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

**ISSN 2349-8870
Volume: 4
Issue: 5
128-135
Year: 2017**

CHALCONE – IS A TOOL OF SYNTHESIS OF VARIOUS DRUG

Avinash Bhagvat[1], Anand Khadke[2], Anuradha Patil[3] and Bhagyashri Jadhav*[4]

[1,2]Assistant Professor, Yashoda Technical Campus Satara Faculty of Pharmacy.
[3]JSPM's Jayawantrao Sawant College of Pharmacy.
[4]Student, Yashoda Technical Campus Satara Faculty of Pharmacy.

***Corresponding Author: Bhagyashri Jadhav**
Student, Yashoda Technical Campus Satara Faculty of Pharmacy.

Article Received on 14/03/2017 Article Revised on 25/04/2017 Article Accepted on 26/04/2017

ABSTRCT

1,3-Diphenylprophenyl-2-en-1-one synthesized by the two method, first is Claisen-Schmidt reaction the condensation of substituted acetophenone with substituted aldehyde and the second is Aldol Condensation reaction with para-substituted acetophenone and para-substituted benzaldehyde. Chalcone are used as primary product in many synthesis. Various basic nuclei are also synthesized from chalcone like pyrazolines, Isoxazole, cyanopyridines, pyrimidines.

KEYWORDS: Chalcone, pyrazolines, Isoxazole, cyanopyridines, pyrimidines.

INTRODUCTION

The chemistry of chalcones has generated intensive scientific studies throughout the world. Especially interest has been focused on the synthesis and biodynamic activities of chalcones. The name "Chalcones" was given by Kostanecki and Tambor.[1] These compounds are also known as benzalacetophenone or benzylidene acetophenone. In chalcones, two aromatic rings are linked by an aliphatic three carbon chain. Chalcone bears a very good synthon so that variety of novel heterocycles with good pharmaceutical profile can be designed. Chalcones are -unsaturated ketone containing the reactive keto ethylenic group –CO-CH=CH-. These are coloured compounds because of thepresence of the chromophore -CO-CH=CH-, which depends in the presence of other auxochromes. Different methods are available for the preparation of chalcones.[2-4] Themost convenient method is the Claisen-Schimdt condensation of equimolar quantities of arylmethyl ketone with aryl aldehyde in the presence of alcoholic alkali

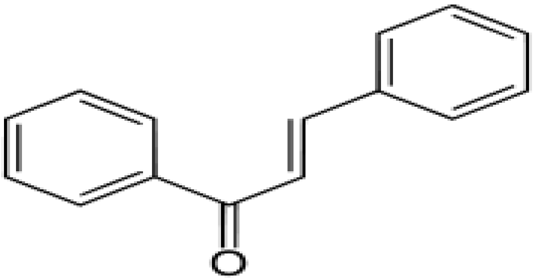


Figure 1. Chalcone

Chalcones are used to synthesize several derivatives like cyanopyridines, pyrazolines isoxazoles and pyrimidines having different heterocyclic ring systems.[6-9]

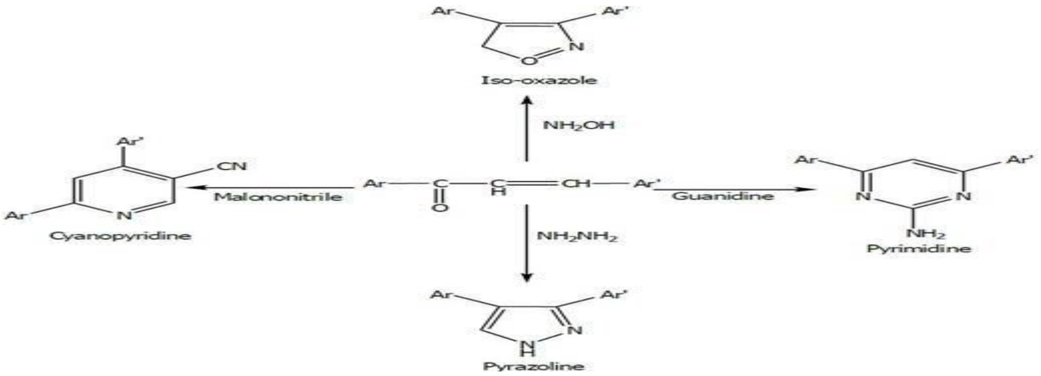


Figure 2. Synthesize several derivatives like cyanopyridines, pyrazolines isoxazoles and pyrimidines.

Method of Synthesis of Chalcone

CLAISEN-SCHMIDT REACTION

A variety of methods are available for the synthesis of chalcones, the most convenient method is the one that involves the Claisen-Schmidt condensation of equimolar quantities of a substituted acetophenone with substituted aldehydes in the presence of aqueous alcoholic alkali.[10-17] In the Claisen-Schmidt reaction, the concentration of alkali used, usually ranges between 10 and 60 %.[18-19] The reaction is carried out at about 50 oC for 12-15 hours or at room temperature for one week. Under these conditions, the Cannizaro reaction[20] also takes place and thereby decreases the yield of the desired product. To avoid the dis proportionation of aldehyde in the above reaction, the use of benzylidene-diacetate in place of aldehyde has been recommended.[21a]

[1] Alkali: Alkali has been the most used condensing agents for synthesis of chalcones. It is used as an aqueous solution of suitable concentration viz. 30 %, 40 %, 50 % and 70 %.

[2] Hydrochloric Acid

Dry hydrochloric gas in a suitable solvent like ethyl acetate at 0 oC was used as a condensing agent in a few syntheses of chalcones from aromatic ketones. Methanolic solution of dry hydrochloric acid gas at 0 oC was also used by Lyle, Paradis[21b] and Marathey.[21c]

[3] Other Condensing Agents

Raval and Shah[22] used phosphorous oxychloride as a condensing agent to synthesize of chalcones. Szell and Sipos[23] condensed 2-hydroxy-5-nitroacetophenone with benzaldehyde using anhydrous AlCl3. Kuroda, Matsukuma and Nakasmura[24] obtained chalcone by condensing acetophenone derived from anisole and other polymethoxy benzenes with some methoxy aldehydes in presence of anhydrous aluminium chloride.

Besides the above, other condensing agents used in synthesis of chalcones have been,

(1) Amino acid[25]
(2) Aqueous solution of borax[26]
(3) Perchloric acid[27]
(4) Piperidine[28]
(5) Boron trifloride[29]
(6) Alkali metal alkoxide[30]
(7)Magnesium tert-butoxide[31]
(8) Organocadmium compound[32]

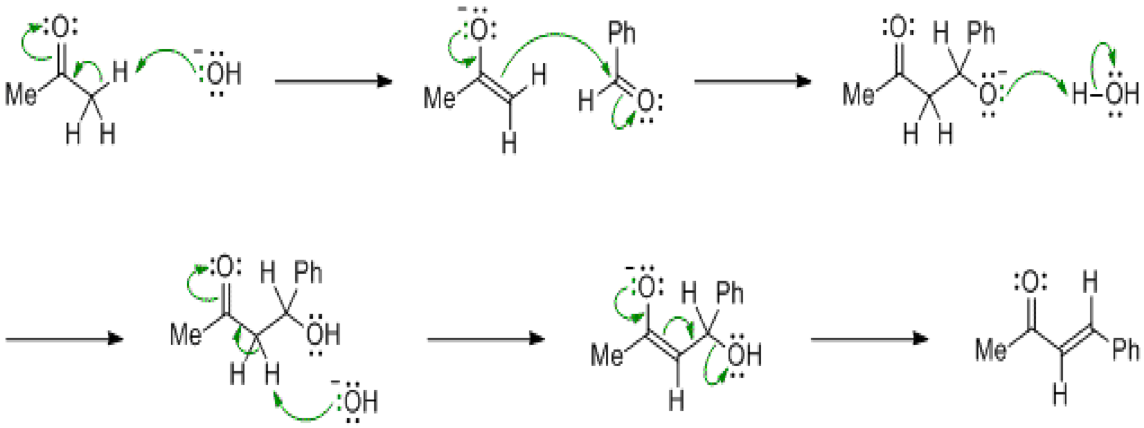


Figure 3. Synthesis of Chalcone Via Claisen Schmidt Reaction

ALDOL CONDENSATION

In this experiment, you will perform a crossed aldol condensation reaction with an unknown para-substituted acetophenone and an unknown para-substituted benzaldehyde under basic conditions to provide a chalcone product. This particular crossed aldol reaction is expected to proceed cleanly since only the substituted acetophenone can form an enolate, as the substituted benzaldehyde does not contain any -hydrogens. Under these equilibrating reaction conditions, the acetophenone enolate is formed in low concentration,α since the equilibrium favors the reactants (this would be expected based upon the reactant and product pKa values given – see reaction scheme below). The nucleophilic acetophenone enolate then reacts with the substituted benzaldehyde, rather than another acetophenone molecule, since aldehydes are more electrophilic than ketones and thus react much more rapidly. As is true of most aldol condensations (especially those involving aromatic aldehydes), the aldol addition product readily -unsaturated carbonyl compound. The double bond formedβ,αundergoes dehydration (via E1cB elimination) to give an is then part of a conjugated system with both the carbonyl group and the aromatic rings. Since this reaction is performed under equilibrating conditions, the lower energy alkene product is obtained – specifically, the highly conjugated trans-alkene. The formation of the highly conjugated alkene product thus serves to drive the equilibrium to the product side. We will use two solvents in today's experiment. The substituted benzaldehyde and acetophenone are soluble in EtOH, whereas NaOH is soluble in water. Hence, a co-solvent system is used in this reaction. The aldol condensation product is less soluble than the starting materials, so it precipitates from the reaction mixture as it is formed. After the reaction is complete, addition of water promotes additional precipitation of the product (the organic compound is even less soluble in water than EtOH). The chalcone is thus isolated via filtration and then purified by crystallization from EtOH.

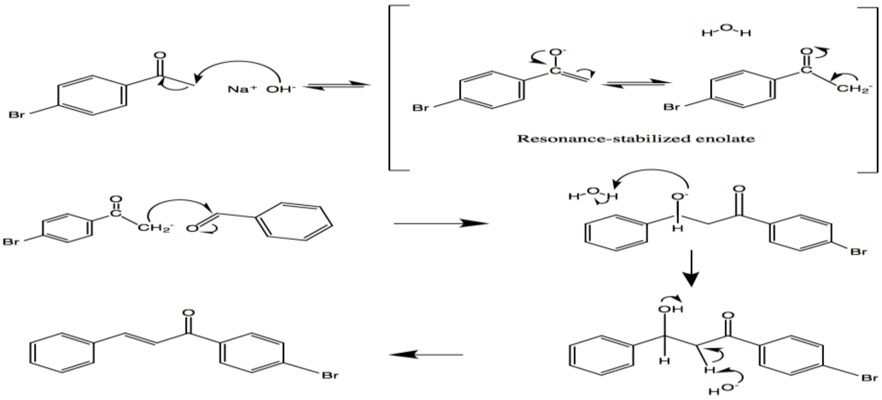


Figure 4. Synthesis of Chalcone Via Aldol Condensation

Various Basic Nuclei synthesis from chalcone

1. Pyrazoline
2. Isoxazole
3. Cynopyridines
4. Pyrimidines

➢ PYRAZOLINE

Synthesis of pyrazoline: synthesis, characterization and biological screening of some novel 1, 3, 5 Trisbstituted 2-Pyrazolines, pyrazolines of nicotinic acid derivatives were synthesized. Nicotinic acid was converted to nicotinic acid hydrazide. 10 different chalcones were synthesized by reacting different aromatic aldehydes with paracetamol. These chalcones on reaction with nicotinic acid hydrazide yielded 10 different 2-pyrazolines. The structure of synthesized compounds was confirmed by spectral data. They were screened for anti-microbial activities.

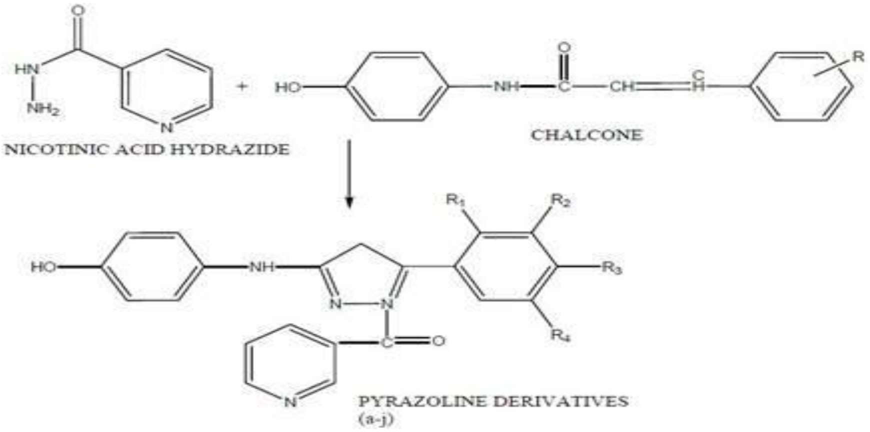


Figure 5. Synthesis Of Pyrazoline Derivatives

- **Pyrazoline Containing Drug**

1. Phenazone

✚**Structure**

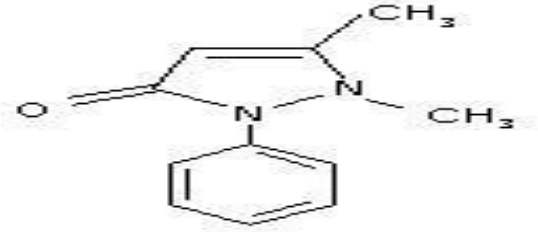


Figure 6. Phenazone

✚**Chemical name**- phenazone API 1,5,-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazole-3-one.

✚**Category**– Analgesic, Antipyretic.

✚**Method Of Synthesis**

Phenazone

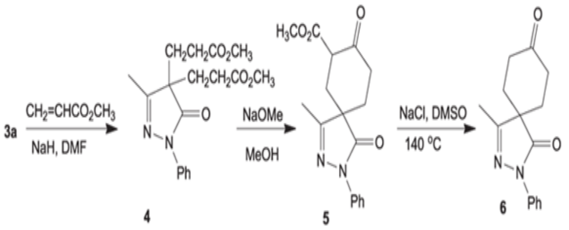


Figure 7. Synthesis of Phenazone

2. Oxyphebutazone

- **Structure**

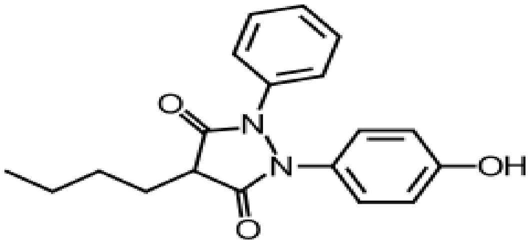


Figure 8. Oxyphebutazone

- **Chemical Name** - 4-Butyl-1-(4-hydroxyphényl)-2-phényl-3,5-pyrazolidinedione, hydrate
- **Category** – Non-steroidal Anti-inflammatory.
- **Method Of Synthesis**

Oxyphebutazone

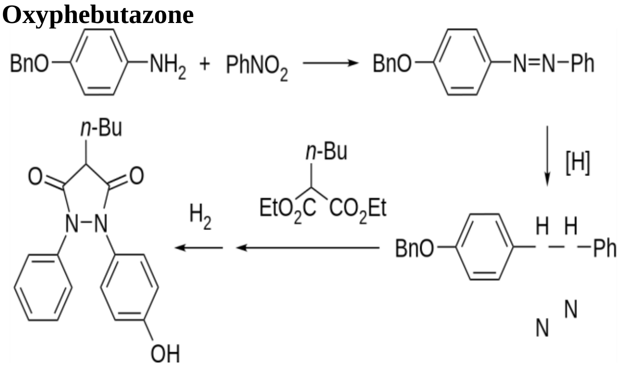


Figure 9. Synthesis of Oxyphebutazone

➢ ISOXAZOLE

Synthesis of Isoxazole

Isoxazole is a five membered heterocyclic compound .Isoxazoles occupy unique position for their antibacterial, anti - inflammatory, antiviral and anti-fungal activities. They are mainly used in controlling of invertebrate pests in agronomic environments. Chalcone on reaction with hydroxylamine hydrochloride and potassium hydroxide in presence of methanol and acetic acid gives isoxazoline derivative.

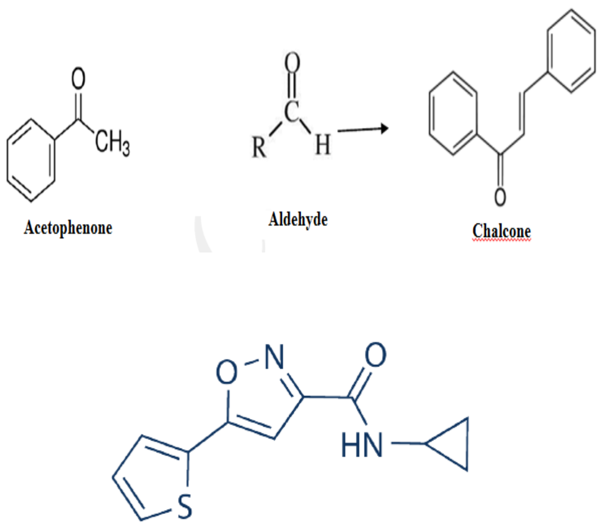


Figure 10. Synthesis of Isoxazole Derivative

- **Isoxazole Containing Derivatives**

1 . Leflunomide

- **Structure**

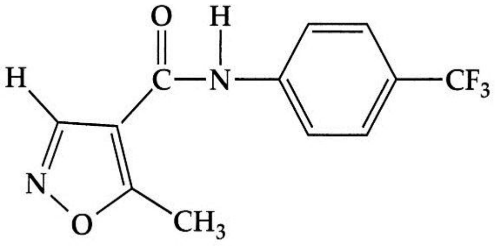


Figure 11. Leflunomide

- **Chemical Name** -Leflunomide, 75706-12-6 ; Arava ; Leflunomidum ; Lefunamide ; Leflunomida.
- **Category–** Anti- rheumatic.
- **Method Of Synthesis** –

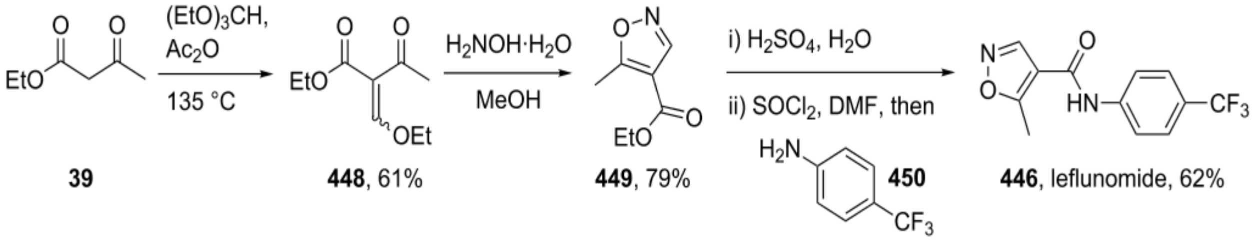


Figure 12. Synthesis of Leflunomide

2. Valdecoxib

- **Structure**

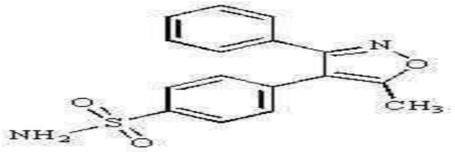


Figure 13. Valdecoxib

Chemical Name :- Valdecoxib ; 181695-72-7,Bextra ; 4 - (5-methyl)-3- Phenylisoxazole-4-yl) benzenesulfonamide.

Category :-Non-Steroidal anti-inflammatory.

Method of Synthesis

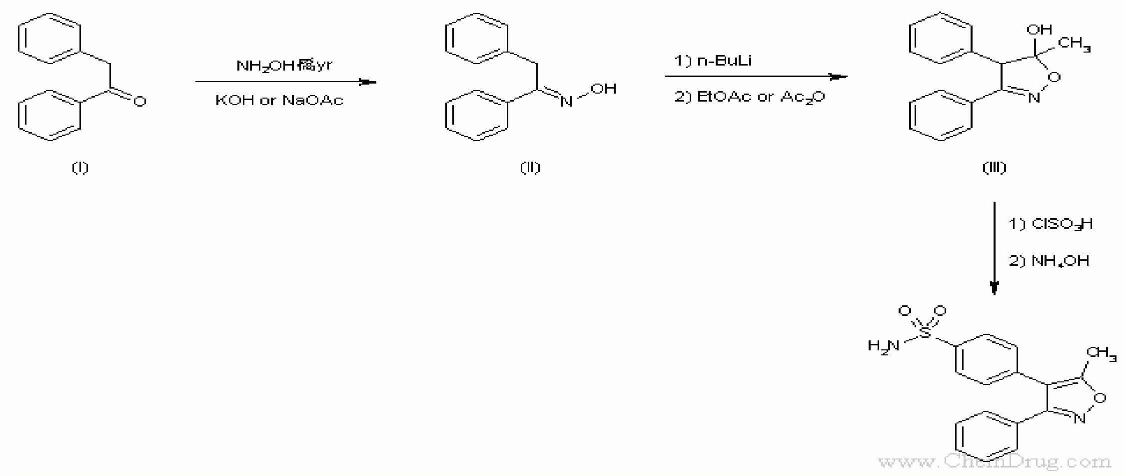


Figure 14.Synthesis Of Valdecoxib

2. Muscimol

Structure

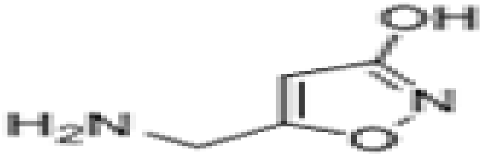


Figure 15.Muscimol

Chemical Name :- Muscimol;Pantherine;Agarin;2763-96-4;Agarine,Pantherin.

Category :- Sedative.

Method Of Synthesis

Muscimol

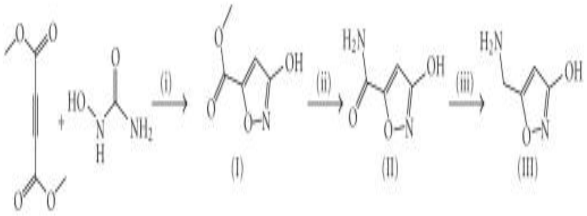


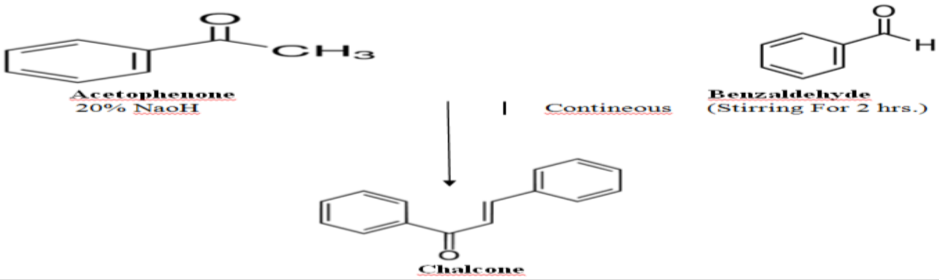
Figure 16. Synthesis of Muscimol

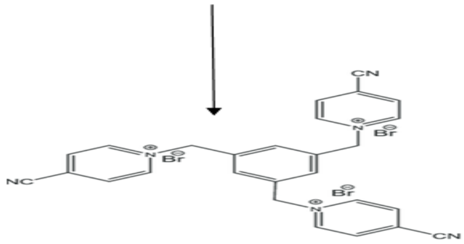
➢ CYANOPYRIDINE

- **Synthesis Of Cyanopyridine**

To a 20 ml solution of 20% sodium hydroxide in distilled water, acetophenone (0.001mol) was added and dissolved. To this benzaldehyde (0.001 mol) was added in small amounts with continuous stirring with the help of a mechanical stirrer or about 2 h. The mixture was left in refrigerator for 24 h. Then the yellowish product thus formed is filtered, dried and recrystallized from ethanol. The synthesized compounds were monitored by TLC[34]

Compound C1-6 (0.01mol) in alcohol (40 mL) malononitrile (0.01mol) and ammonium acetate was refluxed for 8 h. The reaction mixture was then cooled, poured into crushed ice and product separated out was filtered, washed with water, dried and recrystallized from ethyl alcohol.





Cyanopyridine

Figure 17.Synthesis of Cyanopyridine

- **Cyanopyridine Containing Drug –**

1. **Milirinone –**

- **Structure –**

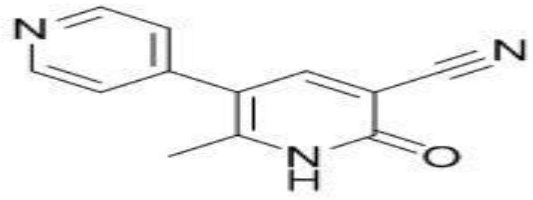


Figure 18. Milirinone

- **Chemical Name** – Milirinone;78415-72-2;Primacor;Corotrope;Milrinona.
- **Category** – Cardiac Stimulant.
- **Method Of Synthesis** –

Milirinone

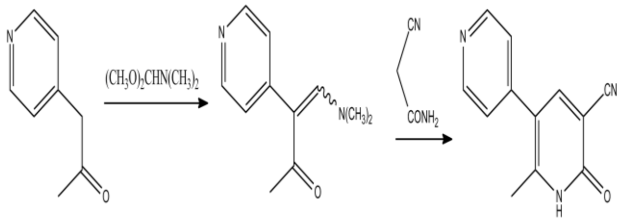


Figure 19.Synthesis Of Milirinone

➢ PYRIMIDINE

Synthesis Of Pyrimidine: The synthesis of chalcone and pyrimidine derivatives was performed following the steps shown in Scheme-1. In the initial step, chalcones (2a-j) were synthesized by condensing 2-(4-carboxyphenylazo)acetoacetate23 1 with appropriate arometic aldehydes in dilute ethanolic sodium hydroxide solution at room temperature. The compounds (3a-j) were synthesized by reacting the appropriate chalcone with urea and potassium hydroxide in ethanol. The purity of the compounds was determined by TLC and elemental analysis. Spectral data (IR, 1 H-NMR, 13C NMR and Mass) of all the newly synthesized compounds were in full agreement with the proposed structure.

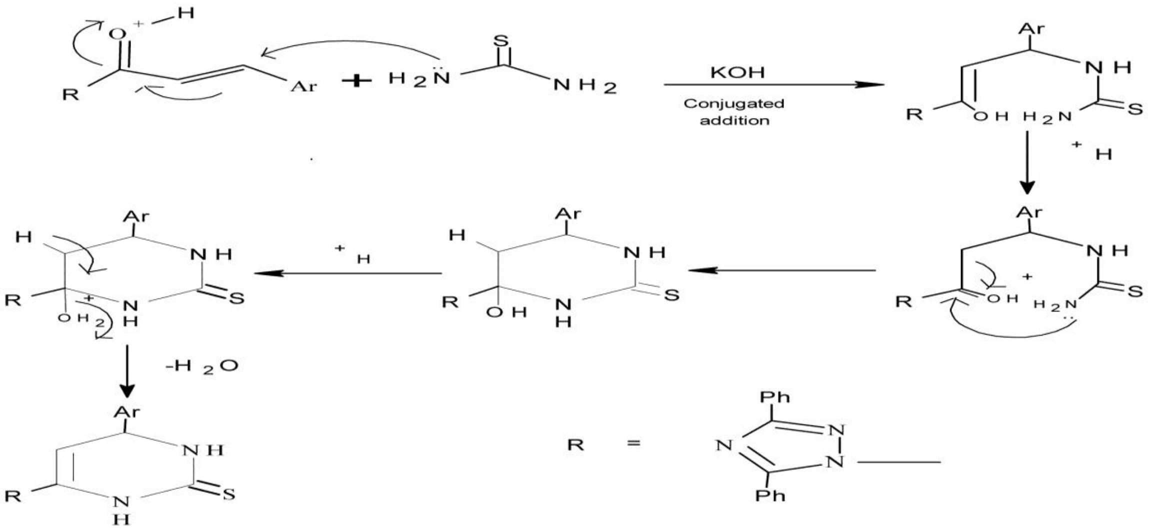


Figure 20. Synthesis of Pyrimidine

- **Pyrimidine Containing Drug**

1. Thonzylamine

- **Structure**

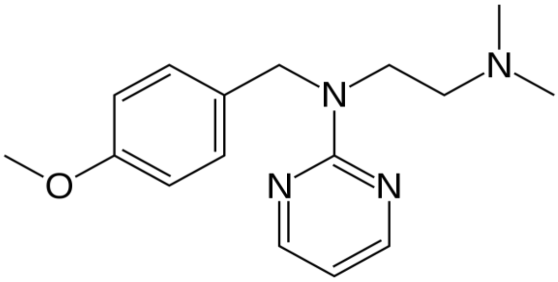


Figure 21. Thonzylamine

- **Chemical Name**

THONZYLAMINE HYDROCLORIDE; Thonzylamine Hcl; Novohetramine; Anahist; Resistab; Thonzylamine Chloride.

- **Category** – Antihistamine

- **Method Of Synthesis**

Thonzylamine

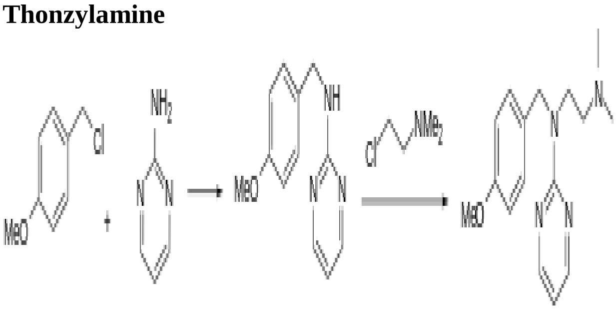


Figure 22. Synthesis Of Thonzylamine

2. Buspiron

- **Structure**

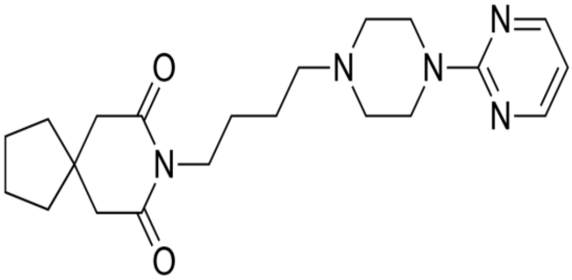


Figure 23. Buspirone

- **Chemical Name** – Buspirone;Ansial;36505-84-7;Buspironum;Buspirona;Bespar.

- **Category** – Antianxiolytic Agent.
- **Method Of Synthesis**

Buspirone

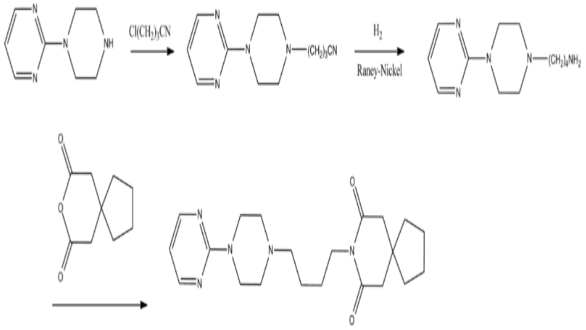


Figure 24. Synthesis of Buspirone

CONCLUSION

The chemistry of heterocyclic compound is to be as an important with the help of chalcone different synthesis are derived and used to synthesis such as Pyrazolines contain Phenazone,. Further Isoxazole contain Leflunomide, Valdecoxib, Muscimol.Further Cyanopyridine contain Milirinone. Further Pyrimidine contain Thonzylamine, Buspiron.

REFERENCE

1. S. V. Kostanecki and Tambor, J. Chem Ber., 1899; 32: 1921.
2. H. Rupe and D. Wasserzug, J. Chem Ber., 1901; 34: 3527.
3. S. A. Hermes, Chem Ber., 1969; 70: 96422h.
4. D. S. Breslow and C. R. Houser, Chem Ber., 1940; 62: 2385.
5. K. Kazauki, K. Hitayama, S. Yokomor and T. Soki, Chem Abstr., 1976; 85: 591.
6. M. A. El.Hashah; M. El-Kady; M. A. Saiyed and A. A. Elaswy, Egypt. J. Chem., 1985; 27: 715.
7. L. S. Crawley and W. J. Fanshawe, J. Heterocyclic chem., 1977; 14: 531.
8. E. C. Taylor and R. W. Morrison, J. Org. Chem., 1967; 32: 2379.
9. P. S. Utale, P. B. Raghuvanshi and A. G. Doshi, Asian J. Chem., 1998; 10: 597.
10. E. P. Kohler and H. M. Chandwell, Org. Synth. Coll., 1922; 2, 1.
11. E. Schraufstalter and S. Deutsch, Chem Ber, 1948; 81: 489.
12. H. E. Smith and M. C. Paulson, J. American Chem. Soc., 1954; 76: 4486.
13. H. Obara, J. Onodera and Y. Kurihara, Bull. Chem. Soc. Japan, 1971; 44: 289.
14. J. Shinoda and S. Sato, J. Pharm. Soc. Japan, 48, 791, (1928), C.A., 23, 836, (1929)
15. E. F. Kurth, J. American Chem. Soc., 1946; 68: 697.
16. T. A. Gaissman and R. O. Clinton, J. American Chem. Soc., 1946; 68: 697.
17. G. J. Martin, J. M. Beler and S. Avakian, U. S. Patent ,2, 769, 817 (1956), C. A., 51, 14815 (1957)
18. Falcao de Fonseca L and Bol Fac Farm, Univ. Coimbra, Ed. Cient, 28, 49, (1968), C. A., 1970; 72: 121124p.
19. S. Fujise and H. Tatsuta, J. Chem. Soc. Japan, 1942; 63: 932.

20. D. N. Dhar and J. B. Lal, J. Org. Chem., 1958; 23: 1159.
21. (a) W. Davey and J. R. Gwilt, J. Chem. Soc., 1008, (1957) (b) R. E. Lyle and L. P. Paradis, J. Am. Chem. Soc., 77, 6667 (1955) (c) M. G. Marathey, J. Uni. Poona, 1952; 1-19.
22. A. A. Raval and N. M. Shah, J. Sci. Res. India, 1962; 21(B): 234.
23. Szell and Sipos, Ann., 1961; 64(1): 113, 34 References.
24. C. Kuroda and T. Matsukuma, C. A., 2442; 26.
25. L. Reichel, Nalanxlissenchaften, 1944; 33: 215.
26. G. V. Jadhav and V. G. Kulkami, Curr. Sci. (India), 1951; 20: 42.
27. V. M. Vlasov, Izv. Sib. Old. Akd. Nauk. USSR, Set: Khim. Nauk., 2, 96 (1971), C.A., 60, 1683 (1964)
28. P. L. Cheng, P. Fournari and Triouflet, J. Bull. Soc. Chem. France, 10, 2248 (1963), C. A., 60, 1683 (1964).
29. D. S. Breslow and C. R. Hauser, J. Am. Chem. Soc., 1940; 62: 2385.
30. S. Fujise and H. Tatsuta, J. Chem. Soc. Japan, 1942; 63: 632.
31. J. L. Guthrit and N. Rabjohn, J. Org. Chem., 1957; 22: 176.
32. H. Gilman and J. P. Nelson, Rec. Trav. Chem., 1936; 55: 518.
33. Organic Chemistry by John McMurry,8e,chapter sections 11.10 (E1cB mechanism)and 23.1-23.5 (Aldol Condensation).
34. Venkatesan J et al. synthesis and biological evaluation of 4, 6-diaryl substituted-4,5- dihydro-2-amino pyrimidines. Indian J.Pharm.Sci. 2007; 69(4); 586-589.
35. Anjani solankee et al. Anti microbial evaluation of some novel isoxazoles, cyanopyridines and pyrimidinthiones. Indian J Chem. 2013; 52 B; 671-676.
36. Anjani Solankee et al. Synthesis and studies of chalcones and its Cyanopyridine and Acetyl Pyrazoline Derivatives. Rasayan J. Chem. 2008; 1(3): 591-595.