JOURNAL OF PHARMA INSIGHTS AND RESEARCH

REVIEW ARTICLE

Synthesis of chalcones and their uses as potential pharmacological agents

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Article DOI: 10.5281/zenodo.10039233
Publication history: Received on 3 Sep 2023; Revised on 18 Oct 2023; Accepted on 23 Oct 2023

Abstract: Chalcone is an α,β-unsaturated ketone and serves as the fundamental framework for numerous significant biological molecules. Due to the existence of α,β-unsaturated ketone functionality, the derivatives of chalcone exhibit enormous therapeutic value, including inhibition of enzymes, anti-bacterial, anti-cancer, anti-inflammatory, anti-fungal, anti-malarial, anti-protozoal, and anti-filarial action. A type of open-chain flavonoids known as chalcone can be produced synthetically as well as via biosynthesis in plants. The Claisen-Schmidt condensation reaction and the additional modern-day invention known as aldol condensation may both be used to produce the simplest chalcone by reacting benzaldehyde and an active methylene ketone in homogenous conditions. 1,3-diaryl-2-propen-1-one, also referred to as chalconoid, is a chemical building block shared by all chalcone compounds. There are two isomers: trans and cis, with trans having greater thermodynamic stability than the cis isomer. By adding various heterocyclic moieties to the structural framework of chalcones, after conducting many investigations, nearly all of them revealed different bioactivities. Chalcones produced from naturally occurring substances are homocyclic and have less bioactivity than compounds made using heterocyclic building blocks. Therefore, the capacity to structurally change chalcones by synthesis provides superior benefits than using natural chalcones, including higher yields, easier handling, cost-effectiveness, and many other things. Despite the reality that the Chalcones have undergone in-depth research, the precise mechanisms of action behind the many biological actions of the chalcones are currently insufficiently understood.

Keywords: Chalcones; Synthesis; Therapeutic activity; Mechanism of action; Bioactivity; Uses

1. Introduction

The primary core of chalcones is produced by the reaction between a ketone with an aldehyde (enone), they are a significant class of biological chemicals [1]. Given the shades of the majority of naturally occurring chalcones, the Greek word "chalcos," which means "bronze," is the source of the name "chalcone" [2]. The reactive, α,β-unsaturated system was found in the rings of the chalcone and showed a variety of potential pharmacological capabilities, such as enzyme inhibitory activity, anti-cancer, anti-inflammation anti-bacterial, anti-malarial, anti-protozoal, and anti-filarial activities. The aromatic ring's structure can be altered to boost effectiveness, lessen toxicity, and expand the range of pharmacological effects. The most well-known sort of secondary metabolic product in plants is chalcones. For plants to survive and guard against molecular harm as well as harm from bacteria, insects, and animals, this is utilized in their defensive systems [3].

In several traditional medical practices, including homeopathy and Chinese medicine, chalcone and its compounds have long been employed. Traditionally, the Aldol condensation and the Clasien-Schmidt condensation, two more recent inventions, were used to react with benzaldehydes and active methyl ketones in homogeneous circumstances [4]. However, new techniques for creating chalcones provide various benefits depending on the kind of catalyst, solvent, base, and reaction circumstances [5]. Herpes simplex virus type 1 (HSV-1) [6] and human immunodeficiency virus type 1 (HIV-1) [7] are sensitive to nitrogen heterocycles with chalcone moiety.

2. Synthesis Methods

Chalcones are unusual as a scaffold with multifunctional biological capabilities because of their, α,β-unsaturated ketone with a diphenyl substitution and other functionalities. Logistical issues frequently arise when chalcones are obtained from natural sources which are plant pigments related to flavones. As a result, they are chemically produced using the following techniques.

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2.1. Claisen-Schimdt condensation

The typical Claisen-Schmidt condensation method is used to create chalcones from an aldehyde and acetophenone in the presence of an acid or base. The following list of expedients has been developed for the synthesis of chalcones.

Different bases have been employed to aid in the synthesis of chalcones in the Claisen-Schmidt condensation process, including NaOH, KOH, LiOH, $Ba(OH)_2$, and organic bases (i.e., piperidine and pyridine). Similar to this, acidic reagents like HCl and $AlCl_3$ have also been enhanced. Chalcone yields are relatively lower in both cases, averaging between 50 and 60 percent depending on the replacement.

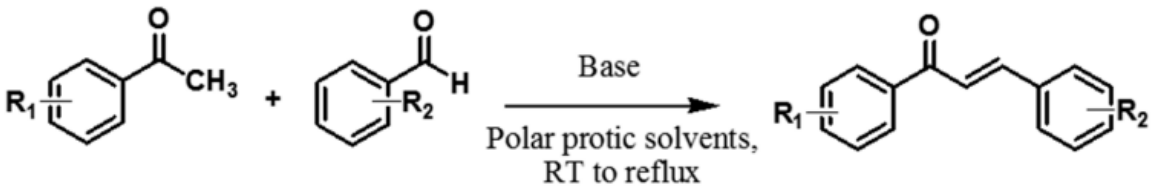

Figure 1 Clasien-Schmidt condensation reaction

Later, several catalysts were also tested to boost yield. [8] [9] For the reaction, substances like chitosan [10] Al-Mg hydrotalcite [11], and Cs-pollucite nanozeolite modified with organosilane have been utilized. The acid-based catalyst, BF3-Et2O, offers various benefits over rivals, including a markedly increased chalcone yield that is beneficial for manufacturing efficacy. [12] Similar to this, other materials have been developed, including nanosized ZnWO4, Fe3O4-MOF core-shell magnetic microspheres, nanosized activated carbons [13], nanoporous AISBA-15 [14], cesium salts of 12-tungstophoric acid [15], ionic liquids [16], (MWCNTs)-COOH-CeO2 hybrids [17], modified fluorapatite [18] and ZnO nanoparticles supported on graphene [19].

Given that the results are produced with greater yields—between 75 and 96%—BF3-etherate can serve as a more effective catalyst for the manufacture of chalcones. Chalcones are produced in greater quantities when heterogeneous catalysts are utilized, and they may be recycled for several cycles of the processes.

2.2. One-Pot synthesis

Vacuum gas stripping method or direct synthesis or telescopic reaction or multicomponent reaction or cascade reaction or tandem reaction. One-pot reactions are a series of numerous synthetic transformations performed in a single pot without the need for intermediate chemical purification. In one-row synthesis, a one-pot method can generate many chemical linkages, permitting the production of very complex compounds. It is a green technique because the use of solvents and chemical waste is kept to a minimum, harsh reaction conditions are minimized, and the synthetic pathways are simplified to the greatest extent possible [20].

The chalcone chemical scaffold can be manufactured via the conventional one-pot Claisen-Schmidt condensation method, in which suitable aldehydes and ketones are combined under basic conditions to yield final chalcones [21]. They can also be generated by different one-pot synthetic methods. Soozani et al. described the synthesis of quinoxaline chalcones in acetonitrile utilizing diethyl amine as the base and Pd/Cu as the catalyst in a one-step reaction of 3-substituted-2-chloroquinoxalines and aromatic aldehydes with calcium carbide [22]. The use of calcium carbide, eliminates the need for protection and deprotection phases, resulting in a more efficient and environmentally friendly one-pot method. Synthesis of (E)-3-(2-aminoquinoxalin-3-yl)-1-arylprop-2-en-1-one derivatives from 2-amino-substituted-3-chloroquinoxalines, calcium carbide, and aromatic aldehydes [23].

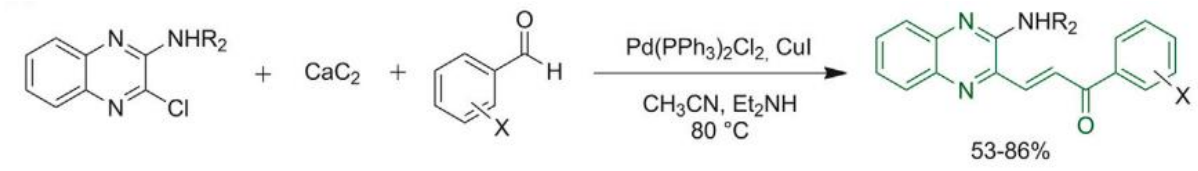

Figure 2 Example of One-Pot synthesis

2.3. Fredel Craft Acylation

Using Cinnamoyl Chloride. Chalcones may be produced using a strong Lewis acid catalyst, such as aluminum trichloride, by the Friedel Crafts acylation of an aromatic ether and cinnamoyl chloride. Shotter et al. described this approach in 1978, with four chalcones produced in reasonable yields Nonetheless, this process has not been frequently employed for chalcone synthesis [24].

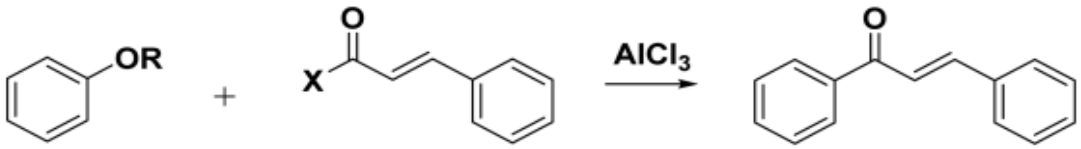

Figure 3 Example of Fredel Crafts Acylation

3. Pharmacological Activity

Chalcones have several biological therapeutic properties which are still being studying to get the complete detail of the therapeutic activity of the chalcones and their derivatives.

3.1. Anti-Bacterial Activity

Today, chemical factories create thousands of chalcone derivatives. Chalcones with several functional groups displayed a broad range of biological actions, namely antibacterial [25]. It was demonstrated that natural substances with the important component known as chalcone (1,3-diphenyl-2-propen-1-ones) are good for human wellness [26]. A wide range of biological actions are brought about by the particular, α,β-unsaturated ketone structure of chalcone [27]. The natural chalcone derivatives xanthohumol and licochalcone exhibit potent antibacterial properties [28].

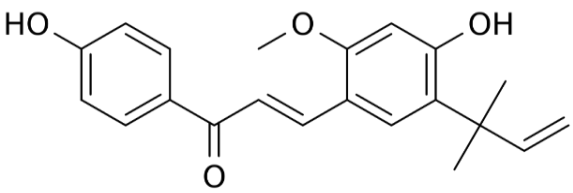

Figure 4 Licochalcone

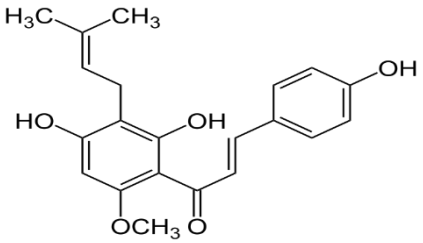

Figure 5 Xanthohumol

Importantly, the microbial cell membrane was depolarized and made permeable as part of the antibacterial actions of our drugs. These findings offer fresh perspectives on the possible application of chalcone peptide mimics as cutting-edge and effective antibacterial agents. In comparison to Gram-negative bacteria, the cationic compounds were more efficient against Gram-positive bacteria. Chalcone displayed unique behaviors in various aryl groups. Both substances with thienyl or furanyl groups and those with various substituted phenyl groups demonstrated good action. It is obvious that some synthetic heterocyclic chalcones function by destroying SA's cell wall, which is analogous to the observed action of the well-known cell membrane-permeant polymyxin B [29]. The most effective inhibitors of strains of MRSA include chalcones with a lipophilic group, like isoprenoid, and groups of methoxy at positions 3', 5', as well as 2' of ring A. A ring with a prenyl group exhibits good activity, but when the prenyl group is cyclized or added to a different ring (the B ring), the activity is reduced.

3.1.1 Structure-activity relationship

Chalcones activity was primarily linked to the existence of phenolic hydroxyl groups, that possess a strong affinity for proteins and may therefore block microbial enzymes. A free hydroxyl group in position 4 (B ring) appears to be a very important requirement. Less active skeletons appear to result from acetylation or methylation of the 2' -OH group. When the 4' hydroxyl group is free, the activity decreases, suggesting that a 40'-methoxyl group is an additional need. However, adding an isoprenyl group to the B ring does not increase the activity. It is discovered that the A-ring's prenyl moiety contributes to a rise in bacterial activity. A ring's methoxy group at position 4' has little impact on activity. Gram-positive and Gram-negative bacteria that were susceptible in the preliminary test, as well as strains that were clinically isolated organisms of multidrug-resistant Gram-positive bacteria, were used to figure out the minimum inhibitory concentration (MIC) for the compounds. Clinical and Laboratory Standards Institute, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically, Approved Standard M7–A6, Clinical and Laboratory Standards Institute, Wayne, PA, USA 2003. Maintenance of antibacterial action requires the, α,β-unsaturated ketone moiety [30]. It is advantageous to increase activity by adding sulfone, triazole, or dithiocarbamate groups to the double bond. In particular for Gram-negative bacteria like P. aeruginosa, the hybrid compounds could widen the antibacterial spectrum and considerably increase activity [31]. Efflux pump inhibiting (EPI), type II fatty acid biosynthetic process (FAS-II), interfering

replication of DNA, filamentous dependent on temperature mutant Z (FtsZ), virulence factor, and protein tyrosine phosphatases are a few of the targets through which natural or synthetic chalcones have demonstrated their antibacterial properties.

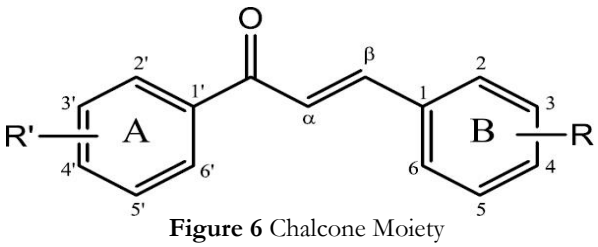

Figure 6 Chalcone Moiety

3.2. Anti-diabetic Activity

Many medications, including insulin secretion substances, reduction of aldol inhibiting agents, R-glycosides inhibitors, and others, have been studied to treat diabetes or its consequences largenides [32]. Recent developments in peroxisome proliferators are activated. Targeting the (PPAR)-receptor, ligands has been created. Type II diabetes (also known as diabetes mellitus not insulin dependent; (NIDDM). These medications enhance the state of insulin. Triggering the differentiation of preadipocytes to tiny adipocytes can increase insulin-induced glucose absorption.

These substances have been employed as fluorescence substrates that can be useful for the detection of fluorides28 and saccharide s like glucose that may be applied to the creation of biosensors for diabetes [33].

The production costs, efficacy, and affordability of diabetes treatments are obstacles to advancement, despite the wide range of in vestigations that have been done to find a permanent cure. Therefore, finding and researching novel and potent potential medications that are easily attainable by diabetes people is still necessary. Five chalcone derivatives were created in an attempt to identify compounds with potential anti-diabetic properties. These researchers' respective anti-diabetic activities were investigated in real-time. The structure-activity relationship between the strength of the association (SAR) was assessed through anti-diabetic action and structural alteration.

3.3. Challenges and Opportunities

Chalcones have been used therapeutically for thousands of years to cure a variety of diseases like tumors, autoimmune disorders, a nd Type 2 diabetes by using medicinal herbs and plants [34]. The solvent polarization, PH, and contact with the surfactants or peptides have an important influence on the fluorescent intensity of chalcones based on molecules. However, the ability of fluorescent chalcones to identify various disorders has been investigated. The chalcones analogs can be utilized to scan human histamine H3 transmitters (hH3R) in stable infected HEK293 cells.

Simple chalcones are artificially hybridized through other templates, like stilbenes [34]. The prime disadvantage of this chalcone reaction is its slow reactivity rate it often takes several days to complete. the nonsolvent microwave technique has the following benefits it allows more versatility for the reaction temperature because it does not have to be limited through the boiling point and volatility of the solvents. It drastically reduces reaction time; it significantly increases reaction in water that of common solvent systems. Other well-known reactions have been researched for the manufacture of chalcones such as cross-coupling Friedel crafts acylation etc

4. Conclusion

In this review, we have covered the many biological activities of chalcones as well as their synthesis techniques. Chalcones is the precursor of many heterocyclic moieties of useful pharmaceutical compounds, as the foregoing description makes evident. Further research is necessary to confirm the therapeutic actions of chalcone derivatives, which may also be a promising chemical with anti-inflammatory and anticancer potential. Even though certain changes showed very little benefit, there may be a link between structure and activity, therefore additional research is required for a more thorough assessment that takes into account the molecular mechanisms behind activities.

References

[1] A j Leusink JGN. Reaction of Organo-tin hydrides with α, β-unsaturated ketones. Tetrahedron letters. 1966; 7(20): 2221-2226.
[2] Sahu NK, Balbhadra SS, Choudhary J, Kohli DV. Exploring pharmacological significance of chalcone scaffold: a review. Curr. Med. Chem. 2012; 19: 209-225.
[3] Matos MJ, Vazquez-Rodriguez S, Uriarte E, Santana L. Potential pharmacological uses of chalcones: A patent review (from June 2011–2014). Expert Opin. Ther. Pat. 2015; 25: 351-366.
[4] Sun YF, Cui YP. The synthesis, characterization and properties of coumarin-based chromophores containing a chalcone moiety.. Dyes Pigments. 2008; 78: 65-76.
[5] Gomes MN, Muratov EN, Pereira M, Peixoto JC, Rosseto LP, Cravo PVL, et al. Chalcone Derivatives: Promising Starting Points for Drug Design. Molecules. 2017; 22: 1210.
[6] El-Barbary AA KAPENC. s-Glucosylated hydantoins as new antiviral agents. J Med Chem. 1994; 37: 73-77.
[7] El-Subbagh HI AZSMMBFAOA. Synthesis and biological evaluation of certain a, b-unsaturated ketones and their corresponding fused pyridines as antiviral and cytotoxic agents.. J Med Chem. 2000; 43: 2915-2921.
[8] Nair AD, Athira CK, Manikandan P, Ramani. P. One-Pot Synthesis of Modified 4-Aryl-4H-Chromenes and Their Preliminary Anti-Cancer Studies. J.Indian Chem.soc. 2019;: 96,19-22.
[9] Pandurangan N, Bose C, Banerji. A. Synthesis and Antioxygenic Activities of Seabuckthorn Flavone-3-Ols and Analogs. 2011; 21: 5328-5330.
[10] Hernawan , Purwono B, Triyono , Hanafi. M. The Use of Chitosan as a Solid Base Catalyst for the Chalcones Synthesis. 2020.
[11] Climent MJ, Corma A, Iborra S, Velty. A. Activated Hydrotalcites as Catalysts for the Synthesis of Chalcones of Pharmaceutical Interest. 2004;: 474-482.
[12] Narender T, Reddy P. K. A Simple and Highly Efficient Method for the Synthesis of Chalcones by Using BorontrifluorideEtherate. 2007; 48: 3177-3180.
[13] Winter C, Caetano JN, Araújo ABC, Chaves AR, Ostroski IC, Vaz BG, et al. Winter, C.; Caetano, J.N.; Araújo,Activated Carbons for Chalcone Production: Claisen-Schmidt Condensation Reaction. 2016; 303: 604-610.
[14] Elamathi P, Chandrasekar G, Balamurali. ElM.M. Nanoporous AlSBA-15 Catalysed Claisen–Schmidt Condensation for the Synthesis of Novel and Biologically Active Chalcones. 2020;: 817-829.
[15] Rafiee E, Rahimi. A Green Approach to the Synthesis of Chalcones via Claisen-Schmidt Condensation Reaction Using Cesium Salts of 12-Tungstophosphoric Acid as a Reusable Nanocatalyst. 2013;: 361-367.
[16] Das S, Porashar B, Saikia S, Borah R. Brönsted Acidic Ionic Liquids Catalysed Sequential Michael-Like Addition of Indole with Chalcones via Claisen-Schmidt Condensation. 2020; 5: 3041-3047.
[17] Heidarzadeh T, Nami N, Zareyee D. Preparation of (MWCNTs)-COOH/CeO2Hybrid as an Efficient Catalyst for ClaisenSchmidt Condensation. J. Appl. Chem. Res. 2021; 15: 44-57.
[18] Jioui I, Dânoun K, Solhy A, Jouiad M, Zahouily M, Essaid B, et al. Jioui, I.; Dânoun, K.; Solhy, A.;Modified Fluorapatite as Highly Efficient Catalyst for the Synthesis of Chalcones via Claisen–Schmidt Condensation Reaction. J. Ind. Eng. Chem. 2016; 39: 218–225.
[19] Li Z, Zhao H, Han H, Liu Y, Song J, Guo W, et al. Li, Z.; Zhao, H.; Han, H.; Liu, Y.; Song,Graphene-Supported ZnO Nanoparticles: An Efficient Heterogeneous Catalyst for the Claisen-Schmidt Condensation Reaction without Additional Base. Tetrahedron Lett. 2017; 58: 3984-3988.
[20] Sydnes M. One-pot reactions: A step towards greener chemistry. Curr. Green Chem.. 2014; 1: 216-226.
[21] Murugesan A,GRM,aLCH. Efficient synthesis of ethyl-piperazinyl quinolinyl-(E)-chalcone derivatives via Claisen-Schmidt reaction by using TiO2-BPTETSA catalyst. J. Taiwan Inst. Chem. Eng. 2017; 80: 852-866.
[22] Soozani A,KA,aBM. One-pot synthesis of quinoxaline chalcones from commercially available calcium carbide through palladium-catalyzed coupling reactions. ChemistrySelect 2. 2017; 2: 9701-9705.
[23] Soozani A,KA,aBM. One-pot synthesis of quinoxaline chalcones from commercially available calcium carbide through palladium-catalyzed coupling reactions. ChemistrySelect. 2017; 2: 9701-9705.
[24] Shotter RG, Johnston KM, Jones JF. Reactions of unsaturated acid halides IV1: Competitive friedel-crafts acylations and alkylations of mono halogeno benzenes by the bifunctional cinnamoyl chloride. Tetrahedron. 1978; 34: 741-746.
[25] Bhale SB. Synthesis and antimicrobial screening of chalcones containing imidazo[1,2-a] pyridine nucleus. Res. J. Chem. Sci. 2013; 3: 38-42.
[26] Tran T.D. . Synthesis and antibacterial activity of some heterocyclic chalcone analogues alone and in combination with antibiotics,. Molecules,. 2012; 17: 6684-6696..
[27] Go XW. Chalcones: an update on cytotoxic and chemoprotective properties. Curr. Med. Chem. 2005; 12: 481-499.
[28] Zhuang WZ. Chalcone: A Privileged Structure in Medicinal Chemistry,. Chem. Rev. 2017; 117: 7762-7810.
[29] Sivakumar PM, Priya S, Doble M. Synthesis, biological evaluation, mechanism of action and quantitative structure-activity relationship studies of chalcones as antibacterial agents.. Chem. Biol. Drug Des. 2009; 73: 403-415.
[30] Moore B.S. Editorial: are natural products the solution to antimicrobial resistance? Nat. Prod. Rep. 2017; 34: 685-686.
[31] Nowakowska Z. A review of anti-infective and anti-inflammatory chalcones. Eur. J. Med. Chem. 2007; 42: 125-137.
[32] Tripathi BK, Srivastava AK. Diabetes mellitus: Complications and therapeutics.. Med. Sci. Monit. 2006; 12: 130-147.

[33] DiCesare N, Lakowicz JR. Chalcone-analogue fluorescent probes for saccharides signaling using the boronic acid group. Tetrahedron Lett. 2002; 43: 2615-2618.
[34] Singh P, Anand A, Kumar V. Recent developments in biological activities of chalcones: a mini review. Eur. J. Med. Chem. 2014; 85: 758-777.

Author's short biography

Adhi Kesava Naidu Neelams

Adhi Kesava Naidu Neelam has a lifelong fascination with science. Because of his success in scientific studies in high school, he decided to pursue a degree in pharmacy. He went on to obtain his pharmacy bachelor's degree and worked towards it. Following graduation, he plans to further his education to enhance both public health and pharmacy. With an eye on becoming a pharmacist, he hopes to use his curiosity and drive for self-improvement to further his career

Sai Venkat Tarigoppala:

Sai Venkat Tarigoppala is a student. Whose work is focused on contextualization the force and consequences of chalcones. His research on writing is rooted within synthesis on their pharmacological activities of chalcones in the second year of his B. Pharm course and he was seeking to leverage his curiosity and self-improvement to develop their valuable skills towards the field of pharmacy and health care system.

Author Name: Likitha Muthyam

Likitha Muthyam while studying her under graduation B. Pharmacy she had interest on reading different articles which upon turn her to study about chalcones and their uses in medicines.

Author Name: Prasanna Lakshmi Marredi

Prasanna Lakshmi Marredi student of pharmacy. She was developed an interest in studying various articles on variety of publications this inspires her to learn more about chalcones and their pharmacological activities.

Vijaya Durga Neelam

Vijaya Durga Neelam completed her master's in Organic Chemistry and now, she is an Asst. Professor of Organic Chemistry, with one year of experience. Her research interests broadly include the facts behind chemical reactions