Novel Oxygen Fused Bicyclic Derivatives and Antioxidant Labelling: Bioactive Chalcone Based Green Synthesis

Keyur D. Bhatt 1,* , Vishal Rana 1, Nihal Patel 1, Jaymin Parikh 1, Shibu G. Pillai 2

1 Faculty of Science, Department of Chemistry, Ganpat University, Kherva-384012, Mehsana, Gujarat, India
2 Department of Chemical Engineering, Institute of Technology, Nirma University, S. G. Highway, Ahmedabad, Gujarat, 382481, India
* Correspondence: drkdmbhatt@outlook.com (K.D.B.); Scopus Author ID 55258010600
Received: 23.12.2021; Accepted: 20.01.2022; Published: 25.03.2022

Abstract: Chalcone has become a matter of focus because of its wide variety of biological actions, such as anti-inflammation, anti-cancer, anti-tuberculosis, etc. Due to its inherent chemical reactivity, chalcone has become an easily accessible building block to construct various naturally and biologically active compounds. In modern times, the title compound is made possible to prepare through Claisen-Schmidt reaction or Aldol reaction. However, it is carried out under a conventional condition with a considerable number of variables (time, temperature, reagents, instrument parameters, etc.). In the present research work, we report a novel series of chalcone-based heterocyclic moieties along with an eco-friendly condensation reaction method permitting a ‘green approach’ to the present work. Thin-layer chromatography (TLC) was used to monitor the ‘reaction’s progress, and Rf values were recorded. All of the synthesized derivative’s FTIR spectra were reported. This research focuses on seeing if green approaches can be used to synthesize the target chemical. In comparison to previous procedures, these approaches were more convenient and generated a greater yield (75-80%), showed maximum efficiency, and were stored without polluting the environment while also providing medicinal benefits. This method provides a faster reaction time, is safer for analysts, is minimal in cost, and is simple to implement. Additionally, the antioxidant activity of synthesized ligands with the DPPH assay has been studied.

Keywords: chalcone; pyrazoline; pyrimidine; green chemistry; antioxidant DPPH.

1. Introduction

The chemistry of chalcone is very rich and is very useful nowadays that why it is gaining intense research interest globally [1,2]. Chalcone is a versatile compound that may be used to precursor various biological compounds [3]. Chalcone is electrophilic species having a ketone functional group attached to the unsaturated double bond, and due to this chromophore (CO-CH=CH) it may be able to show color [4]. Chalcone is a unique structure that consists of two aromatic rings connected by a three-carbon unsaturated carbonyl system. Due to the open-chain model and the feature of skeletal modification to produce a new class of organic compounds such as azachalcones [5,6], isoxazoles [7], pyrazoles [8,9], and indole grounded chalcones [10]. Chalcone derivatives have a wide range of therapeutic properties, including anticancer, antioxidants [11], anti-inflammatory [12,13], antihypertensive [14], antimalarial [15], antiulcer [16], antiviral [17], antiprotozoal [18], cardiovascular activity [19] and mutagenic properties [20]. Chalcones are starting to synthesize many cyclic derivatives like...
pyrazolines, isoxazoles, pyrimidine [21,22]. Chalcone compounds have unsaturated double bonds, which delocalizes the electrons to two aromatic rings that resonate with the unsaturated double bond. Due to this phenomenon, possess a (p-electron system).

Pyrazoline is a partially reduced form of pyrazole. It is a basic five-membered heterocyclic with two neighboring nitrogen atoms within the ring and only one endocyclic double bond [23]. The electron-rich pyrazoline derivatives operate as 'Lewis’s basis for complexation, resulting in a wide range of biological activities. Aside from the synthetic approach, it may be found in nature in pigments, vitamins, and plant and animal cell contents, among other things [24]. Antimicrobial [25,26], anticancer [27,28], and anti-inflammatory effects [29] are all demonstrated by pyrazoline and its substituted pyrazoline derivatives [30]. Pyrimidines are heterocyclic aromatic compounds with six members, comparable to phenyl rings. It has two nitrogen atoms arranged in six-membered rings. Various drugs containing the pyrimidine moiety are receiving a lot of interest since they represent a large class of natural and non-natural chemicals, many of which have biological functions [31].

An antioxidant is a molecule that prevents other molecules from oxidizing. Oxidation is a chemical reaction in which molecules transfer electrons or hydrogen to an oxidizing agent. Antioxidants stop these chain reactions from continuing by eliminating free radical intermediates and preventing subsequent oxidative reactions of hetero atoms [32]. Antioxidants are responsible for the ‘organism’s defensive mechanisms against diseases caused by free radical attacks. Plant-derived antioxidants are implicated in preventing oxidative stress-related degenerative diseases such as cancer, 'Parkinson’s disease, 'Alzheimer’s disease, and atherosclerosis [33].

Green chemistry is the discipline of chemistry that deals with tools, processes, and technologies that are environmentally friendly [34,35]. Chemists and chemical engineers can use it in research, development, and manufacturing to create more environmentally friendly and efficient goods that may also save money. It will now become an indispensable tool in synthetic chemistry [36,37]. ’It’s a fresh approach to organic synthesis and medicinal molecule design, with significant environmental and economic benefits over classic synthetic methods [38]. Green chemistry has offered a new challenge for organic synthesis, requiring the development of novel reaction conditions that limit the usage of dangerous toxic compounds and the emission of volatile organic solvents [39]. They improve traditional procedures regarding selectivity, reaction time, and product separation and purification. Investing in techniques that reduce the need for chemical waste using alternative technologies, such as sonochemistry [40-42] and microwave technology [43], reusable catalysts [44], renewable solvents, or even solvent-free reactions, has been attracting attention in the scientific community [45]. The synthesis of a classical Chalcone with the help of ultrasound is described in this paper. On the other hand, the model response is used to design, develop, and execute a simple and comprehensive internal quality approach for evaluating the performance of a standard ultrasonic probe.

2. Materials and Methods

All Chemicals, reagents, and solvent ware purchased from Sigma-Aldrich were used without further purification (simple or under vacuum distillation or recrystallization are sometimes carried out for purification). The purity of synthesized derivatives, including intermediate, was tested by thin-layer chromatography (TLC) using silica gel (60-100 mesh), chromatography was eluted using a mixture of chloroform-methanol (9.5:0.5), or chloroform-
ethyl acetate (5:5), and the spots were visualized by exposure to iodine vapor. Organic solvents were distilled before use.

2.1. Experimental procedure for the synthesis of chalcone.

2.1.1. Conventional method.

A (1.0 mol) of 2-4 dihydroxy acetophenone and (1.0 mol) of furfural aldehyde are taken into appropriate quantity of ethanol. This solution was stirred for 10-15 minutes to maintain the temperature around 0-5°C, 15% solution of NaOH (20 ml) was added dropwise to the resulting solution within 30 minutes. This reaction mixture is stirred for 6 hrs. The TLC is used to monitor the reaction progress. After completion of the reaction. It is acidified with 30% AcOH solution. The reaction mixture was poured into ice water; the yellow solid was formed, filtered, then dried [18]. The Chalcone (CC1) was obtained according to the published method [46] (Scheme 1). Physicochemical and analytical data are presented in Table 1.

2.1.2. Green route method.

The ultrasound-assisted reaction was carried out in a 100 mL flask which contained a solution of (1.0 mol) 2-4 dihydroxy acetophenone and (1.0 mol) of furfural aldehyde were taken into appropriate quantity of ethanol. This solution is subjected to ultrasound irradiation. During the process, 15% NaOH (20 mL) is added dropwise within 30 minutes, and the yields vary according to the parameters used. The TLC is used to monitor the reaction progress. After completion of the reaction. It is acidified with 30% AcOH solution. The reaction mixture was poured into ice water; the yellow solid was formed, filtered, and dried. Physicochemical and analytical data are presented in Table 1.

2.1.3. General synthetic route.

![Scheme 1. Chalcone formation.](https://biointerfaceresearch.com/

![Scheme 2. Summarized reaction of series of ligand (LL1-LL5).](https://biointerfaceresearch.com/)
2.2. General procedure for the synthesis of pyrimidine and pyrazoline derivatives.

A solution of (1.0 mol) of (E)-1-(2,4-dihydroxyphenyl)-3-(furan-2-yl) prop-2-en-1-one in ethanol (25 mL) was prepared; after that, it was refluxed with (1.0 mol) of 98 % pure hydrazine hydrate derivative, guanidine and urea for 6-7 hrs., separately [47]. To give a series of compound (LL1-LL5). After completion of the reaction, the reaction mixture concentrated to its half volume; the generated solid particle was separated, then was filtered and washed with hot water and recrystallized from cold ethanol. A mixture of petroleum ether and chloroform (8:2) is used to give a series of compound (LL1-LL5). After completion of the reaction, the reaction mixture concentrated to its half volume; the generated solid particle was separated, then was filtered and washed with hot water and recrystallized from cold ethanol. A mixture of petroleum ether and chloroform (8:2) is used to monitor the reaction through TLC (Scheme 2) continuously. Physicochemical and analytical data are presented in Table 2.

Table 1. Physicochemical and analytical data of compounds.

| Sr. No | Compound | Reaction Time | % Yield | Mass Of Compound | Mol. Formula | Color         | Rf Value |
|--------|----------|---------------|---------|------------------|--------------|---------------|----------|
| 1      | (E)-1-(2,4- | 7 Hrs. | 71% | 230.6 | C_{13}H_{10}O_{4} | Yellowish Brown | 0.74     |
|        | dihydroxyphenyl) | 20-25 Min | 80 % |                  |              |               |          |
|        | -3-(furan-2-y) | prop-2-en-1-one | |                |              |               |          |
| 2      | LL2      | 4-(5-(furan-2-yl)-4,5-dihydro-1H-pyrazol-3-yl) benzene-1,3-diol | 244.03 | C_{13}H_{10}N_{2}O_{3} | 68 \% | Reddish | 0.77 |
| 3      | LL3      | 4-(5-(furan-2-yl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl) benzene-1,3-diol | 320.6 | C_{19}H_{16}N_{2}O_{3} | 68 % | Reddish | 0.80 |
| 4      | LL4      | 4-(2-amino-6-(furan-2-yl) pyrimidin-4-yl) benzene-1,3-diol | 269.5 | C_{14}H_{11}N_{3}O_{3} | 69% | Blackish | 0.74 |
| 5      | LL5      | 4-(6-(furan-2-yl)-2-hydroxypyrimidin-4-yl) benzene-1,3-diol | 270.4 | C_{14}H_{10}N_{2}O_{4} | 68% | Blackish | 0.75 |

3. Results and Discussion

Conventionally, chalcone can be prepared by refluxing the ketone and aldehyde in an organic solvent through Claisen-Schmidt reaction or aldol condensation as an acid or base catalyst [48,49].

The following scheme 1 depicts the synthetic techniques used to synthesize the intermediate derivative and target compounds: Another advantage of this approach is its operational simplicity, ease of work-up, and higher yield, which includes washing the mixture followed by solvent evaporation. Chalcone synthesis is a single-step process. The yields of the synthesized compounds have been shown to be significant. In the current method, we provide a mild, efficient, high-yielding approach for the condensation reaction of different aromatic ketone and furfural aldehyde. These reactions were accomplished in reduced reaction times (20-22 minutes) with high yields using this approach (80 %). The green route approach necessitates simple work-up processes, such as simple filtering to separate the products since

https://doi.org/10.33263/BRIAC13X.000
they are insoluble. The necessary chemicals were produced with good yields without any additional purification. Compared to the reaction time and product yield of conventional methods, this technique was chosen as green, environmentally friendly, clean, and safe to boost synthesis.

After completion of preparation of chalcone, it was utilized to synthesize five-membered and six-membered heterocyclic derivatives (Scheme 02). Chalcone can undergo nucleophilic attack through Michael's addition. Cyclization of the Chalcones with guanidine and urea in ethanol gave compound (LL4), (LL5) 4-(2-amino-6-(furan-2-yl) pyrimidin-4-yl) benzene-1,3-diol and 4-(6-(furan-2-yl)-2-hydroxypyrimidin-4-yl) benzene-1,3-diol, respectively. Furthermore, the substituted pyrazoline ring (five-member ring) formed by the nucleophilic attack by hydrazine hydrate and its analogs give compound (LL1-LL3). All chemicals were extracted in high yields (70–85%) and purified using ethanol recrystallization. Thin-layer chromatography (TLC) and elemental analysis were used to determine the purity of the substances. Elemental analysis and spectrum (UV, IR, $^1$HNMR, $^{13}$C NMR, and mass) data validated the structures of the newly synthesized compounds, which were in agreement with the hypothesized structures.

3.1. Antioxidant activity.

Free radicals are extremely reactive atoms or compounds with outermost electrons unpaired [50]. Due to the gain or loss of an unpaired electron, free radicals are continually striving to form stable bonds. The electron configuration of chalcone-based heterocyclic compounds is ready to accept/donate an electron or depends on the current oxidation state and electron configuration [13,51-53]. As a result, ligands are ready to accept/donate electrons to quench radicals based on reaction conditions.

The DPPH is a well-characterized synthetic solid radical that may be used to assess the antioxidant capacity of substances. The ability of ligands to reduce DPPH by receiving hydrogen or electron was measured spectrophotometrically by altering the DPPH color from yellow to brown Fig. 1.

![Figure 1. DPPH with ligand color from yellow to brown.](https://biointerfaceresearch.com/)

Comparing antioxidant activity with common antioxidant reference materials Quercetin and Ascorbic Acid (AA) [54,55] Fig 2-7. Even though the antioxidant activity [56,57] of CC-1 and LL1-5 is slightly lower than that of the conventional antioxidants Quercetin and Ascorbic Acid (AA), it is reasonable to believe that CC-1 and LL1-5 have the potential to be used as good antioxidant agents.
Figure 2. DPPH with CC-1 from concentration 10µL to 200µL.

Figure 3. DPPH with LL-1 from concentration 10µL to 200µL.

Figure 4. DPPH with LL-2 from concentration 10µL to 200µL.

Figure 5. DPPH with LL-3 from concentration 10µL to 200µL.
The comparison with standard antioxidant with ligand CC-1, LL-1, LL-2, LL-3, LL-4, LL-5 ware recorded in UV Visible and bar diagram shows the potent antioxidant properties of synthesized ligands Fig 8.

The percent DPPH radical inhibition with absorbance effect is indicated in Fig 9. Inhibition was found to be low in CC-1 compared with LL1-5, which may be because NH acts as a good oxidant that can easily react and accept/lose electrons.
4. Conclusions

The research work here demonstrates the synthesis of novel chemical entities of pyrazole/pyrazoline and pyrimidine derivative. Substituted pyrazoline and pyrimidine heterocyclic rings are therapeutically potential classes of compounds. The method used in the present study is one of the best methods for introducing functional group modification with ease. It’s important to note that Chalcones have a unique template with an -unsaturated carbonyl system that allows for structural changes. The experimental results show that the ultrasound-assisted reaction is 17 times quicker than the traditional one (20 min vs. 6 hr.). The ring formation reaction of chalcone with hydrazine and its analogs to obtain substituted pyrazoline and pyrimidine heterocyclic moiety (LL1 – LL5) was attempted by employing various reagents and reaction conditions. All the desired products as a novel moiety were successfully carried out under optimized reaction conditions. In addition, the antioxidant activity of synthesized ligands was also successfully evaluated to show free radical scavenging activity up to 60-70 % in 30 min, which is relatively higher in comparison to other moieties.

Funding

This research received no external funding.

Acknowledgments

The authors are thankful to Mehsana Urban Institute of Sciences, Ganpat University, Mehsana, and CARS-GUNI for providing library facilities and support for research work.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Yusuf, M.; Jain, P. Synthetic and biological studies of pyrazolines and related heterocyclic compounds. Arabian Journal of Chemistry 2014, 7, 553-596, https://doi.org/10.1016/j.arabjc.2011.09.013.
2. Zhuang, C.; Zhang, W.; Sheng, C.; Zhang, W.; Xing, C.; Miao, Z. Chalcone: a privileged structure in medicinal chemistry. Chemical reviews 2017, 117, 7762-7810, https://doi.org/10.1021/acs.chemrev.7b00020.
3. Jawad, A.M.; Salih, M.N.M.; Helal, T.A.; Obaid, N.H.; Aljamali, N.M. Review on chalcone (preparation, reactions, medical and bio applications). Int J Chem Synth Chem React 2019, 5, 16-27.
4. Rivera, E.; Andrade, N.; Martin, G.; Melito, G.; Cricco, G.; Mohamad, N.; Davio, C.; Caro, R.; Bergoe, R. Induction of mammary tumors in rat by intraperitoneal injection of NMU: histopathology and estral cycle influence. Cancer letters 1994, 86, 223-228, https://doi.org/10.1016/0304-3835(94)90082-5.
5. Downs, L.E.; Wolfe, D.M.; Schreiner, P.R. Organic Base-Mediated Condensation of Pyridinecarboxaldehydes to Azachalcones. Advanced Synthesis & Catalysis 2005, 347, 235-238, https://doi.org/10.1002/adsc.200404318.
6. Saleem, F.; Khan, K.M.; Chigurupati, S.; Solangi, M.; Nemala, A.R.; Mushtaq, M.; Ul-Haq, Z.; Taha, M.; Perves, S. Synthesis of azachalcones, their α-amylose, α-glucosidase inhibitory activities, kinetics, and molecular docking studies. Bioorganic chemistry 2021, 106, https://doi.org/10.1016/j.bioorg.2020.104489.
7. Prakash, O.; Kumar, A.; Sadana, A.; Prakash, R.; Singh, S.P.; Claramunt, R.M.; Sanz, D.; Alkorta, I.; Elguero, J. Study of the reaction of chalcone analogs of dehydroacetic acid and o-aminophenol: synthesis and structure of 1, 5-benzothiazepines and 1, 4-benzothiazines. Tetrahedron 2005, 61, 6642-6651, https://doi.org/10.1016/j.tet.2005.03.035.
8. Prasad, Y. R.; Rao, A.L.; Prasoon, L.; Murali, K.; Kumar, P.R. Synthesis and antidepressant activity of some 1, 3, 5-triphenyl-2-pyrazolines and 3-{2 "hydroxy naphthalen-1 "yl}-1, 5-diphenyl-2-pyrazolines. Bioorganic & medicinal chemistry letters 2005, 15, 5030-5034, https://doi.org/10.1016/j.bmcl.2005.08.040.
9. Devi, L.; Sharma, G.; Kant, R.; Shukla, S.K.; Rastogi, N. Regioselective synthesis of functionalized pyrazole-chalcones via a base mediated reaction of diazo compounds with pyrylium salts. *Organic & Biomolecular Chemistry* 2021, 19, 4132-4136. https://doi.org/10.1039/D1OB00274K.

10. Gupta, S.; Maurya, P.; Upadhyay, A.; Kushwaha, P.; Krishna, S.; Siddiqui, M. I.; Sashidhara, K.V.; Banerjee, D. Synthesis and bio-evaluation of indole-chalcone based benzopyrans as promising antilagase and antiproliferative agents. *European journal of medicinal chemistry* 2018, 143, 1981-1996. https://doi.org/10.1016/j.ejmech.2017.11.015.

11. Anto, R.J.; Sukumaran, K.; Kuttan, G.; Rao, M.; Subbaraju, V.; Kuttan, R. Anticancer and antioxidant activity of synthetic chalcones and related compounds. *Cancer letters* 1995, 97, 33-37. https://doi.org/10.1016/0304-3835(95)03945-S.

12. Ballesteros, J.; Sanz, M.; Ubeda, A.; Miranda, M.; Iborra, S.; Paya, M.; Alcaraz, M.D. Synthesis and pharmacological evaluation of 2'-hydroxychalcones and flavones as inhibitors of inflammatory mediators generation. *Journal of medicinal chemistry* 1995, 38, 2794-2797. https://doi.org/10.1021/jm00014a032.

13. Guazelli, C.F.; Fattori, V.; Ferraz, C.R.; Borghi, S.M.; Casagrande, R.; Baracat, M.M.; Verri, J.R.W.A. Antioxidant and anti-inflammatory effects of hesperidin methyl chalcone in experimental ulcerative colitis. *Chemico-Biological Interactions* 2021, 333, https://doi.org/10.1016/jcbd.2020.109315.

14. Won, S.-J.; Liu, C.-T.; Tsao, L.-T.; Weng, J.-R.; Ko, H.-H.; Wang, J.-P.; Lin, C.-N. Synthetic chalcones as potential anti-inflammatory and cancer chemopreventive agents. *European journal of medicinal chemistry* 2005, 40, 103-112. https://doi.org/10.1016/j.ejmech.2004.09.006.

15. Domínguez, J.N.; León, C.; Rodrigues, J.; de Domínguez, N.G.; Gut, J.; Rosenthal, P.J. Synthesis and antimalarial activity of sulfonamide chalcone derivatives. *I Farmaco* 2005, 60, 307-311. https://doi.org/10.1016/j.farmac.2005.01.005.

16. Kyogoku, K.; Hatayama, K.; Yokomori, S.; Saziki, R.; Nakane, S.; Sasajima, M.; Sawada, J.; Ohzeki, M.; Tanaka, I. Anti-ulcer effect of isoprenyl flavonoids. II. Synthesis and anti-ulcer activity of new chalcones related to sophoradin. *Chemical and Pharmaceutical Bulletin* 1979, 27, 2943-2953. https://doi.org/10.1248/cpb.27.2943.

17. Ishitsuka, H.; Ninomiya, Y.; Ohsawa, C.; Fujii, M.; Suhara, Y. Direct and specific inactivation of rhinovirus by chalcone Ro 09-0410. *Antimicrobial agents and chemotherapy* 1982, 22, 611-621. https://doi.org/10.1128/AAC.22.4.617.

18. Chen, M.; Christensen, S.B.; Blom, J.; Lemmich, E.; Fich, K.; Theander, T.G.; Kharazmi, A. Licochalcone A, a novel antiparasitic agent with potent activity against human pathogenic protozoan species of Leishmania. *Antimicrobial agents and chemotherapy* 1993, 37, 2550-2556. https://doi.org/10.1128/AAC.37.12.2550.

19. Chen, M.; Zhai, L.; Christensen, S.B.; Theander, T.G.; Kharazmi, A. Inhibition of fumarate reductase in Leishmania major and L. donovani by chalcones. *Antimicrobial agents and chemotherapy* 2001, 45, 2023-2029. https://doi.org/10.1128/AAC.45.7.2023-2029.2001.

20. Rashid, K.A.; Mullin, C.A.; Mumm, R.O. Structure-mutagenicity relationships of chalcones and their oxides in the Salmonella assay. *Mutation Research/Genetic Toxicology* 1986, 169, 71-79. https://doi.org/10.1016/0165-1218(86)90086-8.

21. Rammohan, A.; Reddy, J. S.; Sravya, G.; Rao, C.N.; Zyryanov, G.V. Chalcone synthesis, properties and medicinal applications: a review. *Environmental Chemistry Letters* 2020, 18, 433-458. https://doi.org/10.1007/s10311-019-00959-w.

22. Kumar, S.; Bawa, S.; Drabu, S.; Kumar, R.; Gupta, H. Biological activities of pyrazoline derivatives-A recent development. *Recent patents on anti-infective drug discovery* 2009, 4, 154-163. https://doi.org/10.2174/15748910979318569.

23. Thakor, K.P.; Lunagariya, M.V.; Bhatt, B.S.; Patel, M.N. Synthesis, characterization and biological applications of some substituted pyrazoline based palladium (II) compounds. *Applied Organometallic Chemistry* 2018, 32, https://doi.org/10.1002/aoc.4523.

24. Khanam, H.; Dar, A.M.; Siddiqui, N.; Rehman, S. Synthesis, characterization, antimicrobial and anti-cancer studies of new steroidal pyrazolines. *Journal of Saudi Chemical Society* 2016, 20, 7-12. https://doi.org/10.1016/j.jscs.2012.05.004.

25. Sahu, S.; Banerjee, M.; Samantray, A.; Behera, C.; Azam, M. Synthesis, analgesic, anti-inflammatory and antimicrobial activities of some novel pyrazoline derivatives. *Tropical journal of pharmaceutical research* 2008, 7, 961-968. https://doi.org/10.4314/tjpr.v7i2.14664.

26. Ahmad, A.; Husain, A.; Khan, S. A.; Mujeeb, M.; Bhandari, A. Synthesis, antimicrobial and antitubercular activities of some novel pyrazoline derivatives. *Journal of Saudi Chemical Society* 2016, 20, 577-584. https://doi.org/10.1016/j.jscs.2014.12.004.

27. Karabacak, M.; Altintop, M. D.; Ibrahim Çifçi, H.; Koga, R.; Otsuka, M.; Fujita, M.; Özdemir, A. Synthesis and evaluation of new pyrazoline derivatives as potential anti-cancer agents. *Molecules* 2015, 20, 19066-19084. https://doi.org/10.3390/molecules20109066.

28. Varma, R.R.; Pandya, J.G.; Vaidya, F.U.; Pathak, C.; Bhatt, B.S.; Patel, M.N. Biological activities of pyrazoline-indole based Re (I) carbonyls: DNA interaction, antibacterial, anti-cancer, ROS production, lipid
peroxidation, in vivo and in vitro cytotoxicity studies. Chemico-Biological Interactions 2020, 330, https://doi.org/10.1016/j.cbi.2020.109231.

29. Herencia, F.; Ferrandiz, M. L.; Ubeda, A.; Domínguez, J.; Charris, J.E.; Lobo, G.M.; Alcaraz, M.J. Synthesis and anti-inflammatory activity of chalcone derivatives. Bioorganic & medicinal chemistry letters 1998, 8, 1169-1174, https://doi.org/10.1016/S0960-894X(98)00179-6.

30. Foye, W.O. Principles of medicinal chemistry. Lea & Febiger 1974.

31. Sharma, V.; Chitranshi, N.; Agarwal, A.K. Significance and biological importance of pyrimidine in the microbial world. International journal of medicinal chemistry 2014, 2014, http://dx.doi.org/10.1155/2014/202784.

32. Abdel-Moneim, A.-M. E.; El-Saadony, M.T.; Shehata, A.M.; Saad, A.M.; Aldhumi, S.A.; Ouda, S.M.; Mesalam, N.M. Antioxidant and antimicrobial activities of Spirulina platensis extracts and biogenic selenium nanoparticles against selected pathogenic bacteria and fungi. Saudi Journal of Biological Sciences 2021, https://doi.org/10.1016/j.sjbs.2021.09.046.

33. Darjee, S.M.; Bhatt, K.; Kongor, A.; Panchal, M.K.; Jain, V.K. Thiacalix [4] arene functionalized gold nano-assembly for recognition of isoleucine in aqueous solution and its antioxidant study. Chemical Physics Letters 2017, 667, 137-145, https://doi.org/10.1016/j.cplett.2016.11.048.

34. Murti, Y.; Pathak, D.; Pathak, K. Green Chemistry Approaches to the Synthesis of Flavonoids. Current Organic Chemistry 2021, 25, 2005-2027, https://doi.org/10.2174/1385272825666210728095624.

35. Jain, S.; Kumar, S.; Lamba, B. Y.; Patra, J.; Mahindroo, N. Nanocatalysts: Applications in synthesis of chalcones—a review. Synthetic Communications 2021, 51, 1-12, https://doi.org/10.1080/00397911.2020.1817941.

36. Cancio, N.; Costantino, A.R.; Silbester, G.F.; Pereyra, M.T. Ultrasound-assisted syntheses of chalcones: Experimental design and optimization. Multidisciplinary Digital Publishing Institute Proceedings 2019, 41, https://doi.org/10.3390/ecsoc-23-06475.

37. Bhuiyan, M.; Hossain, M.; Mahmud, M.; Al-Amin, M. Microwave-assisted efficient synthesis of chalcones as probes for antimicrobial activities. Chemistry journal 2011, 1, 21-28.

38. Li, J.-T.; Yang, W.-Z.; Wang, S.-X.; Li, S.-H.; Li, T.-S. Improved synthesis of chalcones under ultrasound irradiation. Ultrasonomics Sonochemistry 2002, 9, 237-239, https://doi.org/10.1016/S1350-4177(02)00079-2.

39. Deshmukh, N.; Shinde, A. An efficient, ultrasound induced ring closure of hydroxy chalcone in 2-ethoxy ethanol as an green reaction medium and study of antimicrobial potential. Chemical Data Collections 2021, 31, https://doi.org/10.1016/j.cdc.2020.100606.

40. Pizzuti, L.; Martins, P.L.; Ribeiro, B.A.; Quina, F.H.; Pinto, E.; Flores, A.F.; Venzke, D.; Pereira, C.M. Efficient sonochemical synthesis of novel 3, 5-diaryl-4, 5-dihydro-1H-pyrazole-1-carboximidamides. Ultrasonomics Sonochemistry 2010, 17, 34-37, https://doi.org/10.1016/j.ulsonch.2009.06.013.

41. Venzke, D.; Flores, A.F.; Quina, F.H.; Pizzuti, L.; Pereira, C.M. Ultrasound promoted greener synthesis of 2-(3, 5-diaryl-4, 5-dihydro-1H-pyrazol-1-yl)-4-phenythiazoles. Ultrasonomics sonochemistry 2011, 18, 370-374, https://doi.org/10.1016/j.ulsonch.2010.07.002.

42. Dandia, A.; Gupta, S.L.; Parewa, V. An efficient ultrasound-assisted one-pot chemoselective synthesis of pyrazolo[3, 4-b] pyridine-5-carbonitriles in aqueous medium using NaCl as a catalyst. RSC Advances 2014, 4, 6908-6915, https://doi.org/10.1039/C3RA47231K.

43. Thirunarayanan, G.; Mayavel, P.; Thirumurthy, K. Fly-ash: H2SO4 catalyzed solvent free efficient synthesis of some aryl chalcones under microwave irradiation. Spectrochimica acta part A: molecular and biomolecular spectroscopy 2012, 91, 18-22, https://doi.org/10.1016/j.saa.2012.01.054.

44. Rajender, B.; Ramesh, G.; Palamiappan, S. Polyaniline coated glass/SS sheet: Novel, convenient, efficient, reusable and green catalyst. Catalysis Communications 2014, 43, 93-96, https://doi.org/10.1016/j.catcom.2013.09.025.

45. Lu, H.-F.; Zhou, J.-T.; Cheng, H.-L.; Sun, L.-L.; Yang, F.-F.; Wu, R.-Z.; Gao, Y.-H.; Luo, Z.-B. An efficient catalyst for ring opening of epoxides with phenol and thiophenol under solvent-free conditions. Tetrahedron 2013, 69, 11174-11184, https://doi.org/10.1016/j.tet.2013.10.098.

46. Eseohe, O.V.; Oghosa, O.M.; Enoghense, O.; Kingsley, O. Evaluation of the Effects of Administration of Aqueous Root Extract of Chrysophyllum albium on Fertility in Male Wistar Albino Rats. International Journal of Pharmacology, Phytochemistry and Ethnomedicine 2018, 10, 13-28, https://doi.org/10.18052/www.sciexpress.com/IJPPE.10.13.

47. Ozdemir, A.; Dilek Aluntup, M.; Canturk, Z.; Asim Kaplanclikli, Z. Synthesis and in vitro evaluation of furan-based chalcone derivatives as antimicrobial agents. Letters in Drug Design & Discovery 2015, 12, 607-611, http://dx.doi.org/10.2174/1570180812999150202112352.

48. Annath, H.; Manayil, J.C.; Thompson, J.; Marr, A.C.; Raja, R. Contrasting structure-property relationships in amorphous, hierarchical and microporous aluminophosphate catalysts for Clausen-Schmidt condensation reactions. Applied Catalysis A: General 2021, 627, https://doi.org/10.1016/j.apcata.2021.118376.

49. Selvaraj, G.G.; Jayaraman, S.; Selvarasu, U.; Velumani, B.P.; Parasuraman, K. An Efficient Synthesis of α, β Unsaturated Ketones via Clausen-schmidt Condensation Reaction using Amino Acid Based Ionic Liquids. Current Catalysis 2021, 10, 103-107, https://doi.org/10.2174/2211544710666210716113451.
50. Eden, W. T.; Alighiri, D.; Wijayati, N.; Mursiti, S. Synthesis of Chalcone Derivative from Clove Leaf Waste as a Natural Antioxidant. *Pharmaceutical Chemistry Journal* 2021, 55, 268-274, https://doi.org/10.1007/s11094-021-02410-3.

51. Alisi, I.O.; Uzairu, A.; Idris, S.O. Ligand-based design of chalcone analogues and thermodynamic analysis of their mechanism of free radical scavenging. *Journal of Molecular Modeling* 2021, 27, 1-12, https://doi.org/10.1007/s00894-021-04717-0.

52. Kabanda, M.M.; Gbashi, S.; Madala, N.E. Proportional coexistence of okanin chalcone glycoside and okanin flavanone glycoside in Bidens pilosa leaves and theoretical investigation on the antioxidant properties of their aglycones. *Free Radical Research* 2021, 55, 53-70, https://doi.org/10.1080/10715762.2020.1859107.

53. Adelusi, T.I.; Du, L.; Chowdhury, A.; Xiaoke, G.; Lu, Q.; Yin, X. Signaling pathways and proteins targeted by anti-diabetic chalcones. *Life Sciences* 2021, 284, https://doi.org/10.1016/j.lfs.2020.118982.

54. Gacche, R.; Dhole, N.; Kamble, S.; Bandgar, B. In-vitro evaluation of selected chalcones for antioxidant activity. *Journal of Enzyme Inhibition and Medicinal Chemistry* 2008, 23, 28-31, https://doi.org/10.1080/14756360701306370.

55. Kumar, C.; Loh, W.-S.; Ooi, C.W.; Quah, C.K.; Fun, H.-K. Structural correlation of some heterocyclic chalcone analogues and evaluation of their antioxidant potential. *Molecules* 2013, 18, 11996-12011, https://doi.org/10.3390/molecules181011996.

56. Vazquez-Rodriguez, S.; Figueroa-Guíñez, R.; Matos, M.J.; Santana, L.; Uriarte, E.; Lapier, M.; Maya, J.D.; Olea-Azar, C. Synthesis of coumarin-chalcone hybrids and evaluation of their antioxidant and trypanocidal properties. *MedChemComm* 2013, 4, 993-1000, https://doi.org/10.1039/C3MD00025G.

57. Iqbal, H.; Prabhakar, V.; Sangith, A.; Chandrika, B.; Balasubramanian, R. Synthesis, anti-inflammatory and antioxidant activity of ring-A-monosubstituted chalcone derivatives. *Medicinal Chemistry Research* 2014, 23, 4383-4394, https://doi.org/10.1007/s00044-014-1007-z.