EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 7
Issue: 2
143-152
Year: 2020

CHALCONES AND HETEROCYCLIC COMPOUNDS: A REVIEW ON SYNTHESIS AND EVALUATION OF THEIR ANTIBACTERIAL, ANTIMICROBIAL, ANTI-INFLAMMATORY AND ANTILESHMANIAL ACTIVITY

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Article Received on 11/12/2019 **Article Revised on 31/12/2019** **Article Accepted on 21/01/2020**

ABSTRACT

Chalcones are an important class of natural products and are considered as the precursors of flavonoids and isoflavonoids. Chemically, chalcones are 1,3-diaryl-2-propen-1-ones in which two aromatic rings are joined by a three carbon bridge having a carbonyl moiety and α, β unsaturation. The compounds with the backbone of chalcones have been reported to possess various biological activities such as antimicrobial, anti-inflammatory, analgesic, anti platelet, anti ulcerative, anti 0malarial, anticancer, antiviral, anti leishmanial, antioxidant, anti-tubercular, anti-hyperglycemic, immunomodulatory, inhibition of chemical mediators release, inhibition of leukotriene B4, inhibition of tyrosinase and inhibition of aldose reductase activities. This paper mainly focuses on chalcones synthesized by Claisen Schmidt condensation which involves the condensation between an aromatic aldehyde or ketone with an aliphatic ketone or aldehyde catalysed by the presence of dilute alkali or acid to form alpha beta unsaturated compound. through reviewing different biological significance of chalcones and their derivatives have been reported along with their chemistry and of synthesis.

KEYWORDS: Chalcone, Aldol condensation, Claisen Schmidt condensation, Pharmacological / Biological activity.

INTRODUCTION

Chalcones are a major class of natural products belonging to the flavonoid family. They are considered as the precursors of flavonoids and isoflavonoids.[1] Chalcone (and related compounds "chalconoids") is an aromatic ketone that forms the central core for a variety of important biological compounds, which are known collectively as chalcones. They are also the precursors of a number of biologically important heterocyclic compounds.[2] Chalcones have been used as intermediates for the preparation of compounds having therapeutic value.[3,4] They are widely distributed in fruits, vegetables, tea, spices, soy based foods and other plant products. Chemically, chalcones are 1,3-diaryl-2-propen-1-ones in which twoaromatic rings or substituted aromatic rings are joined together by a three carbon atom α,β unsaturated carbonyl system. They show antimicrobial, anti-inflammatory, analgesic, anti platelet, anti ulcerative, anti malarial, anticancer, antiviral, anti leishmanial, antioxidant, anti tubercular, anti hy inhibition of leukotriene B4, inhibition of tyrosinase and inhibition of aldose reductase activities. They have the following general structure and formula.

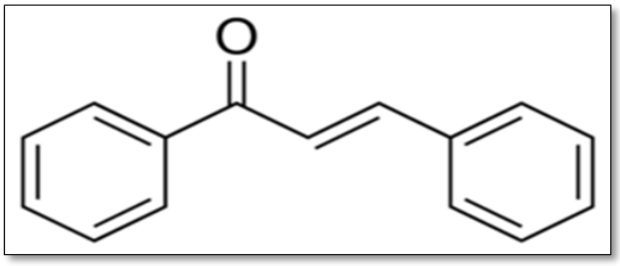


Figure 1: Structure of Chalcone.

Claisen Schmidt Condensation

Claisen Schmidt condensation involve condensation of aldehyde and ketone catalysed by an acid or a base followed by dehydration to yield chalcone as follows:

C6H5CO-CH H2 + O=CHC6H5 → C6H5CO-CH=CHC6H5

Acetophenone Benzaldehyde Benzalacetophenone

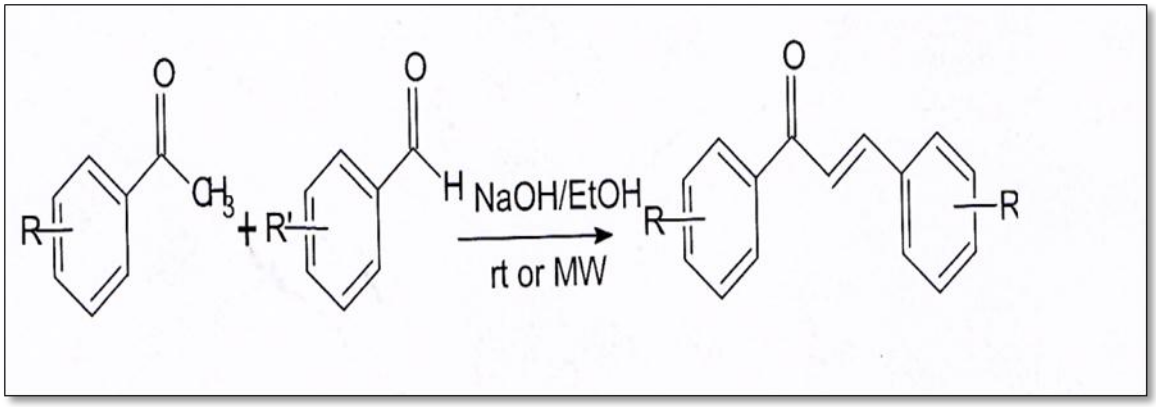


Figure 2: Synthesis of Chalcone.

Aldol Condensation Reaction Method

The starting material for this reaction is acetophenone and benzaldehyde. First acetophenone is treated with a base like KOH which convert it into more active form, its enolate form. It will then react with benzaldehyde to form intermediate. The intermediate will then lose water molecule by heat to form chalcone.

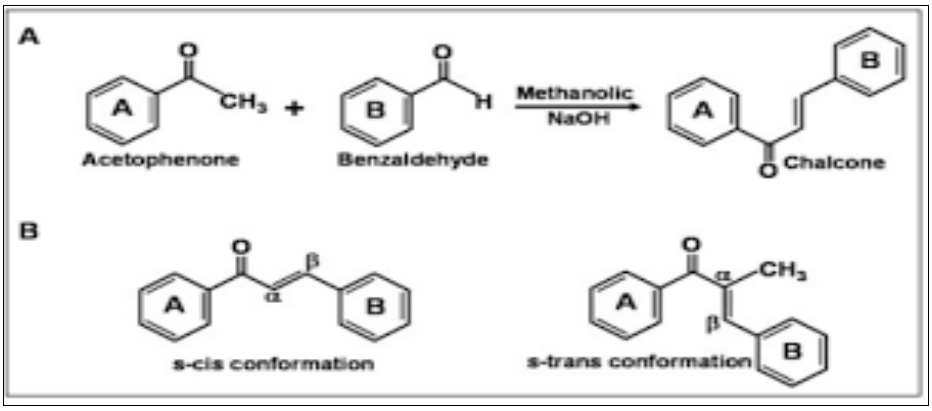


Figure 3: Synthesis of Chalcone.

Importance of Chalcones

- They have close relationship with Flavones, aurones, Tetralones and aziridines
- Chalcones and their derivatives find application as artificial sweeteners, scintillator, polymerization catalyst, fluorescent whitening agent, organic brightening agent, stabilizers against heat, visible light ultraviolet light and aging.
- 3,2,4,6, tetrahydroxy-4propoxy-dihydrochalcone-4-βneohesperdoside has been used as synthetic sweetener and is2200times sweeter than glucose.
- They contain a keto- ethylenic group and therefore reactive towards several reagents e.g. (a) phenyl hydrazine, (b)2-amino thiophenol etc.
- The chalcone have been found useful in elucidating structure of natural products like hemlock tannin, cyanomaclurin, ploretin, eriodictyol and homo eriodictyol, naringeninetc.[5]

Chalcones have been used as intermiates for the preparation of compounds having therapeutic value.[6,7] Many reviews reveal that chalcones derivatives exhibit diverse pharmacological as well as biological activities, such as potential cytotoxic agents, antimicrobial, anti-inflammatory, analgesic, anti platelet, anti ulcerative, anti malarial, anticancer, antiviral, anti leishmanial, antioxidant, anti tubercular, anti hyperglycemic, immunomodulatory, inhibition of chemical mediators release, inhibition of leukotriene B4, inhibition of tyrosinase and inhibition of aldose reductase activities.[8,9]

Medicinal chemists are working on chlcones and their heterocyclic derivatives. A literature survey was done on the synthesis of the said compounds, where the researchers reported different synthetic pathways and their biological activities. These reports are presents below:

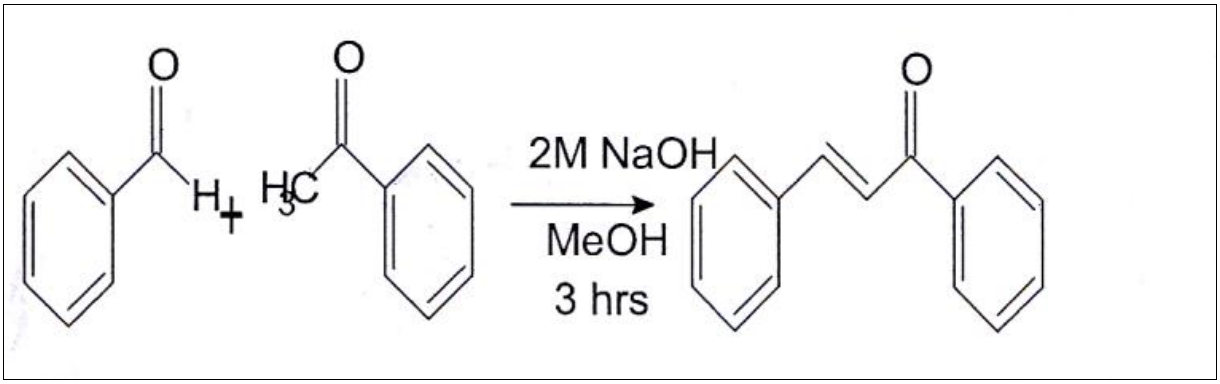


Figure 4: Sivakumar PM *et al* reported the synthesis of α,β unsaturated ketones from substituted aromatic aldehydes and acetophenone.[10]

Reported the antimycobacterial activity against mycobacterial tuberculosis.[11]

The compounds were evaluated for their antimycrobacterial against various types of myco bacteria, and showed comparable activity with of standard drug.

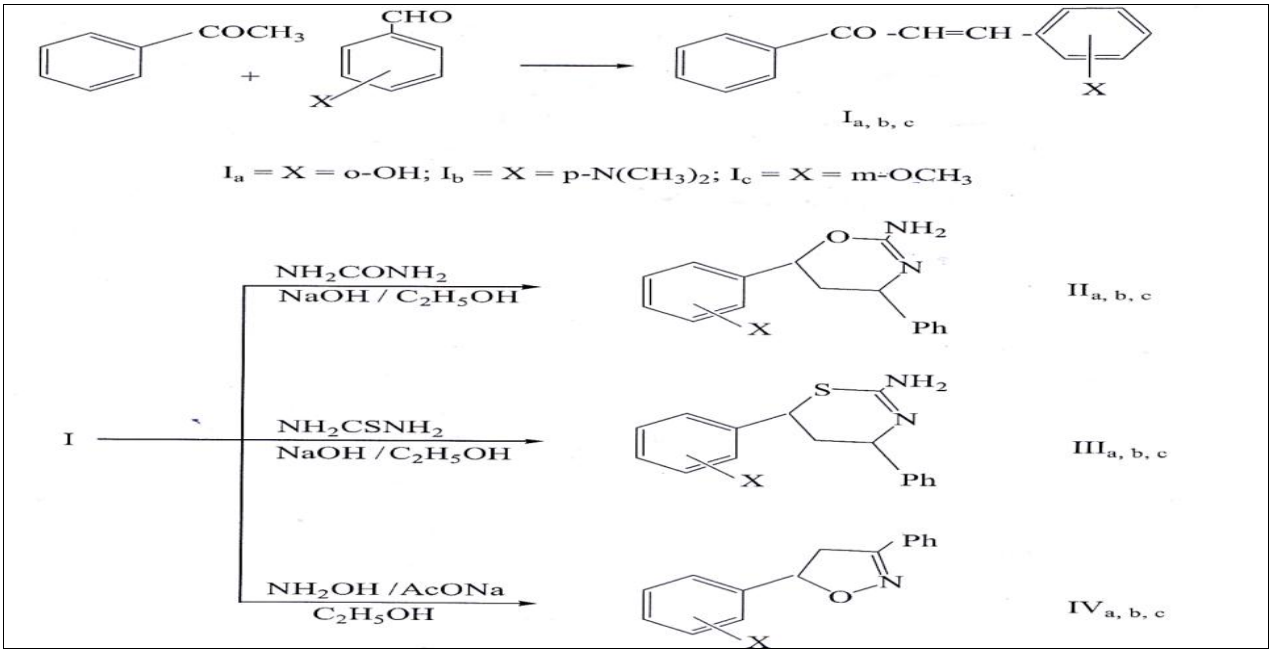
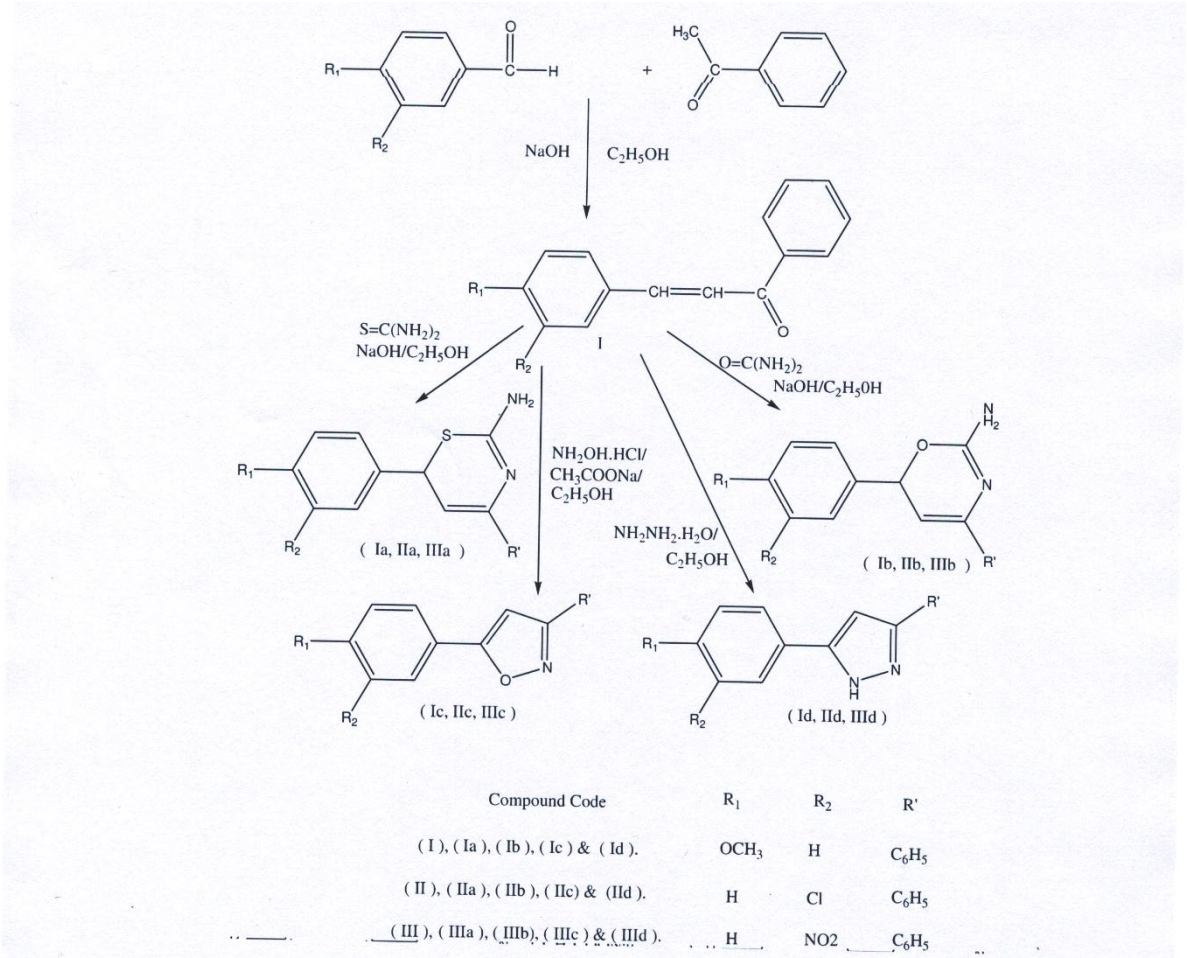


Figure 5: Mhd J.Elarfi etal reported the synthesis of some heterocyclic compound derived from chalcones and evaluated their antibacterial activities.[12]

Antibacterial activity of the heterocyclic derivatives of chalcones have been carried out against several types of bacteria such as, E.coli; s, aureus; and p.argenosa, using nutrient agar medium by well diffusion method.[13] The compounds were evaluated for their antibacterial against various types of bacteria, and showed comparable activity with of standard drug.



Compound Code	R_1	R_2	R'
(I), (Ia), (Ib), (Ic) & (Id).	OCH_3	H	C_6H_5
(II), (IIa), (IIb), (IIc) & (IId).	H	Cl	C_6H_5
(III), (IIIa), (IIIb), (IIIc) & (IIId).	H	NO2	C_6H_5

Figure 6: R. Kalirajan*, S.U.Sivakumar, S. Jubie, B. Gowramma and B. Suresh Synthesis and Biological evaluation of some heterocyclic derivatives of Chalcones.[14]

The synthesized compounds were subjected to antimicrobial screening by cup plate method for zone of inhibition. The Antibacterial activity was tested against various gram positive and Gram negative bacteria and anti fungal activity against various fungal stains compared with standard drug (Ampicillin and Ketoconazole)using solvent control.[15]

Marta kucerrova chlupacova novel pyrazines analogs of chalcones: synthesis and Evalution of their antifungal and antimycobacterial activity.[16]

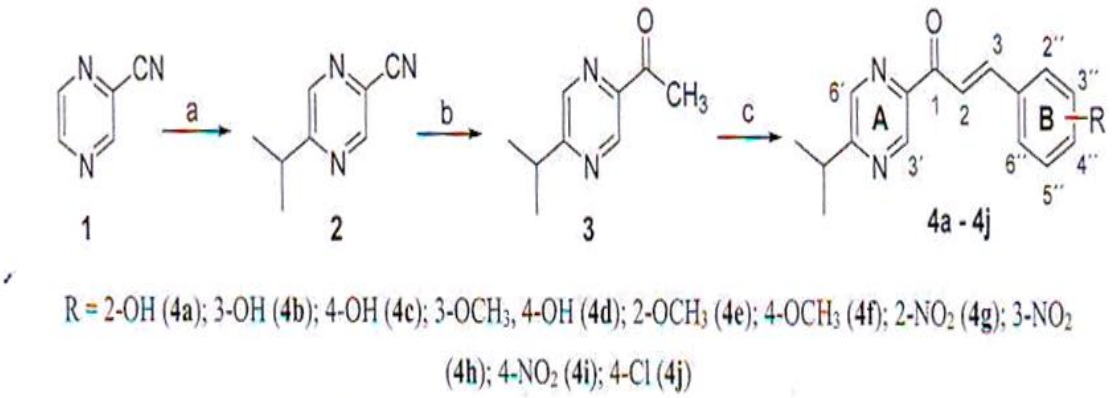


Figure 7: Synthesis of compounds.

A series with various substituents on the phenyl ring and show antifungal and antimycobacterial activity. The compounds that exhibited promising antifungal and anti mycobacterial activity were tested and compared to standard drug.[17,18,19]

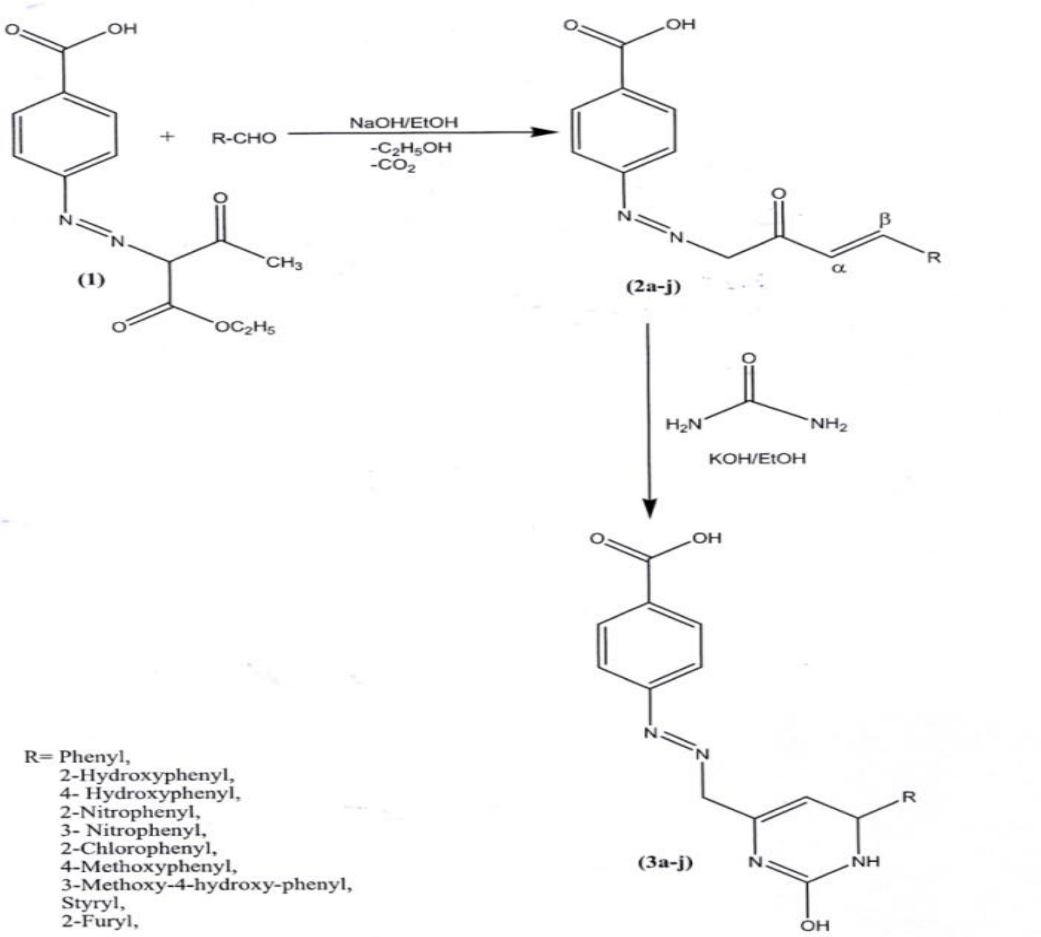


Figure 8: Amit r. Trivedi department of chemistry, Saurashtra university, Rajkot gujrat: Synthesis and biological evalution of some new pyrimidines via a novel chalcones series.[20]

A new class of chalcone and pryimide derivatives evaluted as antitubercular agents. The newly synthesized hetrocycles exhibited as antitublercular activities against mycobacterium tuberculosis. Tomar V etal prepared a series of substituted chalcones by reacting 4-piperazino acetophenone or 3-acetyl -2,5 dichlorothiophene and aromatic aldehyde.[21] Reported the antimicrobial activity against staphylococcus aureus, Esherichia coli, Proteus Vulgaris KLebsiella Pneumonia, Aspergillus Fumigates, Candida albicans microbes. The compounds were evaluated for their antimicrobial activity showed comparable activity with of standard drug.

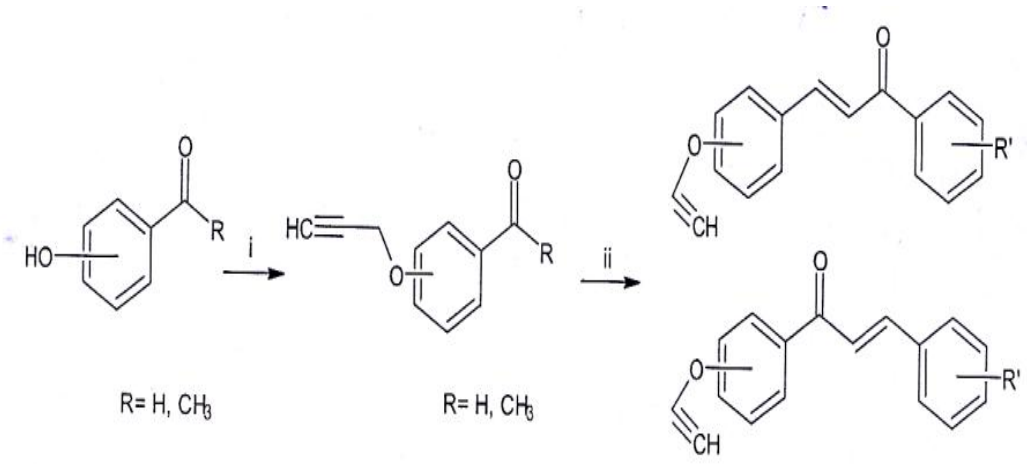


Figure 10: Hans RH et al synthesiszed acetylenic chalcones from commercially available hydroxyacetophenone or benzaldehyde and commercially available vanillin by o-alkylation followed by Claisen –schmidt condensation.[22]

Reported the antimalarial activity and anti tubercular activity against mycobacterium falcirium and mycobacterium tuberculie. The compounds were evaluated for their antimalarial activity and anti tubercular activity showed comparable activity with of standard drug.

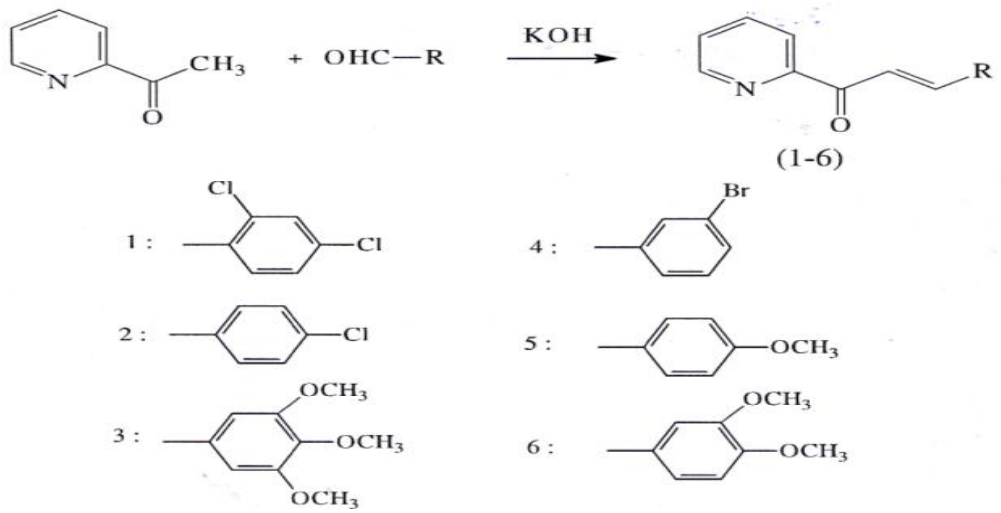


Figure 11: Y. Rajendra Prasad, P. Praveen Kumar P.Ravi kumar and A.srinivasa rao synthesis and antimicrobial activity of some new Chlcones of 2—Acetyl Pyidine.[23]

The presence of a reactive α-β unsatured keto function in chalcones is found to be responsible for their antimicrobial activity which may be altered depending on the types and position of substituent on the aromatic rings. the reaction of 2-acetyl pyridine with different aromatic aldehydes to from chalcones and shows antimicrobial activity.

The compounds were evaluated for their antimicrobial activity showed comparable activity with of standard drug.[24,29]

Anjali solankee, ghanshyam patel and sejal solankee: synthesis and studies of chalcones and its cynopyridine and acetyl pyrazoline derivatives.[30]

Chalcone moiety is the backbone of several antiulcer, cardiovascular and antispasmodic drugs. Pyridine derivatives proven to be of great importance in exhibiting and enhancing the biologiocal activities. Subtituted pyridines derivative like cyanopyridine have found to possess different biological activities such as anticancer, antihypertensive and arthropodicidal.[31,37]

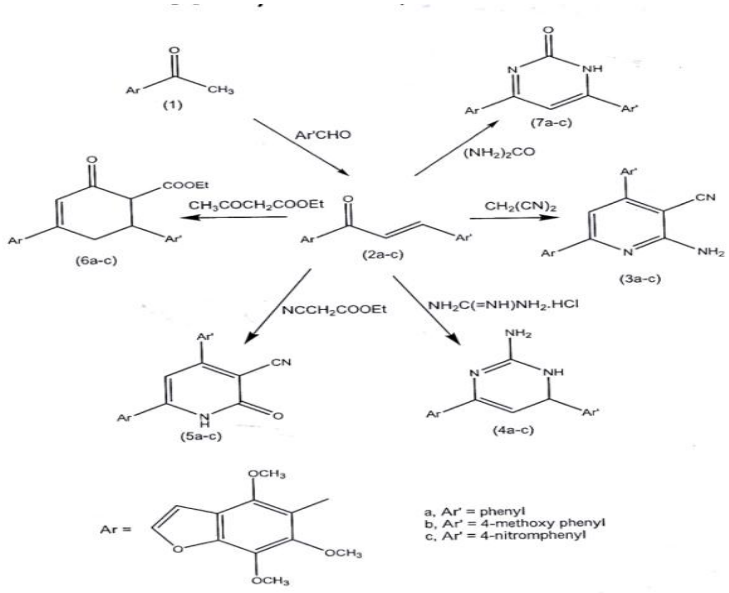


Figure 13: Nehad A.Abdel Latif, ManalM Saeed, Nasreen S. Ahmed, Ras aZ.Batran and Nadia R. A. El-Mouhty synthesis of some pyridine, pyrimidine and cyclohexenone derivatives as antibacterial agents.[38]

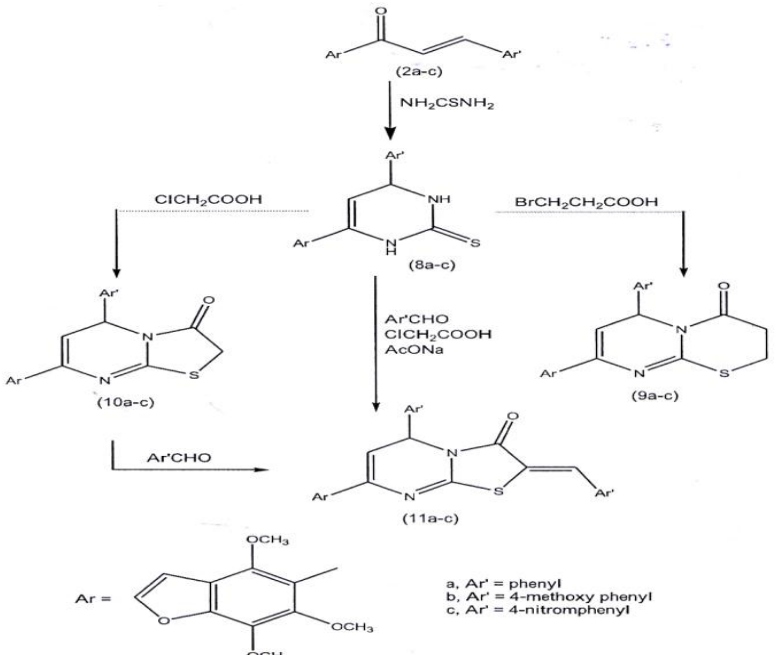


Figure 14: Synthetic Protocol of Target Compounds.

Protocol of Target Compounds

The antibacterial activity of synthesis compounds against, E-coli, Pseudomonas aurignosa, Salmonella typhimurium, Bacillus Subtilis and Staphylococcus aureus were measured by measuring the zone of inhibition in disc diffusion method.

Mohamad F.Ali, Abdulrahim M Khlafulla, Reem mohamed Synthesis of Benzimidazole Derived Chalcones and their Heterocyclic Derivatives.[39]

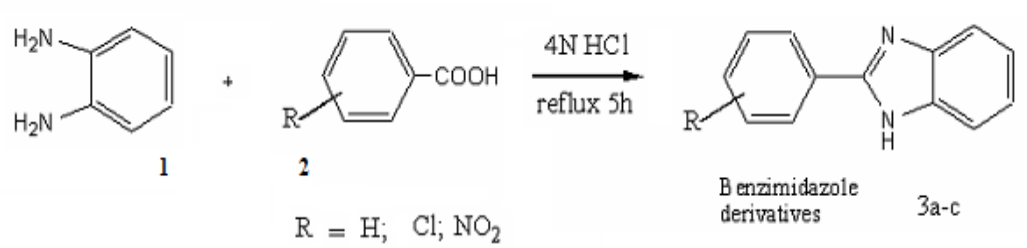
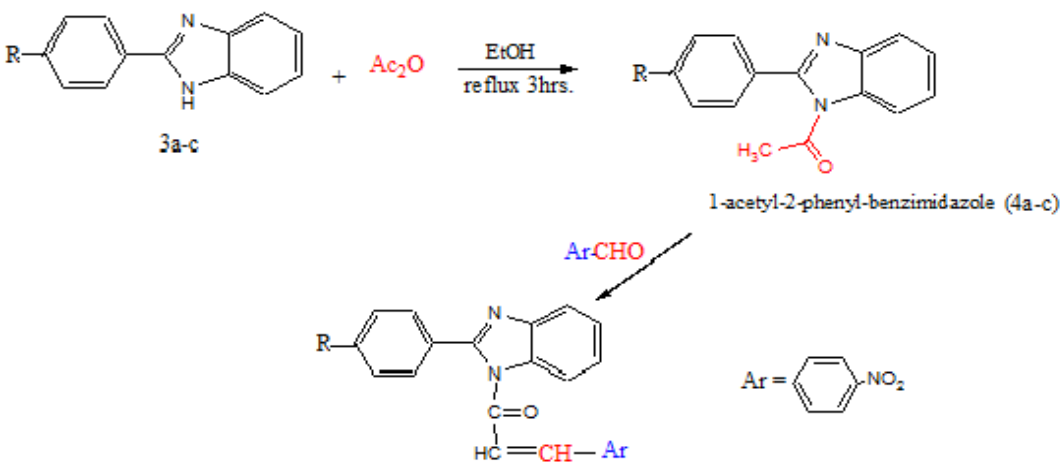


Figure 15: Synthesis of benzimidazole derivative.



Schem 2 : synthesis of chalcone derivatives (5a-c)

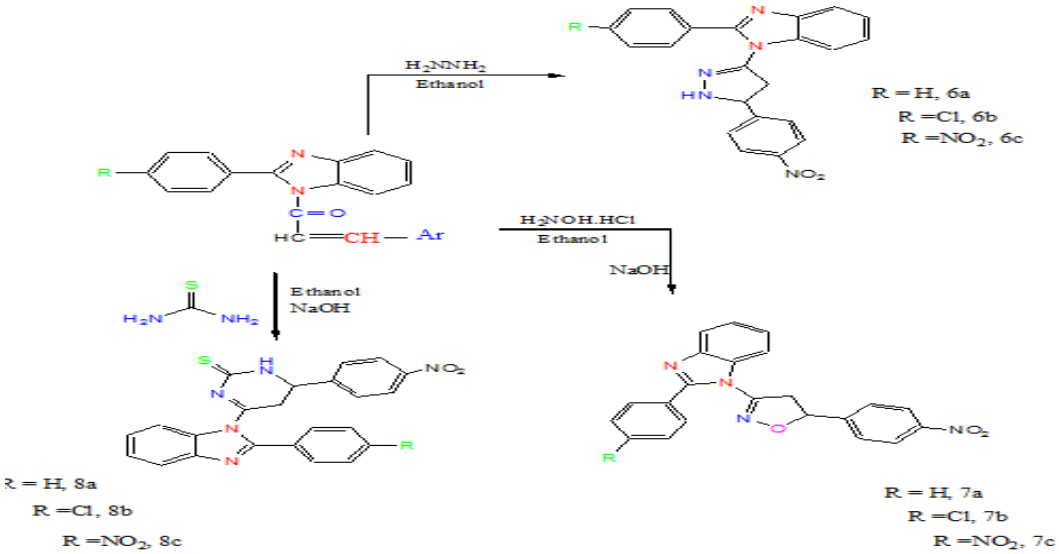


Figure 16: The synthesis route of the cyclized products.

Chemically as chalcones, they consist of open-chain flavonoids in which the two aromatic rings are joined by a three carbon chain.[40] They display a wide range of pharmacological properties, including cytotoxity towards cancer cell lines[41,42], antimitotic[43], antimutagenic[44] and antitumor-promotingactivities; antibacterial[45], antiviral[46], anti-inflammatory[47], antiulcerative[48] and hepatoprotective activities.

D.D Kumbhar Departmentment of chemistry, university of pune ganeshkhind, pune: Synthesis and evalution of chalcones as an antibacterial and anti fungal agents.[49]

The antibacterial activity and antifungal activity of chalcones was evaluated by agar well diffusion method.

TranTD, Nguyen TT, DoTH, HuynhTH, TRanCD, ThaiKM synthesis and antibacterial activity of some hetrocyclic chalcones analogues alone in combination with antibiotics. Chem. Biodevers 2010.[50] The synthesized chalcones were established and had shown activities against both susceptible and resistant staphylococcus aureus strains, but not active against a vanomycin and methicillin resistant. Dimmock and co-workers proposed that the presence of amino function increases the reactivity of chalcones as Michael acceptors and subsequently their anti-proliferative activity. They postulated that the amino function would be protonated at low pH environment normally encountered in tumors. The electron withdrawing effect of the protonated ammonium function would enhance the electrophilicity of the β- carbon in the enone linkage, hence increasing its reactivity as a Micheal acceptor.[3]

Saxena and co-workers grafted chalcones derivatives on estradiol framework some of which showed potent anticancer activity against some human cancer cell lines, potent activity against estrogen receptor- positive and hormone- dependent human breast cancer cell lines, MCF-7. Active anticancer derivatives were also evalutated for osmotic hemolysis using the erythrocyte as a model system. It was observed that chalcones derivatives showing cytotoxicity against cancer cell lines did not affect the fragilityb of erythrocytes and hence may be considered as nontoxic to normal cells: however, nitric oxide production by trimethoxy chalcones derivatives, with various patterns of fluorination, has also been evaluated. One of this compounds, 2,4,6-trimethoxy-20 trifluromethylchalcone, inhibited the production of No and prostaglandin E2 in Lipopolysaccharides stimulated RAW264.7 macrophage cells.[3]

CONCLUSION

From the above review it is evident that chalcones and their hetrocyclic derivatives represent a class of compounds as they show a wide range of pharmacological activites. A number of substitutions are possible in the aromatic rings and ring closure reactions of the chalcones affords hetrocyclic derivatives which are pharmacologically active which further warrants the exploitation of this class of compounds. However, much of the pharmacological potential of chalcones is still not utilized. the purpose of screening of synthetic chalcones, studying importance of chalcones, and synthesis of pharmacologically active chalcones and their biological activities.

REFERENCES

1. Rahman MA Chalcone: a Valuable Insight into the Recent Advances and Potential Pharmacological Activities. Chemical Sciences Journal, 2011; 29: 1-16.
2. Rajat G, Abhijit D, Department of pharmacy, Tripura University, Suramaninnagar, Tripura, World Journal of pharmacy and pharmaceutical Sciences, 2014.
3. Bhat.B, Dhar. K, Sexena.A, Shanmugavel. M, Bioorag. Med. Chem., 2005; 15(3): 177.

4. Michael.L, David.S, Parsad. S, J. Med. Chem., 1990; 331948.
5. Yerragunta V, Kumaraswamy T, SumanD, Anusha V, Patil P, Sahitha T, a Review on chalcones and its importance, pharmatutor, 2013; 1(2): 54-59.
6. B.A. Bhat, K. LDhar, A.k.saxena and M.shanmugavel, Bioorg. med. chem., 2005; 15(3): 177.
7. Pharmacopoeia of India II, A-100, A-108. 1996.
8. Chatterjee.S, Das. S, Ind. J. Pharmacology, 1996; 28: 116.
9. Sivakumar PM, Seenivasan SP, Kumar V, Doble M. Synthesis, antimycobacterial activity evaluation, and QSAR studies of chalcone derivatives. Bioorganic & Medicinal Chemistry Letters, 2007; 17: 1695–1700.
10. KumarD, KumarNM, AkamastsuK, Kusaka E, HaradaH, Ito T, synthesis and Biological Evalution of indolyl Chalcones as antitumour agents. Bioraganic & Medical Chemistry letters, 2010; 20: 3916-9.
11. KumarD, KumarNM, AkamastsuK, Kusaka E, HaradaH, Ito T, synthesis and Biological Evalution of indolyl Chalcones as antitumour agents. Bioraganic & Medical Chemistry letters, 2010; 20: 3916-9.
12. Mhd J.Elarfi, Hussniyia A.Al-Difar synthesis of some heterocyclic compound derived from chalcones Scientic Reviews and chemical communication, 2012; 2(2): 103-107.
13. Barry.A, Antibiotics in Laboratory Medicine Corian (Ed.), Williams & Wilkins, Baltimore, 1991, alves A.J. Etal., Rev. Farm., 1999; 34: 77.
14. Kalirajan. R, Sivakumar. S, Jubie. S, Gowramma. B, Suresh. B Synthesis and Biological evaluation of some heterocyclic derivatives of Chalcones*et al.*/International Journal of Chem Tech Research, Jan – March 2009; 1(1): 27-34, ISSN : 0974-4290.
15. Marta. K.C, novel pyrazines analogs of chalcones: synthesis and Evalution of their antifungal and antimycobacterial activity.et/al molecules, 2015; 20: 1104-111717.
16. Clinical and Laboratory Standards institute. Reference method for broth dilution antifungal Susceptibility Testing Of Yeasts: Approved standard, CLSI document M-27-A3, 3rd ed.: Clinical and Laboratory Standards institute: Wayne, Pa, USA, 2008.
17. Clinical and Laboratory Standards institute. Reference method for broth dilution antifungal Susceptibility Testing Of Filamentous Fungi: Approved standard, CLSI document M-38-A2, 2nd ed.: Clinical and Laboratory Standards institute: Wayne, Pa, USA, 2008.
18. Collins, l., franzblau, S.G. microplate Alamar blue assay versus Bactec 460 system for highb-throughput screening of compounds against mycobacterium tuberculosis and mycobacterium avium. Antimoicrob. agents Chemother, 1997; 41: 1004-1009.
19. Amit R. T. department of chemistry, Saurashtra university, Rajkot gujrat: Synthesis and biological evalution of sme new pyrimidines via a novel chalcones series arkivoc, 2008; (xi): 131-141. ISSN 1551-7012.
20. Tomar V, Bhattacharjee G, Kamaliddina, Kumar A. Synthesis and antimicrobial Evalution Of new Chalcones Contaning Piperazine Moiety. Bioorganic & medicinal Chemistry Letters, 2007; 17: 5321-4.
21. Hans Rh, Guantai Em, Lategan C, Smith Pj, wanc B, Franzblau Sg, Gut j, RosenthalPJ, ChibaleK synthesis antimalarial amd antitubercular activity of acetylenic chalcones. bioorganic & Medical Chemistry letters, 2010; 20: 942-4.
22. Rajendra P, Praveen K, Ravi k Srinivasa .R, Synthesis and antimicrobial activity of some new Chlcones of 2—Acetyl Pyidine university college of pharmaceutical sciences, Andhra university, vishkhapatnam, e-journal of chemistry, Jan 2008; 5(1): 144-148.
23. John Anto R, Sukumaran K, Kuttan G, rao MNA, Subbaraju V and Kuttan R., cancer letters, 1995; 97: 33.
24. Vaya R, Belinky PA and Aviram M, Free Radiac. Biol. Med., 1997; 23: 302.
25. Mukherjee S, Kumar V Prasad AK, Raj HG, Brakhe ME, Olsen CE, Jain Sc and Parmar Vp, Bioorag. Med Chem, 2001; 9: 337.
26. Indyah A, Timmerman H, Samhoedi. M, Sastrohami D, Sugiyanto H and Vander Goot H, Eur. J. Med. chem., 20000; 35: 449.
27. Chen. M, Christensen Sb, Zhai L, Rasmussen MH, Theander TG, Frokjaer S, Steffensen b, Davidson J and Kharazmi a, J. Infect. Dis., 1997; 176: 1327.
28. Nielsen. Sf, Christensen SB, Cruciani G, Kharazmi A and liljefors T, J. Med. Chem., 1998; 41: 4819.
29. Anjali. S, Ghanshyam. P and sejal solankee depratment of chemistry, B.k.m. science College valsad-396001 Rasayan J. chem., 2008; 3: 591-595.
30. Kyogoku. K, Hatayama. K, Yokomori. S, Saziki. R, Chem. Pharm. Bull., 1979; 27(12): 2943; Chem. Abstr., 1980; 93: 26047.
31. Marmo.E, Caputi. A, S. Cataldi, Farmaco, Ed. Prat., 1973; 28(3): 132; Chem. Abstr., 1973; 79: 13501v.
32. Shoji.S, Masatoshi. H, Widago.B, Yakugaku Z, 1960; 80: 620; Chem. Abstr., 1960; 54: 21488e.
33. Makarova N. V., Zemtsova M. N. and Moiseev I.J., Chem. Heterocycl. Comps., 2001; 37(7): 840; Chem. Abstr., 1960; 136: 355209n.
34. Reinhart F. E., Gray J. H., and W. G. Batt, J. Franklin Inst., 1956; 261: 669; Chem. Abstr., 1956; 50: 10930c.
35. Baldwin JJ, Scriabine A., Ludden C.T. and Morgan G., Experientia, 1979; 35(3): 653.; Chem. Abstr., 1979; 91: 83212y.
36. Frasier D. A., Jr. W. C. Holyoke, Jr. M. H. Howard, G. E. Lapone, J. E. Powell and R. J.Pasteris, (E. I. Du Pont De Nemours and Company) PCT Int. Appl. WO97 11,057 (Cl.C07D211/90), 27 Mar (1997); US

Appl. 7, 277, 06 Nov (1995); 107 pp; Chem. Abstr., 1997; 126: 305586f.

37. Nehad A. Abdel Latif, Manal M Saeed, Nasreen S. Ahmed, Rasa Z.B. and Nadia R. A. El-Mouhty Chemistry Department, Faculty of Science, Taif University, 888, vol.3, issue1, January 2014 International journal of innovative Research in sciences Engineering And Technology.
38. Mohamad F.Ali, Abdulrahim M Khlafulla, Reem Mohamad, Synthesis of Benzimidazole Derived Chalcones and their Heterocyclic Derivatives International Journal of Engineering and Applied Sciences (IJEAS) ISSN: 2394-3661, June 2016; 3(6).
39. Rane, R.A.; Telekar V.N., Synthesis and evaluation of novel chloropyrrole molecules designed by molecular hybridization of common pharmacophores as potential antimicrobial agents. *Bioorg. Med. Chem. Lett.*, 2010; *20:* 5681-5685.
40. Konieczny M.T., Konieczny W., Sabisz M.; Skladanowski A.; Wakiec R.; Augustynowicz-Kopec E.; Zwolska Z., Acid-catalyzed synthesis of oxathiolone fused chalcones. Comparison of their activity toward various microorganisms and human cancer cells line. *Eur. J. Med. Chem.*, 2007; *42:* 729-733.
41. Kumar D.; Kumar N.M.; Akamatsu K.; Kusaka E.; Harada H.; Ito, T. Synthesis and biological evaluation of indolyl chalcones as antitumor agents. *Boorg. Med. Chem. Lett.*, 2010; *20:* 3916-3919.
42. Ducki S.; Forrest R.; Hadfield J.A.; Kendall A.; Lawrence N.J.; McGown A.T.; Rennison D. Potent antimitotic and cell growth inhibitory properties of substituted chalcones. *Bioorg. Med. Chem. Lett.*, 1998; *8:* 1051-1056.
43. Edenharder R.; Petersdorff I.V.; Rauscher R., Antimutagenic effects of flavoniods, chalcones and structurally related compounds on the activity of 2-amino-3-methylinidazo[4,5-*f*]quinoline (IQ) and other heterocyclic amine mutagens from cooked food. *Mutat. Res.*, 1993; *287:* 261-274.
44. Pandeya S.N.; Sriram D.; Nath G.; DeClercq E. Synthesis, antibacterial, antifungal and anti-HIV activities of Schiff and Mannich bases derived from isatin derivatives and N-[4-(4′-chlorophenyl)thiazol-2-yl] thiosemicarbazide. *Eur. J. Med. Chem.*, 1999; *9:* 25-31.
45. Biradar J.S.; Sasidhar B.S.; Parveen R. Synthesis, antioxidant and DNA cleavage activities of novel indole derivatives. *Eur. J. Med. Chem.*, 2010; *45:* 4074-4078.
46. Nowakowska, Z. A review of anti-infective and anti-inflammatory chalcones. *Eur. J. Med. Chem.*, 2007; *42:* 125-137.
47. Devi, J.M.; Ali, K.S.; Venkatraman, V.R.; Ramakrishnan, S.K.; Ramachandran, K. A study on the thermal properties of cinnamoylchalcones. *Therochim. Acta*, 2005; *438:* 29-34.
48. Kumbhar. D, Synthesis and evalution of chalcones as an antibacterial and antifungal agents Departmentment of chemistry, University of Pune ganeshkhind, pune: DerPharmacia Letter, 2014; 6(1:224-229ISSN0975-5071).
49. Tran. TD, Nguyen. TT, Do.TH, Huynh.TH, Tran.CD, Thai.KM synthesis and antibacterial activity of some hetrocyclic chalcones analogues alone in combination with antibiotics Chem. Biodevers, 2010.