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Biological evaluation of Aminobenzylated Mannich bases of P- Fluoro benzaldehyde

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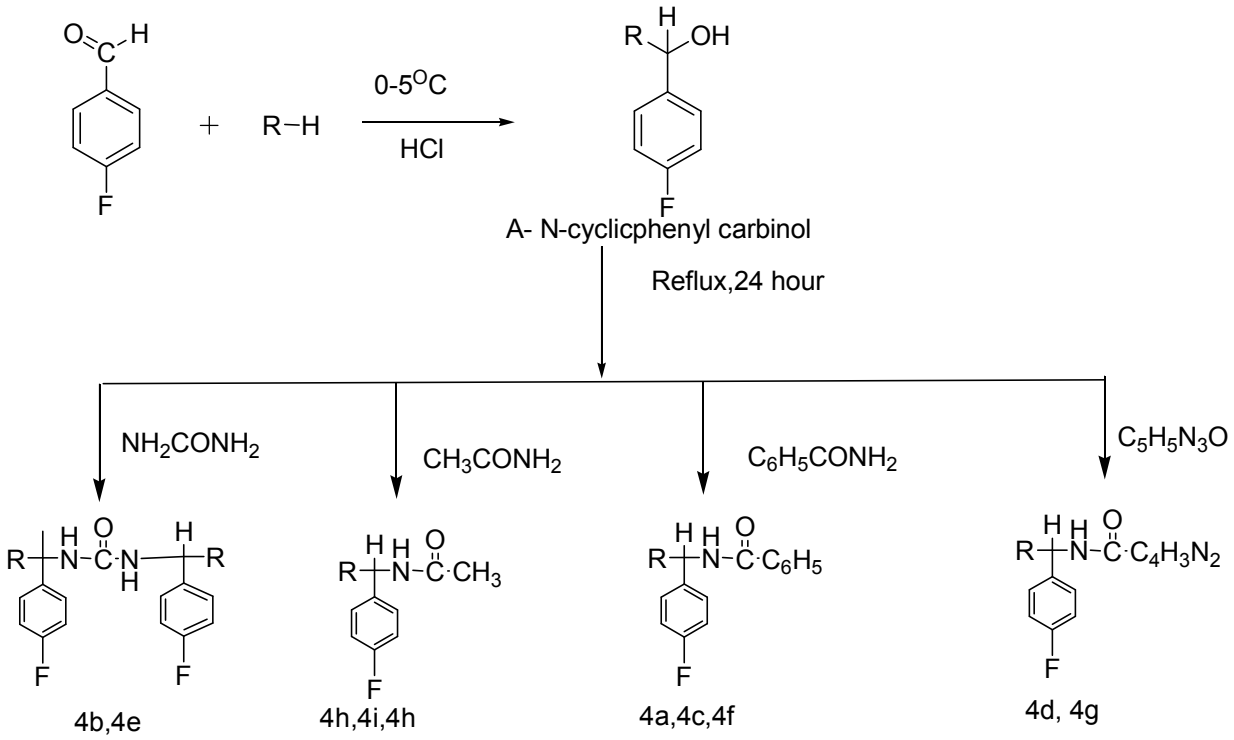
Abstract: In the present study about ten aminobenzylated Mannich bases (4a-4j) of *p*-fluoro benzaldehyde were synthesized using Mannich reaction. The structures of all the synthesized compounds were assigned based on spectral studies and evaluated for their antimicrobial activity against standard drugs.
Key word:- *p*-flouro benzaldehyde, Biological evaluation, Mannich bases, Ketoconazole, Amides.

Introduction

Mannich reaction is one of the most important carbon–carbon bond forming reactions in organic synthesis[1] because it affords synthetically and biologically important intermediate for the construction of pharmaceuticals[2] . Many literatures have shown that Mannich bases posses potent biological activities such as antibacterial[3].antifungal[4], antiinflammatory[5] and anticancer[6] properties but only few aminobenzylated Mannich bases are reported in spite of their pharmacological applications[7]. The incorporation of a fluorine atom or atoms in place of hydrogen in a molecule, particularly in molecules of medicinal interest, is known to impart many beneficial effects upon therapeutic efficacy and pharmacological activity. This is considered to be the result of : 1. Fluorine closely mimicking hydrogen in terms of steric requirements 2. Alteration of electronic effects due to the highly electronegative nature of fluorine 3. Increased lipid solubility of fluorinated drugs 4. Improved oxidative and thermal stability and 5. Enzymic reaction inhibition properties. Consequently, there is considerable interest in the synthesis of fluorinated compounds[8]. In view of these facts and as continuation of our research on pharmaceutically important Mannich bases here by we report the synthesis of a new series of aminobenzylated Mannich bases containing fluorine atom.

p-fluoro benzaldehyde in reaction with cyclic 2^0 amines such as morpholine, N-methyl piperazine, and piperdine gives rise to an intermediate N-cyclic-phenyl carbine (A) which on condensation with active hydrogen compounds urea, pyrazinamide, acetamide and benzamide yields aminobenzylated Mannich bases (scheme 1). The newly synthesized compounds were characterized by IR, ^{1}HNMR, ^{13}CNMR and Mass spectral studies.

Scheme 1: Synthetic Protocol of Aminobenzylated Mannich Bases 4a to 4j



Where,

Compound	R
4a	Morpholine
4b	N-Methyl piperizine
4c	N-Methyl piperizine
4d	Morpholine
4e	Morpholine
4f	Piperdine
4g	N-Methyl piperizine
4h	Morpholine
4i	N-Methyl piperizine
4j	Piperdine

Materials and Method.

All reagents and solvents were used as supplied by commercial sources without further purification. Melting point were measured by open capillaries and are uncorrected. Precoated silica gel TLC plates were used to monitor the progress of the reactions (Table No.1). IR spectra were recorded on FTIR-8400 shimadzu Spectrophotometer. ^{1}HNMR and ^{13}CNMR spectra were obtained by Spect Bruker Spectrophotometer. Chemical shifts of the NMR Spectra were reported in parts per million (ppm) downfield from TMS. The mass spectra was recorded using Shimadzu LC-MS 2010.

Table No. 1: Physicochemical properties of the synthesized compounds 4a to 4j

Sl. No.	Compound	% yield	M.P / B.P	Mol. formula	Mol. Weight	R.F. Value
4a	N-[(*p*-fluorophenyl) (morpholine-1-yl) methyl)] benzamide	45.0	114-116^{0}C	$C_{18}H_{19}N_2O_2F$	314	0.50
4b	1,3-bis[(*p*-fluorophenyl) (N-methyl piperazine-1-yl)] urea	52.5	146-147^{0}C	$C_{25}H_{34}N_6OF_2$	472	0.43
4c	N-[(*p*-fluorophenyl) [N-methylpiperazine-1-yl) methyl] benzamide	39.0	120-122^{0}C	$C_{19}H_{22}N_3OF$	327	0.33
4d	N-[(*p*-fluorophenyl)(morpholine-1-yl)methyl)] pyrazine-2-carboxamide	26.0	185-186	$C_{16}H_{17}N_4OF$	300	0.69
4e	1, 3-bis[(*p*-fluorophenyl) (morpholine-1-yl) methyl] urea	26.5	276-278^{0}C	$C_{23}H_{28}N_4O_3F_2$	446	0.46
4f	N-[(*p*-fluorophenyl) (Piperidine-1-yl) methyl] benzamide	39.5	204-206^{0}C	$C_{19}H_{21}N_2OF$	312	0.39
4g	N-[(*p*-fluorophenyl) [N-methylpiperazine-1-yl) methyl] pyrazine-2-carboxamide	33.0	160-162	$C_{17}H_{20}N_5OF$	329	0.52
4h	N-[(*p*-fluorophenyl) (morpholine-1-yl) methyl] acetamide	61.0	228-231^{0}C	$C_{13}H_{17}N_2OF$	236	0.52
4i	N-[(*p*-fluorophenyl) (N-methyl Piperazine-1-yl) methyl] acetamide	51.0	238-240^{0}C	$C_{14}H_{20}N_3OF$	265	0.40
4j	N-[(*p*-fluorophenyl) (piperadine-1-yl) methyl] acetamide	49.0	152-153^{0}C	$C_{14}H_{19}N_2OF$	250	0.59

General Procedure

To an ethanolic solution of amide (0.005/0.01 mol) ice cold secondary amine (0.01 mol) was added drop wise and stirred to get a clear solution. A drop of hydrochloric acid was added to the above solution to adjust the pH between 3 to 4.5 and stirred at 0 ^{0}c to 5 ^{0}c for about half an hour. 0.01 mol of ethanolic p-fluorobenzaldehyde was added drop wise to the above solution with constant stirring. The resulting mixture was then refluxed at 70 ^{0}c to 80 ^{0}c for about 20-24 hours in a water bath. Then the solvent was distilled off and the residue obtained was collected under suction and recrystallised from chloroform (Scheme 1).

Compound 4a: N-[(*p*-fluorophenyl) (morpholine-1-yl) methyl)] benzamide
I R (KBr, cm^{-1}):3369 (NH), 1604 (amide C=O), 1020 (C-N-C of morpholine), 1111 (Ar-F), 1398(CH-Aliphatic), 1572 (C-C Ar).: ^{1}H NMR (δ in ppm,$CDCl_3$/MeOD): 7.8-7.4 (m,5H,Ar-H), 7.2-7.1 (m,4H,Ar-F), 6.5-6.0 (s,1H,-CONH),), 3.9-3.6 (d,4H, morpholine -OCH_2), 2.7-2.5 (d,4H, morpholine-NCH_2),

Compound 4b: 1,3-bis[(*p*-fluorophenyl) (N-methyl piperazine-1-yl)] urea. I R (KBr, cm^{-1}): 3352(NH), 1653 (amide C=O), 1010 (C-N-C of NMP), 873(CH-Ar,Bending), 2947 (CH-Aliphatic), 1545 (C-C Ar), 1111 (Ar-F).H NMR (δ in ppm,$CDCl_3$/MeOD): 7.9-7.0 (m,8H,Ar-F), 5.7-5.6 (s,2H,-CONH),), 3.8-3.6 (m,8H, -CH_2α in NMP), 3.3-2.9 (m,8H, -CH_2β in NMP), 2.8-2.4 (s,6H,-NCH_3 in NMP), 2.3

Compound 4d: N-[(*p*-fluorophenyl) 9N-methyl piperazine-1-yl) methyl] benzamide .I R (KBr, cm^{-1}): 3367 (NH), 1658 (amide C=O), 1249 (Ar-F), 1400(CH-Aliphatic), 1573 (C-C Ar), 3064(CH-Ar). m/z: 327.

Compound 4g: N-[(p-fluorophenyl) (N-methyl Piperazine-1-yl) methyl]pyrazine-2-carboxamide. I R (KBr, cm^{-1}): 3431 (NH), 1672 (amide C=O), 3090 (Ar-H), 1581 (C-C Ar), 1172 (Ar-F), 1089 (C-N-C of NMP). m/z: 330

Compound 4h: N-[(*p*-fluorophenyl) (morpholine-1-yl) methyl] acetamide. I R (KBr, cm^{-1}): 3273 (NH), 1664 (amide C=O), 1222 (Ar-F), 1371 (CH-Aliphatic), 1518 (C-C Ar), 3124 (CH-Ar), 1091 (C-N-C of morpholine); ^{1}H NMR (δ in ppm,$CDCl_3$/MeOD): 8.6-8.5 (s,1H,NH), 7.5.-7.0 (m,4H,Ar-F), 3.8 (d,4H, morpholine -OCH_2β), 3.4-3.2 (d,4H,morpholine -NCH_2), 2.3-1.8 (s,4H, Ar-CH+CH_3).

Compound 4i: N-[(*p*-fluorophenyl) (N-methyl Piperazine-1-yl) methyl] acetamide .I R (KBr, cm^{-1}):

3273 (NH), 1662 (amide C=O), 1222 (Ar-F), 1373 (CH-Aliphatic), 1518 (C-C Ar), 3130 (CH-Ar), 1091 (C-N-C of NMP); ^{13}C NMR (δ in ppm): 114.5, 114.9, 127.8,127.9, 131 (6 aromatic carbons) 57.7 (1 methine carbon) 47.4, 47.8, 48.3 ,48.7 (4 carbon in NMP), 46.1(1 carbon in NCH_3 of NMP), 171(1 carbon, carbonyl in amide), 20.9(1 carbon of CH_3 in amide).

Antimicrobial screening.

The antimicrobial activity of all the newly synthesized compounds 4a-4j were studied by MIC process using cup-plate agar diffusion method[9]. The antibacterial activities were screened in DMF, using standard amoxicillin/ciprofloxacin (100µg/ml) against Gram positive and Gram negative bacteria such as *E. coli, S.typhi, S.aureas* and *B substlilis*. The compounds were also screened for their antifungal activity in DMF using Ketoconazole (100µg/ml) against *A.niger* and *C. albicans*. After the period of incubation, zones of inhibition were recorded around the wells and results are cited in Table no.2.

Results and Discussion

The IR spectra of the compounds 4a to 4j showed NH and C=O stretching bands of the amide group at 3221-3366 cm^{-1} and 1604-1676 cm^{-1} respectively, indicating the existence of NH bond formed between N-cyclic phenyl carbinol and amide. The formation of the bond was also confirmed by the ^{1}HNMR spectra of the compounds. The singlet at δ 6.5-8.0 ppm in the spectrum of 4a showed the existence of amide group in the compounds. In addition the singlet at δ 2.1-2.0 ppm in the spectrum of compound 4g showed that the existence of benzylic carbon indicating the formation of N-cyclic phenyl carbinol. The MS of the compound 4d showed a molecular ion peak (M^+) at 327 supporting the expected structures.

The compound 4j showed maximum antimicrobial activity but the remaining compounds exhibited comparatively less antibacterial and antifungal activity against all the organisms used for the study in comparison to the standard drugs Amoxicillin, ciprofloxacin and Ketoconazole.

Table No. 2: Antimicrobial activity: zone of inhibition (mm) of compounds (4a to 4j)

Compounds	Bacterial strain-Zone of inhibition (mm)				Fungal strain-Zone of inhibition (mm)	
	S.aureus	*E.Coli*	*S.typhi*	*B.subtillis*	*A.niger*	*C. albicans*
4a	11	15	09	12	08	06
4b	04	11	06	03	02	01
4c	03	07	04	02	02	01
4d	09	10	07	04	03	02
4e	00	00	00	00	00	00
4f	12	17	10	13	10	07
4g	08	09	08	05	05	03
4h	10	10	07	15	04	03
4i	09	15	08	15	07	04
4j	14	16	11	14	11	08
Ciprofloxacin	31	28	33	29	-	-
Amoxicillin	29	20	22	22	-	-
Ketoconazole	-	-	-	-	24	29

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