Synthesis of some 4[5-Substituted-2-Furanyl) Amino]-7-Substituted Aryloxy-6-Fluoro Cinnoline-3-Carboxylic Acids as Antimicrobial Agents

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Eight new substituted cinnoline carboxylic acids were prepared. The structure of these compounds have been confirmed by chemical and spectral analysis. The products were screened for antimicrobial activity. Some of the compounds exhibited comparable antimicrobial activity with standard drugs at same concentration.

CINNOLINE derivatives have wide range of pharmacological and antimicrobial activities. The antibacterial and anti-infective activity of various derivatives of 5-nitrofurfural are also documented[1]. Incorporation of fluorine enhances therapeutic efficacy[2]. Slight variation in substituion patterns of phenol causes a measurable difference in activity[3]. These findings triggered particular interest to incorporate cinnoline, 5-substituted furfurals, fluorine and phenols in one framework, with an aim to improve the antimicrobial activities.

Known 4-amino-7-chloro-6-fluoro cinnoline-3-carboxylic acid[4] (1) on treatment with 5-substituted furfurals gave the corresponding Schiff's bases (2 and 3). Later the active chlorine of compounds 2 and 3 were displaced by various phenols to give the title compounds (2a-d to 3a-d) as shown in table no. 1.

All the melting points were uncorrected. Preparative TLC was performed on Silica Gel (2.0 mm) plates, purchased from Sarabhai and Co. U.V. Spectral data were recorded on a Shimadzu 240 spectrometer, I.R. (KBr) spectra were recorded on Hitachi 270-20 spectrophotometer. The PMR spectra on Hitachi R-1200 (60 MHz) TMS as internal reference (chemical shifts are expressed in δ PPM). Mass spectra on Joel-D300 at 70 eV. Elemental Analysis are quite comparable with their structures.

Substituted 4N-(furfurylidene)-7-chloro-6-fluoro, cinnoline-3-carboxylic acids (2-3)[5] were prepared by a mixture of 4-amino-7-chloro-6-fluoro cinnoline-3-carboxylic acids (1) (12.03 g, 0.05 mole), ethanol (50 ml) and 5-substituted furan-2-als (0.05 mole) were refluxed on a water bath for 3 h in the presence of 2 drops of glacial acetic acid. The excess of solvent was removed by distillation and the resultant solid was collected and crystallized from DMF. Compound 2 shown the M.P-362° and Yield-65% Compound 3 shown the M.P-366° and Yield-62%. I.R. (KBr) spectra shown peaks at 3150 (N-H Str), 2950 (O-H Str), 1600-1630 (C=N Str), 1440 (C-F) 750 (C-Cl). P.M.R. ($CDCl_3$) δ9.7 (S, 1H, N=CH). the signal due to one of the nitrofuran-Proton appeared as doublet at 7.1, while the signal due to nitrofuran and aromatic protons (C_5 and C_8) mingled together and appeared as multiples at 7.2-8.3 integrating for 4 protons.

A mixture of compound number 2/3 (10 moles), Et_4 N+ Cl$^-$ (dried at 80°, 1.65 g, 10 moles), diethylamine (0.73 g; 10 moles, distilled from CaH_2), C-H_3 CN (distilled from CaH_2, 30 ml), and substituted phenols (10 moles were refluxed at 100° for 30 min and then it was concentrated to half the volume by distillation under reduced presure. The residue obtained was poured into water at 5° with vigorous stirring. The resultant mixture was left at room temperature for 5 h. The precipitated title compounds 4N -(furfurylidene)-7-substituted aryloxy-6-fluoro cinnoline-3- carboxylic acid (2a-d and 3a-d) were filtered, washed with water and dried,

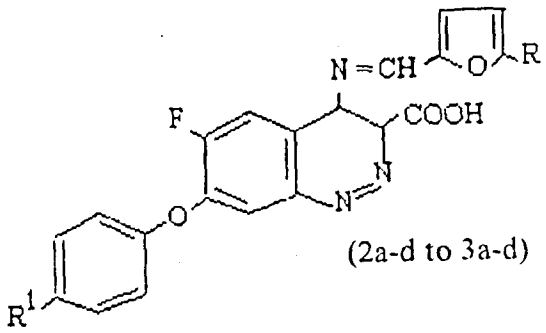


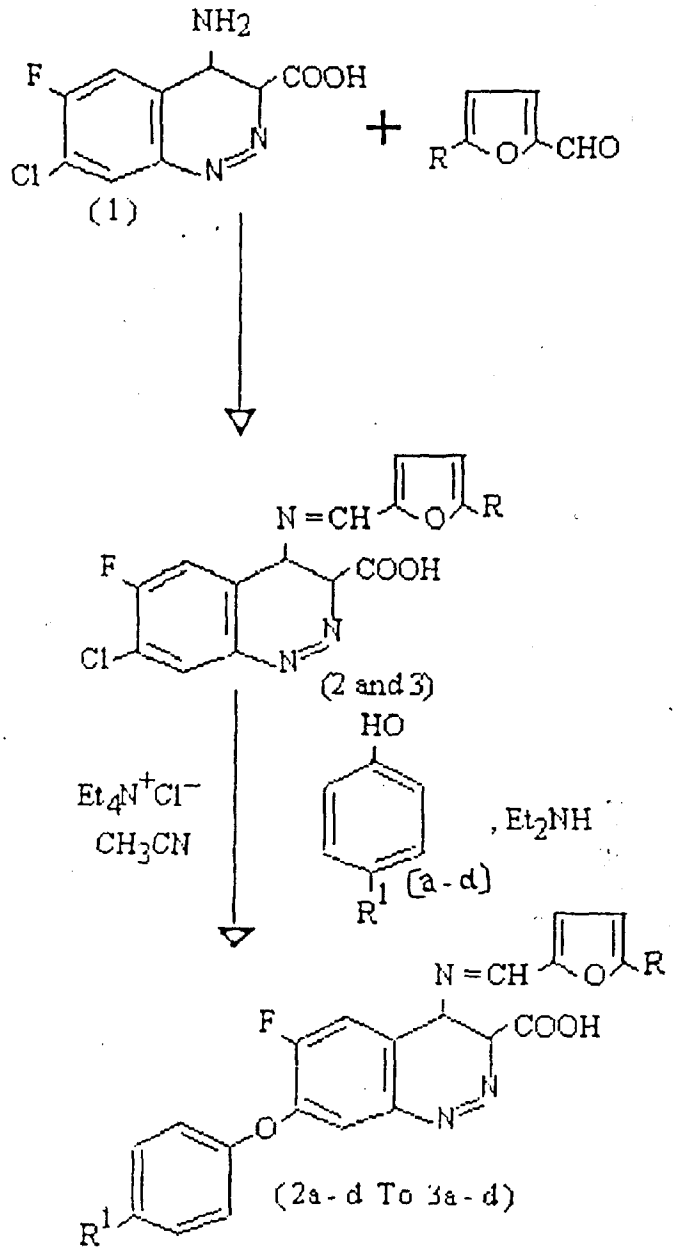
Table -1: Phycial Data of the New compounds 2 and 3

Compound	R	R^1	M.P. °C	MASS m/e	PMR ($CDCL_3$)
2a	$-NO_2$	-Cl	251	450(M^+)	δ 2.1 (3H; S, $-CH_3$) 3.9 (3H, S, $-OCH_3$)
2b	$-NO_2$	$-CH_3$	271		7.1-7.2 (m, 2H, C_5 & C_8 protons of cinnoline)
2c	$-NO_2$	$-NO_2$	262		7.3 (S, 1H, CH=N) 7.8 (m, 4H, ArH Phenyl)
2d	$-NO_2$	$-OCH_3$	276		8.0-8.1 (1H, S, CH=N Schiff Base) 10.2-10.6 (1H, b, -OH of COOH)
3a	$-C_6H_4NO_2$	-Cl	342		δ2.2 (3H; S, $-CH_3$; 4.31-4.35 (3H, S, $-OCH_3$)
3b	$-C_6H_4NO_2$	$-CH_3$	361		7.1-7.2 (m, 2H, C_5 & C_8 Protons of cinnoline)
3c	$-C_6H_4NO_2$	$-NO_2$	353	536 (M^+)	7.3 (S, H, CH=N) 7.8 (m, 4H, ArH Phenyl)
3d	$-C_6H_4NO_2$	$-OCH_3$	357		10.2-10.4 (1H, b, -OH of COOH)

Table -2 Anitmicrobial Activity Results the Compounds 2 and 3

	Antibacterial Activity		*Antifungal Activity*			
Compound	*B. Substilis*	*B. cirroflagellous*	*E. coli*	*P. vulgaris*	*A. niger*	*Candida albicans*
2 a	20	22	24	22	17	19
2 b	17	15	17	16	14	15
2 c	22	25	24	21	18	19
2 d	18	14	16	17	15	13
3 a	18	21	19	17	16	17
3 b	16	17	18	14	15	14
3 c	19	23	21	19	16	17
3 d	17	18	16	14	14	14
Norfloxacin	22	27	27	25	-	-
Nitrofurantoin	28	26	21	23	-	-
Griseofulvin	-	-	-	-	21	24

SCHEME



crystallized from DMF. Percent Yield was found as compound 2a is 60%. 2b is 45%; 2c is 45% 2d is 55%; 3a is 62% 3b is 45%; 3c is 60% 3d is 42%. The formation of the title compounds is also confirmed by a specific. I.R. peak at 1010 cm^{-1} indicating the formation of ether linkage, difference in R_f values and difference in M.P. compared to precursors.

All compounds (2a-d to 3a-d) were screened for antimicrobial activity by the agar cup-plate method[6] at a concentration of 50 μg using DMF as a solvent. The zones of inhibition were measured in mm, and are presented in Table-2. The activity was compared with norfloxacin, nitrofurnation and griseofulvin at same concentration.

From the screening results, it was observed that all the compounds produced considerable zones of inhibition, which were comparable to those of the reference compounds. The compounds 2c and 3c with a nitro substitution at R and R' and chloro-substituent as in 2a and 3a at R' were found to posses significant antibacterial activity and considerable antifungal activity against all the organisms used. Hence these four compounds were tested at lower doses at 10 μg concentration against the same organisms. Compound 2c was found to be significantly active at 10 μg and 30 μg doses against bacteria and fungi which was comparable to standards whereas the compound 2a was active only at 30 μg dose against all organisms. But the compounds 3a and 3c were less active at lower doses.

In conclusion, it may be stated that the compounds 2a-d were better in their antimicrobial activity compared to 3a-d due to the presence of nitrosubstitution at R. The presence of deactivators like nitro and chloro groups at R' enhances considerably the antimicrobial activities of the title compounds, and electron donating (activating) groups such as-methyl and methoxy at R' have shown decreased antimicrobial activity. Finally among the compounds synthesised, the compound 2c with nitro substitution at R and R' was found to be the most promising antimicrobial compound.

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