"A brief review on versatile synthesis and applications of Transition metal Schiff base complexes"

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Abstract

Schiff bases are condensation products of primary amines with carbonyl compounds[1].There are many reported synthetic methods in literature but the non conventional method of Microwave assisted reactions has gained a large importance as it require less time and yields are satisfactory. Microwave synthesis improves the reproducibility and makes handling convenient. The present paper describes the versatile routes for synthesis of Schiff bases and its coordination chemistry. This has claimed importance in bio-inorganic chemistry, biomedical applications, supramolecular chemistry, catalysis, material science, separation of compounds [2].They also have a wide variety of applications such as antitubercular [3], antimalarial[4], vasorelaxing [5], anticancer[6] and analgesic drugs[7].

Keywords: *Schiff Base, antimicrobial, non-conventional, microwave assisted reactions.*

1. Introduction:

Hugo Schiff reported the condensation of primary amines with carbonyl compounds in 1864 to form Schiff bases. Their transition metal complexes have varied applications in clinical, analytical, industrial, catalysis and organic synthesis [8]. Earlier works have reports that some drugs showed increased activity when administered as metal complexes rather than as organic compounds [9].The presence of –C=N– along with other functional groups form more stable complexes compared to compounds with only –C=N– moiety. Schiff-base complexes are considered most important stereo chemical models in main group and transition metal coordination chemistry due to their accessibility and variety. In recent years, environmentally benign synthetic methods have received importance. Organic synthetic procedures which use chlorinated hydrocarbons solvents have created havoc to the ecosystem as they are toxic and volatile in nature [10]. So to reduce such disasters, one must use safer chemicals and solvents. Nowadays a solvent-free approach has proved to be attractive as majority of solvents are either toxic or inflammable and adds to the cost of overall synthesis. But, the solvent free approach improves selectivity, reduces reaction time, and brings ease in separation and purification of products than the conventional methods [11–15]. The development of cleaner methods is a major challenge in Green chemistry. Among the several aspects of green chemistry, the reduction or replacement of volatile organic solvents from the reaction medium is of utmost importance [16,17]. For the increasing economical concerns, it is now necessary for chemists to search environmentally benign methods. Schiff bases derived from aromatic carbonyl compounds have been widely studied with metalloprotein models and asymmetric catalysis, due to the versatility of their steric and electronic properties. The use of water as a solvent [18–20] is one of the best alternative as there are no harsh reaction conditions. In classical synthesis of Schiff bases, it commonly meets the problem of removing solvents from the reaction mixture or liquid. So

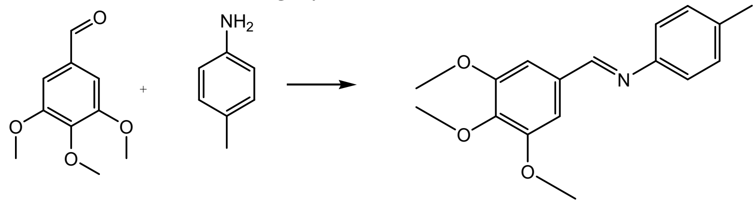
Microwave-assisted reactions have been intensively investigated [21-23] and have been popularly used in organic synthesis.

2. Discussion:

2.1. Novel Routes of Synthesis

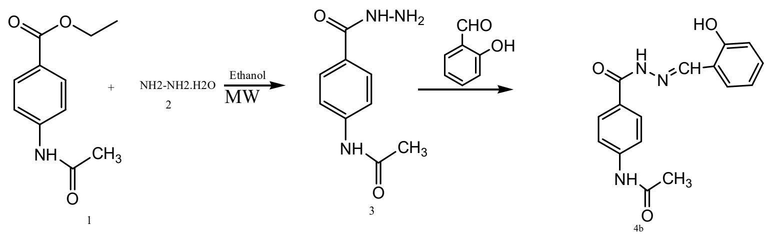
Here we have taken review and presented the report of some novel and clean methods of synthesis for Schiff bases using microwave techniques:

Zhaoqi Yang et al [24] synthesized the Schiff Bases (Scheme-1) by reacting a mixture of p-toluidine and 3,4,5-trimethoxybenzaldehyde with neutral alumina and dichloromethane which was irradiated for 4 min in microwave oven. Microwave irradiation synthesis is use the least time with high yield.



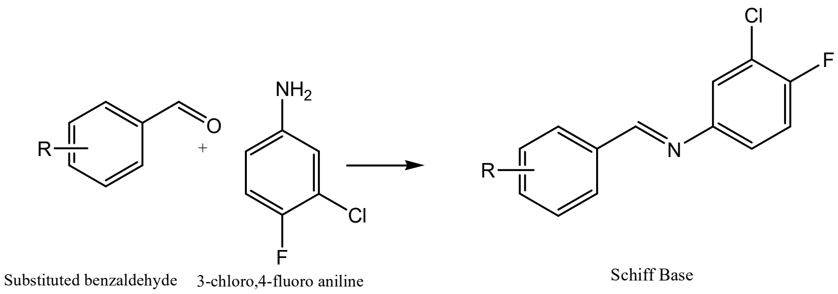
Scheme 1

Eljo P Chacko et al [25] also synthesized Schiff bases by reacting a mixture of N-acetyl p-ethyl benzoate and hydrazine hydrate (Scheme-2) under microwave irradiation for 3 min to form the product with yield 77%.



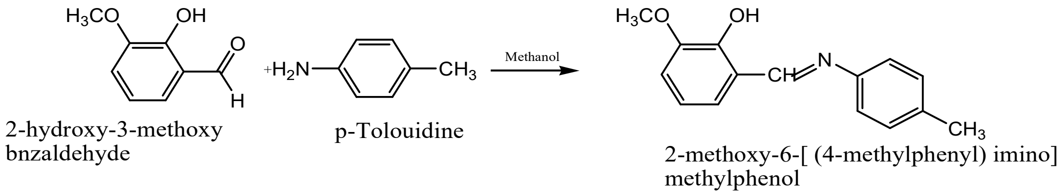
Scheme 2

Arshi Nakvi et al [26] studied three different green methodologies for preparing Schiff bases. A mixture of 3-chloro-4-fluoro aniline and substituted benzaldehydes (Scheme-3) was stirred in 10 ml of water and crystalline product was obtained. The use of Microwave “jump start” synthesis, Grindstone “friction activated” synthesis in greener methodologies, water based reactions have a great virtue as water is cheaper medium for reactions, environmentally benign, easy to handle and without any corrosive or carcinogenic effect.



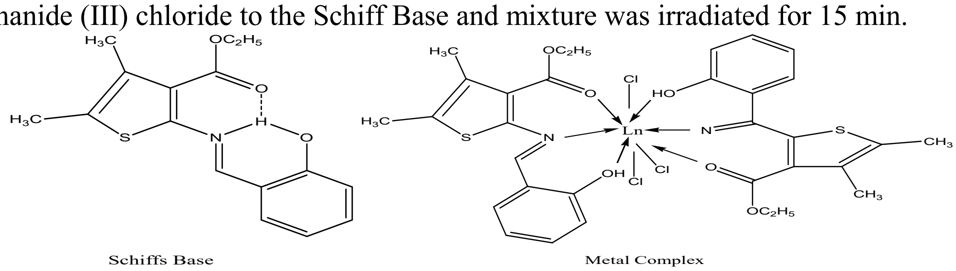
Scheme- 3

Atul Bendale et al [27] prepared imino methyl phenols by condensation of p-toluidine and vanillin (Scheme-4) using different methodologies in presence of U.V light, Sonicator, and mortar and pastel. Among the different methods, the use of sonicator in acetic acid as a catalyst showed maximum yield in short time.



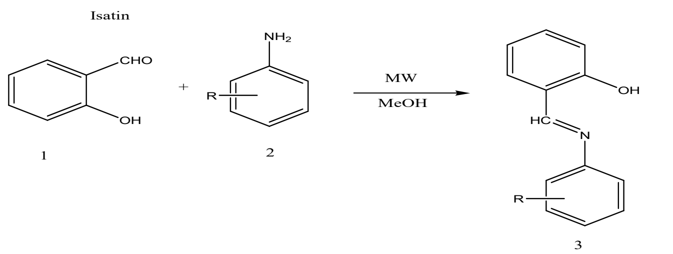
Scheme- 4

B. Sindhu Kumari [28] synthesized carboxy ethyl thiophenes Schiff bases (Scheme-5). Further synthesis of metal complex was achieved by adding ethanolic solution of Lanthanide (III) chloride to the Schiff Base and mixture was irradiated for 15 min.



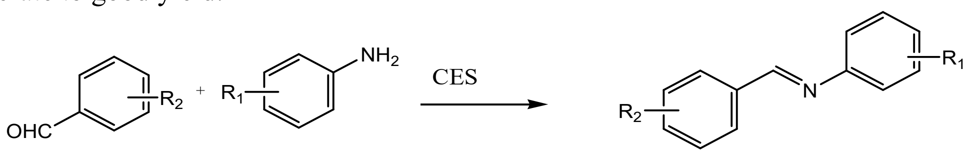
Scheme- 5

Mousumi Chakraborty [29] synthesized Schiff bases by condensation of salicylaldehyde with different substituted aromatic amines in methanol (Scheme- 6) at 80^0C by microwave irradiation to give yellow colored amorphous product. The yield was increased from 48% to 72%.



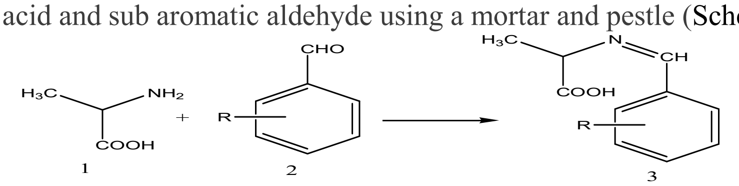
Scheme- 6

Suresh Patil et al [30] synthesized Schiff Bases using 4-methoxyaniline and 4-hydroxy benzaldehyde in calcined eggshells (Scheme-7). This was a new eco friendly grinding method for the synthesis of Schiff bases catalyzed by CES (heterogeneous catalyst) with a moderate to good yield.



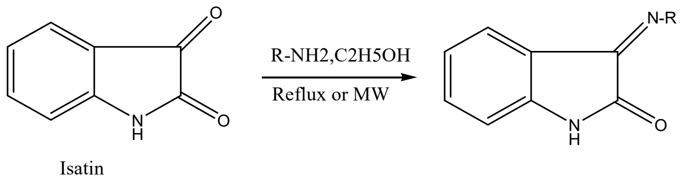
Scheme- 7

Harshita Sachdeva et al [31] synthesized Schiff base by taking equimolar mixture of DL-alanine amino acid and sub aromatic aldehyde using a mortar and pestle (Scheme- 8).



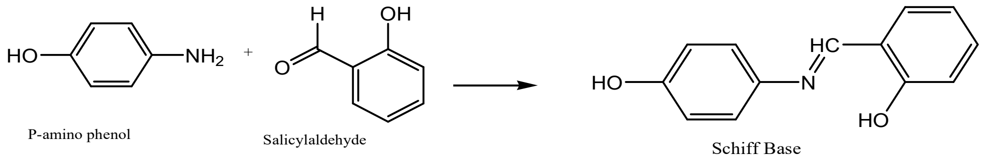
Scheme- 8

J. Panda et al [32] refluxed Schiff Base of Isatin using substituted aniline (Scheme- 9) under microwave irradiation to yield 85% product.



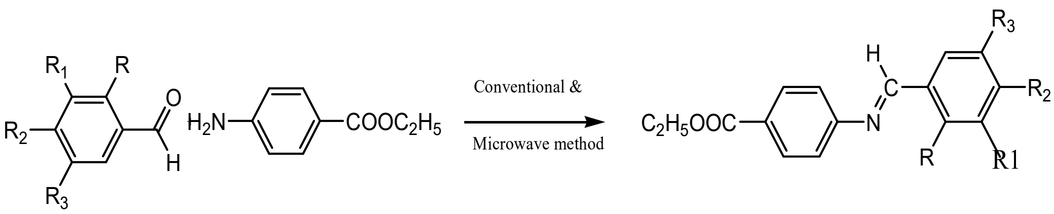
Scheme- 9

Savalia R V et al [33] synthesized the Schiff's Base using equimolar mixture of p-amino phenol and salicylaldehyde by conventional and Microwave irradiation method. It was concluded that Microwave irradiation increases the yield by 20% than the conventional method.



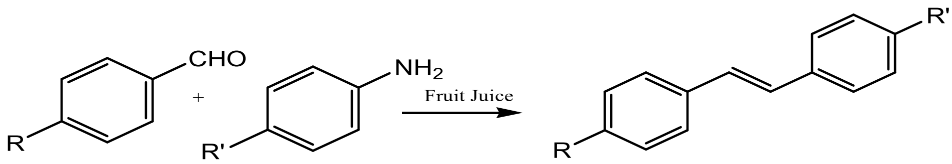
Scheme- 10

O G. Bhusnure et al [34] synthesized Schiff base by adding amino benzoate and 5-Chloro salicyladehyde (Scheme- 11) when irradiated under microwave for 10 s to form the Schiff bases. Beta ethoxy ethanol is a polar molecule, quickly absorbs microwaves and therefore heats up under microwave-assisted solvent free conditions.



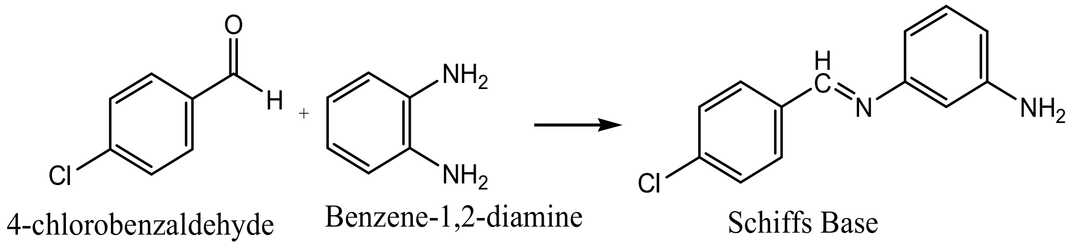
Scheme- 11

Garima Yadav et al [35] synthesized the Schiff Base by using natural acid catalyst like grapes juice, lemon juice (Scheme 12) and mango juice. The growing interest of fruit juice is mainly due to their enzymatic activity, acidic properties, benign environmental character and commercial availability. In near future, the chemistry of natural catalysts will attract significant research activity.



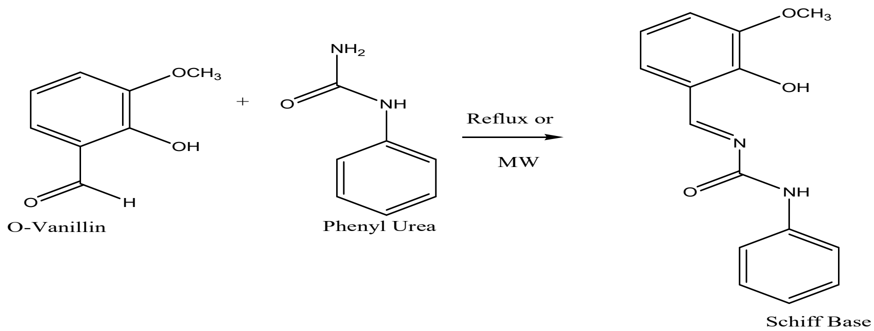
Scheme- 12

Kapadnis et al [36] synthesized Schiff Base and metal complex by grinding and Microwave irradiation methods (Scheme- 13). In Microwave irradiation method, the product obtained with only 8 min and 80.04% yield.



Scheme- 13

Ali Mostafa Hassan et al [37] synthesized the Schiff base by reacting phenyl urea with o-vanillin (Scheme- 14) and refluxed using Microwave irradiation which required 7-13 min short time.



Scheme- 14

2.2. Biological activities of Schiff bases:

a) Antimalarial activity:

Malaria is a disease found in more than 100 countries and has caused serious health problems all over the globe. Every year, 550 million people are affected by this disease, out of which around 3 million people die, 90% of them are in Africa and primarily are children [38]. Human malaria is mainly caused by P. falsiparum, P. vivax, P. ovale, and P. malariae. The female mosquito of the Anopheles genus is the vector of Plasmodium [39]. The priority for search of novel drugs and vaccines to treat malaria is in progress. Schiff bases have shown interesting moieties for the design of antimalarial agents. Ancistrocladidine is a secondary metabolite produced by plants from the families Ancistrocladaceae and Dioncophyllaceae that has an imine group in its molecular structure. It has been active against P. falciparum. Rathelot et al. [40] synthesized 5-nitroisoquinolines and investigated the in vitro activity of these compounds against P. falciparum strain. It was found to be most effective antimalarial agent to inhibit P. falciparum growth by 50%.

b) Antibacterial activity

The development in the field of bio-inorganic chemistry has increased the interest in Schiff base complexes, as many Schiff base complexes serve as promising antibacterial agents. The increasing mortality rate associated with infectious diseases is directly related to bacteria. The development of new antibacterial agents with more efficient mechanisms of action is definitely a need of the hour. Schiff bases have been recognized as promising antibacterial agents [41]. N-(salicylidene)-2-hydroxyaniline is effective against Mycobacterium tuberculosis H37Rv. The synthesis and antimicrobial activity of a series of Schiff bases derived from the condensation of 5-chloro-salicylaldehyde and primary amines has recently been reported [42]. They were most active against Pseudomonas. Bacillus subtilis and Staphylococcus aureus were sensitive to the Schiff bases. Isatin-derived Schiff bases have also been reported to possess antibacterial activity [43]. Twenty-eight bacteria of clinical interest were used in the studies performed by Pandeya and colleagues. These Schiff base were the most potent against E. coli NCTC 10418, Vibrio cholerae, Enterococcus faecalis and Proteus shigelloides. Other isatin derived Schiff bases have been described in the literature, but with no expressive antibacterial activities [44, 45]. The therapeutic safety and effectiveness for isoniazid-derived Schiff base is higher than 40,000, making this Schiff base an excellent lead for the development of antitubercular agents [46]. In 2005, Panneerselvam et al. described the in vitro antibacterial activity of eleven morpholine-derived Schiff bases against S. aureus and Micrococcus luteus. Schiff bases with a 2,4-dichloro-5-fluorophenyl moiety are also effective in the inhibition of bacterial growth. Other molecules of natural or non-natural origin that are platforms for the synthesis of Schiff bases for antibacterial activities include amino acids, coumarins, sulfonamides, or resacetophenones, aminothiazolyl bromocoumarins, crown ethers, o-phthaldehyde, or 2-aminophenol and 1,2,4-triazoles[47]. The antibacterial property of compounds representative of these classes was examined. However, they did not exhibit any notable activity.

3. Conclusion

In this review article, we have discussed the recent progress in the field of Schiff bases, their structure, characterization and biological applications. The ligands and their metal complexes have a significant role in industrial and medicinal fields. Although the research on the Schiff bases is increasing day by day, a number of reports of Schiff base in antimicrobial, antiviral of clinical interest have recently been reported in many articles. But still more research is needed in the development of these metal complex drugs.

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5. Conflict of Interest

This article does not contain any conflict of interest.

6. References

1. *Abu-Hussen, J. Coord. Chem.* ***2006****, 59,157.*
2. *S Karthikeyan, M.; Jagadesh Prasad, D.; Poojary, B.; S. Bhat, Bioorg. Med. Chem.* ***2006****, 14, 7482.*
3. *Singh, K.; Barwa, M. S.; Tyagi, P. Eur. J. Med. Chem.* ***2006****, 41, 1.*
4. *Pannerselvam, P.; Nair, R.R.; Vijayalakshmi, G.; Subramanian, E.H.; Sridhar, S.. Eur. J. Med. Chem.* ***2005****, 40, 225.*
5. *Sridhar, S. K.; Saravan, M.; Ramesh, A. Eur. J. Med. Chem.* ***2001****, 36, 615.*
6. *Pandeya, S. N.; Sriram, D.; Nath, G.; Declercq, E. Eur. J. Pharmacol.* ***1999****, 9, 25.*
7. *Mladenova, R., M.; Manolova, N.; Petrova, T.; Rashkov, I. Eur. Polym. J.* ***2002****, 38, 989.*
8. *Walsh, O. M.; Meegan, M. J.; Prendergast; Nakib, T. A. Eur. J. Med. Chem.* ***1996****, 31, 989.*
9. *H. Keypour, M. Rezaeivala, L. Valencia, P. Perez Lourido and H. Raza Khavasi, Polyhedron,* ***2009****, 28, 3755.*
10. *J. M. DeSimone, "Practical approaches to green solvents," Science, vol. 297, no. 5582,* ***2002,*** *pp. 799–803.*
11. *G. W. V. Cave, C. L. Raston, and J. L. Scott, "Recent advances in solventless organic reactions: towards benign synthesis with remarkable versatility," Chemical Communications, no. 21,* ***2001*** *pp. 2159–2169.*
12 *C. Imrie, P. Kleyi, V. O. Nyamori, T. I. A. Gerber, D. C. Levendis, and J. Look, "Further solvent-free reactions of ferrocenylaldehydes: synthesis of 1,1 -ferrocenyldiimines and ferrocenylacrylonitriles," Journal of Organometallic Chemistry, vol. 692, no. 16,* ***2007,*** *pp. 3443–3453.*
13. *J.Metzger, "Solvent-free organic syntheses," Angewandte Chemie—International Edition, vol. 37, no. 21, ,* ***1998,*** *pp. 2975–2978.*
14. *C. J. Li and T. H. Chan, "Organic syntheses using indium mediated and catalyzed reactions in aqueous media," Tetrahedron, vol. 55, no. 37,* ***1999,*** *pp. 11149–11176.*
15. *T. P. Loh, J. M. Huang, S. H. Goh, and J. J. Vittal, "Aldol reaction under solvent-free conditions: highly stereoselective synthesis of 1,3-amino alcohols," Organic Letters, vol. 2, no. 9,* ***2000,*** *pp. 1291–1294.*

16. *R. S. Varma and V. V. Namboodiri, "Solvent-free preparation of ionic liquids using a household microwave oven," Pure and Applied Chemistry, vol. 73, no. 8, 2001, pp. 1309–1313.*
17. *K. Tanaka and F. Toda, "Solvent-free organic synthesis," Chemical Reviews, 100, (3),**2000,** 1025–1074.*
18. *S. S. Pawar, M. S. Shingare, and S. N. Thore, "A novel approach for ligand promoted palladium (II)-catalyzed suzuki coupling in aqueous media," Lett in Organic Chemistry, vol. 4, no. 7, **2007,**486–490.*
19. *Y. Ren and C. Cai, "Iodine catalysis in aqueous medium: an improved reaction system for knoevenagel and nitroaldol condensation," Catalysis Letters, vol. 118, no. 1-2, **2007,** 134–138.*
20. *V. K. Rao, S. S. Reddy, B. S. Krishna, K. R. M. Naidu, C. N. Raju,and S. K. Ghosh, "Synthesis of Schiff bases in aqueous medium: a green alternative approach with effective mass yield and high reaction rates," Green Chemistry Letters and Reviews, vol. 3, no. 3, **2010,** 217–223.*
21. *Somani R., et al. Optimization of Microwave Assisted Synthesis of some Schiff Bases. International Journal of ChemTech Research 2, **2010**, 172-179*
22. *Kulshrestha A. and Baluja S., Microwave Promoted Synthesis of Some Schiff Bases, Scholars Research Library 2, **2010**, 221-224*
23. *Yang Z. and Sun P., Compare of three ways of synthesis of simple Schiff base. Molbank, **2006**, 12-14*
24. *Zhaoqi Yang, Pinhua Sun, Molbank **2006**, M514 1-3*
25. *Eljo p. Chacko and Gopal krishna rao, Asian Journal of Chemistry, Vol. 19, No. 4 **2007**, 3274-3276*
26. *Arshi Naqvi, Mohd.. Shahnawaaz, Arikatla V. Rao, Daya S. Seth and Nawal K Sharma, E-Journal of Chemistry, **2009**, 6(S1), S75-S78*
27. *A R. Bendale, R Bhatt, A Nagar, A G. Jadhav and G. Vidyasagar, Der Pharma Chemica, **2011**, 3(2): 34-38*
28. *B. Sindhu Kumari, G. Rijulal & K. Mohanan, Synthesis and reactivity in inorganic metal-organic and Nano-metal chemistry, 2011, Page 24-31.*
29. *Mousumi Chakraborty, Sanjay Bawejay, Sunita Bhagatz, T Chundawat, International journal of chemical reactor engineering, Volume 10, **2012**,*
30. *Suresh Patil, S. D. Jadhav, S. K. Shinde, Organic Chemistry International Volume, **2012**, 153159, 1-5*
31. *H Sachdeva, Rekha Saroj, Sarita Khaturia and Diksha Dwivedi, Green Process Synth, **2012**; 1: 469–477*
32. *Jnyanaranjan Panda, V. Jagannath Patro, Biswa Mohan Sahoo, and Jitendriya Mishra, Journal of Nanoparticles, **2013**, Article ID 549502, 1-5*
33. *Savalia R.V., Patel A.P., Trivedi P.T., Gohel HR and Khetani D.B., Research Journal of Chemical Sciences, **2013**, Vol. 3(10), 97-99*
34. *Omprakash. Bhusnure, Yaswant B. Vibhute, Padmaja S Giram, Archana. Vibhute , International Journal of Pharmacy and Pharmaceutical Sciences, Vol 7, Issue 6, **2015**, 124-128*
35. *Garima Yadav, Jyoti V. Mani, International Journal of Science and Research (IJSR), **2015**, Volume 4 Issue 2, 121-127*
36. *Dr. Kapadnis Kailas H., Jadhav Sheetal P., Dr. Patil Anita P., Dr. Hiray Apoorva P.,World journal of Pharmacy and pharmaceutical sciences, **2016**, Volume 5, Issue 2, 1055-1063*
37. *Ali Mostafa Hassan, Ahmed Osman Said, Bassem Hussien Heakal, Ahmed Younis, Miral Ahmed Abdelmoaz, Mahmoud Mohamed Abdrabou, Advanced Journal of Chemistry-Section A, **2020**, 3(5), 621–638*
38. *Bohach GA, Fast DJ, Nelson RD, Schlievert PM. Malaria. In: Rodes J, Benhamou JP, Blei A, Reichen J, Rizzetto M, editors. The textbook of hepatology, Oxford (UK): Wiley Blackwell; **2007**. p. 1029–34.*
39. *Kayser O, Kiderlen AF, Croft SL. Natural products as potential antiparasitic drugs. Parasitol Res **2003**;90 (Suppl 2):S55–62.*
40. *Rathelot P, Vanelle P, Gasquet M, Delmas F, Crozet MP, Timon-David P, et al. Synthesis of novel functionalized 5- nitroisoquinolines and evaluation of in vitro antimalarial activity. Eur J Med Chem **1995**;30(6):503–8.*
41. *de Souza AO, Galetti FCS, Silva CL, Bicalho B, Parma MM, Fonseca SF, et al. Antimycobacterial and cytotoxicity activity of synthetic and natural compounds. Quim Nova, **2007**;30(7):1563–6.*
42. *Shi L, Ge HM, Tan SH, Li HQ, Song YC, Zhu HL, et al. Synthesis and antimicrobial activities of Schiff bases derived from 5-chloro-salicylaldehyde. Eur J Med Chem **2007**;42(4):558–64.*
43. *Pandeya SN, Sriram D, Nath G, de Clercq E. Synthesis and antimicrobial activity of Schiff and Mannich bases of isatin and its derivatives with pyrimidine. IL Farmaco, **1999**;54(9):624–8.*
44. *Pandeya SN, Sriram D, Nath G, de Clercq E. Synthesis, antibacterial, antifungal and anti-HIV activities of Schiff and Mannich bases derived from isatin derivatives and N-[4-(40- chlorophenyl)thiazol-2-yl] thiosemicarbazide. Eur J Pharm Sci ,**1999**;9(1):25–31.*
45. *Jarrahpour A, Khalili D, de Clercq E, Salmi C, Brunel JM. Synthesis, antibacterial, antifungal and antiviral activity evaluation of some new bis-Schiff bases of isatin and their derivatives. Molecules **2007**;12(8):1720–30.*
46. *Hearn MJ, Cynamon MH. Design and Synthesis of antituberculars: preparation and evaluation against M. tuberculosis of an isoniazid Schiff base. J Antimicrobial Chemotherapy, **2004**;53(2):185–91.*
47. *Karthikeyan MS, Prasad DJ, Poojary B, Bhat KS, Holla BS, Kumari NS. Synthesis and biological activity of Schiff and Mannich bases bearing 2,4-dichloro-5-fluorophenyl moiety. Bioorg Med Chem **2006**;14(22):7482–9.*