AMINOBENZYLATED MANNICH BASES OF AMIDES

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ABSTRACT

In the present study aminobenzylated mannich bases of m-nitro Benzaldehyde were synthesized using mannich reaction and the structures of all the newly synthesized compounds have been investigated by IR,^{1}HNMR,^{13}CNMR and Mass spectrometry . The synthesized compounds were also screened for their antimicrobial activity using pathogenic strains of bacteria and fungie against standard drugs.

KEY WORDS: Aminobenzylated Mannich bases, antimicrobial activity, *m*-nitro benzaldehyde, amide, synthesis.

1.INTRUDUCTION

It is reported in the literature that mannich bases have several biological activities such as anti bacterial (Gamal,2009), antifungal (Bela,2009), anti inflammatory (Philip,2009), analgesic (Philip,2009),local anesthetic (Kalirajan,2008) and antitubercular (Bhat,2000) activities. They were synthesized by using mannich reaction (Pandeya,2003) which is a three component condensation reaction consisting of active hydrogen containing compound, aldehyde and a secondary amine. Much work has been done so far on the synthesis of mannich bases but little work was found in aminobenzylated mannich bases (Joshi,2003;Vasoya,2005;Chaluvaraju and Ishwar, 2009). There fore it was thought worth while to synthesize some novel aminobenzylated mannich bases and investigate them for their biological activities and hence in the present study *m*-nitro benzaldehyde was made to react with secondary amines such as morpholine / N - methyl piperazine to form N-cyclic phenyl carbinol (A), Which on condensation with urea/thiourea / acetamide / benzamide in the presence of HCl at a pH of 3 to 4.5 forms various aminobenzylated mannich bases 3a-h (scheme) .

2.MATERIAL AND METHODS

Melting points were measured in open capillaries and are uncorrected. The compounds were checked for purity by TLC. IR spectra were recorded on KBr disk using perkin Elmer spectro meter one model.NMR spectra were obtained on a spect AMX – 400 spectrometer using $CDCl_3$ as solvent and TMS as internal standard . The mass spectra was recorded using Shimadzu LC-MS 2010 Spectra.

General procedure for synthesis of aminobenzylated mannich bases (3a-h).

To the ethanolic solution of 0.1mol of amide was added 0.1mol secondary amine slowly with constant stirring. A drop of HCl was added to the above resulting solution to adjust pH between 3 to 4.5. One half of the 0.1mol of ethanolic *m*-nitro benzaldehyde was added slowly with constant stirring. The reaction mixture was stirred at 0^0C. The remaining portion of *m*-nitro benzaldehyde solution was added in few portion at an interval of one hour. The reaction mixture was further stirred at room temperature for 6-8 hour and poured in to ice cold water. The product obtained was collected under suction and recrystalized from Chloroform.

Compound 3a: 1, 3-bis [(*m*-nitro phenyl) morpholine-1-yl) methyl] urea

IR (KBr,cm^{-1}): 3500 (NH), 1658 (amide C=O), 1045 (C-N-C morpholine), 3266 (CH-Ar), 2738 (CH-Aliphatic), 1536 (C-C ring),1536 (Ar-C-NO_2); ^{1}H NMR ($CDCl_3$,δ ppm): 10.2-10.1(s, 2H, CONH), 8.5-7.3 (m, 8H ,Ar-H), 4.8-4.7(s, 2H,Ar- CH), 4.0-3.5 (t, 8 H, -OCH_2 in Morpholine), 2.7-2.4 (t, 8 H, -NCH_2 in Morpholine); ^{13}C NMR ($CDCl_3$, δ ppm): 159 (NH-CO-NH),127,128,129 (12 aromatic carbons) 89,78 (2 benzylic carbon),68,45 (8 aliphatic carbons); Mass : m/e 498(M^+).

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Compound 3b: 1, 3-bis [(*m*-nitro phenyl) (morpholine-1-yl) methyl] thiourea

IR (KBr,cm^{-1}): 3365 (NH), 1201 (amide C=S), 1087 (C-N-C morpholine), 3068 (CH-Ar), 2883 (CH-Aliphatic), 1531 (C-C ring),1531(Ar-C-NO_2); ^{1}H NMR ($CDCl_3$,δ ppm): 7.7-7.0 (m, 8H, Ar-H), 6.0 (s, 2H CSNH), 5.0-4.8 (s, 2H, Ar- CH), 3.9-3.6 (t, 8 H, -OCH_2 in Morpholine), 3.5-3.4 (t, 8 H, -NCH_2 in Morpholine); ^{13}C NMR ($CDCl_3$, δ ppm): 150 (NH-C0-NH),129,130,131 (12 aromatic carbons), 79 (2 benzylic carbon),65 (8 aliphatic carbons); Mass : m/e 518(M^+).

Compound 3e: 1, 3-bis [(*m*-nitro phenyl) (N-methyl piperazine -1-yl) methyl] urea

IR (KBr,cm^{-1}): 3369 (NH), 1693 (amide C=O), 1203 (C-N-C , NMP), 3066 (CH-Ar), 2883 (CH-Aliphatic), 1610 (C-C ring), 1529 (Ar-C-NO_2); ^{1}H NMR ($CDCl_3$, ppm): 7.5-7.2(m, 8H Ar-H), 6.0 (s, 2H CONH), 6.8-6.6(s, 2H, Ar-CH), 5.7-5.5 (t, 16 H, -CH_2 in NMP), 2.7 (s, 6 H, -NCH_3 in NMP).

Compound 3h : N- [(*m*-nitro phenyl) (N-methylpiperzine-1-yl) methyl] benzamide

IR (KBr,cm^{-1}):3369 (NH), 1693 (amide C=O), 1203 (C-N-C, NMP), 3066 (CH-Ar), 2881 (CH-Aliphatic), 1529 (C-C ring), 1529 (Ar-C-NO_2); ^{1}H NMR ($CDCl_3$, ppm): 8.0-7.2(m, 9 H of Ar-H), 6.1-5.9(s, 1H, CONH), 5.0-4.9 (s, 1H, Ar-CH), 3.8-3.6 (t, 8 H, -CH_2 in NMP), 2.7-2.5 (s, 3H, -NCH_3 in NMP) ; Mass : m/e 346(M^+); NMP: N-Methyl piperazine.

Similarly other derivatives 3c,3d,3f and 3g were synthesized and their physical data are given in table 1.

ANTIMICROBIAL ACTIVITY

All the newly synthesized compounds were screened for antimicrobial activity at conc.400 to 600 mcg/ml against the test organism *S.aureus, B.subtilis, E.coli, P.aeuruginosa , A.niger* and *C.albicans*. Agar cup-plate method (Barry,1976) was used for the inhibition studies.Ciproflaxacin was used as a standard drug for comparison. Antifungal screening was carried by readymade sabourand dextrose agar medium. Ketoconazole was used as standard drug for comparison. DMF was used as solvent control. The antimicrobial activity data is reported in table 2.

3.RESULTS AND DISCUSSION

The antibacterial and antifungal screening revealed that some of the tested compounds showed good inhibition. The antibacterial and antifungal screening indicated that among the tested compounds 3a showed excellent activity against all the tested bacterial strains viz., *S.aureus, B.subtilis, E.coli ,P.aeuruginosa, A.niger* and *C.albicans.*

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Table 1:Physical data of compounds 3a to 3h

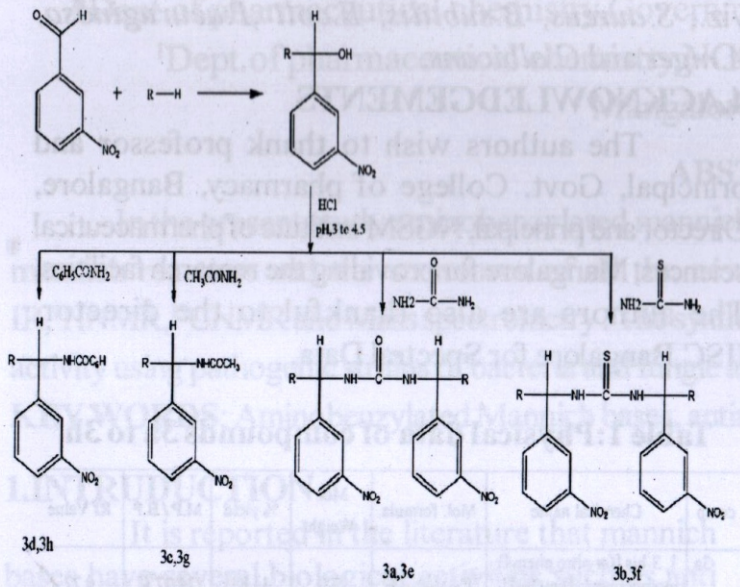
comp	Chemical name	Mol. formula	Mol. Weight	% yield	M.P / B.P	Rf Value
3a	1, 3-bis [(*m*-nitro phenyl) morpholine-1yl) methyl] urea	$C_{23}H_{28}N_6O_7$	500	44.89	74-77^{0}C	0.77
3b	1, 3-bis [(*m*-nitro phenyl) (morpholine-1yl) methyl] thiourea	$C_{23}H_{28}N_6O_6S$	516	60.78	82-84^{0}C	0.62
3c	N- [(*m*-nitro phenyl) (morpholine-1yl) methyl] acetamide	$C_{13}H_{17}N_3O_4$	279	55.50	70-73^{0}C	0.84
3d	N- [(*m*-nitro phenyl) (morpholine-1yl) methyl] benzamide	$C_{18}H_{19}N_3O_4$	341	55.88	58-59 ^{0}C	0.65
3e	, 3-bis [(*m*-nitro phenyl) (N-methyl piperazine - 1yl) methyl] urea	$C_{25}H_{34}N_8O_5$	526	55.76	80-82^{0}C	0.53
3f	1, 3-bis [(*m*-nitro phenyl) (N-methyl piperazine - 1yl) methyl] thiourea	$C_{25}H_{34}N_8O_4S$	542	59.14	38-42^{0}C	0.85
3g	N- [(*m*-nitro phenyl) (N-methylpiperazine-1yl) methyl] acetamide	$C_{14}H_{20}N_4O_3$	292	46.00	50-53^{0}C	0.76
3h	N- [(*m*-nitro phenyl) (N-methylpiperazine-1yl) methyl] benzamide	$C_{19}H_{22}N_4O_3$	345	60.00	63-37^{0}C	0.73

Table 2: Antibacterial, antifungal activity data of compounds 3a to h

Compounds	Microbial Strain – Zone of Inhibition in mm (average)					
	S. aureus	*E.coli*	*P. aeuruginosa*	*B. subtilis*	*A.niger*	*C.albicans*
3a	*15*	*14*	*08*	*14*	*11*	*09*
3b	13	13	07	12	10	09
3c	12	11	07	12	09	08
3d	10	09	06	10	09	07
3e	14	12	07	13	08	07
3f	12	11	08	12	07	06
3g	11	09	07	10	07	05
3h	09	09	08	08	06	05
DMF(control)	-	-	-	-	-	-
Ciprofloxacin	31	28	33	29	-	-
Ketoconazole	-	-	-	-	24	29

Scheme

Synthesis of Aminobenzylated Mannich Bases of Amides



Where R: Morpholine,N (3a to 3d)

R : N-methyl piperazine(3e to 3h)

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