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ANTIMICROBIAL ACTIVITY OF MANNICH BASES OF 1H-INDOLE-2, 3-DIONE: A REVIEW

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ABSTRACT

Resistance in pathogenic microbes is natural problem and it always provoke the researcher to develop more clinically important chemical moiety. Various Mannich bases of aromatic and heterocyclic compounds for their potent diverse microbial broad-spectrum activities have been reported. Mannich bases are results of Mannich reactions, which involve a nucleophilic addition reaction in which a condensation of active hydrogen with amines and aldehyde take place. Due to structure versatility of the 1H-indole-2, 3-dione (isatin), it always attracts the researcher for the preparation of novel moiety with different substitution at position 5 and imine formation with condensation with 3-oxo group. In this brief review we focused on the Mannich bases of 1H-indole-2, 3-dione with antibacterial and antifungal activity.

KEYWORDS: 1H-indole-2, 3-dione, Mannich base, antimicrobial activity, Mannich reaction.

INTRODUCTION

Mannish bases are the end product of Mannich reactions containing β-amino ketone group. Many heterocyclic compounds with active hydrogen(s) are capable of forming Mannich bases with amines and formaldehyde. This involves a nucleophilic addition reaction. Numbers of Mannich bases of aromatic and heterocyclic compounds are synthesized as a leading pharmacophore and active agents. They possess very potential activities like anticancer, antibacterial, antifungal, analgesic, anti-inflammatory, anticonvulsant, antiviral etc.

Number of nitrogen containing heterocyclic compounds has been synthesized with Mannich base, such as 1H-indole-2,3-dione (isatin) and isatin schiff bases reported for their versatile chemotherapeutic activities including some drugs like Methisazoe, sunitinib, semaxanib.[1,2]

Intensive research has done by various modifications on 1H-indole-2, 3-dione moiety, especially at position N-1 with N-alkyl, aryl, acyl, alkylamino, C-3 with imine, hydrazone, spiro, metal complex and C-5 with halogens render the many biological important isatin molecules.[3]

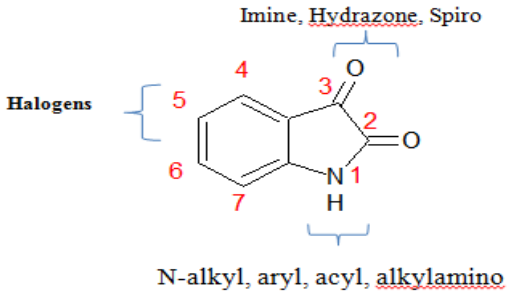


Fig. 1: Structure of 1H-indole-2,3-dione.

Antimicrobial activity of mannich bases of isatin

Mirjana Kupinic *et al*[4] tested the series of N-Mannich bases of isatin and 5-nitroisatin against the 21 pathogenic gram negative and positive bacteria. Various Mannich bases were prepared by using morpholine, piperidine, and substituted diethylamines of different hydrazones (acethydrazide, methylhydrazide and thiosemicarbazide) containing isatins (Fig 2). Both isatin and 5-nitroisatin Mannich bases were found more effective against the most of the strains gram negative bacteria and moderately effective for gram positive bacteria.

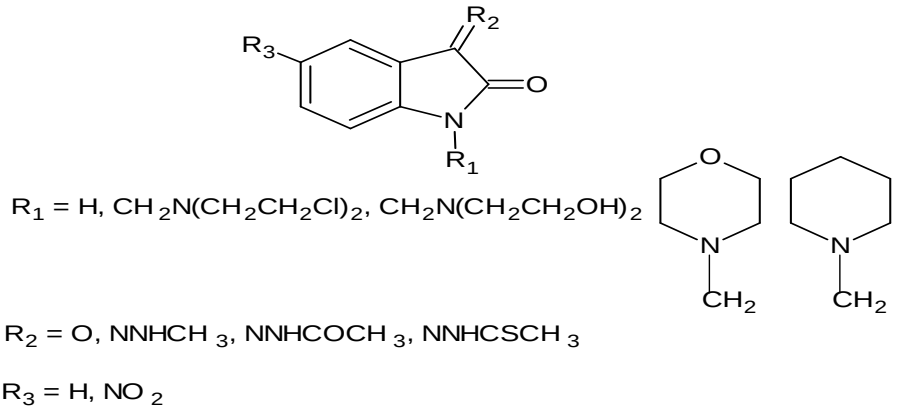


Fig. 2.

Roy W. Daisley and Vasanti K. Shah[5] prepared a series of 5-nitro-3-phenyliminoindol-2(3H)-one and their N-Mannich base analogues with 1-piperidinomethyl (Fig 3). Synthesized compounds were investigated for their antibacterial activity against *E. Coli* as Gram negative and *Staphylococcus aureus*, and *Candida albicans* as Gram positive bacteria using the cup plate method. Effective inhibition of Gram-positive bacteria was observed in Mannich bases than 3-phenylimino compounds, while little or no activity against Gram negative bacteria.

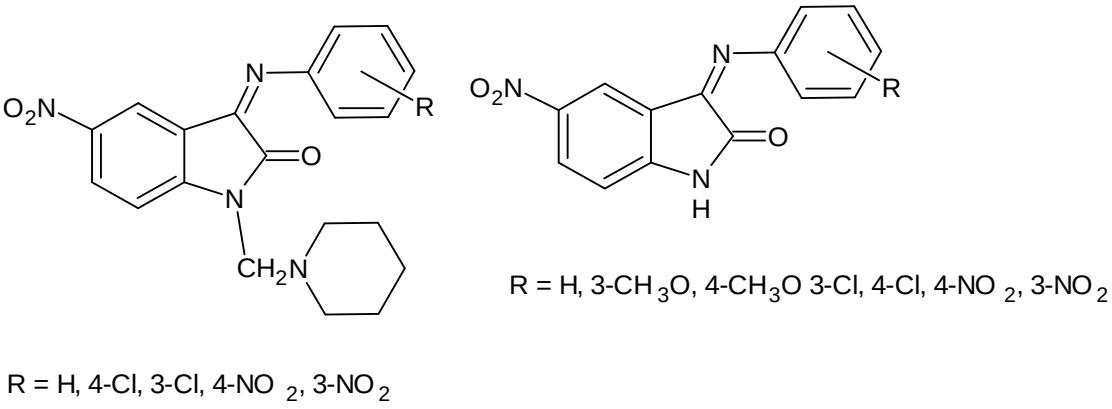


Fig. 3.

Shahina Ali and Mahbub Alam[6] synthesized isatinazine and its Mannich bases were synthesized by mixing the isatinazine, formaldehyde, dimethylformamide along with morpholine or by Isatin-3-hydrazone, 1-morpholinomethyl isatin (Fig 4). Compounds of Mannich bases produced a broad-spectrum antibacterial activity in comparison N-Chloroacetyl isatin, Isatin-3-isonicotinylhydrazone and its 1-acetyl derivative.

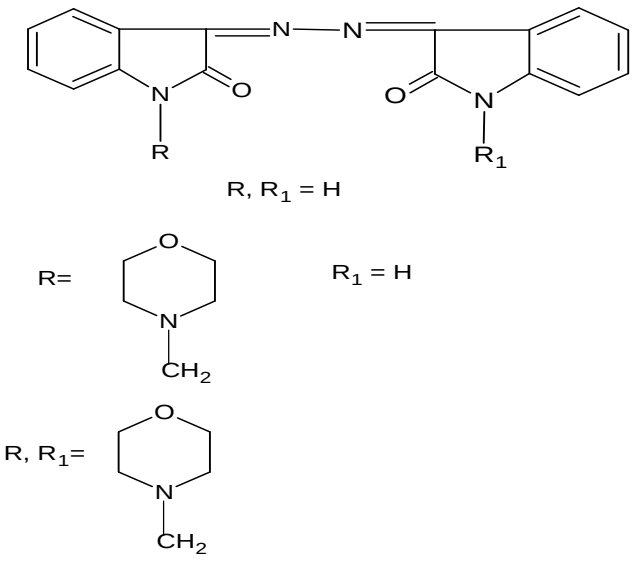


Fig. 4.

S. N. Pandeya *et al*[7] evaluated the antibacterial activity of Mannich bases which was prepared by condensing the isatin with piperazino moiety of ciprofloxacin and lomefloaxacin (Fig 5). It was found that Mannich bases have more or the same antibacterial activity.

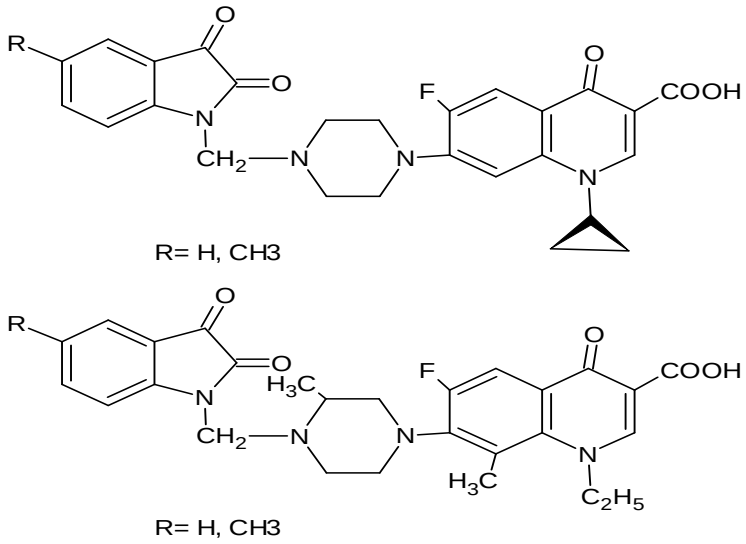


Fig. 5.

S. N. Pandeya *et al*[8] synthesized a series of N-Mannich bases with isatin Schiff bases of trimethoprime (Fig 6). By using agar plate method prepared compounds were screened for antibacterial activity. Most compounds showed antibacterial activity against the *vibrio cholerae* non-O_1, *shigella boydii*, *Enterococcus faecalis* and *Edwardiella tarda* with MIC of 10-15 µg/ml. While some are found active against *Salmonela typhi* and *vibrio cholerae* O_1 with the MIC of 130-160 µg/ml and of 75-150 µg/ml respectively.

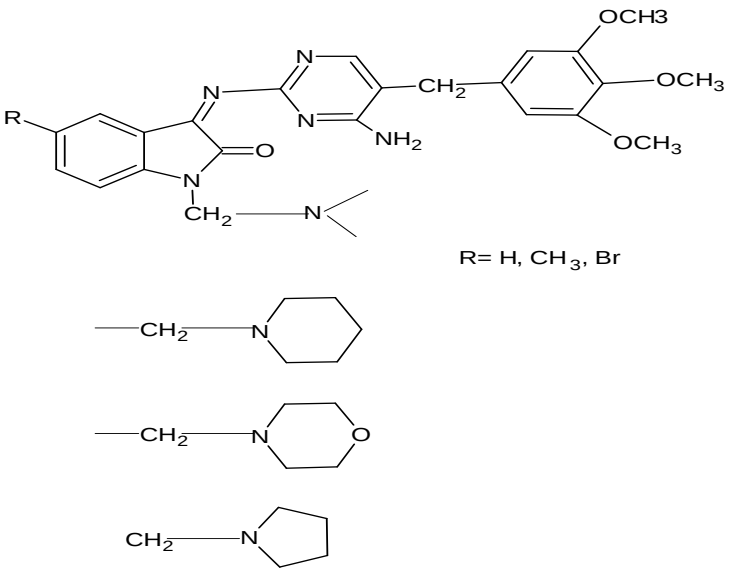


Fig. 6.

S. N. Pandeya *et al*[9] new Mannich base were synthesized by condensing the N-(6-chloro benzothiazol-2-yl) thiosemicarbazide containing Schiff base of isatin with formaldehyde and some aliphatic and heterocyclic secondary amines (Fig 7). All synthesized compounds were tested for antibacterial and antifungal activity. 25 different pathogenic bacteria were used for antibacterial activity of synthesized compounds using sulphamethoxazole and trimethoprim as reference compounds. While for antifungal activity 8 fungi were used with clotrimazole as reference. All synthesized compounds exhibited appreciable antibacterial and antifungal activity.

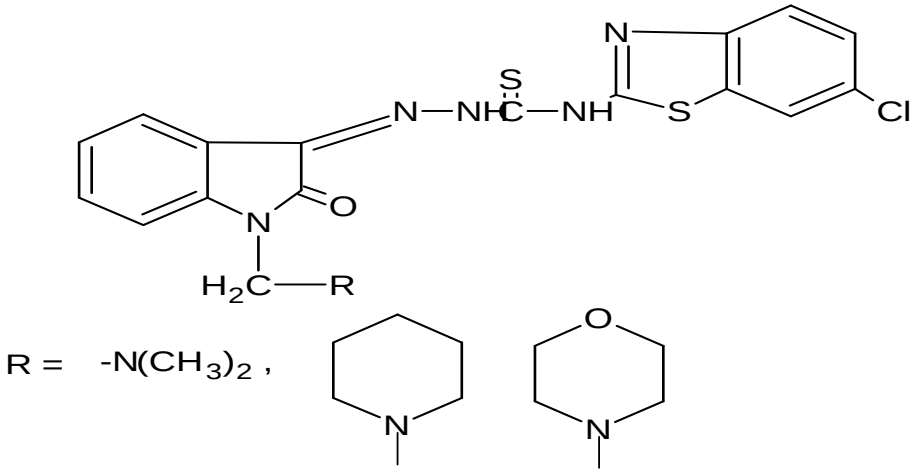


Fig. 7.

S. N. Pandeya *et al*[10] several N-Mannich bases were synthesized by reacting 3-amino-2-methylmercapto quinazolin-4 (3 H)-one containing Schiff bases of 5 substituted istain (Fig 8). All prepared compounds were investigated for in vitro antibacterial and antifungal using 26 and 8 pathogenic bacteria and fungi respectively. Results showed that Mannich bases more effective than their corresponding schiff bases with less MIC values.

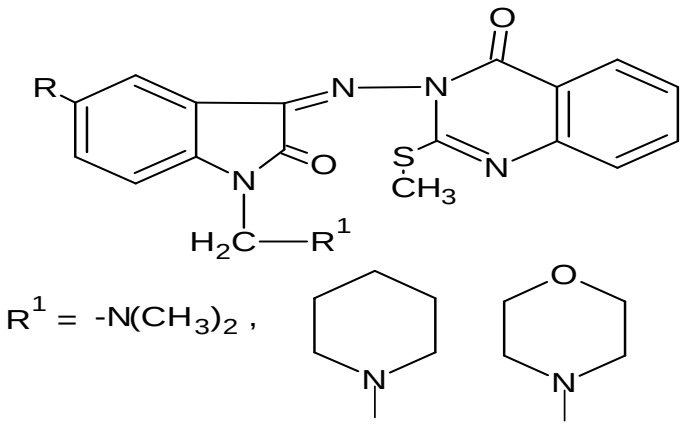


Fig. 8.

Surendra N. Pandeya *et al*[11] 5-substituted isaitn schiff bases was prepared with 3-(4'-pyridyl)-4-amino-5-mercapto-4-(H)-1,2,4-triazole and their N-Mannich bases were prepared by treating them with some secondary amines (Fig 9). Synthesized N-Mannich bases were investigated for antimicrobial activity by using pathogenic 27 bacteria and 8 fungi. When compared with sulphamethoxazole all prepared compounds showed better activity against tested pathogenic microorganism except P. aeruginosa**.** By comparing all synthesized compounds with trimethoprim, then it was exhibited that all the compounds were effective against *S. typhimurium, S. aureus, P. aeruginosa, K. pneumoniae, Aeromonas hydrophile, V. cholerae-01, B. subtilis, P. rettgeri* while 4 compounds showed activity against *Edwardsiella tarda, Enterococcus faecalis*. In comparison with norfloxacin all exhibited more action against S. aureus. In antifungal activity all synthesized compounds showed reasonable activity against all tested fungi. Amongst all compound 1-(Piperidinomethyl)-5-bromo-3-[3'-(4''-pyri-dyl)-5'-mercapto-4'-(H)1',2',4'-triazol4'-yl]- imino-isatin and 1-(morpholinomethyl)-3-(3'-(4''-pyridyl)-5'-mercapto-4'-(H)-1'-2'-4'-triazol-4'-yl] imino isatin showed most favorable anti-bacterial activity and antifungal activity respectively.

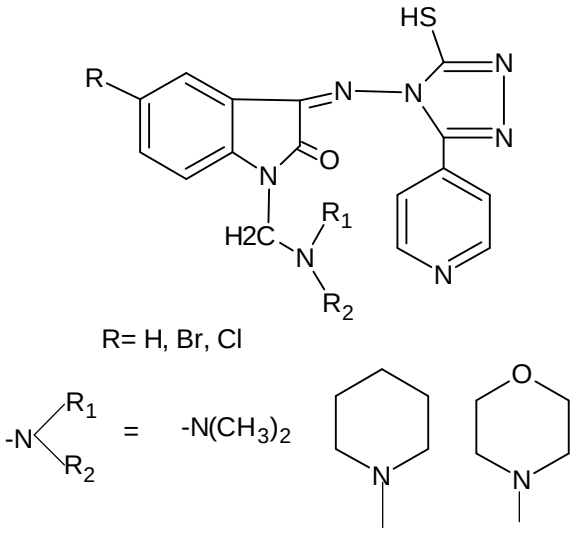


Fig. 9.

Seshaiah Krishnan Sridhara *et al*[12] When aromatic primary amines/hydrazines were reacting with isatin and substituted isatin forming the corresponding Schiff bases and hydarzones. From these relative N-Mannich bases was prepared by diphenylamine (Fig 10). Antimicrobial activity was screened for the seven different pathogenic Gram +ve and Gram -ve bacterial strains. Results showed that compounds containing phenyl hydrazino or substituted phenyl

hydrazino have little or no activity. 4-bromo phenyl substituted compounds found most active against the Gram +ve and Gram -ve bacteria.

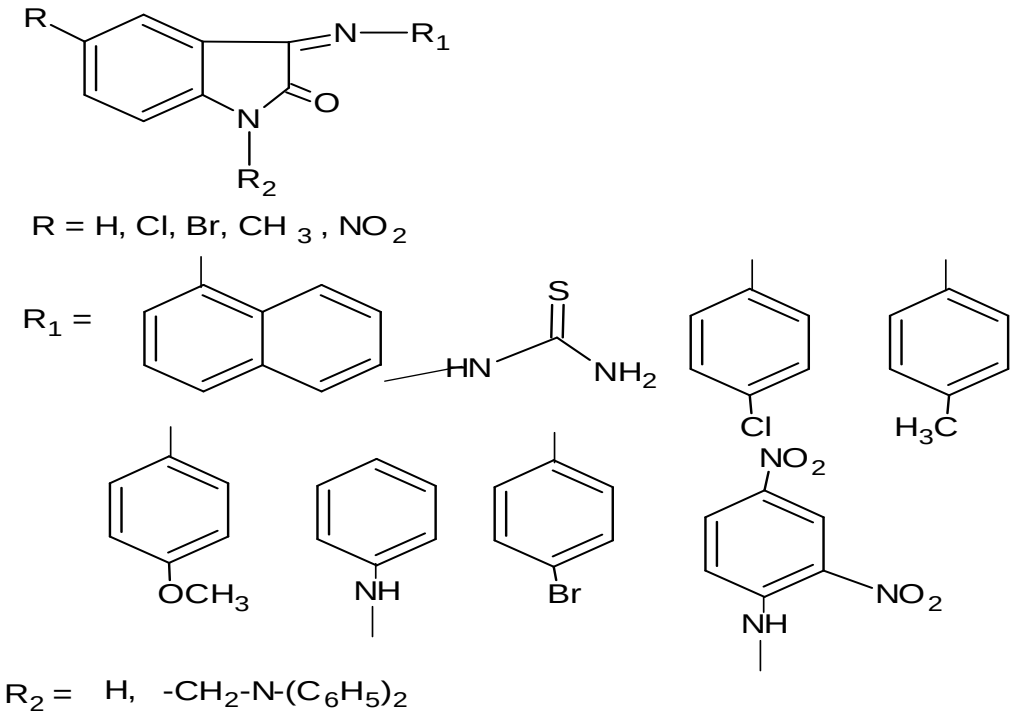


Fig. 10.

Surendra N. Pandeya *et al*[13] New series of N-Mannich bases were prepared from the Pyrimethamine containing schiff bases of isatin (Fig 11). Prepared compounds were confirmed by various analytical techniques and evaluated for the antibacterial and antifungal activity against some pathogenic bacteria and fungi. All prepared N-Mannich bases were found more potent than pyrimethamine.

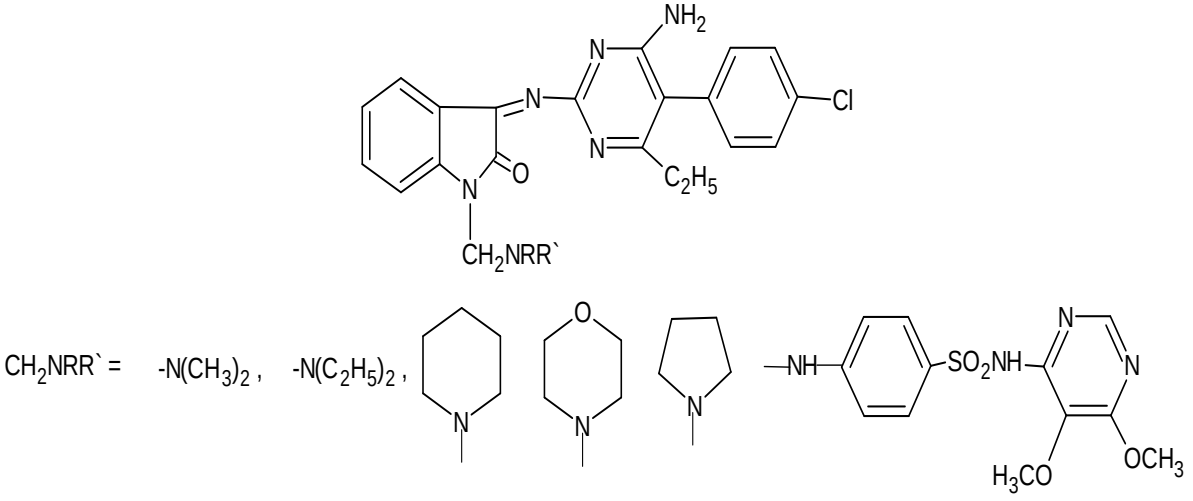
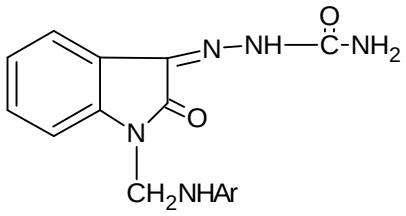


Fig. 11.

S.A. Khan *et al*[14] synthesized the new series of N-Mannich bases by reacting to the 3-semicarbazino isatin with different aromatic amines (Fig 12). Synthesized compounds were tested for antimicrobial activity against the S. aureus, E. coli and C. albicans with amikacin and fluconazole as reference standards. Results showed that p-ethoxyphenyl, p-fluorophenyl and pyridine-3`-yl derivative possess significant effectiveness against *S. aureus* and *C. albicans* while p-ethoxyphenyl, p-chlorophenyl, p-bromophenyl and pyridine-4`-yl containing compounds exhibit good activity against *E. coli.*



Ar = 4`-ethoxyphenyl, 4`-chlorophenyl,4`-bromophenyl, 4`-fluorophenyl, 4`-nitrophenyl

3`-methoxyphenyl, pyridine-4`-yl, pyridine-3`-yl

Fig. 12.

B. N. Singh *et al*[15] N-Mannich bases of sulphadiazinyl schiff base of isatin was prepared with aliphatic and aromatic amines (Fig 13). Antibacterial and antifungal activity was screened and found that most compounds exhibit the antibacterial activity but except piperidine containing Mannich base none of the compounds showed antifungal activity.

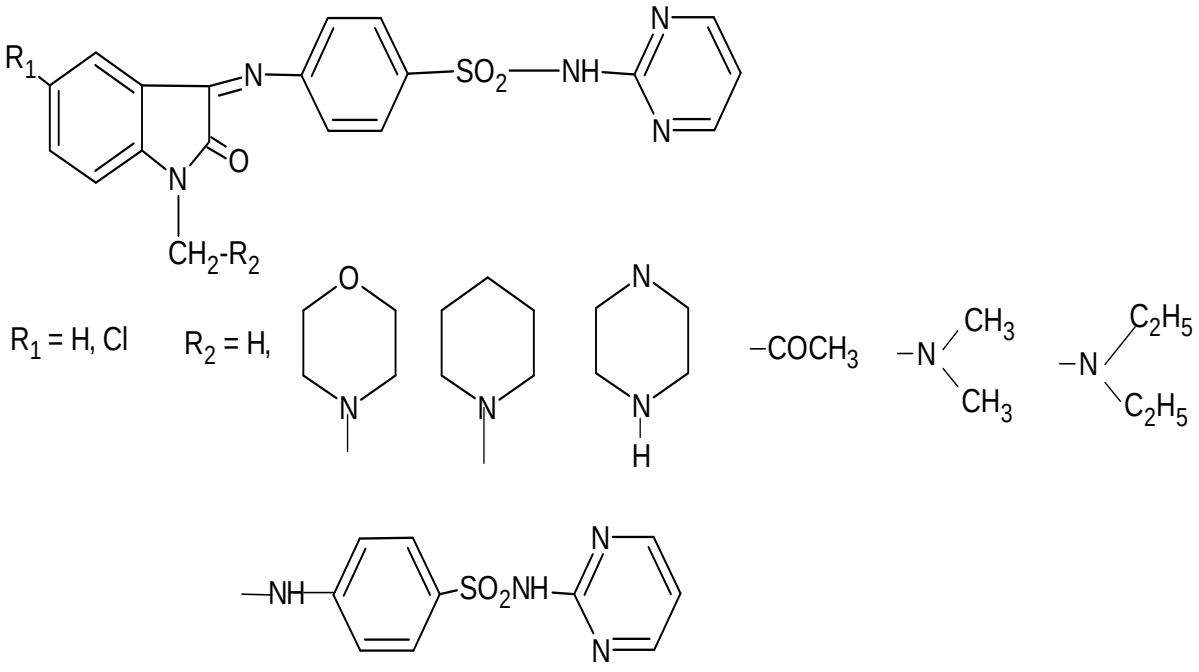


Fig. 13.

V. Ravichandran *et al*[16] prepared the N Mannich base of various aromatic primary amines like 4-chloroaniline, sulfanilamide, 4-amino benzoic acid, 2-amino benzoic acid and phenyl hydrazine containing the schiff base of isatin by condensing the 2-[(2,6-dichlorophenyl)amino]phenylacetic acid (Fig 14). Synthesized compounds were tested for *in vitro* antimicrobial activity against the bacterial strains like *P. aeruginosa* (NCIM 2200), S. aureus (NCIM 2079), *E. coli* (NCIM 2065), *B. subtilis* (NCIM 2063), *B. cereus* (NCIM 2155) and *K. aeruginosa* (NCIM 2239) and fungus strains *C. albicans* (NCIM 3102) and *P. notatum* (NCIM 742). All compounds found average active against previous microbes probably because of the bulky phenyl acetic acid group present at nitrogen atoms in molecules, which may have hindered the compounds for binding to bacterial cells.

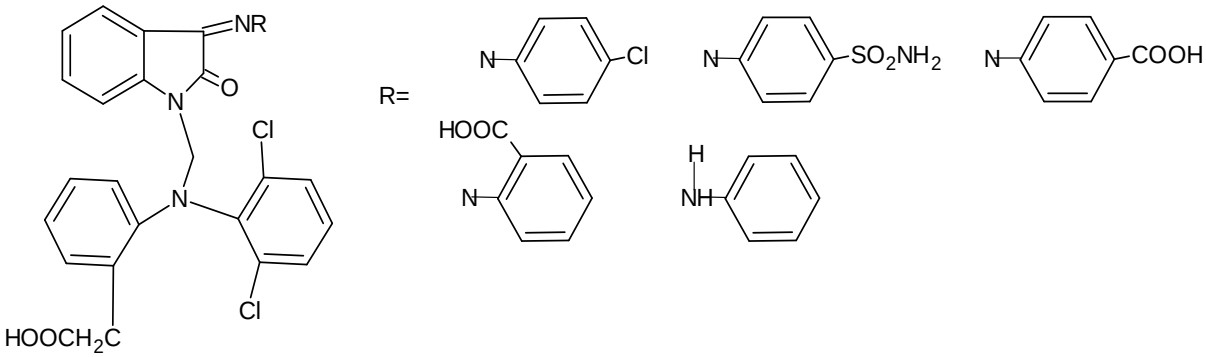


Fig. 14.

V. Vaidhyalingam *et al*[17] prepared a new series of Mannich bases by treating aliphatic and heterocyclic secondary amines with schiff base of pyridine -2-yl)thiosemicarbazide and 5-bromoisatin (Fig 15). These compounds were tested for their antibacterial and antifungal activity against some pathogenic microbes using ciprofloxacin and ketoconazole as reference standards. All compounds showed remarkable action against these bacteria and fungus.

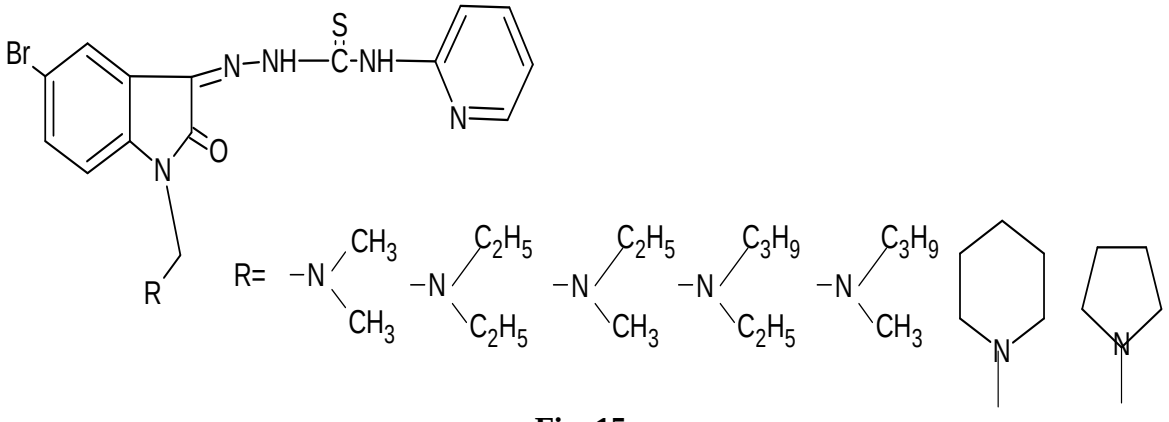


Fig. 15.

S. K. Sahu *et al*,[18] synthesized Mannich bases by using secondary amines like dimethylamine. Diethylamine, diphenylamine, morpholine and piperazine with Schiff bases of 2,3-indolinedione and 3-amino-2-methylquinazoline/6-bromo-2-methylquinazoline-4(3H)-ones (Fig 16). Resultant moieties were assayed for anti-bacterial activity against *S. aureus*, *S. faecalis*, *E. coli* and S. typhi and for antifungal activities against *C. albicans* and *A. niger* using ciprofloxacin and clotrimazole standard. 6-bromo derivative with morpholine and piperazine Mannich base showed the moderate activity against all bacteria while all compounds showed little activity against both fungi. They found that 6 bromo substitution of quinazoline ring does not have any significant effect activity.

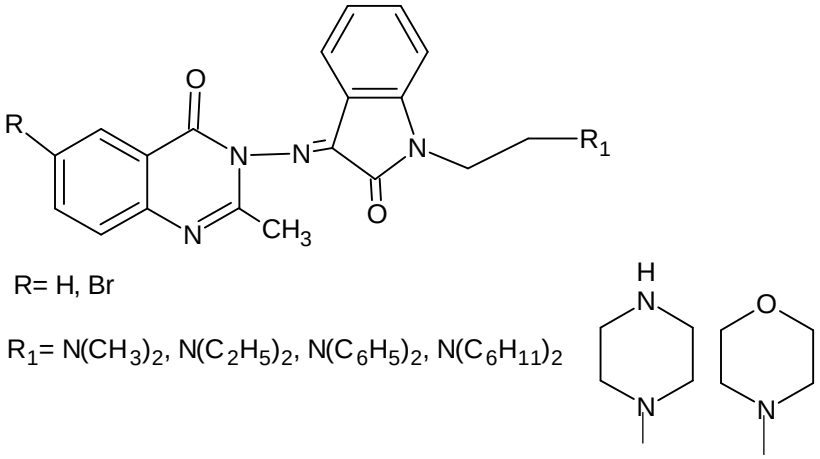


Fig. 16.

Chhajed S.S. and Padwal M. S.[19] antimicrobial activity was investigated by using agar dilution method for the new series of Mannich bases. These were synthesized by condensing various secondary amines with 5-amino, 8-Hydroxy-quinoline schiff base of isatin and chloro isatin (Fig 17). Screening results showed that all compounds have mild and moderate activity, in which piperidine and morpholine derivatives have significant action.

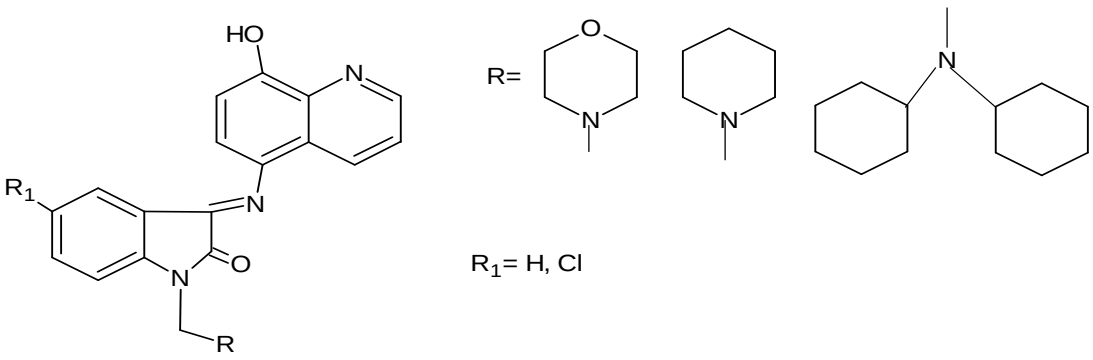
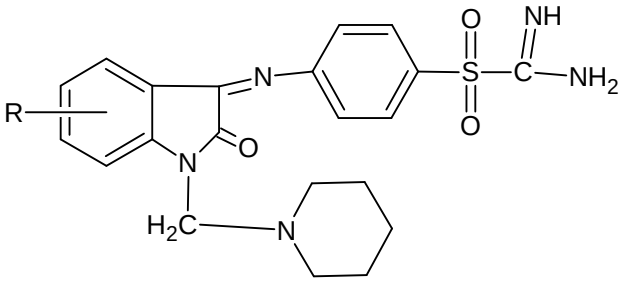


Fig. 17.

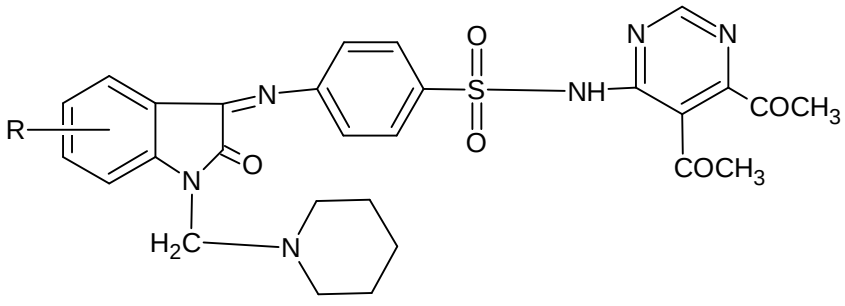
U. K. Singh *et al.*[20] 4-amino-N-carbamimidoyl benzene sulfonamide was used to prepare the schiff base of isatin and substituted isatin. Later their corresponding Mannich bases were synthesized with piperidine (Fig 18). By using tube dilution method antimicrobial activity was investigated on the Mannich bases. Results showed that all compounds have good antibacterial activity in comparison to the standard drug against both gram positive and gram-negative bacterial strains. But none of the compounds showed significant antifungal activity in comparison to standard.



R= H, Cl, Br, NO_2, CH_3

Fig. 18.

Umesh K. Singh *et al*[21] 4-amino-N-(5,6-dimethoxypyrimidin-4-yl) benzene sulfonamide was used for the preparation of schiff bases and relative Mannich bases was synthesized with the help of piperidine (Fig 19). Resulting compounds were screened for the antimicrobial activity against various strains of bacteria and fungus. All compounds showed a considerable enhancement of activity against all the bacteria but no significant activity found for any fungus strain.



R= H, Cl, Br, NO_2, CH_3

Fig. 19.

Ahlam J. Abdulghani and Nada M. Abbas[22] synthesized two new Mannich bases by condensation reaction of dithiooxamide containing schiff bases of isatin with morpholine and

diphenylamine. Metal complexes were also prepared by using these Mannich bases as ligands (Fig 20). Antimicrobial activity was done by using three types of pathogenic bacteria, *Proteus mirabilis, E. coli, and S. aureus*. The morpholine derivative showed potency against all bacteria while diphenylamine derivative showed no activity against any bacteria. However, the metal complexes of morpholine derivatives with nickel (II), palladium (II) and Iron (III) showed no activity, while the palladium (II) complex with diphenylamine derivative showed high potency.

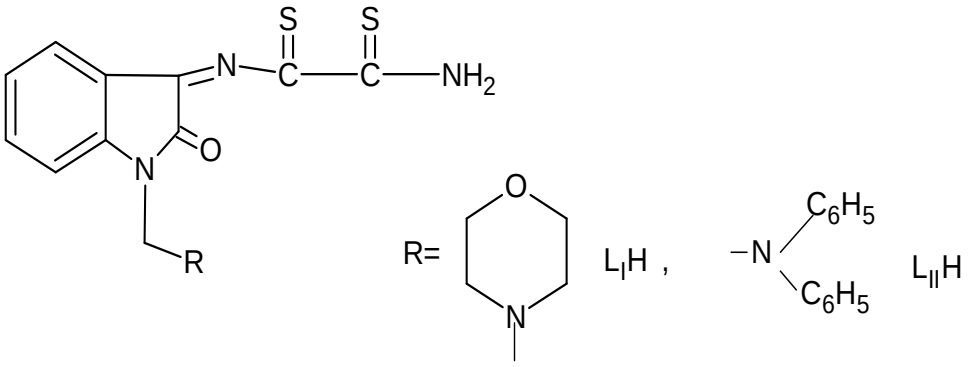


Fig. 20.

Chaluvaraju KC, Zaranappa[23] synthesized Mannich bases of some isatin derivative and screen for antimicrobial properties against *S. aureus, B. subtilis, S. typhi E.coli, A. niger* and *C. albicans*. Results showed that all have synthesized compounds have some antimicrobial activity but very less against all tested fungi (Fig 21).

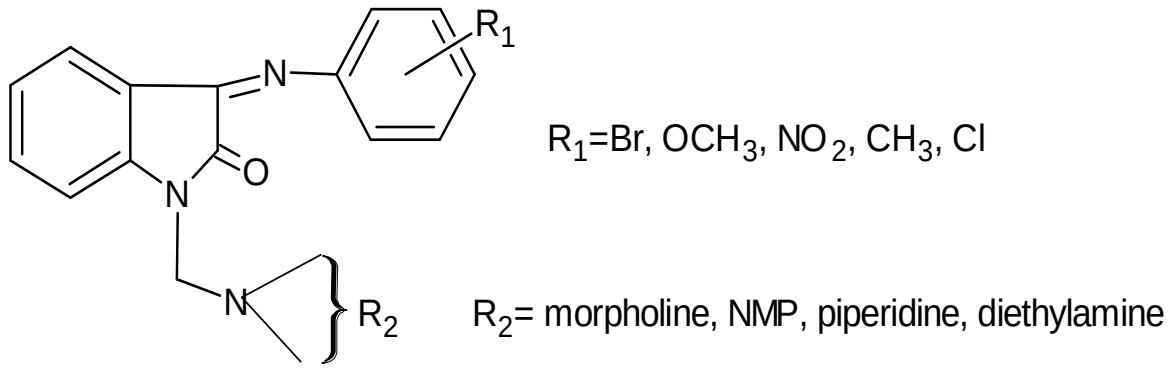


Fig. 21.

Harshita Sachdeva *et al*[24] (2012) synthesized the N-Mannich bases of 1H-indole-2,3-dione by using microwave irradiation method (Fig 22). This reaction was faster and gave good

yield as compared to conventional methods. Compounds also screen for antimicrobial activity and are found significantly effective.

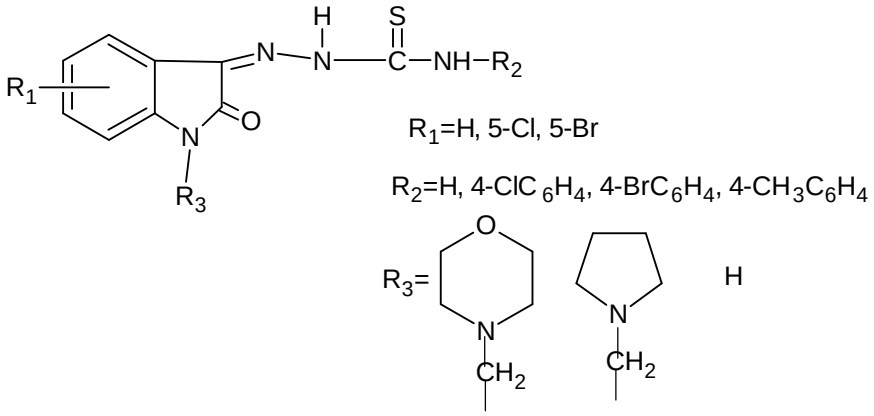


Fig. 22.

N. Saravana Kumar *et al*[25] N-Mannich bases of isatin and its derivative was prepared by reacting the dimethylamine, diethylamine, piperidine and morpholine with the Schiff base of N-{[2-oxo-1H-indol-3-ylidene] amino} pyridine-2-carboximidamide (Fig 23). Antimicrobial screening showed that piperidine containing Mannich base was more effective against *S. aureus* and *E. coli*. while dimethylamine derivative showed good activity for *C. albicans*.

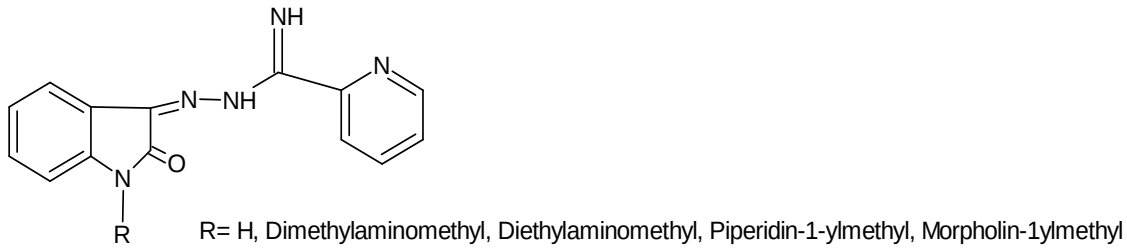


Fig. 23.

Khalaf Ahmed Jasim AL- Bayati[26] When substituted sulfonamides and secondary amines react with 1H-indole-2,3-dione in presence of formaldehyde, a new series of N-Mannich bases were synthesized (Fig 24). The *in vitro* antimicrobial activity showed that substituted sulfonamides based Mannich bases were more effective against selected microbes.

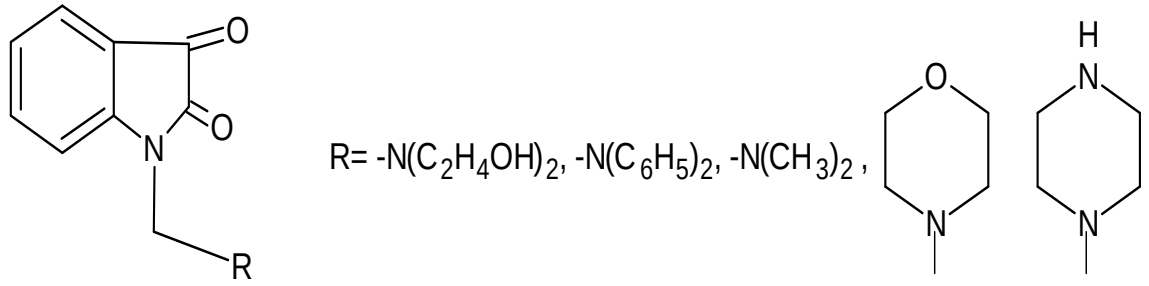


Fig. 24.

S.N. Pandeya *et al*[27] evaluated antimicrobial activity of some N Mannich bases derived from condensation of acetophenone and diethylamine with 8-amino quinoline containing schiff bases of norfloxacin and isatin respectively (Fig 25). Screening of the compounds revealed that most have moderate activity at low concentration. The compounds with Norfloxacin moiety have better activity as compared to other compounds.

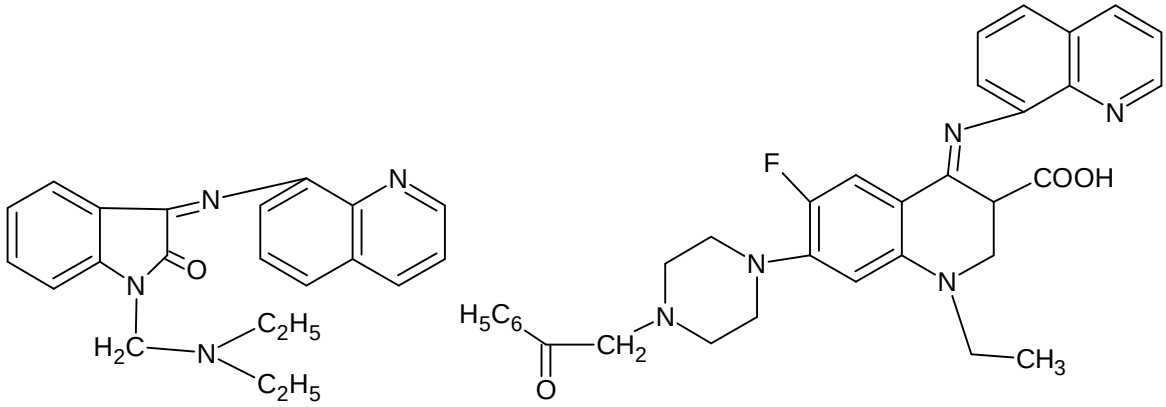


Fig. 25.

K. S. Bhavani Aiswarya *et al*[28] schiff bases of substituted 2- phenoxy-1, 3, 2-dioxa phospholanes was prepared with isain and their corresponding N-Mannich bases was prepared by reacting it with piperidine, morpholine and N-methyl piperazine along with methanal in DMF (Fig 26). Resultant compounds screened against gram positive and gram-negative bacteria. Good results were found in most of the compounds. Similarly antifungal activity tested against *Aspergillus niger* and *Helminthosporium oryzae*.

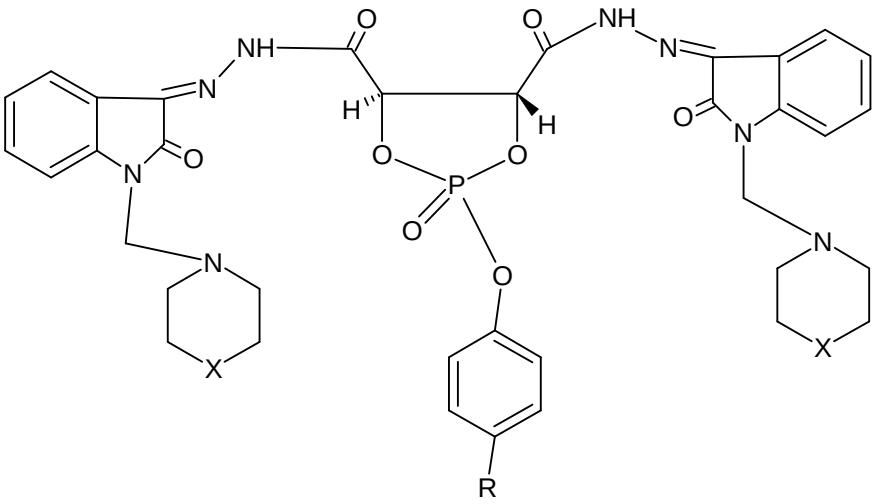


Fig. 26.

J. Panda[29] antimicrobial parameters were derived from newly synthesized N-Mannich bases of isatin. These were prepared from the reaction of schiff bases of isatin with substituted anilines and morpholine (Fig 27). Results showed that chloro and nitro substituted compounds exhibited good antibacterial activity against *P. aeruginosa, E. coli* and *P. vulgaris*.

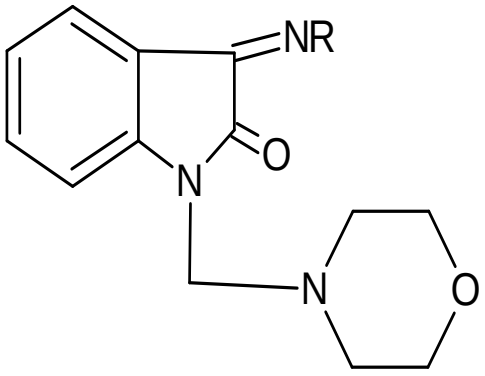


Fig. 27.

R	R
phenyl	4-bromophenyl
2-nitrophenyl	4-fluorophenyl
3-nitrophenyl	3-Cl-4-F-phenyl
4-nitrophenyl	2,6-dichlorophenyl
3-chlorophenyl	2,4-dinitrophenyl
4-chlorophenyl	3,4-dichlorophenyl

Chinnasamy Rajaram Prakash and Sundararajan Raja[30] prepared a novel series of Mannich and Schiff bases of isatin by joining Ciprofloxacin at the N1 position and substituting various aromatic aldehydes at the 3rd position (Fig 28). By using the disc diffusion technique *in-vitro* antibacterial and antifungal properties were investigated for some pathogenic microorganisms. Results showed that electron donating substituent like hydroxy, N-dimethylamino, 3,4,5-trimethoxy and 4-hydroxy-3-methoxy group on phenyl ring exhibited most effective antibacterial and antifungal activity. While electron withdrawing substituents such as nitro and chloro groups do not show significant antimicrobial activity.

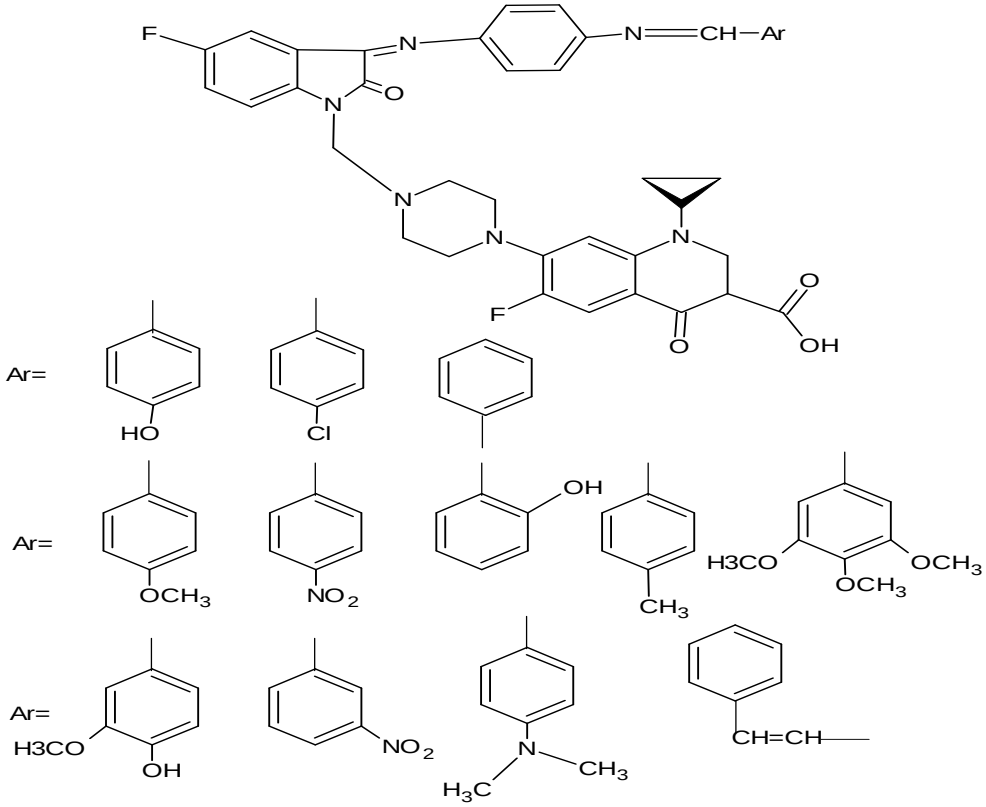
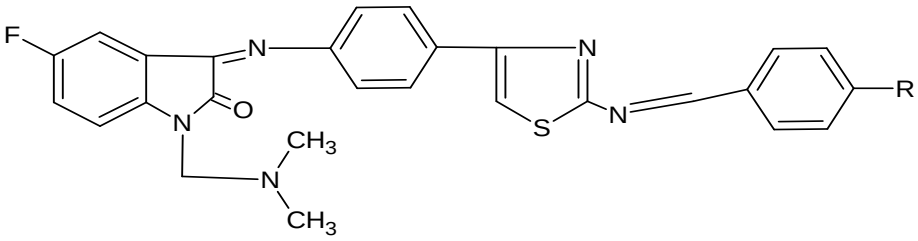


Fig. 28.

Chinnasamy Rajaram Prakash *et al*[31] a new series of Mannich bases was prepared with 3-(4-acetylphenylimino)-5-fluoroindolin-2-one and dimethylamine in formaldehyde. Acetyl moiety of above compound was converted into a thiazole ring by reacting it with thiourea and bromine. 3-(4-(2-(substituted benzylideneamino) thiazol-4-yl)phenyl imino)-1-((dimethylamino)methyl)-5-fluoroindolin-2-one compound was then final obtained by reacting it above compound with different aromatic aldehydes in ethanol (Fig 29). Resultant moiety was investigated for antimicrobial activity against Gram-positive and negative bacteria and fungus. Results showed that some compounds were found active against some

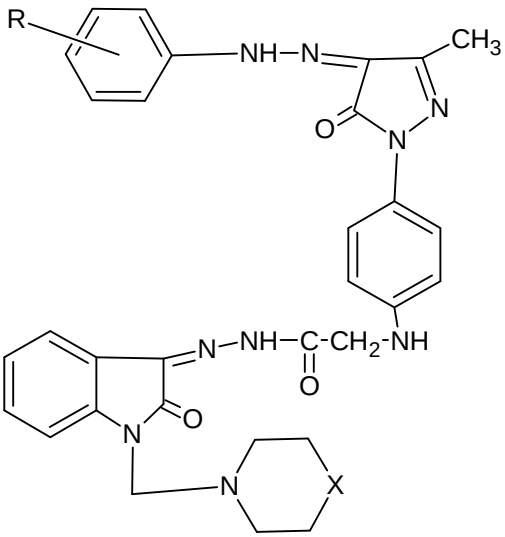
microorganism, some equipotent and while some found least effective against the selected microorganism.



R=H, 4-CH_3,4-OH, 4-$N(CH_3)_2$, 4-OCH_3, 3,4,5-$(OCH_3)_3$, 4-Cl, 2-Cl, 4-NO_2, 3-NO_2, 4-OH, 2-OH

Fig. 29.

Subba Narayana Kanchana *et al*[32] A schiff base of isatin was prepared by reacting it (4Z)-2-(4-((15Z)-4-(2-phenylhydrazono)-4,5-dihydro-3-methyl-5 oxopyrazol -1- yl)phenylamino)-N'-(2-oxoindolin-3-ylidene) acetohydrazide. The resulting compound was subjected for the preparation of Mannich bases with secondary amines (piperidine/ morpholine/N-methylpiperidine) in the presence of formaldehyde (Fig 30). Synthesized compounds were screened for antimicrobial activity and found that some compounds possess good antifungal activity.



X= CH_2, O, N-CH_3 R=H, 4`-Br, 4`-CH_3, 4`-$OCH_3$, 4`-OC_2H_5, 4`-Cl

Fig. 30.

P. Jothi Rani *et al*[33] prepared a series of schiff and Mannich bases by condensing the imesatin derivative with various aromatic aldehydes and secondary amines like piperazine respectively. Imesatin was prepared by reacting isatin with p-phenylene diamine (Fig 31).

Synthesized Mannich bases were subjected to antimicrobial activity and concluded that most compounds have average antimicrobial activity, however the 4-hydroxy and 3,4,5-trimethoxy derivatives exhibited greater activity.

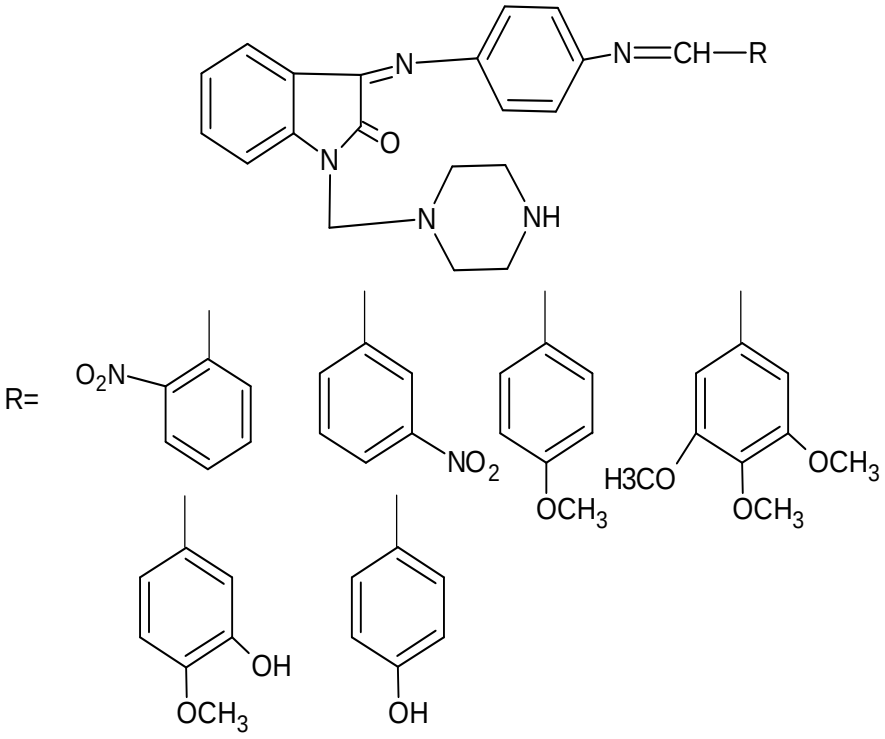


Fig. 31.

P. Sinduja, G. Sammaiah and K. Swathi[34] antimicrobial evaluation of (1-((Bis(2-chloroethyl) amino) methyl)-2-oxoindolin-3-ylidene)-2- (phenylamino) acetohydrazide was performed by cup plate method against the selected Gram positive and negative bacteria. The proposed compound was synthesized by reacting the substituted isatin with bis(2-chloroethyl) amine hydrochloride followed by its condensation with 2-(phenylamino) acetohydrazide (Fig 32). Results revealed all compounds showed activity against the selected strain of bacteria but fluoro substituted compounds with significant activity against selected bacteria. Nitro-containing (R=NO2) compound showed better activity against Gram positive bacteria but less activity against Gram negative bacteria.

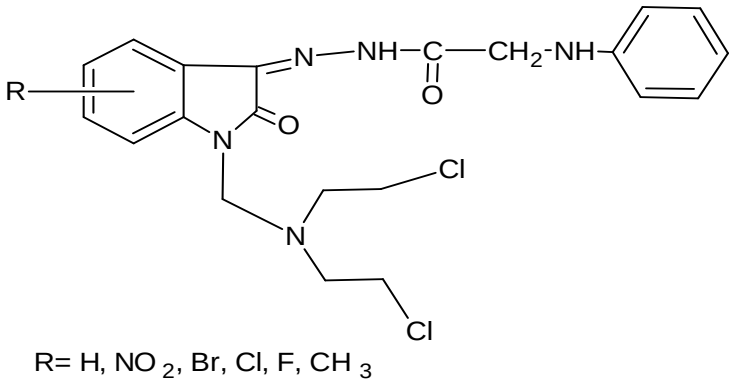


Fig. 32.

CONCLUSION

As mentioned by the work of reviewed in this paper, Mannich bases of 1H-indole-2,3-dione(isatin) and substituted isatin are found to have potent antimicrobial activity. Addition of aminoalkyl side chain on N-1 position of in 1H-indole-2,3-dione (isatin) mainly enhance the bioaccumulation and activity of existing chemical moiety. The remarkable chemotherapeutic activity of Mannich bases is still unexplored. It has been needing the rapid development for the biological efficacy. Because of this it has gain the attention of researcher for design the novel medicinally important derivative. This can be conveniently achieved by the addition of various amines alone and with Schiff bases in 1H-indole-2,3-dione.

REFERENCES

1. Chaudhary Dhruv Kumar, Ahmad Shamim, Maity Supriya and Alam M. Shamsher. Isatin: Diverse biological profile. Der Pharmacia Lettre, 2013; 5(1): 285-295.
2. Bala Suman, Sharma Neha, Kajal Anu, Kamboj Sunil and Saini Vipin. Mannich Bases: An important pharmacophore in present scenario. International journal of medicinal chemistry, 2014; 1-15.
3. K. Vandana, Marathakam Akash, B. S. Thushara and K. Rajitha. A review on isatin derivatives with diverse biological activities. World Journal of Pharmaceutical Research, 2017; 6(16): 318-332.
4. Kupinic Mirjana, Medic-Saric Marica, Movrin Marija, and Maysinger Dusica. Antibacterial and Antifungal Activities of Isatin N-Mannich Bases. Journal of Pharmaceutical Sciences, 1979; 68(4): 459-462.
5. Daisley Roy W. and Shah Vasanti K. Synthesis and Antibacterial Activity of Some 5-Nitro-3-phenyliminoindol-2(3H)-ones and Their N-Mannich Bases. Journal of Pharmaceutical Sciences, 1984; 73(3): 407-408.

6. Ali Shahina and Alam Mahbub. Potential Antimicrobial Agents-I: Structural Modifications and Antimicrobial Activity of some Isatin Derivatives. Arch. Pharm. Res., 1994; 17(2): 131-133.
7. Pandey S. N. and Sriram D. Synthesis and Screening for antibacterial activity of Schiff and Mannich bases of isatin and its derivatives. Acta Pharmaceutica Turcica, 1998; 1: 33-38.
8. Pandey S. N., Sundari C. Gnana, Mariammal N. and Sarvanan P., Balaji S. Sarvana, Kumar R. Senthil and Sriram D. Synthesis and antibacterial activity of Mannich bases of Ciprofloxacin and Lomefloxacin with isatin and its derivative. Indian J. Pharm. Sci., 1998; 60(5): 280-282.
9. Pandeya S. N., Sriram D., Nath G. and De Clercq E Synthesis, Antibacterial, Antifungal and Anti-HIV Activity of Schiff and Mannich bases of Isatin with N-[6-chlorobenzothiazol-2-yl] Thiosemicarbazide. Indian J. Pharm. Sci, 1999; 61(6): 358-361.
10. Pandeya S.N., Sriram D., Nath G. and De Clercq E. Synthesis, antibacterial, antifungal and anti-HIV evaluation of Schiff and Mannich bases of isatin derivatives with 3-amino-2-methylmercapto quinazolin-4 3(H)-one. Pharmaceutica Acta Helvetiae, 1999; 74: 11–17.
11. Pandeya Surendra N., Sriram Dharmarajan, Nath Gopal and Clercq Erik de. Synthesis, Antibacterial, Antifungal and Anti-HIV Evaluation of Schiff and Mannich Bases of Isatin and its Derivatives with Triazole. Arzneim.-Forsch./Drug Res, 2000; 50 (I): 55-59.
12. Sridhar Seshaiah Krishnan, Saravanan Muniyandy and Ramesh Atmakuru. Synthesis and antibacterial screening of hydrazones, Schiff and Mannich bases of isatin derivatives. Eur. J. Med. Chem., 2001; 36: 615–625.
13. Pandeya S. N., Yogeeshwari P., Sriram D. and Nath G. Synthesis, antibacterial and antifungal activities of N-Mannich bases of 3-[N^2- pyrimethaminylimino] isatin. Indian J. Pharm. Sci, 2002; 64(3): 209-212.
14. Khan S. A., Siddiqui N., Imran M. and Haque S.W. Synthesis and antimicrobial screening of novel Mannich bases of isatin derivative. Indian Journal of Pharmaceutical Science, 2004; 830-833.
15. Singh B.N., Shukla S.K. and Singh Meera. Synthesis and Biological Activity of Sulphadiazine Schiff's Bases of Isatin and their N-Mannich Bases. Asian Journal of Chemistry, 2007; 19(7): 5013-5018.

16. Ravichandran V., Mohan S. and Kumar K. Suresh. Synthesis and antimicrobial activity of Mannich bases of isatin and its derivatives with 2-[(2,6-dichlorophenyl)amino]phenylacetic acid. ARKIVOC, 2007; (xiv): 51-57.
17. Vaidhyalingam V., Joseph A. Albin and Aanandhi M. Vijey. Synthesis and Antimicrobial Activity of Some Novel Mannich Bases of Isatin. OCAIJ, 2007; 3(3): 150-154.
18. Sahu S. K., Azam Md. Afzal, Banerjee M., Acharrya S., Behera C. C. and Sic S. Synthesis, Characterization and Biological Activity of 2-Methyl-3-aminoquinazolin-4(3H)-ones Schiff Bases. J. Braz. Chem. Soc, 2008; 19(5): 963-970.
19. Chhajed S.S. and Padwal M. S. Antimicrobial Evaluation of Some novel Schiff and Mannich bases of Isatin and its derivatives with quinoline. International Journal of Chem. Tech. Research, 2010; 2(1): 209-213.
20. Singh U. K., Pandeya S. N., Singh A., Srivastava B. K. and Pandey M. Synthesis and Antimicrobial Activity of Schiff's and N-Mannich Bases of Isatin and Its Derivatives with 4-Amino-N-Carbamimidoyl Benzene Sulfonamide. International Journal of Pharmaceutical Sciences and Drug Research, 2010; 2(2): 151-154.
21. Singh Umesh K., Pandeya Surendra N., Jindal Sunil, Pandey Manoj, Srivastava Birendra K. and Singh Anamika. Synthesis and Antimicrobial Activity of Schiff's and Mannich Bases of 1H−Indole−2,3−Dione Derivatives. Der Pharma Chemica, 2010; 2(2): 392-399.
22. Abdulghani Ahlam J. and Abbas Nada M.: Synthesis Characterization and Biological Activity Study of New Schiff and Mannich Bases and Some Metal Complexes Derived from Isatin and Dithiooxamide. Bioinorganic Chemistry and Applications, 2011; 1-16. doi:10.1155/2011/706262.
23. Chaluvaraju KC, Zaranappa. Synthesis and Biological Evaluation of some Isatin derivatives for Antimicrobial Properties. Research Journal of Pharmaceutical, Biological and Chemical Sciences, 2011; 2(1): 541-546.
24. Sachdeva Harshita, Dwivedi Diksha, Singh Har Lal, Sharma Kanti Prakash. Aqua Mediated One Pot Facile Synthesis of Novel Thioxo-1,2,4-triazin-5(2H)-one and [1,2,4] triazino[5,6-b]indole Derivatives and their Biological Activities. J. Chil. Chem. Soc., 2012; 57(4): 1348-1354.
25. Kumar N. Saravana, Pradeep T., Jani G., Silpa Divya and Kumar B. Vijaya. Design, synthesis, and antimicrobial screening of novel pyridyl-2-amidrazone incorporated isatin Mannich bases. Journal of Advanced Pharmaceutical Technology & Research, 2012; 3: 57-61.

26. AL- Bayati Khalaf Ahmed Jasim. Synthesis and Study of Some New Mannich Bases Derived from Isatin (1H-Indole-2,3-Dione) with Substituted Sulfonamides and Their Antimicrobial Activity. Tikrit Journal of Pure Science, 2012; 17(2) ISSN: 1813 – 1662.
27. Pandeya S.N., Yadav Vandana, Tyagi Alka and Nath G. Molecular Modification of Quinoline Derivatives and Their Antibacterial Activity. Journal of Scientific Research in Pharmacy, 2012; 1(3): 16-18.
28. Aiswarya K. S. Bhavani, Rao P. Jagadeeswara, Spoorthy Y. N., Begum D. Ishrath and Ravindranath L. K. Synthesis and anti-microbial activity of novel Mannich bases containing 2- phenoxy-1, 3, 2-dioxa phospholanes and Indole systems. Journal of Chemical and Pharmaceutical Research, 2012; 4(8): 4052-4059.
29. Panda J.:Synthesis and Biological Evaluation of Some Isatin-based Mannich Bases. International Journal of Pharmaceutical Sciences and Nanotechnology, 2013; 5(4): 1841-1846.
30. Prakash Chinnasamy Rajaram and Raja Sundararajan. Synthesis, characterization and in vitro antimicrobial activity of some novel 5-substituted Schiff and Mannich base of isatin derivatives. Journal of Saudi Chemical Society, 2013; 17: 337-334.
31. Prakash Chinnasamy Rajaram, Raja Sundararajan and Saravanan Govidaraj. Synthesis, Analgesic, Anti-Inflammatory and In Vitro Antimicrobial Studies of Some Novel Schiff and Mannich Base of 5-Substituted Isatin Derivatives. International Journal of Pharmacy and Pharmaceutical Sciences, 2014; 6 (10): 160-166.
32. Kanchana Subba Narayana, Burra Venkataramudu and Nath L. K. Ravindra. Novel Synthesis and Anti-microbial Activity Study of Innovative Mannich Bases Containing 2-Phenoxy-1,3, 2-dioxa Phospholanes and Indole Systems. Orient. J. Chem., 2014; 30(3): 1349-1360.
33. Rani P. Jothi, M. Sundara Pandiyan, A. Senthamil Selvi, A. Aruna and N. Venkatesan. Synthesis, Characterization and Antimicrobial Activity of Schiff and Mannich Bases of Isatin Derivatives. World Journal of Pharmacy and Pharmaceutical Sciences, 2017; 6(1): 1259-1267.
34. Sinduja P., Sammaiah G. and Swathi K. Synthesis and Evaluation of New Isatin Derivatives for Possible Biological Activities. International Journal of Pharmacy and Biological Sciences, 2018; 8(1): 214-219.