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Synthesis, Characterization, *In Silico* prediction and Anti-microbial evaluation of 2-Substituted Benzimidazole Derived Mannich bases

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ABSTRACT

Benzimidazoles and its derivatives are most prominent biological active compounds in nature. Mannich reaction is one of the versatile reaction used in synthetic tools, Substituted Benzimidazole prepared from condensation between various acids and ortho phenylene diamine followed by reacting with secondary amine. The synthesized molecules were in substantial yield and characterized by physiochemically, IR, ^{1}H-NMR spectral data and *in silico* prediction. All the values of the synthesized benzimidazole derivatives were found to be in compliance with standard values stated according to the Lipinski's rule of five. The synthesized compounds were screened with antibacterial activity by standard tetracycline and antifungal activity was determined using standard fluconazole. The results shown significant inhibitory activity against the microbes with the 200 mcg/ml which produce 100% inhibition. Over the series 5D (a) and (b) shown good antibacterial and antifungal effect.

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INTRODUCTION

Nitrogen based heterocyclic compounds like Benzimidazole derivatives are having eminent biologically active principles (Kalyankar TM *et al.,* 2012). It is well known that Benzimidazole derivatives are having therapeutic utility against microbes, inflammation, HIV and cancer and act as analgesic also. Substituted amino group at 1-position of the benzimidazole were reported to be connected with potent anti-inflammatory activity. Therefore, it was suspected that planning to prepare the Mannich base derivatives from 2-substituted benzimidazoles would presumably bring about active compounds of having high biological activities toward many ailments. In this study, we proceed with our work and report the synthesis of a number of Mannich bases got from substituted Benzimidazole, (Mohamed G Elerafi *et al.,* 2010).

Benzimidazoles derivatives broadly used as drugs such as proton pump inhibitor Omeprazole (H.D. Langtry and M.I.Wilde *et al.,* 1998) antihelmenthetic Albendazole (J.C.Hazelton *et al.,* 1995, M.Vijey Aanandhi *et al.,* 2013), antidopaminergic Domperidone (Ludo. E.J. Kennis *et al.,* 1986), specially, the 2-substituted benzimidazoles are known to be effective biologically active compounds Anti inflammatory, Anti tumor, Anti microbial, (Rajasekaran S *et al.,* 2012, Tonelli M *et al.,* 2008, Vitale G *et al.,* 2010). In addition, benzimidazole derivatives are structural basic isosteres of naturally occurring nucleotides, which enables them to connect effortlessly with the biopolymers of the living systems. (P.N.Preston, 1974).

Mannich reaction involves condensation between at least one active hydrogen containing compounds, bases like ammonia, secondary amine and formaldehyde. It has been used as a synthetic tool in the preparation of various therapeutic agents

like, fluoxetine as antidepressant agent, ethacrynic acid a high ceiling loop diuretic, benzoquinamide, a high psychotic agent, Ranitidine a H-receptor antagonists, Triprolidine, H-receptor antagonist and Trihexylphenidyl hydrochloride, an antispasmodic. Mannich bases are physiologically reactive because of the basic function rendering the molecule soluble in aqueous solvent when it is transformed into ammonium salt (Pandeya SN, 2003). Over the past few decades, Mannich bases of heterocyclic molecules have been grabbing the attention of the synthetic chemists for their biological activities ranging from antibacterial, anticancer, antiparkinson to anticonvulsant, analgesic, antispasmodic, anti-HIV anti-malarial as well as intermediates in drug synthesis (Vijayaraghavan S *et al.,* 2009). 2- Substituted benzimidazole derivatives, one of the most important derivatives of benzimidazole are known to possess varied biological activities. In SAR, the biological activities of benzimidazole compounds depend upon the substitution at the N-1 or C-2 position (Devender Pathak et al.,). These observations have been guiding for the development of new mannich bases of 2-substituted benzimidazole derivatives and evaluated for antibacterial and anthelmintic activity. Mannich bases also synthesized from Schiff bases and reported the anti microbial activity (Vinoth Kumar S *et al.,* 2013).

MATERIAL AND METHODS

The melting point apparatus is used to determine the melting points of synthesized compounds and are uncorrected. A TLC with solvent system of Chloroform and Methanol (9:1) and UV-Chamber detectoris used to ascertain the completion of the reaction and the purity of the synthesized compounds. The characterization of synthesized compounds were done by using MB 3000 series FT-IR(KBr- pellet method). AMX-400 NMR spectrophotometer at 400 MHz is used to record 1H-NMR and 13 C-NMR with DMSO as the solvent and tetra methyl silane (TMS) as internal standard. The chemical shifts are expressed in δ ppm. The steps used to synthesize the intermediate and target compounds was depicted in SCHEME 1.

Synthesis of mannich bases

Conventional procedure for the synthesis of derivatives of 2- substituted benzimidazole

Reflux the solutions of O-phenylene diamine and an amino acid (0.01 mol each) for 2 hrs, cool and the mixture were alkalified with 10% NaOH and filter the product. The precipitate dried and recrystallized from ethanol (Vinoth Kumar S *et al.,* 2013).

Conventional procedure for the synthesis of mannich bases

Reflux the solutions of 2- substituted benzimidazole (0.005 mol) in 10ml ethyl alcohol, secondary amine (0.005 mol) and formaldehyde (0.005 mol) for 8 hrs. Cool the resulting solution and the product formed was filtered, dried and recrystallized using DMF (Vinoth Kumar S *et al.,* 2013). Structures and Specific details given to each compound table: 1&2. In silico Prediction (Boudjemma Boumoud *et al.,* 2013)

The synthesized compounds were predicted for molecular physicochemical properties relative to drug design and QSAR like log P, molecular polar surface area (PSA), and the Rule of 5 descriptors. The compounds were also predicted for activity score and drug-likeness for ligands like GPCR, ion channel modulators and kinase inhibitors (interactive virtual screening).

Log P (Octanol /water partition coefficient)

Mol inspiration develops a method to calculate Log P which has a sum of fragment-based contributions and correction factors. Method is able to process practically all organic, most organometallic molecules and is very robust.

Molecular Total Polar Surface Area TPSA

TPSA can be calculated as a sum of O- and N- centered polar fragment contributions. TPSA acts as a very prominent descriptor of drug absorption which includes intestinal absorption, bioavailability and BBB penetration.

Molecular Volume

This calculation method is based on group contributions which have been obtained by fitting sum of fragment contributions to "real" 3D volume for a training set of about twelve thousand, mostly drug-like molecules which were fully optimized by the semiempirical AM1 method.

"Rule of 5" Properties

This was proposed by Lipinski for better bioavailability. The rules include the "drug-like" molecules should have

1. logP ≤ 5
2. molecular weight ≤ 500
3. number of hydrogen bond acceptors ≤ 10
4. number of hydrogen bond donors ≤ 5
5. Polar surface area no greater than 140 Å2

Molecules violating more than one of these rules may have problems with bioavailability.

Number of Rotatable Bonds – nrotb

This focuses on molecular flexibility which descripts oral bioavailability of drugs. Rotatable bond is any single non-ring bond, attached to non terminal heavy (i.e., non-hydrogen) atom.

Anti-microbial activity (M. Vijey Aanandhi *et al.,* 2013)

Dissolve the respective proportions of sodium chloride, peptone, agar-agar, beef and yeast extracts in 100 ml distilled water in a clean conical flask.

Test and adjust the pH of the medium to 7.4 pH using universal indicator paper, which shows green color at this PH. seal the conical flask with non-absorbent cotton and sterilize in autoclave at 121°C (15 lbs pressure) for 30 minutes and pour into sterile petridishes.

The standard drug tetracycline, Fluconazole disc was placed on the media and the whatmann filter disc (5mm diameter) were cut and filled into vials plugged with cotton. These vials were kept in hot air oven at 160°C for 30 minutes for sterilization.

Then it was soaked in synthesized compounds separately and evaporated to dryness and then kept on the media (5mm height). One more disc immersed in DMSO and kept on the media as control. It was kept in the incubator for a period of 24 hrs at 37°C. Observations were made for the zone of inhibition around the synthesized compounds and compared with that of standard. DMSO was used as a solvent for both anti-bacterial and anti fungal activity, and the results are presented in minimal inhibition concentration (MIC) values (µg/ml) in Table 5.

RESULT AND DISCUSSION

In the present work Reflux the solutions of orthophenylene diamine (OPDA) which was condensed with acid and aminoacids such as benzoic acid, glycine, alanine, Phenyl alanine, leucine. Mannich bases were prepared by Reflux the solutions of 2-substituted benzimidazole (0.005 mol) in 10ml ethyl alcohol, secondary amine (0.005 mol) and formaldehyde (0.005 mol) for 8 hrs. Cool the resulting solution and product was confirmed by TLC and was characterized by IR and NMR. The melting point of the synthesized compounds was measured by using open capillary tube method.

Physical and Spectral Data of Synthesized Compounds

N, N-dimethyl-1-(2-phenyl-1H-benzimidazol-1-yl)methanamine: $C_{16}H_{17}N_3$, 65% yield, m.p. 326-328°C, IR (KBr, υ cm-1), 1271.72{C-N Str(aryl)}, 1436.61{CH_2 (bend)}, 1601.01{C=N}, 711.89{C-H (alkyl)}, 1H NMR (DMSO), 2.27(s, 6H, -CH_3), 4.80(s, 2H, -CH_2-), 7.26-7.70(m, 9H, Ar-H). Composition : C(76.46%), H(6.82%), N(16.72%). Composition: C(76.42%) H(6.78%) N(16.62%)

N-ethyl-N-[(2-phenyl-1H-benzimidazol-1-yl)methyl] ethanamine: $C_{18}H_{21}N_3$, 65.5% yield, m.p. 315-318°C, IR (KBr, υ cm-1), 1011.94{C-N Str(alkyl)}, 1272.13{C-N Str(aryl)}, 1434{CH_2 (bend)}, 1600.12{C=N}, 1555.83{C=C}, 712.28{C-H (alkyl)}, 1H NMR (DMSO), 1.00(t, 6H, -CH_3), 2.40(m, 4H, -CH_2-), 4.80(s, 2H, -CH_2-), 7.26-7.70(m, 9H, Ar-H). Composition: C (77.34%), H(7.52%), N(14.94%).

1-[2-(aminomethyl)-1H-benzimidazol-1-yl]-N, N-dimethylmethanamine: $C_{11}H_{16}N_4$, 69% yield, m. p.220-223°C, IR (KBr, υ cm-1): 2872{C-H Str, –CH_3}, 1534{C=C}, 1773{C=N}, 3328{N-H}, 1076 {C-N}, 1H NMR: 2.0(s, 2H, -NH_2), 2.26(s, 6H, -CH_3), 3.92-4.79(s, 4H, -CH_2), 7.26-7.70(m, 4H, Ar-H). Composition: C(64.60%) H(7.81%) N(27.33%).

N-{[2-(aminomethyl)-1H-benzimidazol-1-yl]methyl}-N-ethylethanamine: C13H20N4, 73% yield, m.p. 231-234°C, IR (KBr, υ cm-1): 2865{C-H Str, –CH3}, 1541{C=C}, 1765{C=N}, 3331{N-H}, 1069 {C-N}, 1H NMR: 1.0(t, 6H, -CH_3), 1.9(s, 2H, -NH_2), 2.40-4.80(m, 8H, -CH_2), 7.26-7.72(m, 4H, Ar-H). Composition: C(67.21%) H(8.68%) N(24.12%)

1-{1-[(dimethylamino)methyl]-1H-benzimidazol-2-yl}ethanamine: $C_{12}H_{18}N_4$, 63% yield, m.p. 210-212°C, IR (KBr, υ cm-1): 2870{C-H Str, –CH_3}, 1536{C=C}, 1769{C=N}, 3323{N-H}, 1059{C-N}, 1H NMR: 1.38-2.28(d, 3H, -CH_3), 2.1(d, 2H, -NH_2), 2.26(s, 6H, -CH_3), 3.90-4.81(s, 2H, -CH_2), 4.07 (m, 1H, -CH), 7.27-7.70 (m, 4H, Ar-H). Composition: C(66.02%) H(8.31%) N(25.67%).

N-{[2-(1-aminoethyl)-1H-benzimidazol-1-yl]methyl}-N-ethylethanamine: $C_{14}H_{22}N_4$, 61% yield, m.p. 190-192°C, IR (KBr, υ cm-1): 2876{C-H Str, –CH_3}, 1534{C=C}, 1754{C=N}, 3312{N-H}, 1051{C-N}, 1H NMR: 0.9-1.01(t, 6H, -CH_3), 1.38(d, 3H, -CH_3) 2.1(s, 2H, -NH_2), 2.40(m, 4H, -CH_2), 4.09(m, 1H, -CH), 4.80(s, 2H, -CH_2), 7.26-7.70(m, 4H, Ar-H). Composition: C(68.20%) H(9.02%) N(22.63%)

1-{1-[(dimethylamino)methyl]-1H-benzimidazol-2-yl}-2-phenylethanamine: $C_{18}H_{22}N_4$, 72% yield, m.p. 253-255°C, IR (KBr, υ cm-1): 2869{C-H Str, –CH_3}, 1551{C=C}, 1766{C=N}, 3323{N-H}, 1061{C-N}, 1H NMR: 1.98(s, 2H, -NH_2), 2.27(s, 6H, -CH_3), 3.22-4.80(s, 4H, -CH_2), 4.29(t, 1H, -CH), 7.12-7.70(m, 9H, Ar H). Composition: C(73.40%) H(7.43%) N(19.00%)

N-{[2-(1-amino-2-phenylethyl)-1H-benzimidazol- 1-yl]methyl}-N-ethylethanamine: $C_{20}H_{26}N_4$, 65% yield, m.p. 212-215°C, IR (KBr, υ cm-1): 2876{C-H Str, –CH_3}, 1543{C=C}, 1753{C=N}, 3311{N-H}, 1054{C-N}, 1H NMR: 1.0(t, 6H, -CH_3), 2.17(s, 2H, -NH_2), 2.41(m, 4H, -CH_2), 3.22-4.79(s, 4H, -CH_2), 4.29(t, 1H, -CH), 7.11-7.69(m, 9H, Ar H). Composition: C(74.40%) H(8.11%) N(17.32%).

Table 1: Synthesized compounds

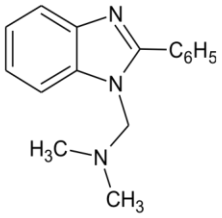
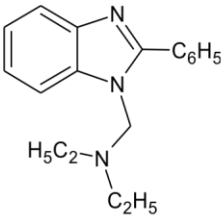
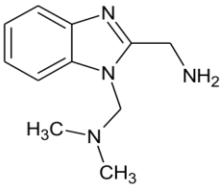
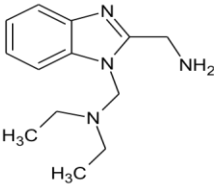
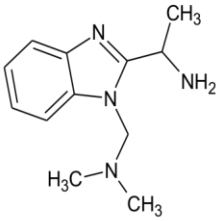
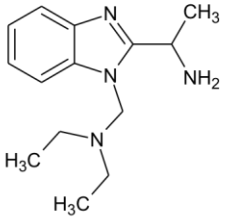
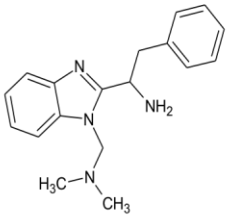
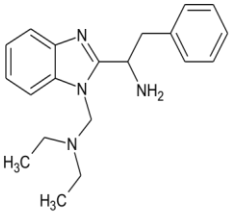
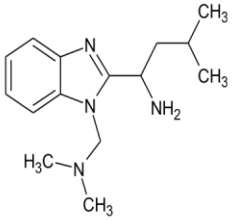
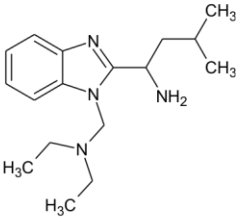
N,*N*-dimethyl-1-(2-phenyl-1*H*-benzimidazol-1-yl)methanamine  5A(a)	*N*-ethyl-*N*-[(2-phenyl-1*H*-benzimidazol-1-yl) methyl]ethanamine  5A(b)	1-[2-(amino methyl) -1*H*-benzimidazol-1-yl]-*N*,*N*-dimethyl methanamine  5B(a)	N-{[2-(amino methyl) -1H -benzimidazol-1-yl]methyl}-N-ethyl ethanamine:  5B(b)	1-{1-[(dimethyl amino)methyl]-1*H*-benzimidazol-2-yl} ethanamine  5C(a)
N-{[2-(1-amino ethyl)-1*H*-benzimidazol-1-yl] methyl}-*N*-ethylethanamine  5C(b)	1-{1-[(dimethyl amino)methyl]-1*H*-benzimidazol-2-yl}-2-phenylethanamine  5D(a)	*N*-{[2-(1-amino-2-phenylethyl)-1*H*-benzimidazol-1-yl]methyl}-*N*-ethylethanamine  5D(b)	1-{1-[(dimethyl amino)methyl]-1*H*-benzimidazol-2-yl}-3-methylbutan-1-amine  5E(a)	1-{1-[(diethyl amino)methyl]-1*H*-benzimidazol-2-yl}-3-methylbutan-1-amine  5E(b)

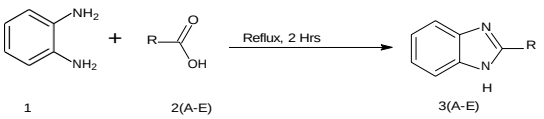
Table 2: Physicochemical parameters of synthesized compounds

Compound name	Molecular Formula	Molecular weight (gms)	Percentage yield	R_f value	Melting point(°C)
5A(a)	$C_{16}H_{17}N_3$	251.32	65%	0.68	326-328°C
5A(b)	$C_{18}H_{21}N_3$	279.37	65.5%	0.72	315-318°C
5B(a)	$C_{11}H_{16}N_4$	204.27	69%	0.75	220-223°C
5B(b)	$C_{13}H_{20}N_4$	232.32	73%	0.78	231-234 °C
5 C(a)	$C_{12}H_{18}N_4$	218.29	63%	0.82	210-212°C
5 C(b)	$C_{14}H_{22}N_4$	246.35	61%	0.84	190-192°C
5D(a)	$C_{18}H_{22}N_4$	294.39	72%	0.67	253-255°C
5D(b)	$C_{20}H_{26}N_4$	322.44	65%	0.73	212-215°C
5E(a)	$C_{15}H_{24}N_4$	260.37	78%	0.62	231-233°C
5E(b)	$C_{17}H_{28}N_4$	288.43	61%	0.71	242-245°C

1-{1-[(dimethylamino)methyl]-1H-benzimidazol-2-yl}-3-methylbutan-1-amine: $C_{15}H_{24}N_4$, 78% yield, m.p. 231-233°C, IR (KBr, υ cm-1): 2864{C-H Str, $-CH_3$}, 1562{C=C}, 1761{C=N}, 3323{N-H}, 1049{C-N}, 1H NMR: 1.02(d, 6H, $-CH_3$), 1.81(t, 2H, $-CH_2$), 1.84(m, 1H, -CH), 2.0(s, 2H, $-NH_2$), 0.97(t, 6H, $-CH_3$), 3.89(t, 1H, -CH), 4.81(s, 2H, $-CH_2$), 7.26-7.70(m, 4H, Ar H). Composition: C(69.19%) H(9.29%) N(21.52%)

1-{1-[(diethylamino)methyl]-1H-benzimidazol-2-yl}-3-methylbutan-1-amine: $C_{17}H_{28}N_4$, 61% yield, m.p. 242-245°C, IR (KBr, υ cm-1): 2877{C-H Str, $-CH_3$}, 1572{C=C}, 1775{C=N}, 3333{N-H}, 1053{C-N}, 1H NMR: 0.97(t, 6H, $-CH_3$), 1.03(d, 6H, $-CH_3$), 1.82(t, 2H, $-CH_2$), 1.83(m, 1H, -CH), 2.0(s, 2H, $-NH_2$), 2.38(m, 4H, $-CH_2$), 3.90(t, 1H, -CH), 4.79(s, 2H, $-CH_2$), 7.27-7.71(m, 4H, Ar H). Composition: C (70.79%) H (9.78%) N (19.42%).

SCHEME OF THE PRESENT WORK



Scheme: 1

3A= R=-C_6H_5 3B= R= -CH_2 NH_2

3C= R=-CH(CH_3) $NH_2$3D= R= -CH(-$CH_2C_6H_5$) NH_2
3E= R= -CH(-CH_2 CH(CH_3) $_2$)NH_2

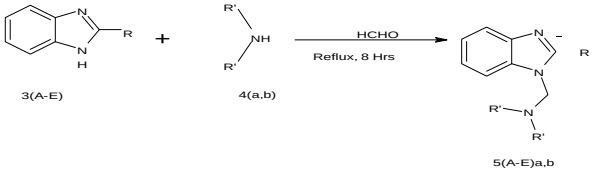


Table 3: Preliminary QSAR Study of Synthesized Compounds

Compound name	Logp	TPSA	MW	nrotb	volume
5A(a)	3.63	21.06	251.32	3	243.36
5A(b)	4.38	21.06	279.37	5	276.97
5B(a)	0.80	47.09	204.27	3	200.04
5B(b)	1.56	47.09	232.32	5	233.65
5C(a)	0.52	47.09	218.29	3	216.63
5C(b)	0.24	47.09	246.35	5	250.24
5D(a)	0.91	47.09	294.39	5	288.28
5D(b)	1.67	47.09	322.44	5	321.88
5E(a)	0.76	47.09	260.37	5	266.82
5E(b)	1.51	47.09	288.43	7	300.43

Table 4: Drug Likeness Score of Synthesized Compounds

Compound name	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
5A(a)	-0.17	-0.12	0.00	-0.54	-0.61	-0.03
5A(b)	-0.09	-0.23	-0.04	-0.49	-0.56	-0.01
5B(a)	-0.52	-0.16	-0.51	-1.57	-0.85	-0.30
5B(b)	-0.35	-0.23	-0.37	-1.35	-0.75	-0.18
5C(a)	-0.41	-0.41	-0.37	-1.15	-0.98	-0.40
5C(b)	-0.27	-0.46	-0.25	-0.99	-0.86	-0.29
5D(a)	0.04	-0.19	-0.03	-0.53	-0.36	-0.13
5D(b)	0.04	-0.28	-0.05	-0.53	-0.37	-0.12
5E(a)	-0.05	-0.24	-0.23	-0.68	-0.46	-0.24
5E(b)	-0.02	-0.32	-0.17	-0.62	-0.42	-0.20

Table 5: In vitro Antimicrobial Activity of the Synthesized Compounds

Compound names	Antibacterial Activity			Antifungal Activity		
	Bacillus subtilis	*Pseudomonas aeuroginosa*	*Staphylococcus aureus*	*Candida albicans*	*A.niger*	*Sacchromyces*
Standard	12	11	14	***10***	***12***	***11***
5A(a)	8.5	10.0	10.0	9.5	7.5	7
5A(b)	9.5	9.0	11.0	8.5	7.5	8
5B(a)	8	7.5	9.5	7.5	7	8
5B(b)	7.5	9.0	7.5	8.0	6.5	7
5 C(a)	10	9.5	9.5	8.5	6.5	7
5 C(b)	9	10	9	7.5	6	6.5
5D(a)	10	9.0	11.0	10.5	8.0	8.5
5D(b)	9.5	9.5	10.5	9.5	7.5	8.5
5E(a)	9	8.5	10.5	9.5	8.5	8
5E(b)	9	10	9	7.5	6	6.5

Standard= Antibacterial activity –Tetracycline; Antifungal activity- Fluconazole

Scheme: 2

R' = a = $-CH_3$, R' = b = $-C_2H_5$,

***In silico* Prediction**

Log p is a good descriptor of hydrophobicity which affects ADME of a drug, its receptor interactions and toxicity. Any title compound did not show significant lipophilic activity. N rotb measures molecular flexibility. Molecular volumes were found to be within lipinski's limit i.e. (less than 500 dalton) all substituted benzimidazole derivatives were found to be in limit with respect to lipinski's rule. All the values of the synthesized benzimidazole derivatives were found to be in compliance with standard values stated according to the Lipinski's rule of five. This demonstrates that all the synthesized compounds possess good permeation and availability shown in table 3 & 4.

***In vitro* Anti-microbial screening**

All the synthesized compounds 5 (A-E) a, b were evaluated for their *in vitro* anti-microbial activity for bacteria like *E. coli* (Gram -ve), pseudomonas aeuroginosa (Gram +ve), staphylococcus aureus (Gram +ve) and Fungal Organisms like sacchromyces species, aspergillus niger, candida albicans using filter-paper disc method shown in Table 5.

The results shows that 5D (a) and (b) has prominent anti-microbial activity. This might be due to the presence of aryl group in its structure

which increases the electronic character favouring better microbial membrane penetration.

The compounds were tested at a concentration level of 200µg/disc and the results were compared with that of tetracycline, fluconazole as a reference drug at 50µg/ml. All the compounds have shown significant antibacterial activity and moderate antifungal activity. Depending on the functional group present in aromatic ring different values were obtained. In future, the potent antimicrobial derivatives can be synthesized by better molecular modifications.

CONCLUSION

A series of Mannich Bases of 2- substituted benzimidazole derivatives were synthesized and their structures were elucidated by spectral data. Substituted benzimidazole mannich bases has significant antimicrobial activity, it was observed that good antibacterial and antifungal effect shown by 5D (a) and (b) because the presence of aromatic group, it exhibited dominating activity over the series. All Other synthesized compounds also made appropriate molecular modification can show as potent antimicrobial agents in future.

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