Review Article: Synthesis, Reactions and Pharmacological Applications of Chalcones and Their Derivatives - A Mini Review

Abdul Razaq Tukur\(^1,2\)*, James Dama Habila\(^1\), Rachael Gbekele-Oluwa Ayo\(^1\), Ogunkemi Risikat Agbeke Lyun\(^1\)

\(^1\)Department of Chemistry, Ahmadu Bello University, Zaria, Nigeria
\(^2\)Department of Chemistry, Al-Qalam University, Katsina, Nigeria

**ABSTRACT**

The shortage of novel antifungal drugs, the emergence of new infectious diseases, the resurgence of several infections and the increased resistance of fungi to available chemotherapeutic agents are the essential issues in drug design and development, which prompted researchers to look for novel compounds that can combat multidrug-resistant organisms. Over the last two decades, chalcones have been proved to be attractive moieties in drug discovery. Chalcones are pharmacologically active compounds that are also described as 1,3-diphenylprop-2-en-1-one derivatives. They have found applications as anticancer, anti-diabetic, anti-HIV, antioxidants, antimalarial, anti-tubercular, anti-viral, anti-inflammatory and antidiuretic agents. Some chalcones have been used as inhibitors of lipoxigenase, \(\beta\)-secretase (BACE1), and acetylcholinesterase (AChE). The synthesis, characterization, various reactions of numerous chalcones and their pharmacological applications have been discussed. This review was motivated by the diverse pharmacological applications of chalcones, their simplicity of synthesis, and the growing resistance of disease causative agents to the currently available chemotherapeutic agents.

**List of content**

1. Introduction
2. Synthesis of chalcones

*Corresponding Author: Abdul Razaq Tukur (abdulrazaqtukur@gmail.com)
1. Introduction

Chalcones also known as 1,3-diaryl-2-propene-1-one, are \( \alpha,\beta \)-unsaturated ketone containing the reactive ketoethylenic group (\(-\text{CO-CH=CH}-\)). Benzalacetophenone or benzyldiene acetophenone are other names for these compounds. In chalcones, an aliphatic three-carbon chain connects two aromatic rings structurally. The term "chalcone" comes from the Greek word "chalcos," which means "bronze," and describes the hue of most natural chalcones. Chalcones are abundant in nature and can be found in fruits and tea [1], *Uvaria siamensis* roots [2], *Stevia lucida* [3] and *Pongamia pinnata* (L.) Pierre roots [4] and based foodstuffs [5, 6]. Kostanecki and Tambor coined the term chalcone [7]. These compounds are colored due to the presence of a chromophore (\(-\text{CO-CH=CH}-\)), which is dependent on the presence of additional auxochromes [8]. Alternative chalcones include phenyl styryl ketones, \( \beta \)-phenyl acetophenone, \( g \)-oxo-diphenyl-apropylene, and \( a \)-phenyl-benzoethylene [9]. They’re non-chiral small molecules having molecular weights between 300 and 600 g/mol and high lipophilicity [10].

The term "chalcone" is frequently used to refer to molecules that contain the 1,3-diphenylprop-2-en-1-one moiety and are employed as intermediates in the manufacture of flavonoids. [11-14] and are a major flavonoid class [15, 16]. They are polyphenolic compounds that change color from yellow to orange and are used to make flavonoids and isoflavonoids. With two aromatic rings joined by a three carbon, \( \alpha,\beta \)-unsaturated carbonyl system, they can be found as either trans \((E)\) or cis \((Z)\) isomers [17].

Because the \( E \) isomer is more thermodynamically stable in most cases, it is the most prevalent structure among the chalcones. The conformation of \((Z)\) isomer is unstable because of substantial steric interactions between the carbonyl group and the A-ring [17]. Various computational techniques have also identified planar and non-planar structures of the most stable conformers. Chalcones are open-chain systems with conjugated double bonds and a completely delocalized \( \pi \)-electron system on the benzene rings and a three-carbon, \( \alpha,\beta \)-unsaturated carbonyl system connecting the two aromatic rings [18]. Molecules with this structure have lower redox potentials and are more likely to interact with electrons via electron transfer [18]. The Claisen–Schmidt condensation reaction, which generates chalcones from the condensation of aryl methyl ketones and aromatic aldehydes in an alkaline medium, is the most effective method of producing chalcones [19].

Due to the delocalization of electron density in the \((C=C-C=O)\) system, compounds with \( \alpha,\beta \)-unsaturated carbonyl system, such as chalcones, have two electrophilic reactive centers, allowing them to engage in additional processes \textit{via} an attack on the carbonyl group (1,2-addition) or engaging the \( \alpha \)-carbon (1,4-conjugate addition) [19] to produce bioactive molecules with promising biological properties used to produce biologically active 5- and 6-membered heterocycles such as pyrroles, indoles, isoxazoles, imidazoles, pyrazoles, indazoles, triazoles, tetrazoles, pyridines, and pyrimidines [19]. Flavones, flavonols, flavanones, aurones, and benzoylecoumarones are examples of flavonoids obtained from chalcones [20-24].

In chalcones, the conjugated double bond allows \( \pi \)-electrons to delocalize, lowering their electrophilic property and allowing them to be employed as intermediates in the synthesis of a wide range of medically essential heterocycles.
As a result, both organic and medicinal chemists are interested in chalcone synthesis. Artificial sweeteners, scintillators, fluorescent whitening agents, and heat stabilizers are made from chalcones and derivatives [26]. They are used as artificial sweeteners in some cases [27]. Due to the presence of the keto-ethylenic group, chalcones become reactive with a range of substances, including phenyl hydrazine and 2-amino thiophenol [28]. For mechanistic research and imaging/diagnosis, fluorescent substituted chalcones with appropriate electron-releasing and electron-withdrawing functional groups on the benzene ring(s) are utilized as chemical probes [29]. The dimethylamino group, in particular, is a typical fluorescent probe substituent found in fluorescent chalcone compounds [29]. Chalcones have also been used to deduce the structure of natural compounds including hemlock tannin, cyanomaclurin [30], ploretin [31], eriodictyol, homo eriodictyol [32] and naringenin [33].

Chalcones can be made in a variety of methods. However, the most typical process involves Claisen-Schmidt condensation in the presence of acid or base under homogeneous conditions [34, 35]. For synthesis of chalcones, strong alkaline media such as natural phosphates, Ba(OH)$_2$, KOH, NaOH and others have traditionally been used [36]. However, the use of several lewis acids ($p$-toluene sulfonic acid, $B_2$O$_3$, RuCl$_3$, AlCl$_3$, BF$_3$ and dry HCl) has also been demonstrated [36]. Chalcones are traditionally made by the combination of substituted or unsubstituted aldehyde and ketone in a base catalyzed Claisen-Schmidt condensation reaction. The traditional synthesis of chalcone has various drawbacks, including harsh reaction conditions, product mixtures, and contamination from tainted reagents [37]. To avoid these complications, more attention has recently been paid to green chemistry methodologies, in which chalcones are synthesized using environmentally friendly methods, uncomplicated, take less time, yield excellent purity with good yield, and have mild reaction conditions [38].

Chalcones (Figure 1) are critical elements of natural sources [39] and were initially isolated from Chinese liquorice (Glycyrrhiza inflata) [40]. They are also abundant in nature, ranging from ferns to higher plants, and many of them have polyhydroxylated aryl rings [41].

Chalcones and their synthetic equivalents serve a variety of biological activities. The biological activities of chalcones are thought to be attributable to the presence of a double bond in conjugation with carbonyl functionality, as removal of this functionality renders them inert [42]. They can easily be cyclized through Michael addition to generate flavanones [43].

The chemistry of chalcones has stimulated a bustle of research around the globe. Chalcone synthesis and biodynamic activities have captivated people's interest. Chalcone has a fantastic synthon, which allows it to make a wide variety of novel heterocycles with intriguing pharmacological effects. Chalcones have shown promising therapeutic efficacy in the treatment of a variety of disorders due to a wide range of structural modifications; in fact, few structurally varied compounds display connection with such a broad range of pharmacological actions, among which scientific study has confirmed that chalcone derivatives show a wide variety of striking biological activities, such as anti-inflammatory [44, 45], anticancer [46], antidiabetic [47], anti-tumor [48-51], anti-fungal [52-54], antibacterial [55, 56], antiviral [57, 58] and antioxidant activities [59, 60]. They have also been reported to show anti-hypertensive effects [61, 62]. Thus, the synthesis of chalcones continued to attract much interest in organic chemistry [63].

![Figure 1](image-url)
1.1 Dietary chalcones

Chalcones are a class of natural compounds found in a variety of fruits and vegetables, such as apples (*Malus domestica*), tomatoes (*Solanum lycopersicum*), and various plants and spices, such as licorice (*Glycyrrhiza inflata*), many of which have been used in traditional herbal medicine for millennia [64]. The production of 4,2′,4′,6′-tetrahydroxychalcone (also known as naringenin chalcone) by chalcone synthase facilitates the common content of chalcones in citrus fruits and many plants [65]. Naringenin chalcone plays an essential function in flavonoid biosynthesis and contributes significantly to the total amount of flavonoids in plants [66]. The chalcone moiety and a strong flavonoid found in Ashitaba (*Angelica keiskei*) include xanthoangeol, xanthoangelol E, and 4-hydroxyderricin [67-69]. Medical trials on chalcones have shown that they are powerful antioxidants that protect organs from free radical damage and assist in halting the aging process at the cellular level.

Although chalcones are found naturally, an efficient and straightforward synthesis could make them more widely available. The presence of a reactive enone moiety (α,β-unsaturated ketone) in chalcones has been reported to undergo conjugate addition with a nucleophilic group, comparable to a thiol group in an essential protein. The type and position of the substituents on the aromatic rings in chalcones can be altered [70]. Several pure extracts of chalcones from plants or crude extracts of plants that contain chalcone, such as licorice, are commercially accessible due to their pharmacological effects [71]. The following are some FDA-approved medications that contain the chalcones moiety:

i. The inhibitory activity of \((E)-1-(2-hydroxyphenyl)-3(thiophen2-yl)prop-2-en-1-one\) (Figure 2), on chemical mediators generated by mast cells, neutrophils, macrophages, and microglial cells was studied in vitro and found to be adequate [72].

![Figure 2](image)

**Figure 2.**

ii. Licochalcone A (Figure 3), an oxygenated chalcone with antileishmanial and antimalarial properties, affects the ultrastructure and function of mitochondria *Leishmania* spp. [72].

![Figure 3](image)

**Figure 3.**

iv. Antiviral action of *O*-hydroxy chalcone [72]. Metochalcone 1-(2,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)-2-propen-1-one (Figure 4) is one of the chalcones available on the market; others include a choleretic drug and an antiulcer medicine (sofalcone), 2-[5-[(3-methyl-2-buten-1-yl)-oxy]-2-[3-4-[(3-methyl-2-buten-1-yl)oxy]phenyl]-1-oxo-2-propen-1-yl] acetic acid [-phenoxy] [73].
2. Synthesis of chalcones

One of the most common types of naturally occurring organic compound is chalcones. For the synthesis of chalcones, various methods have been reported, the most common and well-known of which is the Claisen-Schmidt condensation [74]. Several methods for the synthesis of chalcones have been reported, including microwave-assisted synthesis [75] using PEG-400 [76] or ionic liquids [77], Suzuki reaction [78], and Friedel-Crafts Acylation reaction [79, 80]. Chalcones have simple chemistry that allows for a wide range of substitutions with ease of synthesis. The most significant aspect of each of these approaches is condensing two aromatic systems (with nucleophilic and electrophilic groups) to produce the chalcone scaffold [80].

2.1 Heck reaction

Chalcones are made by carbonylation phenyl halide with styrene in the presence of carbon monoxide while utilizing palladium (Pd) as a catalyst (Scheme 2) [86].

\[
\text{R}^1 + \text{H}_2\text{C} = \text{CH} \rightarrow \text{Pd} \rightarrow \text{CO} \rightarrow \text{O} + \text{H-R}^1
\]

\[\text{Scheme 2. Carbonylative Heck coupling reaction}\]

In the presence of a palladium catalyst, mannich bases and iodoarenes (Scheme 3) generate chalcones [87]. The reaction yield ranges from 24 to 65 %.

2.2 Claisen-Schmidt condensation

For the synthesis of chalcones, the Claisen-Schmidt condensation (Scheme 1) is the most widely used method [81, 82]. Chalcones are made by condensing benzaldehyde and acetophenone derivatives in a liquid solvent between 50 and 100 °C for many hours in the presence of alkaline or acid catalysts [82]. Because of its higher yield, NaOH is the most commonly employed base catalyst. KOH (yield 88 - 94 %), Ba(OH)_2 (yield 88 - 98 %), and NaOH (yield 90 - 96 %) have all been utilized as catalysts in the Claisen-Schmidt reaction [83]. NaOH in EtOH [84], K_2CO_3 in DMF, fly ash in H_2SO_4 and SiO_2 in H_2SO_4 [85] are some of the other catalysts for this condensation [86].
2.3 Synthesis of chalcone from trimethoxyphenol

The trimethoxyphenol acylation reaction (Scheme 4) was carried out in acetic acid in the presence of boron trifluoride diethyl ether complex (BF$_3$-Et$_2$O) [88].

(a) acetic acid, BF$_3$-Et$_2$O, 15 min.; benzaldehyde, EtOH, KOH, 66% yield.
(b) cinnamoyl chloride, BF$_3$-Et$_2$O, 90% yield.

Scheme 4. Chalcone synthesis from trimethoxyphenol

2.4 Synthesis of chalcone from 2,3-epoxy-1,3-diarylpropan-1-ones

Vilsmeier reagent, which is generated from bis (trichloromethyl) carbonate (BTC, triphosgene) and DMF in reasonable yields, was used to synthesize (Z)-2-chloro-1,3-diaryl-2-propen-1-ones by treating 2,3-epoxy-1,3-diarylpropan-1-ones with Vilsmeier reagent (Scheme 5). Sequential ring opening, halogenation, and elimination processes are hypothesized as part of the reaction mechanism [88].

Scheme 5. Chalcone synthesis from 2,3-epoxy-1,3-diarylpropan-1-one

2.5 Syntheses of chalcones by oxidation of benzylic alcohols

In the presence of an oxidant such as hydrogen peroxide chalcone was also synthesized by converting benzylic alcohols into the equivalent ketone (Scheme 6) [89].

Scheme 6. Oxidation of benzylic alcohol

3. Functional group transformation of chalcones

Because of its reactivity and ability to be changed into various functional groups, the enone moiety of chalcone plays a crucial role in
functional group or structural alteration [90]. The carbon-carbon double bond can be reduced into a carbon-carbon single bond under hydrogen gas atmosphere using various catalysts such as Raney nickel, Adam catalyst (PtO₂), Pd/C [90], or rhodium or ruthenium complexes, such as Wilkinson catalyst [(Ph₃P)₃RhCl] and [(Ph₃P)₃RuClH] [90].

Alptuzun and Gozler hydrogenated the chalcone 3-(3,4-dimethoxyphenyl)-1-(3-tolyl)-2-propenone (Figure 5) with Zn/acetic acid in an attempt to create a saturated ketone. They got an intriguing outcome. They did receive the intended product, but only as a by-product (Figure 6). As a result of cyclodimerization, the primary product formed was a cyclopentanol derivative (Figure 7).

4. Chalcones as Michael acceptors

The biological activity of chalcones is influenced or affected by the chemical nature of their structure [91]. Michael acceptors have an electrophile involved in many biological processes and regulates essential signaling pathway. The α,β-unsaturated carbonyl functional moiety in chalcones is considered a Michael acceptor [92]. It participates in covalent
bond formation with thiols or sulfhydryl of cysteine to obtain the Michael adduct or other similar nucleophiles through Michael addition.

Chalcones, for example, can affect Keap1–Nrf2–ARE by forming covalent bonds with cysteine (Scheme 7). The Michael reaction is one of the most effective techniques for forming carbon-carbon bonds and is frequently used in synthetic chemistry. The enone electrophilicity for the reaction is affected by the electron density on the two aromatic rings [93]. Chemical techniques and X-ray crystallography are used to determine the absolute configuration of Michael addition compounds [94].

![Scheme 7. Michael addition through the covalent bond formation with cysteine](image)

5. Conformational properties of chalcones

Chalcones are flexible molecules that can exist in various conformations, and their characteristics are determined by the presence of α,β-unsaturated ketone moiety and an appropriate ring substitution [95]. The conformational equilibrium is one of the most remarkable stereochemical properties of chalcones. Chalcones are flexible molecules that can exist as Z (cis) or E (trans) isomers. The E isomer is the most stable and has the lowest heat of formation [96], whereas the Z configuration is unstable due to the strong steric effect between the carbonyl group and the B-ring [96].

6. Chemical reactions of chalcones

6.1 Epoxidation of chalcones

In 1-butyl-3-methyl imidazolium tetrafluoroborate, the epoxidation of ethylenic groups of natural compounds such as chromone, chalcone, and isoflavone with hydrogen peroxide happens rigorously and with high yield (Scheme 8) [97].

![Scheme 8. Epoxidation of chalcones](image)

6.2 Addition reaction of chalcones with sodiumcyanide (NaCN)

The conjugate addition reaction of sodium cyanide (NaCN) with the chalcones produces substantial yields of α-cyanoketones (Scheme 9) [98].

![Scheme 9. Addition reaction of chalcone with sodiumcyanide (NaCN)](image)
6.3 Reduction reactions of chalcones

In the presence of ruthenium catalysts PR$_3$=PPh$_3$ (triphenyl phosphine) and formic acid, sodium formate or Na$_2$CO$_3$/isopropanol as the hydrogen source, chalcone reduction processes via hydrogenation (Scheme 10) occur. Another catalyst Pd/C (10 %) has also been employed to hydrogenate chalcones [99].

![Scheme 10. Reduction reaction of chalcone via hydrogenation](image)

The reduction of chalcones with trifluoroacetic acid as a proton donor and triethylsilane as a hydride donor yields dihydrochalcones (Scheme 11) [99].

![Scheme 11. Reduction reaction of dihydrochalcone](image)

6.4 Bromination of chalcones

Bromination of chalcones (Scheme 12) can be accomplished using a pure starting material and specific reagents. In the presence of Tetrabutylamonium tribromür (TBATB) and without solvent, the bromination reaction of chalcones proceeds in 87 % yield in 50 seconds [100].

![Scheme 12. Bromination of chalcone](image)

7. Pharmacological applications of chalcones

Chalcone is an aromatic ketone that is the foundation for several major pharmacological applications in drug development [101, 102]. Chalcones have been demonstrated to be pharmacologically active, and several substituted derivatives, such as heterocyclic analogs, have been discovered to have strong biological properties that hinder microorganism development [103-109]. Some chalcone derivatives have been proved to be poisonous to mammals [110] and insects [111], as well as inhibiting enzymes [112] and herbaceous plants [113]. Other biological properties include; anti-inflammatory [114], antioxidant [115, 116],
antimalarial [117], antituberculosis, antihelmints [118], antibacterial, antifungal [119], and anti-ulcer, antitumor, antineoplastic, antispasmodic activities [120]. These are only a handful of the many biological functions related to chalcones. Quinoline-based chalcones have been found to have antimalarial properties [120-122].

7.1 Antimicrobial activity

The presence of a reactive α,β-unsaturated keto function in chalcones was discovered to undergo conjugate addition with a nucleophilic group, such as a thiol group, contributing to their antimicrobial activity, which can vary depending on the type and position of the substituents on the aromatic rings (Figure 8) [123, 124] produced 3-[1-oxo-3-(2, 4, 5-trimethoxyphenyl)-2-propenyl]-2H-1-benzopyran-2-ones (Figure 9) that exhibited significant antibacterial action against *Bacillus subtilis*, *Bacillus pumilis*, and *Escherichia coli* when tested at a concentration of 100 µg/mL. The role of electron-releasing groups like hydroxyl and methoxyl groups in increasing activity was discovered in the study. Chalcones containing halogen substituents such as bromine and chlorine improved antifungal efficacy [125].

![Figure 8](image)

![Figure 9](image)

Kumar *et al.* described the bioisosteric replacement of the crucial 4'-hydroxy group in hydroxychalcones with bioisosters of varying degrees of acidity, resulting in effective and soluble molecules [126]. A powerful molecule with great water solubility was created by replacing the hydroxyl group with a carboxy group. Soluble and potent carboxychalcones with dibromo or trifluoromethyl substitutions on the B-ring (Figure 10) were discovered. When tested against *Candida albicans*, the minimum inhibitory concentrations for these compounds were 2 M and 40 M respectively. The lipophilic feature of the B-ring was enhanced by a dibromo or trifluoromethyl substitution. At the same time, the carboxy group on the A-ring contributed to the needed aqueous solubility.

![Figure 10](image)

Karthikeyan *et al.* used the Claisen Schimdt condensation method to make 3-aryl-1-(2,4-dichloro-5-fluorophenyl)-2-propen-1-one (Figure 11), which showed remarkable
antifungal activity against *Aspergillus niger* [127].

![Figure 11](image)

Jae-Chul *et al.* isolated a retrochalcone, licochalcone-C (*Figure 12*) from *Glycyrrhiza* demonstrating concrete antifungal action [128].

![Figure 12](image)

### 7.2 Anti-cancer activities

The double bond of the enone system is essential for the anticancer activity of chalcone prototypes [129]. Some pyrazoline derivatives (*Figure 13*) were also reported to inhibit different enzymes involved in cell division [130].

![Figure 13](image)

A panel of human tumor cell lines was used to assess a series of novel chalcone-linked imidazolones (*Figure 14*) for their anti-cancer activities [131].

![Figure 14](image)

### 7.3 Anti-leishmanial activity

A novel class of sulfonamide 4-methoxychalcone compounds (*Figure 15*) was synthesized and tested for antileishmanial activity against *Leishmania braziliensis promastigotes* and intracellular *amastigotes* as well as cell toxicity [132].
Ruiz et al. developed a series of 2,6-dihydroxy-4-methoxychalcones (Figure 16) and found that they were effective against leishmaniasis [133].

7.4 Antioxidant activity

The antioxidant and lipoxygenase inhibitory action of a series of 2-hydroxychalcones and their oxidative cyclization products (Figure 17), aurones, was investigated [134].

7.5 Antimalarial activity

Eric et al. produced chalcones derivatives and tested them in vitro for Plasmodium falciparum antimalarial activity [135]. The antimalarial activity of phenylurenyl chalcones and (2E)-1-[acridin-9-ylamino)phenyl]but-2-en-1-one (Figure 18) [136].

7.6 Anti-inflammatory activity

The Claisen-Schmidt condensation of hydroxy substituted acetophenones and chloro substituted benzaldehydes in potassium hydroxide/methanol at room temperature yields 2-hydroxy-3,4-dichlorochalcone (Figure 19) which is then tested for anti-inflammatory properties [137].
7.7 Anti-HIV activity

2,4,6-trihydroxybenzaldehyde chalcones produced from commercially available 2,4,6-trihydroxytoluene (Figure 20) or 2,4,6-trihydroxybenzaldehyde (Figure 21) demonstrated significant anti-HIV activity [138].

8. Conclusions

Chalcones are pharmacologically active compounds that are also characterized as 1,3-diphenylprop-2-en-1-one derivatives. Various approaches for the synthesis and characterization of chalcones have been discussed in this review. Chalcones’ anticancer, anti-diabetic, anti-HIV, antioxidants, antimalarial, anti-tubercular, antiviral, anti-inflammatory, and antidiuretic properties have been reviewed. The synthesis of diverse classes of chalcones with therapeutic uses is presented in this paper, along with suggestions for additional modifications to further utilize their extensive biological applications. In this era of developing drug resistance, molecule’s relatively simple synthetic procedures urge for deeper exploration of their pharmacological prospects.

Acknowledgement

The authors would like to acknowledge the management and staff of the Chemistry Department, Al-Qalam University, Katsina Nigeria for their constant motivation and support.

Conflict of Interest

The authors declare that this paper content has no conflict of interest.

Orcid:

AbdulRazaq Tukur: https://www.orcid.org/0000-0002-1140-8453
James Dama Habila: https://www.orcid.org/0000-0003-3518-5271
Rachael Gbekele-Oluwa Ayo: https://www.orcid.org/0000-0002-1890-1080
Ogunkemi Risikat Agbeke Iyun: https://www.orcid.org/0000-0002-0272-3128
References


[4]. R. Wen, H.N. Lv, Y. Jiang, P.F. Tu, *Phytochemistry*, 2018, 149, 56-63. [Crossref], [Google Scholar], [Publisher]


[9]. N. Aljamali, SH. H. Daylee, A. J. Kadhim, Afaq, *Int. J. Eng. Technol.*, 2020, 2, 33-44. [Crossref], [Google Scholar], [Publisher]


[15]. L. Ni, C.Q. Meng, J.A. Sikorski, *Expert. Opin. Ther. Pat.*, 2004, 14, 1669-1691. [Crossref], [Google Scholar], [Publisher]


[23]. B. Orlikova, D. Tasdemir, F. Golais, M. Dicato, M. Diederich, *Genes Nutr.*, 2011, 6, 125-147. [Crossref], [Google Scholar], [Publisher]


[33]. C. Moolman, R. van der Sluis, R.M. Betec, L.J. Legoabe, *Molecules*, **2020**, *25*, 5182. [Crossref], [Google Scholar], [Publisher]


[36]. M.J. Climent, A. Corma, S. Iborra, A. Velty, *J. Catal.*, **2004**, *221*, 474-482. [Crossref], [Google Scholar], [Publisher]


[50]. [Crossref], [Google Scholar], [Publisher]

[51]. A. Modzelewksa, C. Pettit, G. Achanta, N.E. Davidson, P. Huang, S.R. Khan, Bioorg. Med. Chem., 2006, 14, 3491-3495. [Crossref], [Google Scholar], [Publisher]


[58]. S. Pradip, M. Khushboo, C. Anand, G. Devanshi, S. Sudha, K. Sweta, K. Meena, J. Antivir. Antiretrovir, 2016, 8, 79-89. [Crossref], [Google Scholar], [Publisher]


[60]. F. Herencia, M.P. Lopez-Garcia, A. Ubeda, M.L. Ferrandiz, J. Biol. Chem., 2002, 6, 242-246. [Crossref], [Google Scholar], [Publisher]

[61]. P. Quintana-Espinoza, C. Yanez, C.A. Escobar, D. Sicker, R. Araya-Maturana, J.A. Sqella, Electroanalysis, 2006, 18, 521-525. [Crossref], [Google Scholar], [Publisher]


[65]. I. Rimsha, M. Shikufa, A. Meshari, S. Rahman, S. Zaib, Molecules, 2020, 25, 5381. [Crossref], [Google Scholar], [Publisher]


[67]. W.A. Al-Masoudi, N.A. Al-Masoudi, B.A. Saeed, R. Winter, C. Pannecoque, Russ. J. Bioorg. Chem., 2020, 46, 822-836. [Crossref], [Google Scholar], [Publisher]


[70]. S.A. Khan, B. Ahmad, T. Alam, J. Pharm. Sci., 2006, 19, 290-295. [Crossref], [Google Scholar], [Publisher]

[71]. S.A. Hasan, A.N. Elias, M.S. Farhan, Der Pharma Chem., 2015, 7, 39-42. [Google Scholar], [Publisher]


Sci., 2010, 8, 649-654. [Google Scholar], [Publisher]
[79]. B. Zhou, C. Xing, Med. Chem., 2015, 5, 388–404. [Crossref], [Google Scholar], [Publisher]
[81]. A. Kumar, S. Sharma, V.D. Tripathi, S. Srivastava, Tetrahedron, 2010, 66, 9445–9449. [Crossref], [Google Scholar], [Publisher]
[82]. S.N. Bukhari, M. Jasamai, I. Jantant, Mini Rev. Med. Chem., 2012, 1, 1394–1403. [Crossref], [Google Scholar], [Publisher]
[83]. E. Bagyaraj, K. Moorthi, M. Aboobuckersithique, ChemiXpress, 2017, 10, 1-10. [Google Scholar], [Publisher]
[85]. S.F. Nielsen, T. Boesen, M. Larsen, K. Schonning, H. Kromann, Bioorg. Med. Chem., 2004, 12, 3047-3054. [Crossref], [Google Scholar], [Publisher]
[87]. Z. Wan, D. Hu, P. Li, D. Xie, X. Gan, Molecules, 2015, 20, 11861–11874. [Crossref], [Google Scholar], [Publisher]
[89]. Y.Y. Weng, J.J. Li, W.K. Su, Chin. Chem. Lett., 2011, 22, 1395-1398. [Crossref], [Google Scholar], [Publisher]
[90]. S. Farooq, Z. Ngaini, Curr. Organocatalysis, 2019, 6, 184-192. [Crossref], [Google Scholar], [Publisher]
[93]. S. Tanaka, Y. Kon, T. Nakashima, K. Sato, RSC Adv., 2014, 4, 37674-37678. [Crossref], [Google Scholar], [Publisher]
[95]. B. Sadeghi, M.G. Nejad, J. Chem., 2013, 5, 5-15. [Crossref], [Google Scholar], [Publisher]
[97]. Z. Nowakowska, Spectrosc. Lett., 2005, 3, 477-485. [Crossref], [Google_Scholar], [Publisher]
[100]. P.S. Pallan, C. Wang, L. Lei, F.K. Yoshimoto, R.J. Auchus, M.R. Waterman, F.P. Guengerich, M. Egli, J. Biol. Chem., 2015, 29, 13128–131143. [Crossref], [Google_Scholar], [Publisher]
[101]. A. Mori, T. Mizusaki, Y. Miyakawa, E. Ohashi, T. Haga, T. Maegawa, H. Sajiki, Tetrahedron, 2006, 62, 11925-11932. [Crossref], [Google_Scholar], [Publisher]


[107]. M.M. Alidmat, M. Khairudddeen, S.M. Salhimi, M. Al-Amin, *Biomed. Res. Ther.*, 2021, 8, 4294-4306. [Crossref], [Google Scholar], [Publisher]


[123]. I. Karaman, H. Gezegen, M.B. Gürdere, A. Dingil, M. Ceylan, *Chem. Biodivers.*, 2010, 7, 400-408. [Crossref], [Google Scholar], [Publisher]

Tetrahedron, 2019, 75, 3530-3542, [Crossref], [Google Scholar], [Publisher]


[128]. A. Kumar, V.D. Tripathi, P. Kumar, L.P. Gupta, R. Trivedi, H. Bid, N. Chattopadhyay, Bioorg. Med. Chem., 2011, 19, 5409-5419. [Crossref], [Google Scholar], [Publisher]


[130]. J.C. Jung, Y. Lee, D. Min, M. Jung, S. Oh, Molecules, 2018, 22, 1872. [Crossref], [Google Scholar], [Publisher]

[131]. I. Halperin, B. Ma, H. Wolfson, R. Nussinov, Proteins, 2002, 47, 409-443. [Crossref], [Google Scholar], [Publisher]


[133]. G.M. Nitulescu, D. Draghici, O.T. Olaru, Int. J. Mol. Sci., 2013, 14, 21805-21818. [Crossref], [Google Scholar], [Publisher]

[134]. H.S. ElMonaem, N.I. Abdel-Aziz, M.A. Morsi, F.A. Badria, F. ElSenduny, M.B. El-Ashmawy, M.A. Moustafa, J. Appl. Pharm. Sci., 2018, 8, 75-87. [Crossref], [Google Scholar], [Publisher]


[139]. Z. Frazier, Undergraduate Theses. 2020, 44. [Google Scholar], [Publisher]


AbdulRazaq Tukur: He is the corresponding author and a lecturer with Chemistry Department of Al-Qalam University Katsina, Katsina State, Nigeria. He holds B.Sc. degree in Chemistry, M.Sc. degree in Organic Chemistry and presently a Ph.D. candidate in Organic Chemistry (Organic Synthesis). He is a member of Chemical Society of Nigeria (CSN).
James Dama Habila: He is a co-author and Associate Professor in the Department of Chemistry, Ahmadu Bello University, Zaria, Kaduna State, Nigeria. He specialized in Organic Chemistry (Natural Product and Synthetic Organic Chemistry). He is a member of Chemical Society of Nigeria (CSN) and Institute of Chartered Chemistry of Nigeria (ICCON).

Rachael Gbekele-Oluwa Ayo: She is a co-author and a Professor in the Department of Chemistry, Ahmadu Bello University, Zaria, Kaduna State, Nigeria. She holds Ph.D. degree in Organic Chemistry. Her field of research is Organic synthesis and Natural product chemistry.

Ogunkemi Risikat Agbeke Iyun: She is a co-author and a lecturer in Department of Chemistry, Ahmadu Bello University, Zaria, Kaduna State, Nigeria. She holds Ph.D. degree in Industrial Chemistry.