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Synthesis and antimicrobial activity of 5-{4'-[(5"-aryl)-4", 5"-dihydro-1"-(H/acetyl/phenyl) pyrazole-3"-yl] phenyl carbamido}-dibenz [b.f] azepines

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ABSTRACT

5-{4'-[(5"-aryl)-4",5"-dihydro-1"-(H)-pyrazol 3"-yl] phenyl carbamido} -dibenz [b,f] azepines **(4a-4n)**; 5-{4'-[(5"-aryl)-4", 5"- dihydro-1"-acetyl pyrazole-3"-yl] phenyl carbamido}-dibenz [b,f] azepines **(5a-5n)**; 5-{4'-[(5"-aryl)-4",5"–dihydro-1"-phenyl pyrazole-3"-yl]-phenyl carbamido}- dibenz [b,f] azepines **(6a-6n)** have been synthesized. The products have been assayed for their antimicrobial activity against Gram +ve, Gram -ve bacteria and fungi. Antimicrobial activities of the products compare with known standard drugs. Viz ampicillin, chloramphenicol, norfloxacin and griseofulvin at same concentration 50 μg/ml. The stractures of the products have been elucidated by IR, ^{1}HNMR, Mass spectral data and elemental analysis.

KEYWORDS

Pyrazolines (Heterocyclic chemistry)

INTRODUCTION

Dibenz [b,f] azepines derivatives shows a wide ranging of therapeutic activities, such as analgesic[1], bactericidal[2], cardiovascular[3], bactericidal[4], fungicidal[5], etc. chalcones[6] have been synthesised by the condensation of 5-(4'-acetylphenyl carbamido) dibenz [b,f] azepine with aromatic aldehyde in presence of alkali.

Pyrazoles, acetyl pyrazoles and phenyl pyrazoles showed wide spectrum of biological activities such as analgesic[7] bactericidal[8], cardiovascular[9], antimicrobial[10], anticonvalsnt[11] etc 5-{4'-(5"-aryl)–4", 5" dihydro-1" (H) Pyrazol 3"-yl] Phenyl carbamido}-dibenz [b,f] azepines **(4a-4n)** have been synthesized by chemoselective cyclisation of 5-{4'-[(3"-aryl)-2"-propene-1"-one]-phenyl carbamido}-dibenz [b,f] azepines and hydrazine hydrate. The products 5-{4'-[(5"-aryl)-4",5" dihydro-1"-acetyl pyrazole-3"-yl] phenyl carbamido}-dibenz [b,f] azepines **(5a-5n)** have been synthesized by the condensation of 5-{4'-[(3"-aryl)-2"-propene-1"-one]-phenyl carbamido}-dibenz [b,f,] azepines with hydrazine hydrate in gla. CH_3COOH. The product 5-{4'-[(5"-aryl)-4", 5"-dihydro-1"-phenyl pyrazole-3"-yl]-phenyl carbamido}-dibenz [b,f] azepines **(6a-6n)** have been synthesized by the condesation of 5-{4'-[(3"-aryl)-2"-propene-1"-one]-phenyl carbamido}-dibenz [b,f] azepines with phenyl hydrazine.

Antimicrobial activity

5-{4'-[(5"-aryl}–4",5"-dihydro–1"(H) pyrazol 3"-yl] phenyl carbamido}-dibenz [b,f] azepines **(4a-4n)**; 5-{4'–[(5"-aryl)-4",5"-dhydro-1" acetyl pyrazole-3'-

yl] phenyl carbamido}-dibenz [b,f] azepines **(5a-5n)**; 5-{4'-[(5"-aryl)-4",5"-dihydro-1"-phenyl pyrazole-3"-yl]-phenyl carbamido} dibenz [b,f] azepines **(6a-6n)** have been synthesised and evalulated its antimicrobial activity against *B. megaterium, s.aureus, S. taphimarium-B, E.coli* and *A.niger* using DMF as solvent at 50 μg/ml. concentration by cup plate method[12] After 24 hrs of incubation at 37°C the zones of inhibition were measured in m.m. The activity was compared with the known antibiotics, viz chloramphenicol, ampicillin, norfloxacin, gresiofulvin at same concentration.

EXPERIMENTAL

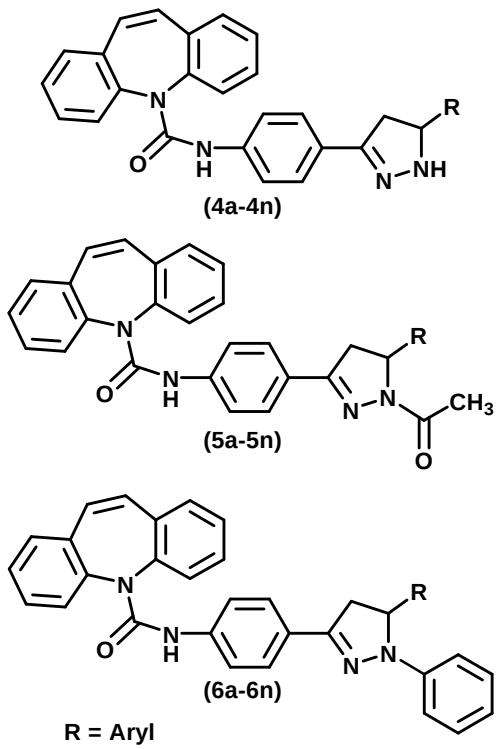
All the melting points were measured by open glass capillary method and are uncorrected. IR absorption spectra (in cm^{-1}) were recorded on a shimadzu IR 435 spectrophotometer using KBr pellet method and ^1H NMR spectra on Hitachi R-1200 (300 MHz) spectrometer using TMS as internal standard (Chemical shift in, δppm) and mass spectra on a Joel 300 ev. The purity of the compounds was routinely checked by TLC using silica gelG.

5-(4′-acetyl phenyl carbamido)-dibenz [b,f] azepine

A mixture of 5-dibenz [b,f] azepine methanoyl chloride (2.55gm, 0.01M),4-amino acetophenone (1.35gm, 0.01M), ethanol (25ml) and pyridine (5.0ml). The reaction mixture was refluxed on a oil bath at 120°C for 12hrs. The products was cooled, poured into crushed ice, filtered, dried and crystallized from ethanol; yield 82.42%, M.P 170°C (Found; C, 77.85; H, 5.02; N, 7.82, $C_{23}H_{18}N_2O_2$ required C, 77.96; H, 5.08; N, 7.90%) IR (KBr): 2958 (C-H str. asym); 2829 (C-H Str. Sym,); 1467, (C-H def. asym); 1388 (C-H def. sym); 3065 (C-H str. aromatic); 801 (C-H str., o.p.p def); 1488 (C=C str.); 1350 (C-N str.); 1691 (>C=O str.) ^1H NMR; 2.5 (3H, - $COCH_3$); (6-7.2) (14H Ar-H).

5-{4'[(3''-(4'''-methoxy phenyl))-2''-propene-1''-one]-phenyl carbamido}-dibenz [b,f,] azepine (3g)

A mixture of 5-(4'-acetyl phenyl carbamido) dibenz [b,f] azepine (3.54 gm, 0.01M) and 4-methoxy benazaldehyde (1.38gm, 0.01M) in ethanol (25ml) and



Scheme 1

aquous NaOH solution. The reaction mixture was stirring vigorously at 24hrs. The contents were poured into crushed ice, acidified filtered dried and crystallized from ethanol. yield; 92.01%, M.P, 105°C (Found; C, 78.80; H, 5.01; N, 5.91; $C_{31}H_{24}N_2O_3$ required C, 78.81; H, 5.08 N, 5.93%) IR (KBr): 2952 (C-H str., asym): 2815 (C-H str. sym.) 1462 (C-H def asym): 1380 (C-H def. Sym.): 3051 (C-H str. aromatic): 805 (C-H str. o.o.p def.): 1480 (C=C str.): 1351(C-N str.): 1592 (>C=O str.); 1501 (C=C str.); 1151 (C-O-C str.) ^1H NMR: 4.0 (S, 3H-OCH_3); 6-2 7.4 (m. 18H, Ar-H) m/z 472, 457,448, 441, 372, 363, 35, 310, 287, 252, 238, 219, 209, 204, 196, 180, 161, 109, 102.

Similarly others compounds **(3a-3n)** were synthesized the data of **(3a-3n)** were published in another journal.

5-{4'-[5''-(4'''-methoxy phenyl)–4'',5''-dihydro-1''-H pyrazole-3''-yl] phenyl carbamido}-dibenz [b,f] azepine (4g)

A mixture of 5-{4'-[3"-(4'"-methoxy phenyl)2"-propene-1"-one] phenyl carbamido}-dibenz [b,f] azepines (4.72g, 0.01M) hydrazine hydrate (1.0 ml) in methanol (15ml) was refluxed for 12hrs. The product was poured into crushed ice filtered, washed with wa-

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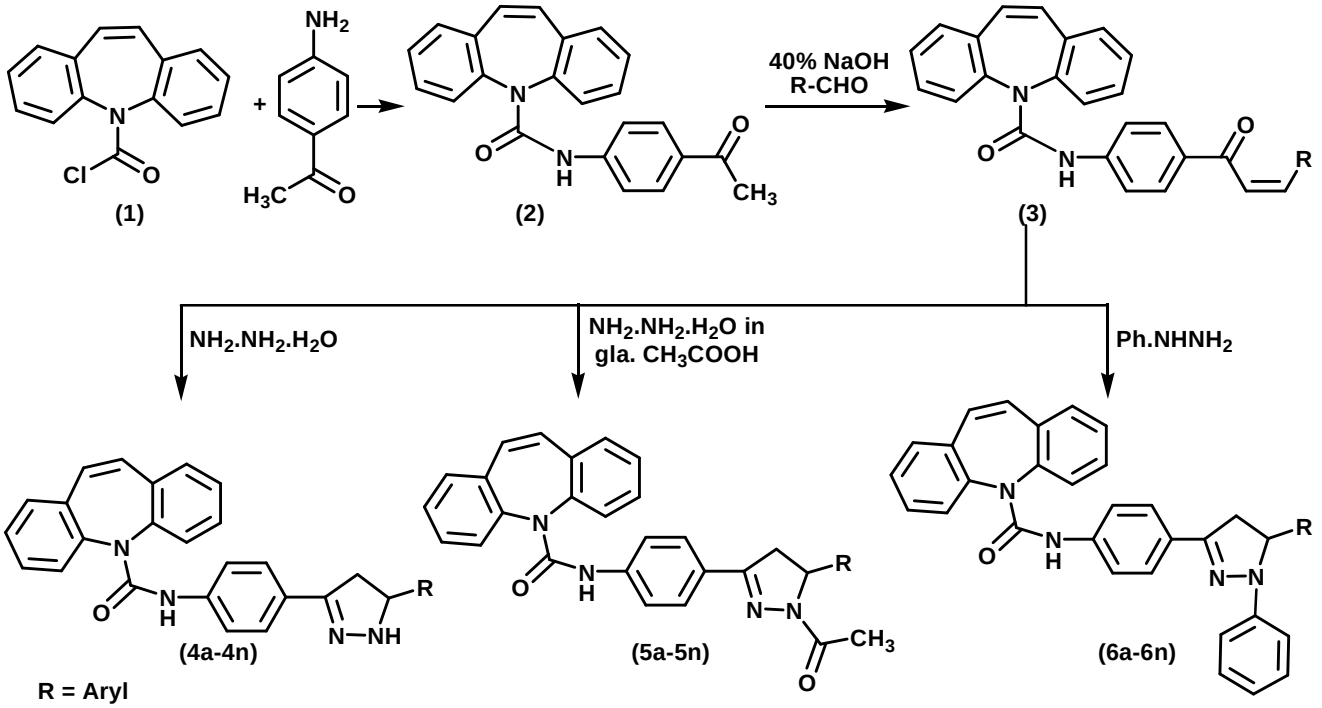

Scheme 2

ter and crystallized from dioxane yield: 69.43% M.P. 60°C (Found; C: 76.40; H: 5.23; N: 11.30: $C_{31}H_{26}N_4O_2$ required C: 76.54; H: 5.34; N 11.52 %) IR (KBr) 2962 (C-H str. sym), 1452: (C-H def. asym), 3010 (C-H str. aromatic); 1504 (C=C str.); 823 (C-H o.o.p. def.); 1697 (>C=O str.); 1232 (C-N str.); 3417 (N-H str.), 1139 1188 (C-O-C str.) ^{1}H NMR 3.8 - 3.9 (S, 3H; -O CH_3), 6.1-7.6 (m 19H, Ar-H) m/z 486, 471, 462, 455, 447, 432, 430, 386, 353, 311, 310, 286, 219, 209, 105, 91.

Similarly other compounds **(4a-4n)** were synthesized and their physical data are recorded in TABLE 1.

5-{4'- [5''-(4'''-methoxy phenyl)]-4',5''- dihydro-1''-acetyl pyrazole-3''-yl] phenyl carbamido}-dibenz [b,f] azepine (5g)

A mixture of 5-{4'-[5"-(4"-methoxy phenyl)]-2" propene-1"-one]-phenyl carbamido}-dibenz [b,f] azepines (4.72gm, 0.01M) hydrazine hydrate (1.0 ml) glacial acetic acid (2.0 ml) and methanol (20 ml) was refluxed for 12 hrs. The reaction mixture was poured into crushed ice, filtered, washed with water and crystallised from dioxane yield 78.69% M.P; 68°C. (Found, C, 74.85; H, 5.24; N, 10.48; $C_{33}H_{28}O_3N_4$ required; C, 75.30; H, 5.30; N, 10.60; %) IR (KBr) 2951; (C-H str. asym), 1566 (C-H str. def), 3040 (C-H- str. aromatic), 1626, 1591 (C=C str,), 823 (C-H o.p.p), 3396 (N-H str.), 1124 (C-O-C str.), 1718 (>C=O str.), 1626 (C=N str.), ^{1}H NMR: 3.8 - 3.9 (S 3H,-OCH_3) 6.2- 7.6 (m 19H, Ar-H) m/z 528, 513, 504, 428, 489, 474, 428, 381, 357, 354, 330, 310, 302, 286, 194, 105.

Similarly other compounds **(5a-5n)** were synthesised and their physical data are recorded in TABLE 1.

5-{4'-[5''-(4'''-methoxy phenyl)-4'', 5''-dihydro-1''-Phenyl pyrazole-3''-yl] phenyl carbamido}-dibenz [b,f] azepine (6g)

A mixture of 5-{4'-[5"-(4'"-methoxy phenyl)-2"-propane-1"-one] phenyl carbamido}-dibenz[b,f] azepines (4.72g, 0.01M), Phenyl hydrazine (1.0 ml) and methanol (20ml) was refluxed for 12 hrs. The reaction mixture is poured into crushed ice, filtered, washed with water and crystallized from dioxane: yield 78.62% M.P 70°C, (Found: C, 78.74; H, 5.20; N, 9.81; $C_{37}H_{30}O_2N_4$ required; C, 79.00; H, 5.33; N, 9.96 %) IR (KBr) 2953 (C-H str.), 1440 (C-H def.), 3030 (C-H str. aromatic), 1491, 1440 (C=C str.), 769 (C-H str. o.p.p.), 3458 (N-H str.), 1222 (C-O-C str.), 1718 (C=O str.), ^{1}H NMR 3.8- 3.9 (S, 3H,-OCH_3), 6.1-7.6 (m 19H, Ar-H). M/z 562, 547, 538, 532, 523,

TABLE 1 : Physical data and antimicrobial activity of (4n-4n), (5a-5n) and (6a-6n)

Comp[d]	R	mp. °C	Antimicrobial activity, zone of inhibition in m.m.				Antifungal activity zone of inhibition	% of nitrogen	
			B.Megaterium	*S.aures*	*S,taphimarium*	*E.coli*	*A.niger*	Calcd.	Found
1	$C_{15}H_{10}NOCl$	152	17	15	18	19	14	5.47	5.41
2	$C_{23}H_{18}N_2O_2$	170	15	18	14	16	18	7.90	7.82
3g	$C_{31}H_{24}N_2O_3$	105	18	19	21	17	21	5.93	5.91
4a	C_6H_5-	58	12	23	21	13	21	12.28	12.12
4b	2-OH.C_6H_4-	70	13	11	23	20	24	11.86	11.81
4c	3-OH.C_6H_4-	98	14	12	24	21	19	11.86	11.70
4d	4-OH.C_6H_4-	105	11	13	25	22	18	11.86	11.84
4e	3-OCH_3, 4-OH;C_6H_3-	110	12	14	26	22	18	11.15	11.01
4f	2-OCH_3.C_6H_4-	70	10	12	19	13	22	11.52	11.22
4g	4-OCH_3.C_6H_4-	60	10	10	18	14	13	11.52	11.30
4h	2-NO_2,.C_6H_4-	85	11	14	21	15	14	13.97	13.92
4i	3-NO_2.C_6H_4-	120	13	11	21	13	15	13.97	13.85
4j	2-CI.C_6H_4-	90	15	21	19	12	23	11.41	11.24
4k	4-N,N $(CH_3)_2$ C_6H_4-	60	16	22	13	22	12	14.02	13.98
4l	C_4H_3O(Furfural)-	50	18	11	12	13	23	12.55	12.40
4m	$C_{10}H_7$ (Napthyl)-	115	21	11	17	21	19	11.06	10.99
4n	$C_{14}H_9$ (Anthra)-	75	23	23	18	19	18	10.07	9.88
5a	C_6H_5-	70	12	13	20	20	21	11.31	11.25
5b	2-OH.C_6H_4-	70	11	12	23	21	11	10.89	10.70
5c	3-OH.C_6H_4-	90	12	14	21	19	12	10.89	10.72
5d	4-OH.C_6H_4-	98	14	21	22	19	15	10.89	10.75
5e	3-OCH_3, 4-OH;C_6H_3-	115	15	21	19	18	16	10.29	10.23
5f	2-OCH_3.C_6H_4-	70	16	24	17	17	11	10.06	10.45
5g	4-OCH_3.C_6H_4-	68	17	25	16	17	25	10.60	10.48
5h	2-NO_2,.C_6H_4-	110	13	11	17	18	13	12.89	12.70
5i	3-NO_2.C_6H_4-	105	11	12	19	20	21	12.89	12.70
5j	2-CI.C_6H_4-	75	13	11	17	21	25	10.52	10.45
5k	4-N,N $(CH_3)_2$ C_6H_4-	60	14	13	18	22	19	12.93	12.80
5l	C_4H_3O(Furfural)-	80	23	11	19	23	22	11.47	11.33
5m	$C_{10}H_7$ (Napthyl)-	122	10	23	12	19	19	10.21	10.11
5n	$C_{14}H_9$ (Anthra)-	75	10	21	22	10	22	9.36	9.18
6a	C_6H_5-	78	12	16	22	12	19	10.52	10.45
6b	2-OH.C_6H_4-	90	13	18	19	13	20	10.21	10.14
6c	3-OH.C_6H_4-	102	23	13	16	14	17	10.21	10.17
6d	4-OH.C_6H_4-	102	22	12	15	22	16	10.21	10.11
6e	3-OCH_3, 4-OH;C_6H_3-	78	11	11	14	15	21	9.68	9.58
6f	2-OCH_3.C_6H_4-	105	10	10	11	17	22	9.96	9.89
6g	4-OCH_3.C_6H_4-	70	12	22	12	19	12	9.96	9.91
6h	2-NO_2,.C_6H_4-	62	13	13	21	16	13	12.13	12.09
6i	3-NO_2.C_6H_4-	95	10	15	14	17	17	12.13	12.11
6j	2-CI.C_6H_4-	76	13	19	12	21	16	9.89	9.70
6k	4-N,N$(CH_3)_2C_6H_4$-	90	15	18	21	13	19	12.17	12.10
6l	C_4H_3O (Furfural)-	50	19	16	19	12	16	10.72	10.66
6m	$C_{10}H_7$ (Napthyl)-	60	18	10	17	11	18	9.61	9.50
6n	$C_{14}H_9$ (Anthra)-	90	16	11	15	16	11	8.86	8.81

TABLE 2 : Compounds showing comparable antimicrobial activity with known standard drugs

Compounds	*B. mega*	*S.aureus*	*S.taph.*	*E.coli*	*A. niger*
1	17	15	18	19	14
2	15	18	14	16	18
3	18	19	21	17	21
(4a – 4n)	4m,4n	4a, 4j, 4k	4b, 4d, 4e, 4i, 4h,	4c, 4d, 4e, 4k, 4m	4a, 4b, 4f, 4j,
(5a-5n)	5l	5d, 5e, 5f, 5g, 5m, 5n	5b, 5c, 5d, 5n	5b, 5j, 5k, 5l	5a, 5g, 5j, 5l, 5n
(6a-6n)	6c,6d	6g, 6j,	6a, 6h, 6k	6d, 6j	6e, 6f

508, 462, 458, 435, 354, 330, 326, 324, 310, 302, 286, 194, 105, 77.

Similarly other compounds **(6a-6n)** were synthesized and their physical data are recorded in TABLE 1.

CONCLUSION

5-{4'-[(5" aryl)-4",5"-dihydro-1"-(H) pyrazole 3"-yl] phenyl carbamido}-dibenz [b,f] azepines **(4a-4n)**; 5-{4'-[(5"-aryl)-4",5" dihydro-1"-acetyl pyrazole-3"-yl] phenyl carbamido}-dibenz [b,f] azepines **(5a-5n)**; 5-{4'-[(5"- aryl)-4",5"-dihydro-1"-Phenyl Pyrazole-3"-yl]-phenyl carbamido}-dibenz [b,f] azepines **(6a-6n)** have been synthesised, the compounds **(4m)**, **(5b)**, **(5n)**, **(6d)**, **(6j)** showed good comparable antibacterial and antifungal activity with compare with known standard drugs ampicillin, chloamphenicol, norfloxacin, and griseofulvin at same concentration 50 μg/ml.

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TABLE 3 : Activity of standard drugs

No.	Drugs 50 μg/ml	*B.megaterium*	*S.aureus*	*S.taphimarium*	*E.coli*	*A.nigar*
1	Ampicillin	22	18	19	27	-
2	Chloramphenicol	24	19	25	26	-
3	Norfloxacin	24	19	25	26	-
4	Griseoflulvin	-	-	-	-	23

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