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Synthesis, Characterization and Biological Activity Studies of Some N-Mannich Bases of 1-Substituted methyl-2-(substituted phenyl)benzimidazoles

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The synthesis of N-Mannich bases of 1-substituted methyl-2-(substituted phenyl)benzimidazoles have been reported. The synthesized derivatives were characterized by elemental analysis and spectral data (IR and ^{1}H NMR). All the synthesized derivatives have been evaluated for their antibacterial, anthelmintic and insecticidal activities against microbes, helminthes and insects as compared to standard drugs. All the synthesized derivatives exhibited significant to good biological activities.

Key Words: Mannich bases, Benzimidazoles, Antibacterial, Anthelmintic, Insecticidal activities.

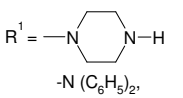
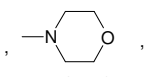
INTRODUCTION

Benzimidazole nucleus is a useful precursor for further molecular exploration and development of new pharmaceutical compounds[1-4] has been studied extensively. Benzimidazole and its derivatives have received much attention owing to the varied biological and pharmaceutical activities including antibacterial[5-7], antifungal[5-7] herbicidal[8], analgesic[9], antioxidant[10], antitumoral agents[11], insecticidal[12], anticancer[13], anti-HIV agents[14], antiviral[14], antiinflammatory[15] and anthelmintic[16] agents. In view of these activities and synthetic importance, benzimidazole core and its various derivatives have long been an area of interest and still constitutes as an active domain for research and industrial field. These versatile biological significance inspired us to synthesize the N-Mannich Bases of 1-substituted methyl-2-(substituted phenyl)benzimidazoles.

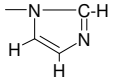
In the present communication we have synthesized N-Mannich bases of 1-substituted methyl-2-(substituted phenyl) benzimidazole (**Scheme-I**), characterized and screened for their antibacterial, anthelmintic and insecticidal activities.

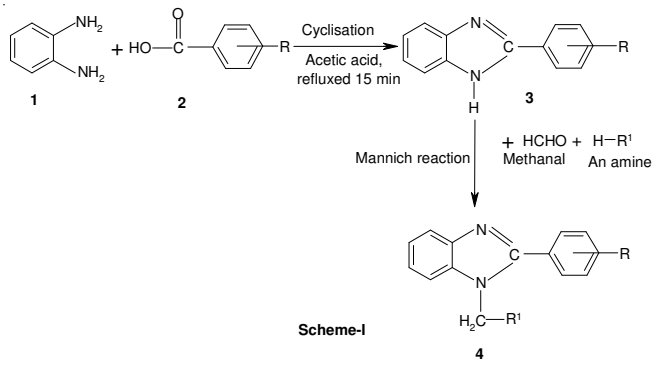
N-Mannich base of 2-substituted phenyl-benzimidazole

where: R = 4-NO_2, 4-OH, 2-OH, 2-Cl

R^1 =  ,  ,

-N (C_6H_5)$_2$, -N (C_2H_4OH)$_2$

- N (C_2H_5)$_2$, 



Scheme-I

EXPERIMENTAL

The melting points (ºC) were recorded by open capillary method and are uncorrected. IR spectra (ν_{max} in cm^{-1}) were recorded on a Shimadzu FTIR 8300 spectrophotometer using KBr pellets. The ^{1}H NMR spectra were recorded on a DRX-300 (300 MHz) instrument using $CDCl_3$ as solvent (chemical shift in δ ppm) and TMS as internal standard. The completion of reactions was monitored by TLC.

Synthesis of 2-(substituted phenyl)benzimidazole 3(a-l): A solution of substituted benzoic acid (0.1 mol) and *o*-phenylenediamine (0.1 mol) in 30 mL of acetic acid was refluxed for 15 min. The product obtained was recrystallized from 20 % acetic acid, dried in vacuum and further recrystallized from DMF. The purity of compounds has been checked by TLC.

Similarly other 2-(substituted phenyl)benzimidazoles were synthesized with the same procedure using different 4-substituted benzoic acid. The purity of the compounds has been checked by TLC.

Synthesis of N-Mannich bases of 2-(substituted phenyl)benzimidazole 4(a-l): To a solution of 2-(substituted phenyl)benzimidazoles (0.02 mol) from **step-1**, in 10-15 mL of ethanol, 0.02 mol of respective secondary amine (piperazine) and 0.02 mol of methanal were added into it with stirring and further stirred it for 1 h at room temperature. Then the reaction mixture was refluxed for 20 min. On cooling, the product formed, was filtered, dried in vacuum and recrystallized through different suitable solvents *viz.*, ethanol, DMF, benzene, acetone and DMSO. The completion of the reaction was monitored by TLC.

Other derivatives of substituted N-Mannich base were prepared with different secondary amine with methanal applying the same procedure.

The physico-chemical data of all the synthesized derivatives are given in Table-1.

Spectral data of derivatives 4(a-l)

1-Piperazinomethyl-2-(4-nitrophenyl)-1*H*-benzimidazole (4a): IR (KBr, ν_{max}, cm^{-1}): 3111 (Ar-H str.), 1610 (C=C str.), 1558 (C=N str.), 3300 (N-H str.), 2874 (C-H str.), 1321 (N=O str. sym.), 1213 (N-C str.); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.39 (d, 1H, N-H piperazine), 2.52-2.55 (τ, 4H(α), CH_2-N-CH_2), 2.85-2.90 (τ, 4H(β), CH_2-N(H)-CH_2), 4.79 (d, 2H, N-CH_2-N), 7.11-8.20 (m, 8H, Ar-H).

1-Diphenylaminomethyl-2-(4-nitrophenyl)-1*H*-benzimidazole (4b): IR (KBr, ν_{max}, cm^{-1}): 3101 (Ar-H str.), 1600 (C=C str.), 1556 (C=N str.), 2877 (C-H str.), 1318 (N=O str. sym.), 1215 (N-C str.); ^{1}H NMR ($CDCl_3$) δ (ppm): 5.48 (d, 2H, N-CH_2-N), 6.88-7.54 (m, 18H, Ar-H).

1-Morpholinomethyl-2-(4-nitrophenyl)-1*H*-benzimidazole (4c): IR (KBr, ν_{max}, cm^{-1}): 3072 (Ar-H str.), 1610 (C=C str.), 1556 (C=N str.), 2868 (C-H str.), 1320 (N=O str. sym.), 1109 (C-O-C str.); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.53-2.66 (τ, 4H CH_2-N-CH_2), 3.59-3.68 (τ, 4H, CH_2-O-CH_2), 4.80 (d, 2H, N-CH_2-N), 7.29-8.10 (m, 8H, Ar-H).

1-Diethanolaminomethyl-2-(4-nitrophenyl)-1*H*-benzimidazole (4d): IR (KBr, ν_{max}, cm^{-1}): 3012 (Ar-H str.), 1610 (C=C str.), 1580 (C=N str.), 2874 (C-H str.), 1317 (N=O str. sym.), 1253 (N-C str.), 3300 (O-H str.); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.59-2.65 (τ, 4H CH_2-N-CH_2), 3.54-3.64 (τ, 4H, C-(CH_2-CH_2-OH)$_2$), 3.78 (d, 2H, C -(CH_2-OH)$_2$), 4.89 (d, 2H, N-CH_2-N), 7.32-8.07 (m, 8H, Ar-H).

1-Imidazolomethyl-2-(4-nitrophenyl)-1*H*-benzimidazole (4e): IR (KBr, ν_{max}, cm^{-1}): 3072 (Ar-H str.), 1600 (C=C str.), 1568 (C=N str.), 2874 (C-H str.), 1319 (N=O str. sym.), 1346 (N-C str.); ^{1}H NMR ($CDCl_3$) δ (ppm): 6.0 (δ, 2H, N-CH_2-N), 6.72 (d, 1H, H-C5), 7.11 (d, 1H, H-C4), 7.40 (δ, 1H, H-C2), 7.51-8.29 (m, 8H, Ar-H).

1-Diethylaminomethyl-2-(4-nitrophenyl)-1*H*-benzimidazole (4f): IR (KBr, ν_{max}, cm^{-1}): 3109 (Ar-H str.), 1610 (C=C str.), 1558 (C=N str.), 2945 (C-H str.), 1317 (N=O str. sym.), 1230 (N-C str.); ^{1}H NMR ($CDCl_3$) δ (ppm): 1.05 (τ, 6H(β), N-(CH_2 CH_3)$_2$), 2.67 (q, 4H(α), N-(CH_2 CH_3)$_2$), 7.25-8.10 (m, 8H, Ar-H).

1-Piperazinomethyl-2-(4-hydroxy phenyl)-1*H*-benzimidazole (4g): IR (KBr, ν_{max}, cm^{-1}): 3045 (Ar-H str.), 1608 (C=C str.), 1548 (C=N str.), 3320 (N-H str.), 2856 (C-H str.), 1174 (N-C str.), 3391 (O-H str.); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.41 (δ, 1H, N-H piperazine), 2.54-2.57 (τ, 4H(α), CH_2-N-CH_2), 2.88-2.91 (τ, 4H(β), CH_2-N(H)-CH_2), 4.81 (δ, 2H, N-CH_2-N), 5.68 (δ, 1H, Ar-OH), 7.28-7.71 (m, 8H, Ar-H).

1-Diphenylaminomethyl-2-(4-hydroxyphenyl)-1*H*-benzimidazole (4h): IR (KBr, ν_{max}, cm^{-1}): 3010 (Ar-H str.), 1606 (C=C str.), 1585 (C=N str.), 2893 (C-H str.), 1365 (N-C str.), 3394 (O-H str.); ^{1}H NMR ($CDCl_3$) δ (ppm): 5.51 (δ, 2H, N-CH_2-N), 6.03 (δ, 1H, Ar-OH), 6.95-7.60 (m, 18H, Ar-H).

1-Morpholinomethyl-2-(4-hydroxyphenyl)-1*H*-benzimidazole (4i): IR (KBr, ν_{max}, cm^{-1}): 3050 (Ar-H str.), 1606 (C=C str.), 1530 (C=N str.), 2870 (C-H str.), 1134 (N-C str.), 1286 (C-O-C str.), 3286 (O-H str.); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.72-2.79 (τ, 4H(α), CH_2-N-CH_2), 3.59-3.63 (τ, 4H(β), CH_2-O-CH_2), 4.79 (δ, 2H, N-CH_2-N), 5.65 (δ, 1H, Ar-OH), 6.95-7.71 (m, 8H, Ar-H).

1-Piperazinomethyl-2-(2'-hydroxy phenyl)-1*H*-benzimidazole (4j): IR (KBr, ν_{max}, cm^{-1}): 3030 (Ar-H str.), 1591 (C=C str.), 1575 (C=N str.), 3350 (N-H str.), 2800 (C-H str.), 1170 (N-C str.), 3300 (O-H str.); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.40 (δ, 1H, N-H piperazine), 2.53-2.55 (τ, 4H(α), CH_2-N-CH_2), 2.87-2.90 (τ, 4H(β), CH_2-N(H)-CH_2), 4.82 (δ, 2H, N-CH_2-N), 5.65 (δ, 1H, Ar-OH), 7.25-7.66 (m, 8H, Ar-H).

TABLE-1
PHYSICAL DATA OF SYNTHESIZED DERIVATIVES **4a-l**

Compd. No.	R	R^1	m.f.	m.w.	m.p. (ºC)	Yield (%)	Elemental analysis (%): Found (calcd.)		
							C	H	N
4a	4-NO_2	Piperazino	$C_{18}H_{19}N_5O_2$	337.0	220	75	63.99 (64.09)	5.60 (5.63)	20.70 (20.77)
4b	4-NO_2	Diphenylamino	$C_{26}H_{20}N_4O_2$	420.0	185	78	74.22 (74.28)	4.72 (4.76)	13.30 (13.33)
4c	4-NO_2	Morpholino	$C_{18}H_{18}N_4O_3$	338.0	173	78	63.88 (63.90)	5.30 (5.32)	16.52 (16.56)
4d	4-NO_2	Diethanolamino	$C_{18}H_{20}N_4O_4$	356.0	152	80	60.62 (60.67)	5.60 (5.61)	15.69 (15.73)
4e	4-NO_2	Imidazolo	$C_{17}H_{13}N_5O_2$	319.0	215	58	63.90 (63.94)	4.02 (4.07)	21.89 (21.94)
4f	4-NO_2	Diethylamino	$C_{18}H_{20}N_4O_2$	324.0	92	56	66.60 (66.66)	6.11 (6.17)	17.20 (17.28)
4g	4-OH	Piperazino	$C_{18}H_{20}N_4O$	308.0	245	88	70.09 (70.12)	6.42 (6.49)	18.12 (18.18)
4h	4-OH	Diphenylamino	$C_{26}H_{21}N_3O$	391.0	266	87	79.72 (79.79)	5.34 (5.37)	10.70 (10.74)
4i	4-OH	Morpholino	$C_{18}H_{19}N_3O_2$	309.0	146	78	69.88 (69.90)	6.10 (6.14)	13.55 (13.59)
4j	2-OH	Piperazino	$C_{18}H_{20}N_4O$	308.0	285	72	70.10 (70.12)	6.43 (6.49)	18.14 (18.18)
4k	2-OH	Diphenylamino	$C_{26}H_{21}N_3O$	391.0	188	86	79.74 (79.79)	5.32 (5.37)	10.71 (10.74)
4l	2-Cl	Piperazino	$C_{18}H_{19}N_4Cl$	326.5	290	55	66.11 (66.15)	5.78 (5.81)	17.11 (17.15)

1-Diphenylaminomethyl-2-(2'-hydroxyphenyl)-1*H*-benzimidazole (4k): IR (KBr, ν_{max}, cm^{-1}): 3020 (Ar-H str.), 1614 (C=C str.), 1579 (C=N str.), 2866 (C-H str.), 1303 (N-C str.), 3240 (O-H str.); ^1H NMR ($CDCl_3$) δ (ppm): 5.50 (δ, 2H, N-CH_2-N), 6.01 (δ, 1H, Ar-OH), 6.92-7.66 (m, 18H, Ar-H).

1-Piperazinomethyl-2-(2'-chloro phenyl)-1*H*-benzimidazole (4l): IR (KBr, ν_{max}, cm^{-1}): 3011 (Ar-H str.), 1604 (C=C str.), 1589 (C=N str.), 3270 (N-H str.), 2875 (C-H str.), 1170 (N-C str.), 711 (Ar-Cl str.); ^1H NMR ($CDCl_3$) δ (ppm): 2.38 (δ, 1H, N-H piperazine), 2.53-2.55 (τ, 4H(α), CH_2-N-CH_2), 2.86-2.89 (τ, 4H(β), CH_2-N(H)-CH_2), 4.80 (δ, 2H, N-CH_2-N), 7.10-7.48(m, 8H, Ar-H).

Antimicrobial activity[17,18]: The synthesized derivatives (**4a-l**) were screened for their *in vitro* antibacterial activity against, *Bacillus subtilis, Escherichia coli, Klebsiella pneumoniae* and *Staphylococcus aureus*, by measuring the zone of inhibition in mm. The antibacterial activity was performed by standard filter paper disc diffusion method, using 4 % solution of synthesized derivatives and standard drug streptomycin in DMSO. Nutrient agar was employed as culture medium. The results are presented in the Table-2.

TABLE-2
RESULTS OF ANTIBACTERIAL ACTIVITY OF SYNTHESIZED DERIVATIVES **4a-l**

Compd. No.	Antibacterial			
	B. subtilis	*E. coli*	*K. pneumoniae*	*S. aureus*
4a	++	+++	+++	++++
4b	+++	+++	++	++
4c	+++	++	++	++++
4d	++	++	+	-
4e	++	+++	+++	+++
4f	++	++	++	+
4g	+++	++	+++	+++
4h	++	++	++	+
4i	+++	++++	+++	++++
4j	++++	+++	++	++
4k	+++	++	+	++
4l	+++	+++	++	+++
Streptomycin	++++	++++	+++	++++

Zone of inhibition was measured in mm; ++++ = (18-20 mm) strong activity; +++ = (15-18 mm) good activity, ++ = (10-15 mm) moderate activity, + = (8-10) slight active, – = (< 8) inactive.

***In vitro* anthelmintic activity[19]:** *In vitro* anthelmintic screening studies of synthesized derivatives **4a-l**, were performed by the Watkins technique, against common Indian earthworm '*P. posthuma*'. For this purpose 4 % and 2 % solutions of the synthesized benzimidazole derivatives and standard drug piperazine hydrochloride in ethylene glycol were used for experiment. The experiments were performed in duplicate and average values of paralytic time and lethal time in minutes have given in the Table-3.

Insecticidal activity[20,21]: Adult cockroaches (*P. americana*) were selected for the testing of *in vitro* insecticidal activity. 4 % Solution of synthesized benzimidazole derivatives and standard drug cypermethrin (w/v) in actone were used for experiment. The time of death of cockroaches was noted as Knock Down value in minutes. For each sample three replication were performed and same experiments were performed with standard drug.

TABLE-3
RESULTS OF ANTHELMINTIC ACTIVITY OF SYNTHESIZED DERIVATIVES **4a-l**

Compd. No.	Concentration			
	4 %		2 %	
	Mean paralytic time (min)	Mean lethal time (min)	Mean paralytic time (min)	Mean lethal time (min)
4a	5	12	7	14
4b	6	13	7	15
4c	7	14	8	16
4d	8	15	9	20
4e	7	14	8	15
4f	8	14	9	18
4g	7	13	7	14
4h	8	13	8	16
4i	7	15	9	17
4j	7	14	8	15
4k	9	18	10	19
4l	6	15	8	17
Streptomycin	6	13	7	15

RESULTS AND DISCUSSION

All the synthesized N-Mannich bases of benzimidazole derivatives **4a-l** have given appreciable yield with satisfactory elemental analysis. It is inferred from the Tables 2-4, that synthesized derivatives **4a-l** have exhibited significant anthelmintic activity, while moderate to good antibacterial and insecticidal activities against helminthes, bacteria and insect selected, as compared to standard drugs. Due to increase of basic moiety, derivatives associated with piperazino, morpholino, imidazolo and diphenylamino substituents along with nitro and chloro groups produced better activity than the rest. On passing toxicity tests these derivatives may prove to be a good antibacterial, insecticidal and potent anthelmintic agents of future.

TABLE-4
RESULTS OF INSECTICIDAL ACTIVITY OF SYNTHESIZED DERIVATIVES **4a-l**

Comp. No.	R	R^1	Mean Known Down value (min)
4a	4-NO_2	Piperazino	10
4b	4-NO_2	Diphenylamino	12
4c	4-NO_2	Morpholino	13
4d	4-NO_2	Diethanolamino	14
4e	4-NO_2	Imidazolo	12
4f	4-NO_2	Diethylamino	13
4g	4-OH	Piperazino	9
4h	4-OH	Diphenylamino	11
4i	4-OH	Morpholino	13
4j	2-OH	Piperazino	11
4k	2-OH	Diphenylamino	12
4l	2-Cl	Piperazino	9
Cypermethrin	–	–	8

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