CHALCONES : A BRIEF REVIEW

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Abstract:

Chalcones are a class of natural open chain flavonoids that are linked by a three carbon spacer between two aromatic rings. Chalcones and their heterocyclic analogues enjoy a range of biological activities such as antimicrobial, antioxidant, cytotoxic, anticancer, antiprotozoal, antihistaminic, antiulcer and anti-inflammatory activities which makes these compounds as a special attraction for investigation. Additionally the bielectrophilic, ketovinyl chain between the two rings is highly reactive and acts as an important chemical synthon for constructing different five, six and seven member heterocyclic scaffolds containing different hetero atoms like nitrogen, oxygen and sulfur atoms by abridgment with a variety of binucleophilic reagents. This review highlights on the chemical and biological potentials of chalcones.

Keywords: Flavonoids; Chalcone; Biological Activities; Chemical Synthon

Introduction:

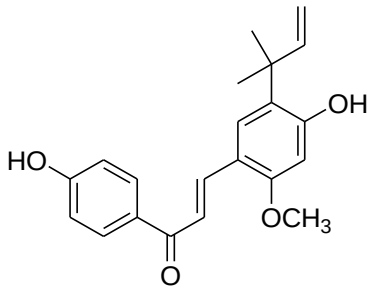
Flavonoids with 1, 3-diarylpropane skeleton can be classified as an outstanding class of naturally occurring compounds. Chalcones or 1,3-diphenyl-2-propen-1-one derivatives are open chain unsaturated carbonyl system in which two aromatic rings are joined by three carbons having α, β- unsaturated system[1]. Chalcones are called “anthochlor pigments”, coined to identify a group of yellow pigments that turn red in the presence of alkali[2]. Chalcones are considered as the precursors of flavonoids and isoflavonoids[3] and are secondary metabolites of terrestrial plants that exhibit various biological activities[4]. Chalcones are popular intermediates for synthesizing various heterocyclic compounds[5] like flavones, isoxazoles, pyrazoles, tetrahydro-2-chromens[6] etc. Chalcones either natural or synthetic are known to exhibit various biological activities. Kostanecki[7] was the first to give the term chalcone and did pioneer work in the synthesis of naturally occurring compounds. The chalcones have been reported to possess various biological activities such as antimalarial[8], antibacterial[9], anti-cancer[10], antileishmanial[11], antifibrogenic[12], anti-inflammatory[13],

immunomodulatory[14], cytotoxic, analgesic, anti-platelet, anti-ulcerative, antiviral, antioxidant, anti-tubercular, anti-hyperglycemic, inhibition of chemical mediators release, inhibition of leukotriene B4, inhibition of tyrosinases, inhibition of aldose 4 reductase activities[15] and anti-trypanosoma cruzi[16] activities. Some chalcone derivatives show herbicidal activity[17] and substituted chalcones have exhibited fungi static and fungicidal activity. The presence of a reactive α, β- unsaturated keto function in chalcones is found to be responsible for their biological activities[15].

Naturally occurring chalcones:

Naturally occurring chalcone have been reported to have multiple biological and pharmacological activities. The biological activity mainly depends on the substitution group of the chalcones. Licochalcone A **1** is a naturally occurring chalcone isolated from the roots of Glycyrrhiza glabra (licorice) which was proved to have in vitro and in vivo antimalarial and antileshmanial activities.

On the other hand 3-methoxy-4-hydroxylonchocarpin **2** isolated from the roots of Lonchocarpus utilis inhibits NADH ubiquinone oxidoreductase activity[1].



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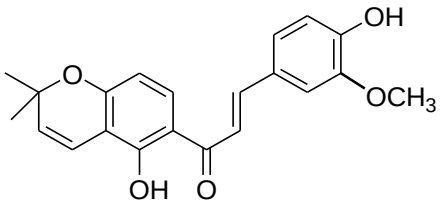

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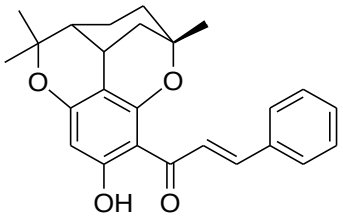
Hua et al.[18], isolated three conjugated monoterpene-chalcone conjugates, including two novel compounds isorubraine **3** and sumadain **4**, and a known compound rubraine **5** from the seeds of Alpinia katsumadai. The seeds of Alpinia katsumadai are used in Traditional Chinese Medicine (TCM) as an antiemetic agent and for the treatment of stomach disorders. The bioactivities of the compounds were evaluated for cytotoxic activities by MTT method in one human liver cancer cell line HepG2, and two human breast cancer cell lines MCF-7 and MDA-MB-435.

Alpinia rafflesiana is a species belonging to Zingiberaceae family which is reported to contain several types of flavonoids including chalcones[19]. Furthermore, it have been accounted that the rhizomes and the fruits of Alpinia rafflesiana stores many biologically active compounds that are related to chalcones. Habsah et al.[19], reported that 2, 3, 4, 6-tetrahydroxychalcone **6** which was

isolated from the fruit of Alpinia rafflesiana using methanol showed free radical scavenging activity with IC_{50} 55 μM due to the existence of the catechol group in its structure.



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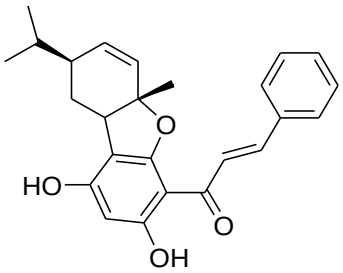

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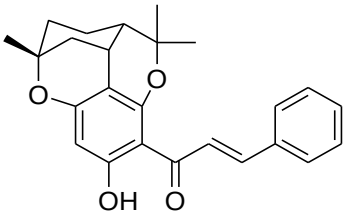

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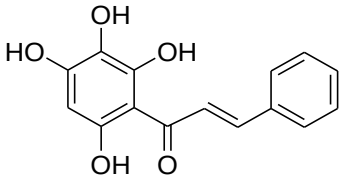

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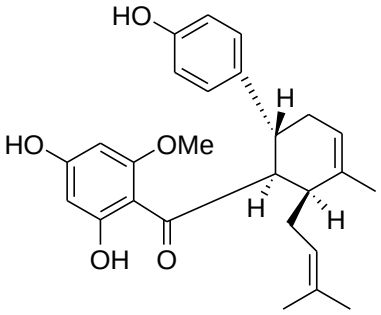
Boesenbergia pandurata or Kaempferia pandurata of Zingiberaceae is used by the local community in Malaysia for various purposes such as an ingredient for tonic, postnatal medications, to treat fungal infections, dry cough, rheumatism, muscular pains and as flavour in their dishes. Chemical studies by Jantan et al.[20] and Cheenpracha et al.[21] on the specie gave several chalcones such as cyclohexenyl chalcone (panduratin C) **7**, panduratin A **8**, hydroxypanduratin A **9**, helichrysetin **10**, 2, 4, 6- trihydroxydihydrochalcone **11**, uvangoletin **12** and cardomonin **13**. Cheenpracha et al., found that the methanol extract of Boesenbergia pandurata rhizome was active in anti HIV-1 protease activity.



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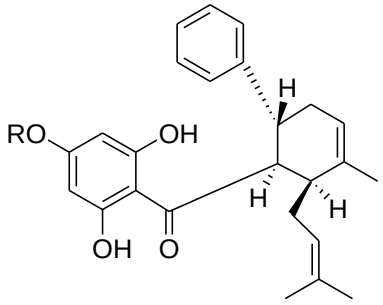
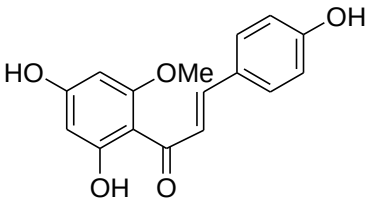


8 R = Me
9 R = H



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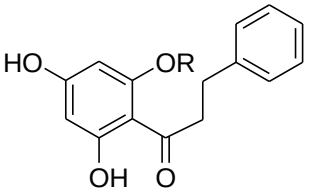
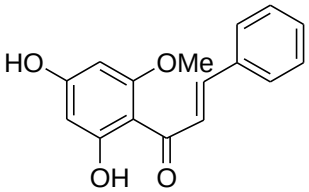


11 R = H
12 R = Me



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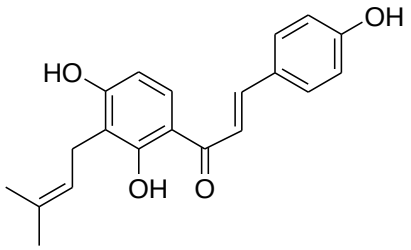
Phytochemical studies on the leaves of Artocarpus lowii done by Jamil et al.[22] discovered new prenylated dihydrochalcones identified spectroscopically as 2, 4, 4'-trihydroxy-3-prenylchalcone **14** and 2, 4'-dihydroxy- 3, 4-(2,2-dimethylchromene) chalcone **15** with 2, 4-dihydroxy-4'-methoxy-3- prenyldihydrochalcone **16** as the new compound. These compounds exhibited strong free radical scavenging activities.



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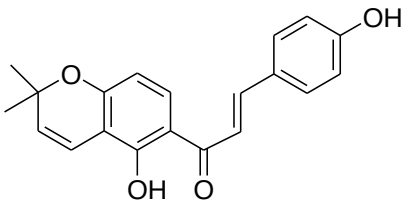

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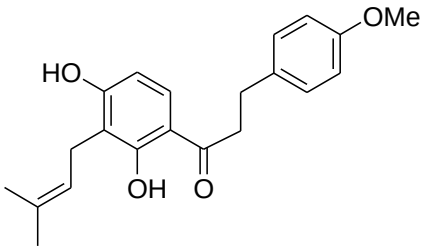

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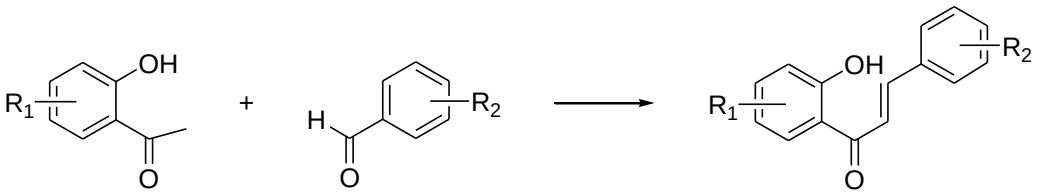
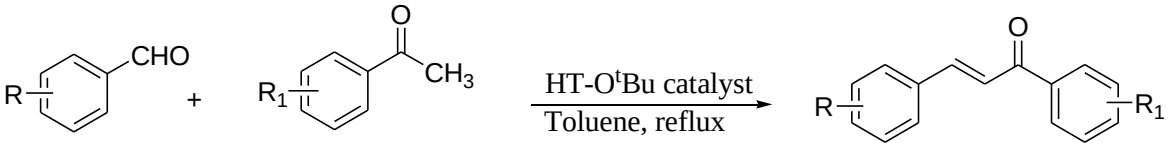
Synthetic preparations of chalcones:

There are a number of methods for the synthesis of chalcones including the classical methods of Claisen-Schmidt, Wittig reaction and Friedel-Crafts acylation[23].

The Claisen-Schmidt condensation between acetophenone and benzaldehyde derivatives is an important C-C bond forming reaction which allows α, β-unsaturated ketone such as chalcones to be obtained[24]. It is the most frequently used means of establishing the C6-C3-C6 flavonoid nucleus. The classical Claisen-Schmidt reaction is routinely carried out using aqueous sodium or potassium hydroxide or ethanolic sodium ethoxide at 50^0C over a period of several hours. The benzaldehyde derivative is often used in slightly more than equivalent amounts. The extensive conjugation of the products causes them to absorb light in the visible region, lending them a yellow colour[25].

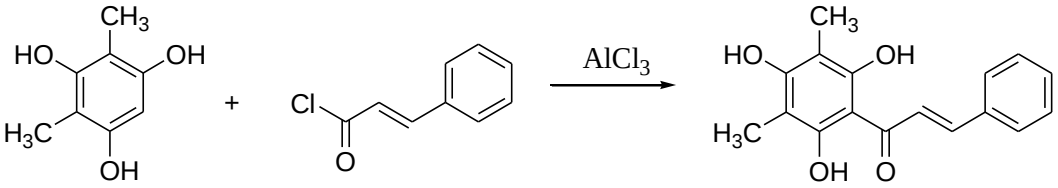


M. Lakshmi Kantam et al. have developed a simple and efficient heterogeneous procedure for the synthesis of chalcones by the Claisen–Schmidt condensation between arylaldehydes and ketones using Mg-Al-OtBu hydrotalcite (HT-OtBu) as catalyst[26].



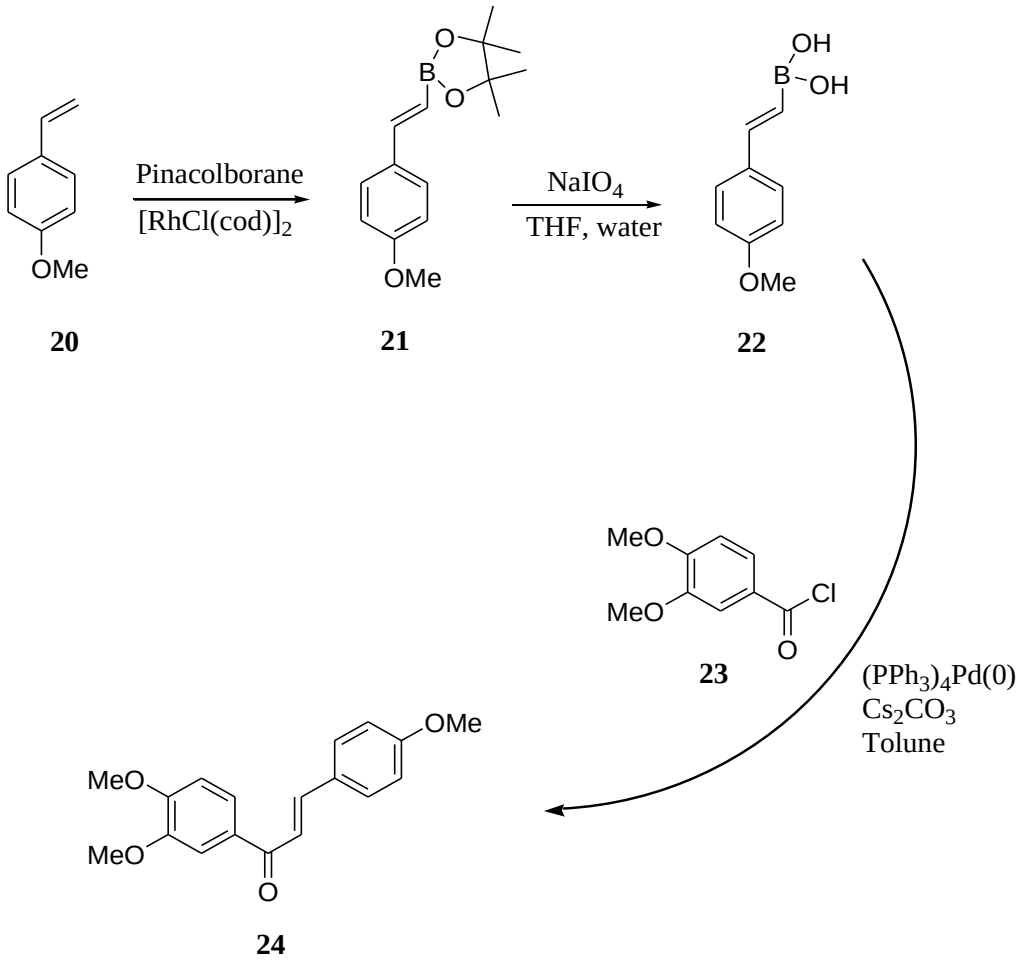
Besides the Claisen-Schmidt reaction, chalcones can also be synthesized by direct Friedel-Crafts acylation of a phenol. In this approach the phenol becomes the A-ring while the acylating agent provides both the B-ring carbons and the three carbon bridge to form C6-C3-C6 unit[27].

Friedel-Crafts acylation of 2, 4-dimethyl-1, 3, 5-triolbenzene **17** with 3- phenylpropionyl chloride **18** gave 2, 4, 6-trihydroxy-3, 5-dimethylchalcone **19**[27].

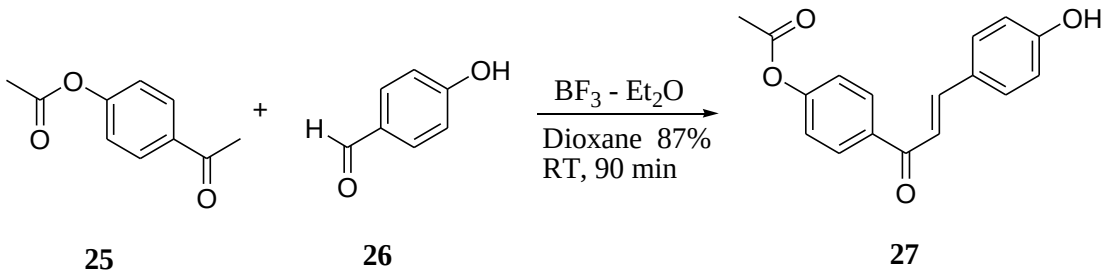


17 **18** **19**

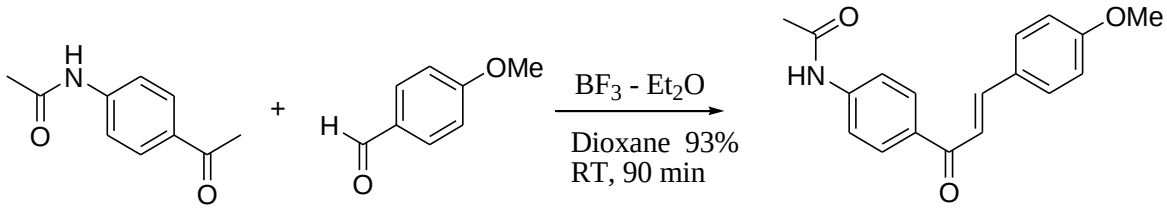
An efficient synthesis of chalcones was carried out based on the Suzuki coupling reaction between benzoyl chlorides 53 and phenylvinylboronic acid **22**[28]. **22** was prepared by dehydrogenative borylation of para-methoxystyrene **20** by pinacolborane oxidative addition-dehydrogenation catalyzed by the rhodium complex, $[RhCI(cod)]_2$ (cyclooctadiene rhodium chloride dimer) to give **21**. Oxidative cleavage of **21** using sodium periodate in THF/water gives **22** required for the Suzuki coupling step. The coupling between **22** and **23** afforded 3, 4, 4'-trimethoxychalcone **24** using anhydrous toluene as solvent and catalyzed by tetrakis(triphenylphosphine) palladium(0) and base; cesium carbonate as shown below.



Narender and Reddy[4] developed a new methodology by using BF_3- Et_2O to synthesize several substituted chalcones. The advantages of this method over the existing methods are high yields, simple work-up, short reaction times and no side reactions. This method is a solvent free reaction and applicable for reactions involving liquid reactants which are base sensitive functional groups such as esters and amides.



25 **26** **27**

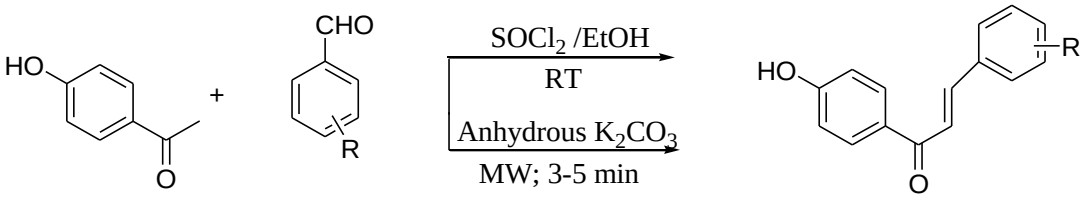


28 **29** **30**

A condensation reaction between O-acylated **25** or N-acylated **28** actophenones and the respective aromatic aldehyde **26** or **29**, produced O-acylated **27** or N-acylated chalcones **30** in high yields by using BF_3-Et_2O.

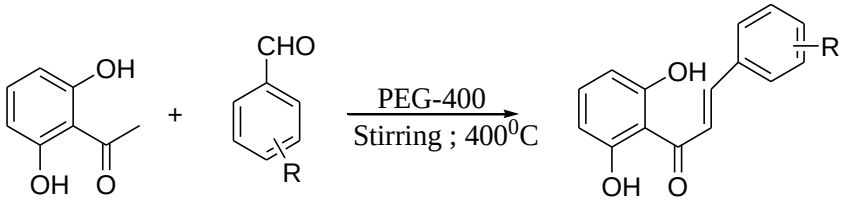
The combination of supported reagents and microwave irradiation can be used to carry out a wide range of reactions in short times and with high conversions and selectivity, without the need of solvents. This approach proved beneficial since it offers several advantages over conventional heating techniques and accelerates the organic reactions.

Jaypal et al.[29] have prepared chalcones **31-33** using anhydrous K_2CO_3 as a catalyst under microwave assisted solid phase solvent free conditions. The authors have also reported the synthesis of chalcones **31-33** via aldol condensation using $SOCl_2$/EtOH as catalyst at room temperature[30].



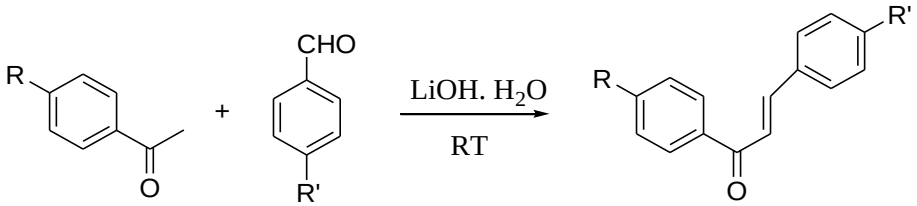
31 R = 2-chloro
32 R = 4-chloro
33 R = 3-nitro

A recyclable alternative reaction solvent PEG-400 was used by the authors to synthesise chalcones **34-37** via Claisen Schmidt reaction in excellent yields[31]. The advantage of the reaction lies in its shorter reaction time and reduced use of volatile organic compounds (VOCs).



34 R = 4-chloro
35 R = 4-hydroxy
36 R = 3-hydroxy
37 R = 4-nitro

According to Bhagat et al.[32], commercially available $LiOH{\cdot}H_2O$ was found to be a highly efficient dual catalyst for Claisen-Schmidt condensation of various aryl methyl ketones with aryl/heteroaryl aldehydes by providing an easy synthesis of 1, 3-diaryl-2-propenones under mild conditions. The reactions were carried out at room temperature and in short times affording high yields.



Chalcones as synthon in chemical synthesis:

Chalcones are resourceful precursor for the synthesis of heterocyclic compounds. Chalcones undergo cyclization reactions with different reagents to form diverse classes of heterocyclic compounds ranging from five membered to seven membered rings containing nitrogen, oxygen and sulfur heteroatoms. In the cyclization reactions the highly reactive bielectrophilic ketovinyl chain condenses with a variety of binucleophilic reagents to generate an assortment of heterocyclic systems such derivatives pyrazolines, phenylpyrazoline and isoxazole (5-membered heterocyclics)[33] derivatives aminopyrimidines and cyanopyridines (6-membered heterocyclics)[34] and derivatives of 1,5-benzodiazepines, 1,5-benzoxazepines, and 1,5-bezothiazepines (7-membered heterocyclics)[35].

References:

1. Ávila, H. P., Albino Smania, E. D. F., Monache, F. D., Smânia Júnior, A. 2008. Structure-activity relationship of antibacterial chalcones. Bioorganic Medicinal Chemistry. 16: 9790–9794.
2. Yoichi K., Shigeyuki K., Seigo S., Kazumi S., Nariaki F. and Shigeru O., 2005, Metabolism of the α,β-unsaturated ketones, chalcone and trans-4-phenyl-3-buten-2-one, by rat liver microsomes and estrogenic activity of the metabolites Drug Metabolism and Disposition, 33(8):1115-1123
3. Barton D. H. R. and Ollis D. W., Comprehensive Organic Chemistry ed., Haslam Pergamon Press, Oxford, Volume 5
4. Narender, T. and Reddy, K. P. 2007. A simple and highly efficient method for the synthesis of chalcones by using borontrifluoride-etherate. Tetrahedron Letters 48:3177–3180
5. Wang S., Yu G., Lu J., Xiao K., Hu Y. and Hu H., 2003, A Regioselective Tandem reaction between chalcones and 2-acetamido-acetamide promoted by Cs_2CO_3 for the preparation of 33-unsubstituted 2-pyridones, Synthesis, 487
6. Sarda S.R., Puri, V.A., Rode, A.B., Dalawe, T.N., Jadhav, W.N. and Pawar R.P., 2007, Sulfated tin oxides: a suitable reagent for synthesis of 2,4-diphenyl- 4,6,7,8-tetrahydrochromen-5-one, ARKIVOC, xvi, 242-247.
7. Harbone J. B., Marby T. J. and Marby H., The Flavanoids, Chapman and Hall Ltd., London, **1975**, 492

8. Liu M., Wilairat P. and Mie-Lin G., J. 2001, Antimalarial Alkoxylated and Hydroxylated Chalones: Structure–Activity Relationship Analysis, Med. Chem., 44(25):4443-4452)

9. Opletalova V, 2000, Chalcones and Their Heterocyclic Analogues as Potential Therapeutic Agents of Bacterial Diseases, Cesk.Slov.Farm.49:278-284

10. Konieczny MT, Konieczny W, Sabisz M, Skladanowski A, Wakiec R, Augustynowicz- Kopec E and Zwolska Z, 2007, Synthesis of Isomeric, Oxathiolone fused Chalcones, and Comparison Their Activity towards various Microorganisms and Human Cancer Cells Line, Chem. Pharm. Bull. 55: 817-820,

11. Narendra T., Khaliq T., Shweta, Nishi, Goyal N. and Gupta S., 2005, Synthesis of chromenochalcones and evaluation of their in vitro antileishmanial activity, Bioorg. Med. Chem., 13(23):6543-6550

12. Lee S. H., Nan J. X., Zhao Y. Z., Woo S. W., Park E. J., Kang T. H., Seo G. S., Kim Y. C., Sohn D. H., 2003, The chalcones butein from Rhus verniciflua shows antifibrogenic activity, Planta. Med., 69(11):990-994

13. Jin F., Jin X. Y., Jin Y. L., Sohn D. W., Kim S. A., Sohn D. H., Kim Y. C., Kim H. S., 2007, Structural requirements of 2',4',6'-tris(methoxymethoxy) chalcones derivatives for anti-inflammatory activity: the importance of a 2'-hydroxy moiety, Arch. Pharma. Res., 30(11):1359-1367

14. Barford L., Kemp K., Hansen M. and Kharazmi A., 2002, Chalcones from Chinese liquorice inhibit proliferation of T cells and production of cytokines, Int. Immunopharmacol, 2(4):545-555

15. Rajendra Prasad Y., Lakshmana Rao A. and Rambabu R., 2008, Synthesis and Antimicrobial Activity of Some Chalcone Derivatives, E-Journal of Chemistry, 3:461-466

16. Aponte J. C., Verastegui M., Malaga E., Zimic M., Quiliano M., Vaisberg A. J., Gilman R. H. and Hammond G. B., 2008, Synthesis, cytotoxicity, and anti-Trypanosoma cruzi activity of new chalcones, J. Med. Chem., 51(19):6230-6234

17. Trivedi A.R., Dodiya D.K., Ravat N.R. and Shah V. H., 2008, Synthesis and Biological Evaluation of Some New Pyrimidines via a Novel Chalcone Series, ARKIVOC, xi:131-141

18. Hua Z. S., Luo J. G., Wang X. B., Wang J. S., Yi Kong L., 2009, Two novel momoterpene-chalcone conjugates isolated from the seeds of Alpinia katsumadai Bioorganic & Medicinal Chemistry Letters, 19:2728-2730

19. Mohamed, H.; Abas, F.; Permana, D.; Lajis, N.H.; Ali, A.M.; Shukari, M.A.; Hin, T.Y.Y.; Kikuzaki, H.; Nakatani, H., 2004, DPPH free radical scavenger components from the fruits of Alpinia rafflesiana Wall. ex. Bak. (Zingiberaceae). Z. Naturforsch., 59c:811–815

20. Jantan I., Basni I., Ahmad A. S., Mohd Ali N. A., Ahmad A. R. and Ibrahim H., 2001, Constituents of the rhizome oils of Boesenbergia pandurata (Roxb.) Schlecht from Malaysia, Indonesia and Thailand, Flavour and Fragance Journal, 16(2):110-112

21. Cheenpracha S., Karalai C., Ponglimanont C., Subhadhirasakulb S. and Tewtrakul S., 2006, Anti-HIV-1 protease activity of compounds from Boesenbergia pandurata Bioorganic & Medicinal Chemistry, 14:1710-1714

22. Jamil, S., Mohd Sirat, H., Jantan, I., Aimi, N., Kitajima, M., 2008, A new prenylated dihydrochalcone from the leaves of Artocarpus lowii., Journal of Natural Medicine, 62:321–324.

23. Petrov O, Ivanova Y and Gerova M., 2008, $SOCl_2$ /EtOH: Catalytic system for synthesis of chalcones, Catalysis Communications, 9:315-316

24. Climent M. J., Corma A., Iborra S. and Velty A., 2004, Activated hydrotalcites as catalysts for the synthesis of chalcones of pharmaceutical interest, J Catal., 221:474-482

25. Mandge S., Singh H. P., Gupta S. D. and Hari Narayana Moorthy N. S., 2007, Synthesis and characterization of some chalcones derivatives, Trends in Applied Sciences Research 2, 1:52-56

26. Lakshmi Kantam M., Veda Prakash B. and Ch. Venkat Reddy, 2005, An Efficient Synthesis of Chalcones by a Solid Base Catalyst, Synth. Commun., 35:1971

27. Bohm, A. B., Introduction to Flavonoids, Harwood Academic Pub., London. **1998**, p 243-284

28. Edrarir, S., Cotelle, N., Bakkaour, Y., Rolando, C., 2003, An Efficient Synthesis of Chalcones Based on the Suzuki Reaction, Tet Letts., 44: 5359-5363

29. Jayapal M. R. and Sreedhar N.Y., 2010, Anhydrous K_2CO_3 as Catalyst for the synthesis of Chalcones under Microwave Irradiation, J. Pharm. Sci. & Res., 2 (10):644-647

30. Jayapal M. R. and Sreedhar N.Y., 2010, Synthesis and characterization of 4 hydroxy chalcones by aldol condensation using $SOCl_2$/EtOH, Int J Curr Pharm Res, 2(4):60-62

31. Jayapal M. R., Prasad K. S. and Sreedhar N. Y., 2010, Synthesis and Characterization of 2,6-Dihydroxy Substituted Chalcones Using PEG-400 as a Recyclable Solvent, J. Pharm. Sci. & Res., 2(8):450-458

32. Bhagat, S., Sharma, R., Sawant, D.M., Sharma, L. and Chakraborti, A.K., 2006. $LiOH{\cdot}H_2O$ As a Novel Dual Activation Catalyst for Highly Efficient and Easy Synthesis of 1,3-Diaryl-2-Propenones by Claisen-Schmidt Condensation Under Mild Conditions, J. Mol. Catal. A, 244: 20–24

33. Fathalla OA, Awad SM, Mohamed MS, 2005, Synthesis of new 2-thiouracil-5-sulphonamide derivatives with antibacterial and antifungal activity, Arch Pharm Res 28(11), 1205-1212.

34. Ramiz MM, El-Sayed WA, El-Tantawy Al, Abdel-rahman AA, 2010, Antimicrobial activity of new 4,6-disubstituted pyrimidine, pyrazoline, and pyran derivatives, Arch Pharm Res 33(5): 647-654.

35. Braun RU, Zeitler K, Mueller TJ, 2000, A novel 1,5-benzoheteroazepine synthesis via a one-Pot coupling-isomerization-cyclocondensation sequence, Org Lett, 2(26): 4181-4184.