A REVIEW ON PHARMACOLOGICAL ACTIVITIES OF SOME MANNICH BASES

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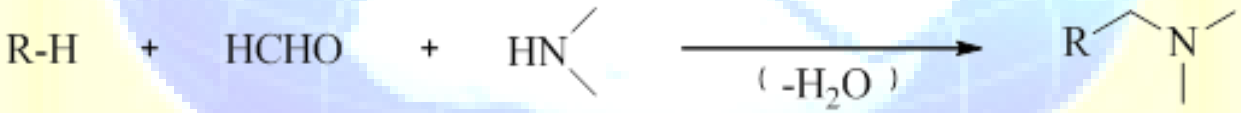
Introduction

The classical Mannich reactionis a three-component condensation between compounds containing an active hydrogen atom, aldehyde and amine. The reaction involves the elimination of water molecule and leads to the formation of compounds called Mannich bases as illustrated in the following scheme(*B***abu. K and Pitchai. P2014)**.



Mannich bases have found numerous applications in the treatment of natural macromolecular materials such as leather, paper and textiles, the production of synthetic polymers, as additives used by the petroleum industry, water treatment, analytical reagents, cosmetics, dyes, etc. (Gheorghe Roman,2014).Several Mannich bases had been prepared from different combination and their various activities have been evaluated.Mannich bases have been found to possess significant antibacterial, antifungal activities (**Suba Sharma and Shamim Ahmad2013).**Anticancer ,antitubercular , analgesic anticonvusant ,antioxidant and anti-inflammatory activities of mannich bases were also known (G.L. Almajan et al.2009).Mannich

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bases plays an important role polymer industry, removal of water effluents, corrosion inhibitionetc.biologica(*ChandrabhanVerma et al.,2013).*But this review focuses mainly some pharmacological activities some ofmannich bases.Numerous researches have been conducted on mannich bases and their medicinal activities have studies intensively,some of these mannichbases that has medicinal applications includes are discuss below.

Antimalarial activity

Malaria is one of the most common widespread infectious parasitic diseases mainly affecting people from developing countries like Centraland South-America, Asia, and Sub-Saharan Africa (Ajay,2014). According to the World Health Organization (WHO), approximately 250 million clinical cases of malaria occur in every year, and this leads to deaths of millions of people, especially children below 5 years.

The most common causes of malaria includes; species of the protozoan parasite Plasmodium: *P. falciparum, Plasmodium vivax, Plasmodium malariae,* and *Plasmodium ovale,* which are transmitted by over 70 species of Anopheles mosquitoes(Ajay,2014).In africancountries, *P. falciparum* is the most common causative agent which account to about 80% ofmalaria cases,*P. vivax* is the most widespread species, occurring largely in Asia, including the Middle East and the Western Pacific, and in Central and South America. This parasite species causes a relatively less lethal form of the disease compared with *P. falciparum*(Ajay,2014).

There have been severalMannich bases reported from the literature and are widely used as effective drugs for the treatment of malaria. Chloroquinedescribed in structure(1) has been widely used for the treatment of malaria since in the early 1950s,and it was found to be highly active against *Plasmodium falciparum*,however in some cases the drugs tends to be resistance to malaria and therefore other Chloroquine analogues which shows high activity than Chloroquine have been reported.Amodiaquinedescribed in structure(2), a new Mannich base 4-aminoquinoline, that is effective against chloroquine-resistant strains of *P. falciparum* was also reported (Selva, 2012). Butthe clinical use of AQ has been restricted due to it isadverse side effects, the drug toxicity involves the formation of an electrophilic metabolite,

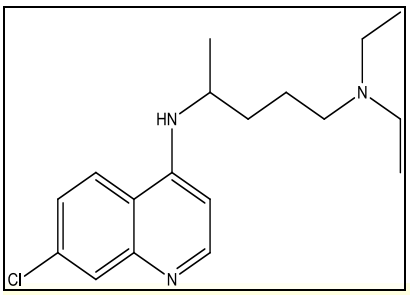
amodiaquinequinoneimine (AQQI), which binds to cellular macromolecules leading to hepatotoxicity and agranulocytosis(Sanjib*et al.,2009*).However, another study had reported a new series of amodiaquine (AQ) analogues as antimalarial agents and was found to have a high antimalarial activity against *Plasmodium falciparum*(Rudrapal and Chetia, 2011).

The synthesis of amodaquineanaloques such as Isoquine (IQ) andtebuquine (TQ) as described in structure (3) and (4) respectivelyhave been reported, isoquine possess higher antimalarial activity than AQ. Tebuquine (TQ), is also another analogue of AQ with a p-chlorophenylmoiety substituted at the 5-position of the 4-hydroxyaniline side chain of AQ. TQ is significantly more active than AQ and CQ in both in vitro and in vivo tests. Many otherQuinoline containing compounds were also prepared for the treatment of malaria, Jain et al., 2004 have reported a synthesis of 8-quinolinamine analogues which showed high antimalarial activity (Ajay, 2014).

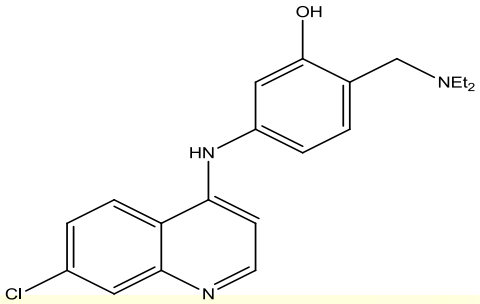
The synthesis of new PhthalimideMannich Base and it's metal complexes (2-dimethyl-aminomethyl)isoindoline-1,3-dione derived from condensation reaction of phthalimide, formaldehyde and dimethylamine at room temperature were reported to possess a wide range of antimalarial antibacterial, antifungal activities (M.YosuvaSuvaikin et al.,2013).

Antimalarial activity of **Substituted Triazoles Derivatives were reported,** the nitrogen containing heterocyclics was found to effective in inhibiting the *in vitro* growth of *P. falciparum.* Triazoles and its derivatives were also found to possess a great importance in medicinal chemistry and can be used for the synthesis of numerous heterocyclic compounds with different biological activities (**Mohammad Asif,2014).**
A series of quinolylhydrazones were synthesized and their antimalarial activity was evaluated against the chloroquine-sensitive strain of *Plasmodium falciparum*(***Raghav and singh 2011).***

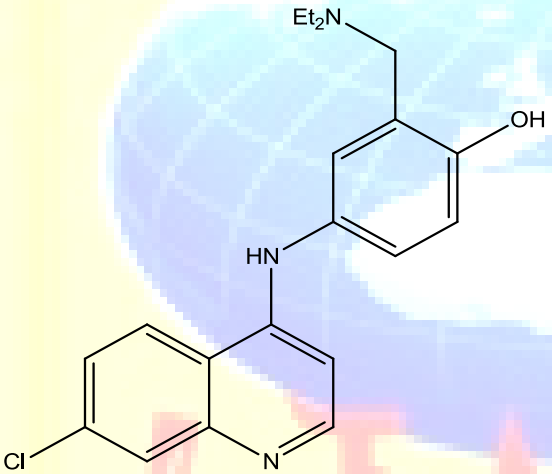
The synthesis of new mannichbase derived from condensation reaction between phthalimide, Morpholine and formaldehyde ***N-(morpholinomethyl)phthalimide(MMP) described in structure (5), and it'smetal complexes were reported, both the ligand and the metal complexes possess antimalarial activity (*L. Muruganandam*et al ., 2012).***



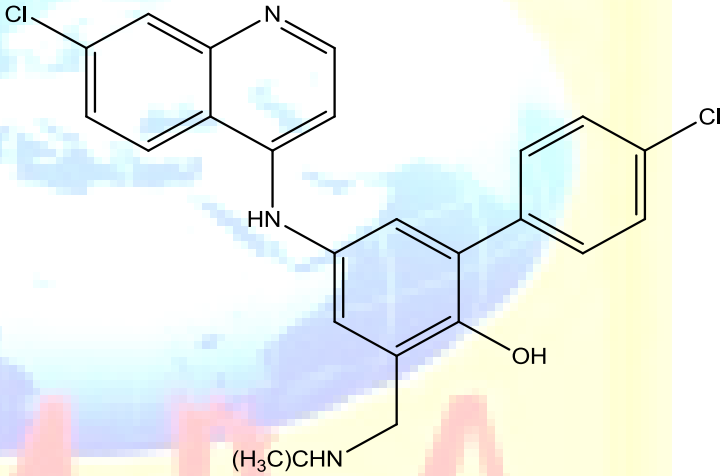
(1) Chloroquine



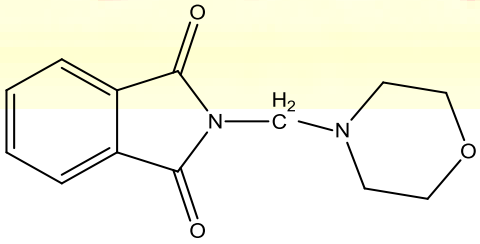
(2) Amodiaquine



(3) Isoquine



(4)Tebuquine



(5) MMP

Antioxidant Activity

An antioxidant is a molecule that has the ability to inhibits the oxidation of other molecules.oxidation isa chemical reaction that involves the transfer of electrons or hydrogen from one substance to another, the excess of reactive oxygen species produced in living organisms can cause damage to the cells by initiating chain reactions that lead to lipid peroxidation, DNA damage or protein oxidation.Mannich bases have been reported to be effective antioxidant (Gheorghe, 2014).

Mannich basederived from phenolic compounds have been reported as potential antioxidants, a phenolic mannich base containing morpholine and amine moiety have been reported to have antioxidant activity which has been assessed by means of xanthine oxidase inhibition test for the cell-free system, and by inhibition of lipid peroxidation using rat liver homogenate(Gheorghe Roman,2014).Mannich bases derived from benzamide, 1-((1H-benzod] imidazole-1-yl)methyl)urea (BIUF) as described in structure (6)and 1- (3-hydroxynaphthalen-2-yl)methyl)thiourea (TNTUF) as described in structure (7) were synthesized and were found to be active antioxidant agents due to presence of electron releasing amide group . But BIUF was found to more active than TNTUF due to the presence of two N atoms in the benzimidazole attached to amide group(Suman Bala, 2014).

The synthesis of Mannich base (SBA) as described in structure (7), derived from succinimide,benzaldehyde and aniline, 1-[anilino(phenyl)methyl]pyrrolidine-2,5-dione have been reported and the antioxidant activity of the compound was determined by it is ability to inhibit linoleic acid peroxidation using *ferric thiocyanate (FTC)* method ,where various concentrations of the mannich bases were used, and the compound showed significant antioxidant activity in the inhibition of linoleic acid peroxidation, similarly the DPPH (2,2-diphenyl-picrylhydrazine) scavenging activity of the compound was observed (Rajeswari *et al*.,2011). Mannich bases of cinnamaldehyde derived from o-toluidine, urea and thiourea have been synthesized and also its in vitro scavenging activities were evaluated. The antioxidant activity was determined by measuring it's reducing power. The DPPH is a stable free radical, which has been widely accepted as a tool for estimating free radical scavenging activities of antioxidants, the compounds were able to reduce the stable radical DPPH to the yellow colored 1, 1-diphenyl-1, 2-picryl hydrazine, and the reducing ability of a compound is an indication that

the compound possess a significant antioxidant activity., Similarly, the antioxidant activity of a compound has been assigned to various mechanisms such as prevention of chain initiation ,binding of transition metal ion catalyst and decomposition of peroxides (Vishnu*et al.*, 2013).

Scavenging activity

The Scavenging activity of a compound isusually expressed as:

Scavenging activity(%) =Ao-As/Ao × 100

Where,As is the absorbance of the DPPH in the presence of the tested compounds and standard

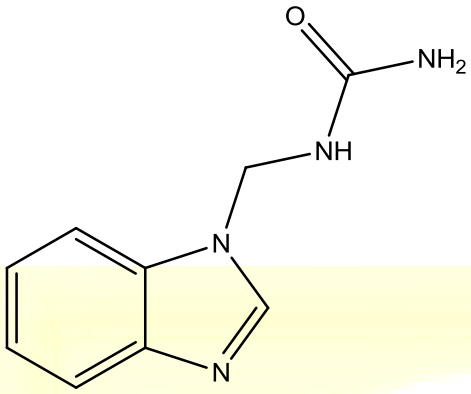
A0 is the absorbance of the DPPH in the absence of the tested compound and standard(Koparir ,2013).

The synthesis of novel mannichbase ***3-(phenyl(p-tolylamino)methyl) naphthalene-2-ol (TNPTB)*** derived from β-naphthol, p-toluidine and benzaldehyde, described in structure (9), was also also reported and the compound was found to have significant antioxidant activity (**K.gokulakrishnan et al.,2014).**

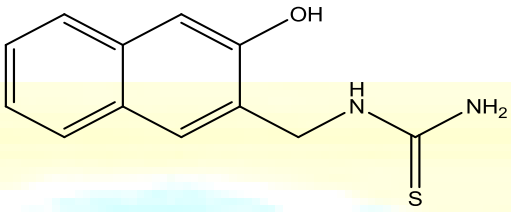
A novel series of Mannich bases of pyrazolines was synthesized and evaluated for the antioxidantactivity using DPPH radical with ascorbic acid and rutin employed as standarddrugs for comparison.The compounds were found to have highantioxidant capacities as compared to both of the standarddrugs(P. C. Jagadish., 2013)

Thiazolinederivatives were synthesized and evaluated for their antioxidant activity. The antioxidant activity of derivatives of compound have been found to exhibit the significant DPPH radical scavenging activity, comparable to that of vitamin E(Shih *et al., 2004).*

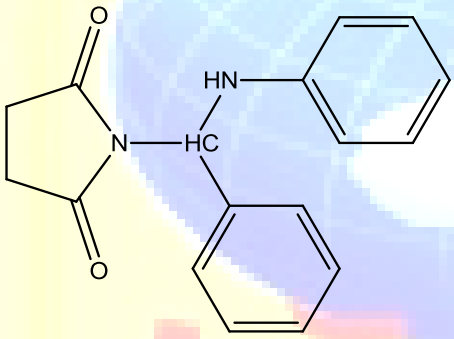
Mannich bases of 2-benzylthio benzimidazole**derivatives** N-1-((substitited amino)methyl)-2-benzylthio benzimidazole as described in structure (10), were also synthesized .The radical scavenging ability of synthesized compound was tested by DPPH assay method using ascorbic acid as standard, and the compound were found to posses a good antioxidant activity(**Sumayya K K et al., 2013).**



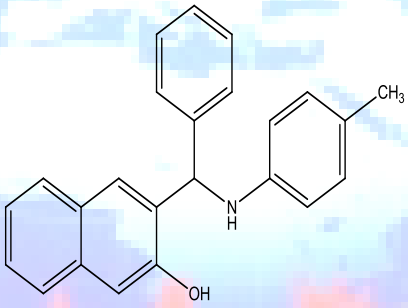
(6) **BIUF**



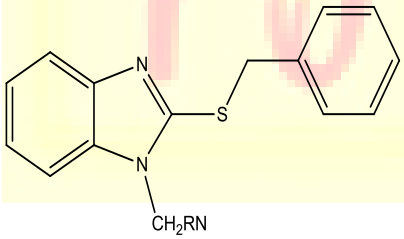
(7) TNTUF



(8) SBA



(9) *TNPTB*



(10)

Anticonvulsant activity

Epilepsy is the most prevalent neurological disorder, affecting approximately 50 million people worldwide, which have been characterized by recurrent seizures of cerebral origin with episodes

of sensory, motor or autonomic phenomena, which proceed with or without loss of consciousness (Kaminski*et al.*, 2013). The synthesis of Several Mannich bases which are used as an anticonvulsant have been reported, and are considered as potential drugs used in the treatment of seizures in epilepsy(N. S. Pandeya and N. Rajput 2012)

Mannich base of 3-phenyl-pyrrolidine-2,5-diones were synthesized and their anticonvulsant activity were evaluated in several animal models of epilepsy and theresults also revealed that majority of compounds showed protection in the maximal electroshock tests (MES) (Kaminski, *et al.,* 2013). Mannich derivative 1-(4- chlorobenzylidene)-3-(1 (morpholinomethyl)-2, 3-dioxoindolin-5-yl) ureaas described in structure (11), havebeen reported to have a significant antiepileptic property with the absence of neurotoxicity (Selva, 2012).The synthesis of mannich bases of substituted amino phenol and acetophenone by treatment with formaldehyde and active hydrogen compound have alsobeen reported and their anticonvulsant activity were determined(Muthumani *et al.*,2010).

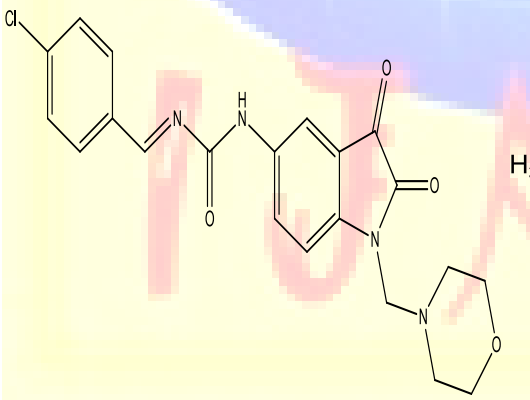
(Byrtus et al., 2011) reported the synthesis of Mannich bases derived from 5-cyclopropyl-5-phenyl- and 5 cyclopropyl-5-(4-chlorophenyl)-imidazolidine-2,4-dione derivatives have been reported and the anticonvulsant activity was determined using maximal electroshock and subcutaneous pentylenetetrazole(SCPTZ)seizure tests.

Active triazole derivatives were reported to have good anticonvulsantactivites (**M. ShamsherAlam*et al., 2012).*** 1,2,4-triazole derivatives were also reported and the Compounds were evaluated *in vivo* for their anticonvulsant and muscle relaxant activities using PTZ and rotarod tests, respectively(Ali *et al*., (2007). Synthesis of 3-(4-chloro-phenylimino)-5-methyl-1, 3- dihydro-indole-2-one was reported by Sridhar *et al.,2002* The synthesized compound were found to be active in MES test (Siddiqui*et al ., 2010).* Synthesis of 3-cycloalkanone-3, 4-hydroxy-2-oxindoles derivatives were also reported and compound showed the MES test and PTZ test, thus act as a potential anticonvulsant (Veerasamy*et al.,2010).*Mannich bases of 3-arylsuccinimides derived from other secondary aliphatic amines, such as morpholine, 4-benzylpiperidine, 4-cyclohexylpiperazine and mannich bases derived from 4-(2-hydroxyethyl)piperazine or 4- benzylpiperidine were reported tobe effective anticonvulsant (J. Obniskaet al., 2012).

phenolicMannich bases of 3- hydroxy-4-pyranones has been investigated extensively and evaluated using MES and scPTZ tests, the compounds showed an excellent anticonvulsant activity , without being neurotoxic (M.D. Aytemir et al.,2004).synthesis of various semicarbazones of acetophenonemannich base have also been reported to have good anticonvulsant activity using MES test model(Raja *et al.,2007)*

A series mannich bases of 2-mercaptobenzimidazole derivatives were synthesized using mannich reaction by the reaction between compounds having secondary amine and formaldehyde. *The anticonvulsant activity of the compounds were studied on mice in which the MES was measured using* electroconvulsiometer *where by most of the synthesized compounds exhibited highly significant anticonvulsant activity* (**K. Anandarajagopal*et al., 2010)***

Yogeeswari*et al., 2004* synthesized a series of 3-chloro-2 methyl phenyl substituted semicarbazones described in structure (12), and evaluated for anticonvulsant activitivity. The anticonvulsant activity of the compound was tested using MES, and scPTZ test models after intraperitoneal administration to mice at doses of 30 , 100, 300 mg/kg (**Sagar Kumar and Vinit Raj 2013)**



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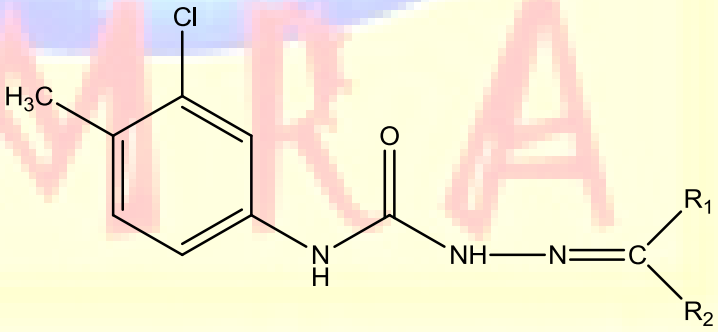
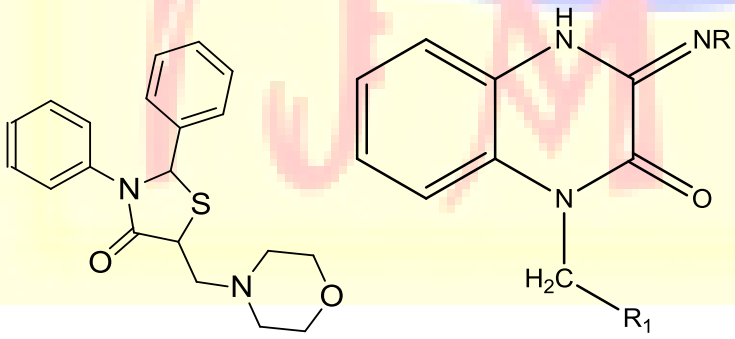


(12)

Antitubercular activity

Tuberculosis (TB) is a common and an infectious disease that is caused bya strain of bacteria called *Mycobacterium tuberculosis* (*M. tuberculosis*).Tuberculosis is among the major global health problems which cause serious damage to the body that can leads to death and it's

considered as the second leading cause of death from an infectious disease worldwide, after the human immune deficiency virus (HIV) (Anju *et al.*,2014). There have been several drugs for the treatment of tuberculosis among which includes Ethambutol, Streptomycin, Rifampicin etc.(Anju*et.,al* 2014). The use of Mannich base compounds alsoplayed a significant role in the treatment of tuberculosis. Numerous Mannich base were synthesized and their antitubercular activity were evaluated (M. A. Ali and M. Shaharyar(2007). The synthesis of Mannich base by treating 4-thiazolidinone derivatives with morpholine and formaldehydedescribed in structure(13), was reported and the compound was tested for in vitroantitubercular activity against *Mycobacterium tuberculosis* by alamar blue assay method (Anju *et.,al* 2014).The synthesis of Mannich base of Quinoxaline derivatives formed by condensation of o-phenyl ene diammine, and oxalic acid followed by the treatment with primary amine, as described in structure (14), was also reported and evaluated for antitubercular activity against *Mycobacterium tuberculosis*(H37 Rv ATCC27294) using Microplate Alamar Blue Assay method, and the compound was found to be effective against the selected sample(Ramalakshmi*et al.*,2013). Mannich base of substituted 1,3,4-oxadiazole was synthesized and evaluated for their antitubercular activity against *Mycobacterium tuberculosis* H37Rv strain using Middle brook 7H-9 agar medium (Somani *et al.*, 2013).



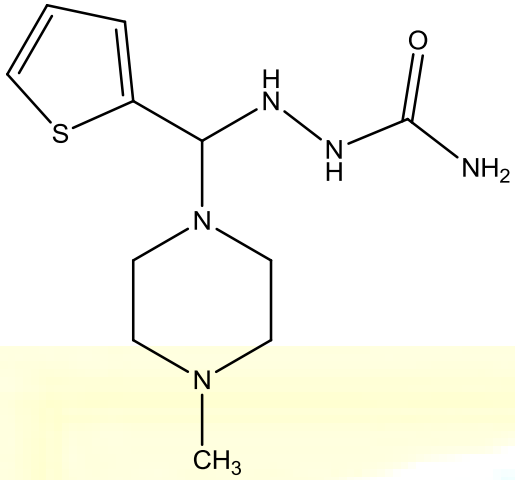
(13) **(14)**

Anticancer activity

Cancer is one of the most complex diseases characterized by the uncontrolled, rapid and pathological proliferation of abnormal cells which ultimately leads to tissue damage and eventually leads to dead, cancer is primarily caused by environmental factors.The cancer-causing agents (carcinogens) can be present in food, water, air, and in chemicals etc. (Oyaizu M. 1986).The most commonly used method for cancer treatment is by surgery or radiotherapy,but nowadays, drugs capable of targeting the cancerous tissues with some side effects are used(Vishnuvardhanaraj G, *et al.,2013).*

Mannich base compounds have been reported to have a significant role in cancer treatment. Several Mannich bases have been prepared by treating N-methylpiperazine and Indole-3-aldehyde as fixed component and varying the number of compounds possessing active hydrogen atoms such as acetamide, urea, thiourea, semicarbazide and thiosemicarbazide by Mannich condensation and the compounds were tested for their anticancer activity *in vitro* against2 human cancer cell lines; human liver (HUH7) and breast (MCF7), majority of the compounds been synthesized were found to have significant anticancer activity against liver and breast cancer cell lines with lower concentrations than the standard drug 5-fluorouracil(***Padmashali et al.,2013).***

Synthesis of novel Mannich bases 2-((4-methylpiperazin-1-yl)(thiophen-2-yl)methyl)hydrazinecarboxamide (MPTMHC) and 2-((4-methylpiperazin-1-yl)(thiophen-2-yl)methyl)hydrazinecarbothioamide (MPTMHCT) as described in structure **(15)** and **(16)** respectively have been reported. The anticancer activity was studied against human lung cancer (A549) cell and colon cancer (HCT15) cell lines and the compounds were found to possess good anticancer activity (***Padusha et al.,2013)***



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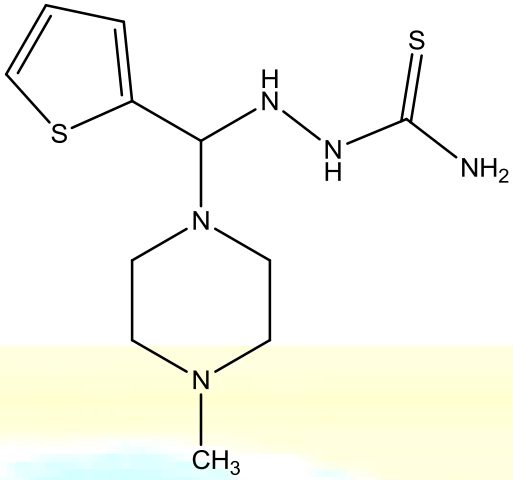

(16)

A series of novel Mannich bases of 2-propoxybenzylideneisonicotinohydrazide was also reported,the anticancer activity was studied against A549 human lung cancer using gemcitabine as standard drug, and the compound was found to possess good activity than the standard drug (phogat et al., 2012). Veerendra et al.,2003 have also reported some Mannich bases derived from 1,2,4-triazoles to have anticancer activity. Mannich bases derived from chalcones were also reported and some of the compounds showed good antitumor activity against renal cancer UO-31 by *in-vitro* disease-oriented human cells screening panel assay (**Hanan H. Kadry**et al.,2013)

Conclusion

This review summarizes pharmacological applications of some mannich base which includes; antimalarial, antioxidant, anticonvulsant,antitubercular and anticancer activities and all the reported compounds were evaluated and found to possess significant activities.

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