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Synthesis and Antimicrobial Activities of Amino Benzylated Mannich Bases of Pyrazinamide

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Abstract: A series of aminobenzylated mannich bases of pyrazinamide (2a to 2j) have been prepared by mannich reaction of aromatic aldehydes with pyrazinamide and secondary amines. The chemical structure of all the synthesized compounds have been elucidated by spectral studies (IR, H^1 NMR). Also they have been assayed *in vitro* for their biological activity against *E.coli, B.substilis, S.aureas* bacterial species and *A. niger* and *C. albicans* fungal micro organisms.

Key Words: Aminobenzylated Mannich Bases, Biological Activities, Pyrazinamide, amoxicillin Ciprofloxacin and Ketoconazole.

Introduction

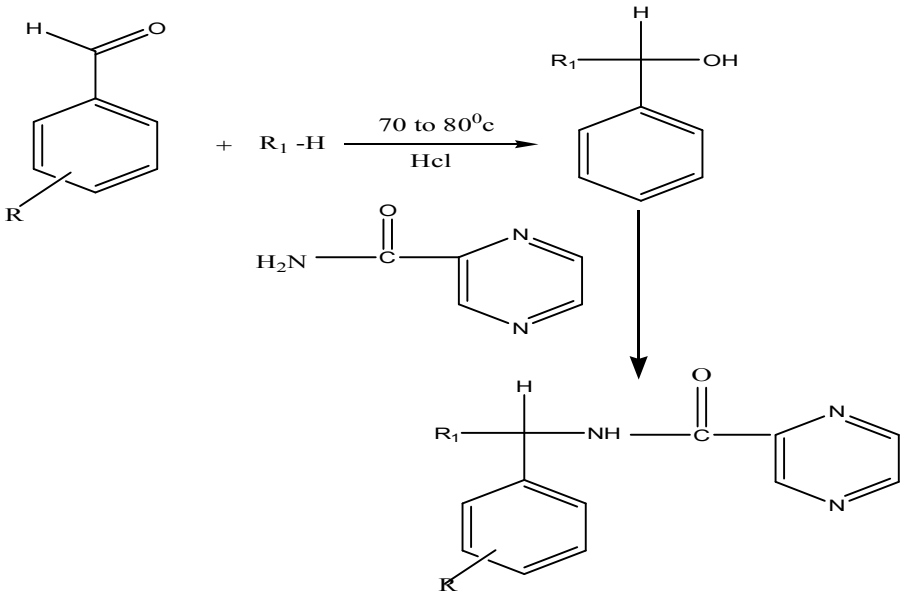
Pyrazinamide (PAZ) had been reported to posses antitubercular activity and a considerable amount of work has been reported on the synthesis and antimicrobial activity of pyrazinamide mannich bases[1,2]. Further a considerable amount of work has been reported on the synthesis and pharmacological activity of various mannich bases for analgesic [3], anthelmentic,[4] local anesthetics[5] and antimicrobial activity, [6] as well as intermediates in drug synthesis. In this context literature survey has revealed a very few reports on antimicrobial activity of aminobenzylated mannich bases derived from different amides such as urea, thiourea,acetamide and benzamide[7,8,9] .Keeping in view of the importance of these two organic moieties, pyrazinamide and mannich bases in the field of medicine and biology here an attempt has now been made to synthesize some aminobenzylated mannich bases connecting both the moieties and investigate their possible antimicrobial activity.

The present study describes the synthesis of aminobenzylated mannich bases via mannich reaction. Aromatic Aldehydes in reaction with cyclic secondary amines such s morpholine,N- methyl piperazine, piperidine *etc* gives rise to N-cyclic phenyl carbinol which on condensation with pyrazinamide yield aminobenzylated mannich bases 2a to 2j (scheme 1).

Experimental

Melting points were measured on buchi melting point apparatus in open capillaries and were uncorrected. The compounds were checked for purity by TLC on silica gel HF_{254}, 200 mesh. The solvent system employed was chloroform : methanol (80:20) and the spots were identified by placing the plate in UV chamber (λmax 254nm). IR spectra were recorded on KBR disks using Perkin Elmer FT-IR spectrophotometer 1 model. H^1NMR spectra were obtained on a Brucker Advance II NMR spectrophotometer (400 mHz) using $CDCl_3$ as solvent and TMS as internal standard.

Scheme 1: Synthetic Protocol of Aminobenzylated Mannich Bases (2a-2j)



Where,

Compound	R	R_1
2a	Hydrogen	Morpholine
2b	2,5-dimethoxy	Morpholine
2c	4-hydroxy	Morpholine,
2d	Hydrogen	N-Methyl piperizine
2e	2,5-dimethoxy	N-Methyl piperizine
2f	4-hydroxy	N-Methyl piperizine
2g	2,5-dimethoxy	Piperdine
2h	4-hydroxy	Piperdine
2i	3-nitro	Piperdine
2j	2,4-dimethoxy	Piperdine

Synthesis of Aminobenzylated Mannich Bases of Pyrazinamide (2a to 2j)

Equimolar quantity (0.005mol) of secondary amine was added to ethanolic solution of (0.005mol) pyrazinamide 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 .One half of the (0.005mol) ethanolic aromatic aldehyde solution was added slowly with constant stirring to the above resulting solution and the reaction mixture was stirred at 70 to 80 ^{0}C on a magnetic stirrer for 10 to 12 hours. The remaining aldehyde was added in two portions at an interval of one hour. The reaction mixture was kept overnight in the refrigerator. The excess solvent was removed by distillation under pressure and they kept for crystallization in the refrigerator. The resulted product was washed with petroleum ether and recrystellised from chloroform.

Compound 2a:N-((1-morpholino-1-yl-phenyl) methyl)pyrazine-2-carboxamide.

Yield:35%;m.p.136-139^{o}C;Rf:0.625:IR(KBr,cm^{-1}):1670(C=O) 3427 (NH): ^{1}HNMR(400 MHz,$CDCl_3$, δ/ppm): 9.2-9.1 (1H, s,C_2-H pyrazine),8.8-8.7 (2H, d,C_5,C_6-H pyrazine),7.8-7.5 (5H, m ,Ar-H), 6.7-6.6 (1H, s,Ar-CH),5.9 (1H, s,-NH).

Compound 2b:N-(2,5-dimethoxy phenyl (morpholino-1-yl)methyl)pyrazine-2-carboxamide.
Yield:49%; m.p161-165^{o}C;Rf :0.58. IR(KBr, cm^{1}):1647 (C=O), 3428 (NH).^{1}HNMR (400 MHz ,$CDCl_3$, δ/ppm): 9.3-9.1 (1H, s, C_2-H pyrazine),8.8-8.7 (2H, d, C_5,C_6-H pyrazine) 7.25-7.15 (2H, s,Ar-H),6.9-6.8 (1H, s,Ar-CH),5.6-5.5 (1H, s,-NH),3.3-3.1 (6H, t,-OCH_3+-OCH_3).

Compound 2C:N-((4-Hydroxy phenyl)(morpholino-1-yl)methyl)pyrazine-2-carboxamide.
Yield:26%; m.p 142-148^{o}C;Rf : 0.69. IR(KBr ,cm^{1}):1647 (C=O), 3428 (NH).^{1}HNMR (400 MHz, $CDCl_3$,δ/ppm):9.2-9.1 (1H, s, C_2-H pyrazine),8.7-8.6(2H, d, C_5,C_6-H pyrazine),8.2 (1H,s,Ar-OH),7.8-7.5 (4H, m,Ar-H),6.7-6.6 (1H, s,Ar-CH),6.0 (1H, s,-NH).

Compound 2d:N-(1-methyl piperizine -1-yl-phenyl)methyl)pyrazine-2-carboxamide.
Yield:36%; m.p 128-131^{o}C;Rf : 0.64. IR(KBr, cm^{1}):1674(C=O)3419(NH).^{1}HNMR(400 MHz, $CDCl_3$, δ/ppm):9.3-9.2(2H, s, C_2-H pyrazine +NH), 8.8-8.6 (2H, d, C_5,C_6-H pyrazine),7.9-7.4 (5H, m,Ar-H),5.2-4.6 (1H, s, Ar-CH),2.3-2.0 (3H, s ,-CH_3).

Compound2e:N-(2,5dimethoxyphenyl(1-methylpiperazin-1-yl)methyl)pyrazine-2-carboxamide.
Yield:41%; m.p 156-159^{o};Rf:0.52. IR(KBr, cm^{1}):1670 (C=O) 3414 (NH).^{1}HNMR (400 MHz, $CDCl_3$, δ/ppm): 9.3-9.2(1H, C_2-H pyrazine),8.8-8.7 (2H, d, C_5,C_6-H pyrazine),7.2-7.1(5H, m ,Ar-H),6.9-6.8 (1H, s,Ar-CH),5.6-5.5 (1H, s,-NH), 3.1-3.0 (6H, t,-OCH_3+-OCH_3).

Compound 2f:N-((4-Hydroxy phenyl)(1-methyl piperzin -1-yl)methyl)pyrazine-2-carboxamide.
Yield:30%; m.p 171-175^{o}C;Rf:0.67. IR(KBr, cm^{1})) ^{1}:1605 (C=O)3414(NH).^{1}HNMR(400 MHz, $CDCl_3$, δ/ppm):9.8-9.7 (1H, s,-NH),9.3-9.2 (1H, s, C_2-H pyrazine),7.9-7.7 (2H, d, C_5,C_6-H pyrazine),7.3-6.8, (4H, m ,Ar-H), 6.8-6.7 (1H, s,Ar-OH),5.2-4.7 (1H, s,Ar-CH),2.2-2.1 (3H, s,-CH_3).

Compound 2g:N-(2,5dimethoxyphenyl(pieridin-1-yl)methyl)pyrazine-2-carboxamide.
Yield:38%; m.p 159-161^{o}C;Rf:0.8. IR(KBr, cm^{1}):1656 (C=O) 3507 (NH).^{1}HNMR (400 MHz, $CDCl_3$, δ/ppm) :8.5-8.3 (2H, s,C_2-H pyrazine+NH),7.3-6.8(5H, m,Ar-H+Het-H),6.7-6.6(1H, s,Ar-CH), 4.0-3.8 (6H, t,-OCH_3+-OCH_3).

Compound 2h:N-((4-Hydroxy phenyl) pieridin-1-yl)methyl)pyrazine-2-carboxamide
Yield:51%; m.p:220-222^{o}C;Rf:0.59. IR(KBr, cm^{1}):1698 (C=O),3504(NH).^{1}HNMR (400 MHz, $CDCl_3$, δ/ppm):9.5-9.2(1H, s, C_2-H pyrazine),8.8-8.5(2H, s,C_5,C_6-pyrazine) 7.9 (1H,s,NH),7.2-7.1(4H,m,Ar-H)6.0-5.8(1H,s,Ar-CH)

Compound 2i:N-((3-nitro phenyl) pieridin-1-yl)methyl)pyrazine-2-carboxamide
Yield:45%; m.p:250-252^{o}C;Rf:0.47. IR(KBr, cm^{1})):1704 (C=O), 3477 (NH),1525(Ar-No_2^{1}HNMR (400 MHz, $CDCl_3$, δ/ppm):8.9-8.5 (3H,d,C_2,C_5,C_6-H pyrazine) 8.3-8.2(1H,s,NH),8.2-7.8(4H, s,m,Ar-H),7.1-7.0 (1H,s,Ar-CH),

Compound 2j:N-((2,4-Hydroxy phenyl) pieridin-1-yl)methyl)pyrazine-2-carboxamide
Yield:60%; m.p:273-275^{o}C;Rf:0.52. IR (KBr, cm^{1})) ^{1}:1671 (C=O), 3259 (NH).^{1}HNMR (400 MHz, $CDCl_3$, δ/ppm):8.3-8.2 (1H, s,-NH),7.7-7.1(6H,m,Ar-CH,+HCN-H),6.7-6.6 (6H,s,Ar-CH),4.0-3.5 (6H,s,-OCH_3+-OCH_3).

Results and Discussion

Antimicrobial Activity: The antimicrobial activity was assayed using the cup-plate agar diffusion method by measuring the zone of inhibition in mm[10]. All the compounds were screened invitro for their antimicrobial activity against bacterial strains *E.coli, B.substilis*,*S.aureas* and the fungi *A. niger* and *C. albicans* at a concentration of 20 to 100µg/ml. standard drugs amoxicillin ciprofloxacin and ketoconazole were used for comparison purposes (table no 1) it is observed the compound 2e,2f were active against *E.coli ;* compounds 2a,2e,and 2f were active against *B. substillus;* compounds 2a,2f were active against *S. aureas* and compounds 2e,2g,2i displayed maximum activity against *A.niger* and compounds 2c,2e against *C. albicans.*

Table no.1: Antimicrobial screening result of compounds 2a to 2j at 20 to 100µgm/ml conc.(avg values)

Compounds	Antibacterial activity (zone of inhibition in mm)			Antifungal activity (zone of inhibition in mm)	
	B.subtilis	*E.Coli*	*S. aureus*	*A. niger*	*C. albicans*
2a	17	16	15	4.0	5.0
2b	14	12	14	3.0	6.0
2c	16	14	14	6.0	13.0
2d	13	18	13	5.0	7.0
2e	17	19	15	7.0	13.0
2f	17	12	18	5.0	10.0
2g	15	10	12	6.0	9.0
2h	11	09	12	7.0	11.0
2i	14	12	14	7.0	12.0
2j	13	20	15	6.0	10.0
Amoxicillin	20	23	29	00	00
Ciprofloxacin	23	22	21	00	00
Ketoconazole	00	00	00	23.0	28.0

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