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CHAPTER 16

General Introduction, Synthetic Methods and Applications of Chalcones in Pharmaceutical

Gajanan Kottapalle

Department of Chemistry, Digambarrao Bindu ACS College, Bhokar Dist. Nanded 431801 Maharashtra, India

Corresponding author Email: gdkottapalle12@gmail.com

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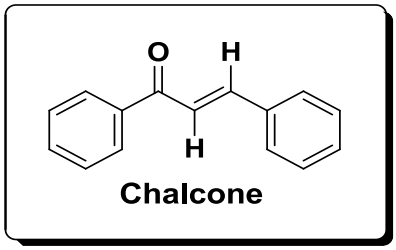
Introduction

Chalcones have been the subject of extensive scientific study throughout the world due to their chemistry. In recent years, chalcones have gained a lot of attention in terms of their synthesis and biodynamic properties. The name "Chalcones" was specified by Kostanecki and Tambor[1]. Alternative names for chalcones are benzylidene acetophenone, Phenyl styryl ketone, benzalacetophenone, β-phenyl acrylophenone and α-phenyl-β-benzoylethylene. This compound is composed of two aromatic rings linked by an aliphatic chain of three carbons with a ketone group and with a reactive ketoethylenic group –CO-CH=CH-. Due to the presence of chromophore -CO-CH=CH- chalcones are coloured compounds, the colour of compounds enhances in the presence of other auxochromes[2]. They undergo variety of chemical reactions and are used initial material for the synthesis of various heterocyclic compounds in which chalcones act as basic building blocks for their preparation. Chalcones are the key precursor so that selection of novel heterocycles with good pharmaceutical activities can be designed. It is represented as:



Chalcone

Chalcones have an α,β-unsaturated carbonyl group are one of the significant biocides and helpful synthons for various chemical transformations. An important group of natural products, chalcones, have a growing pharmacological potential[3]. These compounds are precursors of flavonoids and isoflavonoids which are class of naturally occurring compounds rich in plants. Several pharmacological and medicinal applications are associated

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with maximum chalcones[4]. Chalcones are also widely used in dyes and cosmetic compositions, in addition to pharmaceutical industries[5,6]. In addition to their biological importance, chalcone derivatives have good crystallizability and nonlinear optical (NLO) properties[7]. Chacones possess an antimicrobial and antihyperglycemic activity due to the presence of the naphthyl ring[8,9].

The benefits of Chalcones to human beings have attracted much attention due to their abundance in nature[10]. Biologically active molecules, both synthetic and natural, contain the main structural design of chalcones. Several offensive diseases such as cancer, tuberculosis, diabetes, HIV, malaria, and many others are being treated with chalcones manufactured synthetically or isolated from their natural sources. Chalcones and their derivatives have also been seen to find applications in large varieties of diverse areas such as artificial sweeteners, scintilator, stabilizer against heat and visible light. In agriculture, they are used to destroy phytopathogenic organism, eco-friendly plant growth regulators and defense agents. Similarly in industry chalcones are used as anti-sunburn oil. The compounds synthesized from chalcones include such as flavonones, flavonols, flavones and their derivatives like pyrazolines, isoxazolines, benzodiazepines, benzothiazepines, pyridines, thiopyrimidines, etc.

Synthetic Methods of Chalcones

The chemistry of chalcones has generated demanding scientific studies throughout the world, known bioactive heterocyclic five, six and seven-membered compounds are synthesized from chalcones, which have a unique structure that facilitates their synthesis as the core structure of various known organic compounds. There are numerous synthetic methods reported in literature some of them discussed below:

1) By Claisen-Smidth Condensation

Several methodologies have been reported in literature but Claisen-Schmidt condensation is the most frequently used methodology for the synthesis of chalcones.

In the Claisen-Schimdt condensation equimolar quantities of aryllketone(presence of active –CH -group) and aryl aldehyde (absence of ∝–H atom) get condensed in the presence of NaOH or KOH generally in ethanol solution. Occasionally piperidine is also used as base for this condensation reaction. Normally hydroxyl chalcones were prepared from the corresponding hydroxy substituted acetophenones and aromatic aldehydes substituted by various groups in the presence of NaOH, KOH and piperidine as a base in ethanol as solvent[11,12].

A potential substitute for conventional homogeneous/heterogeneous acidic catalysts is the preparation of chalcones by the use of ionic liquid, which is an efficient and environmentally friendly method. Ionic liquids (ILs) with sulfonic acid functions were prepared and employed as catalysts and solvents for the synthesis of chalcones from acetophenone and benzaldehyde using Claisen-Schmidt condensation.[13].

2) By Heck Coupling Reaction

Synthesis of chalcones between an α, β-unsaturated ketone and an aryl-iodide by using the Heck coupling reaction in which equimolecular quantities of compound 1-(3,4-dimethoxyphenyl)-prop-2-en-1-one and o-acetoxy-iodobenzene were dissolved in acetonitrile; Et_3N, $Pd(OAc)_2$ and PPh_3 were added and the mixture was stirred refluxing (85°C) under argon. The reaction completed after 2.5 hrs. Several differently substituted chalcones have been prepared by this method with very satisfactory yields, confirming the versatility of this method[14].

3) By Microwave Irradiation Method

It produces products efficiently in high yields, requires minimum purification, and requires a short reaction time. Using a Knoevenageal condensation of benzoylacetonitriles and aromatic aldehydes, substituted chalcones are formed after a microwave irradiation of 15 minutes. Over twenty coloured, solid chalcone products have been

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isolated as a result of diversifying aromatic groups and substituting electron-withdrawing, electron-donating, and heterocyclic groups[15].

4) Solvent Free Synthesis by Grinding

At room temperature without solvents, the Claisen–Schmidt condensation reaction can be completed using methyl ketones or aromatic aldehydes. A comparison of this procedure to classical reactions shows that it is simple, efficient, economical, and environmentally friendly.

At room temperature, the appropriate methyl ketones, aromatic aldehydes, and sodium hydroxide mixture is ground thoroughly with a pestle until it melts. It took 3–5 minutes for the initial reaction mixture to solidify. As the reaction progressed, TLC was used to monitor its progress for another 5–10 minutes. A solution of sodium hydroxide was removed from the solid by washing it with cold water and recrystallizing it to yield chalcone derivatives[16].

It is also reliable with the green chemistry methodology because it does not need heating or microwave irradiation. In both reactions and separation of the product, except for recrystallization, there is no use of organic solvents.

Synthetic Applications of Chalcones

Chalcones represent an important class of natural products with a variety of biological activities. Both naturally occurring and synthetic chalcones exhibit number of pharmacological activities few of them discussed here:

1) Antibacterial Activity

Various factors are causing antibiotic resistance to rise, which has prompted researchers to look for compounds that are active against multidrug-resistant pathogens. It is useful for discovering new therapeutic agents because chalcone-based compounds exhibit a variety of pharmacological properties. Globally, antibiotics are becoming less effective as resistance increases. As a result, the quest for new antibacterial agents has become more and more popular. Consequently, we need new antibacterial drugs that have increased strength, new targets, low cost, improved pharmacokinetics, and minimal side effects. Xu et.al. concluded that there have been significant advances in the field of medicinal chemistry to understand the structure-activity relationships of potent antibacterial agents. In this group of neutral protective compounds, there are various synthetic structures, which suggest that further structural optimization could lead to the discovery of a possible drug[17].

Various substituted chalcones tested for their antibacterial activity against bacterial strains, *Bacillus cereus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* and found various compounds exhibit good to moderate antibacterial activity[18].

2) Anticancer Activity

Cancer is a main health dilemma in developing as well as under developed countries familiar by uncontrolled cell growth. In spite of, intensive advancement in the treatment of cancer, the current chemotherapy is useless because of drug resistance and failure of many drugs to distinguish between common cells and the cancerous cells. Approximately 70% of deaths occur in low and middle earning countries due to cancer. Therefore, improvement of new molecules with fewer toxicity, better efficiency and better selectivity afford main contribution for the development of nontoxic drugs helpful in the chemotherapy of cancer. Targeted agents have more effective and less toxicity profiles above conventional chemotherapeutic agents.

It has been shown that natural compounds like chalcones are relatively nontoxic, and that certain chalcone moieties may be effective in targeting molecular events that could cause cancer. Since chalcones have anticancer activities, considerable effort has been made to identify new potential oncology drugs based on chalcones.

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Keeping in view the biological significance of chalcones Kotha and et. al. as part of the chalcone system, two-hydroxyphenyl groups and heterocyclic moieties are synthesized. They also converted the chalcones to flavonols and evaluated the anticancer activity of all the synthesized compounds. Several different structures have been reported to inhibit microbial growth, in recent years as a potential therapeutic approach, indicating the development of new antibiotics has been regarded as a potential therapeutic approach[19].

3) Antitubercular Activity

A bacterial disease caused by *Mycobacterium tuberculosis*, tuberculosis is the most common continuous transmissible disease. Worldwide, TB is mainly caused by morbidity, which results in death. A recent study indicated that tuberculosis is directly associated with the leading cause of death caused by HIV/AIDS. In retroviral-infected patients all over the world, current tuberculosis chemotherapy has little chance of success. It is becoming increasingly difficult to treat tuberculosis in the world due to the emergence of emerging resistance to existing antitubercular agents. Therefore potent novel antitubercular agents with new mode of action is needed to treat critical tuberculosis cases[20]. Hence, a choice of halogenated chalcones display superior antitubercular activity[21]. Hans and et.al. proposed a series of acetylenic chalcones were evaluated for antitubercular activity. Most compounds were more active against non-replicating than replicating cultures of *Mycobacterium tuberculosis* H37Rv, an unusual pattern with respect to existing anti-TB agents[22].

4) Antimicrobial Activity

It is also known that chalcones are effective antimicrobial agents. Substituted chalcones have been synthesized using Claisen-Schmidt condensation by condensing benzaldehyde derivatives with acetophenone derivatives in dilute ethanol at room temperature. The antimicrobial activity of the synthesized chalcone was evaluated by filter paper disc diffusion method. The compound 3(4-methoxy phenyl) 1(4-iodophenyl) 2-propen-1-one showed excellent activity against *S. aureus* at concentration 500μg/ml and 1000 μg/ml[23].

References

1. S.V. Kostanecki, Tambor, *J. Chem.Ber*., **1899**, *32*, 1921-1926.
2. C. Anuba, T. F. Abbs Fen Reji, *Inter. J. Res. Engi. Biosci*., **2015**, *3*, 61- 65.
3. V. Sharma, G. Singh, H. Kaur, A.K. Saxena, M. Paul, S. Ishar, *Bioorg. Med. Chem. Lett.*, **2012**, *22*, 6343-6346.
4. Y.R. Prasad, A.L. Rao, R. Rambabu, *E. J. Chem*., **2008**, *5*, 461-466.
5. A.M. Asiri, *Bull. Korean Chem. Soc*., **2003**, *24*, 426-430.
6. S. Forestier, C. Moire, G. Lang, *US Patent*,**1989**,*4*,867-964.
7. S. Shettigar, K. Chandrasekharan, Umesh, B. K.Sarojini, B. Narayana, *Polymer*, **2006**, *47*, 3565-3567.
8. R.G. Damazio, A.P. Zanatta, L.H. Cazarolli, L.D. Chiaradia, A. Mascarello, R.J. Nunes, R. A.Yunes, F.R. Barreto Silva, *E. J. Med. Chem*., **2010**, *45*, 1332-1337.
9. P.Y. Rajendra, P.Ravi Kumar, C. H. AshaDeepti, M.VenkataRamana, *E. J. Chem*., **2006**, *3*, 236-241.
10. K. Sukumaran, R. Kuttan, *J. Ethnopharma.*, **1991**, *36*, 93-96.
11. 11.Y. R. Prasad, P. R. Kumar, C. A. Deepti, M. V. Ramana, *E-Jour. Chem*., **2006**, *3*, 236-241.
12. B. Tiwari, A.S. Pratapwar, A.R. Tapas, S.R. Butle, B.S. Vatkar, *Inter. J.Chem. Tech. Res.*, **2010**, *2*, 499-503.
13. H. Qian, D. Liu, *Ind. Eng. Chem. Res*., **2011**, *50*, 1146–1149.

ISBN: 978-93-95369-85-5

14. A. Bianco, C. Cavarischia, M. Guiso, *Nat. Prod. Res*., **2006**, *20*, 93–97.
15. S. J. Deshpande, P.R. Leger, S.R. Sieck, *Tetrahedron Lett*., **2012**, *53*, 1772–1775.
16. N. M. Rateb, H. F. Zohdi, *Syn. Comm*., **2009**, *39*, 2789–2794.
17. M. Xu, P. Wu, F.Shen, J. Ji, K.P. Rakesh, *Bioorg.Chem*., **2019**,*91*, 103133.
18. H.P. Avila, E.F.A.Smania, F.D. Monache, A.S.Junior, *Bioorg. Med. Chem.*, **2008**, *16*, 9790-9794.
19. R.R. Kotha, R.G. Kulkarni, A.K. Garige, S.G. Nerella, A. Garlapati, *Med. Chem*., **2017**, *7*, 353-360.
20. E. L. Corbett, C. J. Watt, N. Walker, D. Moher, B.G.Williams, M.C. Raviglione, C. Pye, *Arch.Inter.Med.*, **2003**, *163*, 1009-1021.
21. Y.M. Lin, M.T. Flavin, L.M. Zhou, W. Nie, F.C. Chen, *Bioorg. Med. Chem*., **2002**, *10*, 2795-2798.
22. R.H. Hans, E.M. Guantai, C. Lategan, P.J. Smith, B. Wan, S.G. Franzblau, J. Gut, P.J. Rosenthal, K. Chibale, *Bioorg. Med. Chem. Lett*., **2010**, *20*, 942–944.
23. A.N. Choudhary, V. Juyal, *Int. J. Pharm. Pharm. Sci*., **2011**, *3*,125-128.

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