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MANNICHBASES: AN OVERVIEW OF HETEROCYCLIC COMPOUND WITH VARIOUS BIOLOGICAL ACTIVITIES

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ABSTRACT: In Organic chemistry, largest families of organic compounds belong to heterocyclic compounds. In place of a carbon atom incorporation of an oxygen, a nitrogen, a sulfur, or an atom of a related element gives rise to a heterocyclic compound..Heterocyclic compounds are of very essential for our day-to-day life. It has a broad range of applications in medicinal chemistry as well as in agrochemicals products. A Mannich base is a beta-amino-ketone, which is formed in the reaction of an amine, formaldehyde and a carbon acid, and it is a carbon-carbon bond-forming nucleophilic addition reaction and is a key step in synthesis of a wide variety of natural products, pharmaceuticals, and so forth. This literature study enlightens the fact, that Mannich bases of heterocyclic compounds are highly reactive and are recognized to possess potent diverse activities like, anti-inflammatory, anticancer, antibacterial, antifungal, anticonvulsant, anthelmintic, anti-tubercular, analgesic, anti-HIV, antimalarial, antipsychotic, antiviral activities and so forth. In this review various biological activities of Mannich bases of heterocyclic compound derivatives reported is discussed.

INTRODUCTION: Mannich basesis a beta-amino ketone [1, 2]. It is one type of nucleophilic addition reaction, which is formed by anamine, formaldehyde (or an aldehyde) and a carbon acid [3]. Mannich bases additionally go about as significant pharmacophores or bioactive leads with different potential specialists that have amino alkyl group. The instances of clinically helpful Mannich bases of aminoalkyl group are Ranitidine, Fluoxetine, Biperiden, Cocaine, Trihexyphenidyl, Procyclidine, Atropine [4–6].

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The literature survey had demonstrated that Mannich bases are very reactive and it very well may be effortlessly changed over to different mixes, for instance, its diminished to frame physiologically dynamic amino alcohols [7] and furthermore it is generally utilized for development of Nitrogen-containing mixes. It gained more significance because of their application in antibacterial activity [8, 9] and used in detergent substances [10], polymers, surface dynamic agents and resins [11].

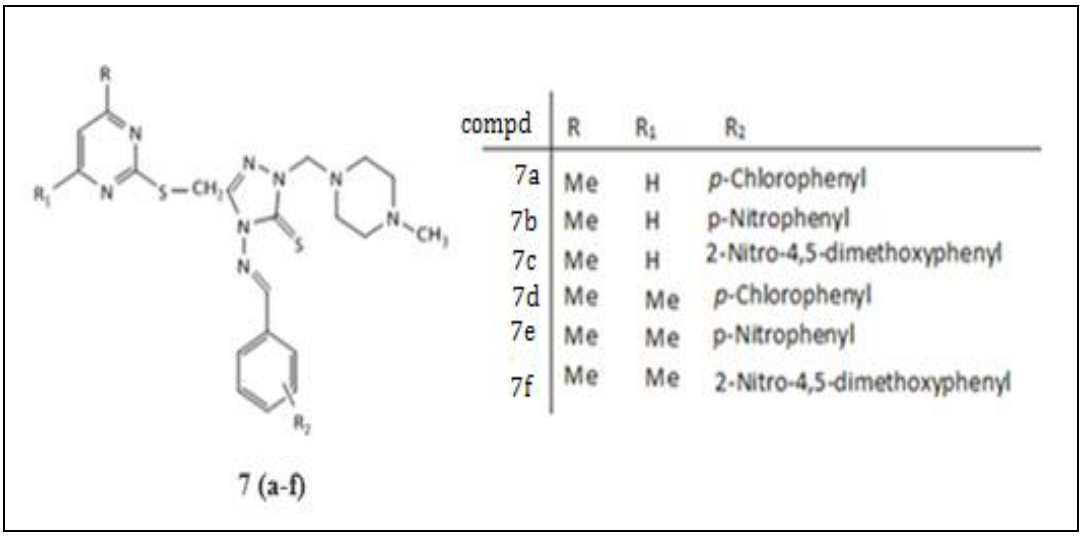
The heterocyclic compounds have a fundamental interest in medicinal chemistry, and the most unpredictable parts of chemistry are typically called heterocyclic chemistry [12]. The heterocyclic compounds containing Sulphur, Nitrogen, and Oxygen are referred to as heteroatoms, assuming significant jobs in the drug discovery process [13].

These compounds especially having five and six-membered ring, have pulled in consideration of pharmacy network throughout the years, because of their remedial value [14] and at the same time these compounds are luxuriously utilized as intermediate in organic synthesis [15-17] and the synthetic routs are monitored by the pharmacological estimation of nitrogen, sulphur and oxygen containing heterocycles [18-24].

Mannich bases with heterocyclic mixes are known to have intense exercises like anticonvulsant [25, 31]anti-inflammatory [26], antibacterial [27, 28], antifungal [28, 29], analgesic [30], antiviral [32], anthelmintic [33], antipsychotic [34], antimalarial [35], antitubercular [36], [37], anti-HIV70, and anticancer [31, 38, 39], activity and soforth. Starting here of view, the current examination effectively depicts a survey on heterocyclic compounds demonstrating distinctive pharmacological activity by utilizing Mannich bases.

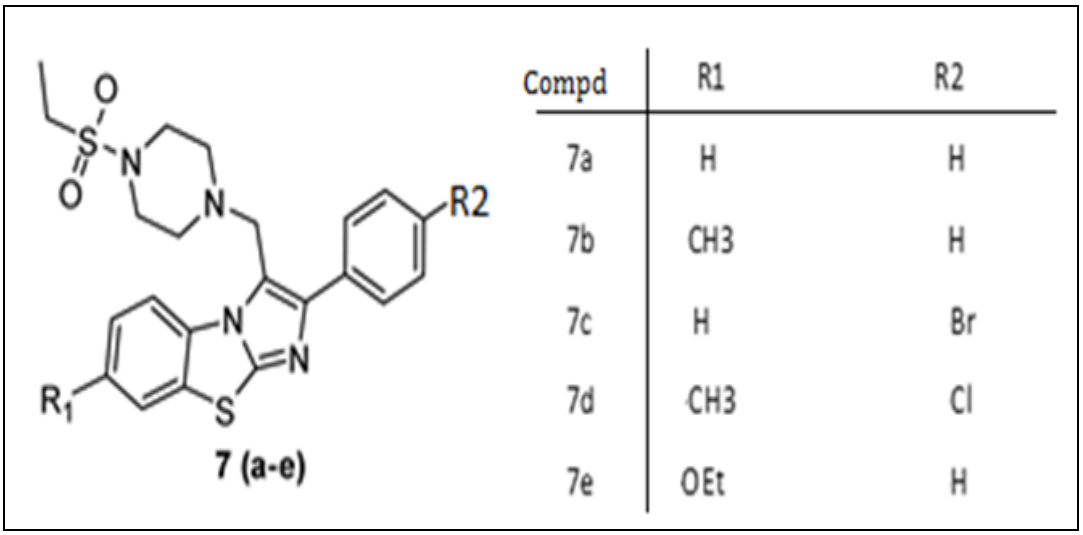
2. Biological Activities:

2.1 Anti-Microbial Activity: Lingappa *et al.*, (2008) [40] Prepared a progression of novel compound 3-(4,6-disubstituted -2 thiomethyl-pyrimidyl) – 4 - amino-5-mercapto -1, 2, 4 - triazoles 7(a-f) **Fig. 1** and it has been evaluated for antifungal and antibacterial activity. The synthesized compound on reaction with amines N Mannichbase 7 (a-f) obtained rather than S Mannich base, and it also been reacted with aldehydes to obtain schiffs base. The novel blend shows excellent antifungal and antibacterial activity.



compd	R	R_1	R_2
7a	Me	H	*p*-Chlorophenyl
7b	Me	H	p-Nitrophenyl
7c	Me	H	2-Nitro-4,5-dimethoxyphenyl
7d	Me	Me	*p*-Chlorophenyl
7e	Me	Me	p-Nitrophenyl
7f	Me	Me	2-Nitro-4,5-dimethoxyphenyl

FIG. 1: 3- (4, 6 – DISUBSTITUTED -2 THIO METHYL PYRIMIDYL)- 4- AMINO-5-MERCAPTO-1,2-4-TRIAZOLES) & DERIVATIVES



Compd	R1	R2
7a	H	H
7b	CH3	H
7c	H	Br
7d	CH3	Cl
7e	OEt	H

FIG. 2: IMIDAZO [2, L-B] BENZOTHIAZOLES & DERIVATIVES

Maddili SK *et al.,* (2017) [41] Synthesised imidazole [2, l-b] benzothiazoles were set up through one-pot multi-part response within the sight of water as an eco-accommodating dissolvable **Fig- 2**. All the integrated mixes were affirmed from1HNMR IR, 13CNMR, and Mass spectroscopy. These discoveries showed that compound 7c showed great antifungal adequacy while compound 7b uncovered noteworthy enemy of microbial activity. What is more restricting conduct of compound 7b was explored by restricting investigation between calf thymus DNA and compound 7b by UV-Vis ingestion spectroscopy and further research about HSA communications was completed.

Sharma P *et al.,* (2019) [42] Synthesized novel heterocyclic 1, 3, 4-thiadiazole **Fig. 3** and the organized blends were portrayed by1H NMR, IR, UV Spectroscopy. The result has shown that the blends are unique against pathogens under assessment and were nontoxic. The quieting development of the compound was evaluated by the paw edema method using the standard medicine diclofenac sodium. Compounds 7b and 8c shown amazing moderate and agony easing pharmacological activities. Which shows extraordinary lipophilic properties inside electron rich morpholine ring in Mannich base.

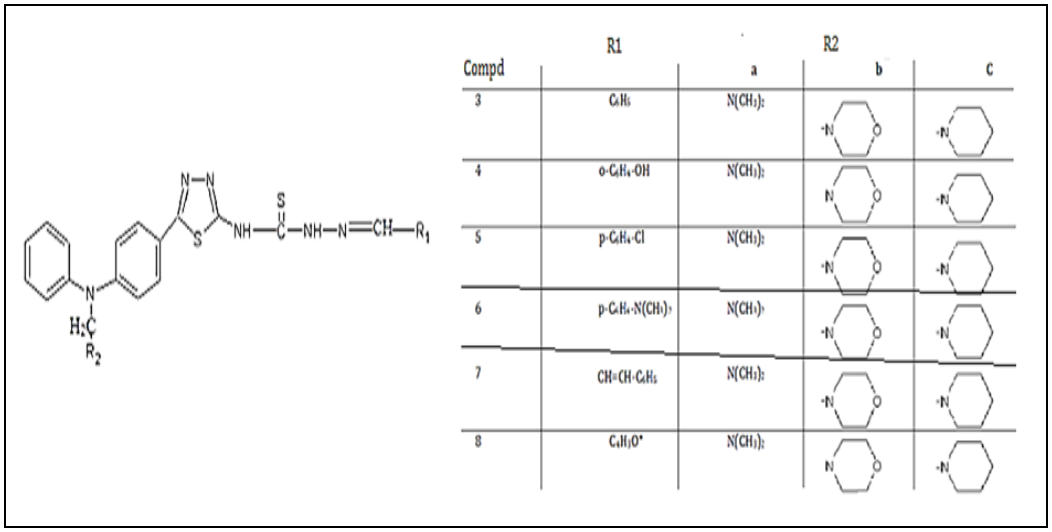


FIG. 3: 4-(5-(4-(N-PHENYL-N-(R2-SUBSTITUTED) METHYLAMINO) PHENYL)-1,3,4-THIADIAZOL-2-YL)-1-R1-SUBSTITUTED – THIOSEMICARBAZIDE & DERIVATIVES

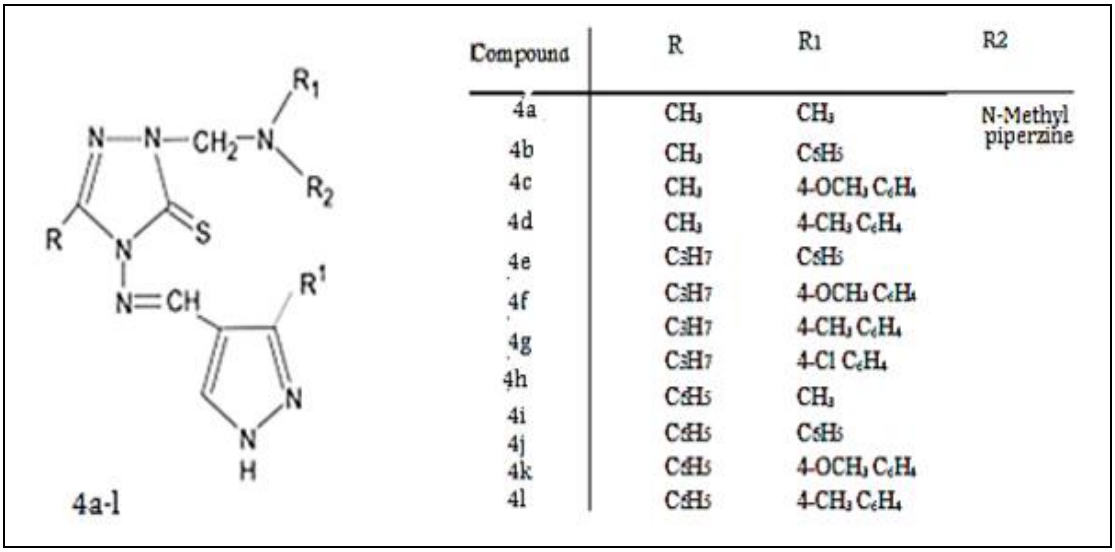
Alptüzün V *et al.,* (2009) [43] Synthesized some subbed benzylidene hydrazinyl pyridinium subsidiaries bearing benzyl, ethylphenyl, and propylphenyl bunches on the pyridinium nitrogen. The synthesized compounds were tested for their antifungal and antibacterial activity. Antimicrobial test outcomes showed that mixes containing a 3-phenylpropyl chain showed the most powerful antimicrobial action, and the compound 3d was the most dynamic in the arrangement against every tried bacterium and parasites strains.

MV Aanandhi *et al.,* (2013) [44] Synthesized a benzimidazole subordinates in two stagesfrom o-phenylenediamine. The Compounds 3a-c were portrayed by IR, 1H NMR, Mass and essential examination and evaluated for their antifungal and antibacterial activity. Out of the synthesized mixes 3a, 3b and 3cshows incredible antibacterial activity and the mix 3 ademonstrated great antifungal activity than others.

Lohitha P *et al.,* (2015) [45] Mannich Bases of 1, 3-Di Acetyl Indole subsidiaries were recently synthesized and were described by 1H NMR, Mass and IR, spectra. Blended Mannich bases of 1, 3-Di Acetyl Indole subordinates were explored for their antifungal and antibacterial action utilizing the cup-plate technique. A portion of the recently integrated Mannich bases of 1, 3-Di Acetyl Indole subordinates were found to have great and huge antibacterial and antifungal action.

Isloor AM *et al.,*(2009) [46] By the aminomethylation of 4-(3-substituted 1H-pyrazol-3-yl)methyl amino-5-substituted 4H-1,2,4-triazole-3-thiols(3) with formaldehyde and N-methylpiperzinesynthesized novel Mannich bases derivatives 4 (3 - substituted

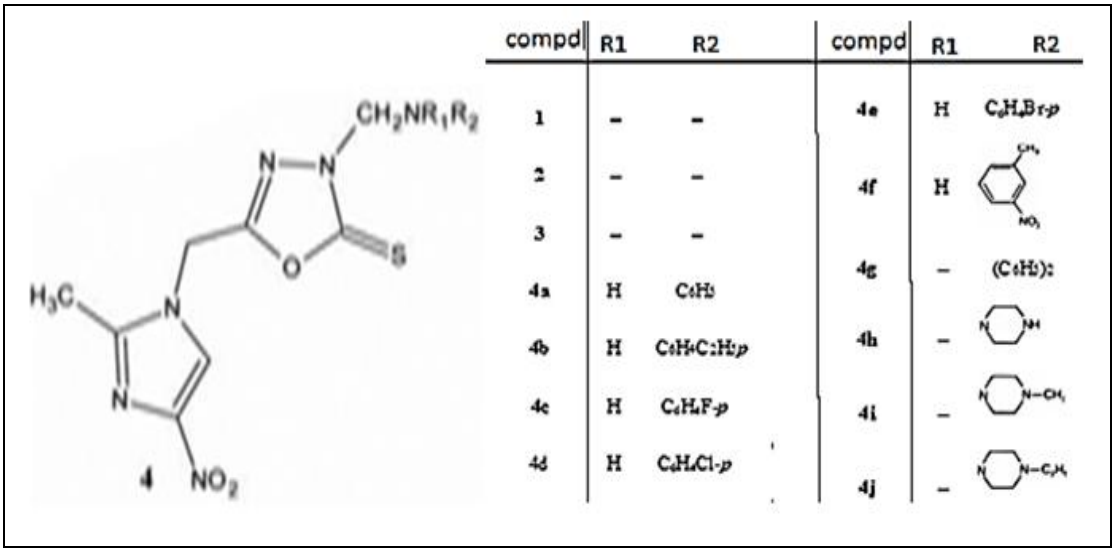
1H – pyrazol – 4 - yl)methyleneamino] – 5-Substituted 2-[(4-methylpiperzine-1-yl)methyl] - 2H-1,2,4-triazole-3(4H)-thione from 1,2,4-triazoles **Fig. 4**. These as of late joined structures were depicted by, 1H NMR, Mass and IR spectra and evaluated for their antibacterial and antifungal activity. Blends 4c, 4e, 4h, and 4k exhibited higher obstruction when compared with standard compounds.



Compound	R	R1	R2
4a	CH_3	CH_3	N-Methyl piperzine
4b	CH_3	C_6H_5	
4c	CH_3	4-OCH_3 C_6H_4	
4d	CH_3	4-CH_3 C_6H_4	
4e	C_3H_7	C_6H_5	
4f	C_3H_7	4-OCH_3 C_6H_4	
4g	C_3H_7	4-CH_3 C_6H_4	
4h	C_3H_7	4-Cl C_6H_4	
4i	C_6H_5	CH_3	
4j	C_6H_5	C_6H_5	
4k	C_6H_5	4-OCH_3 C_6H_4	
4l	C_6H_5	4-CH_3 C_6H_4	

FIG 4: 1,2,4-TRIAZOLE DERIVATIVE OF MANNICH BASES

Frank PV *et al.,* (2013) [47] by using 2-methyl-4-nitro-imidazole as a beginning material synthesized, a new 5 - (2- Methyl – 4 – Nitro -1- Imidazomethyl)-1, 3, 4-Oxadiazole – 2 – thione. **Fig. 5** and was presented to Mannich reaction with appropriate amines to yields another course of action of 3-substituted amino methyl-5 - (2- Methyl – 4 – Nitro -1- Imidazomethyl)-1,3,4-Oxadiazole – 2 – thiones. The synthesized compounds were evaluated for their antifungal and antibacterial activity. Huge quantities of these blends demonstrated extraordinary antifungal activity.



compd	R1	R2	compd	R1	R2
1	–	–	4e	H	C_6H_4Br-*p*
2	–	–	4f	H	
3	–	–	4g	–	$(C_6H_5)_2$
4a	H	C_6H_5	4h	–	
4b	H	$C_6H_4C_2H_5$-*p*	4i	–	
4c	H	C_6H_4F-*p*	4j	–	
4d	H	C_6H_4Cl-*p*			

FIG. 5: 5 - (2- METHYL – 4 – NITRO -1- IMIDAZOMETHYL)-1,3,4-OXADIAZOLE – 2 - THIONES& DERIVATIVES

Bogdanov, A.V *et al.,* (2016) [48] Synthesized a is indigo derivatives **Fig. 6** by using isatin with monosubstituted piperazines and formaldehyde. Subsidiaries of 1-piperazinomethylisatins, combine to form new is indigo subordinates. The synthesized subordinates were assessed for the antimicrobial activity, and it shows an excellent action.

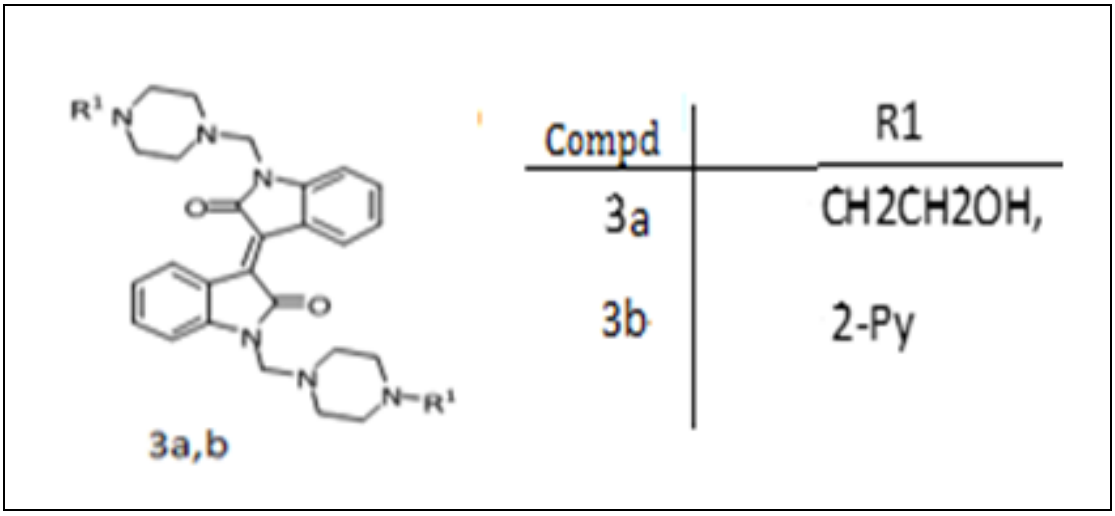
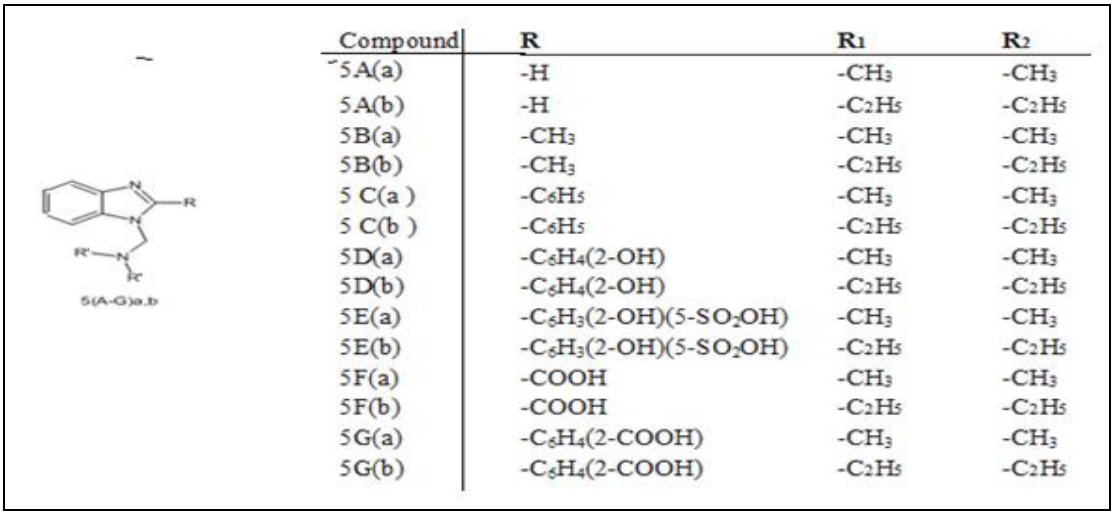


FIG. 6: ISOINDIGO SUBORDINATES

Kumar SV *et al.*, (2013) [49] Benzimidazole mixes were synthesized from the build-up response between ortho phenylenediamine and various acids **Fig. 7**. The excellence of the blends was resolved (TLC).

Among the readied blends, compound (b) and 5Ewas developed to be the most extraordinary against each attempted microorganism, and these 2 blends indicated complete bacterial DNA cleavage and non-harmful.



Compound	R	R1	R2
5A(a)	-H	$-CH_3$	$-CH_3$
5A(b)	-H	$-C_2H_5$	$-C_2H_5$
5B(a)	$-CH_3$	$-CH_3$	$-CH_3$
5B(b)	$-CH_3$	$-C_2H_5$	$-C_2H_5$
5 C(a)	$-C_6H_5$	$-CH_3$	$-CH_3$
5 C(b)	$-C_6H_5$	$-C_2H_5$	$-C_2H_5$
5D(a)	$-C_6H_4$(2-OH)	$-CH_3$	$-CH_3$
5D(b)	$-C_6H_4$(2-OH)	$-C_2H_5$	$-C_2H_5$
5E(a)	$-C_6H_3$(2-OH)(5-SO_2OH)	$-CH_3$	$-CH_3$
5E(b)	$-C_6H_3$(2-OH)(5-SO_2OH)	$-C_2H_5$	$-C_2H_5$
5F(a)	-COOH	$-CH_3$	$-CH_3$
5F(b)	-COOH	$-C_2H_5$	$-C_2H_5$
5G(a)	$-C_6H_4$(2-COOH)	$-CH_3$	$-CH_3$
5G(b)	$-C_6H_4$(2-COOH)	$-C_2H_5$	$-C_2H_5$

FIG. 7: SUBSTITUTED BENZIMIDAZOLE DERIVATIVES FROM ORTHO PHENYLENE DIAMINE& DERIVATIVES

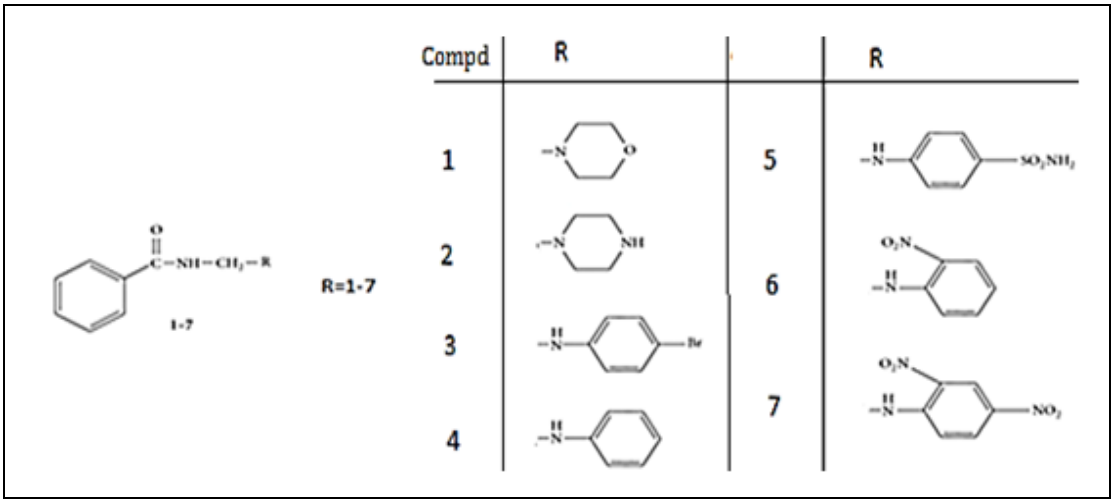


FIG. 8: BENZAMIDE SUBSTITUTED MANNICHBASE DERIVATIVES

Bala S *et al.,* (2014) [50] Benzamide substituted Mannich bases were synthesized **Fig. 8** and affirmed by UV-Visible, FTIR, TLC, Mass and NMR spectroscopic frameworks and screened for their *in-vitro* antibacterial activity by test tube weakening system utilizing cefixime and amoxicillin as standard. The blends 5, 6 and 7 where seen as the most impressive antibacterial executives among all the solidified blends.

Analgesic Activity: GangulaMohan Rao *et al.,* (2013) [51] By the Mannich reaction on 2 - [(2,4-dinitrophenyl) sulphanyl]-5(6) substituted-1H-benzimidazoles with suitable amines and paraformaldehyde in presence of con HCL and ethanol synthesized a new benzimidazole derivatives (16a-19f). The mixed blends have been evaluated for calming action and pain-relieving activity. Huge amounts of synthesized compounds were found to show incredible activity Among that, compound (18e)2-(2,4 -dinitrophenyl) sulphanyl6-methoxy-1-pyrrolidin-4-yl methyl -1H - benzimidazole was viewed as more strong pain relieving than standard drug pentazocine.

Goekce M *et al.,* (2005) [52] Novel pyridazinone derivatives were synthesized and screened for anti-inflammatory activity and pain relieving activity. The structures of these new pyridazinone were confirmed by their1H-NMRand IR spectra and simple examination. Among the blends (IVe)2 - [4 -(4-fluorophenyl) -1-piperazinyl] methyl] -6- (4-methoxyphenyl)-3(2H) pyridazinone was viewed as a most reassuring mitigating movement and pain-relieving action. Lohitha P *et al.,* (2011) [53] Synthesized hydrazones of indole by rewarding indole-3-carbaldehyde with hydrazine hydrate. Furthermore, the organized assistants were treated with different aldehydes of Schiffs bases and different amines of Mannich bases in the nearness of formaldehyde and dimethylformamide. The planned mixes were depicted by MASS, FT-IR, and 1H NMR spectra. Schiff's bases of indole derivates were exhibited commendable antifungal and antibacterial activity; jointly, Mannich bases of indole assistants were researched for calming movement and pain-relieving action. It has been announced that the recently blended Mannichbases like B3, B6, and B7 with electron attracting groups like, chloronitro, displays better calming and pain-relieving movement.

Malinka W *et al.,* (2005) [54] Synthesized the series of 4-aryl piperazine assistants of Mannich base **Fig. 9** and their non-4-aryl piperazine analogs (3 and 4). The synthesized compounds were analyzed for their analgesic action. In the arrangement of 4-arylpiperazine subordinate an electron attracting substituent moiety produces a more significant pain relieving impact than their unsubstituted precursors (compare 4e and 4f). The introduction of second electron attracting substituent (EWG) doesn't cause an increase in activity (compare 4a and 4c).

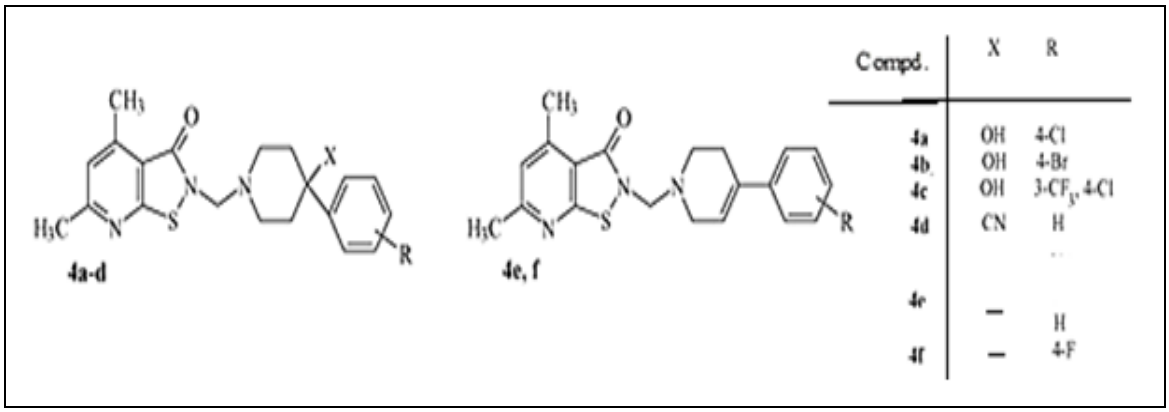


FIG. 9: 4-ARYLPIPERIDINE (4A–F) ANALOGUES

Chakkaravarthi K *et al.,* (2013) [55] 1-(1H-benzo(d)imidazole-1-yl)methyl urea (BIUF) and 1-(3-hydroxynaphthalen-2-yl) methyl thiourea (TNTUF)(Fig10) were synthesized and depicted by 13C NMR,1H NMR, UV-Vis, FT-IR, MASS and Elemental assessment. The synthesized compounds were shown better antimicrobial and anti-oxidant activity. The combined Mannich base compound BIUF shows up better antimicrobial and antioxidant activity than TNTUF due to the presence of two N atoms, and heteroatoms combined with an amide group.

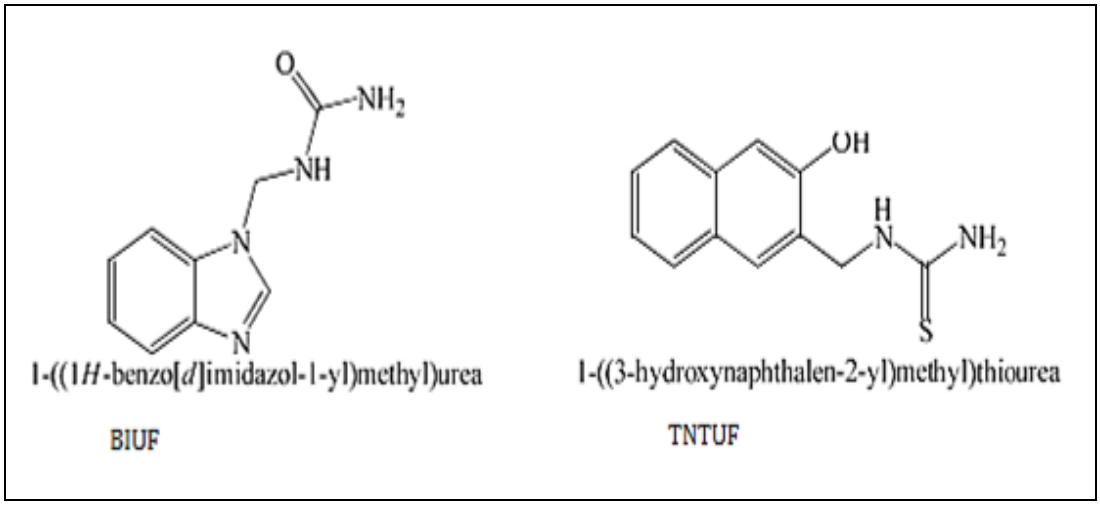


FIG. 10: BIUF AND TNTUF

Jagadish PC *et al.,* (2013) [56] Microwave-assisted Mannich base of pyrazoline derivatives 3(a–e) **Fig. 11** were synthesized and depicted by NMR, UV, Mass, IR spectroscopy. The results were excellent in microwave-assisted procedure over old-style warming one. All the blends were found in consistency with Lipinski rule of five, and the mixture contains para hydroxy substitution (3e) exhibited the best anti-oxidant activity.

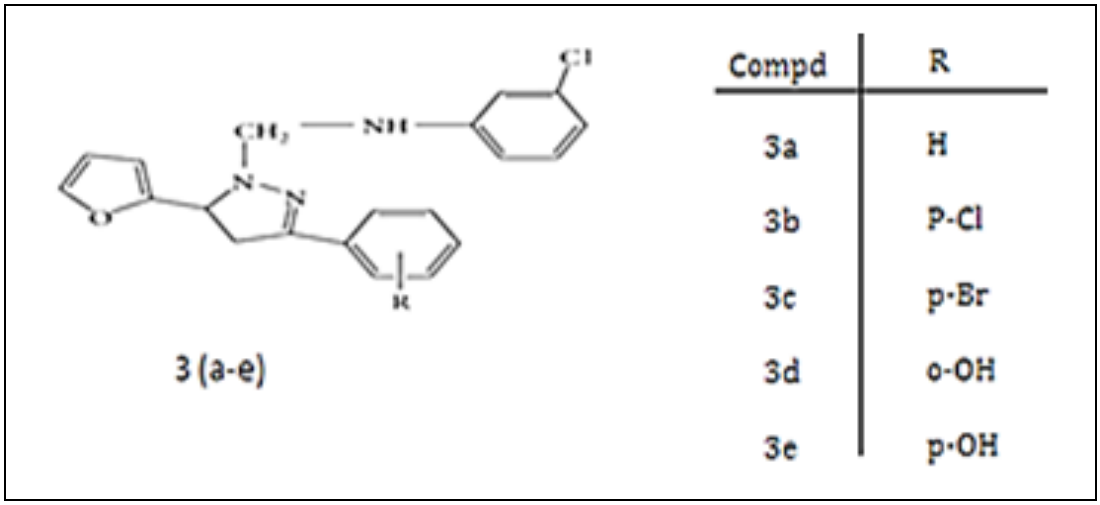


FIG. 11: 5-FURAN-2-YL-3-ARYL-1-[(3-CHLORO-PHENYL) METHYL AMINO]-2-PYRAZOLINE& DERIVATIVES

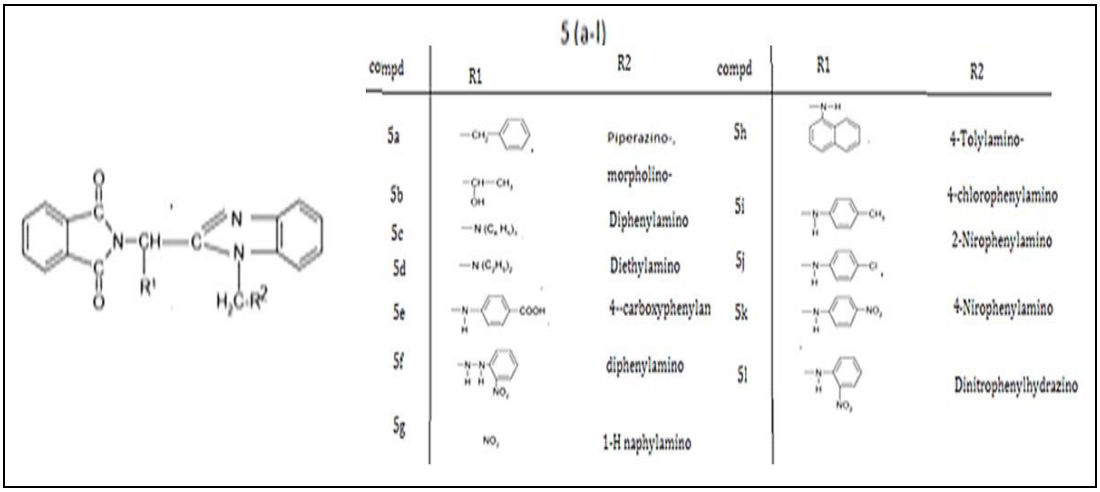


FIG. 12: BENZIMIDAZOLYL SUBBED 1H-ISOINDOLE-1,3(2H) DIONE& DERIVATIVES

2.4 Anthelmintic Activities: Bamnela RI *et al.*, (2012) [57] Benzimidazolyl substituted isoindole derivatives 5(a-i) with different amines and methanol **Fig. 12**. have been synthesized and evaluated for their anthelmintic, insecticidal, and antimicrobial activities against microorganism and compared with standard medication. All the incorporated N-Mannich bases have appreciable anthelmintic, insecticidal, and antimicrobial activity.

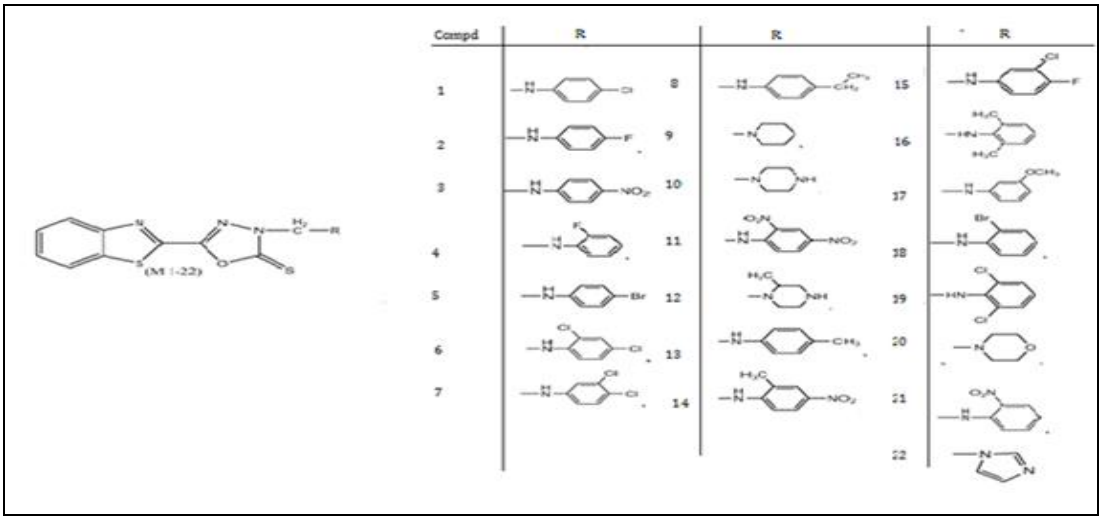


FIG. 13: NEW BENZOTHIAZOLE CLUBBED OXADIAZOLE-MANNICH BASE DERIVATIVES.

2.5 Anti-diabetic Activity: Bhutani R *et al.*, (2018) [58] Orchestrated new benzothiazole clubbed oxadiazole-Mannich bases (M-1to M-22) **Fig. 13** and confirmed the structure by, NMR, Mass, IR and Elemental assessment. Among the joined blends, nine blends were picked dependent on docking score and surveyed for their in vivo of diabetic activity using an Oral glucose tolerance test (OGTT). Results exhibited that compound M-14 demonstrated the most decline of blood glucose level identical to that of the standard drug glibenclamide.

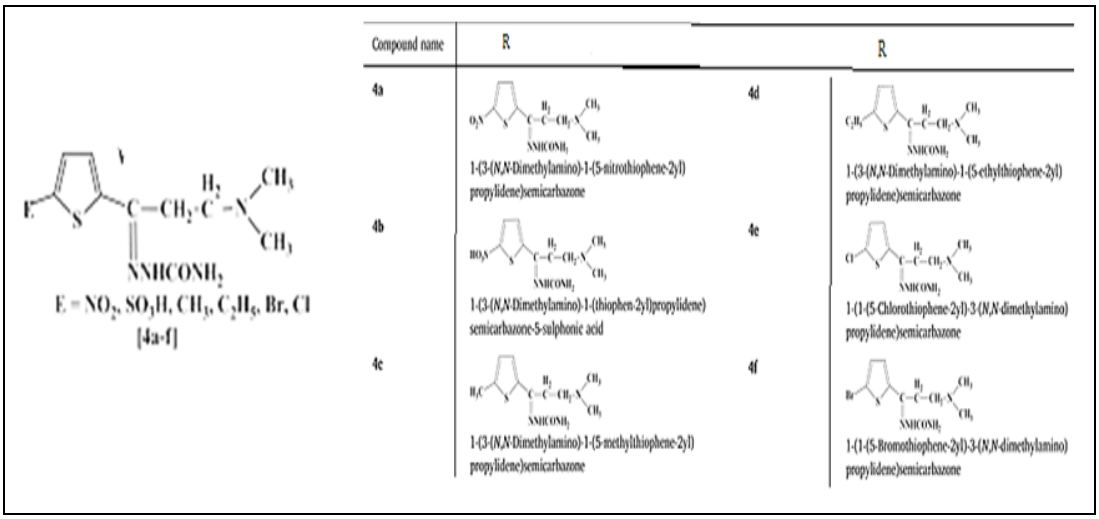


FIG. 14: 1-(3 -(N, N-DIMETHYL AMINO)-1-(5-SUBSTITUTED THIOPHENE-2-YL) PROPYLIDENE & DERIVATIVES

Gopi C *et al.*, (2018) [59] By using N,N-dimethyl amine hydrochloride, semicarbazide, 1-(thiophen 2-yl) ethanone and formaldehyde synthesized a novel 1-(3 -(N, N-dimethyl amino)-1-(5-substituted thiophene-2-yl) propylidene semicarbazone derivatives **Fig. 14**. The prepared analogs were portrayed by 1H NMR, 13C NMR, FT-IR, Mass spectroscopy and it has been evaluated for anti-diabetic and anti-inflammatory activity.

The result reveals that most of the blends were basically reduced in the blood glucose level and irritation of paw volume when comparative evaluations done with standard drug.

2.6 Carbonic Anhydrase Inhibitory: Gul HI *et al.,* (2016) [60] By using starting material as 4-(1H-benzimidazol -2-yl) phenolnew phenolic mono and bis Mannich bases benzimidazole 2-(aminomethyl)-4-(1H-benzimidazol-2-yl)phenol and 2,6-bis (aminomethyl) -4- (1H-benzimidazol -2-yl) phenol **Fig. 15** were synthesized. Amines utilized for the affiliation included pyrrolidine, dimethylamine, N-methyl piperazine, morpholine and piperidine. These novel blends show moderate CA inhibitory properties, which was tested with the human carbonic anhydrase.

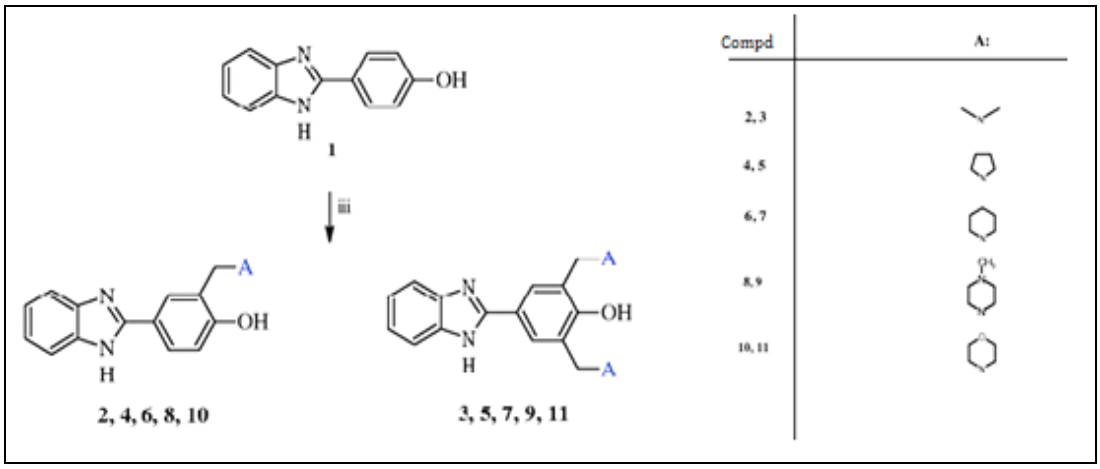
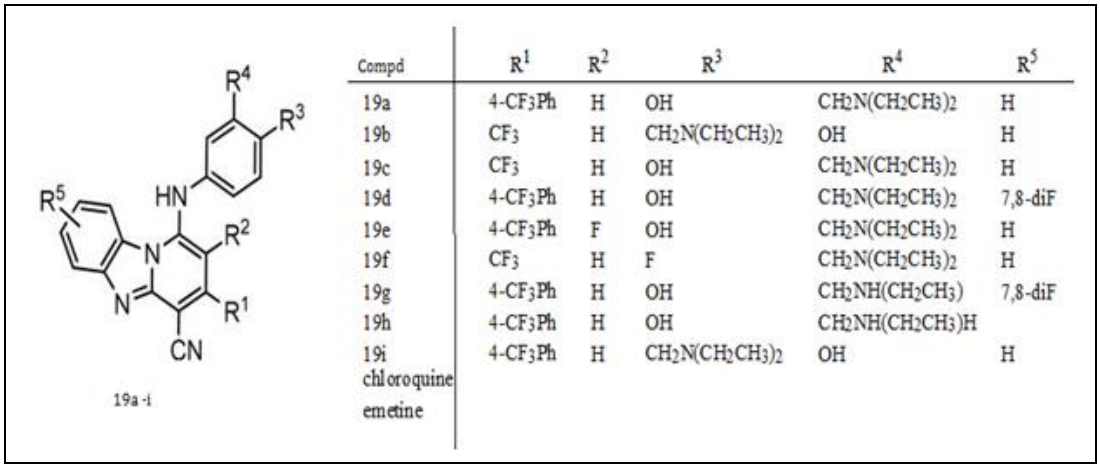


FIG. 15: MONO AND BIS MANNICH BASES OF BENZIMIDAZOLE DERIVATIVES

2.7 Antimalarial activity: Barlin GB *et al.,* (1992) [61] Di-Mannich base (4 and 5) and mono-Mannich base (6)s ubsidiaries have been synthesized and examined for their activity against the chloroquine – sensitivity. All the 7 di Mannich base subsidiaries of (5) uncovered a higher dynamic than chloroquine, while the di-Mannich base subordinates (4) had been marginally less dynamic. The mono-Mannich base subsidiaries (6) were less lively than chloroquine.

Okombo J *et al.,* (2019) [62] Integrated a novel pyrido (1,2-a) benzimidazoles **Fig. 16** bearing Mannich base side chains and their metabolitieswere consolidated and evaluated for *in-vitro* microsomal metabolic sufficiency, antiplasmodium activity, open metabolite (RM) improvement, and *in-vivo* antimalarial in a mouse model. The *in-vivo* adequacy of these subordinates is likely a result of their dynamic metabolites, two of which demonstrated extreme in vitro anti-plasmodium activity.RM (rapid metabolism) getting examinations recognized glutathione adducts just subordinates bearing 4-aminophenol moiety. As with AQ(amodiaquine), exchanging the spot of 4-hydroxy and Mannich base side or substituting the 4-hydroxy with fluorine atom seems to block bioactivation of the AQ-like auxiliaries anyway to the disservice of anti-plasmodium activity, which was in general brought down.



Compd	R^1	R^2	R^3	R^4	R^5
19a	4-CF_3Ph	H	OH	$CH_2N(CH_2CH_3)_2$	H
19b	CF_3	H	$CH_2N(CH_2CH_3)_2$	OH	H
19c	CF_3	H	OH	$CH_2N(CH_2CH_3)_2$	H
19d	4-CF_3Ph	H	OH	$CH_2N(CH_2CH_3)_2$	7,8-diF
19e	4-CF_3Ph	F	OH	$CH_2N(CH_2CH_3)_2$	H
19f	CF_3	H	F	$CH_2N(CH_2CH_3)_2$	H
19g	4-CF_3Ph	H	OH	$CH_2NH(CH_2CH_3)$	7,8-diF
19h	4-CF_3Ph	H	OH	$CH_2NH(CH_2CH_3)H$	
19i	4-CF_3Ph	H	$CH_2N(CH_2CH_3)_2$	OH	H
chloroquine					
emetine					

FIG. 16: PYRIDO (1,2-A) BENZIMIDAZOLES DERIVATIVES

2.8 Anti-cancer Activity: Hu G *et al.*, (2012) [63] Planned to make novel anticancer fluoroquinolones from antibacterial analogs by introducing the heterocyclic ring as a bioisostere of the C-3(COOH) group. To this end, two plans of (11) S-triazole subordinates bearing functionalized side chains of Mannich bases and Schiff bases were organized and orchestrated. Structures were depicted by basic assessment and extraordinary data obtained when it is assessed with *in-vitro* antitumor activity. Blends having the free phenol bundle were particularly unique and warranted further new development.

Mistry BM *et al.*, (2017) [64] N-Mannich base of an isoquinoline alkaloid, berberine, bearing substituted benzothiazole moieties were synthesized **Fig. 17** and fused for *in-vitro* anti-oxidant activity towards (DPPH) and (ABTS) and *in-vitro* cytotoxicity by using different cell lies. Their structures have been clarified by 1H NMR, 13C NMR, and FT-IR, regular examinations (CHN). Cytotoxicity of the blends towards conventional cell lines was investigated using the (MDCK) non – dangerous development cell line.(OCH_3) functional group of (5e), (COOH) group (5c), and Cyano group (5m) analogs showed outstanding antioxidant activity.

Analogs of (5a) and (5g) show the extraordinary cytotoxicity for the HeLa cell line and 6 cyano group (5m) for the CaSki cell line.

Moreover, compounds (5a) and (5e) appeared with the tremendous cytotoxicity, and compound 5(a) were found active in both antioxidant and cytotoxicity activity.

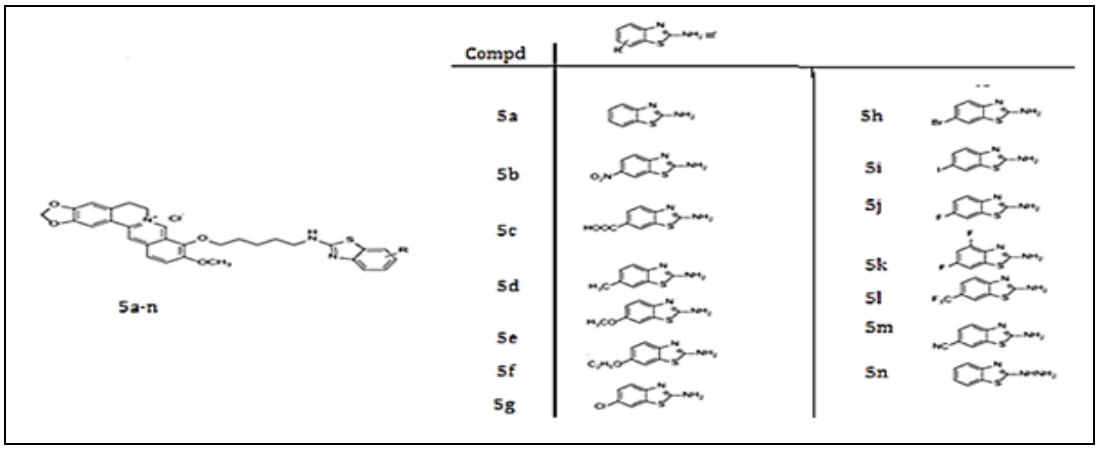


FIG. 17: ISOQUINOLINE ALKALOID, BERBERINE, BEARING SUBSTITUTED BENZOTHIAZOLE MOIETIES.

R.M *et al.*, (2011) [65] Benzothiazole derivatives were synthesized **Fig. 18** and surveyed for their anti-cancer activity. These blends demonstrated better cytotoxicity activity in HeLa, HepG2, MCF 7 cell lines.

The two promising compounds 3c and 3fwere studied in the HepG2cell line. Among that, the compound 3f of the course of action could be considered as the potential lead for its progression as a novel anticancer agent.

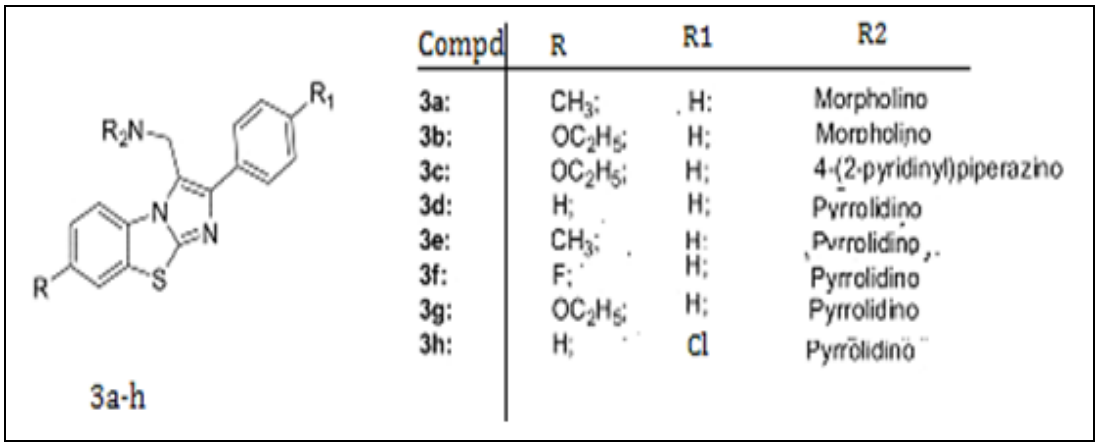


FIG. 18: 2-ARYLIMIDAZO (2,1-B) BENZOTHIAZOLE & DERIVATIVES

2.9Anticholinesterase Activity: Alpan AS *et al.,* (2017) [66] Benzimidazole subordinates **Fig. 19** having a phenolic group have been synthesized and evaluated for their antioxidant and anticholinesterase activities. By using Ellman's strategy the, acetylcholinesterase and butyrylcholinesterase inhibitory movement were studied. Compound 4b was the unique molecule on the acetylcholinesterase protein and besides specific. In like manner, the antioxidant activity was also investigated, and the results exhibit that an enormous segment of the blends had great antioxidant activity.

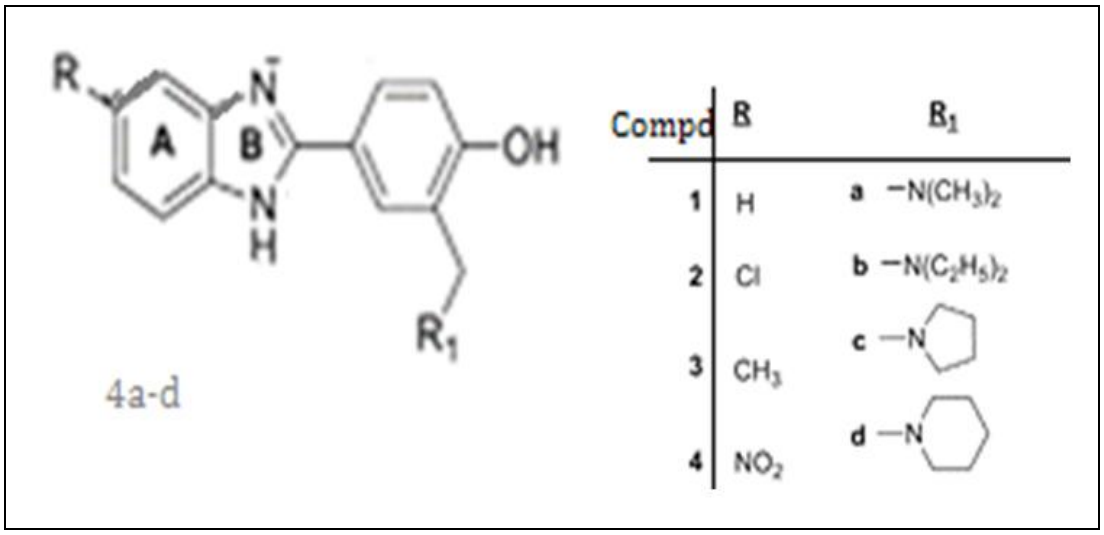


FIG. 19: BENZIMIDAZOLE SUBORDINATES

3.0 Antitubercular, Antiprotozoal, and anti-HIV Activity: Ali MA *et al.,* (2007) [67] Combined oxadiazole Mannich bases **Fig. 20** by responding dapsone, oxadiazole subsidiaries, and proper aldehyde within sight of methanol. The purity of the synthesized compounds were checked by chromatography (TLC), and confirmed the structure by 1H NMR and IR. The orchestrated mixes were assessed for their antimycobacterial activity against mycobacterium tuberculosis. Among the synthesized blends, compound (4) had great anti-tuberculosis activity.

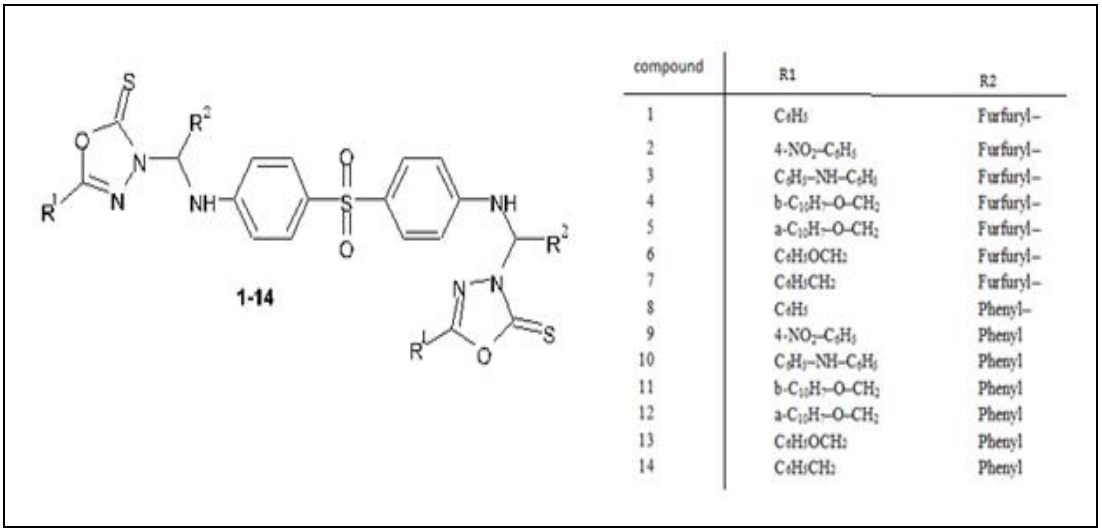


FIG. 20: OXADIAZOLE MANNICH BASES DERIVATIVES

Sriram D *et al.,* (2006) [68] . Synthezied progression of pyrazinamide (PAZ) **Fig. 21** by using formaldehyde, PAZ, and different substituted piperazines. The incorporated blends were surveyed for *in-vitro* and *in-vivo* antimycobacterial activity against Mycobacterium tuberculosis. Among the fused blends, compound (17) was viewed as the most encouraging compound.

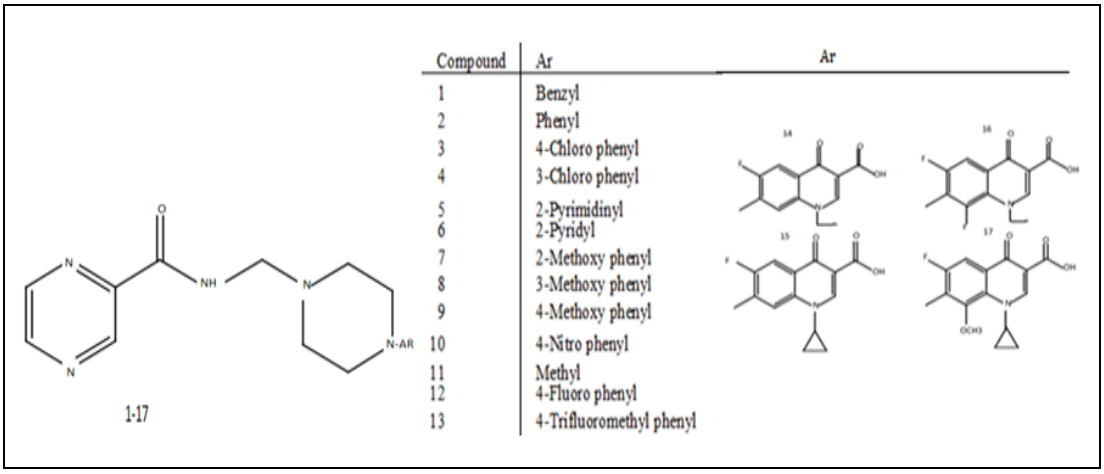


FIG. 21: PYRAZINAMIDE (PAZ)& DERIVATIVES.

Patel VM *et al.*, (2018) 69 With microwave-assisted and conventional method, 4-(4-fluorobenzylidene) amino) -5-(pyridin-4-yl) – 4H -1,2,4-triazole -3- thiol(Fig-22)were synthesized and examined for *in-vitro* antitubercular, antimicrobial and antiprotozoal action. The compound 4kwas viewed a general unique, and 4 g indicated ground-breaking, and the compound4bdemonstrated sublime power against M. tuberculosis in the fundamental screening. The computational exam revealed for that Mannich auxiliary (4b) showed a high loving towards the dynamic site of protein which gives a strong stage to new structure-based arrangements attempts.

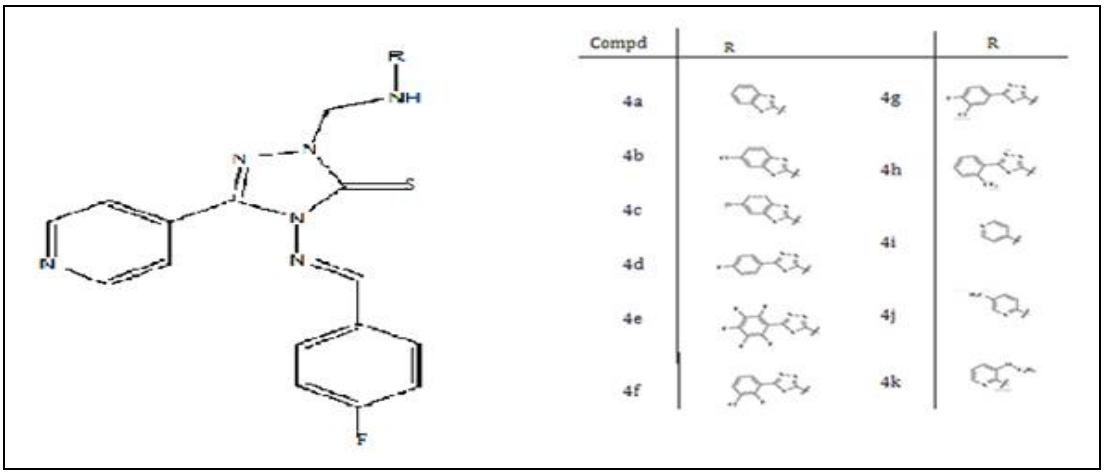


FIG. 22: 4- (4- FLUORO BENZYLIDENE) AMINO) -5- (PYRIDINE-4-YL)-4H-1,2,4-TRIAZOLE-3-THIOL &-DERIVATIVES

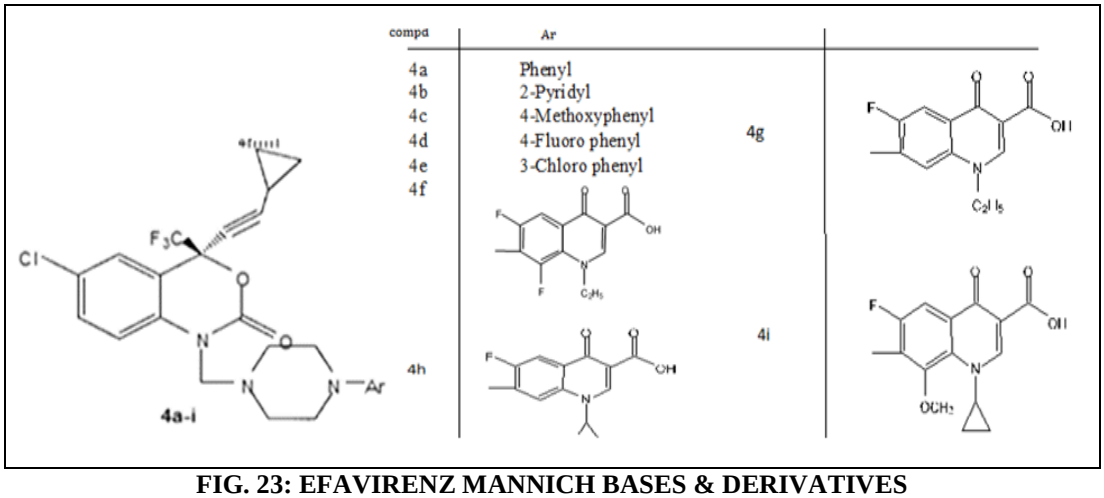


FIG. 23: EFAVIRENZ MANNICH BASES & DERIVATIVES

Sriram D *et al.,* (2009) [70]. Microwave-assisted efavirenz Mannich base derivatives **Fig. 23** has been synthesized by reacting formaldehyde, secondary amine, and aryl-substituted piperazines. The synthesized blends were evaluated for their *in-vitro* against HIV and antimycobacterial action. Among that, compounds having fluroquinolone moiety were found to be challenging and (4i) limited to *M. tuberculosis* with the least inhibitory concentration.

RESULTS AND DISCUSSION: As validated through the body of work reviewed in this paper, Mannich bases and their subordinates in heterocyclic compounds have amazing biological activities. This review shall give researchers access and detailed understanding on various application of Mannich bases a novel heterocyclic subsidiary into diverse areas for new process or application. This review provides an overview of Mannich base subordinates of heterocyclic compounds and highlights their different biological properties.

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