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Synthesis and antimicrobial activity of 5-{4'-[(6''-aryl)-2''-hydroxyl-3'',4''-dihydro pyrimidine-4''-yl]-phenyl carbamido}/5-{4'-[(6''-aryl)-2''-mercapto-3'',4''-dihydropyrimidine-4''-yl] phenyl carbamido} dibenz [b,f] azepines

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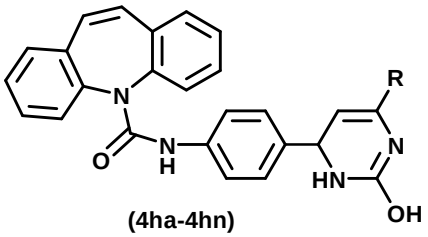
ABSTRACT

5-{4'-[(6"-Aryl)-2"-hydroxy-3",4"-dihydro pyrimidine 4"-yl] phenyl carbami-do} diben [b,f] azepines **(4ha-4hn)**; 5-{4'-[(6"-aryl)-2"-mercapto-3",4"-dihydropyrimidine-4"-yl] phenyl carbamido}-dibenz [b,f] azepines **(5ma-5mn)** have been synthesised. The products have been assayed for their antimicrobial activities. Some of the products showed moderate activity in comparison with known standard drugs. Viz ampicillin, chloramphenicol, norfloxacin and greseofulvin at same concentration 50 μg./ml. Constitution of the products have been characterized by IR, ^{1}HNMR, Mass spectral studies and elemental analyses.

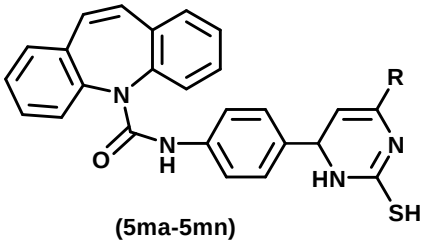
INTRODUCTION

Dibenz [b,f] azapines derivatives showed a wide range of therapeutic activities. i.e. antithyroid[1], herbicidal[2], anti-inflammatory[3], bactericidal[4], antifungal[5] etc. chalcones[6] have been synthesed by the condensation of 5-(4'-acetylphenyl carbamido)-dibenz [b,f] azepines with aromatic aldehyde in presence of aqueous alkali.

Hydroxy pyrimidines and thiopyrimidines have proven to be of great importance in exhibiting and enhancing the biological activities such as antitumor[7], antimalarial[8], anthelmintic[9], antiviral[10], antimicrobial[11] etc. Hydroxy pyrimidine and thiopyrimidine[12,13] have been synthesised by chemo selective cyclisation of 5-{4'-[(3"-aryl)-2"-propene-1"-one]-phenyl carbamido} -dibenz [b,f] azepines **(3a-3n)** with urea in presence of acidic medium to afforded 5-{4'-[(6"-aryl)-2"-hydroxy-3",4"-dihydro pyrimidine-4"-yl]-phenyl carbamido}-dibenz [b,f] azepines **(4ha-4hn)**. The products 5-{4'-[6"-(aryl)-2"- mercapt-3",4"-dihydro pyrimidine-4"-yl] phenyl carbamido}-dibenz [b,f]-azepines **(5ma-5mn)**



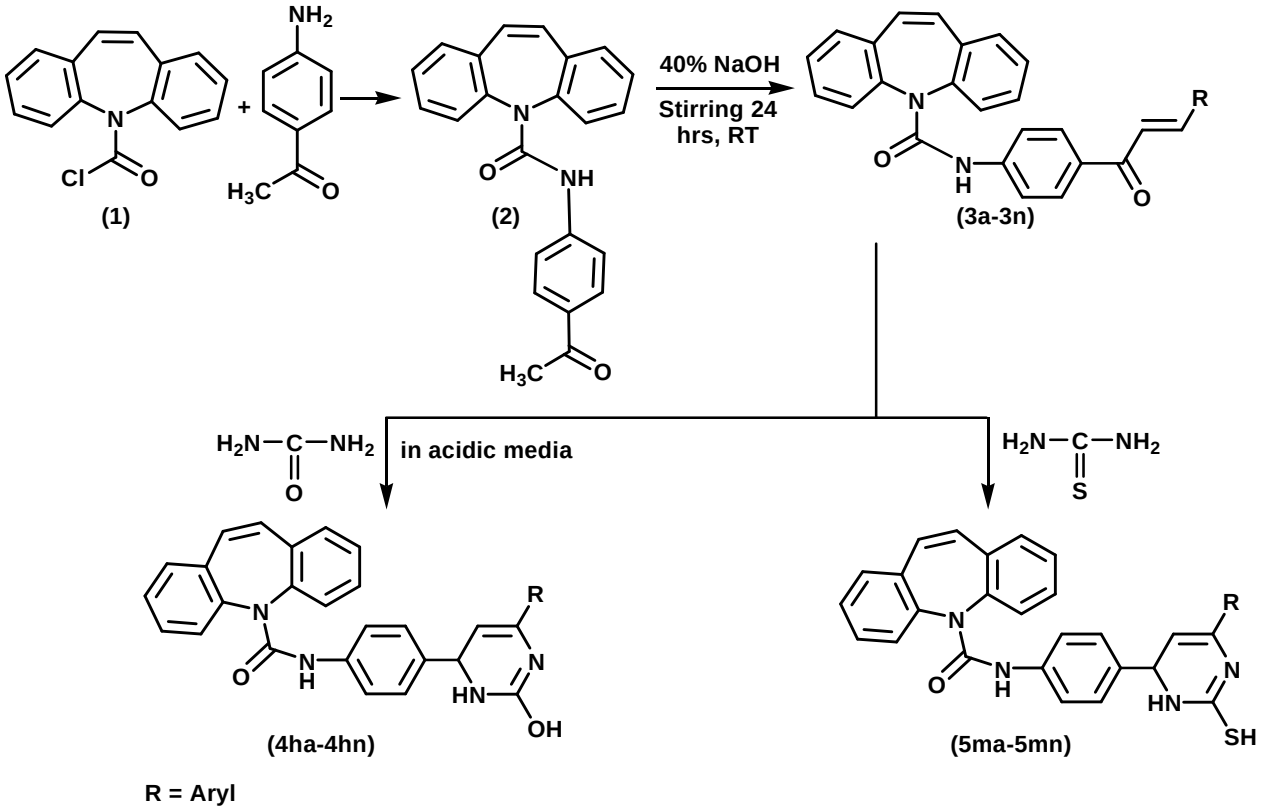
(4ha-4hn)



(5ma-5mn)

R = Aryl

Scheme 1



Scheme 2

have been synthesised by the condensation of 5-{4'-[(3"-aryl)-2"-propene-1"-one]-phenyl carbamido}-dibenz [b,f] azepines with thiourea in presence of alkali.

The products **(4ha-4hn)** and **(5ma-5mn)** were assigned the IR, ^{1}HNMR, mass spectral data, TLC and elemental analyses. The physical data and antimicrabial activities are represented in TABLE 1 and comparable antimicrobial activities are represented in TABLE 2.

Antimicrobial activity

5-{4'-[(6"-aryl)-2"-hydroxy-3",4"-dihydro pyrimidine-4"-yl]-phenyl carbamido} dibenz [b,f] azepines **(4ha-4hn)**; 5-{4'-[(6"-aryl) mercapto-3",4"-dihydro pyrimidine-4'-yl] phenyl carbamido} **(5ma-5mn)** were evalulated *in vitro* for antibacterial activity against *B. megaterium, B. aureus, S. taphimarium, E. coli and A. niger* using DMF as solvent at 50 μg./ml. concentration by cupplate method[14]. After 24hrs of incubation at 37°C, the zones of inhibition were measured in mm. The activity was compared with the known antibiotics, viz, chloramphenicol, ampicillin, norfloxacin, gresiofulvin at same concentration.

Antimicrobial of activity compounds **(4ha-4hn)**, **(4ma-4mn)** are represented in TABLE 1 and comparable antimicrobial activity represented in TABLE 2.

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,^{1}H NMR spectra on Hitachi R-1200 (300-mHz) spectrometer using DMSO-d6 method, as internal standard (chemical shift in, δppm) and mass spectra on a Joel 300 ev. The purity of the compounds were routinely checked by TLC using silica gel-G.

5-(4'-acetyl phenyl carbamido)-dibenz [b,f] azepine (2)

A mixture of 5-dibenz [b,f] azepine methanoyl chloride (2.55g, 0.01M), 4-amino acetophenone (1.35g, 0.01M) in ethanol (25ml) and pyridine (5.0ml) was refluxed on a oil bath at 120°C for 12hrs. The products

TABLE 1 : The physical data and antimicrobial activities of compounds (4ha-4hn) and (5ma-5mn). Zone of inhibition in m.m.

Comp[d]	R	m.p. °C	Antibacterial activity				Antifungaractivities	%of Nitogen	
			B.megaterium	*S. aureus*	*S.taphimarium*	*E. coli*	*A. niger*	Calcd	Found
4ha	C_6H_5 -	82	18	12	15	19	15	11.57	11.50
4hb	2 – OHC_6H_4 -	90	20	14	18	22	17	11.20	11.18
4hc	3 - OHC_6H_4 -	100	19	17	21	23	19	11.20	11.19
4hd	4 - OHC_6H_4 -	124	21	18	18	21	21	11.20	11.15
4he	3-OCH_3, 4-OHC_6H_3 -	130	16	19	14	17	14	10.56	10.51
4hf	2 - OCH_3, C_6H_4 -	95	17	16	15	16	15	10.89	10.81
4hg	4 - OCH_3, C_6H_4 -	112	18	15	17	18	17	10.89	10.80
4hh	2 - NO_2 C_6H_4 -	118	12	17	16	19	22	12.98	12.90
4hi	3 - NO_2 C_6H_4 -	110	14	19	19	21	20	12.98	12.92
4hj	2 – Cl C_6H_4 -	80	19	20	20	23	21	12.00	11.99
4hk	4 - N,N$(CH_3)_2$ C_6H_4 -	118	15	16	17	18	15	13.00	12.91
4hl	C_4H_3O (Furfuryl) -	85	17	14	14	17	18	11.81	11.79
4hm	$C_{10}H_7$ (Napthyl) -	105	20	13	18	19	17	10.48	10.42
4hn	$C_{14}H_9$ (Authryl) -	110	19	15	13	18	14	9.58	9.53
5ma	C_6H_5 -	70	15	12	14	19	14	11.02	11.00
5mb	2 – OH C_6H_4 -	96	18	13	12	15	15	10.85	10.78
5mc	3 – OH C_6H_4 -	108	20	15	13	14	18	10.85	10.79
5md	4 – OH C_6H_4 -	78	22	14	22	20	19	10.85	10.82
5me	3-OCH_3 4-OHC_6H_3 -	118	14	18	13	15	13	10.25	10.15
5mf	2 - OCH_3 C_6H_4 -	115	17	15	15	18	14	10.56	10.47
5mg	4 - OCH_3 C_6H_4 -	90	17	14	18	20	15	10.56	10.52
5mh	2 - NO_2 C_6H_4 -	90	18	15	15	21	20	12.84	12.81
5mi	3 - - NO_2 C_6H_4 -	122	21	19	19	23	21	12.84	12.83
5mj	2 – CI C_6H_4 -	75	22	20	21	23	23	11.87	11.84
5mk	4-N,N.$(CH_3)_2$ C_6H_4 -	150	16	14	15	15	18	12.89	12.82
5ml	C_4H_3O – Furfural -	62	15	11	14	18	17	11.42	11.39
5mm	$C_{10}H_7$ – Naphtnyl -	80	14	15	17	19	16	10.18	10.15
5mn	$C_{14}H_9$ – Anthryl -	120	18	13	15	17	18	9.33	9.32

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

Compounds	*B.megaterium*	*S. aureus*	*S.taphimarium*	*E. coli*	*A.niger*
(4ha-4hn)	4hb,4hd,4hm	4hd,4hc,4hi,4hj	4hc,4hi	4hb,4hc,4hd,4hi,4hj	4hd,4hh,4hi,4hj
(5ma-5mn)	5mc,5md,5mi,5mj	5me,5mi,5mj	5md,5mi,5mj	5mj,5mg,5mh,5mi,5mj	5md,5mh,5mi,5mj

was cooled; poured into crushed ice, filtered, dried and crystallized from ethanol; yield 85.42%, 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; o.p.p def.); 1488 (C=C str.); 1350 (C-N str.); 1691 (>C=O str.) ^{1}H NMR; 2.5 (S,3H,-$COCH_3$); (6-7.2) (m,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 (3.54g, 0.01M) and 4-methoxy benazaldehyde (1.36g, 0.01M) in ethanol 25 ml and 40% NaOH solution was stirring vigorously at 24hrs. The contents were poured into crushed ice, acidified, filtered, dried, and crystallized from ethanol. yield; 79.86%, M.P, 105°C (Found; C, 75.80; H, 5.01; N,

TABLE 3 : Activity of standard drugs

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

5.80; $C_{31}H_{24}N_2O_3$ required C, 75.86; 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.) ^{1}H NMR: 3.8 (S,3H, -OCH_3); 6.2-7.4 (m.18H,Ar-H). m/z: 472, 457, 448, 441, 372, 363, 310, 287, 252, 238, 219, 209, 204, 196, 180, 161, 109, 102.

Similarly others compounds **(3a-3n)** were synthesized, the data were published in our continuous publication.

5-{4'-[6''-(4'''-methoxyphenyl)-2''-hydroxy-3'',4''-dihydro pyrimidine-4''-yl]-phenyl carbamido}-dibenz[b,f] azepine (4hg)

A mixture of 5-{4'-[3"-(4'"-methoxyphenyl)-2"-propene-1"-one] phenyl carbamido}-dibenz [b,f] azepine (4.72gm, 0.01M) and urea (0.60gm, 0.01M) was refluxed at 90°C for 14hrs in presence of acid as a catalyst and in methanol. The reaction mixture was poured into crushed ice. The product was isolated crystallized from dioxane yield 78.49%. M.P. 112°C (Found: C, 74.65; H, 5.02; N, 10.80 %) M.F. $C_{32}H_{26}O_3N_4$ required C, 74.70; H, 5.05; N, 10.89 %, IR(KBr): 2962 (C-H str., sym.); 1446 (C-H str. Asym.); 1388 (C-H def. asym.); 3050 (C-H str., aromatic); 1490 (C=C str.); 756 (C-H.o.o.p def.); 3345 (N-H str.); 1691 (C=O str.); 1299 (C-N str.); 1606 (C=N str.) 1091 (C-O-C str.); 3000-3350 (-OH bend) ^{1}HNMR: (S, 3H, - OCH_3); 6.92-8.09 (m, 20, Ar-H); M/z: 514, 499, 490, 483, 460, 414, 408, 326, 311, 288.

Similarly other compounds **(4ha-4hn)** were prepared and their physical data are recorded in TABLE 1.

5-{4'-[6''-(4'''-methoxyphenyl)-2''-mercapto-3'',4''-dihydo pyrimidine-4''-yl] phenyl carbamido}-dibenz [b,f] azepines (5 mg)

A mixture of 5-{4'-[3"-(4'"-methoxyphenyl)-2"-propene 1"-one]-phenyl carbamido}-dibenz [b,f] azepine (4.72gm, 0.01M) and this urea (0.66gm, 0.01M) was refluxed at 90°C for 14 hrs in presence of basic medium like alcoholic KOH and methanol. The reaction mixture was poured into crushed ice filtered and dried. The product was isolated, crystallised from dioxane. Yield 68.71 %, M.P. 90°C (Found: C, 72.41; H, 4.89; N, 10.52) M.F. C_{32} $H_{25}N_4$ SO_2 required C, 72.45; H, 4.90; N, 10.56 %. IR (KBr): 2962 (C-H str., Sym.); 1433 (C-H str. asym.); 1380 (C-H def., asym.); 3090 (C-H str., aromatic); 1504 (C=C str. ring skeleton); 1659 (>C=O str.); 1233 (C-N str.); 1585 (C=N str.); 1161 (C-O-C str.); 2612 (C-S H str.). 1H, 4.90, N, 10.56 % ^{1}HNMR 3.8-3.9 (S, 3H, Ar-OCH_3); 7.02-8.09 (m, 20H, Ar-H). M/z: 530, 515, 516, 506, 476, 430, 412, 135, 176.

Similarly other compounds **(5ma-5mn)** were prepared and their physical data are recorded in TABLE 1.

CONCLUSION

5-{4'-[(6"-aryl)-2"-hydroxy-3",4"-dihydropyrimidine-4"-yl]–phenyl carbamido}-dibenz [b,f] azepines **(4ha-4hn)**; 5-{4'-[(6"-aryl)-2"-mercapto-3", 4"-dihydro pyridime-4"-yl] phenyl carbamido}-dibenze [b,f] azepines **(4ma-4mn)** have been synthesised. Some of the compounds **(4hb)**, **(4bc)**, **(4hi)**, **(4hj)**, **(5md)**, **(5mi)**, **(5mj)** showed good comparable antibacterial and antifungal activity with compare with known standard drugs. ampicillin, chloramphenicol, norfloxacin and griseofulvin at same concentration 50 µg./ml.

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