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Synthesis and Biological Screening of 11-{4'-[(5"-ARYL)-4"-5" DIHYDRO-1"- (H)-PYRAZOL-3"-YL] PHENOXY}-DIBENZO [b,f] THIAZEPINES

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Abstract:
11-{4'-[(5''-aryl)-4"-5"dihydro-1"-(H)-pyrazol-3"-yl] phenoxy}-dibenzo [b,f] thiazepines (4a–4j) have been synthesized by the condensation of 11-{4'-[(3"-aryl)- 2"- propene-1"-one]-phenoxy} dibenzo [b,f] thiazepines with hydrazine hydrate.
The constitution of the newly synthesized products have been confirmed by elemental analysis, IR, ^{1}H NMR, Spectroscopy and further supported by mass spectroscopy. The products have been evaluated for their biological activity against gram +ve bacteria, gram –ve bacteria and fungi. Some of the products showed moderate activity compared with known standard drugs.

Key words: *Chalcones, Pyrazolines, MIC*

1. Introduction

Dibenzothiazepine derivatives have been reported as a valuable medicine e.g. quetiapine and tianeptine in the treatment of depression and schizophrenia (anti pscychotic) respectively. Pyrazoline derivatives are associated with a wide range of biological activity like analgesic[1], bactericidal[2], cardiovascular[3], antimicrobial[4], anticonvulsant[5] etc. In order to design better drug potentials and to study their pharmacological profile some pyrazoline derivatives were synthesized.

2. Antimicrobial Activity

All the compounds (3a-3j) and (4a-4j) were tested for their antimicrobial activity with MIC by Broth Dilution Method[6,7] against the Gram positive bacteria *Staphylococus aureus*, *Streptococcus pyogenes* and Gram negative bacteria *Escherichia coli*, *Pseudomonas aeruginosa* and for antifungal activity against *Candida albicans* using DMSO as a solvent after 24 hrs of incubation at 37^{o}C, the lowest concentration inhibiting growth of the organism is recorded as the MIC. The activity was compared with known standard drugs viz. Ampicillin, Chloramphenicol, Ciprofloxacin and Griseofulvin drugs which is represented in Table – II

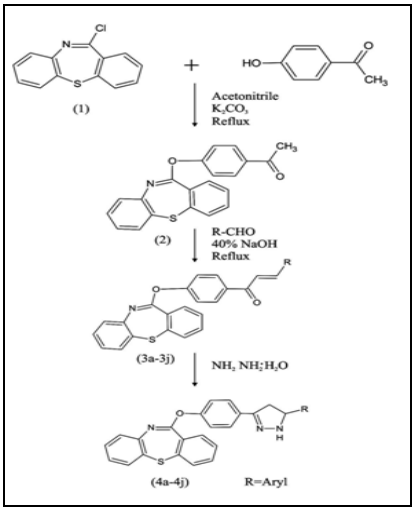

Figure 1: Reaction Scheme

3. Experimental Section

All the melting points were measured in open glass capillary method. IR absorption spectra (in cm^{-1})were recorded on a Shimadzu FT-IR-8400 spectrophotometer using KBr pallet method and ^1H NMR spectra on BRUKER (500-MHz) using TMS as internal standard (chemical shift in □ppm) and mass spectra on a Joel 300 eV. The compounds were routinely checked by TLC using silica gel-G

3.1. 11-(4'-Acetyl phenoxy) dibenzo [b,f] thiazepine (2)

A mixture of 11-chloro dibenzo [b,f] thiazepines (2.45g, 0.01M), 4-hydroxy acetophenone (1.36g, 0.01M) in acetonitrile (25ml) and potassium carbonate (4 gm) was refluxed on a water bath at 80-85^oC for 24 hrs. The product was cooled, poured in to crushed ice, filtered, dried and crystallized from ethanol.Yield:76.85%; m.p.160^oC (Found: C:72.98; H:4.28; N: 4.01, $C_{21}H_{15}O_2NS$ required C:73.04; H: 4.35; N: 4.06%)

3.2. Synthesis of 11-{4'-[3"-(4'''-methoxy phenyl)-2"-propene-1"-one]-phenoxy} dibenzo [b,f] thiazepine (3b)

A mixture of 11-(4'-acetyl phenoxy) dibenzo [b,f] thiazepine (3.45g, 0.01M) and 4-methoxy benzaldehyde (1.36g, 0.01M) in ethanol 25 ml and 40% NaOH solution (25ml) was refluxed on a water bath for 8 hrs. The contents were poured in to crushed ice, acidified, filtered, dried and crystallized from ethanol. Yield: 88.40%, M.P.: 212^oC (Found: C:75.13; H:4.50; N:3.00; $C_{29}H_{21}O_3NS$ required C:75.16; H:4.54; N: 3.02%)

IR (KBr) : 2953 (C-H str. asym); 2831 (C-H str. sym); 3064 (C-H str. aromatic); 1421, 1508 (C=C ring skeletal); 1342 (C-N str.), 1662 (>C=O), 1462 (CH=CH str.), 1217 (C-O-C str.) 1653 (C=N str.); 761 (C-S-C str).

^1H NMR (DMSO): 3.3 (S, 3H;-OCH_3), 6.9 (d, 2H; HC=CH), 7-8 (m, 16H; Ar-H)

m/z:- 77,161, 209,210, 303, 330, 345, 430, 448, 463.

Similarly other compounds (3a-3j) were synthesized and their physical data are recorded in Table-I.

3.3. Synthesis of 11-{4'-[5"-(4'''-methoxy phenyl)-4"-5"-dihydro-1"-(H) pyrazol- 3"-yl] phenoxy}- dibenzo [b,f] thiazepines (4b)

A mixture of 11-{4'-[3"-(4'''-methoxy phenyl)-2"-propene-1"-one] phenoxy} dibenzo [b,f] thiazepine (4.63 gm, 0.01M), hydrazine hydrate (1.0ml) in methanol (15ml) was refluxed for 12 hrs. The reaction mixture was poured into crushed ice, filtered, dried and crystallized from dioxan. Yield: 69.88 % ; m.p. 114^oC (Found: C:72.93; H: 4.81; N:8.76, $C_{29}H_{23}O_2N_3S$ required: C: 72.96 ; H: 4.82; N: 8.80%).

IR (KBr):- 2980 (C-H str. asym); 2835 (C-H str.sym); 3059 (C-H str. aromatic); 1510 (C=C ring skeleton); 1342 (C-N str.); 3356 (N-H str.); 761 (C-S-C str.); 1658 (C=N str.); 1249 (C-O-C str.)

^1H NMR (DMSO): 3.8(s,3H;-OCH_3), 2.8(t,1H), 2.5(d,2H), 4.8(s,1H;-NH),
7-8 (m,16H, Ar-H)

m/z:- 69,77,122,140,210,226,303,370,384,448,477

Similarly other compounds (4a-4j) were synthesized and their physical data are recorded in Table-I.

Comp[d]	R	MF	M.P °C	Antibacterial activity MIC(µg/ml)				Antifungal activity MIC	% of Nitrogen	
				S. Aureus	S. pyogenes	E. Coli	P. Aeruginosa	C. Albicans	Calcd.	Found
3a	C_6H_5-	$C_{28}H_{19}O_2NS$	204	*500*	500	200	250	1000	3.23	2.97
3b	4-OCH_3-C_6H_4-	$C_{29}H_{21}O_3NS$	212	*500*	250	500	500	250	3.02	3.00
3c	3-Cl- C_6H_4-	$C_{28}H_{18}O_2NSCl$	170	*500*	500	200	200	200	2.99	2.96
3d	4-Cl- C_6H_4-	$C_{28}H_{18}O_2NSCl$	175	*500*	500	125	200	200	2.99	2.94
3e	4-F- C_6H_4-	$C_{28}H_{18}O_2NSF$	208	*250*	250	200	200	1000	3.10	3.07
3f	4-NO_2- C_6H_4-	$C_{28}H_{18}O_4N_2S$	181	*250*	200	250	250	1000	5.86	5.84
3g	3-NO_2- C_6H_4-	$C_{28}H_{18}O_4N_2S$	193	*500*	500	200	200	250	5.86	5.80
3h	3,4-$(OCH_3)_2$-C_6H_3-	$C_{30}H_{23}O_4NS$	191	*250*	200	500	500	500	2.83	2.80
3i	4-CH_3- C_6H_4-	$C_{29}H_{21}O_2NS$	208	*125*	125	250	250	500	3.13	3.09
3j	3,4-$(Cl)_2$- C_6H_3-	$C_{28}H_{17}O_2NSCl_2$	196	*100*	100	200	200	500	2.78	2.75
4a	C_6H_5-	$C_{28}H_{21}ON_3S$	142	*125*	125	100	125	1000	9.40	9.37
4b	4-OCH_3-C_6H_4-	$C_{29}H_{23}O_2N_3S$	114	*250*	250	125	125	1000	8.80	8.76
4c	3-Cl- C_6H_4-	$C_{28}H_{20}ON_3SCl$	125	*200*	250	200	200	250	8.72	8.70
4d	4-Cl- C_6H_4-	$C_{28}H_{20}ON_3SCl$	147	*62.5*	100	250	250	250	8.72	8.71
4e	4-F- C_6H_4-	$C_{28}H_{20}ON_3SF$	136	*125*	200	200	200	1000	9.03	9.00
4f	4-NO_2- C_6H_4-	$C_{28}H_{20}O_3N_4S$	194	*62.5*	200	250	250	200	11.38	11.36
4g	3-NO_2- C_6H_4-	$C_{28}H_{20}O_3N_4S$	139	*100*	200	125	125	1000	11.38	11.32
4h	3,4-$(OCH_3)_2$-C_6H_3-	$C_{30}H_{25}O_3N_3S$	150	*250*	200	200	250	1000	8.28	8.25
4i	4-CH_3- C_6H_4-	$C_{29}H_{23}ON_3S$	138	*200*	500	250	250	1000	9.11	9.09
4j	2,4-$(Cl)_2$- C_6H_3-	$C_{28}H_{19}ON_3SCl_2$	123	*500*	500	100	100	250	8.14	8.11

Table 1: The physical data and biological screening of compounds (3a-3j) and (4a-4j)

Compounds	S. aureus	S. pyogenes	E.coli	P.aeruginosa	C.albicans
(3a-3j)	3e, 3f, 3h,3i, 3j	3i, 3j	3d	-	3b, 3c, 3d,3g
(4a-4j)	4a, 4b, 4c,4d, 4e, 4f,4g,4h,4i	4a, 4d	4a,4b,4f	4a,4b,4g,4j	4c,4d,4f,4j

Table 2: Compounds showed moderate activity compared with known standard drugs

Drugs	S. aureus	S. pyogenes	E.coli	P.aeruginosa	C.albicans
1. Ampicillin	250	100	100	100	-
2. Chloramphenicol	50	50	50	50	-
3. Ciprofloxacin	50	50	25	25	-
4. Griseofulvion	-	-	-	-	500

Table 3: Activity of standard drugs: MIC (□g/ml)

4. Conclusion

11-{4'-(3"-aryl)-2"-propene-1"-one]-phenoxy} dibenzo [b,f] thiazepines(3a-3j) and 11-{4'-[(5"-aryl)-4"-5"-dihydro-1"-(H)-pyrazol-3"-yl] phenoxy}-dibenzo [b,f] thiazepines (4a-4j) have been synthesized. The compounds 3b,3c,3d,3g,3i,3j,4a,4c,4d, 4e,4f,4g,4i,4j shows good antibacterial and antifugal activity with compared to known standard drugs.

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