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Synthesis and antimicrobial activity of (2- methoxy/ 2-amino)-6-{4'-[(4'''-chlorophenyl) (phenyl) methyl amino] phenyl}-4-aryl nicotinonitrile

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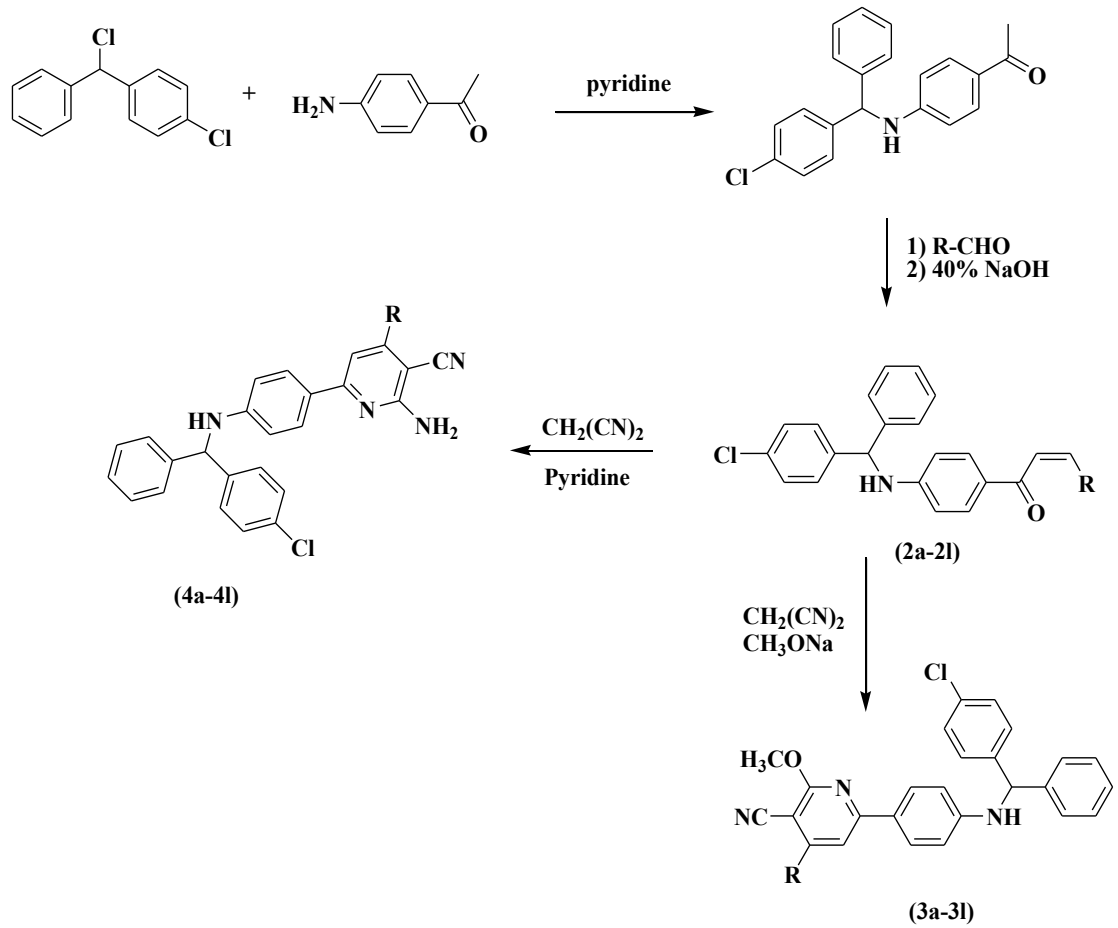
ABSTRACT

2- Methoxy – 6 - {4' - [(4'''- Chlorophenyl) (phenyl) methyl amino] phenyl} - 4 - aryl nicotinonitrile (**3a-3l**) and 2-Amino-6-{4'-[(4'''-Chlorophenyl)(phenyl)methyl amino]phenyl}-4-aryl nicotinonitrile (**4a-4l**) have been synthesized. The products have been assayed for their antimicrobial activity against Gram +ve, Gram -ve bacteria and fungi. The structure of the products has been elucidated by IR, ^{1}H-NMR, mass spectral data, elemental analysis and thin layer chromatography.

1. INTRODUCTION

2-Methoxy-3-cyanopyridine and 2-amino-3-cyanopyridine derivatives showed wide range of biological activities like, antiallergic[1], fungicidal[2], antidiabetic[3], anticancer[4], anti-HIV[5], antiinflammatory[6], antitumor[7], antineoplastic[8], analgesic[9], bactericidal[10], herbicidal[11], cardiovascular[12], diuretic[13], antiamoebic[14] etc. The products of methoxy cyanopyridines (**3a-3l**) and amino cyanopyridines (**4a-4l**) have been synthesized and assigned with IR, ^{1}H-NMR, mass spectral data and elemental analysis. The physical data and antimicrobial activities are represents in Table I.

Reaction Scheme



2. ANTIMICROBIAL ACTIVITY

2 - Methoxy – 6 - {4'- [(4'"- Chlorophenyl) (phenyl) methyl amino] phenyl}- 4 - aryl nicotinonitrile (**3a-3l**) and 2 – Amino – 6 - {4' - [(4'"- Chlorophenyl) (phenyl) methyl amino] phenyl}-4-aryl nicotinonitrile (**4a-4l**) products were evaluated in vitro for their antibacterial activities against *Bacillus Megatarium , Staphylococcus aureus, Escherichia coli ,Salmonella typhy* and antifungal activity against *Aspergillus nige*r using DMF as solvent at 50 µg / ml. 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 (**3a-3l**) and (**4a-4l**) showed moderate to good and remarkable activities compare with known standard drugs at same concentration. The physical data and antimicrobial activities are represented in Table-I. Comparable antimicrobial activities of synthesized compounds (**3a-3l**) and (**4a-4l**) are represented in Table-II.

3. EXPERIMENTAL

All the melting points were measured in open glass capillary method and are uncorrected. IR absorption spectra (in cm^{-1}) were recorded on a shimadzu FT-IR 8400-spectrophotometer using KBr pallet method and ^{1}H-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.

(A) 4'-[(4'"-Chlorophenyl) (phenyl)-methyl amino phenyl-1-yl] ethanone (1)

A mixture of (4'-chlorophenyl) (phenyl)-methyl chloride in methanol (2.37 gm, 0.01 mole) and 4-amino acetophenone (1.47 gm, 1.2 mole) is heated in the presence of basic catalyst as

pyridine (2 ml) for 8 hrs. The completion of the reaction is checked by TLC and poured the reaction mixture in ice cold water filter it and wash with water, dry and recrystallized from methanol yield 65 %; m.p.134 ^{o}C.

(B) 4'-[(4'''-Chlorophenyl) (phenyl) methyl amino] phenyl-3-(4''''-Methoxyphenyl) prop-2-en-1 one (2h)

A mixture of 4'-[(4'''-Chlorophenyl) (phenyl)-methyl-4-methoxy-amino]-phenyl-1-yl - ethanone (3.35 gm, 0.01 mole) 4-methoxy benzaldehyde (1.36 gm, 0.01 mole) and methanol (25 ml). Stirred the content at room temperature for 24 hrs in presence of catalytic amount of 40% NaOH. The resulting solution was poured on to crushed ice. The solid was separated out filtrated and crystallized from ethanol yield 52%, m.p.102ºC. Ana. calcd. for $C_{29}H_{24}ClNO_2$; Requires C:76.73; M, 5.33 N:3.09%, Found C, 76.71; H, 5.3l, N:3.07%.

Similarly, other chalcones (**2a-2l**) have been Synthesized. Its physical data, elemental analysis, antimicrobial activity published in another journal from our continuous publication.

(C) 2-Methoxy-6- {4'-[(4'''-chlorophenyl) (phenyl) methyl amino] phenyl} - 4-(4''''-methoxy phenyl) nicotinonitrile (3h)

A mixture of 4-{[4'''-(Chlorophenyl) (phenyl) methyl] amino-phenyl}-3-(4''''-methoxyphenyl)-prop-2-en-1-one (4.53 gm, 0.01 mole), malononitrile (0.67 gm, 0.01 mole) in methanol (10 ml) and sodium methoxide. The content was heated under reflux with stirring for 12 hrs. The reaction mixture was cooled and poured on to crushed ice; the separated solid was filtered out and crystallized from ethanol. Yield 55%, m .p. 238^{o}C. Ana. cald. for $C_{33}H_{26}ClN_3O_2$; Requires C, 74.50; H, 4.93; N, 7.90%; Found: C, 74.45, H, 4.92; N, 7.88%. IR-(KBr, cm^{-1}); 2928 (C-H str.; asym); 2872 (C-H str.; sym); 1390 (C-H def.; sym.); 3055 (C-H aromatic); 1492(C=C str. aromatic); 3287 (N-H Str.); 819 (C-Cl str.); 1618 (C=N Str.); 1170 (C-N Str.); 1176 (C-O-C Str.); 2166 (CN Str.). ^{1}H-NMR (DMSO-d6, δ ppm); 3.60 (3H, s, Ar-OCH_3); 5.02-5.07 (1H, dd, C-H); 7.03 (1H, s, C-H); 7.26-7.60 (11H, m, Ar-H); 7.60-7.68 (2H, d, Ar-H); 7.87-7.95 (4H, d, Ar-H); 8.20 (1H, s, N-H). m/z: 109, 123, 149, 163, 197, 215, 263, 279, 289, 305, 323, 413, 429, 461, 503, 532.

Similarly, other compounds (**3a-3l**) have been synthesized. The physical data are recorded in Table No.I.

(D) 2-Amino-6- {4'-[(4'''-chlorophenyl) (phenyl) methyl amino] phenyl} - 4-(4''''-methoxy phenyl) nicotinonitrile (4l) :

A mixture of 4'-{[4'''-(Chlorophenyl) (phenyl) methyl] amino phenyl}-3-(4''''-methoxyphenyl) prop-2-en-1-one (4.53 gm, 0.01 mole), malononitrile (0.67 gm, 0.01 mole) ammonium acetate and methanol (25ml) were heated under reflux with stirring for 12 hr. The reaction mixture was cooled and poured into crushed ice; the separated solid was filtered out and crystallized from ethanol. Yield 60%; m.p. 177^{o}C. Ana. calcd. for $C_{32}H_{25}ClN_4O$; Requires: C,74.34; H, 4.87; N, 10.84%; Found: C, 74.30, ; H, 4.82; N,10.80%. IR (KBr, cm^{-1}); 2984 (C-H str.; asym.); 2840 (C-H str.; sym); 1382 (C-H def.;sym); 3084 (C-H aromatic); 1615 (C=C str.; aromatic); 3157 (N-H Str.), 689 (C-Cl str.); 1651 (C=N str.); 1108 (C-N str.); 1125 (C-O-C Str.); 2166 (CN Str.); 3299-3157 (-NH_2 Str.)**.** ^{1}H-NMR (DMSO-d6, δ ppm); 3.74 (3H, s, Ar-OCH_3); 5.44 (1H, d, C-H); 7.02-7.25(17H, m, Ar-H); 8.87 (1H, s, Ar-H); 10.07 (1H, s, N-H);10.73 (2H, s, N-H). m/z: 268, 284, 301, 328, 348, 350, 364, 382, 466, 488, 517, 520.

Similarly, other compounds (**4a-4l**) have been synthesized. The physical data are recorded in Table-I.

Table-I

The physical data and antimicrobial activity of compounds (**3a-3l**) and (**4a-4l**) [zone of inhibition in mm]

Comp.Id	R	Molecular Formula	M.P. ° C	Antibacterial activity				Antifungal activity	% of Nitrogen	
				B.Mega	*S.aureus*	*E.Coli*	*S.typhi*	*A. niger*	Calcd.	Found.
3a	C_6H_5-	$C_{32}H_{24}ClN_3O$	136	14	16	11	12	16	8.37	8.34
3b	4-Cl-C_6H_4-	$C_{32}H_{23}Cl_2N_3O$	237	10	12	17	10	15	7.83	7.80
3c	4-F-C_6H_4-	$C_{32}H_{23}ClFN_3O$	175	11	15	14	13	19	8.08	8.04
3d	4-Br-C_6H_4-	$C_{32}H_{23}BrClN_3O$	236	15	15	16	14	13	7.23	7.20
3e	2-OH-C_6H_4-	$C_{32}H_{24}ClN_3O_2$	286	17	14	15	16	16	8.11	8.08
3f	3- OH-C_6H_4-	$C_{32}H_{24}ClN_3O_2$	236	11	16	11	13	20	8.11	8.10
3g	4-OH-C_6H_4-	$C_{32}H_{24}ClN_3O_2$	266	10	14	15	12	14	8.11	8.07
3h	4-OCH_3-C_6H_4-	$C_{33}H_{26}ClN_3O_2$	238	13	11	12	11	17	7.90	7.88
3i	3-OCH_3-4-OH-C_6H_4-	$C_{33}H_{26}ClN_3O_3$	234	21	11	17	16	16	7.67	7.64
3j	4-N-$(CH_3)_2$-C_6H_3-	$C_{34}H_{29}ClN_4O$	139	14	16	11	12	16	10.28	10.25
3k	$C_{10}H_7$-(Naphthayl)	$C_{36}H_{26}ClN_3O$	231	18	12	17	10	15	7.61	7.60
3l	$C_{14}H_9$-(Anthranyl)	$C_{40}H_{28}ClN_3O$	237	11	15	14	13	19	6.98	6.95
4a	C_6H_5-	$C_{31}H_{23}ClN_4$	210	17	14	15	11	13	11.50	11.48
4b	4-Cl-C_6H_4-	$C_{31}H_{22}Cl_2N_4$	206	12	16	14	12	16	10.74	10.71
4c	4-F-C_6H_4-	$C_{31}H_{22}ClFN_4$	194	13	11	12	10	15	11.09	11.05
4d	4-Br-C_6H_4-	$C_{31}H_{22}BrClN_4$	156	15	16	15	12	14	9.90	9.88
4e	2-OH-C_6H_4-	$C_{31}H_{23}ClN_4O$	188	10	17	12	14	17	11.14	11.11
4f	3- OH-C_6H_4-	$C_{31}H_{23}ClN_4O$	201	15	13	17	13	16	11.14	11.13
4g	4-OH-C_6H_4-	$C_{31}H_{23}ClN_4O$	198	12	11	13	15	16	11.14	11.10
4h	4-OCH_3-C_6H_4-	$C_{32}H_{25}ClN_4O$	177	16	15	13	13	12	10.84	10.80
4i	3-OCH_3-4-OH-C_6H_4-	$C_{32}H_{25}ClN_4O_2$	151	17	16	11	10	21	10.51	10.50
4j	4-N-$(CH_3)_2$-C_6H_3-	$C_{33}H_{28}ClN_5$	167	14	15	16	13	13	13.21	12.81
4k	$C_{10}H_7$-(Naphthayl)	$C_{35}H_{25}ClN_4$	234	13	16	14	11	16	10.43	10.40
4l	$C_{14}H_9$-(Anthranyl)	$C_{39}H_{27}ClN_4$	256	17	11	15	16	19	9.54	9.51

Table-II

Comparable antimicrobial activity compare with known standard drugs.

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					
(3a-3l)	3e,3I,3k	3a,3f,3j	3b,3d,3e,3h,3k	3d,3e,3i	3c,3f,3h,3l
(4a-4l)	4a,4i,4l	4b,4d,4e,4i,4k	4a,4d,4f,4j,4l	4e,4g,4l	4e,4i,4l

4. CONCLUSIONS

2-Methoxy-6-{4'-[(4'''-Chlorophenyl) (phenyl)methyl amino]phenyl}-4-aryl nicotinonitriles (**3a-3l**) and 2-amino-6-{4'-[(4'''-Chlorophenyl)(phenyl)methyl amino] phenyl}-4-aryl nicotinonitriles (**4a-4l**) have been synthesized. Compounds containing **3d, 3e, 3k, 3l** and **4b, 4d, 4g, 4l, 4i** showed moderate antimicrobial activity compare with known standard drugs.

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