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Microwave Assisted Synthesis and Biological Studies of Novel Mannich Bases

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In this work, microwave irradiation was employed for the synthesis of Mannich bases using piperidin-4-one, heteroaldehyde and amide moieties. The structures of compounds were characterized through analytical (elemental analysis, melting point and TLC) and spectral methods (IR, ^{1}H NMR, ^{13}C NMR and Mass). Further the compounds were screened for the antibacterial and antifungal activities.

Key Words: Microwave assisted synthesis, Mannich bases, Biological activities.

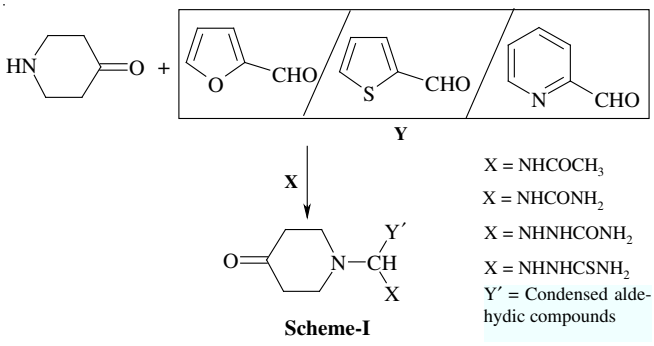
INTRODUCTION

In recent years, considerable interest has been paid on the synthesis of Mannich bases by the use of microwave[1] in the presence of solid supports. Mannich reaction is a multi-component reaction involving aldehyde, amine and compound containing active hydrogen. Many reports are available in the literature for synthesis of Mannich bases using aliphatic and aromatic aldehydes[2-5]. However, the synthesis of Mannich base many primary and secondary amines have been employed, but no report is available using piperidin-4-one as an amine. Literature survey revealed that piperidin-4-one derivatives and amide moieties have widely been investigated for various biological activities[6-13].

EXPERIMENTAL

The compounds were synthesized using domestic microwave oven BPL-700T. Melting points were determined by an open capillary tube and are uncorrected. Purity of the compounds was checked by TLC using silica gel G coated glass plates with chloroform and ethyl acetate (1:1) as irrigant and iodine vapour as visualizing agent. The IR spectra were recorded in KBr on a FT-IR spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AMX400 NMR spectrophotometer using TMS as internal standard and chemical shifts are expressed in ppm. The elemental analyses were performed on a Perkin-Elmer series C, H, N and S analyzer-2000. Mass spectra were recorded on a JEOL-8X 102. All the analytical data of compounds I-XII were tabulated and shown in Table-1.

General procedure for the preparation of compounds I-IV: In a pyrex test tube was placed a mixture of furan-2-carbaldehyde (0.01 mol), piperidin-4-one (0.01 mol) and compounds containing amide moiety [acetamide, urea, semi- and thiosemicarbazide (0.01 mol)]. The test tube was then placed in domestic microwave oven and zapped the contents for 2.5-5.0 min at 540 Watts. Upon completion of the reaction (monitored by TLC), the solid obtained was washed with cold ethanol, filtered, washed again by cold ethanol, dried and crystallized from ethanol. All the reactions are briefly summarized in **Scheme-I**.



Scheme-I

General procedure for the preparation of compounds V-VIII: In a pyrex test tube was placed a mixture of thiophene-2-carbaldehyde (0.01 mol), piperidin-4-one (0.01 mol) and compounds containing amide moiety [acetamide, urea, semi- and thiosemicarbazide (0.01 mol)]. The test tube was then placed in domestic microwave oven and zapped the contents for 3.0-5.0 min at 600 Watts. Upon completion of the reaction (monitored by TLC), the solid obtained was washed with cold

TABLE-1
ANALYTICAL DATA OF THE SYNTHESIZED MANNICH BASES

Compd.	Yield (%)	m..w.	m.p. (ºC)	m.f.	Elemental analysis (%): Found (calcd.)			
					C	H	N	S
I	50	233	136	$C_{12}H_{16}N_2O_3$	61.05 (61.00)	6.64 (6.83)	11.80 (11.86)	–
II	50	235	112	$C_{11}H_{15}N_3O_3$	55.56 (55.69)	6.35 (6.39)	17.68 (17.71)	–
III	50	257	144	$C_{11}H_{16}N_4O_3$	52.35 (52.37)	6.38 (6.38)	22.23 (22.21)	–
IV	50	281	186	$C_{11}H_{16}N_4O_2S$	49.24 (49.24)	6.05 (6.01)	20.87 (20.88)	11.92 (11.95)
V	62	250	204	$C_{11}H_{15}N_3O_2S$	57.13 (57.12)	6.31 (6.39)	11.13 (11.10)	12.74 (12.71)
VI	70	253	226	$C_{11}H_{15}N_3O_2S$	52.13 (52.15)	5.92 (5.97)	16.55 (16.59)	12.63 (12.66)
VII	50	265	215	$C_{11}H_{16}N_4O_2S$	49.23 (49.24)	6.03 (6.01)	20.83 (20.88)	11.92 (11.95)
VIII	60	284	236	$C_{11}H_{16}N_4OS_2$	45.40 (46.45)	5.67 (5.67)	19.73 (19.70)	22.53 (22.55)
IX	76	242	172	$C_{13}H_{17}N_3O_2$	63.15 (63.14)	6.92 (6.93)	16.90 (16.99)	–
X	72	241	185	$C_{12}H_{16}N_4O_2$	58.02 (58.02)	6.52 (6.50)	22.57 (22.57)	–
XI	70	264	155	$C_{12}H_{17}N_5O_2$	54.72 (54.72)	6.52 (6.51)	26.64 (26.60)	–
XII	75	275	232	$C_{12}H_{17}N_5OS$	51.54 (51.59)	6.12 (6.13)	25.05 (25.07)	11.45 (11.48)

ethanol, filtered, washed again by cold ethanol, dried and crystallized from ethanol.

General procedure for the preparation of compounds IX-XII: In a pyrex test tube was placed a mixture of pyridin-2-carbaldehyde (0.01 mol), piperidin-4-one (0.01 mol) and compounds containing amide moiety [acetamide, urea, semi- and thiosemicarbazide (0.01 mol)]. The test tube was then placed in domestic microwave oven and zapped the contents for 4-7 min at 540 Watts. Upon completion of the reaction (monitored by TLC), the solid obtained was washed with cold ethanol, filtered, washed again by cold ethanol dried and recrystallized from ethanol.

N-[Furan-2-yl(4-oxopiperidin-1-yl)methyl]acetamide (compound-I): IR (KBr, ν_{max}, cm^{-1}): 3449 (NH and CH stretching), 1635 (C=O), 1235 (C-N-C), 1118 (C-O-C). ^{1}H NMR (DMSO) δ: 7.8 (s, H, NH), 6.3-6.5 (m, Ar) 5.8 (s, H, CH), 2.3-2.6 (m, piperidin-4-one), 2.0 (s, H, CH_3). ^{13}C NMR (DMSO) δ: 197 (C=O, piperidin-4-one), 124 (Ar), 70 (CH). MS: m/z: 236.

1-[Furan-2-yl(4-oxopiperidin-1-yl)methyl]urea (compound-II): IR (KBr, ν_{max}, cm^{-1}): 3354 (NH and CH stretching), 1644 (C=O), 1170 (C-N-C), 1119 (C-O-C). ^{1}H NMR (DMSO) δ: 5.8 (s, H, NH), 6.3-6.5 (m, Ar), 6.2 (s, H, CH), 3.2-2.8 (m, piperidin-4-one), 2.4 (t, 4H CH (CO)) 2.2 (t, 4H, CH(N)), 2.0 (s, H, CH_3). ^{13}C NMR (DMSO) δ: 180 (C=O piperidin-4-one), 120 (Ar), 64 (CH). MS: m/z: 237.

2-[Furan-2-yl(4-oxopiperidin-1-yl)methyl]hydrazinecarboxamide (compound-III): IR (KBr, ν_{max}, cm^{-1}): 3457 (NH stretching), 3154 (ter. NH), 3079 (Ar CH), 1692 (C=O), 1157 (C-N-C), 1119 (C-O-C). ^{1}H NMR (DMSO) δ: 7.3 (s, 2H, NH_2), 7.5-7.7 (m, Ar), 6.3-6.4 (s, H NH-CO), 5.0 (s, H, CH), 2.3 (t, 4H CH (CO)) 2.2 (t, 4H CH(N)), 2.0 (s, H, NH). ^{13}C NMR (DMSO) δ: 170 (C=O piperidin-4-one), 132 (Ar), 63 (CH). MS: m/z: 252.

2-[Furan-2-yl(4-oxopiperidin-1-yl)methyl]hydrazinecarbothioamide (compound-IV): IR (KBr, ν_{max}, cm^{-1}): 3410 (NH stretching), 3220 (ter. NH), 3139 (Ar CH), 2980 (Aliph. CH), 1277 (C=S), 1147 (C-N-C), 1124 (C-O-C). ^{1}H NMR (DMSO) δ: 8.2 (s, 2H, NH_2), 7.5-7.7 (m, Ar), 6.3-6.4 (s, H NH-CS), 5.4 (s, H, CH), 2.3 (t, 4H CH (CO)) 2.2 (t, 4H CH(N)), 2.4 (s, H NH). ^{13}C NMR (DMSO) δ: 184 (C=O piperidin-4-one), 142 (Ar), 66 (CH). MS: m/z: 284.

N-[(4-Oxopiperidin-1-yl)(thiophen-2-yl)methyl]acetamide (compound-V): IR (KBr, ν_{max}, cm^{-1}): 3100 (CH stretching), 1700 (C=O), 1654 (amide-I), 1580 (amide-II), 1125 (C-S-C). ^{1}H NMR (DMSO) δ: 8.0 (s, H, NH), 7.4-6.8 (m, Ar), 6.0 (s, H CH), 2.3 (t, 4H CH (CO)) 2.2 (t, 4H CH(N)), 1.9 (s H CH_3). ^{13}C NMR (DMSO) δ: 202 (C=O piperidin-4-one), 170 (C=O amide), 134, 126, 120 (Ar), 72 (CH-N), 47, 43 (CH_2(O), CH_2(N)). MS: m/z: 253.

1-[(4-Oxopiperidin-1-yl)(thiophen-2-yl)methyl]urea (compound-VI): IR (KBr, ν_{max}, cm^{-1}): 3330 (NH stretching), 3020 (CH str.), 1693 (C=O), 1644 (amide-I), 1565 (amide-II), 1143 (C-S-C). ^{1}H NMR (DMSO) δ: 8.0 (s, 2H, NH_2), 6.2-7.4 (m, ArH), 5.8 (s, H CH), 2.8 (t, 4H CH (CO)) 2.4 (t, 4H CH(N)). ^{13}C NMR (DMSO) δ: 180 (C=O piperidin-4-one), 164 (C=O amide), 130, 126, 120 (Ar CH), 68 (CH-N), 45, 42 (CH_2(O), CH_2(N)), MS: m/z: 252.

2-[(4-Oxopiperidin-1-yl)(thiophen-2-yl)methyl]hydrazinecarboxamide (compound-VII): IR (KBr, ν_{max}, cm^{-1}): 3384, 3244, 3159 (NH/NH, NH_2 str.), 1674 (C=O), 1640 (amide-I), 1583 (amide-II), 1143 (C-S-C). ^{1}H NMR (DMSO) δ: 9.2 (s, 2H, NH_2), 8.4 (s, H NH-CO), 7.3-8.3 (m, ArH), 5.2 (s, H NH), 4.8 (s, H, CH-NH), 2.8 (t, 4H CH (CO)), 2.4 (t, 4H, CH(N)). ^{13}C NMR (DMSO) δ: 180 (C=O piperidin-4-one), 170 (C=O amide), 130, 126, 120 (Ar CH), 72 (CH-N), 47, 44 (CH_2(O), CH2(N)). MS: m/z: 268.

2-[(4-Oxopiperidin-1-yl)(thiophen-2-yl)methyl]hydrazinecarbothioamide (compound-VIII): IR (KBr, ν_{max}, cm^{-1}): 3420, 3380, 3121 (NH/NH, NH_2 str.), 1664 (amide-I), 1585 (amide-II), 1121 (C=S). ^{1}H NMR (DMSO) δ: 10.2 (s, 2H, NH_2), 9.4 (s, H, NH-CS), 8.3 (m, ArH), 7.0 (s, H NH-CH) 5.2 (s, H, CH-NH), 2.8 (t, 4H CH_2(CO)), 2.4 (t, 4H, CH_2(N)). ^{13}C NMR (DMSO) δ: 200 (C=O piperidin-4-one), 170 (C=S amide), 130, 126, 120 (Ar CH), 78 (CH-N), 45, 40 (CH_2(O), CH_2(N)). MS: m/z: 285.

N-[(4-Oxopiperidin-1-yl)(pyridin-2-yl)methyl]acetamide (compound-IX): IR (KBr, ν_{max}, cm^{-1}): 3020 (CH stretching), 1705 (C=O), 1690 (amide-I), 1580 (amide-II), 1235 (C-N-C). ^{1}H NMR (DMSO) δ: 8.3 (s, H, NH-CH), 7.4-6.8 (m, Ar), 5.4 (s, H, CH), 3.2 (d, 4H, CH (CO)) 2.8 (t, 4H CH(N)), 2.0 (t, 3H, CH_3). ^{13}C NMR (DMSO) δ: 190 (C=O piperidin-4-one), 168 (C=O amide), 134, 126, 120 (Ar CH), 72 (CH-N), 47, 43 (CH_2(O), CH_2(N)), MS: m/z: 246.

1-[(4-Oxopiperidin-1-yl)(pyridin-2-yl)methyl]urea (compound-X): IR (KBr, ν_{max}, cm^{-1}): 3300 (NH stretching), 2980 (CH str.), 1673 (C=O), 1652 (amide-I), 1582 (amide-II). ^1H NMR (DMSO) δ: 7.0-6.6 (m, ArH), 6.0 (s, 2H, NH_2), 5.6 (s, H, NH-CH), 4.8 (s, H CH-NH), 3.2 (t, 4H, CH (CO)) 2.8 (t, 4H, CH(N)). ^{13}C NMR (DMSO) δ: 190 (C=O piperidin-4-one), 164 (C=O amide), 130, 126, 120 (Ar), 73 (CH-N), 45, 42 (CH_2(O), CH_2(N)), MS: m/z: 246.

2-[(4-Oxopiperidin-1-yl)(pyridin-2-yl)methyl]hydrazinecarboxamide (compound-XI): IR (KBr, ν_{max}, cm^{-1}): 3353, 3244, 3132 (NH/NH, NH_2 str.), 1681 (C=O), 1648 (amide-I), 1562 (amide-II), 1230 (C-N-C). ^1H NMR (DMSO) δ: 9.2 (s, 2H, NH_2), 7.8 (s, H NH-NH), 7.3-6.8 (m, Ar) 6.2 (s, NH-CH), 5.3 (t, H, CH-NH), 2.8 (t, 4H, CH (CO)), 2.4 (d, 4H, CH(N)). ^{13}C NMR (DMSO) δ: 194 (C=O piperidin-4-one), 170 (C=O amide), 140, 126, 120 (Ar), 72 (CH-N), 47, 44 (CH_2(O), CH_2(N)), MS: m/z: 266.

2-[(4-Oxopiperidin-1-yl)(pyridin-2-yl)methyl]hydrazinecarbothioamide (compound-XII): IR (KBr, ν_{max}, cm^{-1}): 3380, 3300, 3150, 3032 (NH/NH, NH_2, CH str.), 1700 (C=O) 1670 (amide-I), 1565 (amide-II), 1135 (C=S). ^1H NMR (DMSO) δ: 9.2 (s, 2H, NH_2), 9.4 (s, H NH-CS), 8.3 (m, ArH), 5.0 (s, H, CH-NH) 4.8 (t, H, NH-CH), 2.8 (t 4H, CH_2(CO)), 2.4 (d 4H CH_2(N)). ^{13}C NMR (DMSO) δ: 200 (C=O piperidin-4-one), 170 (C=S amide), 130, 126, 120 (Ar CH), 78 (CH-N), 45, 40 (CH_2(O), CH_2(N)), MS: m/z: 276.

Antimicrobial activity: The synthesized compounds **I-XII** were screened for antibacterial and antifungal activities against certain pathogenic bacteria by disc diffusion method at concentration of 10 µg/mL in DMSO using gram positive *S. aureus, B. substilis*, gram negative *E. coli, P. aeruginosa* and anti fungal activity against *C. albicans*. The zone of inhibition was measured in mm and the activities were compared with ciprofloxacin 1 µg/disc for bacteria and clotrimazole 10 µg/disc for fungi as standard drugs. The antibacterial results showed maximum inhibition against *S. aureus*, *B. substilis* for the compounds **V-VIII**. The compounds **IX-XII** possess maximum inhibition against the entire selected organism when compared with the standard. The compounds **I-IV** showed significant activity compared to that of standard. The order of activity for the compound is (**IX-XII**) > (**V-VIII**) > (**I-IV**). The zone of inhibition value of the above compounds are shown in Table-2.

TABLE-2
ANTIMICROBIAL DATA OF THE SYNTHESIZED MANNICH BASES

Compd.	Diameter zone of inhibition (mm)				
	Gram positive		Gram negative		Fungi
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*	*C. albicans*
I	19	17	16	18	10
II	19	18	17	19	12
III	20	20	17	18	11
IV	17	18	13	19	09
V	19	18	14	16	10
VI	18	18	12	15	10
VII	15	13	09	NI	08
VIII	12	10	NI	10	09
IX	22	20	18	21	13
X	21	19	17	22	NI
XI	21	22	18	19	12
XII	23	20	17	21	17
Standard	23	20	17	21	17
Solvent	20	19	16	19	12

Standard = Ciprofloxacin 1 µg/disc for bacteria, clotrimazole 10 µg/disc for fungi; Solvent = Dimethyl sulfoxime; NI = No Inhibition

RESULTS AND DISCUSSION

In the present study, 12 compounds of piperidin-4-one derivatives have been prepared by microwave irradiation method. If the same compounds are prepared by conventional method, it will require 7-8 h for refluxion. From this study, it is found that microwave irradiation synthesis is found to be more efficient over conventional method. It has been observed that all the reported compounds are found to possess antimicrobial and antifungal activities. The preparation of various Mannich bases containing heterocyclic component might make a contribution to the development of antibacterial and antifungal drugs.

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