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Synthesis and antimicrobial activity of 2-amino/2(1H) one/2(1H) thione-4-{4'-[(4'''-chlorophenyl) (phenyl) methyl amino] - phenyl}-6-aryl pyrimidines

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ABSTRACT

2-Amino-4-{4'-[(4'''-chlorophenyl) (phenyl) methyl amino]-phenyl}-6-aryl pyrimidine (5a-5l)/4-{4'-[(4'''-chlorophenyl) (phenyl)methylamino]-phenyl}-6-aryl pyrimidin-2(1H)-one (6a-6l) /4-{4'-[(4'''-chlorophenyl) (phenyl) methyl amino] - phenyl}-6-aryl pyrimidine -2(1H)-thione (7a-7l) have been synthesized. The products have been assayed for their biological activity against Gram +ve, Gram -ve bacteria and fungi. Some of the compounds showed moderate activity in concentration 50 µg/ml.

KEYWORDS

Pyrimidines

INTRODUCTION

Pyrimidine derivatives shows wide range of biological activities e.g. Antiallergic[1], fungicidal[2], antidiabetic[3], anticancer[4], anti-HIV[5], anti-inflammatory[6], antitumor[7], antineoplastic[8], analgesic[9], bactericidal[10], herbicidal[11], cardiovascular[12], diuretic[13], antiamoebic[14] etc. In view of getting we have synthesized pyrimidine derivatives. The compounds of **(5a-5l)**, **(6a-6l)** and **(7a-7l)** have been synthesized and characterised with IR, ^{1}HNMR, Mass spectral data, and elemental analysis. The physical data and antimicrobial actitivities are represented in TABLE 1

ANTIMICRIBIAL ACTIVITY

2-Amino-4-{4'-[(4'''-chlorophenyl) (phenyl) methyl amino]-phenyl}-6-aryl pyrimidine (5a-5l)/4-{4'-[(4'''-chlorophenyl) (phenyl)methylamino]-phenyl}-6-aryl pyrimidine-2(1H)-one (6a-6l) /4-{4'-[(4'''-chlorophenyl) (phenyl) methyl amino] - phenyl}-6-aryl pyrimidine -2(1H)-thione (7a-7l) products were evaluated in vitro for their antimicrobial activities against *Bacillus Megatarium, Staphylococcus aureus, Escherichia coli, Salmonella typhy, and Aspergillus niger* using DMF as solvent at 50 µg / ml. concentration by cup plate method[15]. After 24 hrs of incubation at 37°C, the zones of inhibition were measured in mm. The activity was compared with the known antibiotic, viz, Ampicillin, Chloramphenicol, Norfloxacin, and Gresiofulvin at same concentration.

All the synthesized compounds **(5a-5l)**, **(6a-6l)** and **(7a-7l)** showed moderate to good and remarkable activities with known standard drugs at same concentration. The physical data and antimicrobial activities are represented in TABLE 1.

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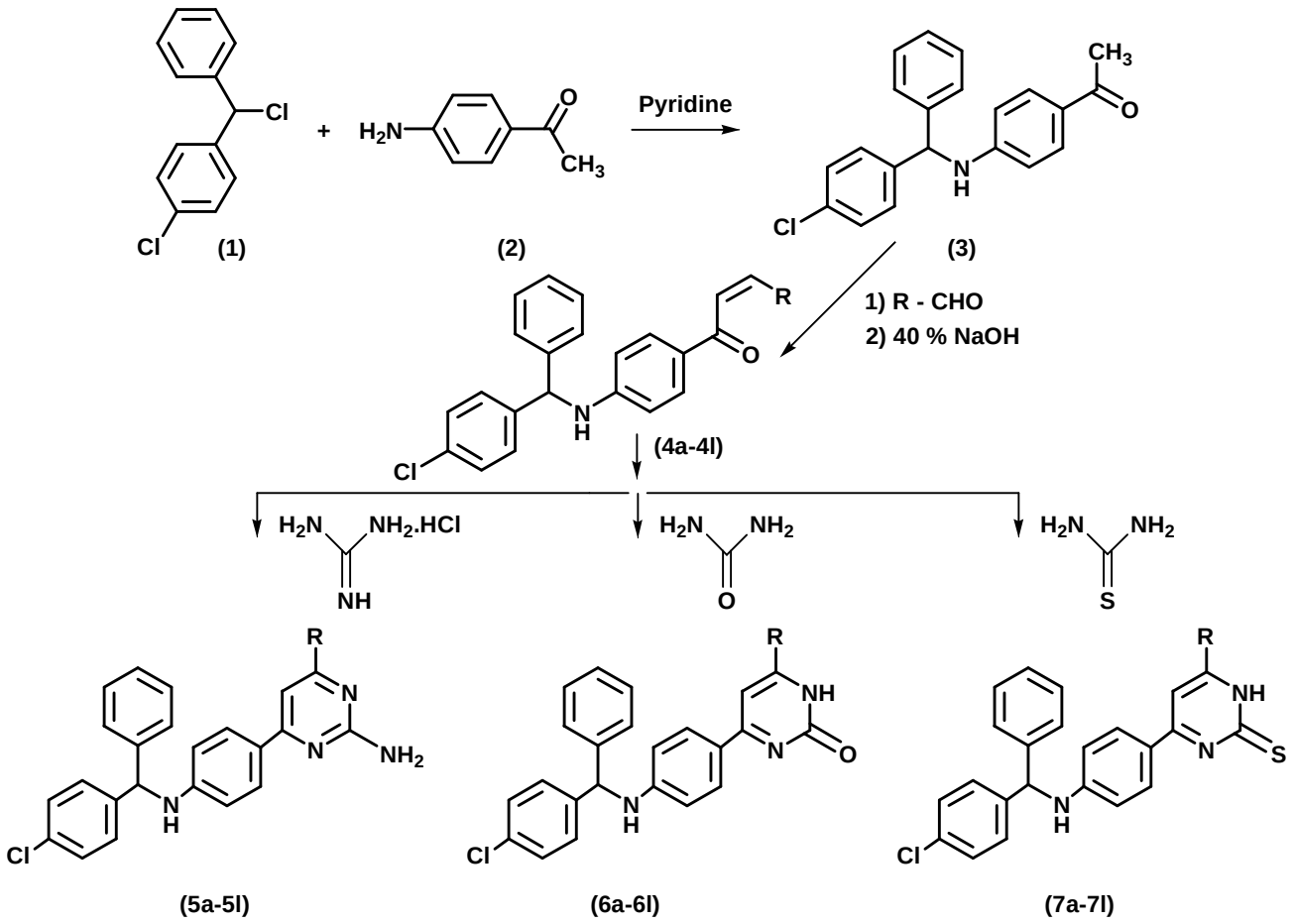

R = Aryl

Reaction scheme

EXPERIMENTAL

All the melting points were measured in open glass capillary method and are uncorrected. I.R. absorption spectra (in cm^{-1}) were recorded on a shimadzu FT-IR 8400-spectrophotometer using KBr pallet method and ^1H NMR spectra on BRUKER spectrometer (300 MHz) using TMS as internal standard (chemical shifts in δ ppm) and compounds were routinely checked by TLC using silica gel G.

4'-[(4'''-Chlorophenyl) (phenyl)-methyl-amino] phenyl ethanone (3)

A mixture of (4'-Chlorophenyl) (phenyl)-methyl) chloride in methanol (2.37 gm, 0.01 M) and p-amino acetophenone (1.47 gm, 1.2 M) and methanol (20ml). The reaction mixture refluxed in the presence of basic catalyst pyridine (2 ml) for 8 hrs. The completion of the reaction is checked by TLC. The reaction mixtured poured into ice cold water filter it and wash with water and dry it. The yield is 65 %, m.p.134 °C.

4'-[(4'''-Chlorophenyl) (phenyl) methyl amino] phenyl-3-(4''''-aryl) prop-2-ene-1- one (4h)

A mixture of 4'-[(4'''-Chlorophenyl) (phenyl)-methyl-amino] phenyl-1-yl} -ethanone (3.35 gm, 0.01 M)4-methoxy benzaldehyde (1.36 gm, 0.01 M) and methanol (25 ml). Stirr the content at room temperature for 24 hr. in presence of catalytically amount of 40% NaOH. The resulting solution was poured on to crush ice, thus the solid separated was filtrated and crystallized from ethanol.

Yield 52 %, m. p.102° C. ($C_{29}H_{24}ClNO_2$). Required C,76.73; H,5.33; N,3.09 found C,76.71; H,5.31; N,3.07%.

Similarly other compounds (4a-4l) have been synthesed. The physical data and antimicrobial activity published in other journal.

2-Amino-4-{4'-[(4'''-chlorophenyl) (phenyl) methyl amino] - phenyl}-6-(4''''-methoxy phenyl) pyrimidine (5h)

A mixture of 4'-[(4'''-Chlorophenyl)(phenyl) methylamino]phenyl-1'-yl-3-(4''-methoxy phenyl)-2-propene-1-one (4.53 gm, 0.01 M) and guanidine hydrochloride (1.10gm, 0.01 M) in methanol (20 ml) was refluxed on water bath in presence of alcoholic KOH for 8 hr. The excess solvent was distilled out and the residue was neutralized with 20 % HCl, the solid was filtered out and crystallized from ethanol. Yield 62 %, m.p. 134°C Anal. Calcd. for $C_{30}H_{25}ClN_4O$ Requires: C,73.09; H, 5.11; N,11.37 Found: C,73.07; H, 5.10; N, 11.32%.

IR (KBr); 2969 (C-H str. asym); 2909 (C-H str. sym); 1372 (C-H def.sym); 3052 (C-H aromatic); 1485(C=C str. aromatic); 3244 (N-H Str.), 760 (C-Cl str.). 1648 (C=N Str.), 1186 (C-N Str.), 1176 (C-O-C Str.), 3250&3335 (NH_2 Str.). ^{1}HNMR (DMF); 2.95(1H,s,N-H),3.37(2H,s,Ar-NH_2).3.85(3H,s,Ar-OCH_3); 5.60-5.61(1H,d,C-H);7.16-7.17(2H,d,C-H); 7.27-7.28 (2H,d,Ar-H);7.36-7.79 (14H,m,Ar-H);7.71 (1H,s,N-H). m/z: 51, 63, 78, 96, 111, 138, 164, 192, 200, 221, 262, 266, 301, 310, 373, 390, 392, 426,

TABLE 1 : The physical data and antimicrobial activity of compounds (5a-5l), (6a-6l) and (7a-7l)

Comp.	R	Molecular Formula	M.P. °C	Antibacterial activity				Antifungal activity	% of Nitrogen	
				B.Mega	*S.aureus*	*E.Coli*	*S.typhi*	*A.niger*	Calcd.	Found.
5a	C_6H_5-	$C_{29}H_{23}ClN_4$	189	17	15	14	14	14	12.10	12.08
5b	4-Cl-C_6H_4-	$C_{29}H_{22}Cl_2N_4$	106	14	11	16	12	17	11.26	11.24
5c	4-F-C_6H_4-	$C_{29}H_{22}ClFN_4$	205	11	12	9	8	17	11.65	11.61
5d	4-Br-C_6H_4-	$C_{29}H_{22}BrClN_4$	171	21	16	13	11	17	10.34	10.32
5e	2-OH-C_6H_4-	$C_{29}H_{23}ClN_4O$	109	13	14	15	12	14	11.70	11.67
5f	3- OH-C_6H_4-	$C_{29}H_{23}ClN_4O$	211	11	14	12	10	13	11.70	11.66
5g	4-OH-C_6H_4-	$C_{29}H_{23}ClN_4O$	162	16	16	16	12	17	11.70	11.67
5h	4-OCH_3-C_6H_4-	$C_{30}H_{25}ClN_4O$	134	11	14	17	13	16	11.37	11.32
5i	3-OCH_3-4-OH-C_6H_4-	$C_{30}H_{25}ClN_4O_2$	142	11	10	12	16	10	11.01	11.00
5j	4-N-$(CH_3)_2$-C_6H_3-	$C_{31}H_{28}ClN_5$	269	13	11	17	14	21	13.84	13.80
5k	$C_{10}H_7$-(Naphthayl)	$C_{33}H_{25}ClN_4$	232	15	13	14	12	16	10.92	10.90
5l	$C_{14}H_9$-(Anthranyl)	$C_{37}H_{27}ClN_4$	183	11	14	17	11	15	9.95	9.91
6a	C_6H_5-	$C_{29}H_{22}ClN_3O$	101	14	13	17	12	18	9.06	9.04
6b	4-Cl-C_6H_4-	$C_{29}H_{21}Cl_2N_3O$	202	16	11	15	13	16	8.43	8.40
6c	4-F-C_6H_4-	$C_{29}H_{21}ClFN_3O$	167	10	16	16	17	18	8.72	8.70
6d	4-Br-C_6H_4-	$C_{29}H_{21}BrClN_3O$	145	11	12	20	11	10	7.74	7.72
6e	2-OH-C_6H_4-	$C_{29}H_{22}ClN_3O_2$	165	13	10	15	15	17	8.76	8.74
6f	3- OH-C_6H_4-	$C_{29}H_{22}ClN_3O_2$	148	18	11	15	10	10	8.76	8.75
6g	4-OH-C_6H_4-	$C_{29}H_{22}ClN_3O_2$	210	16	13	10	13	15	8.76	8.73
6h	4-OCH_3-C_6H_4-	$C_{30}H_{24}ClN_3O_2$	189	21	14	13	11	17	8.51	8.50
6i	3-OCH_3-4-OH-C_6H_4-	$C_{30}H_{24}ClN_3O_3$	194	17	12	12	14	20	8.24	8.23
6j	4-N-$(CH_3)_2$-C_6H_3-	$C_{31}H_{27}ClN_4O$	155	14	10	15	12	10	11.03	11.00
6k	$C_{10}H_7$-(Naphthayl)	$C_{33}H_{24}ClN_3O$	134	15	17	17	10	10	8.17	8.14
6l	$C_{14}H_9$-(Anthranyl)	$C_{37}H_{26}ClN_3O$	225	17	15	15	16	19	7.45	7.41
7a	C_6H_5-	$C_{29}H_{22}ClN_3S$	204	11	13	8	14	20	8.76	8.74
7b	4-Cl-C_6H_4-	$C_{29}H_{21}Cl_2N_3S$	212	9	12	16	11	11	8.17	8.15
7c	4-F-C_6H_4-	$C_{29}H_{21}ClFN_3S$	106	11	11	11	13	23	8.44	8.41
7d	4-Br-C_6H_4-	$C_{29}H_{21}BrClN_3S$	126	10	16	10	10	12	7.52	7.50
7e	2-OH-C_6H_4-	$C_{29}H_{22}ClN_3OS$	166	12	14	14	9	13	8.47	8.44
7f	3- OH-C_6H_4-	$C_{29}H_{22}ClN_3OS$	152	15	14	15	14	18	8.47	8.43

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Comp.	R	Molecular Formula	M.P. °C	Antibacterial activity				Antifungal activity	% of Nitrogen	
				B.Mega	*S.aureus*	*E.Coli*	*S.typhi*	*A.niger*	Calcd.	Found.
7g	4-OH-C_6H_4-	$C_{29}H_{22}ClN_3OS$	184	11	13	17	13	14	8.47	8.45
7h	4-OCH_3-C_6H_4-	$C_{30}H_{24}ClN_3OS$	193	13	12	12	16	15	8.24	8.23
7i	3-OCH_3-4-OH-C_6H_4-	$C_{30}H_{24}ClN_3O_2S$	228	16	11	15	13	19	7.99	7.95
7j	4-N-$(CH_3)_2$-C_6H_3-	$C_{31}H_{27}ClN_4S$	216	12	15	13	10	17	10.71	10.67
7k	$C_{10}H_7$- (Naphthayl)	$C_{33}H_{24}ClN_3S$	201	13	17	15	14	16	7.93	7.90
7l	$C_{14}H_9$-(Anthranyl)	$C_{37}H_{26}ClN_3S$	209	14	14	11	13	21	7.24	7.20

Zone of inhibition in mm

TABLE 2 : Comparable antimicrobial activity with known standard drug

Compounds (50 µg/ml)	*B.mega*	*S. aureus*	*E.Coli*	*S. typhi*	*A.niger*
Ampicillin	21	19	19	21	-
Chloramphanicol	24	20	25	23	-
Norfloxacin	25	20	25	24	-
Greseofulvin	-	-	-	-	25
Maximum antimicrobial activity					
(5a-5l)	5a, 5d, 5g, 5k	5a, 5d, 5g	5h, 5j, 5k	5a, 5i, 5j	5b, 5c, 5d, 5g, 5j
(6a-6l)	6f, 6h, 6i, 6l	6c, 6h, 6k, 6l	6a, 6d, 6k	6c, 6e, 6l	6a, 6c, 6i, 6l
(7a-7l)	7f, 7i, 7l	7d, 7e, 7f, 7j, 7k	7b, 7f, 7g, 7k	7a, 7f, 7h, 7k	7a, 7c, 7i, 7l

447, 449, 462, 478.

Similarly other compounds **(5a-5l)** have been synthesized. The physical data and antimicrobial activity are repesented in TABLE 1

4-{4'-[(4'''-chlorophenyl) (phenyl) methyl amino]-phenyl}-6- (4''''-methoxy phenyl) pyrimidin-2(1H)-one (6h)

A mixture of 4'-[(4'''-Chlorophenyl)(phenyl) methylamino] phenyl -3-(4''''-methoxy phenyl) prop-2-ene-1-one (4.53 gm, 0.01 M) and urea (1.0gm, 0.01 M) in methanol (20 ml). The reaction mixture was refluxed in water bath in presence of alcoholic KOH for 10 hr. The excess of solvent was distilled out and the residue was neutralized with 20 % HCl. The separated solid was filtered out and crystallized from ethanol. Yield 54%, m.p. 189°C Anal. Calcd. for $C_{30}H_{24}ClN_3O_2$, Requires: C, 72.94; H, 4.90; N,8.51 Found: C, 72.94; H, 4.90; N,8.50 %.

IR (KBr); 2958 (C-H str. asym); 2875 (C-H str. sym); 1366 (C-H def. sym); 3079 (C-H aromatic); 1512(C=C str. aromatic); 3398 (N-H Str.), 758 (C-Cl str.). 1575 (C=N Str.), 1205 (C-N Str.), 1651 (C=O Str.); 1239(C-O-C Str.). ^{1}HNMR (DMF); 3.25(1H,s,-NH);3.83(3H,s,Ar-OCH_3);5.60-5.61 (1H,d,C-H); 6.62-8.35(20H,m, Ar-H); 8.57(1H,s,N-H). m/z: 51, 63, 78, 132, 152, 159, 170, 195, 202, 219, 229, 263, 277, 292, 294, 318, 335, 347, 365, 388, 404, 408, 427, 444, 464, 477, 479.

Similarly other compounds **(6a-6l)** have been synthesized. The physical data and antimicrobial activity are represented in TABLE 1

4-{4'-[(4'''-Chlorophenyl) (phenyl)methylamino] -phenyl}-6-(4''''-methoxy phenyl) pyrimidin-2(1H)-thione (7h)

A mixture of 4'-[(4'''-Chlorophenyl)(phenyl) methylamino]phenyl-3-(4''''-methoxy phenyl)-2-propene-1-one (4.53 gm, 0.01 M) and thiourea (0.78 gm, 0.01 M) in methanol (20 ml). The reaction mixture was refluxed in water bath in presence of alcoholic KOH for 10 hr. The excess of solvent was distilled out and the residue was neutralized with 20 % HCl, the separated solid was filtered out and crystallized from ethanol. Yield 57 %, m.p. 193°C Anal. Calcd. for $C_{30}H_{24}ClN_3OS$ Requires: C, 70.64; H, 4.74; N, 8.24 Found: C, 70.62; H, 4.72; N, 8.23 %.

IR (KBr); 2922 (C-H str. asym); 2854 (C-H str. sym); 1380 (C-H def. sym); 3060 (C-H aromatic); 1509 (C=C str. aromatic); 3244 (N-H Str.), 760 (C-Cl str.). 1168 (C=N Str.), 1205 (C-N Str.), 1574 (C=S Str.); 1246(C-O-C Str.). ^{1}HNMR (DMF);

3.85(3H,s,Ar-OCH_3); 4.01(1H,s,-NH);5.60-5.61 (1H,d,C-H); 7.00-7.03(19H,m, Ar-H); 7.12(1H,s,N-H). m/z: 107, 120, 137, 154, 165, 185, 204, 221, 233, 245, 273, 289, 307, 322, 367, 391, 414, 429, 439, 452, 502, 517.

Similarly other compounds **(7a-7l)** have been synthesized. The physical data and antimicrobial activity are represented in TABLE 1

SUMMARY

2-Amino-4-{4'-[(4'''-chlorophenyl) (phenyl) methyl amino]-phenyl}-6-aryl pyrimidine (5a-5l)/4-{4'-[(4'''-chlorophenyl) (phenyl)methylamino]-phenyl}-6-aryl pyrimidine-2(1H)-one (6a-6l) /4-{4'-[(4'''-chlorophenyl) (phenyl) methyl amino] - phenyl}-6-aryl pyrimidine -2(1H)-thione (7a-7l) have been synthesized.

Compounds containing **(5a)**, **(5d)**, **(5g)**, **(5k)**, **(6c)**, **(6i)**, **(6k)**, **(6l)** and **(7a)**, **(7f)**, **(7j)**, **(7k)** shows more comparable antimicrobial activity compare to other compounds. Antimicrobial activity compared with known standard drugs.

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