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Mannich Bases of 2-Substituted Benzimidazoles - A Review

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Abstract: Mannich bases are the end products of mannich reaction and are known as beta amino ketone carrying compounds. Mannich reaction is a carbon carbon bond forming nucleophilic addition reaction which helps in synthesizing N-methyl derivatives and many other drug molecules. Mannich base derivatives of benzimidazoles possess many pharmacological properties such as anti-oxidant, anti-inflammatory, anticancer, antiviral, anthelmintic and play an important role in medical field. As these drugs are clinically useful in treatment of microbial infections and exhibit other therapeutic activities also, so this encouraged the development of more potent, novel and clinically significant compounds. In this review synthesis and various biological activities of new mannich bases of benzimidazole derivatives reported is discussed.

Keywords: Mannich Bases, Substituted Benzimidazoles, Pharmacological Activities.

1. INTRODUCTION

The fusion of benzene and imidazole forms a heterocyclic aromatic organic compound called Benzimidazole which is bicyclic in nature. It is an important pharmacophore and a privileged structure in medicinal chemistry. Heterocyclic compounds are more biologicaly active as compared to others (Padmavati

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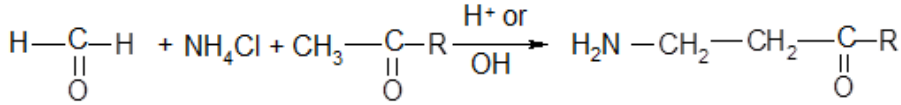
et al., 2007). Benzimidazole is one such compound which attract the attention of synthetic chemists for the designing more potent Benzimidazole derivatives having wide diverse of biological activity (Walia *et al.*, 2011).

Literature reveals that benzimidazole-containing compounds show biological activities as anti-allergic agents (Nakano *et al.*, 2000), PARP inhibitors- as anticancer agents (White *et al.*, 2000) and as cytomegalovirus (HCMV) inhibitors (Zhu *et al.*, 2000). They are also reported as anthelmintic agents and in diverse human therapeutic areas such as treatment of ulcers, anti inflammatory agents and as antihistaminics (Spasov *et al.*,1999). Benzimidazole derivatives are named as "privileged sub structures" for drug design because of their diverse uses (Evans *et al.*, 1988; Mason *et al.*, 1999).

Mannich reaction has been studied by several groups of workers in the field of medicinal chemistry, mainly because of the various pharmacological properties of the Mannich Bases so formed. A variety of Mannich Bases have been reported to possess analgesic (Malinka *et al.*, 2005), anti-inflammatory (Kalluraya *et al.*, 2005; Koksal *et al.*, 2007), local anaesthetic, anticancer (Ivanova *et al.*, 2007; Gul *et al.*, 2000), anti convulsant (Vashishta *et al.*, 2004), antipsychotic (Scott *et al.*, 1992), antiviral (Edwards *et al.,* 1983), anthelmintic (Bennet *et al.*,1996), antimalarial (Barlin *et al.*, 1990), antibacterial (Ashok *et al.*, 2007; Pandeya *et al.*, 2000), antifungal (Pandeya *et al.*, 2000; Singh *et al.*, 2007) and several other activities. The earliest examples of the Mannich reactions were published in succession by Tollens and co-workers, Petrenko Kritschenko and by Mannich and Krosche. Mannich was the first to recognize reaction as the general one and a detailed investigation began in 1917 (Thompson *et al.*, 1968).

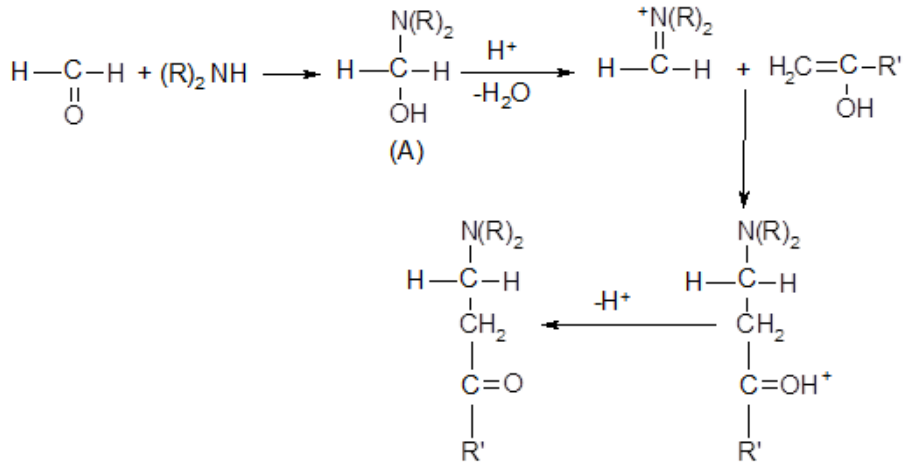
1.2 MANNICH REACTION



In Mannich reaction, formaldehyde or paraformaldehyde is condensed with ammonia in the form of its salt and a compound containing active hydrogen. This may formally be considered as an addition of ammonia to give H_2N-CH_2-OH, followed by a nucleophilic substitution. Instead of ammonia, the reaction may be carried out with salts of primary or secondary amines or with amides, in which cases the product is substituted on the nitrogen with R, R_2 and RCO respectively (March, 1992).

Mechanism of formation of Mannich Bases (Cummings *et al.*, 1960).

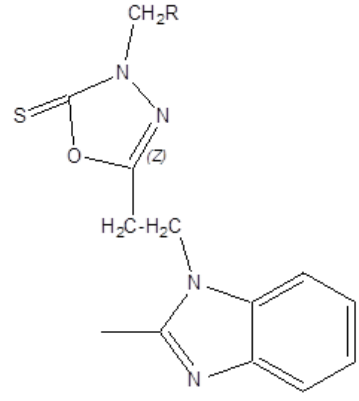
The Acid Catalysed Reaction



Mannich Bases possess several pharmacological properties which may be due to their reactive chemical nature, so they can be easily transformed into numerous other compounds. Studies on the chemistry of Mannich Bases are of interest in various areas of application. A large number of amino alkyl derivatives have been prepared in order to correlate their structure with pharmacological activities.The examples of clinically useful mannich bases having amino alkyl chain are cocaine, atropine, trihexiphenidyl, procyclidine, ranitidine, ethacrynic acid, fluoxetine, biperiden (Racane *et al.*, 2001; Ashiyama *et al.*, 1999; Bhusare *et al.*, 2001).

2. MANNICH BASES OF BENZIMIDAZOLE DERIVATIVES

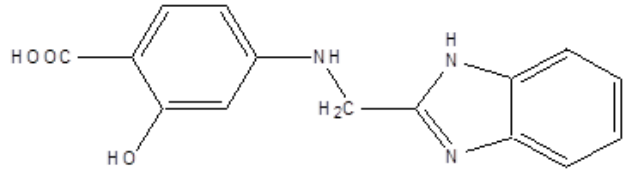
1) Some secondary amines (4-methyl morpholine, diethylamine, 1,4-dimethylpiperazine) and formaldehyde were used for the synthesis of Mannich base derivatives of benzimidazole (1). The synthesized compounds were then checked for their anti microbial activity against gram positive and gram negative bacterial strains, yeast and fungi. Some of the synthesized compounds were found active against bacterial strains but none of the compound was active against yeast and fungi (Afaf *et al.*, 2000).



R=-N(C2H5)2,4-methyl morpholine,1,4-dimethylpiperazine

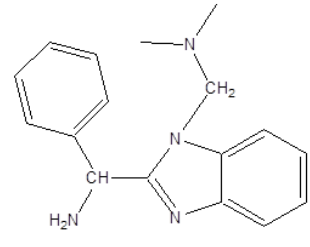
1)

2) Benzimidazole salicylic acid mannich base (2) was synthesized by the reaction of benzimidazole, 4-amino salicylic acid and formaldehyde. Complexes of mannich bases with transition metals were also prepared and studied (Kamlesh *et al.*, 2009).



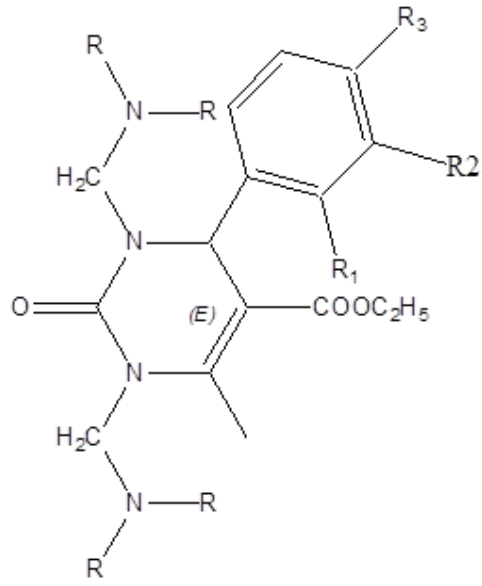
2)

3) Derivatives of 1,2 disubstituted benzimidazole were synthesized by employing mannich base reaction. Diamine and glycine in acidified ethanol were first heated and then substituted benzimidazole was dissolved in secondary amine and formaldehyde (Anil, 2009).



3)

4) Novel series of N-mannich base derivatives of 3,4 dihydropyrimidine-2-H-one (4) with different heterocyclic amines and formaldehyde was also synthesized. All the compounds showed good biological activities against two bacterial and two fungal strains (Shah *et al.*, 2009).

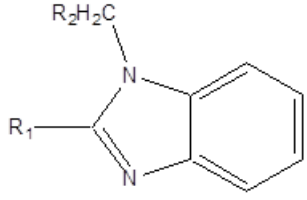


R_1= OH R_2, R_3 =H

R=Benzimidazole, 2-methyl benzimidazole, 2-phenyl benzimidazole, benzotriazole, Pthalimide, Morpholine, Tetrahydrocarbazole

4)

5) Various derivatives were synthesized. All the synthesized compounds were evaluated for anti-inflammatory and analgesic properties. All the compounds showed good corneal penetration but some of the compounds were found even more potent than paracetamol and diclofenac (Jasudason *et al.*, 2009).

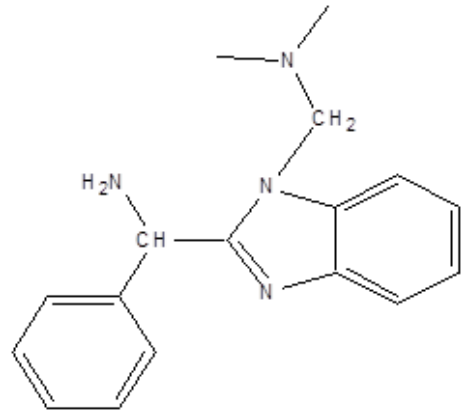


R_1=H,CH_3,CH=CHC_6H_5

R_2=-$N(CH_3)_2$-$N(C_2H_5)_2$,1-methylpiperiine,4-methylmorpholine

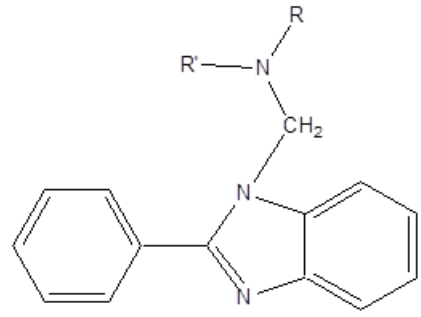
5)

6) Mannich bases of 2-substituted benzimidazole derivatives (6) were synthesized by the reaction of amino phenyl acetic acid and ortho phenylene diamine, they were then reacted with formaldehyde and secondary amine (dimethyl amine) and evaluated for anti-inflammatory activity (Reddy, 2010).



6)

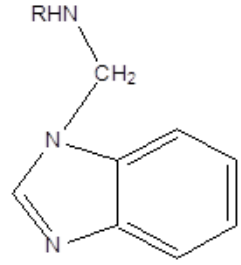
7) Secondary amine, 2- substituted phenyl benzimidazoles and formaldehyde were employed for the synthesis of novel mannich bases (Elerafi *et al.*, 2010).



R'=piperidine
R=morpholine

7)

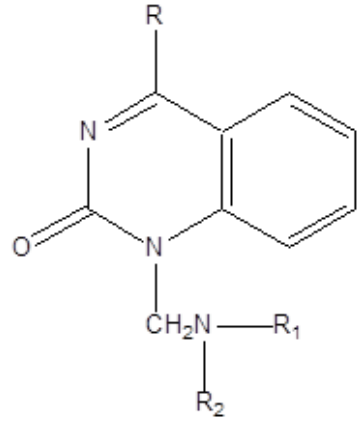
8) Some active hydrogen containing compounds such as sulphamethoxazole, sulphanilamide, sulphadimidine, 2-amino pyrimidine, Pthalimide, benzamide, anthranilic acid were reacted with formaldehyde and benzimidazole to synthesize N-substituted benzimidazole derivatives (8) which were then evaluated for anti HIV and antiviral activities (Selvam *et al.*, 2010).



R=Sulphanilamide, sulphadimidine, sulphamethoxazole,
2-amino pyrimidine, Pthalimide, anthranilic acid, benzamide

8)

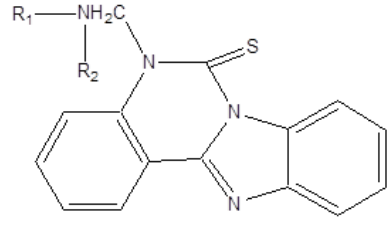
9) New mannich Schiff bases of 2-phenyl benzimidazole were also synthesized (9) by refluxing anthranilic acid with alkyl amide and results in the formation of 2-alkyl-4-(3H)-quinzolinone which further underwent mannich reaction. All the compounds showed good potency towards antimicrobial agents (Misra *et al.*, 2010).



R=H, CH_3, C_6H_5
R=CH_3, C_6H_5

9)

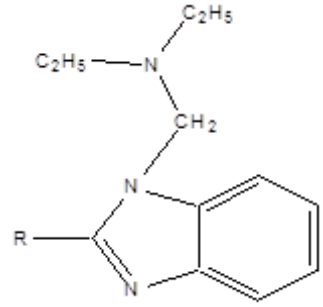
10) Mannich base derivatives of benzimidazoles (10) were synthesized through cyclization reaction. All the compounds were evaluated for anti microbial activities. Some of the compounds emerged as moderate antibacterials whereas some possessed negligible antifungal activitiy (Saraswathi *et al.*, 2010).



R1,R2=CH3,C6H5,4-methylmorpholine,1-methylpieridine

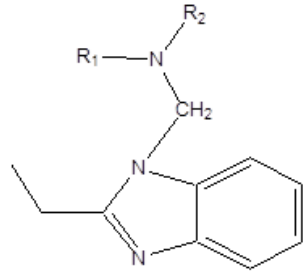
10)

11) Novel mannich bases of 2-substituted benzimidazole (11) were synthesized by reacting orthophenylene diamine with carboxylic acid for 6-8 hrs at 100°C and then mannich base was formed by reacting the above formed product with diethylamine and formaldehyde (Murugesan *et al.*, 2011).



11)

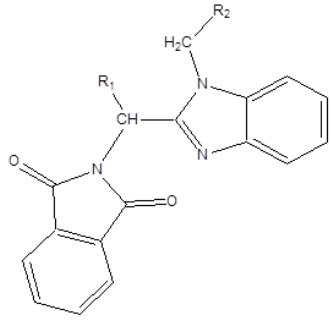
12) A series of 2-ethyl benzimidazole derivatives (12) have been synthesized by the condensation reaction of benzimidazole, primary and secondary amine and formaldehyde (Mariappan *et al.*, 2011).



NR1R2=Diethylamino,piperidino,morpholino,diethanolamino,2-chloroanilino,3-chloroanilino,4-bromoanilino

12)

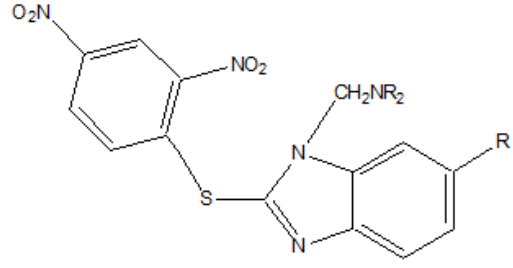
13) N-Mannich bases of benzimidazolyl substituted 1H-isoindole-1-(2H)-dione were synthesized (13). All the synthesized compounds were screened for anthelmintic activity. Piperazine hydrochloride was used as standard drug. All the synthesized compounds showed significant anthelmintic activity where as the derivatives substituted with piperazino, morpholine, diphenylamino, chloro, nitro and dinitro groups showed better activity than other derivatives (Rita and Shrivastava, 2012).



R1=benzyl
R2=piperazino,morpholino,diphenylamino,
2-nitrophenyl-amino,4-nitrophenyl-amino,2,4 dinitrophenyl-amino

13)

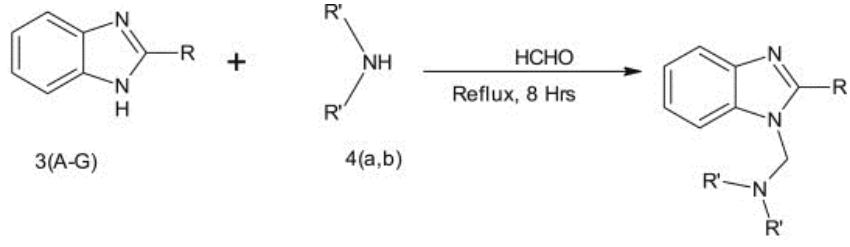
New derivatives of [1-(N,N-disubstituted)amino methyl-2-(2,4-dinitrophenyl) sulphanyl]-6-substituted-1 H-benzimidazoles (14) were synthesized by mannich reaction on 2-[(2,4 dinitrophenyl)sulphanyl]-5(6)-substituted-1 H-benzimidazoles with appropriate secondary amine and paraformaldehyde in presence of conc. hydrochloric acid in ethanol. The synthesized compounds were evaluated for analgesic and anti-inflammatory activity (Mohan Rao *et al.*, 2013).



14)

15) A series of mannich bases of 2-substituted benzimidazole derivatives were synthesized. The preliminary in vitro antibacterial and, antifungal

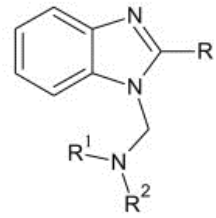
toxicological screening results of novel benzimidazole derivatives [5(A-G) a, b] reported good to moderate antimicrobial activity. The compound 5E (a) and (b) exhibited broad spectrum of antibacterial activity and antifungal activity (Kumar *et al.*, 2013).



3(A-G) 4(a,b) 5(A-G)a,b

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

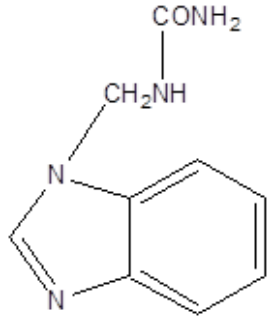
Synthesized compounds



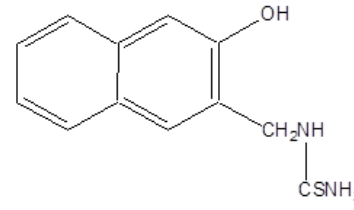
Compound s	**R**	**R^1**	**R^2**
5A(a)	-H	$-CH_3$	$-CH_3$
5A(b)	-H	$-C_2H_5$	$-C_2H_5$
5B(a)	$-CH_3$	$-CH_3$	$-CH_3$
5B(b)	$-CH_3$	$-C_2H_5$	$-C_2H_5$
5 C(a)	$-C_6H_5$	$-CH_3$	$-CH_3$
5 C(b)	$-C_6H_5$	$-C_2H_5$	$-C_2H_5$
5D(a)	$-C_6H_4$(2-OH)	$-CH_3$	$-CH_3$
5D(b)	$-C_6H_4$(2-OH)	$-C_2H_5$	$-C_2H_5$
5E(a)	$-C_6H_3$(2-OH)(5-SO_2OH)	$-CH_3$	$-CH_3$
5E(b)	$-C_6H_3$(2-OH)(5-SO_2OH)	$-C_2H_5$	$-C_2H_5$
5F(a)	-COOH	$-CH_3$	$-CH_3$
5F(b)	-COOH	$-C_2H_5$	$-C_2H_5$
5G(a)	$-C_6H_4$(2-COOH)	$-CH_3$	$-CH_3$
5G(b)	$-C_6H_4$(2-COOH)	$-C_2H_5$	$-C_2H_5$

15)

16) Two Mannich bases 1-(1H-benzodimidazolyl) methyl urea (BIUF) and 1(3-Hydoxynaphthlen -2-yl) methyl thoiurea (TNTUF) (16, 17) were synthesized and evaluated for antioxidant activity by employing hydrogen peroxide radical scavenging, DPPH radical scavenging and reducing power assays (Chakkaravarthi *et al.*, 2013).

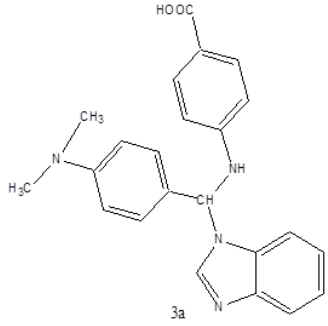


16)

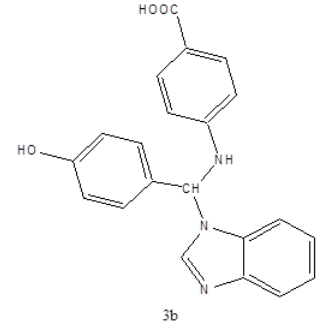


17)

17) A series of mannich bases of benzimidazole derivatives were synthesized from o-phenylenediaamine in two steps via benzimidazole intermediates. The anti fungal and anti bacterial activities of synthesized compounds 3a-c (18, 19, 20) were also checked andit was found that compounds 3a, 3b and 3c showed excellent antibacterial activity and compound 3a showed good antifungal activity than others (Aanadhi *et al.*, 2013).



18)



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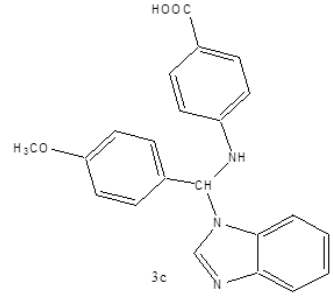
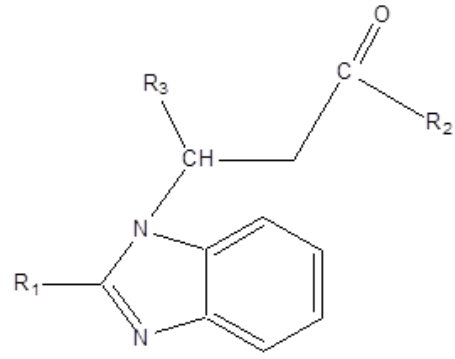


20)

18) A series of novel mannich bases of 2-substituted benzimiazoles were synthesized by the reaction of 2- substituted benzimidazoles with corresponding aldehyde and acetophenones and evaluated for analgesic and anti-inflammatory activity (Kumar *et al.*, 2015)



R_1= H, R_2 = -C_2H_5, R_3 = H

21)

CONCLUSION

As demonstrated by the frame of work reviewed in this paper, Mannich bases and their derivatives are found to have diverse activities. This review summarized various biological activities of mannich base of 2- substituted benzimidazole derivatives. It can be concluded that synthesis of mannich base derivatives provides a good opportunity to medicinal chemists for evolving better drugs with lower cytotoxicity.

ACKNOWLEDGEMENT

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

REFERENCES

[1] Aanadhi, M.V., Verma, A.K., Sujatha, R., Kamal Raj, R. (2013) Synthesis and characterization of novel mannich bases of benzimidazole derivatives for antibacterial and antifungal activity. International Journal of Pharmacy and Pharmaceutical Sciences, **5(2)** : 295-297.

[2] Afaf, H.E., Fahmy,H.H., Abdelwahed, S.H.A. (2000) Synthesis and antimicrobial properties of some new benzimidazole derivatives.Molecules, **5**: 1429-1438. http://dx.doi.org/10.3390/ 51201429

[3] Anil, R. (2010) Mannich bases of benzimidazole-synthesis and antimicrobial properties.A short review. European J.of Chemistry, **7(1)**: 222-226.

[4] Ashok, M., Holla, B.S., and Poojary. B. (2007) Convenient one pot synthesis and antimicrobial evaluation of some new Mannich bases carrying 4-methylthiobenzyl moiety. European J. of Medicinal Chemistry, **42(8)**: 1095-1101. http://dx.doi.org/10.1016/j.ejmech.2007.01.015

[5] Barlin,G.B., and Jiravinya, C. (1990) Potential antimalarials.X.Di-mannich bases of 4-(7'-trifluoromethyl-1',5'-naphthyridin-4'-ylamino)phenol and N-(4'-Diethylamino-1'-methylbutyl)-7-trifluoromethyl-1,5-naphthyridin-4-amine.Australian J. of Chemistry, **43(7)**: 1175-1181. http://dx.doi.org/10.1071/CH9901175

[6] Bennet-Jenlins, E., and Baryant, C. (1996) Novel sources of anthelmintics. International J. for Paracitology, **26(8-9)** : 937-947. http://dx.doi.org/10.1016/S0020-7519(96)80068-3

[7] Bhusare,S.R., Pawar,R.P., Vibhute,Y.B. (2001) Synthesis and antibacterial activity of some new 2-(substituted phenyl sulphonamido)-6-substituted benzothiazoles. Indian J.of Heterocyclic Chemistry,**11(1)**: 79-80.

[8] Chakarrarvarthi, K., Gokulakrishnan, K., Suman, T., Tamilvendan, D. (2013) Synthesis,spec tral,antimicrobial and antioxidant studies on diamide mannich base derivatives.International Journal of Pharmacy and Pharmaceutical Sciences, **6(1)**: 492-495.

[9] Cummings, T.F., and Shelton, J.R. (1960) Mannich reaction Mechanisms.Journal of Organic chemistry, **(25)**: 419-423. http://dx.doi.org/10.1021/jo01073a029

[10] Edwards, M.L., Ritter, H.W., Stemeric, D.M., Stewart K.T. (1983) Mannich bases of 4-phenyl-3-buten-2-one:a new class of antiherpes agent. J.of Medicinal Chemistry, **26(3)**: 431-436. http://dx.doi.org/10.1021/jm00357a020

[11] Elarafi, M.G.,Ibrahim, M.N. (2010) Synthesis and spectral studies of mannich bases derived from 2-substituted benzimidazoles. International J. of Chem.Tech.Resr. **4**: 2097-2099.

[12] Evans, B.E., Rittle, K.E., Bock, M.G., Hirshfield J. (1988) Methods for drug discovery, development of potent selective, orally effective cholecystokinin antagonist. J.Med.Chem. **31**: 2235-2246 http://dx.doi.org/10.1021/jm00120a002

[13] Gul,H.I., Vepsalainen, J., Gul, M., Erciyas, E. and Hanninen, O. (2000) Cytotoxic activities of mono and bis mannich bases derived from acetophenone against Renca and Jurkat cells. Pharmaceutica Acta Helvetiae, **74(4)**: 393-398. http://dx.doi.org/10.1016/S0031-6865(00)00022-4

[14] Ivanova, Y., Momekov, G., Petrov, O., Karaivanova, M. and Kalcheva, V. (2007) Cytotoxic Mannich bases of 6-(3-aryl-2-propenoyl)-2-(3H)-benzoxazolones.European J.of Medicinal Chemistry, **52(11-12)**: 1382-1387. http://dx.doi.org/10.1016/j.ejmech.2007.02.019

[15] Jesudason, E.P., Sridhar, S.K., Padma, E.J., Shanmugapandiyan, P., Inayathullah, M., Arul, V., Selvaraj, D., Jayakumar, R. (2009) E.Journal of Medicinal Chemistry, **44**: 2307-2312. http://dx.doi.org/10.1016/j.ejmech.2008.03.043

[16] Kalluraya, B., Chimbalkar, R.M. and Hedge, J.C. (2005) Anticonvulsant activity of nicotinyl/ isonicotinyl substituted 1,2,4-triazol-5-thione Mannich bases.Indian Journal of heterocyclic Chemistry, **15(1)**: 15-18.

[17] Kamlesh, V., Arun, S. (2009) Design docking and synthesis of some 6-benzimidazoyl pyrans and screening of their antitubercular activity. European Journal of Chemistry, **6(1)**: 281-288.

[18] Kashiyama, E., Hutchinson, I., Chua, M.S. *et al.* (1999) Antitumour benzothiazoles.8.1 Synthesis,metabolic formation and biological propertie of the C and N oxidation products

of antitumour-2-(4-aminophenyl)-benzothiazoles. Journal of Medicinal Chemistry. **42(20)**: 4172-4184. http://dx.doi.org/10.1021/jm990104o

[19] Koksal, M., Gokhan, N., Kupeli, E., Yesilada,E., Erdogan, H.(2007) Analgesic and anti-inflammatory activities of some new mannich bases of 5- nitro-2-benzoxazolinones. Archives of Pharmacal Research, **30(4)**: 419-424. http://dx.doi.org/10.1007/BF02980214

[20] Kumar, S.V., Subramanian, M.R., Chinnaiyan, S.K. (2013) Synthesis, characterisation and evaluation of N-mannich bases of 2-substituted Benzimidazole derivatives. Journal of Young Pharmacists, **5**: 154-159. http://dx.doi.org/10.1016/j.jyp.2013.11.004

[21] Kumar, N., Sharma, C.N., Ranawat, M.S., Singh, H.P., Chauhan, L.S., Dashora, N. (2015) Synthesis, analgesic and anti-inflaammatory activities of novel mannich bases of benzimidazoles. Journal of Pharmaceutical Investigation, **45**: 65-71. http://dx.doi.org/10.1007/s40005-014-0145-0

[22] Malinka, W., Swiatek, P., Filipek, B., Sapa, J., Jezierska, A., Koll, A. 2005) Synthesis analgesic activity and computational study of new isothiazolopyridines of mannich base type.Farmaco, **60(11-12)**: 961-968. http://dx.doi.org/10.1016/j.farmac.2005.08.005

[23] March, J. (1992) Advanced Organic Chemistry: Reaction Mechanisms and Structure, Fourth edition, A Wiley-Interscience Publication, John Wiley and Sons, New York: 900-902.

[24] Mariappan, G., N.R.Bhuyan, N.R., Kumar, P., Kumar, D., K.Murali, K. (2011) Synthesis and biological evaluation of mannich bases of benzimidazole derivatives.Indian Journal of Chemistry, **50 B**: 1216-1219.

[25] Mason, J.S., Morize, I., Menard, P.R. (1999) New 4-point pharmacophore method for molecular similarity and diversity applications: Overview of the method and applications including a novel approach to the design of combinatorial libraries containing privileged sub-structures. J.Med. Chem. **42**: 3251-3264. http://dx.doi.org/10.1021/jm9806998

[26] Misra, P.S., Shanmugasundaram, P., Chaudhary, R., Anandhi, M.V. (2010) Synthesis of 2-phenyl benzimidazole derivatives and their Schiff bases as possible antimicrobial agents. Rasayan Journal of Chemistry. **3(1)**: 51-54.

[27] Mohan Rao G, Narsimha Reddy Y, Vijaya Kumar B, Evaluation of analgesic and anti-inflammatory activities of N-Mannich bases of substituted 2-mercapto-1-H-benzimidazoles. International J. of Applied Biology and Pharmaceutical Technology, 2013, **4(1)**,38-46.

[28] Murugesan S., *et al.* (2011) J. of Pharmacy Research, **498**: 2679-2681.

[29] Padmavati, V., Subbaiah, D.R.C.V., Mahesh, K., Lakshmi, T.R. (2007) Synthesis and bioassay of amino-pyrazolone,amino isoxazolone and amino-pyrimidinone derivatives. Chem.Pharm. Bull. **55**: 1704-1709. http://dx.doi.org/10.1248/cpb.55.1704

[30] Pandeya, S.N., Sriram, D., Nath,G., and De Clercq, E. (2000) Synthesis , antibacterial, antifungal and anti-HIV activities of norfloxacin mannich bases. European J. of Medicinal Chemistry, **35(2)**: 249-255. http://dx.doi.org/10.1016/S0223-5234(00)00125-2

[31] Racane, L., Kulenovic, V.T., Jakic, L.E., Boykin, D.W., and Zamola, G.K. (2001) Synthesis of bis substituted amidino-benzothiazoles as potential anti-HIV agents. Heterocycles, **55**: 2085-2098. http://dx.doi.org/10.3987/COM-01-9305

[32] Reddy B.A (2010) Synthesis,Characterization and biological evaluation of 1,2 disubstituted benzimidazole derivatives using mannich bases.European journal of Chemistry, **7(1)**: 222-226.

[33] Rita, R., and Shrivastava, P. (2012) Synthesis and Characterization of some N-Mannich bases as potential antimicrobial,anthelmintic and insecticidal agents.Chemical Science Transactions, **1(2)** : 431-439. http://dx.doi.org/10.7598/cst2012.184

[34] Saraswathi, M., Rohini, R.M., Nayeem, N. (2010) Synthesis and evaluation of mannich bases of benzimidazo [1,2-c] quinazolin- 6(5h)-thione for antimicrobial activity. Pak.J.of Pharmaceutical Sciences, **23(4)**: 459-462.

[35] Scott, M.K., Martin, G.E., Distefano, D.L., *et al.* (1992) Pyrrole Manncih bases as potential antipsychotic agnts. J. of Medicinal chemistry, **35(3)**: 552-558. http://dx.doi.org/10.1021/jm00081a018

[36] Selvam P., *et al.* (2010) International J.of Pharmaceutical Sciences and Research, **1(9)**: 105-119.

[37] Shah, T.B., Gupte, A., Patel,M.R., Patel, H.,Patel, V.C. (2009) Synthesis and in vitro study of biological activity of heterocyclic N-Mannich bases.Indian Journal of Chemistry, **48B**: 88-96.

[38] Singh, B.N., Shukla, S.K. (2007) Synthesis and biological activity of sulphadiazine schiff's bases of isatin and their N-Mannich bases. Asian J. of Chemistry. **19(7)**: 5013-5018.

[39] Spasov, A.A., Yozhitsa, I.N., Bugaeva L.I.(1999) Benzimidazole derivatives: Spectrum of Pharmacological activity and toxicological properties (a review). Pharm. Chem. Journal, **33**: 232-243. http://dx.doi.org/10.1007/bf02510042

[40] Thompson, B.B. (1968) The Mannich Reaction, Mechanistic & Technological considerations. J of Pharamaceutical Sciences, **57(5)**: 715-733. http://dx.doi.org/10.1002/jps.2600570501

[41] Vashishtha, S.C., Zello, G.A., Nienaber K.H., el al (2004) Cytotoxic and anticonvulsant aryloxy aryl mannich bases and related compounds.European Journal of Medicinal Chemistry, 2004, **39(1)**: 27-35. http://dx.doi.org/10.1016/j.ejmech.2003.09.011

[42] Walia, R., Md Hedaitullah, Naaz, S.F., Iqbal, K., Lamba, H.S. (2011) Benzimidazole Derivatives-An Overview. International Journal of Research in Pharmacy & Chemistry, **1(3)**: 565-574.

[43] White, A.W., Almassy, R., Calvert,A.H., Golding, B.T. (2000) Resistance modifying agents,Synthesis and Biological properties of Benzimidazole inhibitors of DNA repair enzyme Poly(ADP Ribose) polymerase.Journal of Med.Chem. **43**: 4084-4097. http://dx.doi.org/10.1021/jm000950v

[44] Zhu, Z., Lippa, B., Drach, J.C. (2000) Design Synthesis and biological evaluation of tricyclic nucleosides (Dimensional probes) as analogues of certain antiviral polyhalogenated Benzimidazole Ribonucleosides.Journal of Med. Chemistry, **43**: http://dx.doi.org/10.1021/jm990290y