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Review

AN EXPLORATION ON THE SYNTHESIS AND BIO-APPLICATIONS OF DERIVATIVES OF HETEROCYCLIC MANNICH BASES

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Abstract: The Mannich reaction is a three-component reaction of an aldehyde, a primary or secondary amine and a ketone which is one of the most powerful C-C bond forming reactions in organic synthesis. It leads to β-amino carbonyl compounds, which are useful for the syntheses of nitrogen containing compounds, such as natural products and medicinally relevant compounds. The versatility and potential of these compounds to introduce both functional and structural diversity using the Mannich reaction have stimulated the creativity of chemists. Keeping in view of the importance of this organic moiety in the field of medicine and biology here an attempt has been made to review the synthesis and biological importance of heterocyclic Mannich base derivatives.

Keywords: Amines, β-amino carbonyl compounds, Biological activity, Heterocyclic Mannich base derivative, Ketones, Mannich reaction**.**

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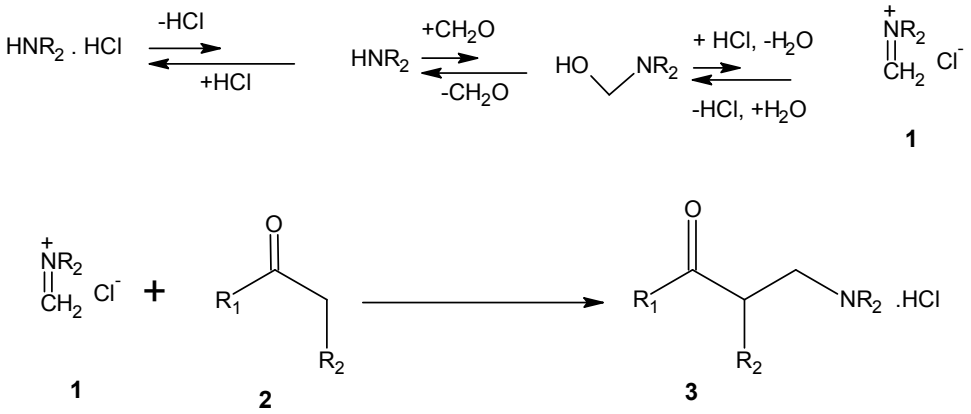
1. INTRODUCTION

The Mannich reaction is an organic MCR reaction which consists of an amino alkylation of an acidic proton placed next to a carbonyl functional group with formaldehyde and ammonia

or any primary or secondary amine. The Mannich reaction occupies an important position in the field of organic synthesis and has been one of the most important reactions in organic chemistry. The presence of heterocyclic ring in drugs constitutes a part of pharmacophore. Heterocyclic Mannich bases are very reactive; they can be easily transformed into numerous other compounds. Mannich bases represent easily obtainable intermediates for the synthesis of other compounds such as heterocycles, amino-alcohols. N-Mannich bases have been developed as water soluble prodrugs of many drugs. They were considered as chemically reversible prodrugs for NH- acidic compounds. They exhibit diverse pharmacological action like antimicrobial, anticancer, antimalarial, anti-inflammatory, antibacterial, antifungal antihistamine and antiviral activities [1]. The increasing popularity of the Mannich reaction has been fuelled by ubiquitous nature of nitrogen-containing compounds in drugs and natural products [2]. The review provided by Xiao-Hua *et al.,* [3] was an overview of the recent history of the applications of various catalytic systems in asymmetric Mannich reaction, including metal-based asymmetric organocatalysis, asymmetric organocatalysis, other chiral catalysis and no chiral catalysis systems. Subramaniapillai [4] in his review article gave an insight into the recent applications of Mannich reaction and its variants in the construction of bioactive molecules. The tutorial review by Verkade *et al*., [5] provided an overview of the recent history of the asymmetric organocatalysed Mannich reaction, including scope and limitations, and application of different catalyst systems. The review by Xiao-hua Cai *et al.,* [6] provided an overview of asymmetric Mannich reactions in recent years under different organocatalytic systems, including: chiral amines, chiral bifunctional thiourea, chiral Bronsted acids and other chiral organocatalytic systems. Literature survey reveals several synthetic protocols for the synthesis and biological activities of Mannich bases.

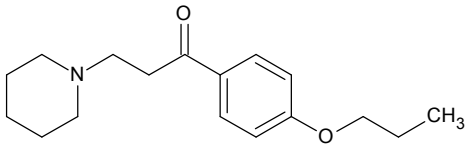
2. MECHANISM



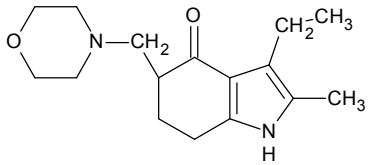
Scheme 1. Simplified mechanism of Mannich reaction

A simplified mechanism is given in **Scheme 1**. It is assumed that methylene iminium salts **1** are formed in a small concentration by a series of equilibrium reactions. These then react with the enol tautomer of the carbonyl compound **2** also present in very small equilibrium concentrations, to give the hydrochloride of the β-aminocarbonyl compound **3**, which are called Mannich bases [7].

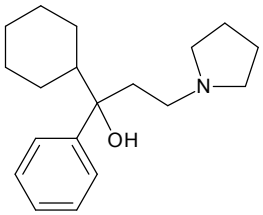
Scheme 2 shows some of the heterocyclic Mannich base derivatives which are commonly used as pharmaceutical agents.



Falicain (Aneasthetic)



Moban (Neuroleptic)

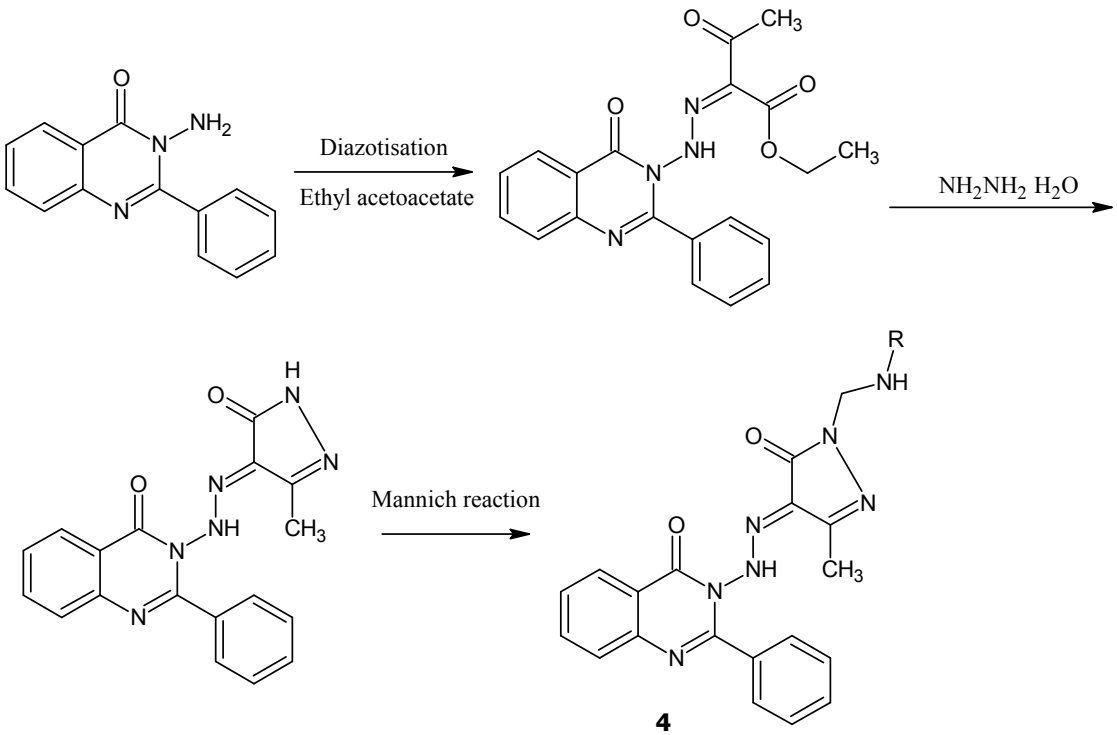


Osnervan (Antiparkinson)

Scheme 2. Heterocyclic Mannich bases as Pharmaceutical agents

3.1 MANNICH BASES OF PYRAZOLE DERIVATIVES

In the investigation conducted by Sivakumar *et al*., [8] a series of 12 Mannich bases of pyrazol-5(4*H*)-one moiety containing 3-(hydrazinyl)-2-phenylquinazolin-4(3*H*)-one **4 (Scheme 3)** had been synthesized and characterized by physicochemical as well as spectral means. The synthesized Mannich bases were screened for their preliminary antimicrobial activity against Gram-positive and Gram-negative bacteria as well as fungal strains by the determination of zone of inhibition. All the Mannich bases were found to be more potent antibacterial agents against Gram-positive bacteria,

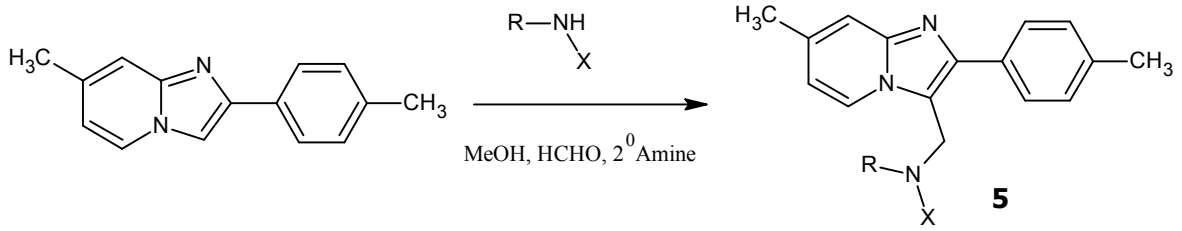


Where, R = aniline; 2-nitroaniline; 4-aminophenol; 4-chloroaniline; pyridin-2-amine; 4-aminobenzoic acid; 4-amino-2-hydroxy benzoic acid; 4-amino-3-hydroxynaphthalene-2-sulfonic acid; acetamide; 2-cyanoacetamide; benzamide; pyridin-2-amine.

Scheme 3. Synthesis of Mannich bases of pyrazol-5 (4*H*)-one moiety containing 3-(hydrazinyl)-2-phenylquinazolin-4 (3*H*)-one

3.2 MANNICH BASES OF IMIDAZOLE DERIVATIVES

A series of Mannich bases **5** were prepared by the reaction of 7-methyl-2-(p-methyl phenyl)imidazo[1,2-a]pyridine with secondary amines and p-formaldehyde in appropriate solvent **(Scheme 4)** by Sanghani and Ganatra [9]. The newly synthesized compounds were characterized by elemental analysis, IR, ^{1}H NMR and mass spectra. All the synthesized compounds were tested for their antibacterial activities against Gram positive and Gram negative bacteria, and antifungal activities.

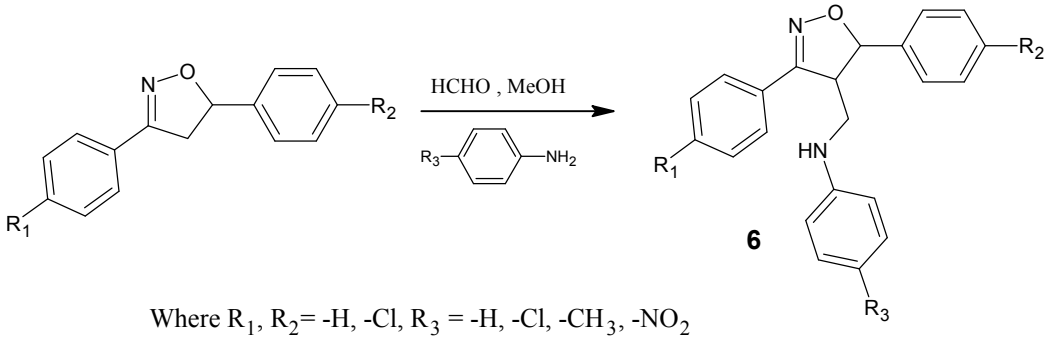


Where R= C_4H_8O-, -C_4H_8, $C_5H_{11}N$-, $C_6H_{13}N$-, -C_5H_{10}, -C_7H_{14} $C_4H_{11}N$-, $C_9H_{19}N$-, -C_2H_7, -C_6H_{10}

Scheme 4. Mannich base of 7-methyl-2-(p-methylphenyl)imidazo[1,2-a]pyridine

3.3 MANNICH BASES OF ISOXAZOLINE

Sudhir *et al*.,[10] prepared Isoxazolines derivatives, namely 3,5-bis(4-Substituted phenyl)-4,5-dihydroisoxazole and refluxed them with substituted primary amines and formaldehyde for 6-10 h to afford *N*-((3,5-bis(4-Substituted phenyl)-4,5-dihydroisoxazol-4-yl)substituted)-4-substituted benzenamine **6**, which are Mannich bases **(Scheme 5)**. The synthesized compounds were characterized on the basis of their spectral (IR, ^{1}HNMR) data and evaluated for the antimicrobial activity by using Zone of Inhibition by cup plate method and Minimum Inhibitory Concentration by broth dilution method.

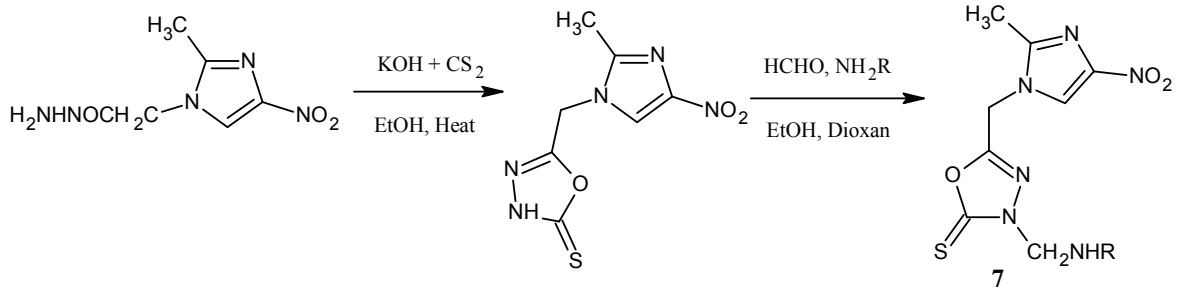


Where R_1, R_2= -H, -Cl, R_3 = -H, -Cl, -CH_3, -NO_2

Scheme 5. Synthesis of *N*-((3,5-bis(4-Substituted phenyl)-4,5-dihydroisoxazol-4-yl)substituted)-4-substituted benzenamine

3.4 MANNICH BASES OF OXADIAZOLE

Frank *et al.,* [11] in the short communication reported the synthesis of new 5-(2-methyl-4-nitro-1-imidazomethyl)-1,3,4-oxadiazole-2-thione from 2-methyl-4-nitro-imidazole. It was subjected to Mannich reaction with appropriate amines to yield a new series of 3-substituted aminomethyl-5-(2-methyl-4-nitro-1-imidazomethyl)-1,3,4-oxadiazole-2-thiones **7 (Scheme 6)**. The structure of the title compounds was elucidated by elemental analysis and spectral data. The newly synthesized Mannich bases were screened for their antibacterial and antifungal activity. Many of these compounds exhibited potent antifungal activity.



7

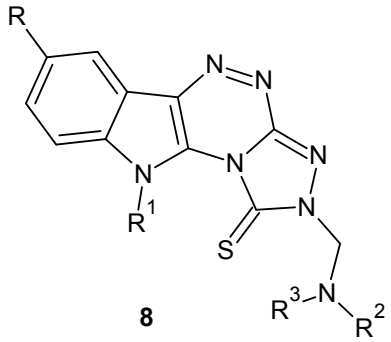
Where R is C_6H_5, p-$C_6H_4C_2H_5$, p-C_6H_4F, p-C_6H_4Cl, p-C_6H_4Br, $(C_6H_5)_2$

m-Nitrotoluene,Piperazine, N-methyl piperazine, N-ethyl piperazine

Scheme 6. Synthesis of 5-(2-methyl-4-nitro-1-imidazomethyl)-1,3,4-oxadiazole-2-thione

3.5 MANNICH BASES OF TRIAZOLE DERIVATIVES

Holla and Udupa [12] reported that the novel Mannich bases derived from 5-mercapto-1,2,4-triazolo[3,4-c]-1,3,4-triazino[5,6-b]-indoles **8 (Scheme 7)**. These compounds were tested for their *in vitro* antibacterial activity.

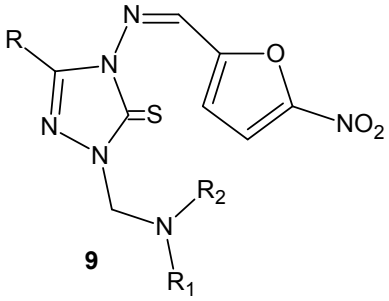


8

(Where R= H, Cl, CH_3; R^1 = H,CH_3; NR^2R^3 = morpholino, piperidino, 2,4-dichloroanilino)

Scheme 7. Mannich bases derivatives of 5-mercapto-1,2,4-triazolo[3,4-c]-1,3,4-triazino[5,6-b]-indoles

Mannich bases of some 3-substituted-4-(5-nitro-2-furfurylidene) amino-1, 2, 4-triazol-5-thiones **9 (Scheme 8)** were synthesized by Kalluraya *et al.,*[13]. These compounds were found to be active against Gram positive bacteria at 5µg/ml concentrations.

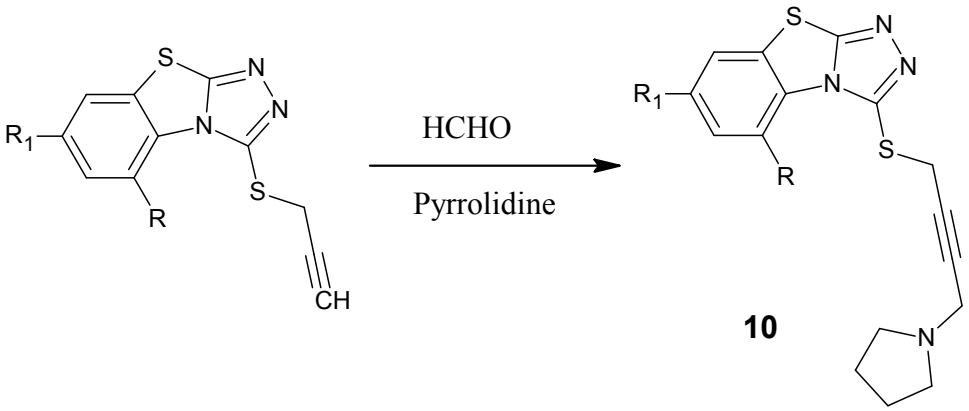


9

(Where R=alkyl, aryl, aryloxymethyl ; NR^1R^2 = morpholino, piperidino, p-chloroanilino, p-anisidino)

Scheme 8. Mannich bases of 3-substituted-4-(5-nitro-2-furfurylidene) amino-1, 2, 4-triazol-5-thiones

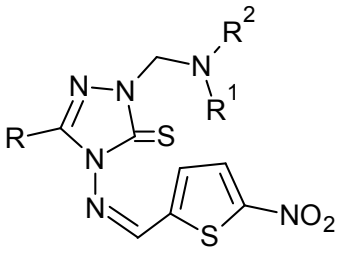
Deshpande and Deshmukh [14] reported the synthesis of Mannich bases from Propargyl derivatives of some 3-substituted-1, 2, 4-triazolo [3, 4-b] benzothiazoles **10 (Scheme 9)**.



10

Scheme 9. Mannich bases from propargyl derivatives of 3-substituted-1, 2, 4-triazolo [3, 4-b] benzothiazoles

Kalluraya and D'Souza [15] reported the synthesis of some 1-aminomethyl-3-substituted -4-(5-nitro-2-thienylidene) amino-1, 2, 4-triazole-5-thiones **11 (Scheme 10)**.

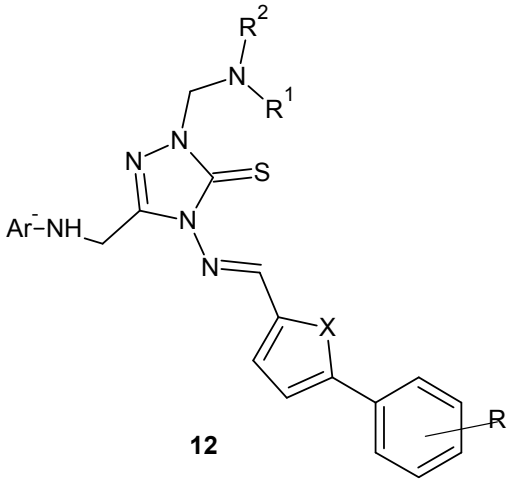


11

(Where R=alkyl, aryl, aryloxymethyl ; NR^1R^2 = morpholino, piperidino, p-chloroanilino, diphenylamino)

Scheme 10. 1-aminomethyl-3-substituted -4-(5-nitro-2-thienylidene) amino-1, 2, 4-triazole-5-thiones

Kalluraya *et al*., [16] reported the synthesis and biological activities of 3- substituted anilinomethyl-4-(5-substituted-2-furfurylidene) amino-1, 2, 4-triazolo-5-thiones and their Mannich bases **12 (Scheme 11)**.

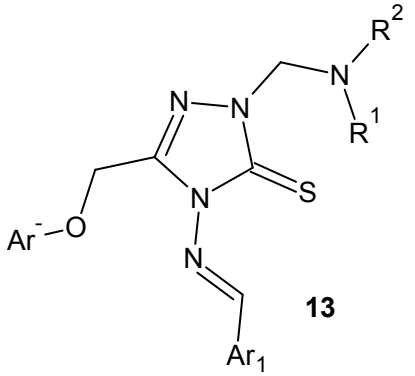


12

(Where Ar = 4-$CH_3C_6H_4$, 2- $OCH_3C_6H_4$; R=4-Cl, 4- NO_2, X=O, S ;
NR^1R^2 = morpholino, piperidino, diphenylamino)

Scheme 11. Mannich bases of 3- substituted anilinomethyl-4-(5-substituted-2-furfurylidene) amino-1, 2, 4-triazolo-5-thiones

1-Aminomethyl-3-aryloxymethyl-4-(arylidene) amino-1, 2, 4-triazol-5-thiones **13 (Scheme 12)** were reported by Holla *et al.,* [17].

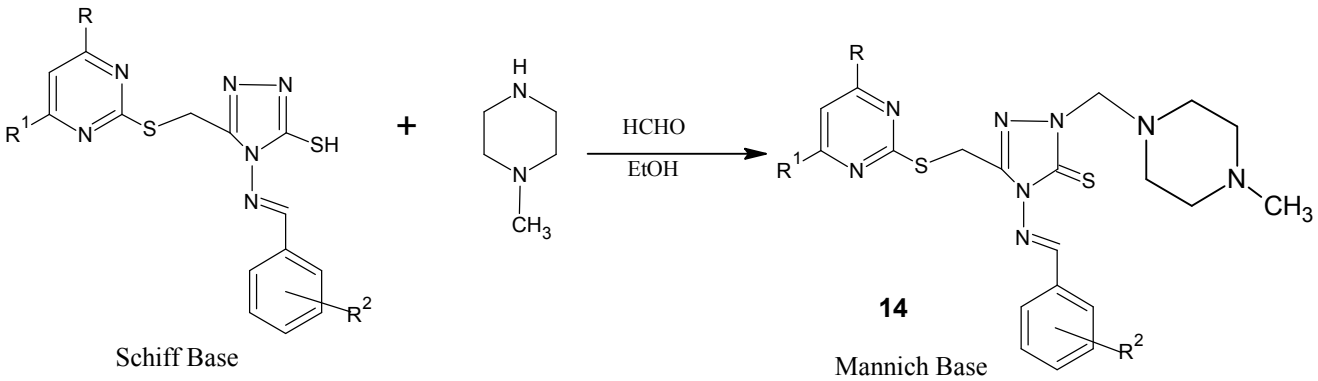


13

(Where Ar = 4-$CH_3C_6H_4$, 2-$CH_3C_6H_4$, 4-ClC_6H_4 ; Ar_1 = 2,4-$Cl_2C_6H_3$, 4-ClC_6H_4, 2,6-$Cl_2C_6H_3$, 2-Furyl ; NR^1R^2 = morpholino, piperidino, 2-chloranilino, 4-chloranilino)

Scheme 12. 1-Aminomethyl-3-aryloxymethyl-4-(arylidene) amino-1, 2, 4-triazol-5-thiones

The synthesis of novel Mannich bases from mercaptotriazole **14 (Scheme 13)** and their antimicrobial properties was reported by Lingappa *et al.,*[18].They synthesized a new series of 3-(4, 6-disubstitted-2-thiomethylpyrimidyl)-4-amino-5-mercapto-1,2,4-triazoles, which on reaction with aldehydes in the presence of acid catalyst form Schiff's bases. When these compounds were subjected to Mannich reaction, N-Mannich bases are obtained rather than S-Mannich bases. The structure of the new compounds was confirmed by spectral and analytical data. Few of these Mannich bases showed significant antifungal and antibacterial activity.



Schiff Base

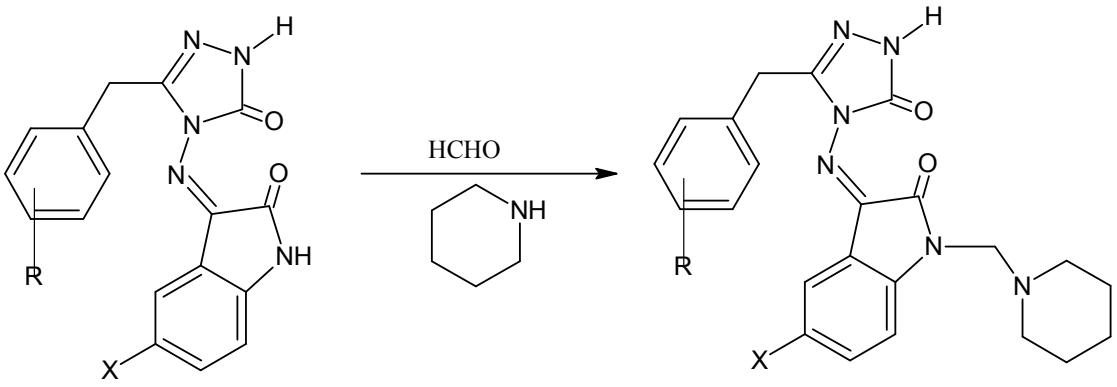
14

Mannich Base

(Where R = CH_3; R^1= H, CH_3; R^2 = p- chloro phenyl, p- nitro phenyl, 2-nitro-4,5-dimethoxy phenyl)

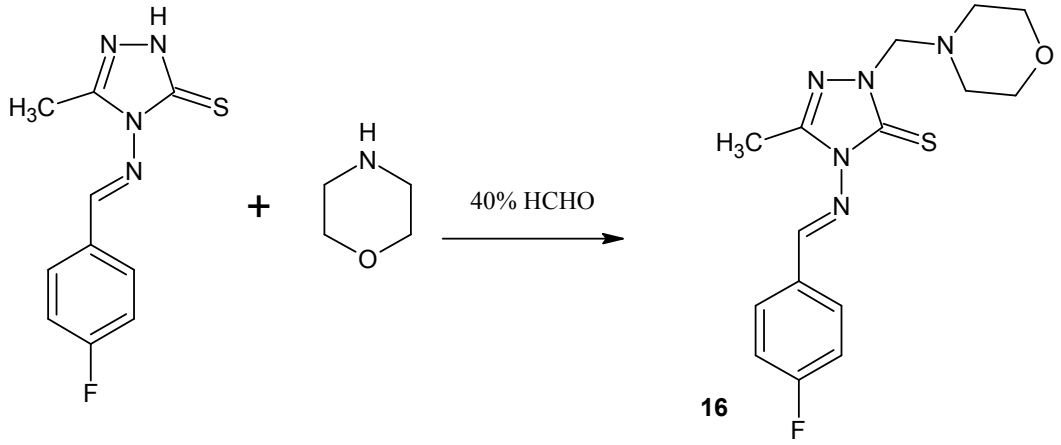
Scheme 13. Schiff's bases and Mannich bases of 3-(4, 6-disubstitted-2-thiomethylpyrimidyl)-4-amino-5-mercapto-1,2,4-triazoles

The article "Synthesis of Schiff and Mannich bases of Isatin derivatives with 4-amino-4, 5-dihydro-1*H*-1, 2, 4-triazole-5-ones" was reported by Bekircan and Bektas [19]. Schiff bases of substituted 4-amino-4,5-dihydro-1*H*- 1,2,4-triazole-5-ones, Isatin and 5-chloroisatin were subjected to Mannich reaction to form Mannich bases using formaldehyde and piperidine **15 (Scheme 14)**. Their chemical structures were confirmed by IR, ^{1}H NMR and ^{13}C NMR data and by elemental analysis.

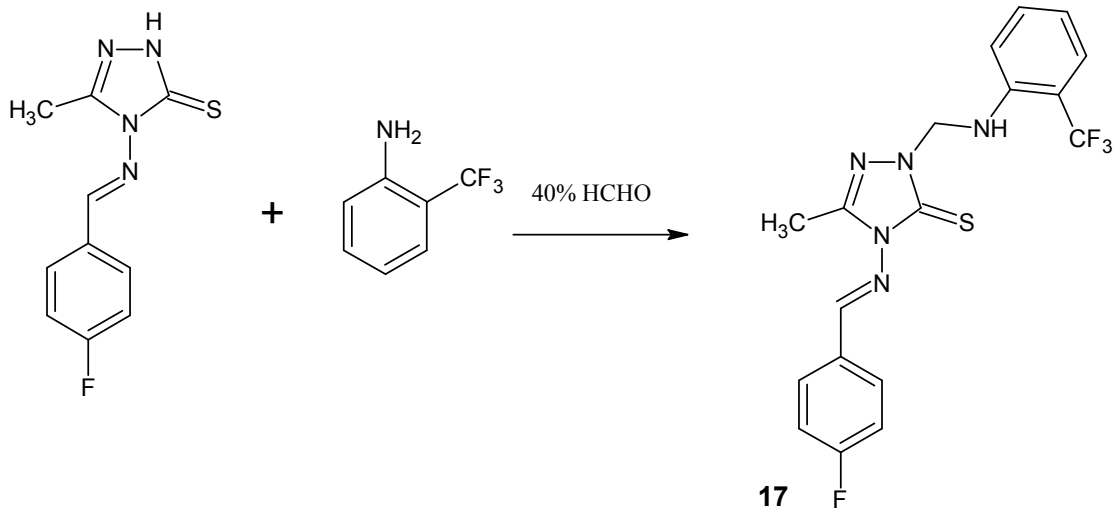


Scheme 14. Mannich base of substituted 4-amino-4,5-dihydro-1*H*- 1,2,4-triazole-5-ones,Isatin and 5-chloroisatin

Synthesis and antibacterial activity of some new Mannich bases was reported by Holla *et al.*, [20]. 4-{[(1*Z*)-(4-fluorophenyl)methylene]amino}-5-methyl-2-(morpholin-4-ylmethyl)-2,4-dihydro -3*H*-1,2,4-triazole-3-thione **16** (**Scheme-15a**) was obtained by the Mannich reaction between 4-[(*E*)-(4-fluorobenzylidene)amino]-5-methyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione and morpholine and 4-{[(1*Z*)-(4-fluorophenyl)methylene]amino}-5-methyl-2-({[2-(trifluoromethyl)phenyl] amino}methyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione **17** (**Scheme-15b**) was synthesized by the reaction between 4-[(*E*)-(4-fluorobenzylidene)amino]-5-methyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione and o-trifluoromethylaniline. Both of them displayed good antibacterial activities against *E. coli*, *S. typhase*, *K. pneumonia* and *P. aeruginosa*.

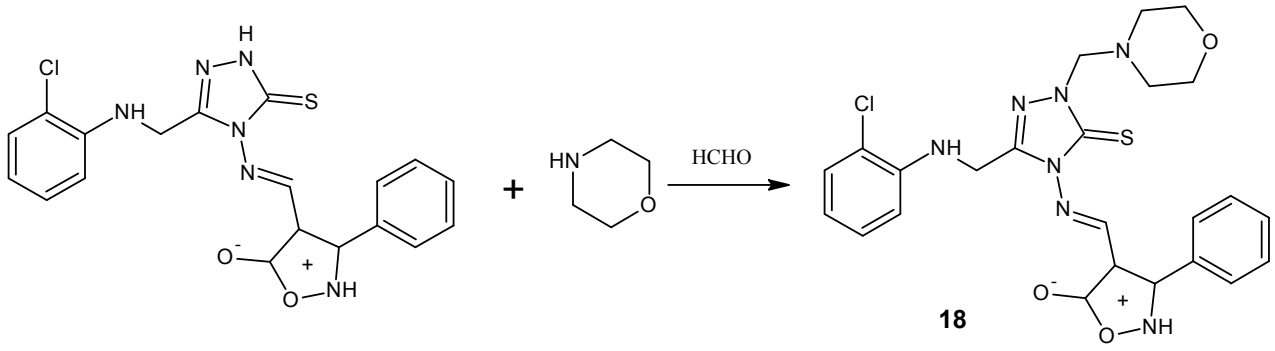


Scheme 15a. Synthesis of 4-{[(1*Z*)-(4-fluorophenyl)methylene]amino}-5-methyl-2-(morpholin-4-ylmethyl)-2,4-dihydro -3*H*-1,2,4-triazole-3-thione



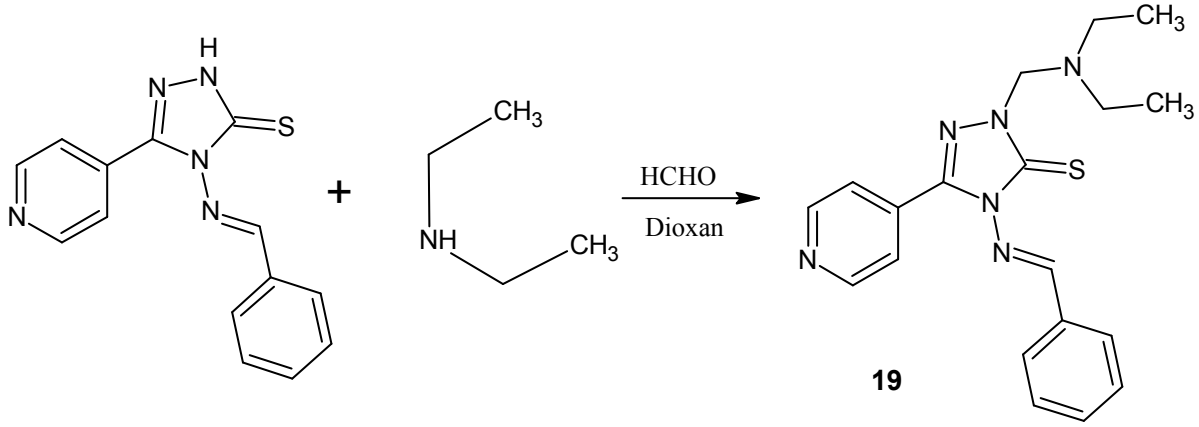
Scheme 15b. Synthesis of 4-{[(1*Z*)-(4-fluorophenyl)methylene]amino}-5-methyl-2-({[2-(trifluoromethyl)phenyl] amino}methyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione

3-(4,6-Dimethyl-2-thiomethylpyrimidyl)-4-(4-chlorobenzylidene)-amino-1-(N-methylpiprazinomethyl)-1,2,4-triazole-5-thione **18 (Scheme 16)**, which is a sydnone and triazole-containing Mannich derivative was prepared by Kalluraya *et al.,* [21] which exhibited good antibacterial activity against *E. Coli.*



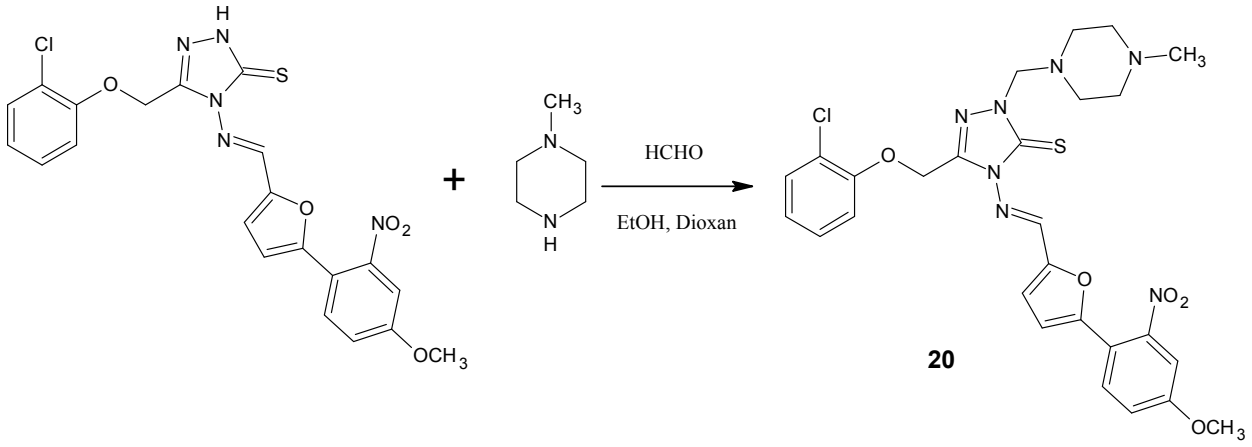
Scheme 16. Synthesis of 3-(4,6-dimethyl-2-thiomethylpyrimidyl)-4-(4-chlorobenzylidene)-amino-1-(N-methylpiprazinomethyl)-1,2,4-triazole-5-thione

Synthesis and biological evaluation of some Mannich bases and azetidin-2-ones of 3-pyridyl-4-amino-5-mercapto-1,2,4-triazole was reported by Priyadarsini *et al.,* [22]. They synthesised 1-diethylaminomethyl-3-(4'-pyridyl)-4-benzylideneamino-1,2,4-triazole-5-thione **19** by the reaction between 4-[(*E*)-benzylideneamino]-5-(pyridin-4-yl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione and diethylamine **(Scheme 17)**. It showed moderate antitubercular properties against *M. tuberculosis.*



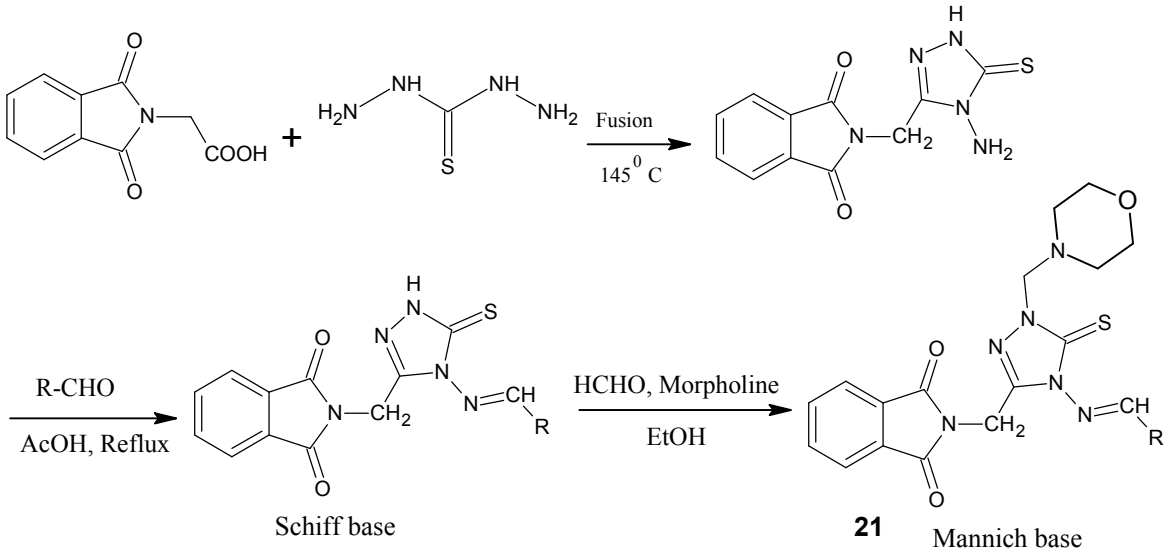
Scheme 17. Synthesis of 1-diethylaminomethyl-3-(4'-pyridyl)-4-benzylideneamino-1,2,4-triazole-5-thione

Holla *et al.,* [23] studied the synthesis, characterization and anticancer activity on some Mannich bases derived from 1,2,4-triazoles such as 1-[(4-methylpiperazin-1-yl)methyl]-3-(2-chlorophenoxymethyl)-4-[5-(4-methoxy-2-nitrophenyl)-2-furfurylidene]-amino-1,2,4-triazole-5-thione **20 (Scheme 18)** which was found to be a potent anticancer agent against twenty four cancer cell lines.



Scheme 18. Mannich base of 1-[(4-methylpiperazin-1-yl)methyl]-3-(2-chlorophenoxymethyl)-4-[5-(4-methoxy-2-nitrophenyl)-2-furfurylidene]-amino-1,2,4-triazole-5-thione

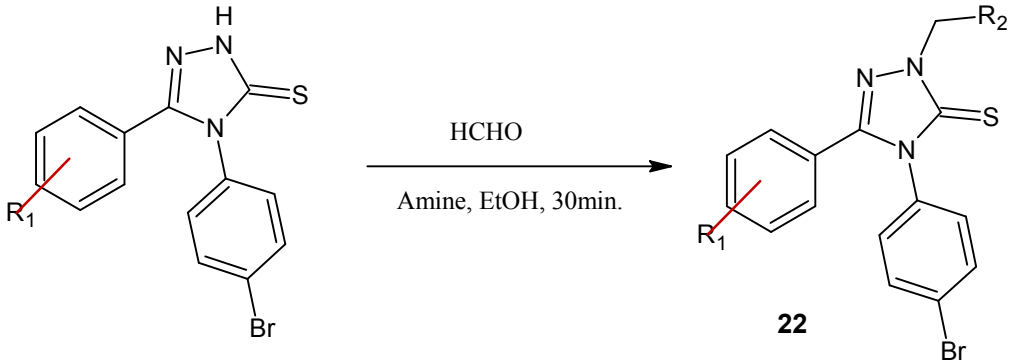
In the research article, Yunus *et al.,* [24] described the syntheses and antimicrobial activity studies of a series of novel Schiff bases and their Mannich bases **21** starting from 4-amino-3-(N-phthalimido-methyl)-1,2,4-triazole-5-thione **(Scheme 19)**. All the synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, and MS. All the synthesized compounds were screened for four Gram negative strains, one Gram-positive strain of bacteria, and one diploid fungal strain. They found that the antimicrobial activity increased remarkably on the introduction of azomethine functionality in parent triazole (**1**). The antimicrobial activity further improved when morpholine group was added to them except for *Enterobacter cloacae*, where loss of activity was observed.



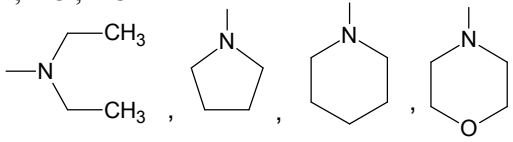
Where R = phenyl, 2-hyroxyphenyl, 3-pyridyl, 3-nitrophenyl, 4-chlorophenyl, 4-bromophenyl, 4-pyridyl, 4-methoxyphenyl, 4-fluorophenyl

Scheme 19. Synthesis of Mannich bases of 4-amino-3-(N-phthalimido-methyl)-1,2,4-triazole-5-thione

The research done by Plech *et al.,* [25] proved that chemical character of the C-5 substituent significantly determines the antibacterial activity of the Mannich bases derived from 4, 5-disubstituted 1,2,4-triazole-3-thiones **22 (Scheme 20)**. This activity was considerably increased by an introduction of chlorine atom to the phenyl ring. The obtained compounds were particularly active against opportunistic bacteria (*Bacillus subtilis* and *Bacillus cereus*). The antibacterial activity of few Mannich bases was similar or higher than the activity of commonly used antibiotics such as ampicillin and cefuroxime.

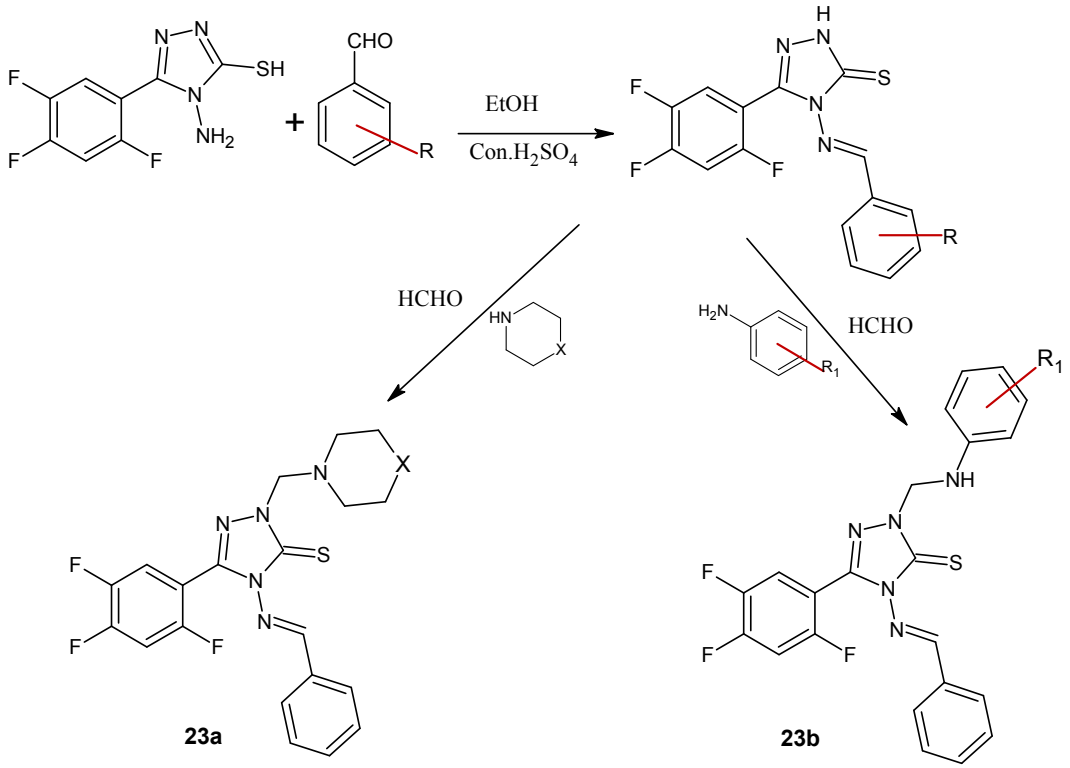


Where R_1 = H, 2-Cl, 4-Cl

and R_2 = 

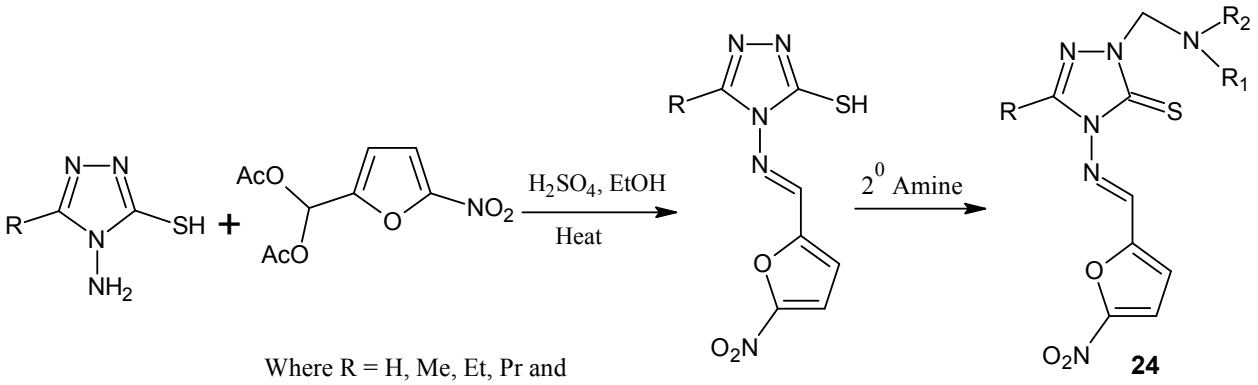
Scheme 20. Mannich bases derived from 4, 5- disubstituted 1,2,4-triazole-3-thiones

Karthikeyan *et al.,* [26] prepared a series of 2,4-dichloro-5-fluorophenyl bearing Mannich base **23**a, **23b** from triazole Schiff bases by aminomethylation with formaldehyde and secondary/substituted primary amines **(Scheme 21)**. All newly synthesized compounds were screened for their antifungal activity.



Scheme 21. Synthesis of 2,4-dichloro-5-fluorophenyl bearing Mannich base

A series of Schiff bases, 3-substituted-4-(5-nitro-2-furfurylidene)amino-5-mercapto-1,2,4-triazoles and their Mannich bases **24 (Scheme 22)** were synthesized by Shivananda and Prakash [27]. The structures of these Schiff bases and Mannich bases were confirmed on the basis of elemental analysis, ^{1}H NMR and mass spectral data. These compounds were also screened for their antifungal activity against *C. albicans*.

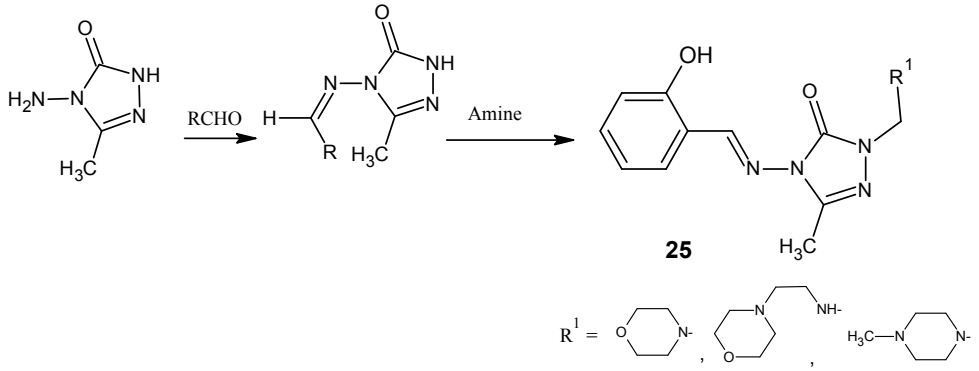


Where R = H, Me, Et, Pr and

NR_1R_2 = Morpholine, 2-Aminopyridine, 3-Cl-4-F-Aniline, N-methylpiperazino

Scheme 22. Synthesis of Mannich base of 3-substituted-4-(5-nitro-2-furfurylidene)amino-5-mercapto-1,2,4-triazoles

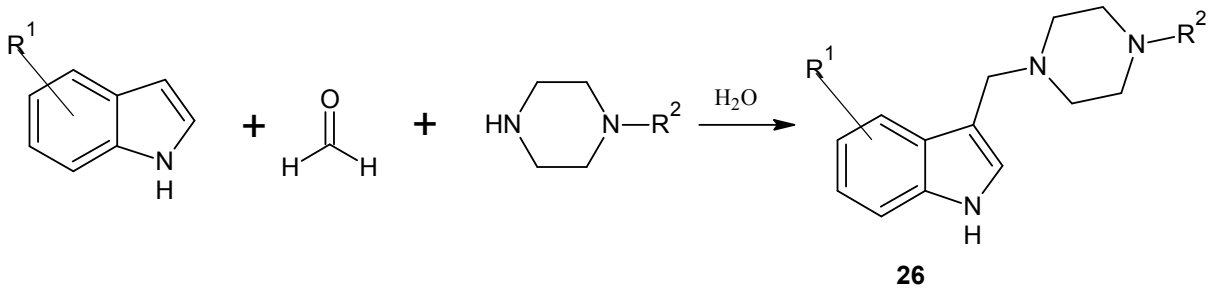
Fandakli *et al.,* [28] converted 1,2,4-triazol-3-one containing an imine group to respective Schiff base by the action of aldehydes and then to Mannich bases **25**, using several primary or secondary amines including morpholine or piperazine nucleus **(Scheme 23)**. All newly synthesized compounds were screened for their antimicrobial activity in comparison with ampicillin.



Scheme 23. Synthesis of Mannich base of 1,2,4-triazol-3-one

3.6 MANNICH BASES OF INDOLE DERIVATIVES

An efficient and simplified first green protocol for three component Mannich reactions of Indoles in water without using any catalyst **(Scheme 24)** was described by Khan *et al.* [29]. Different functionalized Indole Mannich base **26** synthesized in relatively short time with moderate to good yields. The advantages of this methodology are higher selectivity, simplicity, and shorter reaction time.

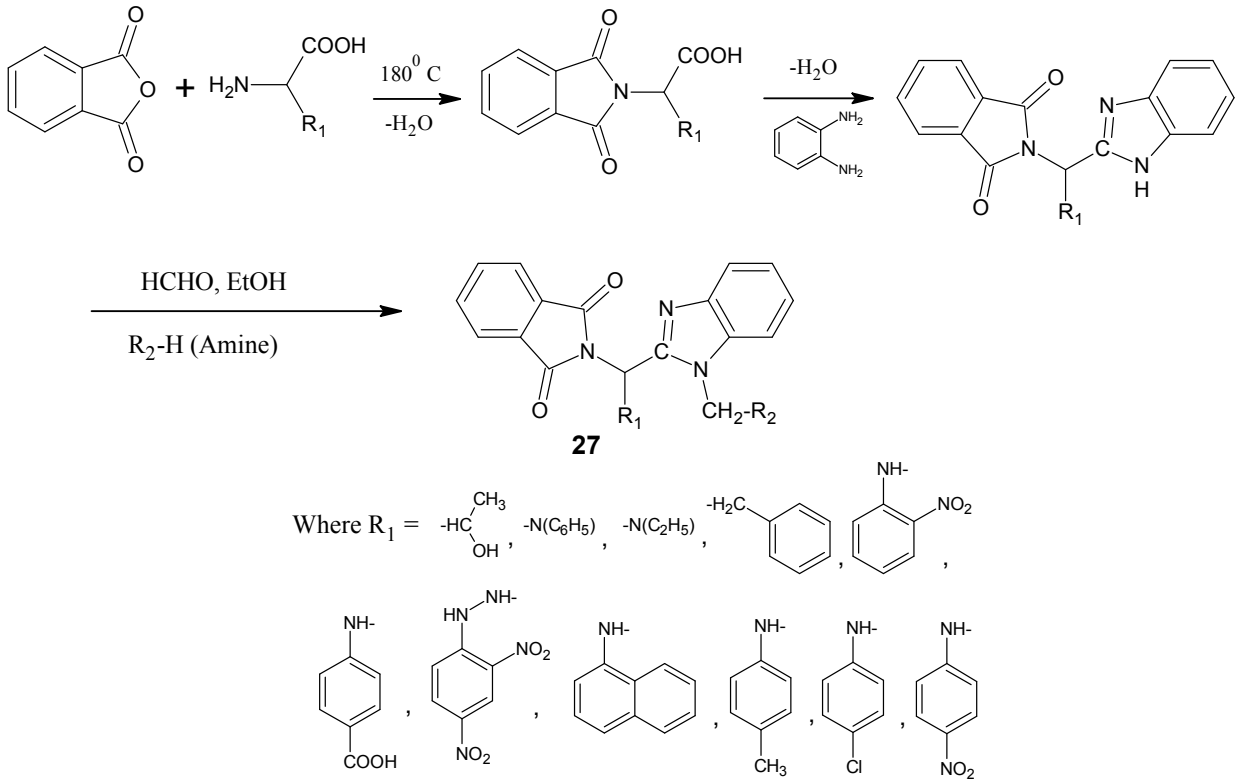


26

(Where R_1= CN, H, Br, OMe and R_2 = alkyl or aryl)

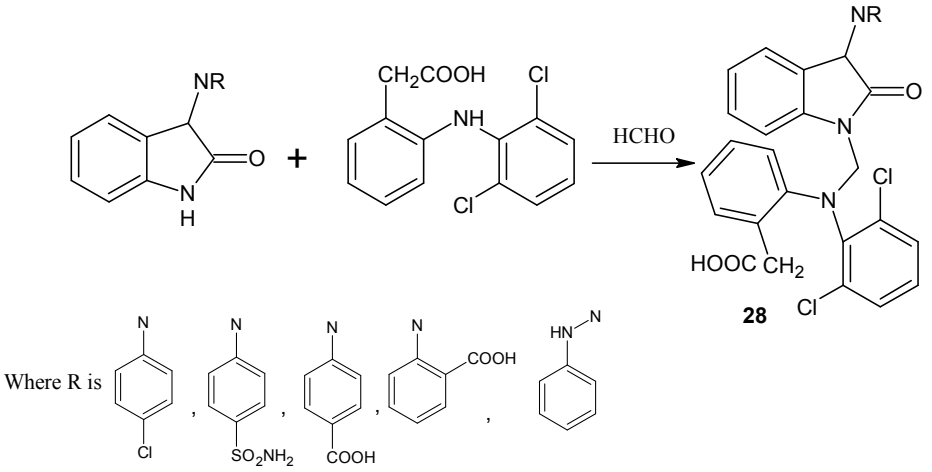
Scheme 24. Synthesis of Indole Mannich base

Bamnela *et al.,* [30] in the research article derived a series of *N*-Mannich bases of benzimidazolyl substituted 1*H*-isoindole-1,3(2*H*)dione **27** by the reaction of different substituted amino acids with phthalic anhydride to yield 2-(substituted) 1*H*-isoindole-1,3(2*H*) diones, further condensation with *o*-phenylenediamine yields 2-substituted benzimidazolyl 1*H*-isoindole-1,3(2*H*) diones, followed Mannich reaction with ethanol and different amines **(Scheme 25)** to yields final products. The chemical structures of synthesized *N*-Mannich bases were determined by elemental analysis and spectral data (FTIR &^{1}H NMR). All the synthesized derivatives have been evaluated for their antimicrobial, anthelmintic and insecticidal activities against microbes, helminthes and insects selected as compared to standard drugs by using disc diffusion method and Watkins technique respectively. All the synthesized *N*-Mannich bases possess the significant antimicrobial, anthelmintic and insecticidal activities.



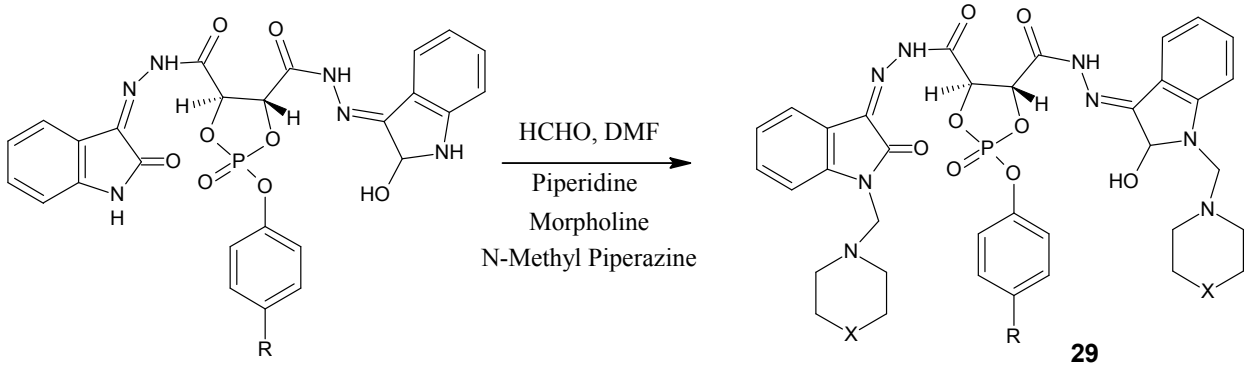
Scheme 25. Synthesis of *N*-Mannich bases of benzimidazolyl substituted 1*H*-isoindole-1,3(2*H*)dione

In the general paper produced by Ravichandran*et al.,* [31] preparation of a series of 2,3-dihydro-2-oxo-1,3-disubstituted indoles **28** by the reaction of 2,3-dihydro-2-oxo-3-substituted indoles with 2-[(2,6-dichlorophenyl)amino]phenylacetic acid in the presence of formaldehyde **(Scheme 26)** had been explained. The newly synthesized compounds were characterized on the basis of elemental analysis, IR, ^{1}H NMR and mass spectra. All the synthesized compounds were tested for their antibacterial activities against Gram positive and Gram negative bacteria, and antifungal activities.



Scheme 26. Synthesis of 2,3-dihydro-2-oxo-1,3-disubstituted indoles

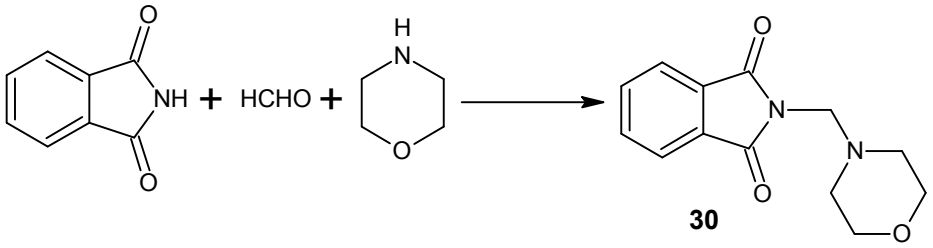
Aiswarya *et al.,* [32] synthesised new Mannich bases of 2-phenoxy-1,3,2-dioxaphospholanes derivatives (4R, 5R) – N'4, N'5-bis-(2-oxo-1-(piperidin-1-ylmethyl) / (morpholino methyl) / (4-methyl piperazin-1-ylmethyl) indolin-3-ylidene) – 2-(4-substituted phenoxy)-1,3, 2-dioxa phospholane-4, 5-dicarbohydrazide-2-oxide **29**. This product was obtained by the Mannich reaction of the corresponding (4R, 5R) – N'4, N'5-bis-(2-oxo indolin-3-ylidene) – 2-(4-substituted phenoxy)-1, 3, 2-Dioxaphospholane-4, 5-dicarbohydrazide-2-oxide with different Secondary amines namely: piperidine, morpholine and N-methyl piperazine in the presence of formaldehyde in DMF (Dimethylformamide) **(Scheme 27)**.The structure of these newly synthesized compounds was characterized by IR, Mass, ^{1}H, ^{13}C and ^{31}P NMR spectral data. These newly synthesized compounds 6(a-g) were screened for their antibacterial and antifungal activity.



Where R = 4-H,4-CH_3, 4-Cl, 4-Br, 4-NO_2 and X = -CH_2, -O, -N-CH_3

Scheme 27. Synthesis of Mannich bases of 2-phenoxy-1,3,2-dioxaphospholanes derivatives

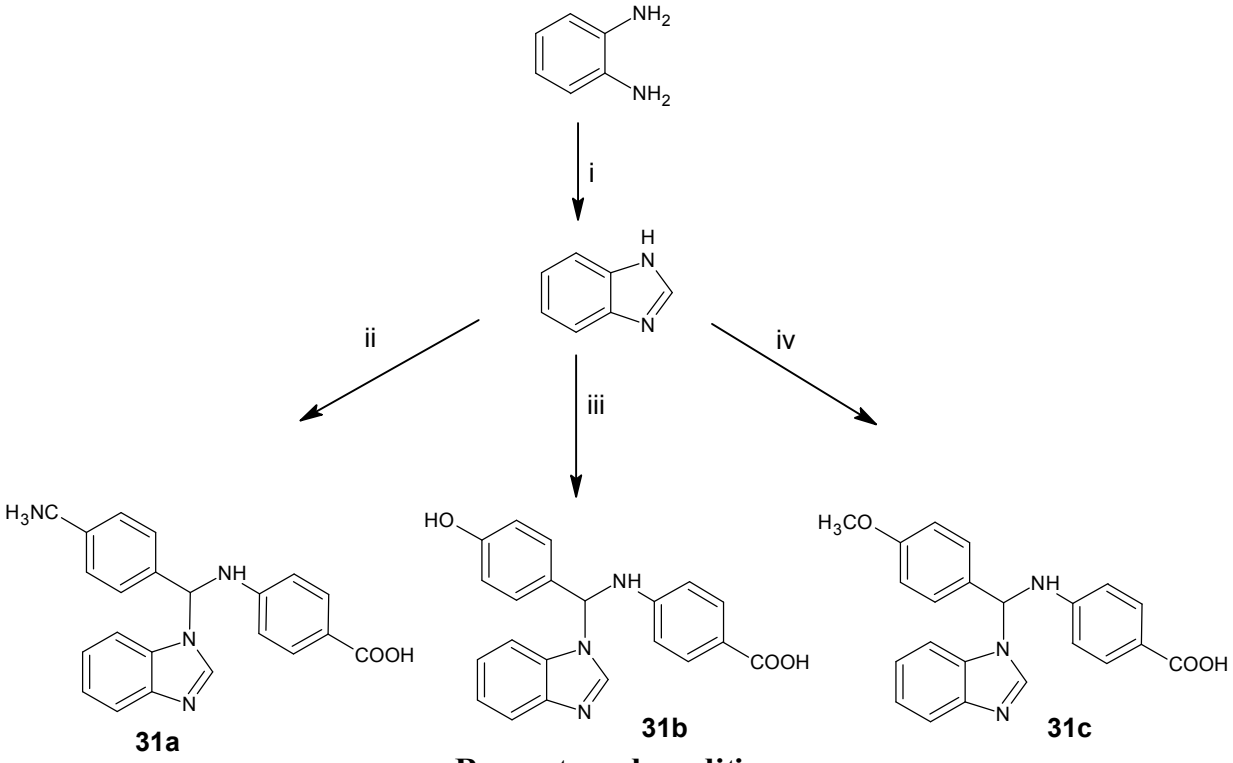
A new Mannich base 2-(morpholin-4-ylmethyl)isoindole-1,3-dione **30** and its coordination complexes with manganese(II) and cobalt(II) ions **(Scheme 28)** have been synthesized and characterized by Ramesh & Sabastiyan [33]. The structural features of the complexes were investigated by elemental analysis, IR, UV-Vis, ^{1}H and ^{13}C NMR, mass, magnetic, conductance, TG/ DTA and cyclic voltammetric data. 2-(Morpholin-4-ylmethyl)isoindole-1,3-dione was found to act as a neutral bidentate chelating ligand binding to the metal ion through a carbonyl oxygen and tertiary amino nitrogen atoms. The non-electrolytic nature of the complexes was evidenced by their very low molar conductance values. On the basis of magnetic moments and electronic spectral data, the Mn(II) and Co(II) complexes were assigned an octahedral geometry excepting and the Co(II) chloro complex which was assigned a tetrahedral geometry. The antimicrobial activity of the ligand and a selected few complexes had been studied by agar-well diffusion method. Both the organic ligand and the complexes possessed significant antimicrobial activity comparable to that of the standard drugs.



Scheme 28. Synthesis of Mannich base of 2-(morpholin-4-ylmethyl)isoindole-1,3-dione

3.7 MANNICH BASES OF BENZIMIDAZOLE DERIVATIVES

A series of Mannich bases of benzimidazole derivatives **31a, 31b, 31c** were synthesized by Aanandhi *et al.,* [34] from o-phenylenediaamine in two steps via benzimidazole intermediates **(Scheme 29)**. The synthesized compounds were characterized by IR, ^{1}H NMR, mass and elemental analysis and were evaluated for their anti fungal activity against a panel of two pathogenic fungal strains namely, *Aspergillus niger, and Candida albicans* by two fold serial dilution method, antibacterial activity against *B. subtilis, S .aureus, E. Coli, S. Typhi.* All the compounds showed significant inhibitory activity against the microbes with the 100µg/ml which produces 100% inhibition against the microorganism. Anti bacterial activity was determined using Ciprofloxacin as a standard and antifungal activity was determined using standard Ketoconazole.

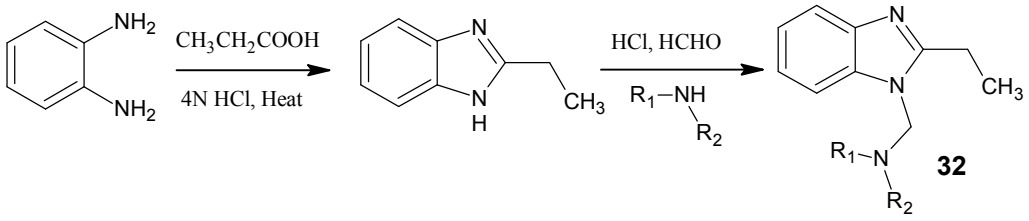


Reagents and conditions:

i) Formic acid and 10%NaoH, ii) p-Aminobenzoic acid, P-Dimethyl amino benzaldehyde and ethanol, iii) p-Aminobenzoic acid, p-Hydroxy benzaldehyde and ethanol, iv) p-Aminobenzoic acid, p-Methoxy benzaldehyde and ethanol

Scheme 29. Synthesis of Mannich bases of benzimidazole derivatives

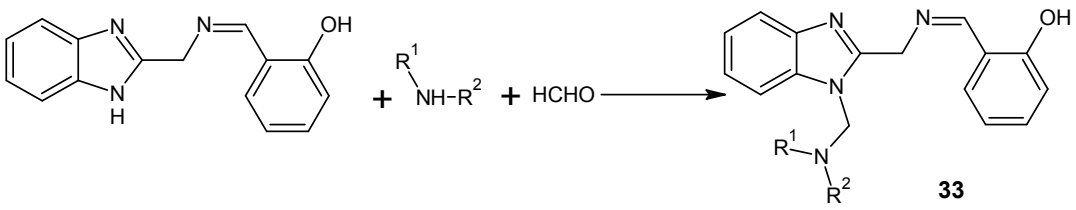
[1-(N-substituted amino)-2-ethyl benzimidazole derivatives **32** have been synthesised by the condensation of 2-ethyl benzimidazole with substituted primary and secondary amines **(Scheme 30)**. The synthesized compounds were characterized by UV-Vis, IR, ^{1}H NMR, mass spectral data and were evaluated for their anti –inflammatory and analgesic activities. This has been reported by Mariappan *et al.,* [35].



Where –NR_1R_2 is Diethylamino, Piperidino, Morpholino, diethanolamino, 2-Chloroanilino, 3-Chloroanilino, 2,3-Dichloroanilino, 3,4-Dichloroanilino, 4-Fluoroanilino, 4-Bromoanilino.

Scheme 30. Synthesis of Mannich base of 2-ethylbenzimidazole derivatives

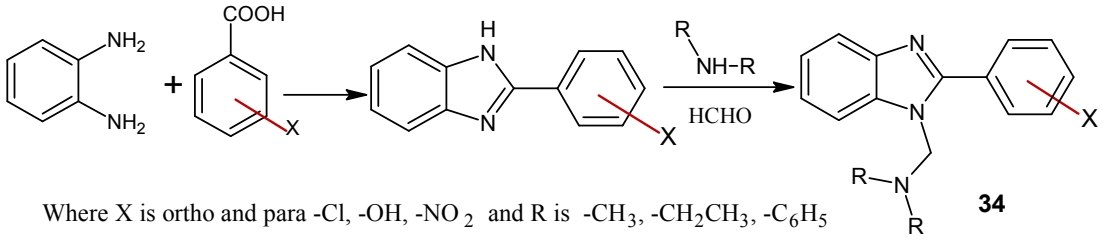
Ur Rehman *et al.,* [36] prepared novel Mannich base derivatives of Benzimidazole **33** through the condensation reaction of benzimidazole derivative with formaldehyde and primary and/ secondary amine **(Scheme 31)**. They also synthesised Zinc(II), copper(II), nickel(II) and cobalt(II) complexes of Mannich bases. All the compounds were fully characterized by, elemental analyses, magnetic moment determination, molar conductivity measurement, thermo gravimetric analysis, spectral and analytical data. Experimental results showed that metal complexes act as bi-dentate ligands towards divalent metal ions via azomethine-N and deprotonated-O while suggesting an octahedral geometry. All the compounds were screened for in-vitro antibacterial and antifungal activity against various bacterial and fungal strains. Almost all the compounds showed good potent activity against microorganisms. It was also seen that compounds with complexed form were more active as compared to un-complexed form. The prepared compounds were also screened for their cytotoxicity and results showed that only Ni(II) complexes exhibit some cytotoxicity while all other compounds were almost inactive.



Where R^1 is -H, $-CH_2CH_3$, $-C_6H_5$ and R^2 is -H, $-CH_2CH_3$, $-CH_2CH_2NH_2$, $-C_6H_5$, $-C_6H_4CH_3$, $-C_5NH_5$, $-C_4N_2H_5$

Scheme 31. Synthesis of Mannich base derivatives of Benzimidazole

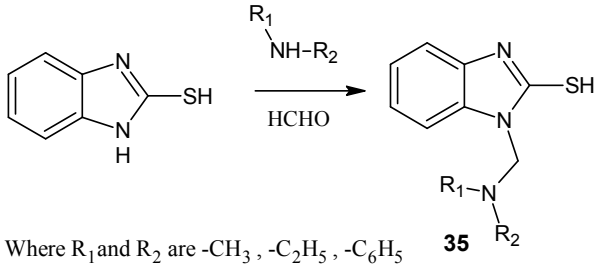
Al Messmary *et al.,* [37] prepared a number of 2-substituted benzimidazoles by reaction of substituted benzoic acid with o-phenylenediamine, and then the products obtained were treated with secondary amines in the presence of formaldehyde to synthesize Mannich bases **34 (Scheme 32)**. The final products were characterized by physical and spectral analysis.



Where X is ortho and para -Cl, -OH, $-NO_2$ and R is $-CH_3$, $-CH_2CH_3$, $-C_6H_5$

Scheme 32. Synthesis of Mannich base derivatives of 2-substituted benzimidazole

Arora *et al.,* [38] reported the synthesis of the Benzimidazole **35** by reaction between o-phenylenediamine with twice molar quantities of formic acid .The compound was subjected to sulphonation which results in the formation of 2-mercaptobenzimidazole then the products obtained were treated with secondary amines in the presence of formaldehyde in order to synthesize Mannich bases **(Scheme 33)**. Both conventional and microwave irradiated synthesis of derivatives had been carried out to compare their yield and reaction time.

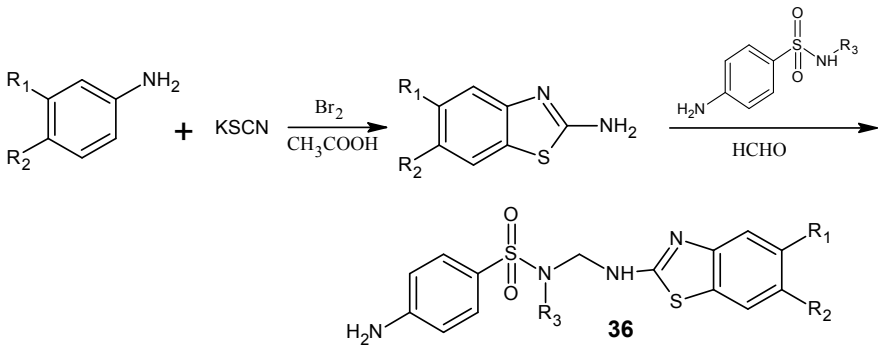


Where R_1 and R_2 are $-CH_3$, $-C_2H_5$, $-C_6H_5$ **35**

Scheme 33. Synthesis of N-Mannich bases of 2-mercaptobenzimidazole

3.8 MANNICH BASES OF BENZOTHIAZOLE DERIVATIVES

Mannich bases of sulphadiazine, sulphamethoxazole, sulphacetamide **36** with 2- amino -3 -methyl benzothiazole, 2 -amino chloro benzothiazole and 2 -amino 5 -chloro 6- fluro benzothiazole **(Scheme 34)** were synthesized by Nayeem & Denny [39]. The structures of the various derivatives were characterized by various spectral data's and by elemental analysis. The synthesized compounds were screened for their anti tubercular activity using Lowenstein-Jensen (L.J) medium against *Mycobacterium tuberculosis* H37 RV strains and the anti microbial activity against bacteria i.e. *Escherichia coli, Bacillus subtilis, Pseudomonas aeruginosa Klebsiella neumonia*and fungi *Candida albicans* and *Aspergillus niger*.

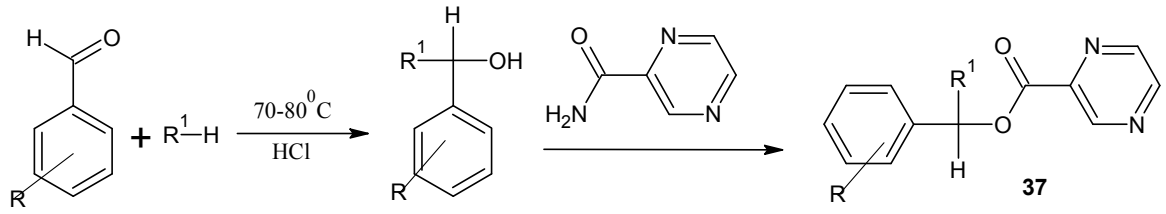


Where R_1 = H,Cl, CH_3, R_2 = H, F and R_3 = H, $C_4H_3N_2$, $COCH_3$

Scheme 34. Synthesis Mannich bases of Sulphadiazine, Sulphamethoxazole, Sulphacetamide

3.9 MANNICH BASES OF PYRAZINE DERIVATIVES

Chaluvaraju and Ishwar Bhat [40] synthesized a series of aminobenzylated Mannich bases of pyrazinamide **37** by Mannich reaction of aromatic aldehydes with pyrazinamide and secondary amines **(Scheme 35)**.They elucidated chemical structure of all the synthesized compounds by IR, ^{1}H NMR spectral studies. These compounds 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.

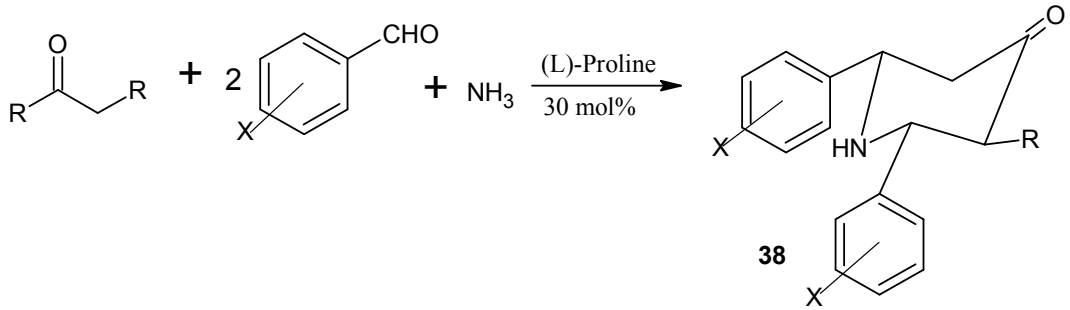


R= Hydrogen, 2,4-dimethoxy, 4-hydroxy, 3-nitro, 2,5-dimethoxy and R^1= Morpholine, Piperdine, N-Methyl piperizine.

Scheme 35. Aminobenzylated Mannich bases of pyrazinamide

3.10 MANNICH BASES OF PIPERIDINE DERIVATIVES

(L)-Proline catalyzed Mannich reaction of ketones, aromatic aldehydes and ammonia **(Scheme 36)** was reported by Srinivasan *et al.*, [41]. This furnished 3-substituted 2,6-diarylpiperidin-4-ones **38** in enhanced yields (up to five times) compared to the reaction involving ketone, aldehyde and ammonium acetate. The catalytic efficiency of proline was ascribable to the involvement of an enamine intermediate that could result from the reaction of ketones with proline and the absence of the formation of bicyclic side product in this reaction.

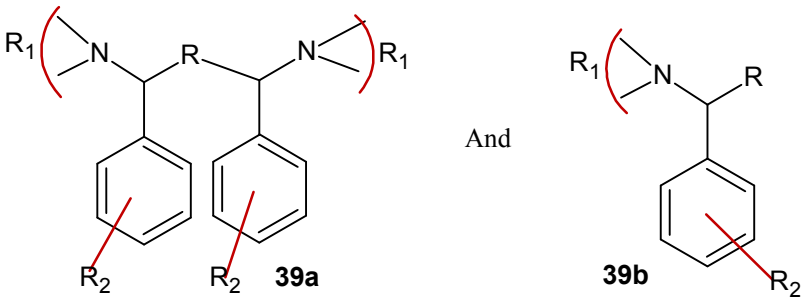


R= CH_3, $CH(CH_3)_2$, $COOC_2H_5$; X = H,p-Cl, p-CH_3,o-OCH_3 , o-Cl , p-OCH_3

Scheme 36. (L)-Proline catalyzed Mannich bases

3.11 MANNICH BASES OF PIPERAZINE DERIVATIVES

Studies were conducted on the anthelmintic property of about 15 synthesized aminobenzylated Mannich bases bearing N-methyl piperazine **39a, 39b (Scheme 37)** using Indian earthworms *Pheritima Posthuma* against piperazine citrate as standard reference by Chaluvaraju & Bhat [42]. Three concentrations of each compound (0.1, 0.2, 0.3% w/v) were studied, which involved the determination of paralysis and death time of the worms. The compound 1g exhibited the most significant anthelmintic activity among all the compounds screened against the worms as compared to standard drug.



Where R = Urea, Thiurea, Acetamide, Benzamide, Pyrizinamide

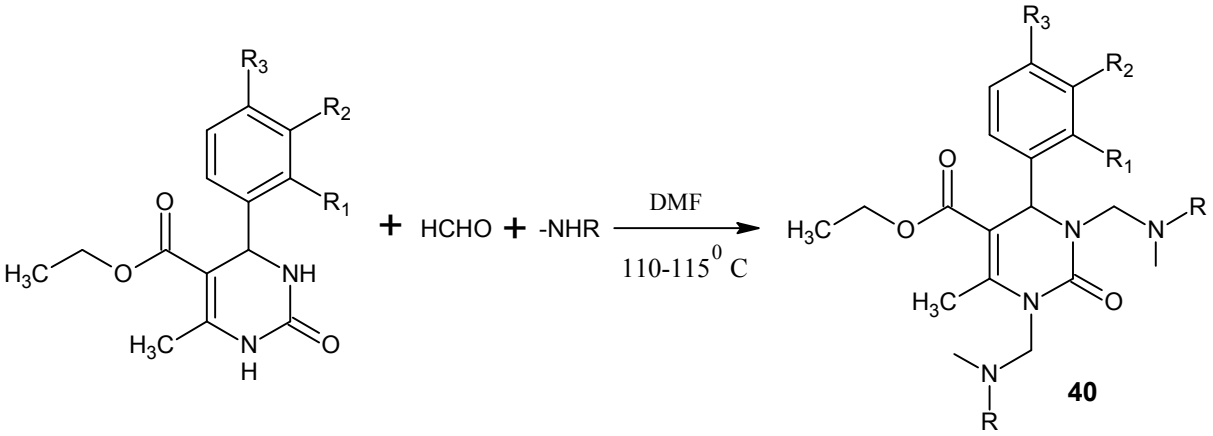
R_1 = N-methyl piperazine and R_2 = H, P-$N(CH_3)_2$, 2,5-$(OCH_3)_2$, 4-OH, 3-NO_2

Scheme 37. Aminobenzylated Mannich bases bearing N-methyl piperazine

3.12 MANNICH BASES OF PYRIMIDINE DERIVATIVES

Three series of N-Mannich bases of 3, 4-dihydropyrimidin-2 (1*H*)-ones (DHPMs) **40** had been prepared by Mannich reaction of DHPMs with seven different heterocyclic secondary amino compounds and formaldehyde **(Scheme 38)** by Shah *et al.,* [43]. The precursors DHPMs were derived by Biginelli reaction of aromatic aldehyde with ethyl acetoacetate and urea. The chemical structure of all the three series of N-Mannich bases had been elucidated by elemental and spectral studies. *In vitro* biological activity against *E. Colii* and *B. subtilis*

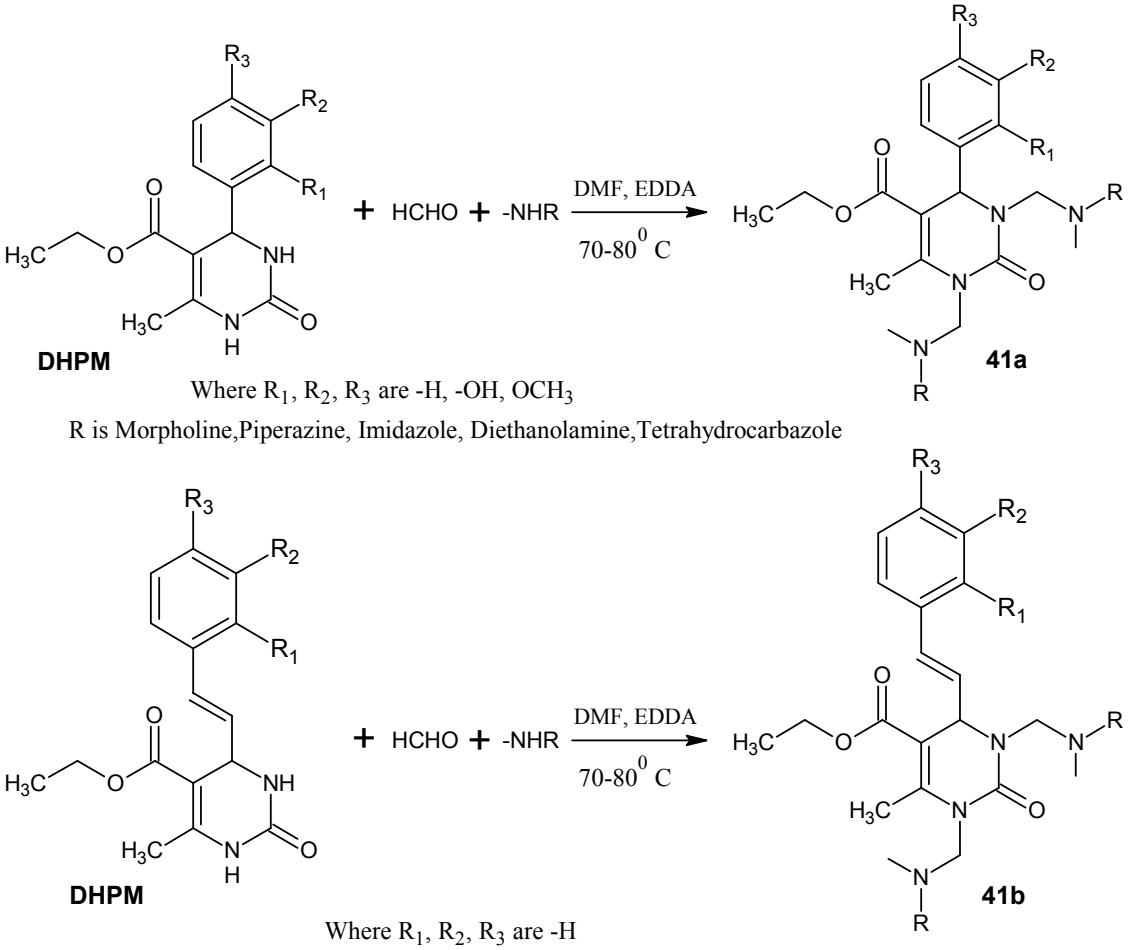
bacterial species and *A. niger* and *C. albicans* fungal microorganisms were assayed.



Where R_1 = -H, -OH, R_2 = -H, $-OCH_3$ and R_3 = -H, -OH, $-OCH_3$
R is Benzimidazol,2-Me benzimidazol, 2-Ph benzimidazol,
Benzotriazol, Phthalimide, Morpholine, Tetrahydrcarbazole

Scheme 38. Synthesis of N-Mannich bases of 3, 4-dihydropyrimidin-2 (1*H*)-ones (DHPMs)

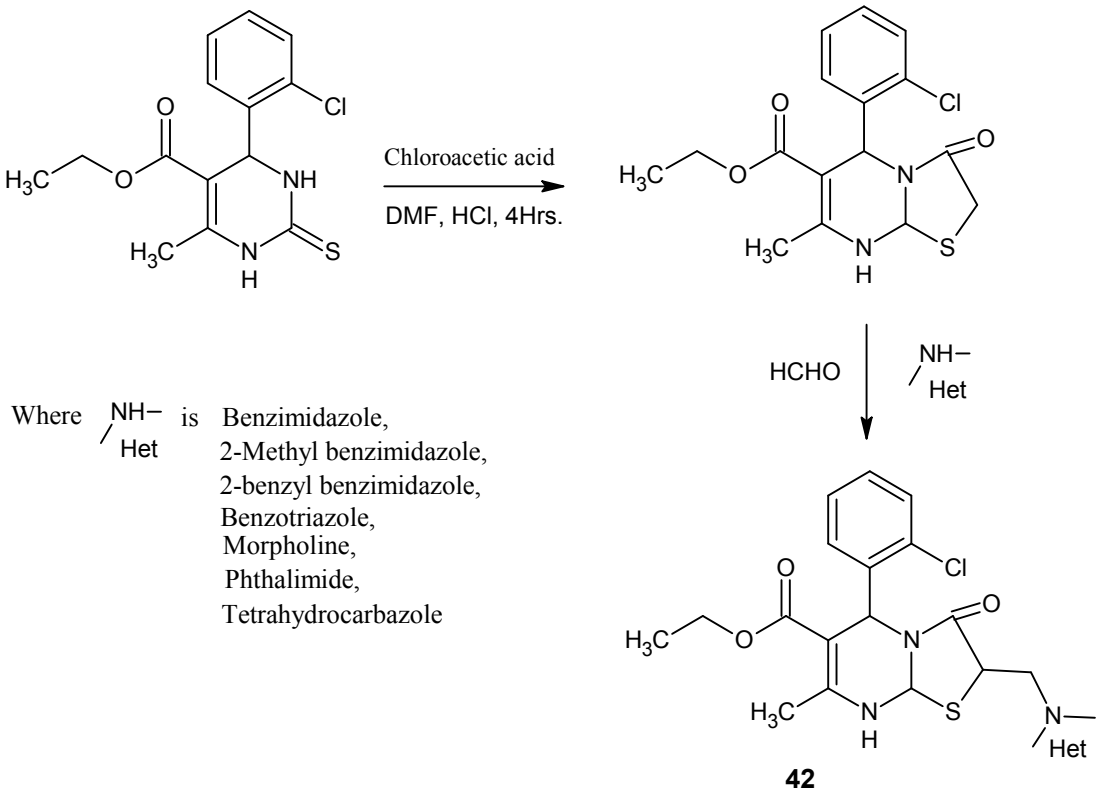
Rajendran *et al.,* [44] in the research article described the synthesis of N-Mannich bases of 3, 4-dihydropyrimidin-2 (1*H*)-ones (DHPMs) **41a, 41b** using Ethylene diammonium diacetate (EDDA) as catalyst **(Scheme 39)**. The heterocyclic precursor DHPMs were synthesized by Bignelli reaction of aromatic aldehyde, ethyl acetoacetate and urea using ionic liquid. Three series of N-Mannich bases have been synthesized by Mannich reaction of 3, 4-dihydropyrimidin-2(1*H*)-one with different heterocyclic secondary amines namely morpholine, piperazine tetrahydrocarbazole, diethanolamine, imidazole and formaldehyde. The Mannich bases have been characterized by elemental and spectral studies. The results indicated that the catalyst EDDA exhibited excellent catalytic activity for the Mannich condensation with better yield and high degree of purity under mild reaction conditions than those reactions with conventional catalyst.



Scheme 39. Synthesis of N-Mannich bases of 3, 4-dihydropyrimidin-2 (1*H*)-ones (DHPMs)

Patel *et al.,* [45] synthesised Mannich bases **42** of ethyl 5-(2-chlorophenyl)-7-methyl-3-oxo-3,5-dihydro-2*H*-thiazolo[3,2-a]pyrimidine-6-carboxylate by Mannich reaction respectively with seven different heterocyclic secondary amino compounds and formaldehyde **(Scheme 40)**. These Mannich bases were derived by the cyclization reaction of ethyl 4-(2-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate with chloroacetic acid in dimethylformamide (DMF). Chemical structure of all the newly synthesized Mannich bases were analysed by elemental analysis and spectral studies (FTIR, ^{1}H &^{13}C NMR). They were assayed *in vitro* for their biological activity against *Escherichia coli* and *Bacillus subtilis* bacterial species as well as *Aspergillus niger* and *Candida albicans* fungal microorganisms. Evaluation of the title compounds as antimicrobacterial agent indicate that ethyl-5-(2-chlorophenyl)-7-methyl-2-(morpholinomethyl)-3-oxo-3,5-dihydro-2*H*-thiazolo [3,2-a]pyrimidine-6-carboxylate (9e) have shown promising antimicrobacterial

activity against both bacterial and fungal microorganisms and thus could be promising novel drug candidates.

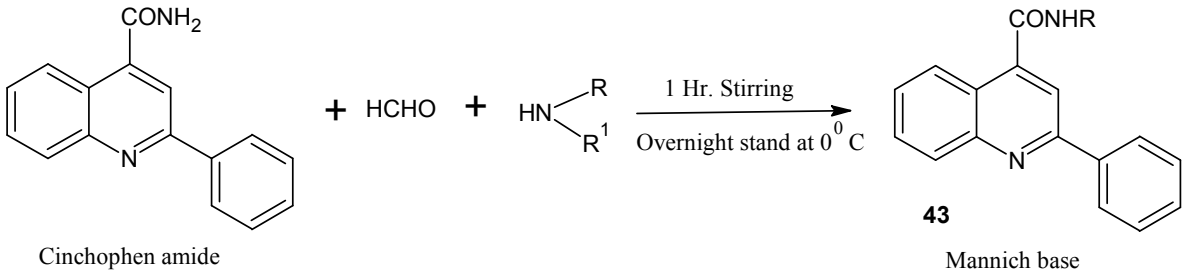


Scheme 40. Synthesis of Mannich bases of ethyl 5-(2-chlorophenyl)-7-methyl-3-oxo-3,5-dihydro-2*H*-thiazolo[3,2-a]pyrimidine-6-carboxylate

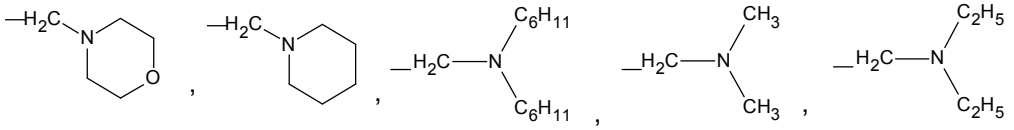
3.13 MANNICH BASES OF QUINOLINE DERIVATIVES

Jumade *et al.* [46] reported the synthesis of new Mannich bases of Quinoline derivative **43** for antimicrobial activity. Here, cinchophen having carboxylic acid (-COOH), group was converted to amide (- $CONH_2$) and it is utilized to synthesize Mannich bases. At first cinchophen was synthesized by Doebnear synthesis and then it was converted to cinchophen chloride, using oxalyl chloride. Cinchophen chloride was converted to cinchophen amide, using ammonia. The Mannich bases have been synthesized by reaction of cinchophen amide with formaldehyde and secondary amine **(Scheme 41)**. The prepared Mannich bases were subjected to physicochemical studies like melting point determination, TLC and % yield. The structures of Mannich bases were characterized by UV, IR, Mass and NMR spectroscopy. Antibacterial screening of newly synthesized Mannich bases was carried out against *E. coli*,

P. aureoginosa, *S. aureus* and antifungal activity against *C. albicans* and *A. niger* according to cup-plate method.

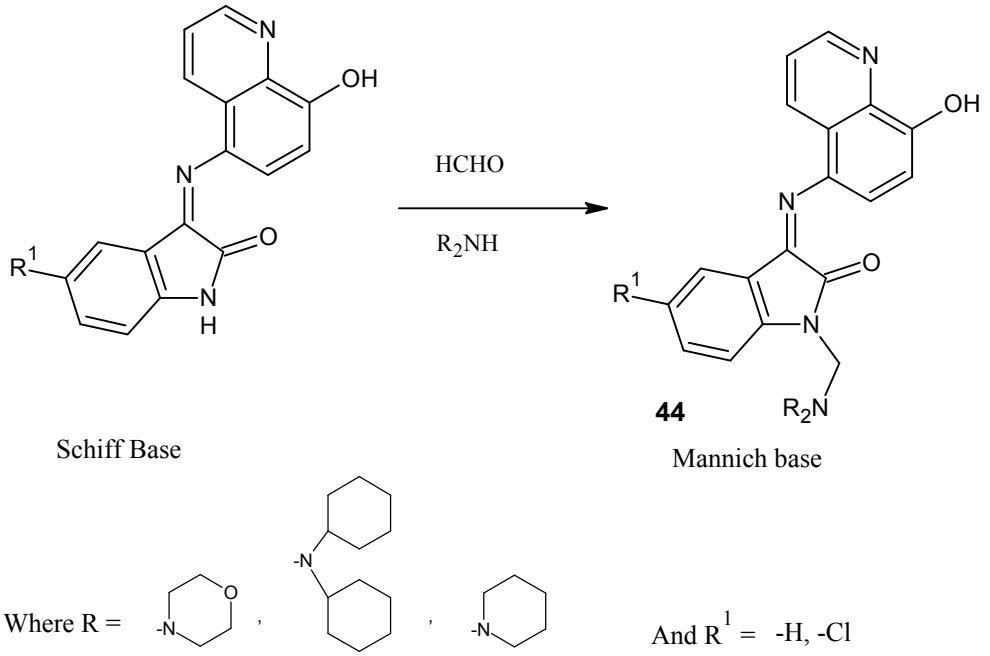


Where R=



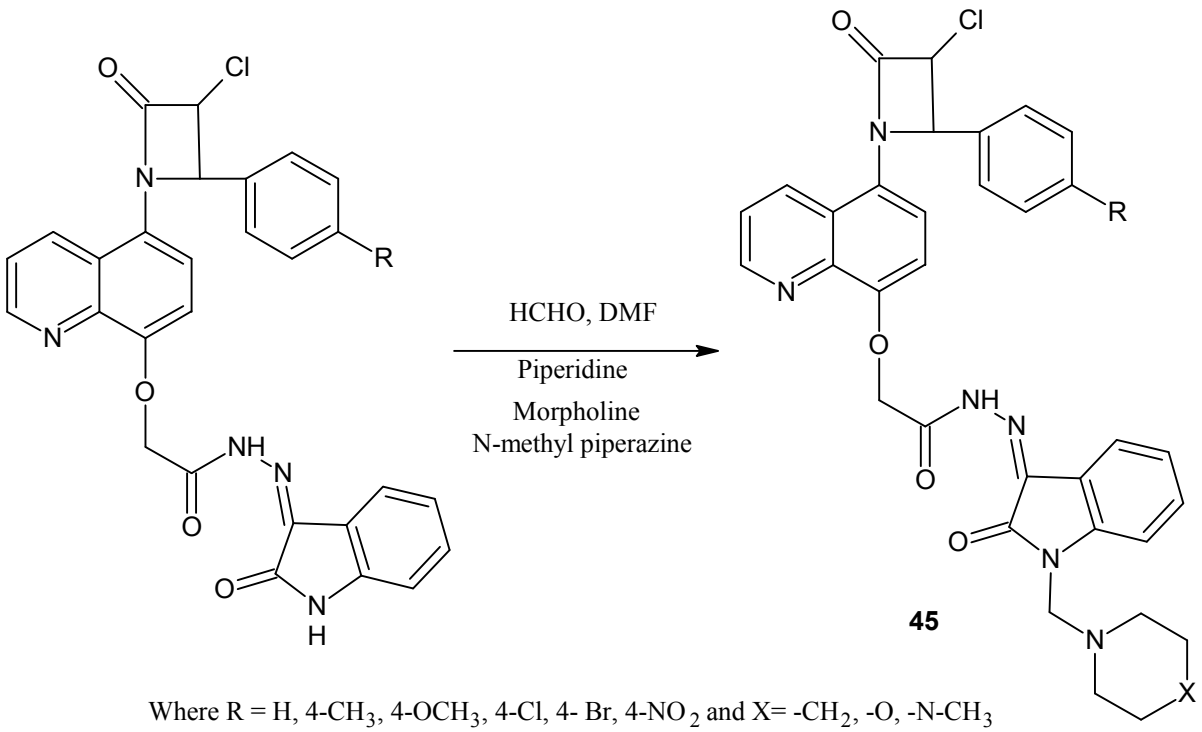
Scheme 41. Mannich bases of Quinoline derivative

Antimicrobial evaluation of some novel Schiff and Mannich bases **44** of Isatin and its derivatives with Quinolin was done by Chhajed & Padwal [47]. The Schiff bases of Isatin, its chloro derivative and 5-amino, 8-Hydroxy-quinoline were converted to *N*-Mannich bases by reacting them with formaldehyde and several secondary amines **(Scheme 42)**. The structure of synthesized compounds was confirmed by IR, NMR and mass spectral analysis. Investigation of antimicrobial activity of the compounds was made by the agar dilution method. Gram positive bacteria such as *Staphylococcus aureus*, *Streptococcus faecalis* and *bacillus Subtilis*, two gram negative bacteria such as *Escherichia coli* and *Pseudomonas aeruginosa* and two fungal species such as *Aspergillus Niger* and *Candida albicans* were tested for the activities. The compounds were significantly active against these bacteria and fungi.



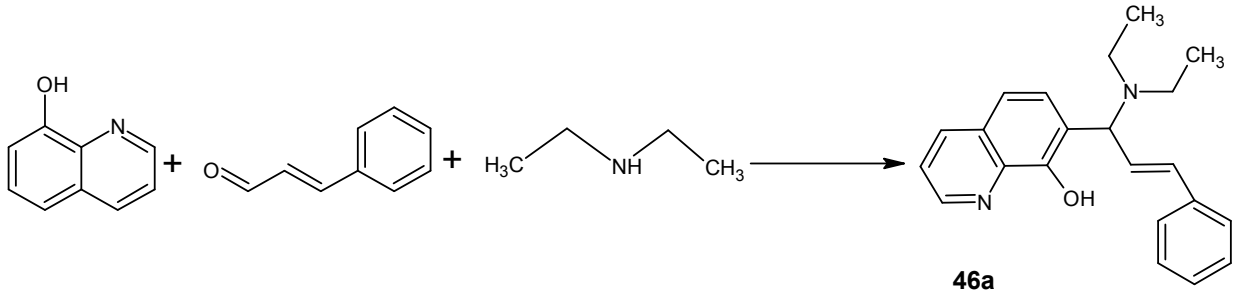
Scheme 42. Mannich bases of Isatin and its derivatives with Quinoline

Madhu *et al.,* [48] subjected (*Z*)-2-(5-(3-chloro-2-oxo-4-ptolylazetidin-1-yl)quinolin-8-yloxy)-N'-(2-oxoindolin-3-ylidene)acetohydrazide to Mannich reaction with cyclic secondary amines such as piperidine / morpholine / N-Methyl Piperazine in presence of formaldehyde in DMF to get corresponding Mannich bases (*Z*)-2-(5-(3-chloro-2-oxo-4-p-tolylazetidin-1-yl)quinolin-8-yloxy)-N'-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidine)acetohydrazide **45 (Scheme 43)** in excellent yields. The structures of these newly synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, Mass, IR and elemental analysis. The prepared compounds had been screened on some strains of bacteria and fungi.



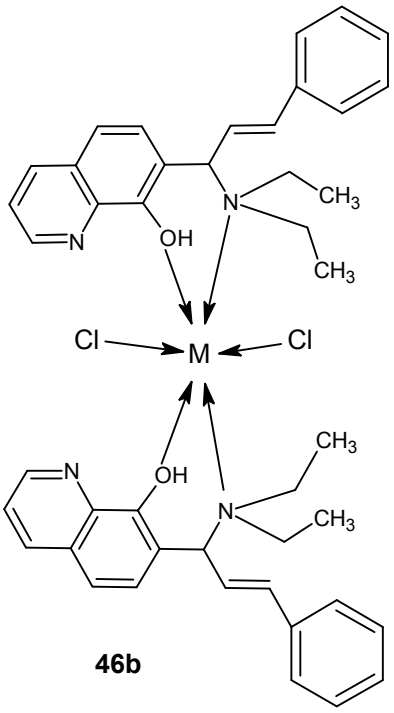
Scheme 43. Mannich bases of (Z)-2-(5-(3-chloro-2-oxo-4-p-tolylazetidin-1-yl)quinolin-8-yloxy)-N'-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidine)acetohydrazide

Muthukumar*et al.,* [49] synthesised the Mannich base 7-diethylaminocinnamyl-8-hydroxyquinoline **46a** by the condensation of 8-hydroxyquinoline, diethylamine and cinnamaldehyde in 1:1:1 mole ratio (**Scheme 44a)**. Transition metal complexes, $[ML_2Cl_2]$ **46b** were prepared by the interaction of $MCl_2.nH_2O$ (M = Co, Ni and Cu) with the Mannich base **(Scheme 44b)**. The synthesized ligand and complexes were characterized by elemental analysis, molar conductance, magnetic susceptibility and spectral measurements. On the basis of spectral and magnetic data, an octahedral geometry has been assigned to all the complexes studied. The free ligand and its metal chloro complexes have been screened against a number of microorganisms in order to assess their antimicrobial potency.



46a

Scheme 44a. Mannich bases of 7-diethylaminocinnamyl-8-hydroxyquinoline



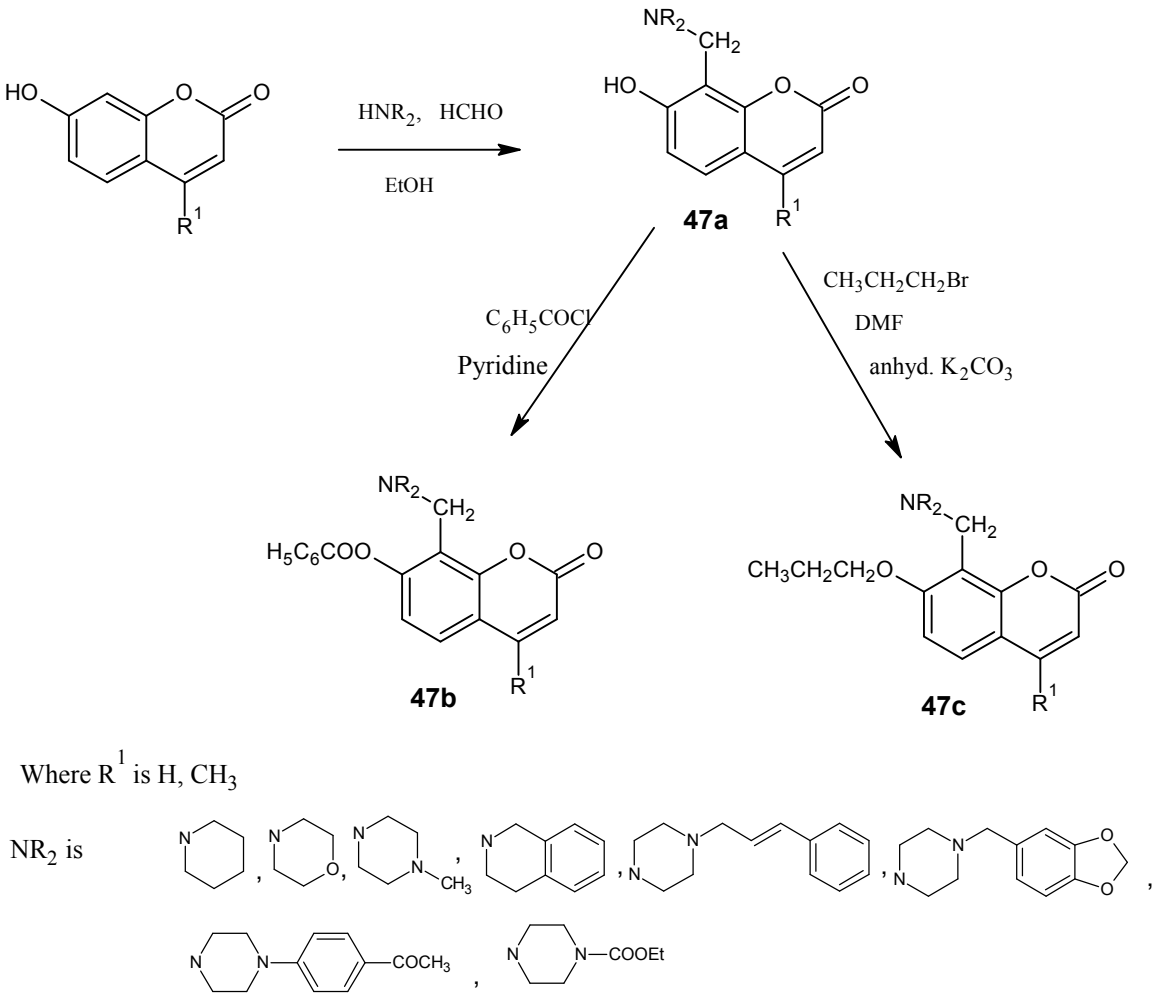
46b

Where M is Co(II), Cu(II), Ni(II), Mn(II)

Scheme 44b. Structure of Transition metal complexes of Mannich bases

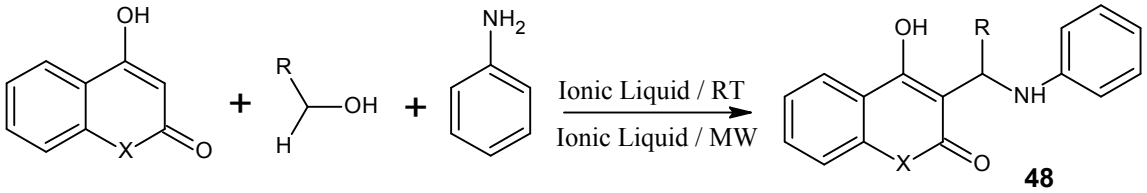
3.14 MANNICH BASES OF COUMARIN

Some Mannich bases of 7-hydroxycoumarin **47a** and their simple derivatives **47b** and **47c (Scheme 45)** were prepared and tested against viruses containing single-stranded, positive-sense RNA genomes (ssRNA+). This study was directed toward Flaviviridae and, in particular, HCV surrogate viruses (BVDV, YFV). The work was reported by Mazzei *et al.*, [50].



Scheme 45. Mannich bases of 7-hydroxycoumarin

Synthesis of a series of 3-substituted aminophenyl-4-hydroxycoumarins **48** *via* Mannich reaction by using [BMIM]BF_4 ionic liquid under microwave irradiation **(Scheme 46)** was reported in the research article by Onkara *et al*., [51]. Compounds were characterized by IR, ^{1}H NMR and mass spectroscopy. All the compounds were tested for their antibacterial activity against B. *subtilis,* Bacillus. *sp,* E. *coli and* P. *putida*. Most of the compounds showed moderate to good antibacterial activity. Docking study of the synthesized compounds was done with the help of VLife MDS 3.5 software using GA docking method to study their observed activity.

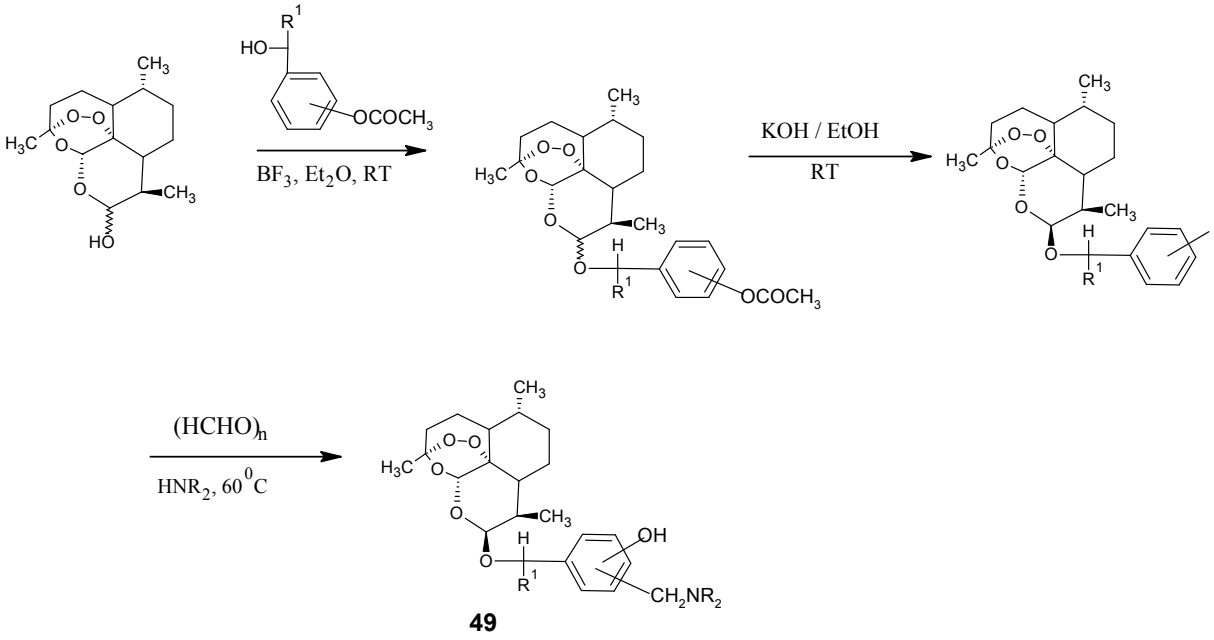


Where X = O, S and R = -H, -C $_6H_5$, -$C_6H_5CH_3$, $C_6H_5OCH_3$, -C_6H_5Cl, $C_6H_5NO_2$

Scheme 46. Synthesis of 3-substituted aminophenyl-4-hydroxycoumarins *via* Mannich reaction

3.15 MANNICH BASES OF ARTEMISININ DERIVATIVES

Novel artemisinin derivatives **49** bearing Mannich base group were prepared **(Scheme 47)** and tested for their antimalarial activity by Li *et al*., [52]. These water-soluble artemisinin derivatives were more stable than sodium artesunate and few compounds were found to be more active against *Plasmodium berghei* in mice than artesunic acid by oral administration.

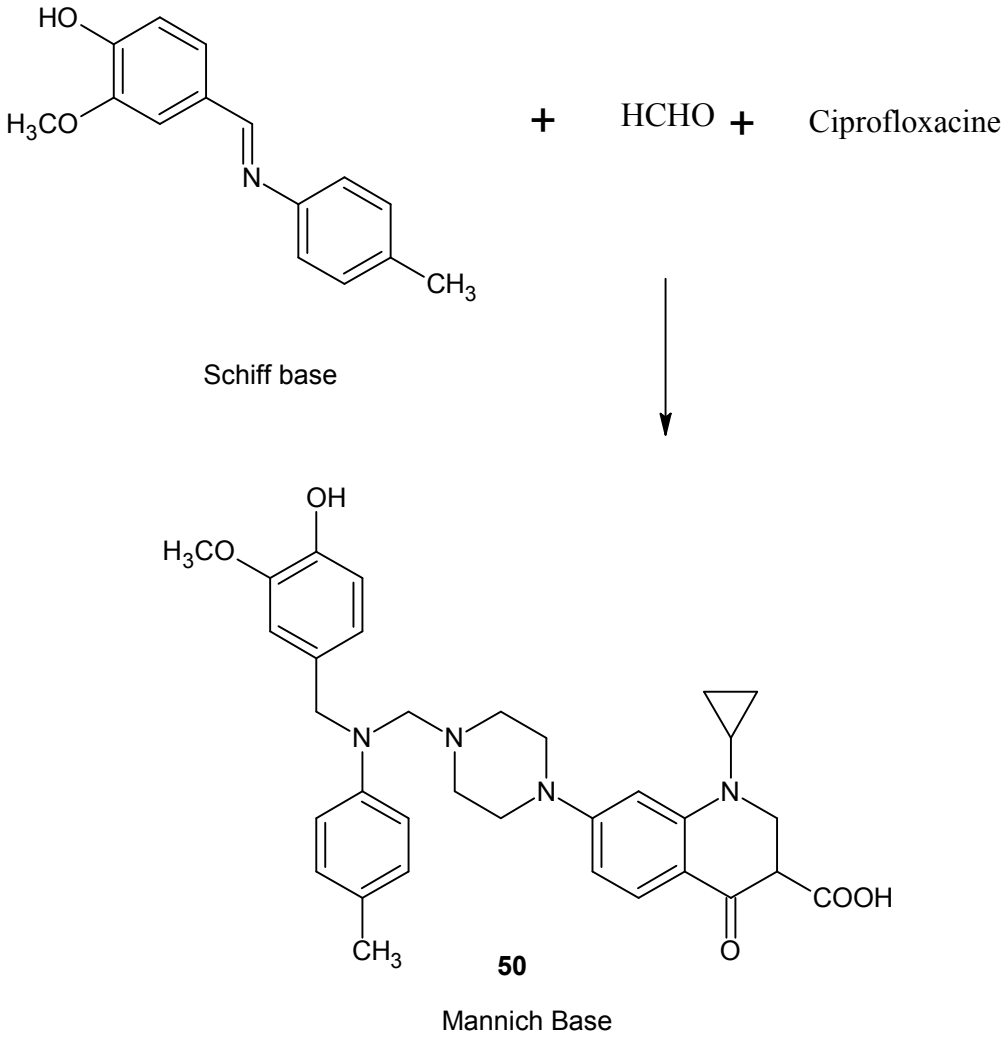


Scheme 47. Artemisinin derivatives bearing Mannich base group

3.16 MANNICH BASES OF CIPROFLOXACIN DERIVATIVES

Mannich bases of ciprofloxacin **50** were synthesized upon the modification of Schiff base 2-methoxy-4{*E*-[(methylphenyl)imino]methyl]}phenol using different aldehydes **(Scheme 48)**

by Bendale *et al.,*[53].Schiff bases are obtained by joining some aldehydes profitably to the triazole group through the Schiff reaction. Ciprofloxacin was incorporated to the new series of Schiff bases of 1, 2, 4- triazole via Mannich reaction. The new compounds have been evaluated *in vitro* for their antimicrobial activity against *Staphylococcus Aureus and E. coli.* All the compounds showed *in vitro* gram positive and gram negative activity which was comparable or superior to that of activity of parent drug (ciprofloxacin).

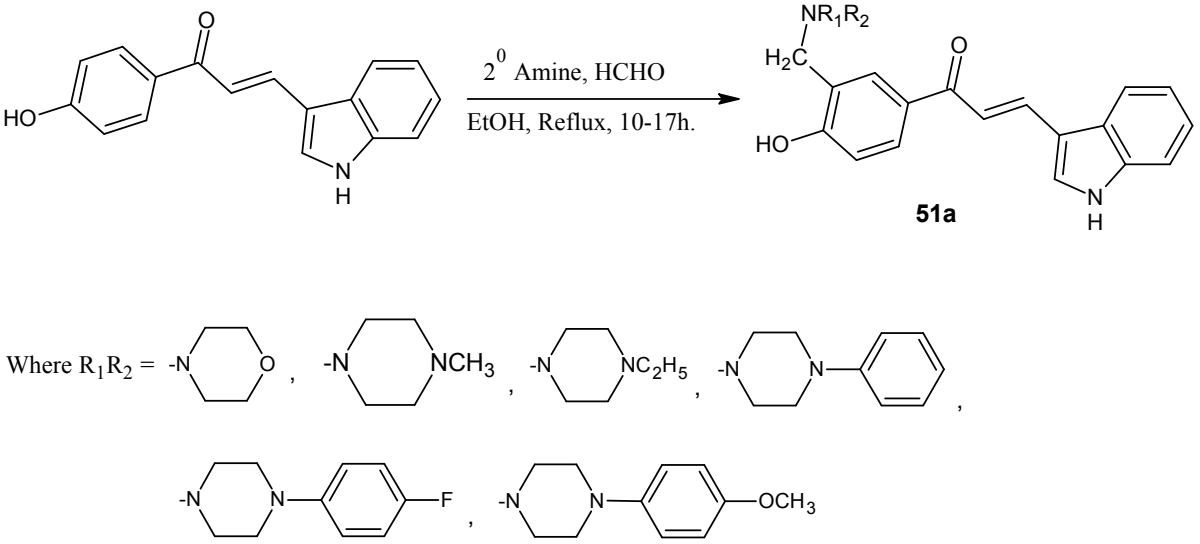


Scheme 48. Mannich bases of ciprofloxacin

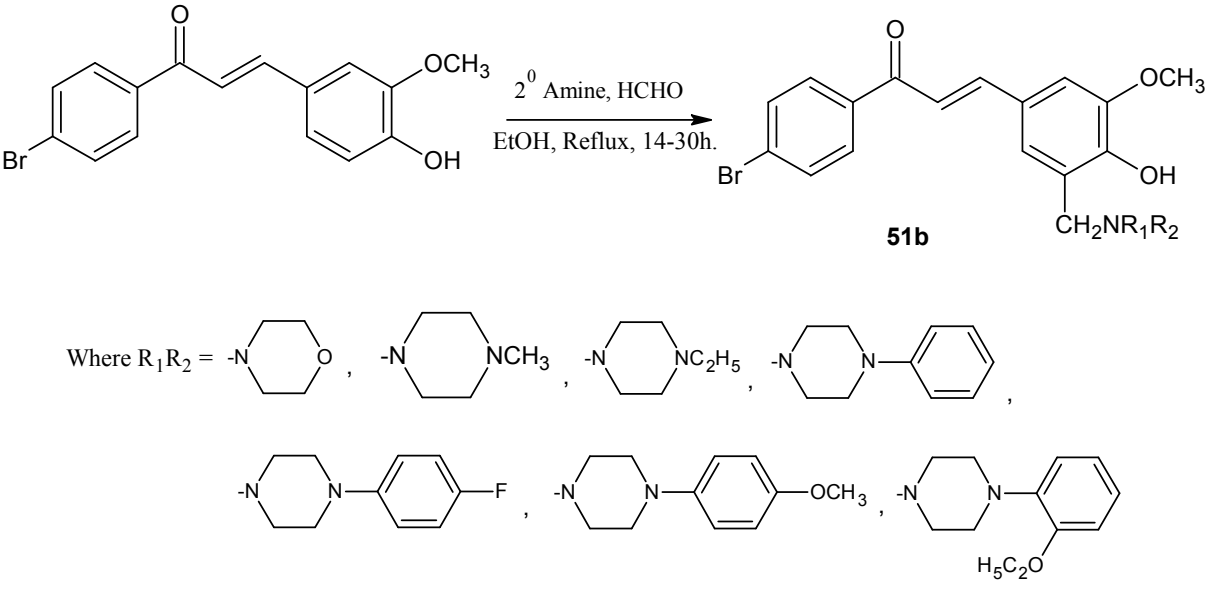
3.17 MANNICH BASE OF CHALCONE

Two series of Novel Mannich bases **51a** and **51b** were synthesized by Kandeel *et al.,* [54] from chalcones **(Scheme 49a & 49b)** and evaluated for their *in vitro* cytotoxic activity. Among the newly synthesized compounds, four derivatives were selected by the National Cancer Institute (NCI) to be evaluated for their *in-vitro* antitumor activity by *in-vitro* disease-

oriented human cells screening panel assay. All the tested compounds exhibited a broad spectrum of antitumor activity against renal cancer UO-31.



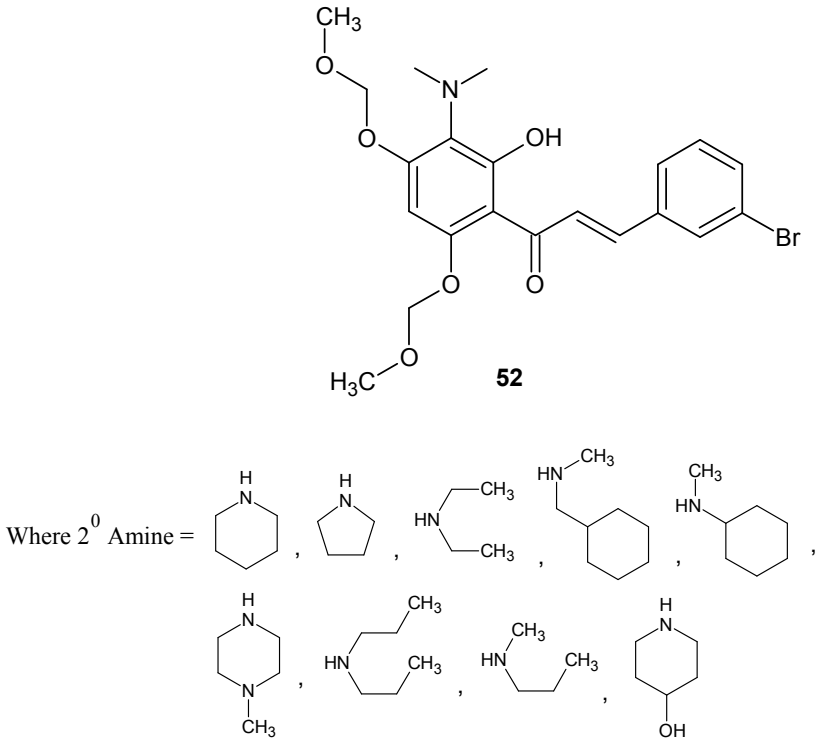
Scheme 49a. Synthesis of Mannich base of Chalcone, 1-(4-hydroxyphenyl)-3-(1Hindol-3-yl)prop-2-en-1-one



Scheme 49b. Synthesis of Mannich base of Chalcone, 1-(4-bromophenyl)-3-(4-hydroxy-3-methoxyphenyl)prop-2-en-1-one

A series of Mannich base derivatives of 2-hydroxy-chalcones **52** were obtained expediently in good to excellent yields by microwave-assisted Mannich reaction **(Scheme 50)** done by

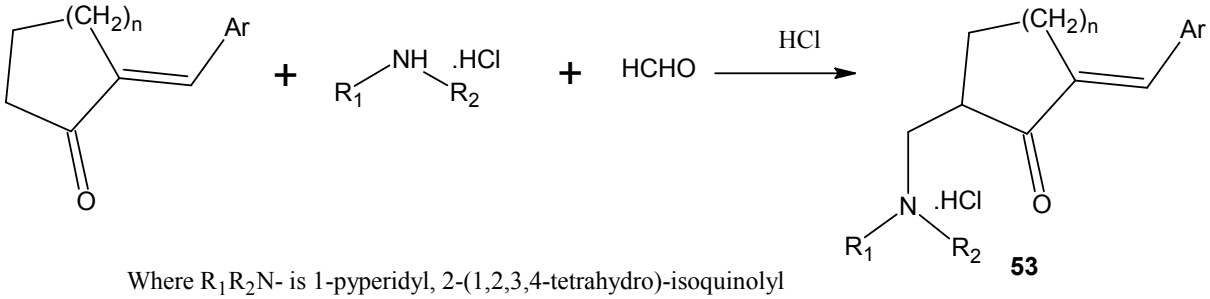
Dong *et al*., [55]. The regioselectivity of the reaction occurred preferentially at the C-3 position of the 2-hydroxy-chalcone backbone. A better yield in shorter time was obtained by microwave process, in comparison with conventional results. Further vasorelaxation assay showed that 2-hydroxy-3-((4-methylpiperazin-1-yl)methyl)-4,6-dimethoxymethoxy-3[1]-bromo-chalcone significantly decreased maximal PE-induced contraction.



Scheme 50. Mannich Base Derivatives of 2-Hydroxy-chalcones

3.18 MANNICH KETONES

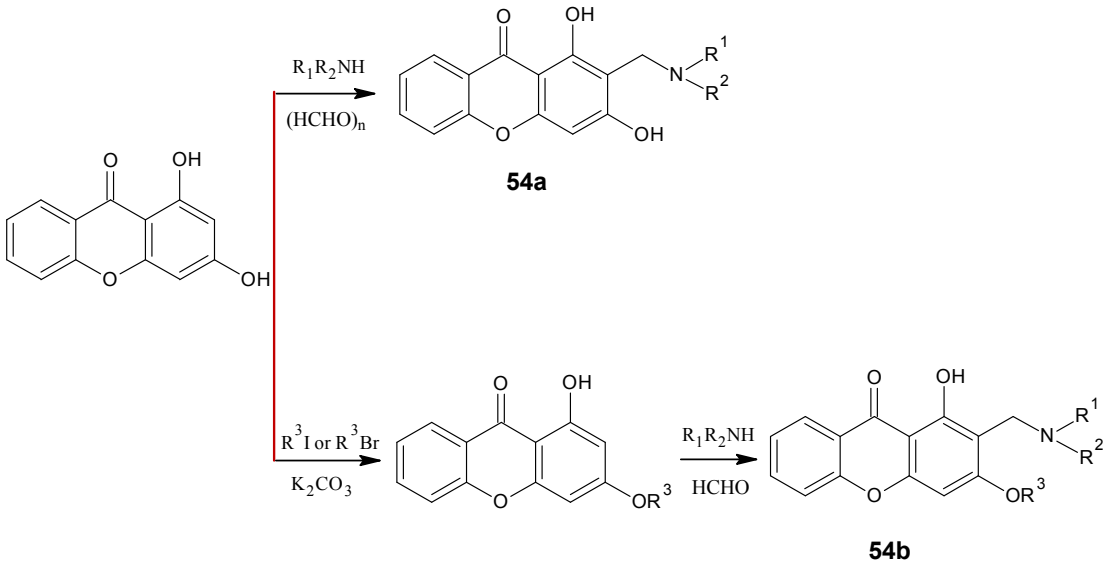
Grobuschek *et al.*, [56] reported chiral separation of bioactive cyclic Mannich ketones **53 (Scheme 51)** by HPLC and CE using cellulose derivatives and cyclodextrins as chiral selectors. In HPLC, stationary phases containing cellulose derivatives or h-cyclodextrin were used and in CE different cyclodextrins, such as h-CD, g-CD, carboxymethyl-h-CD and succinyl-h-CD were added to the background electrolyte as chiral selectors. These Mannich ketones showed a marked antibacterial and antifungal activity.



Where R_1R_2N- is 1-pyperidyl, 2-(1,2,3,4-tetrahydro)-isoquinolyl

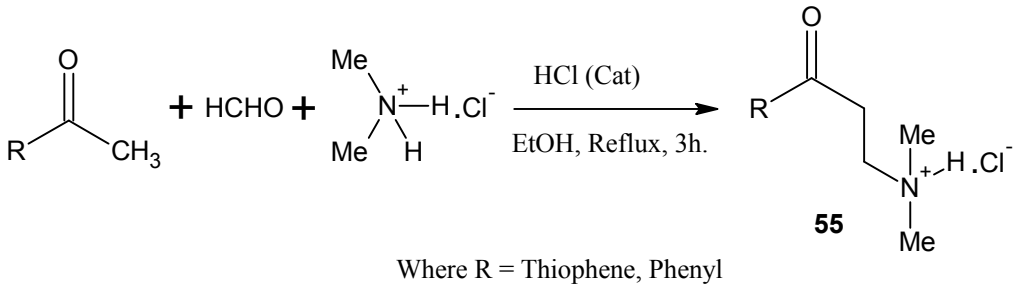
Scheme 51. Cyclic Mannich ketones

A series of novel 1, 3-dihydroxyxanthone Mannich bases derivatives **54a** and **54b** were synthesized **(Scheme 52)**, structure elucidated and evaluated for anti-cholinesterase activity by Qin *et al*., [57]. The result showed that most of the target compounds exhibited moderate to good inhibitory activities with the IC50 values at micromole level concentration against both acetylcholinesterase (AChE) and utyrylcholinesterase (BuChE). The results of a mixed-type manner in enzyme kinetic experiment and molecular docking study for 2-((diethylamino)methyl)-1-hydroxy-3-(3-methylbut-2-enyloxy)-9*H*-xanthen-9-one demonstrated that the Mannich base derivatives were likely to bind to the active site (AS) and the peripheral anionic site (PAS) of cholinesterases.



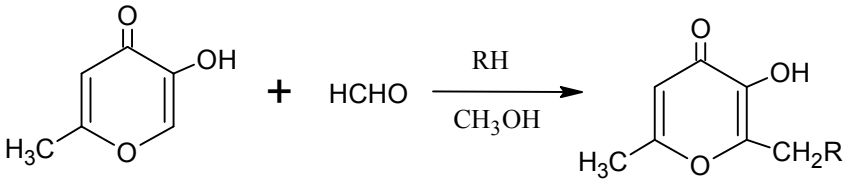
Scheme 52. Mannich bases derivatives of 1, 3-dihydroxyxanthone

Lahbib *et al.,* [58] in their investigation, synthesized two Mannich base hydrochlorides (2-thienyl-β-dimethylaminoethyl ketone hydrochloride) and (β-dimethylaminopropiophenone hydrochloride) **55 (Scheme 53)**, and then evaluated their effect on relative weight, haematological parameters, biochemical parameters, and neurotoxicity in rats at the dose of 5 mg/kg.

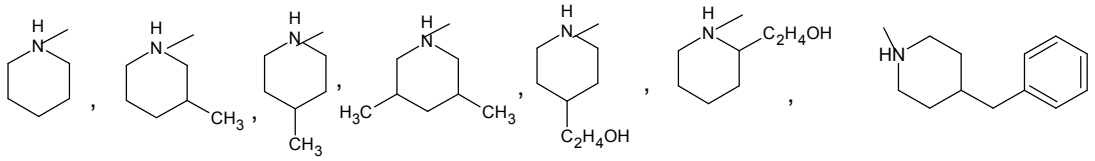


Scheme 53. Synthesis of Mannich bases Hydrochloride

Aytemir & Çalış [59] reported synthesis of some novel Mannich bases derived from Allomaltol **56** and evaluation of their anticonvulsant activities. They synthesized new 3-hydroxy-6-methyl-2-substituted 4*H*-pyran-4-one derivative and evaluated their anticonvulsant activities. Mannich bases were prepared by the reaction of suitable piperidine derivatives with allomaltol and formaline **(Scheme 54)**. The structure of the synthesized compounds was confirmed by IR, ^{1}H NMR, Mass and elementary analysis. Anticonvulsant activities of the compounds were examined by maximal electroshock (MES) and subcutaneous Pentylenetetrazole (scMet). Neurotoxicity was determined by rotarod toxicity test.



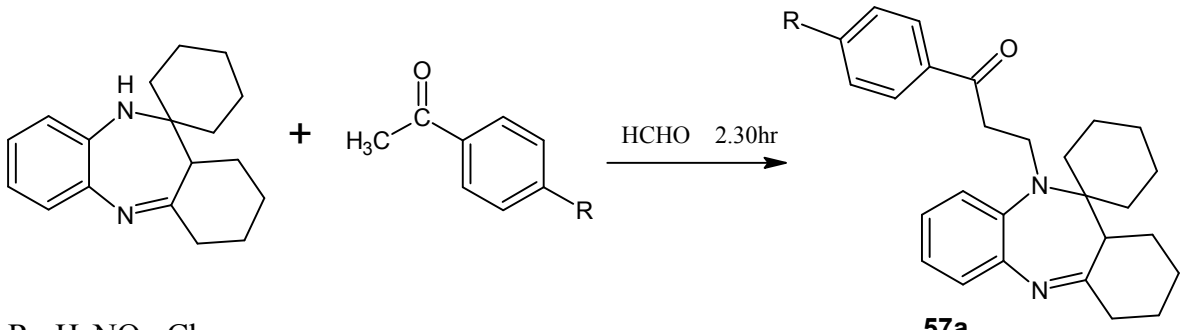
Where R=



Scheme 54. Mannich bases derived from Allomaltol

3.19 MANNICH BASES OF BENZODIAZEPINES

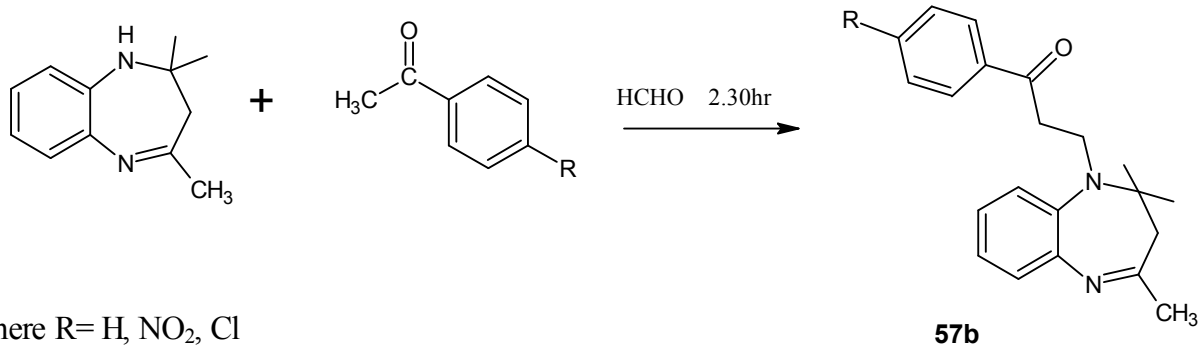
Synthesis and anticonvulsant activity of various Mannich bases **57a** and **57b** of 1,5-benzodiazepines was reported by Pandeya & Rajput [60]. Mannich bases were synthesized by the reaction of benzodiazepines with acetophenone, p-nitroacetophenone, p-chloroacetophenone and formaldehyde **(Scheme 55a & 55b)**. All the synthesized derivatives were evaluated at the dose of 30mg/kg b.w for anticonvulsant activity by isoniazid induced convulsion model. Some have shown good anticonvulsant activity.



Where R= H, NO_2, Cl

57a

Scheme 55a. Synthesis of Mannich base derivatives of fused ring benzodiazepines



Where R= H, NO_2, Cl

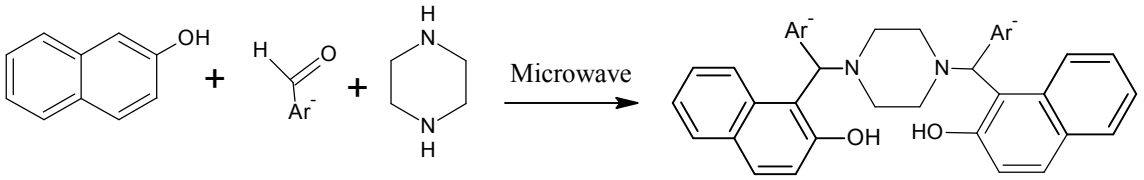
57b

Scheme 55b. Synthesis of various Mannich base derivatives of 1,5- benzodiazepines

3.20 BIS- MANNICH BASES

Huang *et al* [61] reported microwave-assisted synthesis of novel 2-naphthol *bis*-Mannich bases **58 (Scheme 56)**. Mannich bases of 2-naphthol have the ability to chelate strongly to metal ions. Hence, they have great potential to be used as chiral catalysts, metallo-enzyme inhibitors and/or scavenger of heavy metal poisons. Here an efficient and expeditious microwave assisted-synthesis of novel bis-Mannich bases of 2-naphthols were derived from aromatic aldehydes and diamines namely piperazine and *N,N'*-dialkylethylenediamines under

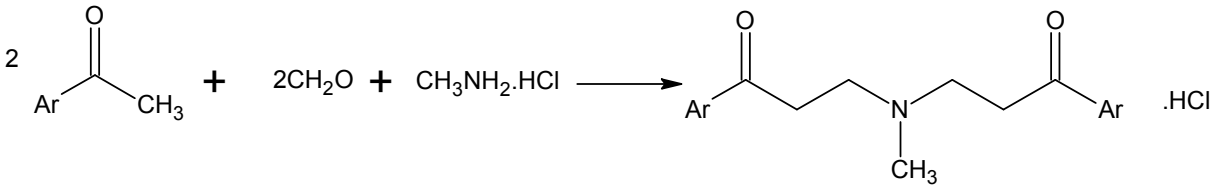
solvent-free conditions. These compounds were also prepared under conventional reflux in ethanol. The compounds of this series displayed interesting NMR behaviour.



58

Scheme 56. Synthesis of *N,N'*-bis[aryl-(2-hydroxynaphthalen-1-yl)-methyl]-piperazines

Synthesis and evaluation of anticonvulsant activities of some bis Mannich bases and corresponding piperidinols **59 (Scheme 57)** was reported by Gul *et al.,* [62]. Some acetophenone derived bis Mannich, piperidinols and quaternary piperidine derivative were synthesized and studied for anticonvulsant activity. Chemical structures of the compounds were confirmed by UV, IR, ^{1}H NMR, ^{13}C NMR, mass spectra and elemental analysis. Their anticonvulsant activities were determined by maximal electroshock (MES), subcutaneous Metrazol (scMet) tests and rotarod test for neurological deficits.



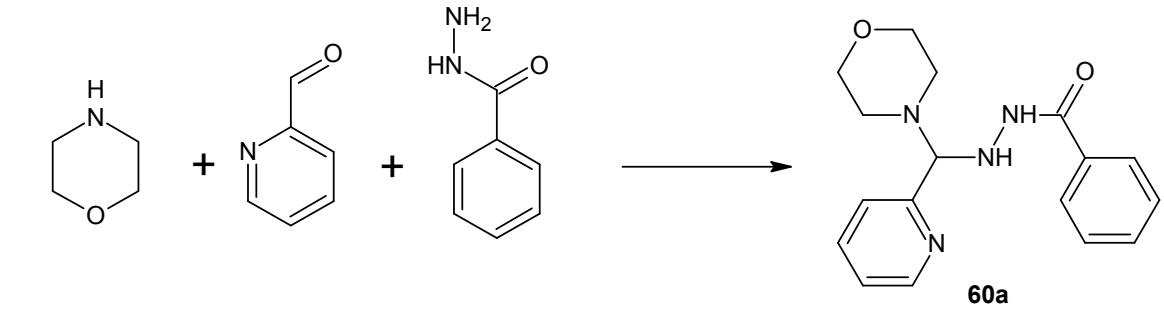
59

Where Ar = C_6H_5, p-$CH_3C_6H_4$, p-$CH_3OC_6H_4$, p-ClC_6H_4, $2C_4H_3S$

Scheme 57. Synthesis of Bis Mannich bases

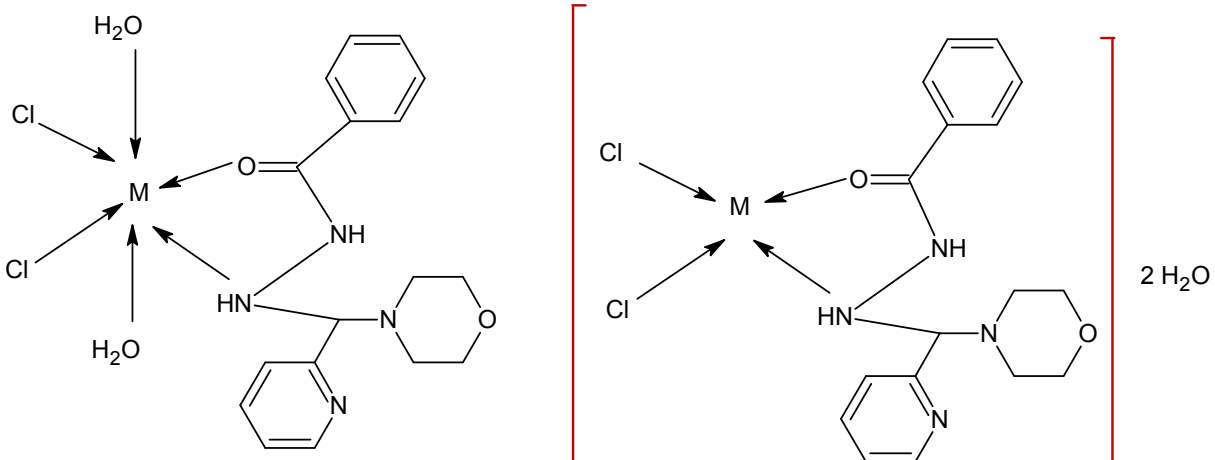
3.21 METAL COMPLEXES OF MANNICH BASES

Synthesis, characterization and antimicrobial studies of Mannich base derived from benzohydrazide **60a** and its metal [Co(II), Cu(II), Mn(II)] complexes **60b** and **60c (Scheme 58)** was reported by Jameel *et al.,* [63]. Both the ligand and its metal complexes were tested against some microorganisms for their antimicrobial activity.



60a

N-[morpholin-4-yl(pyridin-2-yl)methyl]benzohydrazide



60b

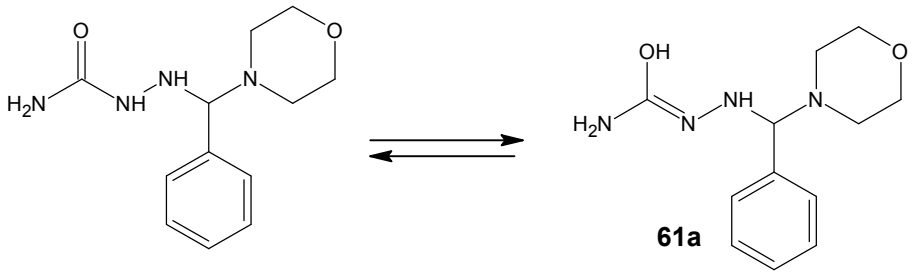
M = Mn(II)

60c

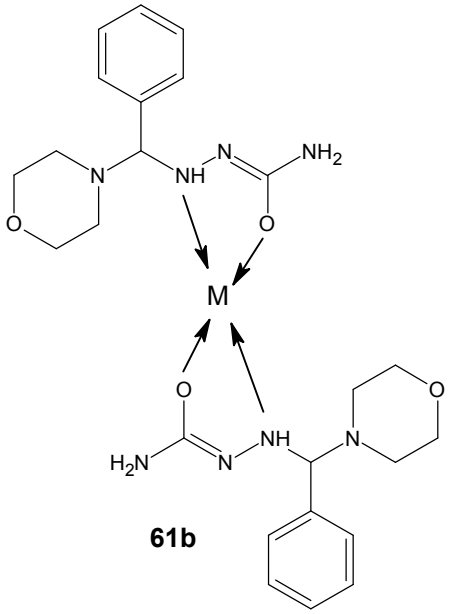
M =Cu (II), Co (II)

Scheme 58. Mannich base of benzohydrazide and its metal [Co(II), Cu(II), Mn(II)] complexes

A new Mannich base, N-(1-morpholinobenzyl) semicarbazide (MBS) **61a**, formed by the condensation of morpholine, semicarbazide and benzaldehyde, and its Cu(II), Ni(II), Co(II) and Zn(II) complexes **61b (Scheme 59a & 59b)** have been synthesized by Raman *et al.,*[64]. Their structures have been elucidated on the basis of analytical, magnetic, electrical conductivity and spectral study as well as elemental analyses. The complexes exhibited square-planar geometry. The monomeric and non-electrolytic nature of the complexes is evidenced by their magnetic susceptibility and low conductance data. The electrochemical property of the ligand and its complexes in acetonitrile solution was studied by cyclic voltammetry. The X-band ESR spectra of the Cu(II) complex in DMSO at 300 and 77 K were recorded and their salient features are reported in the paper.

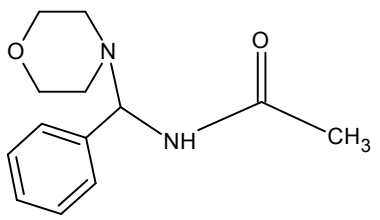


Scheme 59a. Structure of the Mannich base ligand



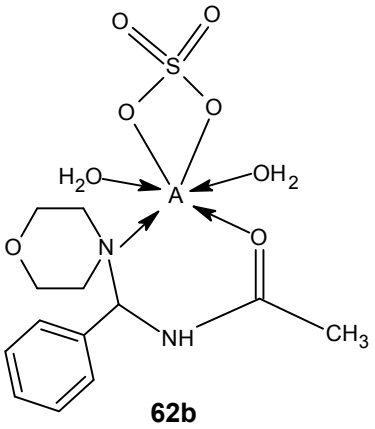
Scheme 59b. The proposed structure of the complexes

Muruganandam & Krishnakumar [65] reported the synthesis and characterisation of new Mannich base *N*-[morpholino(phenyl)methyl]acetamide (MBA) **62a**. Chelates of MBA with cobalt(II), nickel(II) and copper(II) ions **62b**, **62c**, and **62d (Scheme 60)** were prepared and characterized by elemental analyses, IR and UV spectral studies. MBA was found to act as a bidentate ligand, bonding through the carbonyl oxygen of acetamide group and CNC nitrogen of morpholine moiety in all the complexes. Based on the magnetic moment values and UV-Visible spectral data, tetracoordinate geometry for nitrato complexes and hexacoordinate geometry for sulphato complexes were assigned. The antimicrobial studies showed that the Co(II) nitrato complex was more active than the other complexes.



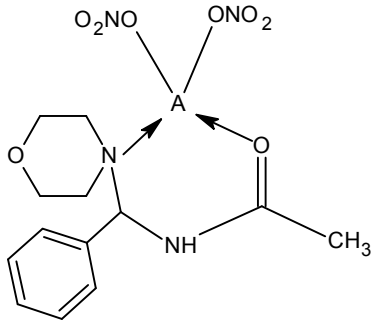
62a

N-[Morpholino(phenyl)methyl]acetamide MBA



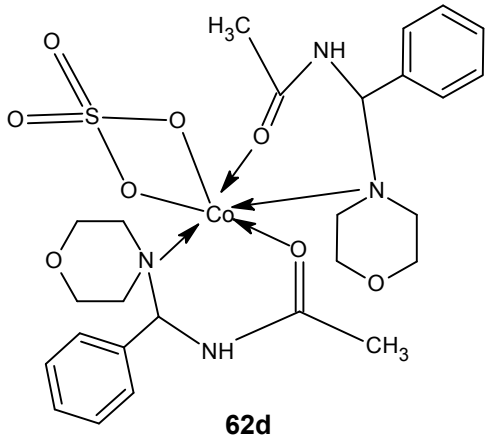
62b

$A.SO_4.MBA.2H_2O$ (A=Cu)



62c

$A.(NO_3)_2.MBA$ (A= Co, Ni and Cu)



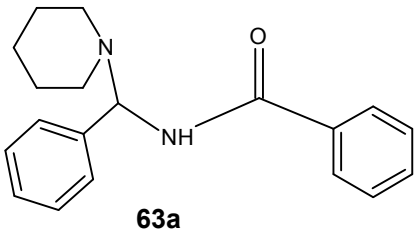
62d

$CoSO_4.2MBA$

Scheme 60. The proposed structure of MBA and it's the complexes

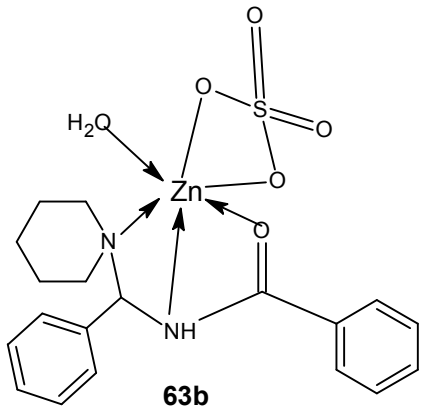
Murugandandam & Balasubramanian [66] synthesized the complexes of ZnII, CdII and HgII with N-[Phenyl(pyrrolidin-1-yl)methyl]benzamide(PBB) **63a**, **63b**, **63c**, and **63d (Scheme 61)**. The resulting complexes were characterized by elemental analysis, conductivity measurements, IR and ^{1}H NMR spectral studies. On the basis of spectral data, it is inferred that the ligand acts as a bidentate and tridentate coordination to the metal ions. The complexes were non-electrolytes. The presence of the coordinated water molecules in some the complexes was indicated by IR spectra and TG analysis of the complexes. From the analytical and spectral data, the stoichiometry of these complexes had been found to be [$M.SO_4.L.H_2O$, $M.Cl_2.L.2H_2O$ and $M.SO_4.L$] {where M = ZnII, CdII and HgII }. It was found that, HgII sulphato complex exhibits tetrahedral geometry and the other three

correspond to octahedral geometry. The antimicrobial activities of the ligand and its complexes were studied by disc diffusion technique.



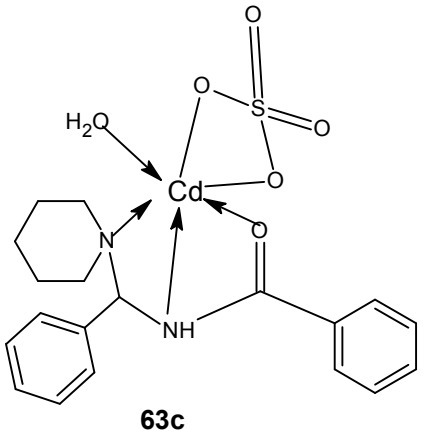
63a

N-[Phenyl(pyrrolidin-1-yl)methyl]benzamide (PBB)



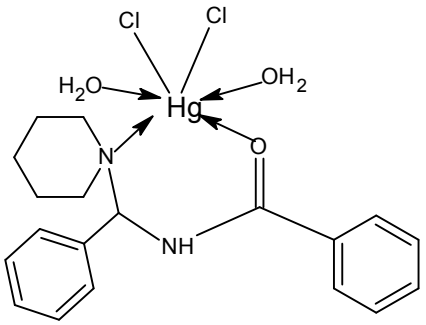
63b

$ZnSO_4.PBB.H_2O$



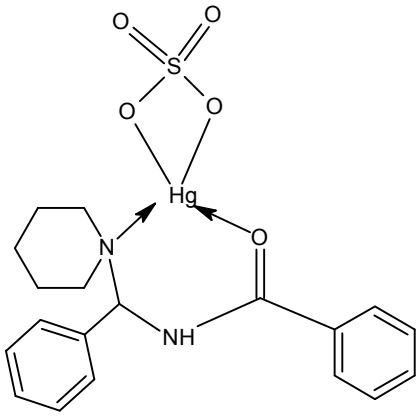
63c

$CdSO_4.PBB.H_2O$



63d

$HgCl_2.PBB.2H_2O$



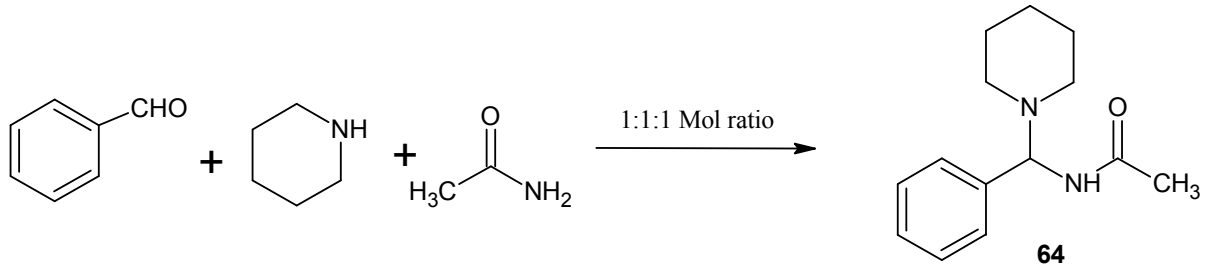
63e

$HgSO_4.PBB$

Scheme 61. The proposed structure of PBB and it's the complexes

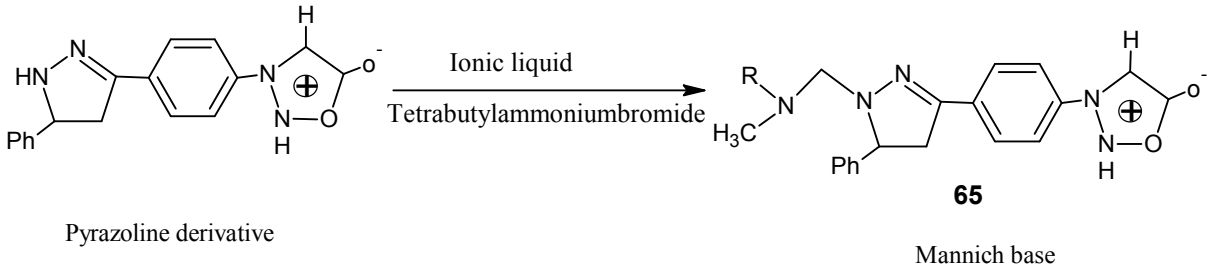
3.22 GREEN SYNTHESIS OF MANNICH BASES

Calcium chloride catalyzed microwave synthesis of some Mannich bases and their characterization was reported by Ravichandran [67]. He reported the synthesis of Mannich bases N-[1-(piperidinobenzyl) acetamide, N-[1(morpholinobenzyl) acetamide, N-[1-(piperidinobenzyl) benzamide, N-[1-(morpholinobenzyl) benzamide **64** under microwave radiation catalysed by calcium chloride **(Scheme 62)**. This method offered several advantages including high yields, shorter reaction times, simple work-up procedures which made it a useful process for the synthesis of Mannich bases.



Scheme 62. Calcium chloride catalyzed microwave synthesis of some Mannich bases

Taj *et al.* [68] reported facile synthesis of Mannich bases of 3-[*p*-(5-arylpyrazolin-3-yl)phenyl]sydnones **65**, as anti-tubercular and anti-microbial agents, under ionic liquid/tetrabutylammonium bromide (TBAB) catalytic conditions. Novel methylene bridged Mannich bases were synthesized in good to excellent yields from the pyrazoline derivative using various primary/secondary amines, 37 % formalin in presence of ionic liquids/TBAB as catalyst **(Scheme 63)**. The structures of the newly synthesized compounds were confirmed by IR, ^{1}H and ^{13}C NMR and GC–MS spectroscopy, as well as elemental analysis. The title compounds were screened for their anti-tubercular and antimicrobial activities. Some of the compounds exhibited very good anti-tubercular, antifungal and antibacterial activities.

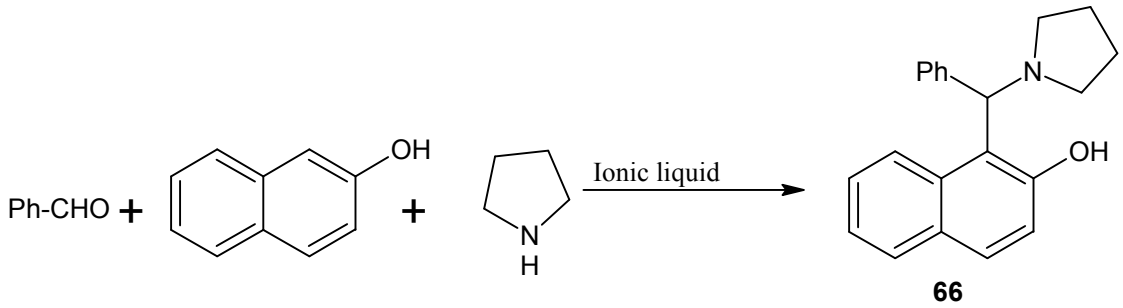


Pyrazoline derivative

Mannich base

Scheme 63. Mannich bases of 3-[*p*-(5-arylpyrazolin-3-yl)phenyl]sydnones

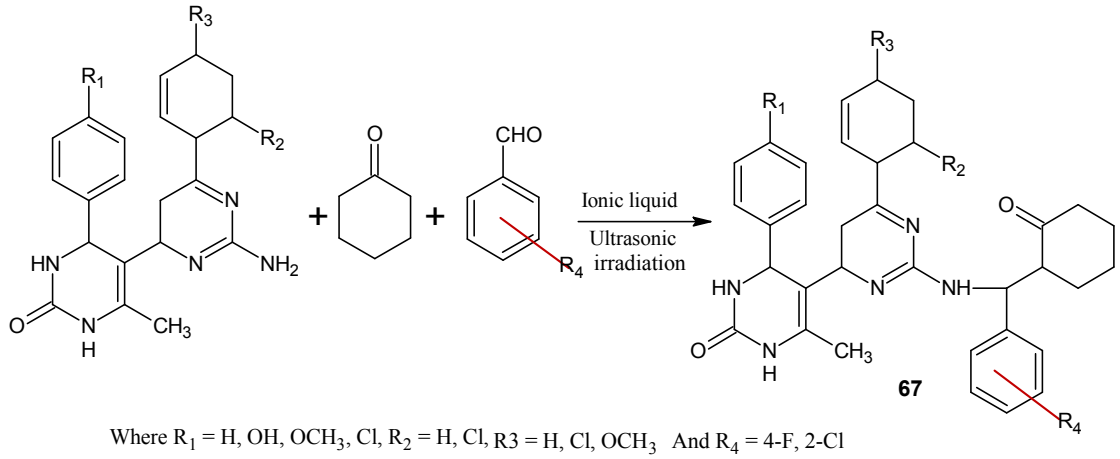
Several ionic liquids were used by Yaghoubi *et al.,* [69] as catalyst for three-component Mannich reactions of aldehydes, amines, and naphthols at room temperature to produce following Mannich base **66**. The used ionic liquids were 1-butyl-3-methylimidazolium tetrafluoroborate ([Bmim]BF_4), 1-octyl-3- methylimidazolium tetrafluoroborate ([Omim]BF_4), 1-ethyl-3-methylimidazolium tetrafluoroborate ([Emim]BF_4), butyldimethylimidazolium tetrafluoroborate ([Bdmim]BF_4), 1-octyl-3-methylimidazolium nitrate ([Omim]NO_3), 1-methylimidazolium sulfuric acid ([Hmim]HSO_4) and 1-methylimidazolium trifluoroacetic acid ([Hmim] Tfa) **(Scheme 64)**. Higher yields were obtained in the presence of [Hmim] Tfa in comparison with other ionic liquids.



66

Scheme 64. Ionic liquid catalyzed Mannich reactions of aldehydes, amines, and naphthols

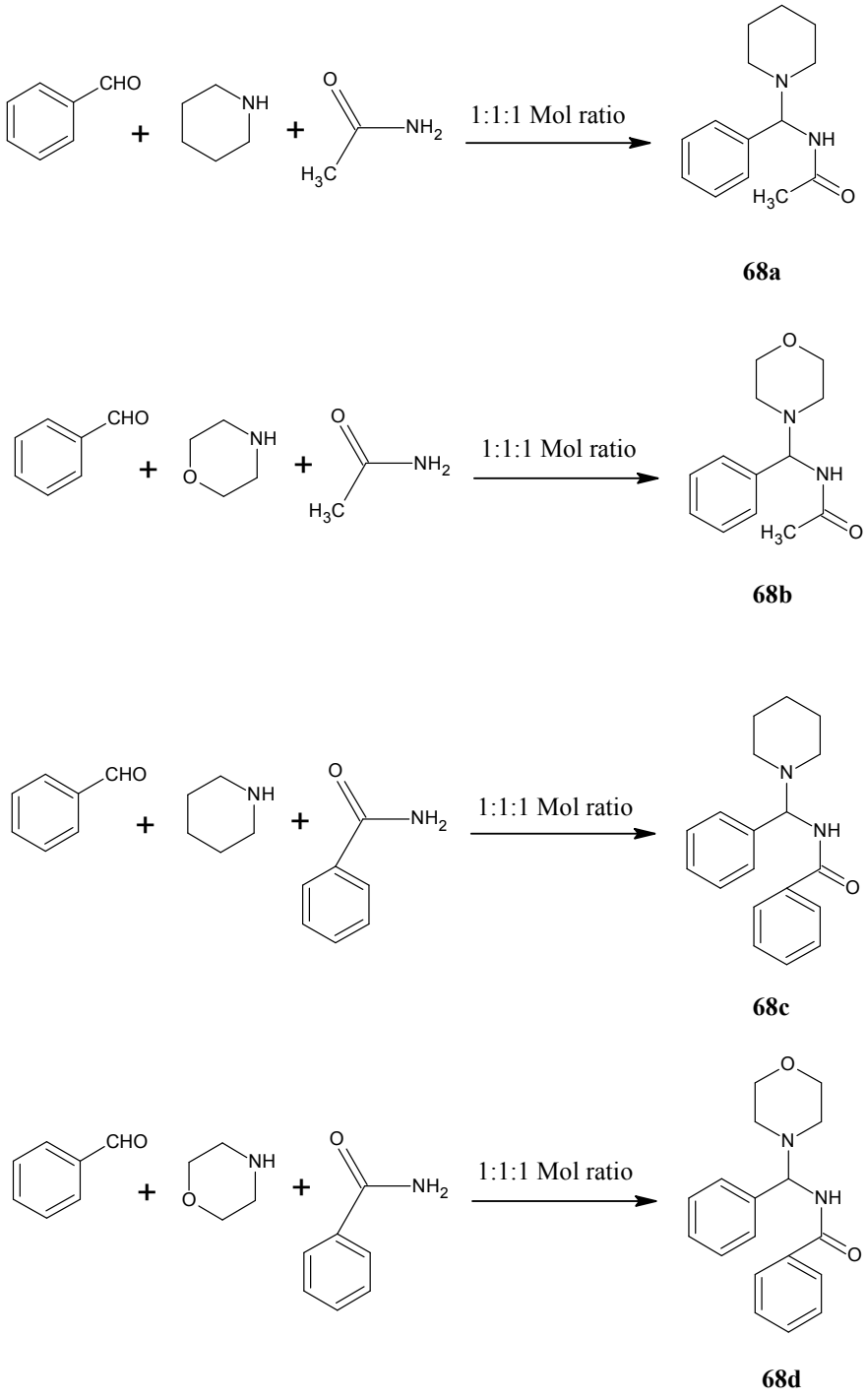
Suryawanshi*et al.*, [70] showed that the ionic liquid [Et_3NH][HSO_4] was found to be a particularly efficient catalyst for the synthesis of β-amino carbonyl pyrimidines through the Mannich condensation reaction of substituted pyrimidin-2(1*H*)-ones, cyclohexanone and 4-fluro/chloro benzaldehyde under ultrasonic irradiation at room temperature to get following Mannich base **67 (Scheme 65)**. The present methodology offered several advantages such as excellent yields, simple procedure and mild conditions.



Where R_1 = H, OH, OCH_3, Cl, R_2 = H, Cl, R3 = H, Cl, OCH_3 And R_4 = 4-F, 2-Cl

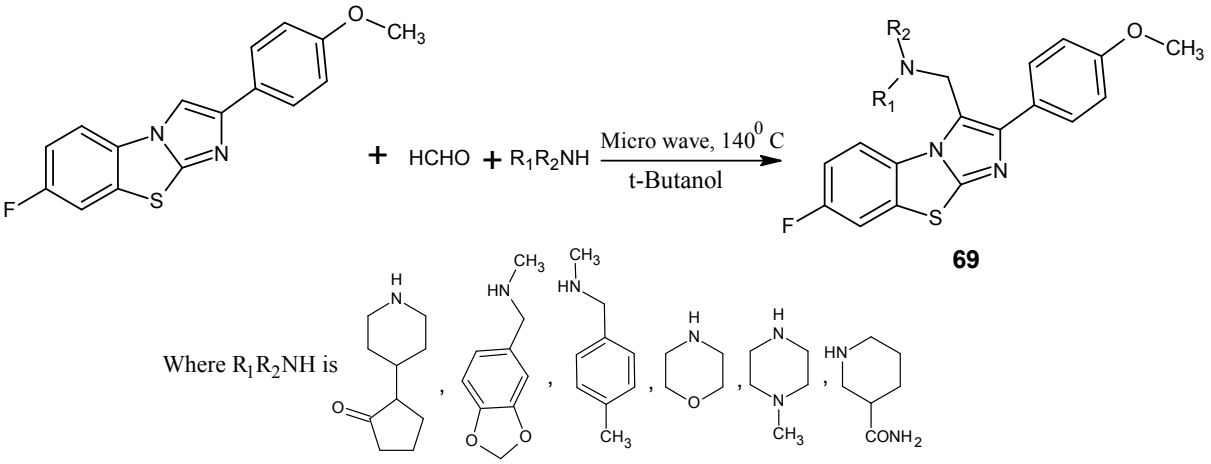
Scheme 65. Ionic liquid [Et_3NH][HSO_4]catalyzed Mannich reaction

Montmorillonite K 10 clay catalyzed Microwave Synthesis of some Mannich bases and their Characterisation was reported by Arunkumar *et al.,* [71]. The synthesis of Mannich bases N-[1-(piperidinobenzyl) acetamide **68a**, N-[1-(morpholinobenzyl) acetamide **68b**, N-[1-(piperidinobenzyl) benzamide **68c**, N-[1-(morpholinobenzyl) benzamide **68d** have been reported under microwave radiation catalysed by Montmorillonite K 10 clay **(Scheme 66)**.



Scheme 66. Montmorillonite K 10 clay catalyzed Microwave Synthesis of some Mannich bases

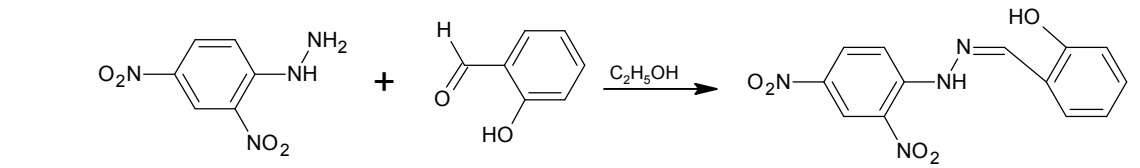
Umesha [72] in his Ph.D. thesis explained the one pot multicomponent Mannich reaction. A mixture of 7-fluoro-2-(4-methoxyphenyl)imidazo[2,1-*b*][1,3]benzothiazole paraformaldehyde and secondary amines were irradiated in microwave at 140°C, t-butanol was used as a solvent medium afforded 7-fluoro-2-(4-methoxyphenyl)-3-(substituted amino-1-ylmethyl)imidazo[2,1-*b*][1,3]benzothiazoles **69 (Scheme 67)**. The structure of synthesised compounds was established on the basis of its elemental and IR ^{1}H NMR and ^{13}C NMR spectral data.



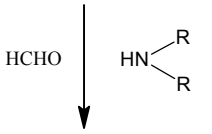
Scheme 67. Synthesis of Mannich base of Imidazo[2,1-*b*]benzothiazoles derivatives

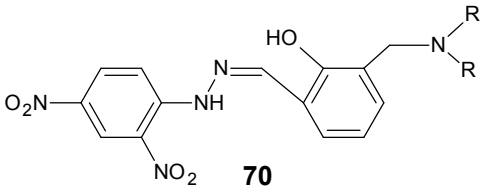
3.23 MISCELLANEOUS SYNTHESIS

A report on synthesis, characterisation and evaluation of Mannich bases as potent antifungal and hydrogen peroxide scavenging agents was published by Malhotra *et al.* [73].They synthesised (*E*)-2-{[-2-(2,4-Dinitrophenyl)hydrazono]methyl}phenol and used it as key intermediate for the synthesis of new Mannich bases **70 (Scheme 68).** All the synthesized compounds were evaluated for their antifungal activity against three fungal strains *Candida albicans*, *Candida tropicalis* and *Aspergillus niger*and antioxidant activity. The structure of these compounds was confirmed by IR, ^{1}H NMR and ^{13}C NMR studies. Most of the compounds exhibited moderate to significant activities.



2,4-Dinitrophenylhydrazine 2-Hydroxybenzaldehyde Substituted hydrazone

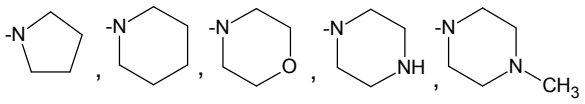




70

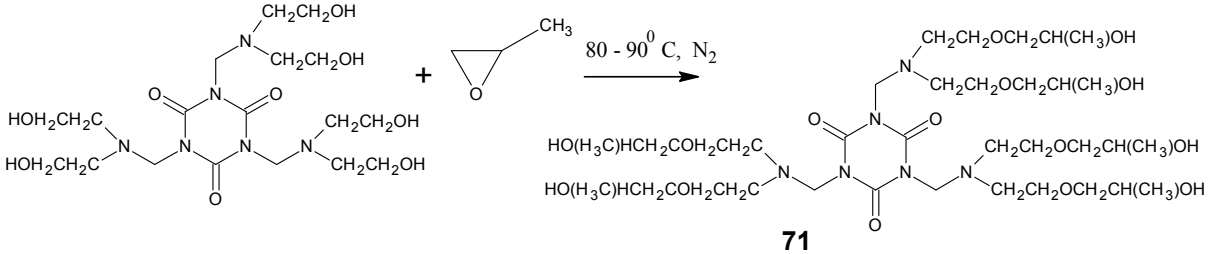
Substituted Mannich base

Where -NRR is $-N(CH_3)_2$, $-N(C_2H_5)_2$, $-N(C_3H_7)_2$, $-N(C_4H_9)_2$, $-N(C_6H_5)_2$,



Scheme 68. Mannich bases of (*E*)-2-{[-2-(2,4-Dinitrophenyl)hydrazono]methyl}phenol

Rotaru*et al.,* [74] presented a paper, which explained the synthesis and characterisation of a new Mannich polyether polyol with high nitrogen content and thermostable isocyanuric structure. The synthesis was performed by the alkoxylation in the absence of any catalyst and a Mannich base **71** obtained by the reaction of cyanuric acid with a Mannich precursor reagent 1,3-oxazolidine **(Scheme 69)**. The Mannich polyol was characterised by ^{1}H and ^{13}C NMR, IR spectroscopy and by the determination of some usual characteristics such as hydroxyl number, viscosity, amine echivalent, water content. The main application of this polyol is the production of "spray" rigid polyurethane foams with higher thermostability and inherent flame retardancy properties.

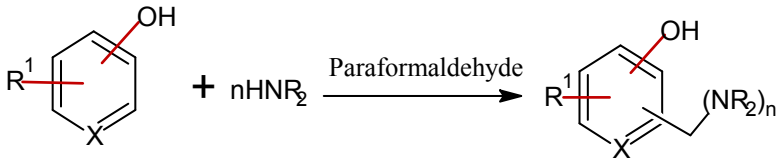


71

Mannich base from Cyanuric acid Mannich polyether polyol with isocyanuric structure

Scheme 69. New isocyanuric Mannich polyether polyol

Chi*et al.,* [75] in their paper reported the result of one-pot Mannich reaction of secondary amines with hydroxy aromatic compounds in an aprotic solvent to form Mannich base **72**. The synthesis of Mannich bases with hydroxypyridines was effectively conducted and the reaction underwent regioselectively at the ortho position to alcohol group **(Scheme 70)**. Also, the reactivity of the Mannich reaction generally depended on the nucleophilicity of hydroxy aromatic rings.

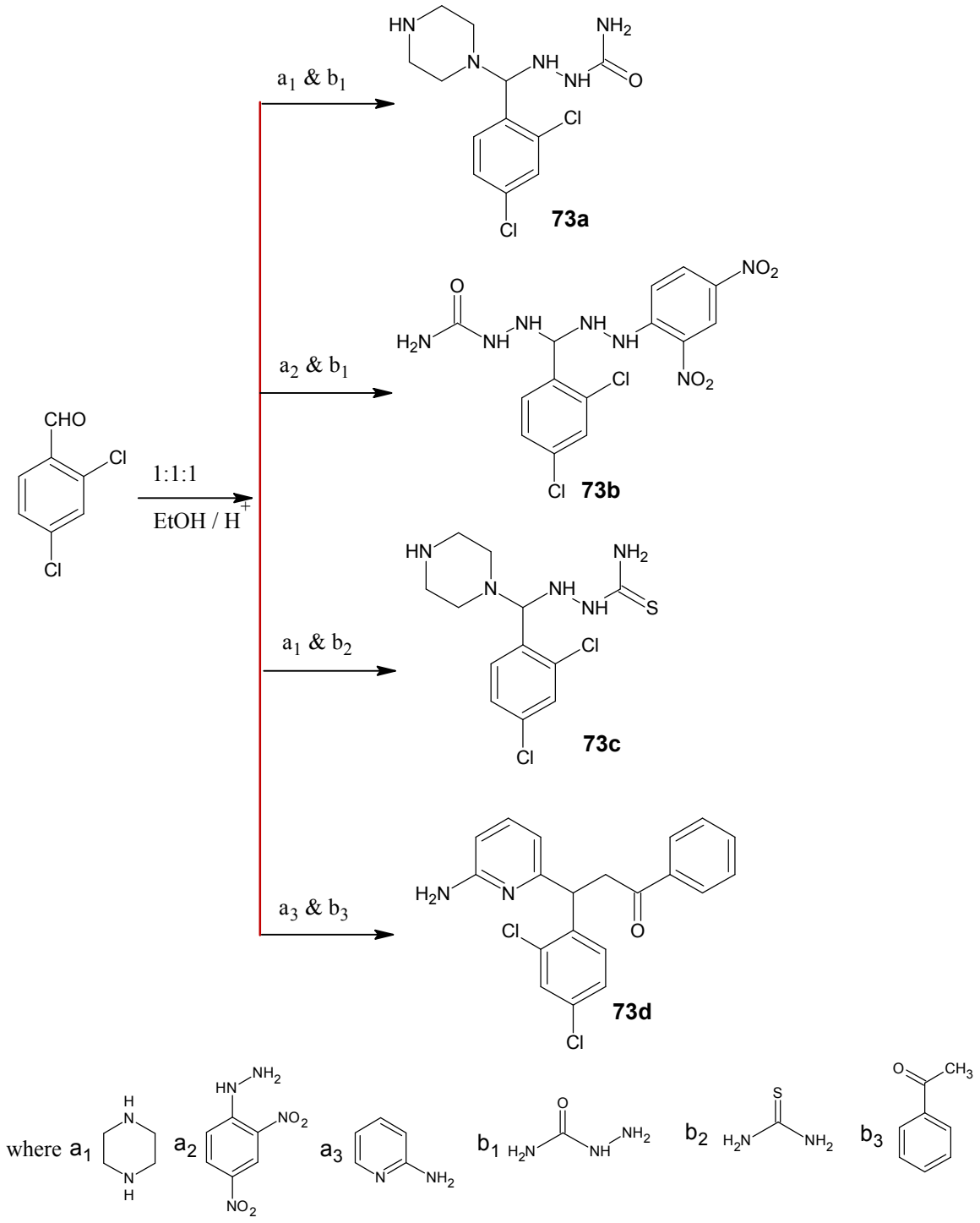


a **b** **72**

Where **a** is 3-Hydroxypyridine, 4-Hydroxypyridine, 2-Hydroxypyridine, 4-Hydroxyquinoline, 8-Hydroxyquinoline, 1- Naphthol, 2- Naphthol, 4-Chloro-1- naphthol, 2,3-Dihydroxynaphthalene, Hydroquinone, 2-Methylresorcinol, 2,6-Dimethylphenol, and **b** is Morpholine, Pyrolidine, 1,4,10,13-Tetraoxa-7,16-Diazacyclooctadecane, 1,4,7,10,13-Pentaoxa-16-azacyclooctadecane, N-Methylpiperazine.

Scheme 70. One-pot Mannich reaction of secondary amines with hydroxy aromatic compounds

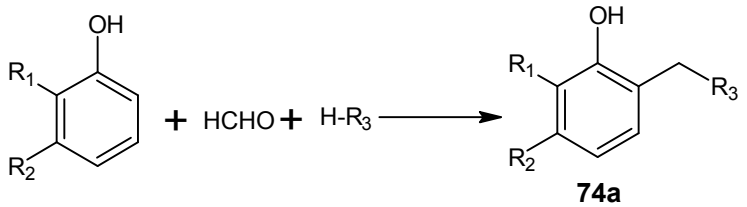
In this report Murugesan *et al.,* [76] prepared new Mannich bases **73a**, **73b**, **73c**, and **73d** by treating 2,4-dichlorobenzaldehyde, 2-aminopyridine, 2,4-dinitrophenylhydrazine with active hydrogen containing compound such as semicarbazide, thiourea, and acetophenone **(Scheme 71)**. The synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and analytical methods like elemental analysis, melting point and TLC techniques. Further the synthesized compounds were screened for antimicrobial activities.



Scheme 71. Synthesis of Mannich bases of 2,4-dichlorobenzaldehyde, 2-aminopyridine, 2,4-dinitrophenylhydrazine

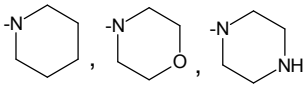
In this study, some Mannich bases of substituted aminophenol and acetophenone had been synthesized **74a** and **74b (Scheme 72a & 72b)** by Muthumani *et al.,* [77] and their

anticonvulsant and antimicrobial activities were evaluated. The synthesized compounds were characterized by UV, IR and ^{1}H NMR spectroscopy.

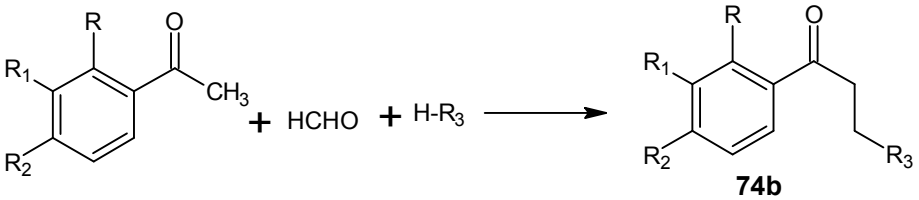


74a

Where R_1 and R_2 are -H, -NH_2

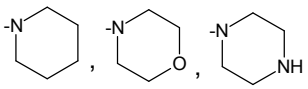
R_3 is -$N(CH_3)_2$, -$N(C_2H_5)_2$, -$N(C_2H_4OH)_2$, 

Scheme 72a. Synthesis of Mannich bases of substituted aminophenol



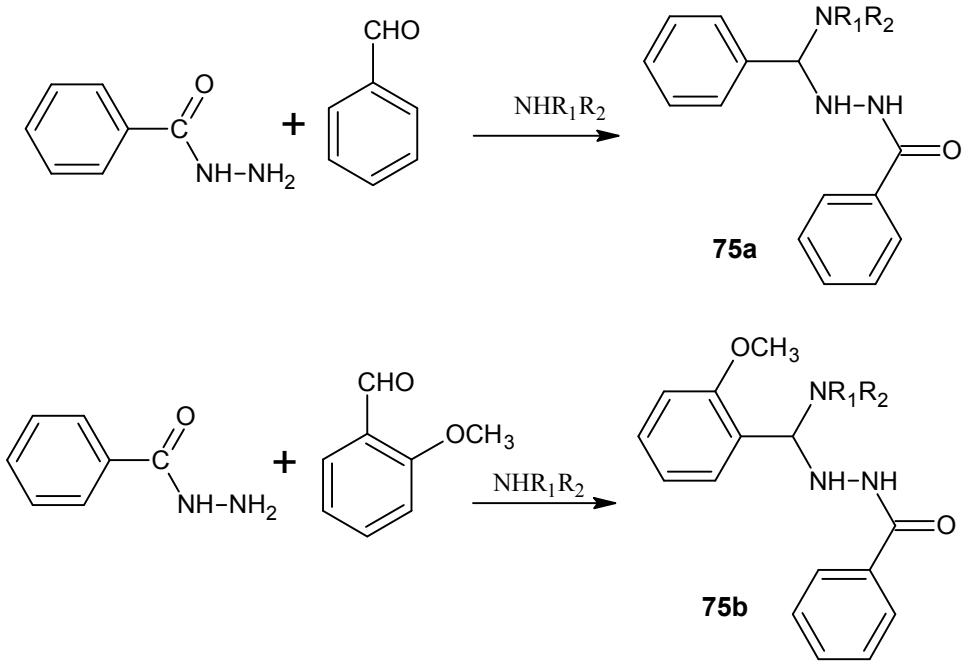
74b

Where R = -H, -OH, R_1 = -H, -OCH_3, R_2 = -OH, -OCH_3

R_3 is -$N(CH_3)_2$, -$N(C_2H_5)_2$, -$N(C_2H_4OH)_2$, 

Scheme 72b. Synthesis of Mannich bases of substituted acetophenone

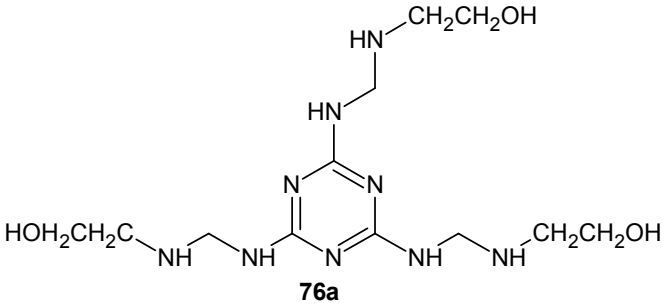
Jameel *et al.,* [78] studied the synthesis, structure and antimicrobial properties of Mannich bases derived from Benzyhydrazide **75a** and **75b (Scheme 73)**. The structures of the synthesized Mannich bases were characterized by IR, ^{1}H NMR &^{13}C NMR elemental analysis, melting point and TLC. The antimicrobial activities of synthesized compounds such as *Staphylococcus aureus, P.aeruginosa, Bacillus spp.* and *Escherichia coli* were also tested against certain organisms.



NHR_1R_2 = Morpholine, N-methyl piperazine, N,N-diethylamine

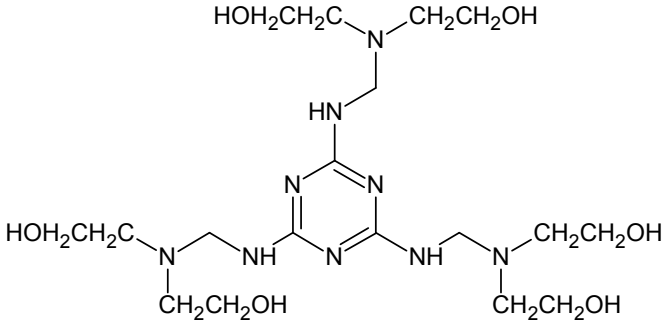
Scheme 73. Synthesis of Mannich bases derived from Benzyhydrazide

The corrosion inhibition of mild steel using two new Mannich bases namely 2,2',2''((((1,3,5-triazine-2,4,6-triyl)tris(azanediyl)tris(methylene)tris(azanediyl)triethanol**(INH-1) 76a** and 2,2',2'',2''',2''''((((1,3,5-triazine-2,4,6-triyl)tris(azanediyl)tris(methylene)tris(azanediyl)hexaethanol**(INH-2) 76b (Scheme 74)** has been investigated using weight loss and electrochemical methods by Verma *et al*., [79].These compounds showed maximum efficiency of 92% and 95% at 25ppm concentration respectively. Potentiodynamic polarization suggested that the inhibitors depict mixed type behaviour. The Electrochemical impedance spectroscopy (EIS) measurement showed that inhibitors were adsorbed at mild steel surface and obeyed Langmuir adsorption isotherm. Various thermodynamic parameters were also determined to investigate the mechanism of corrosion inhibition. The results obtained from weight loss and electrochemical methods were in good agreements.



76a

2,2,2((((1,3,5-triazine-2,4,6-triyl)tris(azanediyl)tris(Methylene)tris(azanediyl)triethanol

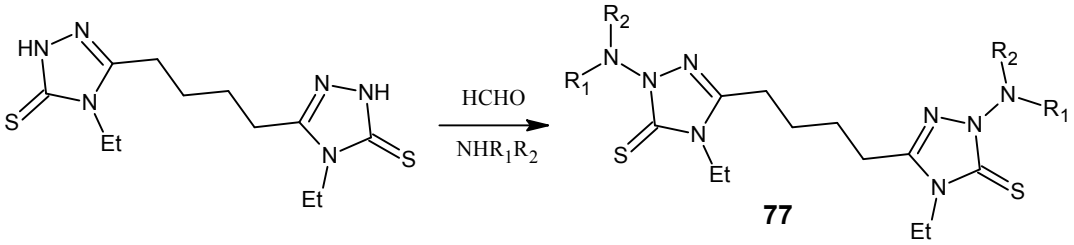


76b

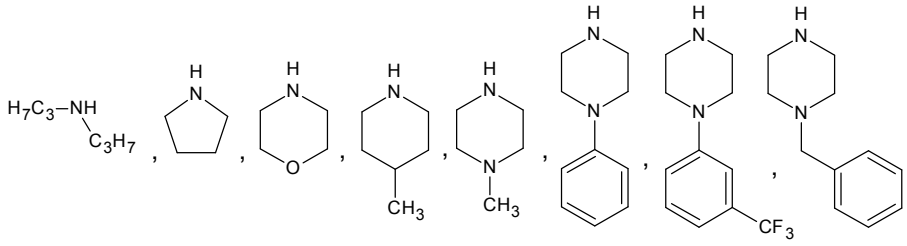
2,2,2,2,2,2((((1,3,5-triazine-2,4,6-triyl)tris(azanediyl)tris(Methylene)tris(azanediyl)hexaethanol

Scheme 74. Structure and names of Mannich bases INH-1and INH-2

A series of Mannich bases containing bis-1,2,4-triazole **77 (Scheme 75)** were prepared under conventional cyclic condensation by Koparir [80]. The structures of newly synthesized compounds were established based on analytical and spectral studies. These compounds were evaluated for their antioxidant, antifungal and antibacterial activities. Most of the compounds were found with good activity when compared with standard.

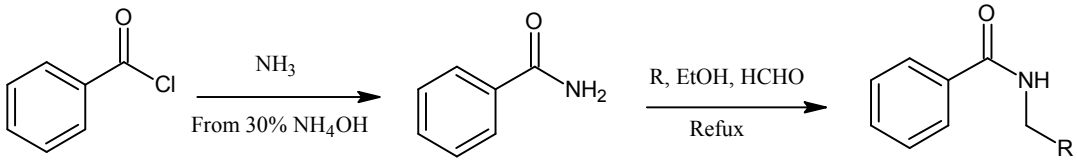


77

Where NHR_1R_2 = 

Scheme 75. Synthesis of Mannich bases containing bis-1,2,4-triazole

Bala *et al.,* [81] reported the design, synthesis, characterization, and computational studies on benzamide substituted Mannich bases **78 (Scheme 76)** as novel, potential antibacterial agents. A series of benzamide substituted Mannich bases were synthesized. The synthesized derivatives were authenticated by TLC, UV-Visible, FTIR, NMR, and mass spectroscopic techniques and further screened for *in vitro* antibacterial activity by test tube dilution method using amoxicillin and cefixime as standard drugs. The physicochemical similarity of the compounds with standard drugs was assessed by calculating various physicochemical properties using software programs. The percent similarity of synthesized compounds was found to be good. The compounds were subjected to QSAR by multilinear regression using Analyze it version 3.0 software, and four statistically sound models were developed with R^2 (0.963–0.997), R^2_{adj} (0.529–0.982), and Q^2 (0.998–0.999) with good F (2.35–65.56) values.

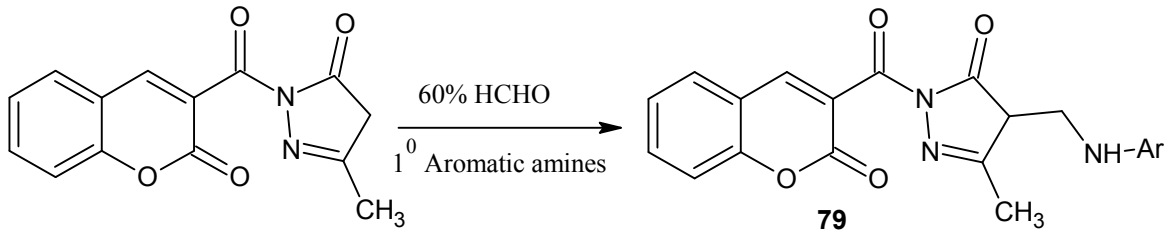


78

Where R is Morpholine, Piperazine, Phenylamine, 4-Bromophenylamine, 4-Sulfamoylphenylamine, 2-Nitrophenylamine, 2,4-dinitrophenylamine

Scheme 76. Synthesis of benzamide substituted Mannich bases

Sivakumar *et al.,*[82]described an efficient synthesis of some Mannich base of 5-methyl-2-[(2-oxo-2*H*-chromen-3-yl)carbonyl]-2,4-dihydro-3*H*-pyrazol-3-one **79** from 5-methyl-2-[(2-oxo-2*H*-chromen-3-yl)carbonyl]-2,4-dihydro-3*H*-pyrazol-3-one (**Scheme 77)** by using conventional and non-conventional (microwave) techniques. Microwave assisted reactions required shorter reaction time and gave good yield. The newly synthesized compounds were screened for their anti-inflammatory, analgesic activity, antioxidant, and antibacterial effects by comparing with standard drug.



Where Ar = 4-benzoic acid, 4-Phenol, 4-Nitro benzene, 4-Salicylic acid, 4-Benzene sulphonic acid, 2-Benzene sulphonic acid, 2-Pyridine, 4-Chloro benzene, 4-Methoxy benzene

Scheme 77. Synthesis of Mannich base of 5-methyl-2-[(2-oxo-2*H*-chromen-3-yl)carbonyl]-2,4-dihydro-3*H*-pyrazol-3-one from benzamide substituted Mannich bases

4. CONCLUSION

Heterocyclic Mannich bases are well known and important nitrogen compounds. Several methods have been applied for their synthesis. Most of the derivatives of heterocyclic Mannich bases have been found to possess considerable biological activities, which stimulated the research activity in this field. This manuscript is a brief review about different methods for the synthesis of biologically active derivatives of heterocyclic Mannich bases.

5. REFERENCES

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