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

P. J. Kathiriya, H. D. Purohit, D. M. Purohit*

Shree M. & N. Virani Science College, Kalawad Road, Rajkot-5 Gujarat, India

*E-mail address: purohitdm@yahoo.com

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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 malono nitrile in the presence of sodium methoxide. The biological activities of these compounds have been determined against various Gram +ve, Gram –ve bacteria and fungi. The constitutions of the products are supported by IR, ^{1}H NMR, Mass spectra and elemental analysis.

1. INTRODUCTION

Methoxy pyridines derivative possess broad spectrum of pharmacological activities which are reflected by their use as analgesic[1], anticonvulsant[2], antimicrobial[3], antipyratics[4], antiinflammatory[5], antitumor[6], antineoplastic[7] etc. In view of getting potent therapeutic agents to synthesized titles compounds.

2-{4'-[(4"-aryl)-3"-cyano-2"-methoxy-pyridine-6"-yl]-phenyl amino}-6-[Bis(2"'-chloro ethyl) amino]-4-methoxy-1,3,5-triazine 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 malono nitrile in the presence of sodium methoxide.

2–{4'–[(3"–aryl)–2"–propene–1"–one phenyl amino}–6–[(Bis(2"'–chloro ethyl)amino]–4–methoxy–1,3,5–triazine (4a – 4k) have been synthesized by the reaction of 2–(4'–acetyl phenyl amino)–6–[Bis (2"–chloro ethyl)amino]–4–methoxy–1,3,5–triazine (3) with aromatic aldehyde in the present of aq. NaOH solution.

2–(4'–acetyl phenyl amino)–6–[Bis(2"–chloro ethyl)amino]–4–methoxy–1,3,5–triazine (3) have been synthesized by the condensation of 2–(4'–acetyl phenyl amino)–6–chloro–4– methoxy–1,3,5–triazine (2) with 2,2'–dichlorodiethyl amine hydrochloride in the presence of aq. NaOH and dioxane at 110 °C temp.

2–(4'–Acetyl phenyl amino)–6–chloro–4–methoxy–1,3,5–triazine (2) have been synthesized by the reaction of 2–(4'–acetyl phenyl amino)–4,6–dichloro–1,3,5–triazine (1) with sodium methoxide in methanol at room temp.

2–(4'–Acetyl phenyl amino)–4,6–dichloro–1,3,5–triazine (1) have been synthesized by the condensation of 2,4,6–trichloro–S–triazine with 4–amino acetophenone in aq. NaOH and acetone at 0 °C temp.

2. MATERIALS AND METHODS

2.1. Antimicrobial activity :

Methoxy pyridines (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[8]. 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 viz. Ampicillin chloramphenicol, Norfloaxacin, Greseofulvin at same concentration which is represented in Table-I and comparable anti microbial activity represented in Table no. II.

3. METHOD SECTION :

All the melting points were taken in open glass capillaries and are uncorrected. IR absorption spectra were recorded on a Shimadzu-FT-IR 8400 spectro-photometer 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 compounds were routinely checked by TLC using silica get G.

4. EXPERIMENTAL AND SPECTRAL SECTION :

(A) **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 °C temp. for 5 hrs. The content was poured into crushed ice, filltered and washed with water. The isolated product was crystallized from dioxane yield : 82%, MP. 112 °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 : 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.) NMR : 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.

(B) **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, filltered 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 : 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.) NMR : 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 Hb, Hc), 9.95 (s, 1H, N–Hf) Mass : (m/z) 77, 103, 136, 145, 174, 202, 221, 240, 264, 278.

(C) **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–metholy–1,3,5–triazine (2.78 gm, 0.01 m), 2,2'–di chloro diethyl amine hydrochloride (1.43 gm, 0.01m); dioxane (25 ml) and aq. NaOH. The reaction mixture was refulx at 110 °C temp. for 6 hrs. The content was cooled and poured into crushed ice, Filltered 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 : 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.p. def.), 1511 (C=C Str.) 1121 (C–N str.), 3342 (N–H Str.) 1242 (C–O–C Str.), 1702 (C=O str.) NMR : 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.

(D) **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, filltered 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 : 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.) NMR : 3.62–3.86 (s, 6H, Ar-OCH_3), 7.01–7.03 (D. D. 4H, Ar–Hb), 8.08–8.72 (D. D. 4H, Ar– Hc), 4.79–4.80 (t, 4H, CH_2–Cl), 2.50–2.51 (t, 4H, -NCH_2), 9.95 (s, 1H, –NHf), 4.80–4.83 (s, 2H, CH=CHg) Mass : (m/z) 112, 130, 156, 212, 262, 271, 280, 285, 325, 335, 371, 428, 461, 502.

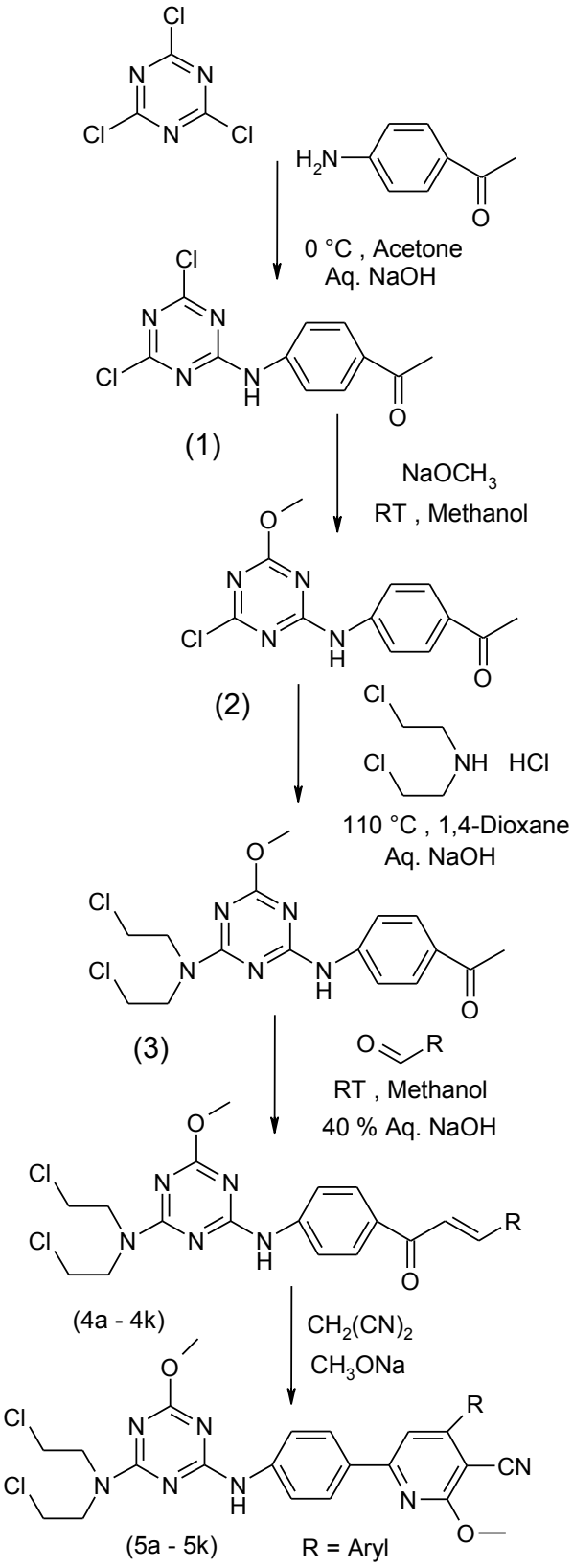
Similarly other chalcones (4a – 4k) where prepared and their physical data and antimicrobial activities data published in other journal.

(E) **2–{4'– [4"– (4""–Methoxyphenyl) –3"–cyano–2"–methoxy) –pyridine–6"–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, 0.01M); methanol (25 ml) malono nitrile (0.66 gm, 0.01 M); sodium methoxide, (0.44 g., 0.01M). The reaction mixture was refluxed 10 hrs. at 170º C. in dioxane. The product was poured into crushed ice, filtered and dried, crystallised from dioxane, yield : 78%, M.P. : 188º C. (Found : C : 5780; H : 4.69; N : 16.81; $C_{28}H_{27}O_3N_7Cl_2$ required C : 57.83; H : 4.71 ; N : 16.89%). IR : 2910 (C–H str. asym), 2876 (C–H str. sym.) 1458 (C–H def. asym), 1363 (C–H def. sym.), 3024 (C–H str. aromatic) 1298 (C–H i. p. def.), 837 (C–H o.o.p. def.), 1458 (C=C str), 1215 (C–N str.), 1593 (C=N str.), 3413 (N–H str.), 1635 (N–H ben.), 1244 (C–O– C str. asym.), 1045 (C–O– C str. sym.), 792 (C–Cl str.), 2216 (C=N str.), 1581 (C–N str.). NMR : 3.76-3.96 (s, 6H, Ar–OCH_3), 7.41-7.84 (DD, 4H, Ar-H_b), 7.93-8.24 (D.D. 4H, Ar–H_C), 4.00-4.96 (t, 4H, -CH_2–Cl), 2.63-3.23 (t, 4H, -NCH_2), 10.09 (s, 1H, Ar–NH), 7.97 (s, 2H, Ar-NH_2). Mass : (m/z) 143, 141, 151, 157, 188, 247, 279, 337, 347, 388, 424, 452, 580.

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

REACTION SCHEME :



RESULTS AND DISCUSSION :

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

Table-I

Compd	R	Mol. Formula	M.P. °C	Yield (%)	N(%)		Antibacterial activity				Antifungal Activity
					Calc.	(Found)	*B. Mega*	*B. Subtilis*	*E. Coli.*	*P. Fluoroscens*	*A. awamori*
5a	C_6H_5	$C_{27}H_{25}Cl_2N_7O_2$	201	64	17.81	17.80	13	12	14	16	17
5b	2-OH C_6H_4	$C_{27}H_{25}Cl_2N_7O_3$	212	68	17.31	17.30	14	13	16	19	19
5c	3-OH C_6H_4	$C_{27}H_{25}Cl_2N_7O_3$	179	72	17.31	17.29	17	14	18	20	23
5d	4-OH C_6H_4	$C_{27}H_{25}Cl_2N_7O_3$	153	75	17.31	17.27	18	17	18	21	21
5e	4-OCH3 C_6H_4	$C_{28}H_{27}Cl_2N_7O_3$	188	78	16.89	16.81	15	13	16	17	18
5f	4-OH, 3-OCH_3 C_6H_4	$C_{28}H_{27}Cl_2N_7O_4$	176	80	16.44	16.42	20	14	14	15	15
5g	4-Br, C_6H_4	$C_{27}H_{24}BrCl_2N_7O_2$	205	85	15.58	15.53	16	19	21	22	16
5h	3-NO_2 C_6H_4	$C_{27}H_{24}Cl_2N_8O_4$	164	79	18.82	18.81	17	18	18	18	17
5i	4-NO_2 C_6H_4	$C_{27}H_{24}Cl_2N_8O_4$	179	78	18.82	18.80	19	20	20	20	20
5j	4-N,N$(CH_3)_2$ C_6H_4	$C_{29}H_{30}Cl_2N_8O_2$	171	81	18.88	18.83	15	18	16	17	14
5k	C_4H_3O (Furfuryl)	$C_{25}H_{23}Cl_2N_7O_3$	119	85	18.14	18.09	19	17	17	19	18

* Zone of inhibition in mm.

Table-II
Comparable antimicrobial acivity.

	Compd	*B. Mega*	*B. Subtillis*	*E. Coli*	*P. Fluorescens*	*A. awamori*
	5a-5k	5f, 5i, 5k	5g, 5h, 5i	5c, 5g, 5i	5d, 5g, 5i	5c, 5d, 5i
1	Ampicillin (50 µg)	23	18	17	27	-
2	Chloramphenicol (50 µg)	24	19	25	26	-
3	Norfloxacin (50 µg)	24	19	25	26	-
4	Greseofulvin (50 µg)	-	-	-	-	23

5. CONCLUSION

The compounds 5c, 5d, 5g, 5i showed moderate antimicrobial activity then other synthesized compounds, compare with known standard drugs.

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