5- 21
	2-OCH_3-C_6H_4-20	4-CH_3-C_6H_4 -22	3,4-$(OCH_3)_2$-C_6H_3-21	2-NO_2-C_6H_4-21	4-CH_3-C_6H_3- 20
	4-OCH_3-C_6H_4-23	4-NO_2-C_6H_4 -23	3,4,5-$(OCH_3)_3$-C_6H_2-23	4-NO_2-C_6H_4-23	3-NO_2-C_6H_4-20
		4-NH_2-C_6H_4-20	4-NH_2-C_6H_4-21		4-NH_2-C_6H_4-21
Comparable activity with known standard drugs					
Ampicilin 50µg	29	28	31	33	-
Chloramphenicol 50µg	28	31	28	29	-
Norfloxacin 50µg	32	30	26	29	-
Griseofulvin 50µg	-	-	-	-	26

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