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Synthesis and antimicrobial activity of 2-{4'-[(6"-ARYL)2"-HYDROXY-3",4"-DIHYDRO-PYRIMIDINE-4"-YL]-PHENYL AMINO}-6-[BIS (2'"-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE

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ABSTRACT

The titled compounds (5a-5k) have been synthesized by the condensation of 2-{4'-[(3"-aryl)-2"-Propene-1"-one]-Phenyl amino}-6-[bis-2""-chloroethyl) amino]-4-methoxy-1,3,5-triazine with urea in presence of conc. HCl (0.3ml) The biological activities of these compounds have been examined against various Gram +ve, Gram –ve bacteria and fungi. The structure of the products was confirmed by IR, ^{1}H NMR, Mass spectra and elemental analysis.

1. INTRODUCTION

Pyrimidine nucleus possess broad spectrum of pharmacological activities which are reflected by their use as analgesic[1], anticonvulsant[2], antimicrobial[3-4], antipyratics[5], antiinflammatory[6], antitumor[7], antineoplastic[8], antimalarial[9], antithyroid[10], anthelmintic[11], Anti-HIV[12-13], antiviral[14], antagonists[15-17] etc. With a view to getting of synthesis pyrimidine derivatives.

2. ANTIMICROBIAL ACTIVITY

Hydroxy pyrimidines (5a-5k) were evaluated in vitro for antimicrobial activity against *B. Mega, B. Subtillis, E. Coli, P. Fluoresences* and for antifungal activity against *A. awamori* using DMF as solvent at 50 µg concentration by cup-plate method[18]. After 24 hrs. of incubation at 37 ^{0}C temp., the zone or inhibition were measured in mm. The activity was compared with the known antibiotics e.g. Ampicillin, chloramphenicol, Norfloaxacin, Griseofulvin at same concentration which is represented in Table-I and comparable anti microbial activity represented in Table no. II

3. MATERIAL AND METHODS

All the melting points were taken in open glass capillaries and are uncorrected. IR absorption spectra were recorded on a Shimadzu-FT-IR 8400 Spectrophotometer using KBr pellet and ^{1} H NMR spectra on a Bruker DPX-200 spectrometer (300 MHz) using DMSO as solvent and TMS as internal standard. Purity of the products was routinely checked by TLC.

Synthesis of 2–(4'–Acetyl phenyl amino)–4,6–dichloro–1,3,5-triazine (1):

A mixture of 2,4,6–trichloro–S–triazine (1.845 gm, 0.01 M), 4-amino acetophenone (1.35 gm, 0.01 M) in acetone (25 ml) and aq. NaOH solution till solution basic. The reaction mixture was stirring at 0 $^{\circ}$C temp. for 5 hrs. The content was poured into crushed ice, filtered and washed with water. The isolated product was crystallized from dioxane. yield : 82%, m.p. 112 $^{\circ}$C. (Found : C, 46.61 , H, 2.79, N, 19.75, $C_{11}H_8N_4OCl_2$ required C, 46.64, H, 2.82, N, 19.79%). IR : (cm^{-1}) : 2952 (C–H str., asym.), 2870 (C–H Str., Sym), 1420 (C–H def.), 3056 (C–H str., aromatic), 1509 (C=C str.), 1118 (C–N str.), 1620 (N–H bend), 768 (C–Cl Str.), 1700 (C=O str.) ^{1} H NMR : (δ ppm) :

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3.10–3.20 (s, 3H, Ar–$COCH_3$); 6.50–6.63 (m, 4H, Ar–H), 9.95 (s, 1H, N–H). Mass : (m/z) 77, 103, 139, 145, 172, 198, 221, 240, 259, 283. TLC : Hexane : Acetone (6:3), R_f = 0.56

Synthesis of 2–(4'–Acetyl phenyl amino)–6–chloro–4–methoxy–1,3,5–triazine (2):

A mixture of 2–(4'–acetyl phenyl amino)–4,6–dichloro–1,3,5–triazine (2.83 gm, 0.01 M); sodium methoxide (0.56 gm, 0.01 M) in methanol. The reaction mixture was stirring at room temp. for 7 hrs. The content was poured into crushed ice, filtered and wash with water. The isolated product was crystallized from dioxane. yield : 86%, m. p. 178^{0}C. (Found C, 51.65 H, 3.91, N, 20.09, $C_{12}H_{11}N_4O_2Cl$ required C, 51.70, H, 3.94, N, 20.10%) IR : (cm^{-1}) : 2950 (C–H str. asym), 2871 (C–H Str. Sym.) 1421 (C–H def.), 3051 (C–H str. aromatic), 1510 (C=C str.) 1120 (C–N Str.), 1618 (–NH Str.), 1244 (C–O–C Str.), 761 (C–Cl str), 1702 (C=O str.) ^{1}H NMR : (δ ppm) : 3.10–3.20 (s, 3H, Ar–$COCH_3$), 3.62–3.86 (s, 3H, Ar–OCH_3), 7.10–7.03 (d.d. 4H Ar H), 9.95 (s, 1H, N–H). Mass : (m/z) 77, 103, 136, 145, 174, 202, 221, 240, 264, 278. TLC : Hexane : Acetone (5:5), R_f = 0.63

Synthesis of 2–(4'–Acetyl phenyl amino)–6–[bis (2''–chloroethyl) amino]–4–methoxy–1,3,5 triazine. (3):

A mixture of 2–(4'–acetyl phenyl amino)–6–chloro–4–methoxy–1,3,5–triazine (2.78 gm, 0.01 M), 2,2'–di chloro diethyl amine hydrochloride (1.43 gm, 0.01 M); dioxane (25 ml) and aq. NaOH. The reaction mixture was refluxed at 110 °C temp. for 6 hrs. The content was cooled and poured into crushed ice, Filtered and washed with water. The isolated product was crystallized from dioxane. yield 79%, m. p. 249 °C. (Found : C, 49.88, H, 4.91, N, 18.19, $C_{16}H_{19}N_5O_2Cl_2$ required C, 50.00, H, 4.94, N, 18.22%) IR : (cm^{-1}) : 2921 (C–H str., asym), 2850 (C–H str., sym.), 1431 (C–H def.), 3062 (C–H str. aromatic), 1166 (C–H i.p. def.), 842 (C–H, o.o.p. def.), 1511 (C=C Str.) 1121 (C–N str.), 3342 (N–H Str.) 1242 (C–O–C Str.), 1702 (C=O str.) ^{1}H NMR : (δ ppm) : 3.10–3.22 (s, 3H, Ar–$COCH_3$), 3.62–3.86 (s, 3H, –OCH_3), 7.01–7.03 (d.d. 4H, (Ar-H), 4.79–4.80 (t, 4H, –CH_2–Cl), 9.95 (s, 1H, –NH), Mass : (m/z) 77, 103, 145, 172, 210, 228, 265, 282, 302, 326, 355, 370, 384. TLC : Hexane : Methanol (4:6), R_f = 0.73

Synthesis of 2–{4'–[3''–(4'''–Methoxy phenyl)–2''–propene–1''–one]phenyl amino}–6–[bis(2'''–chloro ethyl amino] –4–methoxy–1,3,5–triazine. (4e):

A mixture or 2–(4'–acetyl phenyl amino)–6–[bis(2''–chloro ethyl) amino]–4–methoxy– 1,3,5–triazine((3.84 gm, 0.01 M), 4–methoxy benzaldehyde (1.36 gm, 0.01 M), methanol (25 ml). and 40% aq. NaOH solution till becomes basic medium. The reaction mixture was stirring 24 hrs. at room temp. The contents were poured into crushed ice, acidified, filtered and crystalized from dioxane. yield 79%, m. p. : 198 °C. (Found C, 57.31, H, 4.90, N, 13.91, $C_{24}H_{25}O_3N_5Cl_2$ required C, 57.37, H, 4.98, N, 13.94%) IR: (cm^{-1}) : 2923 (C–H str., asym.), 2852 (C–H str., sym), 1436 (C–H str., asym), 1371 (C–H str., Sym.) 3097 (C–H str., aromatic) 1276 (C–H i.p. def.), 821 (C–H, o.o.p. def.), 1677 (C=O str.), 1118 (C–N Str.), 3311 (N–H str.) 3045 (C=C str.), 1245 (C–O–C Str.), 768 (C–Cl str.) ^{1}H NMR (δ ppm) : 3.62–3.86 (s, 6H, Ar-OCH_3), 7.01–7.03 (d.d. 4H, Ar–H), 8.08–8.72 (d.d. 4H, Ar– H), 4.79–4.80 (t, 4H, CH_2–Cl), 2.50–2.51 (t, 4H, -NCH_2), 9.95 (s, 1H, –NH), 4.80–4.83 (s, 2H, CH=CH) Mass : (m/z) 112, 130, 156, 212, 262, 271, 280, 285, 325, 335, 371, 428, 461, 502. TLC : Hexane : Acetone (3:7), R_f = 0.69

Similarly other chalcones (4a – 4k) where prepared and their physical data and antimicrobial activities data published in onther journal.

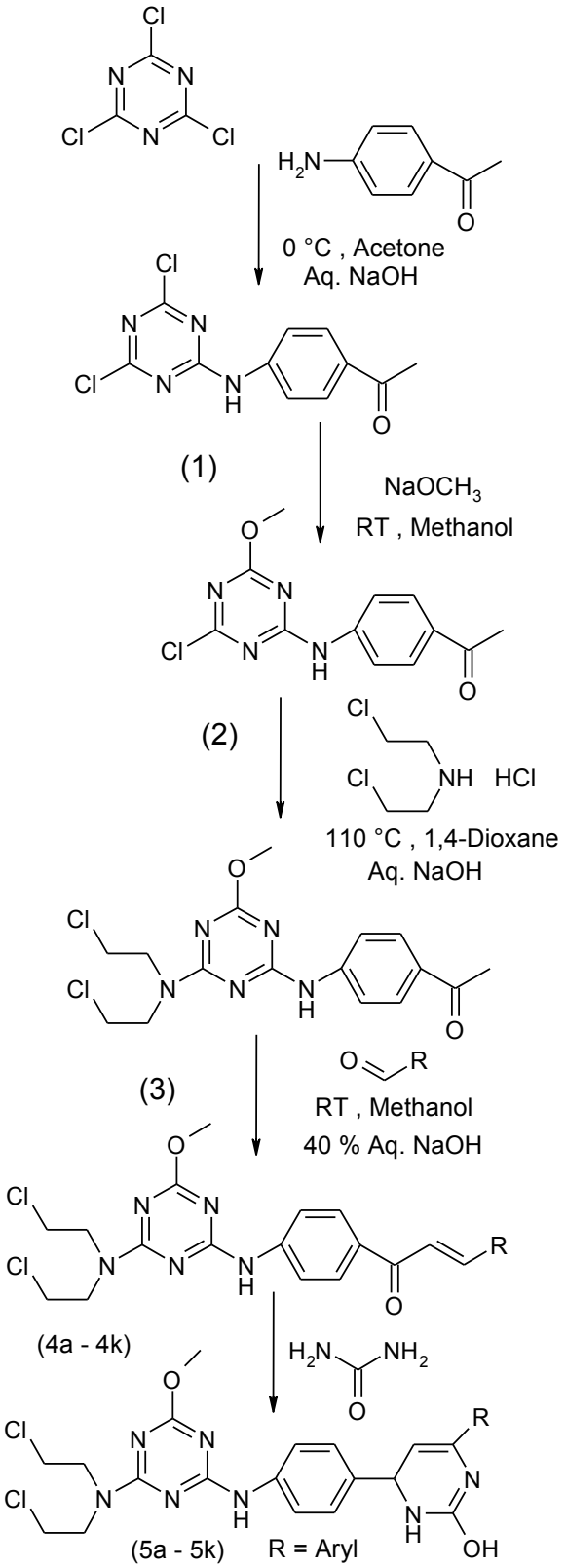
Synthesis of 2–{4'–[6''–(4'''–Methoxy phenyl)–2''–hydroxy-3'',4''-dihydro-pyrimidine-4''-yl]-phenylamino}–6–[bis(2'''–chloroethyl)–amino]–4–methoxy–1,3,5-–triazine (5e) :

A mixture of 2-{4'-[3"-(4'''-methoxy Phenyl) – 2" – Propene – 1"-one] Phenyl amino}-6-[bis (2'''-chloro ethyl) amino]-4-methoxy – 1,3,-5 – triazine (5.02 gm, 0.01 M) and urea (0.60 g, 0.01 M)

was refluxed at 90º C. for 12 hrs. in presence of conc. HCl (0.3 ml) in methanol the reaction mixture was poured into crushed ice, filtered and dried the product was isolated, crystallised from dioxane. Yield : 78%. m.p. 110º C. (Found : C : 55.11; H : 4.95; N : 17.99; $C_{25}H_{27}O_3N_7Cl_2$ required C : 55.14; H : 4.96; N : 18.01%). IR : (cm^{-1}) : 2925 (C–H str. asym), 2876 (C–H str. sym.) 1460 (C–H def. asym), 1355 (C–H def. sym.), 3081 (C–H str. aromatic) 1180 (C–H i. p. def.), 806 (C–H o.o.p. def.), 1473 (C=C str), 1141 (C–N str.), 1589 (C=N str.), 3407 (N–H str.) 1247 (C–O– C str. asym.), 1068 (C–O– C str. sym.), 767 (C–Cl str.), 3350 (N–H str.), 1116 (C–N str.), 1616 (C=N str.). ^{1}H NMR (δ ppm) : 3.50 – 3.69 (s, 6H, Ar–OCH_3), 7.49-7.90 (d.d., 4H, Ar-H), 7.92-9.27 (d.d. 4H, Ar–H), 4.62-4.65 (t, 4H, -CH_2–Cl), 2.32-2.92 (t, 4H, -NCH_2), 9.69 (s, 2H, Ar–NH), 9.78 (s, 2H, Ar-NH_2). Mass : (m/z) 143, 141, 151, 157, 188, 247, 279, 337, 347, 388, 424, 452, 543. TLC : Hexane : Acetone (3:7), R_f = 0.74

Similarly other (5a – 5k) have been synthesized and their physical data represented in Table no. I.

REACTION SCHEME:



4. RESULTS AND DISCUSSION

Table-I

The physical data and antimicrobial activity of compounds (5a -5k)

Compd	R	Mol. Formula	M.P. ^{0}C	Yield (%)	N(%)		Antibacterial activity				Antifungal Activity
					Calc.	(Found)	*B. Mega*	*B. Subtillis*	*E. Coli.*	*P. Fluoroscens*	*A. awamori*
5a	C_6H_5 -	$C_{24}H_{25}C_{12}N_7O_2$	180	81	19.06	(19.03)	20	12	18	15	19
5b	2-OH C_6H_4 -	$C_{24}H_{25}Cl_2N_7O_3$	228	79	18.48	(18.41)	23	14	17	19	20
5c	3-OH C_6H_4 -	$C_{24}H_{25}Cl_2N_7O_3$	262	83	18.48	(18.43)	21	18	19	23	19
5d	4-OH C_6H_4 -	$C_{24}H_{25}Cl_2N_7O_3$	280	85	18.48	(18.47)	24	19	22	23	22
5e	4-OCH3 C_6H_4 -	$C_{25}H_{27}Cl_2N_7O_3$	110	78	18.01	(17.99)	19	18	16	20	18
5f	4-OH, 3-OCH_3 C_6H_4 -	$C_{25}H_{27}Cl_2N_7O_4$	192	76	17.49	(17.43)	17	16	15	18	17
5g	4-Br, C_6H_4 -	$C_{24}H_{24}BrCl_2N_7O_2$	224	79	16.53	(16.51)	22	15	17	22	19
5h	3-NO_2 C_6H_4 -	$C_{24}H_{24}Cl_2N_8O_4$	265	81	20.03	(20.01)	18	17	20	21	21
5i	4-NO_2 C_6H_4 -	$C_{24}H_{24}Cl_2N_8O_4$	249	84	20.03	(20.02)	23	19	16	24	20
5j	4-N,N$(CH_3)_2$,C_6H_4 -	$C_{26}H_{30}Cl_2N_8O_2$	213	79	20.10	(20.08)	19	20	17	16	16
5k	C_4H_3O (Furfuryl) -	$C_{22}H_{23}Cl_2N_7O_3$	211	83	19.44	(19.41)	17	16	14	21	18

* Zone of inhibition in mm.

Table-II

Antimicrobial activity compared with known standard drugs.

	Compd	*B. Mega*	*B. Subtillis*	*E. Coil*	*P. Fluorescens*	*A. awamori*
	5a-5k	5b, 5d, 5i	5d, 5i, 5j	5c, 5d, 5h	5c, 5d, 5i	5b, 5d, 5h
1	Ampicillin (50 µg)	23	19	19	23	-
2	Chloramphenicol (50 µg)	24	19	22	23	-
3	Norfloxacin (50 µg)	23	20	20	24	-
4	Griseofulvin (50 µg)	-	-	-	-	22

5. CONCLUSION

The titled compounds (5a – 5k) have been synthesisid and evaluated in vitro their antimicrobial screening. The compounds 5b, 5c, 5d, 5i, 5h, showed moderated comparable antibacterial and antifungal activity then other synthesized compounds which are compare with known standard drugs e.g. Ampicillin , Chloramphenicol, Norfloxacin, Griseofulvin at same concentration (50 µg/ml)

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