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Review Article

Bis-Chalcones: A Review On Synthetic Methodologies And Anti Inflammatory

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ABSTRACT

Chalcones are bioactive particles of regular and engineered sources, whose physicochemical properties, reactivity, and organic exercises are notable among established researchers. In any case, there are quite a large number particles stringently connected with chalcones with essentially less acknowledgment like bis-chalcones. A few examinations shown that bis- chalcones enjoy upper hands over chalcones in unambiguous bioactivities like calming action. This survey article depicts the compound construction and synthetic properties of bis-chalcones, as well as the strategies revealed in the writing for the amalgamation of these mixtures featuring the latest developments. At long last, the calming movement of bis-chalcones is depicted, accentuating the dynamic structures tracked The act of documenting information and the methods by which individuals and organizations operate.

INTRODUCTION

Chalcones, a well-known class of flavonoid precursors, are abundantly found in plants. They have been extensively studied for their bioactivities, which are associated with low toxicity [1]. However, bis-chalcones, a subclass of chalcones, have received relatively less attention, despite preliminary findings suggesting their potential for greater potency compared to chalcones. Several studies in the literature have reported the synthesis of bis-chalcones, their role as intermediates in the synthesis of complex compounds, and their biological activities. However, only a few studies have demonstrated the potential of bis-chalcones as anti-inflammatory agents. Chronic inflammation is a persistent and uncontrolled condition caused by an imbalance between the excessive production of proinflammatory mediators, such as cytokines and chemokines, and the low production of anti-inflammatory agents [1,2]. The proinflammatory mediators recruit and activate leukocytes, which are responsible for eliminating microorganisms. However, excessive levels of these mediators can lead to cell damage and reactivation of proinflammatory responses. In this context, drugs

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can be used to counteract and reduce the excessive production of these mediators. Although there are several anti-inflammatory drugs available, they are associated with severe side effects. Therefore, the use of bis-chalcones as a potential alternative to current treatments is an intriguing prospect. In this study, we aim to investigate the potential of bis-chalcones as anti-inflammatory agents and evaluate their efficacy and safety compared to existing drugs. By understanding the mechanisms of action and therapeutic potential of bis-chalcones, we can contribute to the development of novel and safer treatment options for chronic inflammation.There are a few calming drugs available, however they are related with extreme incidental effects. Hence, the bis-chalcones platform could be an intriguing change local to the ongoing arrangements. In this specific circumstance, the target of this article is to audit the writing concerning properties and amalgamation of bis-chalcones and their derivatives over the most recent 20 years, and afterward investigate the mitigating exercises depicted for this class of mixtures.

History and discoveries about chalcones

Chalcone is the name given to a simple chemical scaffold present in several compounds natural origin mainly found in plants [3]. The term chalcone derives from the Greek word Chalcos, meaning bronze [3]. This association is due to the yellow and orange colors (like bronze) of vegetable tissues containing these compounds [4]. This word was first mentioned by Stanisław Kostanecki and Josef Tambor, the first scientists responsible for the synthesis of these natural compounds with unique colors [5]. However, therapeutic applications of chalcones exist long before they were first mentioned [3]. Through the use of plants and herbs, these compounds were used for the treatment of different medical disorders, such as cancer, inflammation, and diabetes [3]. Nowadays, chalcones (1,3-diarylprop-2-en-1-ones) (Fig. 1) is a class of compound that has stimulated far reaching interest connected with the Inflammation and diabetes are two health conditions that have been linked to chalcones, a class of compounds known as 1,3-diarylprop-2-en-1-ones. These compounds have garnered significant interest due to their potential in developing new synthetic and biosynthetic pathways, as well as their diverse biological activities. Various natural and synthetic chalcones, as well as compounds inspired by the chalcone structure, have been associated with a range of biological activities such as anti-inflammatory, antioxidant, anticancer, and antidiabetic properties. This has made chalcone derivatives attractive targets for medicinal chemists, leading to a steady increase in research publications on chalcones over the past two decades. Some therapeutic agents derived from chalcones have been approved for clinical use, such as metochalcone 1 for choleretic effects and sofalcone 2 for anti-ulcer properties. Hesperidin methyl-chalcone 3 has been tested and approved for the treatment of chronic venous lymphatic insufficiency, while xanthohumol 4, another chalcone derivative, is currently undergoing clinical trials for its potential chemopreventive and antineoplastic activities.

Bis-chalcones chemical structures

Chalcones are a type of open-chain flavonoids that consist of a three-carbon α,β-unsaturated carbonyl system connected to two aryl rings (A and B, as shown in Fig. 1). The structural variability of chalcones has led various researchers to classify them into distinct groups. These include classical chalcones and hybrid chalcones, which feature the 1,3-diaryl-prop-2-en-1-one core linked to other significant chemical structures, often referred to as pharmacophores. Fused chalcones refer to a distinct category of hybrid chalcones which possess a chalcone moiety linked to another chemical structure, such as indole or oxathiole,

through ring fusion [12]. Bis-chalcones, on the other hand, encompass compounds that feature two chalcone moieties within a single structure. Dihydrochalcones are compounds characterized by a reduced α,β-unsaturated double bond [13]. Chalcone mimics or analogues are compounds that exhibit a structure resembling an α,β-unsaturated ketone system, thereby imitating chalcones [14].

Structural characteristic and chemical reactivity of bis-chalcones

The unique chemical structure of chalcone derivatives, such as their fluorescence and organic activities, is primarily responsible for their known properties (Fig. 1). Chalcones possess an elongated π-framework that connects rings A and B, resulting in a highly planar and rigid structure [15]. The extended conjugation between the carbonyl group and the double bond imparts the molecule with distinct reactive properties, which contribute to the biological activities exhibited by this class of compounds. The core formed structure, with its elongated conjugation, serves as the essential element for the activity of most derivatives, rendering further modifications and enhancements in the chalcone structure ineffective if the core framework is removed [16]. The double bond can exist in different configurations, either (Z) or (E).The (E)- isomer is the most stable and therefore is typically the predominant isomer. However, the (Z)- isomer can exhibit increased biological activity for certain targets, so the interconversion between isomers, often catalyzed by light exposure, is an important aspect to consider. The substituents also play a crucial role in the structure and biological activities of these compounds. Bulky ortho-substituents such as nitro or chloro disrupt the planarity of rings A or B to reduce steric effects caused by these groups, with ring A being more susceptible to distortion. The hydroxy substituent is common among most natural chalcones as well as synthetic ones. It is a weak acid and its pKa value depends on its position in the molecule. When hydroxy groups are introduced in ortho- positions, regions of stability for a hydrogen bond between this group and the carbonyl oxygen are delineated, resulting in a stable planar conformation.The reactivity and bioavailability of the hydroxy group will be affected by the reduced accessibility of this group [19]. Engineered chalcones have the ability to incorporate various substituents in the aromatic rings, such as bromo or fluoro, alkyl, amino, acetamido, and carboxy groups. These substituents can have an impact on the bioactivity of the molecule [15]. The structure and behavior of bis-chalcone derivatives also depend on the position of each chalcone moiety. Bis-chalcones typically have an aromatic ring as the central moiety, which is usually substituted at C1, C3, or C1, C4 [23,24]. Additionally, there are some examples of more complex bis-chalcones where the central moiety is composed of multiple aromatic rings linked together. There are numerous combinations in writing that resemble bis-chalcones due to the presence of an α,β-unsaturated ketone framework, but they cannot be classified as bis-chalcones. Instead, they should be referred to as bis-chalcone mirrors, bis-chalcone analogs, or bis-chalcone "type". These compounds include [25,26]. Compounds containing a fragrant heterocycle [27,28] or even a cycloalkane [29] as the central component (compound 7, Fig. 4) are known for their pleasant aroma. Similarly, compounds with aromatic heterocycles as the B-rings (compound 8, Fig. 4) possess a sweet-smelling characteristic. On the other hand, compounds derived from curcumin, where the central component is a CH2 group (compound 9, Fig. 4), are often referred to as diketones rather than bis-chalcone analogues. This classification is based on the prevalent presence of the thenolic structure in curcuminoids [30]. The primary rationale behind categorizing these designs as bis-chalcone "type" compounds rather than bis-chalcones is that a bis-chalcone

should serve as a precursor to a bis-flavonoid. However, most of these compounds cannot be converted into a flavonoid. Instead, they should be compared to bis-chalcones due to their shared characteristics, such as the presence of two formed α,β-unsaturated ketone systems.

2. Synthesis of bis-chalcones

Synthesis methodologies

Engineered methodologies for producing bis-chalcones rely on the established procedures for chalcone synthesis. Due to the complexity of bis-chalcones, the current synthetic techniques are typically the most robust and straightforward methods previously employed for chalcones. However, significant efforts have been made recently to enhance the reaction conditions. The synthesis of bis-chalcones, given their intricacy, generally involves lengthier processes, necessitates more challenging purifications, and is less efficient compared to the synthesis of mono derivatives.In this regard, novel reaction conditions have been investigated in order to enhance reaction times, purification steps, yields, and the overall sustainability of the process. Among the reactions found to be more beneficial for chalcone synthesis such as Claisen-Schmidt condensation, Wittig reaction, Suzuki reaction, and Mizoroki-Heck coupling reactions, the Claisen-Schmidt condensation, an aldol-type condensation, is the most commonly employed. The Claisen-Schmidt reaction was named after R. L. Claisen and J. G.Schmidt and the two scientists who previously elucidated the process by which a pleasant-smelling aldehyde and a methyl ketone react in the presence of a catalyst [3], have also identified two alternative methods for synthesizing bis-chalcones. The first method involves starting with a diketone that reacts with two equivalents of a fragrant aldehyde, while the second method involves starting with a dialdehyde that reacts with two equivalents of a fragrant ketone.

Solvent-free synthesis

Bis-chalcones synthesis may be significantly influenced by the reaction medium. An environmentally friendly and innovative method for organic synthesis involves conducting the reaction with minimal or no solvents. This can be achieved by using liquid reagents (in excess) or in a solid state by using mortars to thoroughly mix the different powders. While the former method is more conventional, it is less environmentally friendly. The latter approach offers more advantages in terms of being more environmentally friendly, along with increased selectivity and reaction time, but it is more challenging to implement.Furthermore, an example of solvent-free reactions conducted in acidic environments is also presented. Siddiqui et al. [33] developed an innovative, efficient, and cost-effective approach for the synthesis of new heterocyclic bis-chalcone analogues 26 and bis-pyrazolines under solvent-free conditions, using cellulose sulfuric acid (CSA) as a biodegradable and recyclable solid acid catalyst.The aldol condensation reaction between terephthalaldehyde 24 and various heterocyclic ketones 25, which contain different heteroatoms such as nitrogen, oxygen, and sulfur, as well as functional groups like methyl, hydroxy, and carbonyl groups, was investigated by the creators (Plan 9). The optimal conditions for this reaction did not require a solvent, and the reaction was conducted at a temperature of 70 ◦C, resulting in a high yield of 98% in just 3 minutes. Interestingly, the presence of a solvent had a negative effect on the progress of the reaction. The performance of the catalyst was compared to other acid catalysts, both heterogeneous and homogeneous, but no significant improvement was observed. However, it should be noted that no essential conditions were tested for comparison. Furthermore, the reusability of the catalyst was evaluated, and it was found to be successful for up to 8 consecutive runs without

any loss of activity or adverse impact on the reaction yield [33].

Ultrasound assisted synthesis

Ultrasound has been extensively studied in organic synthesis as a triggering method for various reactions, similar to microwaves. The combination of ultrasound irradiation results in superior mixing capabilities and intense microscale energy transfer due to the violent collapse of bubbles generated by the ultrasound waves [57].In addition, this method is compatible with most synergistic strategies, whether they are corrosive or fundamental, heterogeneous or homogeneous [57]. The successful application of this technique in the synthesis of bis-chalcones has been demonstrated. Ganesan et al. [58] effectively incorporated a new series of bis-chalcone analogs 43 by utilizing the 1,4-dihydropyridine derivative 42 and various aromatic aldehydes 11. The reaction was carried out in ethanol using NaOH 20% as the catalyst and an ultrasonic generator in a water bath at room temperature (Scheme 16). The use of ultrasound waves facilitated the reaction, reducing the reaction time and increasing yields up to 83-87%, without the need to raise the temperature. Similarly, Polo et al. [59] employed ultrasound to assist in the synthesis of novel bis-chalcones 45 (Scheme 17). The authors recognized the environmentally friendly potential of this method, along with its effectiveness and convenience. With the use of ultrasound, their reaction times were reduced to 20 minutes instead of 7 hours, and more derivatives were synthesized with significant yields [59].The quantities of KOH utilized in the reaction were not demonstrated, however, Liargkova et al. [60] incorporated new bis-chalcone ethers 47, potential pleiotropic agents, using basic catalysis combined with ultrasound to hasten the reaction time and enhance the yields (Scheme 18). Nevertheless, the reaction times for the synthesis of the bis-chalcone analogs were not specified, hence the impact of ultrasound in reducing the reaction time remains unclear [60]. Asiri et al. [22] also employed ultrasonic radiation for the eco-friendly synthesis of bis-chalcone analogs 49 containing dimethylthiophenyl and dimethylfuranyl as B-rings (Scheme 19). The most remarkable outcome was the brief reaction time (5 min), significantly shorter than the typical reaction times achievable with ultrasound (20 min up to 1 h).

Reactivity of bis-chalcones

Bis-chalcones possess a unique structure that makes them ideal for the synthesis of various active heterocyclic compounds. Their reactivity stems from the α,β-unsaturated ketone framework, which makes them susceptible to a wide range of reactions. Similar to chalcones, bis-chalcones can react with binucleophiles to form different heterocyclic compounds such as pyrazoles, isoxazoles, thiazoles, indoles, pyrazolines, pyrimidines, azepines, thiazepines, and more. Bis-chalcones are considered as potential Michael acceptors, playing a crucial role in organic synthesis.Some reactions, such as alkylation and halogen additions, are similar to other reactions. There are research articles dedicated to the transformation of chalcones into different heterocyclic compounds. This study will focus on the reactivity of bis-chalcones in converting them into other flavonoid-like compounds. Chalcones are well-known flavonoid precursors, so bis-chalcones also exhibit similar characteristics. Isomerization and cyclization reactions under different conditions will lead to the formation of various structures, including flavanones, flavones, flavanols, and even aurones

Bis-chalcones

Flavones represent one of the most widely acknowledged groups of flavonoid derivatives and are commonly found in many pharmacologically active compounds. They are distinctive due to their C2=C3 double bond coupled with a carbonyl group, as well as the presence of an aryl B-ring

attached at C2. Extensive research has been conducted on flavones, revealing numerous benefits associated with this class of compounds such as antioxidant and anti-inflammatory activities. Despite the intriguing nature of bis-flavones, which potentially offer enhanced biological activities due to the presence of two flavone moieties in the same molecule, these compounds have been relatively understudied. Bis-flavones can be obtained through the oxidative cyclization of bis-chalcones.The synthesis of bis-flavones with improved antibacterial and antifungal activities was carried out by Husain et al. [92] through the use of ortho-hydroxy groups and I2 in DMSO under catalytic conditions at temperatures ranging from 120 to 180 ◦C. The most potent bis-flavone (compound 52, R = 2,6-(Cl)2) from Plan 21 exhibited enhanced antimicrobial properties due to the presence of chloro substituents. Additionally, Durgapal et al. [91] successfully prepared another bis-flavone derivative 53 using the same method, where alkyl chains of varying lengths were introduced into each B-ring through O-alkylation. These compounds were then evaluated for their antioxidant activity using the DPPH assay.

Bis-flavones

Flavanol is a highly abundant class of flavonoids that has received significant attention in recent years. However, similar to bis-flavones, the study of bis-flavanols, particularly those derived from bis-chalcones, has been found to be extremely intriguing. Gaur et al. successfully synthesized a novel bis-flavanol, known as compound 56, from bis-chalcone 55. Both compounds were then utilized to form Ru(II) complexes [94]. The synthesis of this compound involved the oxidative cyclization of compound 55 using NaOH and 30% H2O2.

3. Biological activity of bis-chalcones

Bis-chalcones, along with their analogs and derivatives, have recently gained significant attention due to their extensive range of potential biological activities (Fig. 6). Several derivatives of bis-chalcones have been actively investigated for their anti-inflammatory [32,36,39,50,58-60], anticancer [25,61-63], antimicrobial [18,21,64,65], anticonvulsant [48], Antidiabetic [19,41,44,105], antioxidant [34,44,60,106], antitubercular [78], antimalarial [107-110], anti-HIV [100], anticonvulsant [48], antiamoebic [81] properties, as well as their potential as inhibitors for carbonic anhydrases [23,47] and acetylcholinesterases [59,60,86,99].

Anti-inflammatory activity

The subsequent sections outline the components of anti-inflammatory action of bis-chalcones identified in the literature. Each analysis refers to and evaluates the following parameters: the most potent bis-chalcones identified by the researchers (enumeration of the compounds mentioned is independent of the compound section), the method of evaluation of their anti-inflammatory action, and the results obtained. The results presented throughout this review are described based on the information available in the cited articles. Therefore, the different formats in which the results are presented are due to the variable existing data among studies and may include associated errors (standard deviation or standard error of the mean) or not.

Version 1:

The subsequent sections delineate the elements of anti-inflammatory activity of bis-chalcones identified in the literature. Each analysis refers to and assesses the following parameters: the most potent bis-chalcones identified by the researchers (enumeration of the compounds mentioned is independent of the compound section), the method of evaluating their anti-inflammatory activity, and the outcomes obtained. The results presented throughout this review are described based on the

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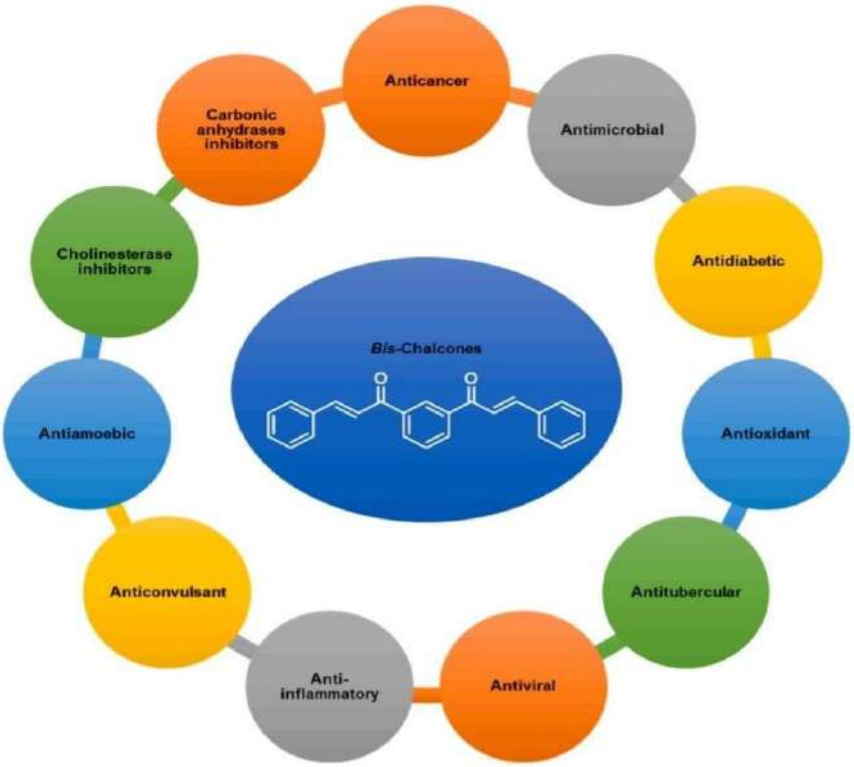


Fig no 1 . Staple bis-chalcones structure and associated biological activites, with highlight on the most prevalent ones in literature.

Modulation of transcripation factors activity

The kappa-light-chain-enhancer of activated B cells (NFκB) is an atomic variable that plays a crucial role in activating the expression of responsive genes associated with proinflammatory responses. As a result, it is a primary target for anti-inflammatory drugs [1]. NFκB is a complex protein network composed of multiple proteins that regulate each other, with its most abundant form being a heterodimer consisting of two monomers, p65 and p50 [72]. Effective modulation of this complex can lead to a reduction in the expression of various inflammatory mediators such as cytokines, tumor necrosis factor-alpha (TNF-α), interleukin (IL), and others.Interleukin-6 (IL-6) and Interleukin-8 (IL-8) are proteins involved in the regulation and control of immune responses. They have the ability to reduce the expression of enzymes that trigger the release of other inflammatory mediators such as cyclooxygenase (COX). Therefore, targeting this complex could be a promising approach to prevent the initiation and propagation of the inflammatory response. Several bis-chalcone analogs have been studied and documented in the literature, employing various methods. Two such analogs, EF24 and EF31 (referred to as 1 and 2, respectively), have been synthesized as more bioavailable alternatives to curcumin and have been extensively investigated for their potential applications [115-118]. Initially, EF24 was evaluated as an anti-inflammatory agent by Kasisnki et al. [119], and subsequently, both compounds were examined by Oliveira et al. [81] in 2012. The latter study focused on assessing the ability of these compounds to inhibit NF-κB in mouse Raw 264.7 macrophages following proinflammatory activation induced by

lipopolysaccharide (LPS). Various mechanisms were explored, including the NF-κB-DNA binding activity and NF-κB nuclear translocation.Cytokines such as TNF-α, IL-1β, and IL-6 are released, while the action of IκKβ is inhibited. Among the compounds tested, EF31 exhibited the highest potency in inhibiting NF-κB-DNA binding induced by LPS, with an IC50 range of 4.5-5.3 μM. It also showed significant inhibition of IκB kinase activity (IC50 ≈ 1.92 μM) and completely blocked NF-κB activity at a concentration of 5 μM. Furthermore, EF31 effectively suppressed the release of cytokines at all tested concentrations (5, 10, and 50 μM). Further experiments with lower concentrations would be necessary to determine if the observed effect is dependent on the inhibitor's concentration [81].

Modulation of eicosanoids production

Eicosanoids play a crucial role in inflammation and are a group of lipid-derived molecules. These mediators are produced from arachidonic acid (AA), a polyunsaturated fatty acid found in cell membranes. The synthesis of eicosanoids begins when cells are activated by mechanical injury or the presence of proinflammatory signaling molecules such as cytokines and chemokines. This activation leads to the release of AA from the lipid bilayers through the action of cytoplasmic phospholipase A2 (cPLA2). AA is then converted into various eicosanoids, which can be classified into different classes including prostaglandins (PGs), leukotrienes (LTs), thromboxanes (TXs), and lipoxins (LXs).

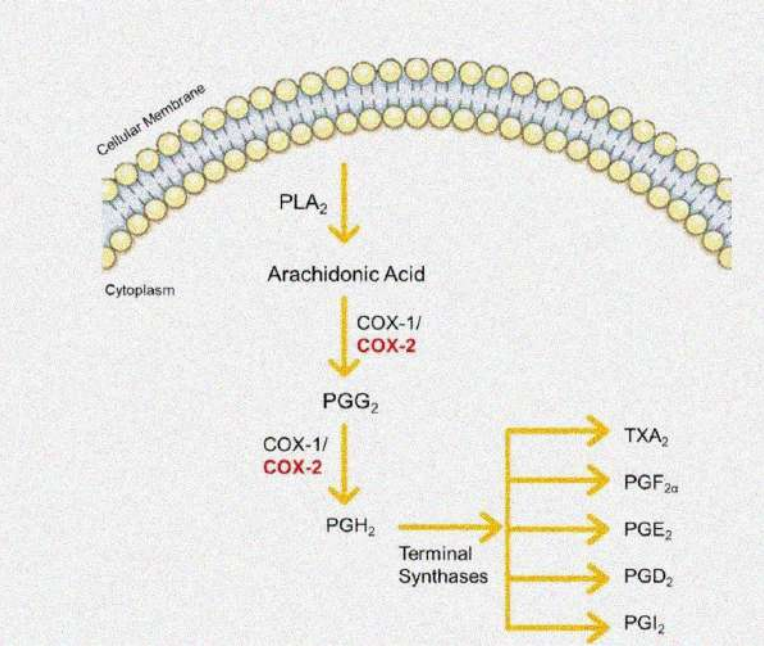


Fig.no 2 Archidonic acid metabolic pathaway through cyclooxygenase.

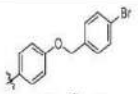
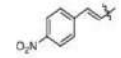
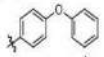
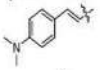
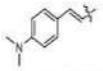
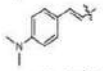
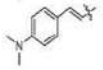
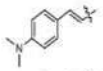
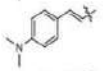
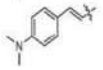
Modulation of pro-oxidant reactive species production

In the context of inflammatory responses, activated macrophages and neutrophils generate several reactive species capable of eliminating microbes. These species can be categorized into reactive oxygen species (ROS) and reactive nitrogen species (RNS). Nitric oxide (NO) is an RNS and a crucial signaling molecule involved in functional and metabolic processes in virtually every organ system. The production of NO is facilitated by nitric oxide synthases (NOS) through the catalysis of the reaction between L-arginine and oxygen.There are 3 isoforms, with iNOS being the inducible form, which is particularly interesting as it is typically overexpressed in

macrophages and neutrophils during inflammatory reactions. In addition to its harmful effects on microbes, nitric oxide (NO) has various physiological functions such as inducing vasodilation and vascular hyperpermeability, modulating cytokine-dependent proinflammatory responses, activating COXs, and S-nitrosylating proteins, among other functions. However, high levels of NO have been linked to various diseases such as septic shock and cardiogenic. Various diseases such as psoriasis, atopic dermatitis, contact dermatitis, Parkinson's disease, cancer progression, and metastasis are associated with oxidative stress and harmful interactions between nitric oxide (NO) and other reactive species with biomolecules, resulting in tissue damage and cell death. To reduce the levels of NO, several strategies can be implemented.

Inhibition of iNOS;

Hunting for •NO to swiftly eliminate it upon release; Suppression of the inflammatory pathway responsible for the excessive expression of iNOS and its consequent effects.

N°	n	R^1	% LOX Inhib. (100 µM)/IC_{50} (µM)	N°	n	R^1	% LOX Inhib. (100 µM)/IC_{50} (µM)
32	3		41	42	3		95/50
33	3		100/55	43	3	5-Me-furan-2-yl	52/96
34	3		93/56	44	3	Ph	76/65
35	3		100/55	45	2		77/62.5
36	3	Thien-2-yl	32	46	4		27
37	3		98/54	47	5		23
38	3		41	48	6		7
39	3		26.5	49	7		65/76
40	3		24.5	50	8		12
41	3	Furan-2-yl	57/85				

In vivo studies

Abdel-Aziz and colleagues (2019) focused their research on a series of bis-chalcone N-arylpyrazole derivatives (64-71, as shown in Table 5). These compounds were evaluated for their anti-inflammatory properties using the mice paw carrageenan-induced edema model. The results were obtained by measuring the edema volume before and after oral administration of the tested compounds (10 mg/kg body weight, single dose) following carrageenan injection. Positive controls such as meloxicam and indomethacin were included in the study. The derivative without any substituents showed the highest reduction in edema volume.

CONCLUSION

The primary objective of this survey was to assess the current state of knowledge regarding bis-chalcones. It led to the recognition that this particular class of compounds is still relatively unexplored compared to their mono-substituted counterparts, known as chalcones. Although numerous articles on bis-chalcones were found in the literature, most of them deviated from the focus of this study's investigation and article selection. Regarding chalcone synthesis, the majority of articles relied on the conventional

Claisen-Schmidt condensation method, with limited emphasis on the development of reaction conditions. In terms of applications, many bis-chalcones find utility in various fields of knowledge, particularly in photochemistry and materials science. Nevertheless, numerous other bis-chalcones remain unexplored.The field of organic examinations has yielded a significant number of articles that focus on various bioactivities such as anticancer, antimicrobial, antidiabetic, and antioxidant properties. However, when it comes to the specific area of anti-inflammatory activity, the number of articles is surprisingly low. This lack of research hinders a thorough investigation of the structure-activity relationship (SAR) of the compounds exhibiting this particular activity. Consequently, this review has successfully identified several gaps in knowledge regarding bis-chalcones. Interestingly, alternative reactivities to Claisen-Schmidt condensation, such as the Wittig reaction, Suzuki coupling, and Mizoroki-Hell coupling, have not been utilized in the synthesis of bis-chalcones. Furthermore, there is a notable absence of studies concerning their anti-inflammatory activity, which is crucial for better understanding and confirming the optimal design to target each inflammatory pathway.

REFERENCE

1. D. Ribeiro, M. Freitas, J.L. Lima, E. Fernandes, Proinflammatory pathways: the modulation by flavonoids, Med. Res. Rev. 35 (2015) 877–936.
2. C.A. Winter, E.A. Risley, G.W. Nuss, Carrageenin-induced edema in hind paw of the rat as an assay for antiinflammatory drugs, PSEBM (Proc. Soc. Exp. Biol.Med.) 111 (1962) 544–547.
3. C. Zhuang, W. Zhang, C. Sheng, W. Zhang, C. Xing, Z. Miao, Chalcone: a privileged structure in medicinal chemistry, Chem. Rev. 117 (2017) 7762–7810
4. N.K. Sahu, S.S. Balbhadra, J. Choudhary, D.V. Kohli, Exploring pharmacological significance of chalcone sccaffold: a review, Curr. Med. Chem. 19 (2012) 209–225.
5. S.v. Kostanecki, J. Tambor, Ueber die sechs isomeren Monooxybenzalacetophenone (Monooxychalkone), Ber. Dtsch. Chem. Ges. 32 (1899) 1921–1926.
6. Sousa, M. Lucas, D. Ribeiro, C.M. Correia, V.L.M. Silva, A.M.S. Silva, E. Fernandes, M. Freitas, Chalcones as modulators of neutrophil oxidative burst under physiological and high glucose conditions, J. Nat. Prod. 83 (2020) 3131–3140.
7. D.K. Mahapatra, S.K. Bharti, V. Asati, Chalcone derivatives: anti-inflammatory potential and molecular targets perspectives, Curr. Top. Med. Chem. 17 (2017) 3146–3169.
8. B.P. Bandgar, S.S. Gawande, R.G. Bodade, J.V. Totre, C.N. Khobragade, Synthesis and biological evaluation of simple methoxylated chalcones as anticancer, anti- inflammatory and antioxidant agents, Bioorg. Med. Chem. 18 (2010) 1364–1370.
9. D.K. Mahapatra, S.K. Bharti, V. Asati, Anti-cancer chalcones: structural and molecular target perspectives, Eur. J. Med. Chem. 98 (2015) 69–114.
10. S. Rocha, D. Ribeiro, E. Fernandes, M. Freitas, A systematic review on anti- diabetic properties of chalcones, Curr. Med. Chem. 27 (2020) 2257–2321.
11. F. Gao, G. Huang, J. Xiao, Chalcone hybrids as potential anticancer agents: current development, mechanism of action, and structure-activity relationship, Med. Res. Rev. 40 (2020) 2049–2084.
12. X.-J. Zhang, L.-Y. Li, S.-S. Wang, S. Que, W.-Z. Yang, F.-Y. Zhang, N.-B. Gong, W. Cheng, H. Liang, M. Ye, Y.-X. Jia, Q.-Y. Zhang, A.-C. Oxyfadichalcones, Three

chalcone dimers fused through a cyclobutane ring from Tibetan medicine Oxytropis falcata Bunge, Tetrahedron 69 (2013) 11074–11079.

13. Y. Wang, M.J. Curtis-Long, B.W. Lee, H.J. Yuk, D.W. Kim, X.F. Tan, K.H. Park, Inhibition of tyrosinase activity by polyphenol compounds from Flemingia philippinensis roots, Bioorg. Med. Chem. 22 (2014) 1115–1120.
14. L. Raj, T. Ide, A.U. Gurkar, M. Foley, M. Schenone, X. Li, N.J. Tolliday, T. R. Golub, S.A. Carr, A.F. Shamji, A.M. Stern, A. Mandinova, S.L. Schreiber, S. W. Lee, Selective killing of cancer cells by a small molecule targeting the stress response to ROS, Nature 475 (2011) 231–234.
15. M.L. Go, X. Wu, X.L. Liu, Chalcones: an update on cytotoxic and chemoprotective properties, Curr. Med. Chem. 12 (2005) 483 499.
16. P. Singh, A. Anand, V. Kumar, Recent developments in biological activities of chalcones: a mini review, Eur. J. Med. Chem. 85 (2014) 758–777.
17. S. Iwata, T. Nishino, H. Inoue, N. Nagata, Y. Satomi, H. Nishino, S. Shibata, Antitumorigenic activities of chalcones (II). Photo-isomerization of chalcones and the correlation with their biological activities, Biol. Pharm. Bull. 20 (1997) 1266–1270.
18. S.N. Lopez, ´ M.a.V. Castelli, S.A. Zacchino, J.N. Domínguez, G. Lobo, J. Charris- Charris, J.C.G. Cort´es, J.C. Ribas, C. Devia, A.M. Rodríguez, R.D. Enriz, In vitro antifungal evaluation and structure–activity relationships of a new series of chalcone derivatives and synthetic analogues, with inhibitory properties against polymers of the fungal cell wall, Bioorg. Med. Chem. 9 (2001) 1999–2013.
19. G. Rastelli, L. Antolini, S. Benvenuti, L. Costantino, Structural bases for the inhibition of aldose reductase by phenolic compounds, Bioorg. Med. Chem. 8 (2000) 1151–1158.
20. U. Tutar, Ü.M. Koçyigit, ˘ H. Gezegen, Evaluation of antimicrobial, antibiofilm and carbonic anhydrase inhibition profiles of 1,3-bis-chalcone derivatives, J. Biochem. Mol. Toxicol. 33 (2019).
21. A.A. Ghoneim, R.M. Elbargisy, A. Manoer, Design and synthesis of heterocyclic compounds from 1,4-diacetylbenzene with expected antimicrobial activity Egypt. J. Chem. 63 (2020) 2901–2910.
22. M.V.B. Reddy, S.S. Chen, M.L. Lin, H.H. Chan, P.C. Kuo, T.S. Wu, Preparation of a series of novel bichalcones linked with a 1,4-dimethylenepiperazine moiety and examination of their cytotoxicity, Chem. Pharmaceut. Bull. 59 (2011) 1549–1554.
23. B. Insuasty, H. Martinez, J. Quiroga, R. Abonia, M. Nogueras, J. Cobo, Synthesis of new bis-3,5-diphenylpyrazolines derivatives linked with alkyl chains J. Heterocycl. Chem. 45 (2008) 1521–1524.
24. S.S. Patole, S.S. Rajput, Synthesis characterisation and biological evaluation of (3Z, 4Z)-3, 4-bis (substituted phenyl benzylidine)-1-(4-subtituted phenyl) pyrolidine-2, 5-dione, Int. J. Pharm. Pharmaceut. Sci. 8 (2016) 289–291.
25. Modzelewska, C. Pettit, G. Achanta, N.E. Davidson, P. Huang, S.R. Khan, Anticancer activities of novel chalcone and bis-chalcone derivatives, Bioorg. Med. Chem. 14 (2006) 3491–3495.
26. K.N. Patel, A.K. Prajapati, B.V. Kamath, A.V. Bedekar, Synthesis and study of mesomorphic properties of unsymmetrical cyclohexanone-derived bis-chalcones, Liq. Cryst. 43 (2016) 729–734.
27. T. Esatbeyoglu, P. Huebbe, I.M. Ernst, D. Chin, A.E. Wagner, G. Rimbach, Curcumin–

from molecule to biological function, Angew. Chem., Int. Ed. Engl. 51 (2012) 5308–5332.
28. S.L. Gaonkar, U.N. Vignesh, Synthesis and pharmacological properties of chalcones: a review, Res. Chem. Intermed. 43 (2017) 6043–6077.
29. S. Farooq, Z. Ngaini, Recent synthetic methodologies for chalcone synthesis (2013-2018), Current Organocatalysis 6 (2019) 184–192
30. Z.N. Siddiqui, T. Khan, An efficient synthesis of novel bis-chalcones and bis- pyrazolines in the presence of cellulose sulfuric acid as biodegradable catalyst under solvent-free conditions, J. Braz. Chem. Soc. 25 (2014) 1002–1011.
31. A.T. Bale, U. Salar, K.M. Khan, S. Chigurupati, T. Fasina, F. Ali, M. Ali, S. Sekhar Nanda, M. Taha, S. Perveen, Chalcones and bis-chalcones analogs as DPPH and ABTS radical scavengers, Lett. Drug Des. Discov. 18 (2021) 249–25.
32. H.A. Abdel-Aziz, K.A. Al-Rashood, K.E.H. ElTahir, H.S. Ibrahim, Microwave- assisted synthesis of novel 3,4-bis-chalcone-N-arylpyrazoles and their anti- inflammatory activity, J. Chin. Chem. Soc. 58 (2011) 863–868
33. M. Draye, G. Chatel, R. Duwald, Ultrasound for drug synthesis: a green approach, Pharmaceuticals 13 (2020) 23.
34. R. Ganesan, V.R. Avupati, M.M. Shabi, Ultrasonic synthesis and in vitro evaluation of some bischalcones as potential cytotoxic agents, Indo Am. J. Pharma. Sci. 4 (2017) 670–687.
35. E. Polo, N. Ibarra-Arellano, L. Prent-Penaloza, ˜ A. Morales-Bayuelo, J. Henao, Galdamez, ´ M. Guti´errez, Ultrasound-assisted synthesis of novel chalcone, heterochalcone and bis-chalcone derivatives and the evaluation of their antioxidant properties and as acetylcholinesterase inhibitors, Bioorg. Chem. 90 (2019), 103034.
36. T. Liargkova, D.J. Hadjipavlou-Litina, C. Koukoulitsa, E. Voulgari, C. Avgoustakis, Simple chalcones and bis-chalcones ethers as possible pleiotropic agents, J. Enzym. Inhib. Med. Chem. 31 (2016) 302–313.
37. A.M. Asiri, S.A. Khan, Synthesis and anti-bacterial activities of a bis-chalcone derived from thiophene and its bis-cyclized products, Molecules 16 (2011) 523–531.
38. O.I. El-Sabbagh, S. Mostafa, H.A. Abdel-Aziz, H.S. Ibrahim, M.M. Elaasser, Synthesis and biological evaluation of some N-arylpyrazoles and pyrazolo[3,4-d] pyridazines as anti-inflammatory agents, Arch. Pharmazie 346 (2013) 688–698.
39. S.M. Gomha, M.M. Edrees, F.M.A. Altalbawy, Synthesis and characterization of some new bis-pyrazolyl-thiazoles incorporating the thiophene moiety as potent anti-tumor agents, Int. J. Mol. Sci. 17 (2016).
40. O.M. Sayed, H. Moustafa, A.E.M. Mekky, A.M. Farag, A.H.M. Elwahy, Synthesis, reactions and DFT calculations of novel bis(chalcones) linked to a thienothiophene core through an oxyphenyl bridge, RSC Adv. 6 (2016) 10949–10961.
41. M.B. Gürdere, E. Kamo, Y. Budak, A. S¸ ahin Yağlioğlu, M. Ceylan, Synthesis and anticancer and cytotoxic effects of novel 1,4-phenylene-bis-N-thiocarbamoylpyr-azole and 1,4-phenylene-bis-pyrazolylthiazole derivatives, Turk. J. Chem. 41 (2017) 179–189.
42. H. Parveen, F. Hayat, S. Mukhtar, A. Salahuddin, A. Khan, F. Islam, A. Azam, Synthesis, characterization and biological evaluation of novel 2,4,6-trisubstituted bis-pyrimidine derivatives, Eur. J. Med. Chem. 46 (2011) 4669–4675.

43. M. Raghu, A. Nagaraj, C.S. Reddy, Synthesis and biological evaluation of novel methylene-bis- 1,5 -benzodiazepines, J. Heterocycl. Chem. 45 (2008) 1115–1120.
44. C.S. Reddy, G.P. Reddy, A. Nagaraj, Synthesis and in vitro study of novel methylenebis(phenyl-1,5-benzothiazepine)s and methylenebis(benzofuryl-1,5-benzothiazepine)s as antimicrobial Agents, Chin. J. Chem. 27 (2009) 1345–1352.
45. R.N. Deshmukh, R.V. Dengle, Synthesis, characterization and in vitro anticancer evaluation of bis-1,5-benzothiazepines against human breast cancer cell line MCF-7, Int. J. Pharmaceut. Sci. Res. 7 (2016) 5024–5029.
46. B.D. Mather, K. Viswanathan, K.M. Miller, T.E. Long, Michael addition reactions in macromolecular design for emerging technologies, Prog. Polym. Sci. 31 (2006) 487–531.
47. Bicer, P. Taslimi, G. Yakali, I. Gulcin, M.S. Gultekin, G.T. Cin, Synthesis, characterization, crystal structure of novel

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