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Chalcone: A Privileged Structure in Medicinal Chemistry

Chunlin Zhuang[†], Wen Zhang[†], Chunquan Sheng[†], Wannian Zhang^{†,§}, Chengguo Xing^{*,‡}, and Zhenyuan Miao^{*,†}

[†]School of Pharmacy, Second Military Medical University, 325 Guohe Road, Shanghai 200433, China

[‡]Department of Medicinal Chemistry, College of Pharmacy, University of Florida, 1345 Center Drive, Gainesville, Florida 32610, United States

[§]School of Pharmacy, Ningxia Medical University, 1160 Shengli Street, Yinchuan 750004, China

Abstract

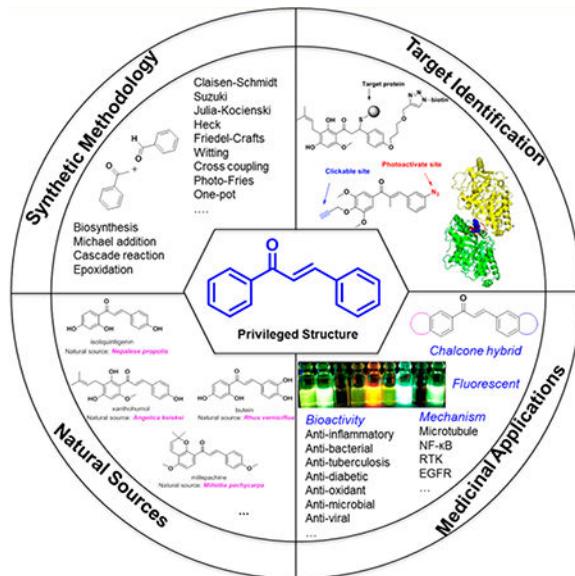
Privileged structures have been widely used as an effective template in medicinal chemistry for drug discovery. Chalcone is a common simple scaffold found in many naturally occurring compounds. Many chalcone derivatives have also been prepared due to their convenient synthesis. These natural products and synthetic compounds have shown numerous interesting biological activities with clinical potentials against various diseases. This review aims to highlight the recent evidence of chalcone as a privileged scaffold in medicinal chemistry. Multiple aspects of chalcone will be summarized herein, including the isolation of novel chalcone derivatives, the development of new synthetic methodologies, the evaluation of their biological properties, and the exploration of the mechanisms of action as well as target identification. This review is expected to be a comprehensive, authoritative, and critical review of the chalcone template to the chemistry community.

Graphic abstract

*Corresponding Authors: Tel.:352-294-8511. chengguoxing@cop.ufl.edu, (C.X.), Tel.: 86-21-81871241. Fax: 86-21-81871241. miaozhenyuan@hotmail.com. (Z.M.).

Notes

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1. INTRODUCTION

A chalcone is a simple chemical scaffold of many naturally occurring compounds and has a widespread distribution in vegetables, fruits, teas, and other plants.^{1–5} The word “chalcone” is derived from the Greek word “*chalcos*”, meaning “bronze”, which results from the colors of most natural chalcones.³ Chalcone compounds have a common chemical scaffold of 1,3-diaryl-2-propen-1-one, also known as chalconoid, that exists as *trans* and *cis* isomers, with the *trans* isomer being thermodynamically more stable (Figure 1).^{3,6} In this article, the phenyl ring attached to the carbonyl group is defined to be the A ring and the other benzene ring is named as the B ring (Figure 1).

The chalcone family has attracted much interest not only from the synthetic and biosynthetic perspectives but also due to its broad interesting biological activities. Therapeutic applications of chalcones trace back thousands of years through the use of plants and herbs for the treatment of different medical disorders, such as cancer, inflammation, and diabetes.^{1–5} Several chalcone-based compounds have been approved for clinical use. For example, metochalcone was once marketed as a choleric drug, while sofalcone was previously used as an antiulcer and mucoprotective drug (Figure 1).^{2,3}

Chalcones have been extensively studied, with many minireviews published^{1,3,4,7–22}. However, the accurate mechanisms of action for the wide-ranging biological activities of chalcones are still not well understood. This review aims to highlight the recent advances in using chalcone as a privileged scaffold in medicinal chemistry, focusing on research articles published in the past 10 years (with a few exceptions). Several aspects of chalcone use will be summarized, including biosynthesis, synthetic methodologies and applications, biological activities, and target exploration.

2. CHALCONES FROM NATURAL SOURCES

Chalcones are the core of many biologically interesting compounds from natural sources and have attracted substantial research attention for decades. How many natural chalcones have been isolated and structurally elucidated? The answer to this question depends on how broadly the net is cast. As in many articles, the term “chalcone” refers generically to chemicals with an α,β -unsaturated ketone system. Thus, the chalcone family has extensive structural diversity and can be roughly classified into two categories: simple/classical chalcones and hybrid chalcones with the core scaffold of 1,3-diaryl2-propen-1-one. Bichalcones, such as rhuschalcone from *Rhus pyroides*, contain two chalcone moieties in a single structure.²³ Dihydrochalcones, such as the fleminchalcones from *Flemingia philippinensis*, are a class of compounds with a reduced α,β -unsaturated double bond.²⁴ Chalcone mimics (e.g., piperlongumines²⁵) and fused chalcones (e.g., oxyfadichalcones²⁶) are not structurally traditional chalcones, although they have a similar α,β -unsaturated ketone system or fused forms derived from chalcones by special biosynthesis pathways. When searching for the classical chalcone shown in Figure 1 in the well-known chemical databases, more than 92 000 chalcones can be found in SciFinder and over 1000 of them have biological data reported in PubChem (accessed August 2016). Therefore, the number of natural chalcones may ultimately not be countable with certainty. Representative classical chalcones, bichalcones, dihydrochalcones, chalcone mimics, and fused chalcones isolated from natural sources in recent years and their potential biological activities are summarized in Table 1. Some of their biological activities and applications will be discussed in the following sections.

3. FLUORESCENT PROPERTIES OF CHALCONES

Because of its conjugated system, chalcones with proper electron-pulling and electron-pushing functional groups on the benzene ring(s) can be fluorescent (Figure 2),^{67–73} making them potential chemical probes for mechanistic investigations and imaging/diagnosis.

As a fluorescent compound, the photophysical parameters, which include the absorption ($\text{Abs } \lambda_m$) and emission ($\text{Emi } \lambda_m$) wavelengths, extinction coefficient (ϵ), and quantum yield (ϕ), are critical for biological applications. The dynamic range of detection is determined by the $\text{Abs } \lambda_m$ and $\text{Emi } \lambda_m$ values. The fluorescence brightness, which is the product of ϵ and ϕ at the maximum absorption wavelength, is associated with the detection sensitivity. Some nonstructural factors are also critical to the fluorescent intensity, such as the solvents and the biological components/additives.^{69,73}

The dimethylamino group is a widely used substituent in fluorescent probes and has also been introduced into fluorescent chalcone compounds (Figure 3). 4-Dimethylaminochalcone (1) was first reported by Jiang et al. as a fluorescent probe for detecting micelle formation.^{74,75} Very recently, the authors have synthesized a small library of fluorescent chalcones to systematically characterize the structural effects on their intrinsic fluorescence and evaluate the influence of several biologically relevant environmental factors.⁷⁶ The 4-dimethylaminochalcone compounds exhibited similar absorptions, with an $\text{Abs } \lambda_m$ between 390 and 460 nm and an $\text{Emi } \lambda_m$ between 450 and 620 nm. The ϵ and ϕ values were between

28 000 and 38 000 and 0 and 0.40, respectively. Several compounds showed good fluorescence brightness, with values exceeding $6000\text{ M}^{-1}\text{ cm}^{-1}$, which is comparable to that of commercial fluorophores (e.g., Cy 3.18– $6000\text{ M}^{-1}\text{ cm}^{-1}$). A structure–fluorescence relationship (SFR) study demonstrated the following: (1) for the chalcone moiety, the molecular planarity played a critical role in the fluorescence, e.g., introducing a methyl group to the α -position of the unsaturated ketone resulted in the loss of fluorescence; (2) for the A ring, weak electron-donating groups (e.g., a methoxyl group) were favorable to the quantum yield, while electron-withdrawing (e.g., a nitro group) or strong electron-donating (e.g., a dimethylamino group) substituents significantly decreased it; (3) for the B ring, disubstituted amino groups were essential for fluorescence, such as piperidine, piperazine, dimethylamino, and diethylamino groups; and (4) for the α,β -unsaturated ketone system, the extension of the double bond decreased the fluorescence and caused a red shift of the maximum emission wavelength. The fluorescence–environment relationship (FER) showed that the fluorescent intensity of chalcone-based compounds depends highly on the solvent polarity, the pH, and the interactions with proteins or detergents. In aprotic solvents, chalcone's fluorescence decreases as the solvent polarity decreases, although the fluorescence is completely lost in protic solvents, such as water or EtOH, at neutral pH. However, it could be partially recovered by the addition of BSA, Triton-X100, or Tween-20. A similar result was obtained by another study, in which 4'-N,N-dimethylamino-4-methylacryloylamino chalcone (2) containing both electron-withdrawing and electron-donating groups was synthesized as a fluorescent sensor for determining the water content in organic solvents.⁶⁹ The fluorescent intensity of compound 2 decreased with an increase in the water concentration in acetone, ethanol, and acetonitrile solutions. Such a sensor was useful for water determination with a low detection limit (<0.01%).⁶⁹ The loss of fluorescence in a protic solvent is potentially due to the formation of hydrogen bonds between the solvent and the nitrogen of chalcone's dialkylamino group, keeping the nitrogen lone pair electrons out of the conjugate system and leading to the nonfluorescent property.⁷⁶

Nevertheless, fluorescent chalcones have been explored for their potential to detect different diseases. Compound 3 was designed based on a phosphorylated chalcone hybridized from 4-dimethylaminochalcone to visualize alkaline phosphatase through emission color changes in living cells.⁷⁷ Stark et al. reported a series of chalcone analogues (4) that could be used to image human histamine H3 receptors (hH3R) in stably transfected HEK-293 cells.⁷⁸ Fluorescent chalcones have also been applied to image stem cells.^{54,79} For example, Lee et al. designed a novel library of 160 fluorescent chalcone amide compounds.⁷⁰ Two amides were introduced into these chalcones on each side of the scaffold to enhance the fluorescence emission intensity. Interestingly, CDg4 (5) was applied as a novel green fluorescent probe for detecting mouse embryonic stem cells (mESCs), where its molecular binding target was identified as the glycogen of the stem cell colony surface. These investigations have provided new possibilities for using nonradioactive alternatives in novel binding assays and as visualization tools.

4. SYNTHESIS

4.1. Biosynthesis

Chalcone synthase (CHS), the first type III polyketide synthase (PKS) superfamily discovered in the 1970s,⁸⁰ is a ubiquitous enzyme in higher plants. CHS has also been detected in several lower plants, such as the liverwort *Marchantia polymorpha*.⁸¹ All other members in this family are labeled “CHS-like” enzymes. CHS is responsible for the biosynthesis of different chalcones. The CHS superfamily enzymes are associated with the biosynthesis of diverse secondary metabolites, including flavonoids, stilbenes, and aurones.⁸² Joseph P. Noel and coworkers developed an important framework for the biosynthetic mechanism by crystallizing CHS from the legume *Medicago sativa*, a process that provided clear structural information about chalcone biosynthesis.⁸³ CHS exists as a homodimer, and the size of each monomer is approximately 42–45 kDa.⁸¹ Cys164, Phe215, His303, and Asn336 are the key residues of the active site and have been conserved among all CHS members and CHS-like enzymes. CHS produces chalcones by transferring a coumaroyl moiety from one 4coumaroyl-coenzyme A (CoA) to Cys164 as the first step. Subsequently, three malonyl-CoA thioesters form an intermediate via a polyketide reaction (Scheme 1). After the generation of a thioester-linked tetraketide, a regiospecific Claisen-type cyclization occurs and forms a new ring system to generate naringenin chalcone (Scheme 1).^{81,84,85} Naringenin chalcone is converted into δ' -deoxynaringenin chalcone (isoliquiritin, Table 1, entry 1) in the presence of chalcone reductase (CHR) and CHS. Other plant secondary metabolites, such as stilbenes, phloroglucinols, resorcinols, and benzophenones, could be biosynthesized in a similar manner with the corresponding catalytic enzymes.^{80,81,85–89} Flavonoids and isoflavonoids are produced by CHS and chalcone isomerase (CHI), respectively, using naringenin chalcones as the substrates.⁸¹ Naringenin chalcones are also the building blocks for the biosynthesis of aurone compounds by a plant catechol oxidase, aurone synthase (AURS).⁹⁰ These conversions from chalcones to flavanones or aurones could also be realized by chemical reactions, such as the Algar–Flynn–Oyamada reaction.⁹¹

Chalcones serving as precursors have generated a range of plant metabolites, revealing interesting biological activities, which will be discussed in the following sections. Taking such experience from nature, simple chalcones have been synthetically hybridized with other templates, such as stilbenes (see section 6.3.2.5).

4.2. Chemical Synthesis

Chalcones are generally prepared by condensation reactions via base or acid catalysis. Although chalcones are one type of easily synthesizable α,β -unsaturated ketone, a growing number of new techniques and procedures have recently been reported because of their interesting biological activities and the development of various catalysts or reaction conditions. The synthetic strategies, general methodologies, catalysts, and conditions used in the synthesis of chalcone scaffolds are summarized below.

4.2.1. Claisen–Schmidt Condensation.

4.2.1.1. Overview: The Claisen–Schmidt reaction is named after two pioneering investigators, R. L. Claisen⁹² and J. G. Schmidt,⁹³ and describes a process in which a benzaldehyde and a methyl ketone are condensed in the presence of catalysts (Scheme 2).

This reaction is deemed one of the most classical reactions in organic chemistry.⁹⁴ The catalysts are either strong bases or acids. In the case of base catalysis, the chalcone is generated from the aldol product via dehydration in an enolate mechanism, while in the case of acid catalysis, it is generated via an enol mechanism.⁹⁵ The main drawback of this reaction is the slow reaction rate; the reaction typically needs several days for completion. The reaction could also result in a complex mixture containing the desirable product, byproducts, and sometimes starting materials. The yield therefore could vary dramatically, depending on the reactants and catalysts, ranging from <10% to near 100% conversion.^{95,96} Nevertheless, this reaction has been employed in most publications because of its experimental simplicity and highly efficient formation of the carbon–carbon double bond with little restriction to the complexity of the molecules. Széll and co-workers synthesized a series of nitrochalcones and showed that the presence of electron-donating groups in the aldehyde favored condensation by acids, while electron-withdrawing substituents favored condensation by base conditions.⁹⁷ Generally, the base condition is more common in chalcone synthesis.

4.2.1.2. Applications.

4.2.1.2.1. Base Condition (Table 2, Entries 1–6): The classical Claisen–Schmidt condensation is base-catalyzed with potassium *tert*-butoxide, sodium hydroxide, or potassium hydroxide in methanol or ethanol at room temperature. This reaction has been widely used for the synthesis of hydroxyl-substituted chalcones, typically with good to excellent yields (60–90%). A group of ferrocenylchalcones has been synthesized under the common base (sodium hydroxide) condition (Table 2, entry 1).⁹⁸ In some cases, an increase in temperature is required, and the base condition also requires modification. For example, the α -carbon of a ketone is difficult to dehydrate when the ketone is electrophilesubstituted (Table 2, entry 2). Such a reaction requires reflux at an elevated temperature or takes a longer time at room temperature.^{55,56,99} However, with a nucleophile substitution on the α -position, mild conditions are generally sufficient (Table 2, entry 3).¹⁰⁰

In some cases, the classical Claisen–Schmidt condensation process has been performed with slight modifications of the catalyst or the solvent system. For example, β -trifluoromethylated chalcones (Table 2, entry 4) can be prepared with alkaline earth metal hydroxides of calcium, barium, or strontium in aprotic solvents for facile water removal.¹⁰¹ Removing the water generated is favorable to the reaction. Thus, the Dean–Stark condition using toluene as the solvent to remove water could accelerate the reaction and has been confirmed to obtain chalcones over a shorter period and at higher yields (data unpublished). Lithium bis(trimethylsilyl)amide (LiHDMs) has also been previously used as a base to catalyze the condensation and obtained chalcones with less than 50% yields (Table 2, entry 5).¹⁰² The NaNO₃ or LiNO₃/natural phosphate/ methanol system is another extremely efficient basic

catalyst for the Claisen–Schmidt condensation process (Table 2, entry 6) from which chalcones are easily obtained in high yields at room temperature.^{6,103}

4.2.1.2.2. Acid Condition (Table 2, Entries 7–11).: Although base catalysts are generally used for the synthesis of chalcones, Brønsted acids,^{97,104} Lewis acids,^{105–108} and solid acids¹⁰⁹ have also been utilized as acid catalysts. The most common application using ethanol saturated with the Brønsted acid HCl is marginally successful, with only a 10–40% yield (Table 2, entry 7).⁹⁰ Dry HCl gas has been shown to be more favorable to the reaction because it acts as not only a catalyst but also a water absorbent.^{97,104}

Aluminum chloride (AlCl_3) has also been used as a Lewis acid for chalcone synthesis (Table 2, entry 8). Two moles of acetophenone per mole of AlCl_3 provide the chalcone product in a high yield (73%).¹⁰⁷ The mechanism of the reaction is not simply the result of the hydrogen chloride evolved by the heating of acetophenone and AlCl_3 ; an intermediate of the general type of $\text{R}-\text{O}-\text{Al}-\text{R}_2$ actually promotes the condensation.

The application of boron trifluoride–etherate ($\text{BF}_3-\text{Et}_2\text{O}$) in the condensation was first reported in a study describing the use of BF_3 gas in chalcone synthesis.¹¹⁰ In 2007, Narendar et al. reported the use of $\text{BF}_3-\text{Et}_2\text{O}$ to obtain 15 chalcones with 75–96% yields with reaction times of less than 3 h (Table 2, entry 9).¹⁰⁵

Petrov et al. reported that 16 chalcones, including 4hydroxyl-chalcone (Table 2, entry 10), were synthesized in a SOCl_2 /ethanol system in high yields (73–96%).⁴⁵⁴ SOCl_2 was used as a convenient alternative to the gaseous HCl in the condensation, where HCl was generated in situ by the reaction of SOCl_2 with absolute ethanol.

Chalcones have also been obtained with *p*-toluenesulfonic acid (*p*-TsOH) as the catalyst and acetic acid as the solvent at 70 °C with yields greater than 70% (Table 2, entry 11).¹⁰⁹ $\text{Zn}(\text{bpy})(\text{OAc})_2$, TiCl_4 , $\text{Cp}_2\text{ZrH}_2/\text{NiCl}_2$, and RuCl_3 have also been utilized as acid catalysts in the condensation.^{106,108,111,112}

4.2.1.2.3. Nonsolvent Condition (Table 2, Entries 12–14).: Solvent-free conditions have also been applied for chalcone synthesis, such as grinding¹¹³ or microwave irradiation.¹¹⁴ Rateb and co-workers reported a method using sodium hydroxide ground with an aldehyde and ketone to obtain a chalcone in an 80% yield (Table 2, entry 12).¹¹³ A nitrochalcone was synthesized under the grinding conditions with a novel base catalyst $\text{KF}-\text{Al}_2\text{O}_3$ with over a 94% yield in 5 min (Table 2, entry 13).¹¹⁵ Microwave irradiation has also been applied in nonsolvent systems to construct the chalcone core.¹¹⁶ A facile, solvent-free ecofriendly method using calcium oxide as a solid base catalyst for the synthesis of chalcones under microwave conditions has been reported.¹¹⁴ Fifteen chalcones with electron-donating as well as electron-withdrawing groups on both the ketone and aldehyde moieties have been produced in 57–88% yields using this method (Table 2, entry 14).¹¹⁴ A green catalyst system of solid sulfonic acid from bamboo was discovered by Xu et al. and catalyzed the condensation under a nonsolvent condition with isolated yields ranging from 60 to 82%.¹¹⁷ The nonsolvent microwave methodology has the following advantages: (1) it avoids the influence of the solvent and reduces the byproducts; (2) it enables greater flexibility for the

reaction temperature because it is unconstrained by the boiling point and volatility of the solvents; (3) it dramatically reduces the reaction time; (4) it significantly improves the reaction yield over those of common solvent systems.

4.2.1.2.4. Other Conditions (Table 2, Entries 15 and 16).: Green chemistry, which has attracted considerable interest in organic synthesis,^{73,101} has recently been applied for chalcone synthesis. Water is an ideal solvent for organic reactions, where the chalcone moiety is prepared in a water system in the presence of a phase-transfer catalyst (PTC). Duan et al. reported a modification of the Claisen–Schmidt condensation using water as the solvent with cetyltrimethylammonium bromide (CTMAB) as the PTC and potassium carbonate as the base catalyst. High yields of the desired chalcones were obtained under these mild conditions.¹¹⁸ In 2013, heterocyclic ring-containing chalcones were obtained using tetrabutylammonium bromide (TBAB) as the PTC with an inorganic alkaline solution as the base under microwave conditions (Table 2, entry 15).¹¹⁹ Ionic liquids have also been utilized. Wu et al. reported the use of 1,3-dibutyl-2-methylimidazolium tetrafluoroborate ($[dbmin]BF_4^-$) as the ionic liquid and hydrotalcite as a solid acidic catalyst to give chalcones with a yield of 98.5% (Table 2, entry 16).¹²⁰ This method has several advantages, such as the low use of catalyst, convenient product separation, and catalyst recycling without reduced activity.

4.3. Synthesis of Chalcones Using Other Well-Known Strategies

Because the Claisen–Schmidt condensation process sometimes leads to a complex mixture that is difficult to purify for the desired chalcone compound, other well-known reactions have been explored for the synthesis of chalcones, including crosscoupling (e.g., Suzuki reaction, Heck reaction, Julia–Kocienski reaction, and Wittig reaction), Friedel–Crafts acylation, photoFries rearrangement, and one-pot synthesis from alcohols.

4.3.1. Cross-Coupling.

4.3.1.1. Suzuki Coupling.: Suzuki coupling^{121,122} was first reported in 1979 by Akira Suzuki, who shared the 2010 Nobel Prize in Chemistry with Richard F. Heck and Ei-ichi Negishi for palladium-catalyzed crosscouplings. Suzuki coupling is a powerful palladium-catalyzed carbon–carbon bond forming reaction. It was first applied for chalcone synthesis in 2003.¹²³

Based on the retrosynthetic analysis, two approaches¹²³ are conceivable for the synthesis of chalcones: coupling cinnamoyl chloride with phenylboronic acid (Scheme 3A) and coupling benzoyl chloride with phenylvinylboronic acid (Scheme 3B). As expected, the reaction conditions affect the reaction yield. Bumagin’s conditions (solvent, acetone/water = 3/1; catalyst, $PdCl_2$, 3%; base, Na_2CO_3) give a moderate yield (23–37%) for coupling between cinnamoyl chloride and phenylboronic acids,¹²⁴ while McCarthy’s conditions (solvent, anhydrous toluene; catalyst, tetrakis(triphenylphosphine)palladium(0); base, $CeCO_3$) provide ~50 and ~90% isolated yields for the above two approaches, respectively.¹²⁵ The Suzuki coupling reaction has been extended to synthesize chalcones with electron-withdrawing substituents or electron-donating substituents, indicating that the electronic property of the substituents on the benzene rings has a minimal effect. Buszek et al. first

reported an interesting example of Suzuki–Miyaura coupling for the synthesis of chalcones from *N*-vinylpyridinium tetrafluoroborate salt with yields of 60–81% (Scheme 4).¹²⁶ These salts represent a novel class of palladium-catalyzed electrophilic coupling partners reacting with a wide range of boronic acids. Additionally, the salts are air-stable and nonhygroscopic crystals that can be easily prepared quantitatively in one step from the activated acetylenes and either pyridinium or trialkylammonium tetrafluoroborates.

4.3.1.2. Heck Reaction: Structurally, chalcone is also a stilbene, which can be obtained by the classical Heck reaction of an arylboronic acid or aryl iodide and an unsaturated ketone in the presence of a base and a palladium catalyst (Scheme 5).^{127–134} Cavarischia et al. first reported the synthesis of aryl vinyl ketones and direct coupling with aryl iodides to rapidly provide chalcone derivatives in excellent yields (75–96%) under catalytic conditions [$\text{Pd}(\text{OAc})_2$, Ph_3P , CH_3CN , TEA].¹³⁵ Heck coupling can also be achieved via rhodium-catalyzed carbon–carbon bond formation, which is a competitive side reaction of the conjugate addition of the phosphine–rhodium catalyzed reaction. Zou et al. reported an approach using this competition between Heck coupling and the conjugate addition reaction to synthesize the chalcone moiety.¹²⁹ In their work, phenylboronic acid reacted with phenyl vinyl ketone using $(\text{PPh}_3)_3\text{RhCl}$ (3%) or RhCl_3 (3%)–(±)2,2-bis-(diphenylphosphino)-1,1-binaphthalene (15%) as the catalyst in a toluene–water biphasic system. The resulting chalcones and dihydrochalcones were obtained in a ratio of approximately 50:50 using $(\text{PPh}_3)_3\text{RhCl}$, in contrast to a >99:1 selectivity of the conjugate adduct if the other catalyst was used.

Carbonylative Heck coupling has also been developed to make chalcones, which was first reported by Beller et al. in 2010 (Scheme 5).¹³³ The desired chalcone was initially obtained under palladium-catalyzed conditions with a yield of only 8%, prompting them to improve the methodology. As expected, phenyl triflate with carbon monoxide and different styrene derivatives under optimized conditions ($[(\text{cinnamyl})\text{PdCl}]_2$, dppp, NEt_3 , toluene, 100 °C, 20 h) gave the corresponding chalcones in fair to excellent yields (71–95%). They also extended this methodology to arylboronic acid¹³² and aryl iodide¹³¹ and synthesized chalcones in satisfactory yields. Skrydstrup and co-workers¹³⁴ further expanded this work and reported a two-chamber system to synthesize chalcones and dihydrochalcones using the carbonylative Heck reaction. In their study, a system was used that enables a measured amount of carbon monoxide generated ex situ in chamber A to be a reagent for a parallel Heck reaction in chamber B. Twenty-two chalcones were synthesized, and a ^{13}C isotope-labeled chalcone was also attained using ^{13}CO gas. This is a new application in chalcone and carbonylative isotope chemistry.

Although the metal-catalyzed Heck reaction is considered a highly efficient approach for chalcone synthesis, its application is limited because of the limited availability of aryl vinyl ketones and the need for pressurized carbon monoxide.^{131–134} However, the work was still notable for several reasons: (1) it represents a connection between the already established carbonylative Suzuki and carbonylative Sonogashira reactions; (2) the change in CO as a function of oxygen, while readily explicable, had not been previously established; (3) it is a powerful tool for the isotope labeling of chalcone-derived compounds by a facile isotope-labeling gas.

4.3.1.3. Wittig Reaction.: The Wittig reaction or Wittig olefination is another easy method to create alkene compounds. Chalcone is a reasonable alkene template for the Wittig reaction strategy (Scheme 6). The initial attempt used triphenylbenzoylmethylene phosphorane and benzaldehyde and required 3 days of reflux in benzene or 30 h in THF with a fair yield of 70%.^{136,137} Further development has indicated that the reaction rate could be significantly enhanced via microwave irradiation. For example, Huang et al. reported the synthesis of various chalcones using eight aromatic aldehydes. Good yields (>80%) were obtained for all of the substrates studied, and the reaction could be finished in 5–6 min using microwave irradiation methods.¹³⁸

4.3.1.4. Julia–Kocienski Olefination.: The Julia–Kocienski olefination (Scheme 7), a modification of the Julia olefination reaction, was first applied to synthesize chalcones by Kumar and co-workers in 2010.¹³⁹ Heteroaryl-sulfonyl phenylethanone was prepared following Jorgensen's method¹⁴⁰. Thirty-one chalcones were obtained by the olefination of the Julia reagents and benzaldehyde in basic media. This reaction was influenced by several factors, such as the base, temperature, Julia reagent, and solvent. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was the most efficient base, while the Julia reagent with benzothiazole being the heteroaryl was the best. Nonpolar solvents were more favorable than polar solvents, generally decreasing the yields along the series THF > DCM > CHCl₃ > CH₃CN > MeOH. The yield dramatically decreased when the temperature was at –78 °C.¹³⁹ However, the trans-isomer was still the main product under such a low-temperature condition, where the stereoselectivity could be explained by the Newman projection.^{139,141}

4.3.1.5. Other Cross-Couplings.: In addition to the above cross-couplings, metal-catalyzed direct cross-coupling (using, for example, silver¹⁴² or palladium^{143–145}) has been thoroughly investigated in recent years as a method for forming chalcones.¹²⁶ As shown in Scheme 8A, Al-Al-Masum and coworkers developed a direct cross-coupling reaction of benzoyl chlorides and potassium styryltrifluoroborates to obtain the corresponding chalcones in the presence of PdCl₂(d^bpbf) as the catalyst and K₂CO₃, taking advantage of microwave irradiation. Eight chalcones were synthesized using this condition, providing good to excellent yields (56–96%).¹⁴⁴

Palladium-catalyzed decarboxylative coupling using 3-benzoylacrylic acids (Scheme 8B) is another recently developed strategy for chalcone synthesis.¹⁴⁶ It has been reported that 3benzoylacrylic acids react with arylboronic acids or aryl halides in the presence of a palladium catalyst and a copper salt oxidant [Cu(OAc)₂·H₂O] to produce chalcone derivatives. A mechanistic investigation found that chalcone was generated by ArPdX-mediated decarboxylation or a Heck-type reaction and demonstrated the limitation of the Heck coupling: the direct use of 3-acylacrylic acids is much better than the use of the corresponding vinyl ketones due to their availabilities and stabilities.¹⁴³ The silver-catalyzed double-decarboxylative protocol (Scheme 8C) is another method to build chalcone scaffolds. Chalcones have been synthesized from α -keto acids and cinnamic acids, which are readily available, in the presence of silver nitrate (AgNO₃), sodium thiosulfate (Na₂S₂O₈), and potassium carbonate (K₂CO₃) under mild aqueous conditions with good yields. A

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mechanism has been tentatively proposed. Ag(II) from Ag(I) by peroxodisulfate oxidation is used to generate an aryl radical from α -keto acid, releasing one molecular carbon dioxide and Ag(I) cation. The aryl radical is added to the cinnamate anion at the α -position, leading to the formation of chalcone with another molecular loss of carbon dioxide and Ag(I).¹⁴² The strategy of using saturated propiophenones to produce unsaturated chalcones has also been demonstrated using a combination of decarboxylation and dehydrogenation (Scheme 8D).¹⁴⁷ The researchers crosscoupled aryl carboxylic acids using a PCy₃-supported palladium catalyst to obtain chalcones in fair yields, which is an extension of the Heck reaction that overcomes the limits of its starting materials.

In summary, the above classical cross-coupling strategies have been developed for the construction of carbon–carbon double bonds under mild conditions with good yields, providing diverse and useful chalcone derivatives in the fields of synthetic chemistry and pharmaceutical chemistry. These strategies have their own advantages and disadvantages and can be selected and utilized depending on the specific circumstances, such as the starting materials, solvents, and catalyst conditions as well as the simplicity of purification.

4.3.2. Other Strategies.

4.3.2.1. Friedel–Crafts Acylation with Cinnamoyl Chloride.: With the use of a strong Lewis acid catalyst, such as aluminum trichloride, chalcones can be synthesized by the Friedel–Crafts acylation of an aromatic ether and cinnamoyl chloride (Scheme 9). This method was reported by Shotter et al. in 1978, with four chalcones made in fair yields.¹⁴⁸ Nevertheless, this reaction has not been widely used for chalcone synthesis.

4.3.2.2. Photo-Fries Rearrangement of Phenyl Cinnamates.: The photochemistry of chalcones has attracted considerable interest since the early 1970s because 2'-hydroxychalcones are the key intermediates of flavonoid biosyntheses in nature.¹⁴⁹ The Fries rearrangement (Scheme 10) is commonly applied to the photosynthesis of these chalcones, where a convenient rearrangement reaction of a phenyl cinnamate to a hydroxy aryl ketone occurs in the presence of Lewis acids. This is an *ortho*- or *para*-selective reaction, which is affected by the reaction conditions, such as temperature and solvents. Obara et al.¹⁵⁰ first reported that phenyl cinnamates could be irradiated using benzene as the solvent under nitrogen with a high-pressure mercury-arc lamp (450 W) to obtain 10% 2'-hydroxychalcone and 2% 4'-hydroxychalcone. Subsequent research has extended this reaction to different substituted chalcones, including dihydroxychalcones,¹⁵¹ *O*-methoxymethyl-protected dihydroxychalcones,¹⁵² and multisubstituted chalcones from natural sources.¹⁵³ Ramakrishnan and Kagan found that methanol, ethanol, and chloroform are also suitable for this rearrangement.¹⁵⁴ Although the yield could be improved to approximately 50% by changing the solvent, complete conversion of the phenyl cinnamates has not been achieved to date. Considering the limits of the reaction, long reaction time, low yield, and difficult operation, this procedure is not widely employed.

4.3.2.3. One-Pot Synthesis of Chalcones.: One-pot synthesis is a methodology to improve the efficiency of a reaction and avoid the purification of intermediates to save time

and increase the overall yield. The chalcone scaffold has recently been synthesized by a one-pot synthesis from alcohol and ketone.

As illustrated in Scheme 11A, chromium(VI) oxide is slowly added to a mixture of a primary alcohol and a ketone, constructing chalcone in moderate to high yields (65–98%). It is apparent that the alcohol is oxidized to the corresponding aldehyde *in situ* and reacts with the ketone to obtain the final product.^{155,156} Xu et al. reported the one-pot reaction of an alcohol and different ketones by changing the reaction temperature from –10 to 100 °C for 10–96 h with a catalyst consisting of copper iodide, 2,2'-bipyridine, and 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (Scheme 11A, condition II).¹⁵⁷ Uozumi and co-workers reported that a novel water-soluble nanopalladium (nano-Pd-V) prepared from PdCl₂ effectively catalyzed the reaction and made chalcones from α -ketones and alcohols in 92% yield (Scheme 11A, condition III).⁴⁵⁵ In 2005, a heterogeneous and recyclable palladium catalyst [Pd/AlO(OH)] was reported to catalyze the alkylation of ketones with primary alcohols (Scheme 11A, condition IV). This catalyst was active without ligands or additives. Enones, such as chalcones, can be selectively produced in the presence of oxygen (1 atm O₂). However, under an argon atmosphere, ketones were the major product.¹⁵⁸ This strategy has been developed with a recyclable gold catalyst that catalyzed the one-pot reaction and obtained chalcones in high yields and selectivity under an oxygen balloon.¹⁵⁹ Mechanically, the alcohol is oxidized to an aldehyde and then reacted with a ketone by condensation. The strength of this application is to extend the classical Claisen–Schmidt condensation using benzyl alcohols instead of aldehydes as starting materials.

In addition to benzyl alcohols, phenols have also been used in one-pot synthesis. An example was published involving the synthesis of chalcones from phenols, which was an extension of the above carbonylative Heck coupling with the activation of phenol in a one-pot manner (Scheme 11B).¹³³

4.4. Synthesis of *cis*-Chalcones

Very few studies have reported the synthesis of *cis*-chalcones, a thermodynamically less stable isomer, compared with the more stable *trans*-chalcones. Yoshizawa et al. (Scheme 12) used siloxypropynes and potassium *tert*-butoxide (*t*-BuOK) at –78 °C to obtain important intermediates, namely, siloxyallenes, which were treated with a strong acid (H₂SO₄) and 1,2-dimethoxyethane (DME) to produce *cis*-chalcones. The *cis*-chalcones were prepared in a high yield (up to 85%) and with an excellent geometry preference (up to 99:1 *cis/trans* ratio).⁴⁵⁶

5. CHEMICAL REACTIONS RELATED TO MICHAEL ACCEPTORS

Michael acceptors, containing an electrophile, are generally biologically active. They are involved in the regulation of many signaling pathways in cells and are important tools in chemical biology research. The chalcone scaffold contains an α,β -unsaturated ketone functional group perceived as a potential Michael acceptor. Biologically, the Michael acceptor of the chalcones can readily form covalent bonds with the sulphydryl of cysteine or other thiols to obtain the Michael adduct (Scheme 13), which may play an important role in their biological activities.^{160–164} For example, chalcones could modulate the Keap1-Nrf2-

ARE pathway through the covalent modification of the cysteines of Keap1 and release Nrf2 to induce phase II enzymes (see section 6.2.1.3). Chemically, the Michael reaction is one of the most efficient methods for carbon–carbon bond formation and is widely applied in synthetic chemistry. The electron density on the two aromatic rings affects the enone’s electrophilicity for the reaction.¹⁶⁴ The Michael-related addition, cascade reaction, and epoxidation will be discussed in this section as well.

5.1. Michael Addition

Chalcone has been widely used in organic synthesis to establish highly enantioselective Michael adducts. The asymmetric catalytic conjugate addition of a stabilized carbanion nucleophile to α,β -unsaturated carbonyl compounds represents one of the most important carbon–carbon bond forming reactions in organic chemistry because the adducts are interesting intermediates for further optimization, such as aminocarbonyls, pyrrolidines, and aminoalkanes.^{165–169}

The first attempt to achieve the enantioselective Michael addition was reported in 1978. Wynberg and co-workers employed *N*-dodecyl-*N*-methylphosphonium fluoride as a catalyst for the 1,4-addition of nitromethane to chalcone to form slightly enantioenriched adducts (enantiomeric excess [ee] 23%).¹⁷⁰ Although the enantioselectivity was not very high, this pioneering work encouraged people to explore more strategies and catalysts. The enantioselective addition to the α,β -unsaturated ketone of chalcones has recently resulted in great successes with different reagents and catalysts (Schemes 14–18 and Table 3).

5.1.1. Sulfa-Michael Addition of Chalcones.—The enantioselective sulfa-Michael addition (Scheme 14) has been recognized as one of the most important methodologies to construct carbon–sulfur (C–S) bonds, mimicking the reaction of chalcones with cysteines in the biological systems.^{171,172} In 2001, the Michael addition of thiophenol to *trans*-chalcone was catalyzed by (+)-cinchonine (9), resulting in nearly optically pure adducts 8 with an ee of 91–95% in multigram quantities.¹⁷³ Wang et al. reported that a chiral bifunctional amine thiourea (10) catalyzed asymmetric Michael addition reactions between chalcones and thioacetic acid and gave the adducts in excellent yields (75–100%) with moderate enantioselectivities (33–65%).¹⁹⁰ The asymmetric Michael addition of thiols to chalcones was also attempted in water. Pitchumani et al. used heptakis(6-amino-6-deoxy)- β -cyclodextrin (per-6-ABCD) as the catalyst, and the adduct was achieved in an enantiomeric excess of up to 61%.¹⁷⁴ In 2011, Vaccaro and co-workers reported the sulfa-addition in water using a highly efficient $\text{Sc}(\text{OTf})_3$ /bipyridine (11) catalytic system to produce compound 8 with an ee of 96%.¹⁷⁵ Both the aqueous medium and catalytic system can be recovered and recycled with no loss in enantioselectivity.

Adamo et al. reported the first example of the catalytic enantioselective addition of sodium bisulfite to α,β -unsaturated ketones by the selection of an appropriate aminothiourea bifunctional catalyst (12). The desired sulfonic acids (7) were synthesized in high yields (87–97%) and with excellent enantioselectivity (84–99%) (Scheme 14).¹⁷⁶

5.1.2. Aminohalogenations of Chalcones.—The aminohalogenations of α,β -unsaturated ketones have also attracted great research interest, and several methods have

recently been developed for the aminobromination (*13*) of chalcones (Scheme 15). Wei et al. reported the aminobromination (*13*) of chalcones with p-toluenesulfonamide (4-TsNH₂) and *N*-bromosuccinimide (NBS) in the presence of 1 mol % silicon powder as the catalyst in high yields (up to 98%) and with excellent regio- and stereoselectivities (*anti:syn* > 95%).¹⁷⁷ They also reported the aminobromination of olefins catalyzed by KI with the TsNH₂–NBS combination. This metal-free condition gave the adduct in good to excellent yields (45–98%) and with high regio- and stereoselectivities (no *syn*-products were detected).¹⁷⁸ Li and co-workers reported a method for the aminochlorination of chalcones with 2-NsNCl₂ in an ionic liquid.¹⁷⁹ Hypervalent iodine compounds, such as PhI(OAc)₂, are usually used as the clean and efficient oxidants.^{180,181} Wang et al. reported the aminohalogenation of chalcone promoted by hypervalent iodine compounds.¹⁸² They also reported the first PhI(OAc)₂-catalyzed aminobromination of chalcones in water with TsNH₂ and NBS.¹⁸³ Ni(OAc)₂ can also be used as the catalyst in the aminobromination of chalcones.¹⁸⁴ These methods have significant strengths, although limitations still exist, such as procedural difficulties, unsuitability for one-pot operation, and high catalyst loading.

5.1.3. Asymmetric Michael Addition of Malonates or Malononitriles to Chalcones.—

The asymmetric Michael addition of malonates to chalcone is another type of carbon–carbon bond formation. A complex named lanthanum–sodiumBINOL, prepared from La(O-i-Pr)₃, (R)-BINOL (3 mol equiv), and NaO-*t*-Bu (3 mol equiv), has been reported to asymmetrically catalyze the addition of malonates to chalcone and give a product with a 77% ee and 93% yield (Scheme 16).¹⁸⁵ A simple bis-sulfonamide type ligand (*17*) and Sr(O-iPr)₂ as the catalyst have been used to obtain the product (*14*) in good yield (91%) and ee (97%).¹⁸⁶ A calcium-BINOL catalyst has also been developed for asymmetric Michael addition, but only 42% ee has been obtained.¹⁸⁷ Recently, Lippur et al. reported a mild condition using CaCl₂, bisoxazoline (*18*), and dimethyl malonate for the asymmetric Michael addition. The condition was suitable for most α,β -unsaturated ketones. However, using chalcones as the starting materials, a low yield (14%) and low enantioselectivity (9%) of the products (*14*) were obtained, likely due to the effect of steric hindrance.¹⁸⁸ Asymmetric phase-transfer catalysis has also been utilized. Maruoka et al. reported that the phase-transfercatalyzed Michael addition of diethyl malonate in the presence of an *N*-spiro quaternary ammonium salt catalyst *19* (3 mol %) and K₂CO₃ (10 mol %) in toluene tolerated both electron-withdrawing and electron-donating groups on the benzyl rings. The corresponding Michael adducts were obtained in excellent yields (>97%) and high ee (85–94%). This catalyst system was also used to afford another Michael adduct *15* in a 98% yield with 81% ee.¹⁸⁹ Wang et al. reported the use of a cinchonine catalyst (*12*) in this reaction and obtained the adduct in 85–95% yields and 87–93% ee.¹⁹⁰ Most of the above strategies have achieved great success with high yields and excellent selectivities, although there are still some areas to be further improved, such as the need for an excess of malonate (4–5.6 equiv) with a long reaction time (from 72 to 144 h).

In addition to compound *14* with two ester groups, an α -stereogenic γ -keto ester (*16*) has also been produced by employing nitro(phenylsulfonyl)-methane in the presence of catalyst *20* and Cl₂CHCOOH.^{188,191} The addition of malononitrile to a chalcone derivative in the presence of a quinine-derived bifunctional thiourea tertiary amine (*21*) as a catalyst results in

compound 15. The mechanism of the Michael addition of malononitrile to chalcones has also been examined using theoretical calculations.¹⁹²

5.1.4. Asymmetric Michael Addition of Nitroalkanes to Chalcones.—The asymmetric Michael addition of nitroalkanes to chalcones was first reported by Sundararajan and coworkers in 2001.¹⁹³ Using a chiral polymer and LiAl as the catalyst system, they obtained *R*-22 with a good yield (90%) but only 51% ee. Subsequent studies have developed several different catalysts for this reaction and provided various chiral products with high yields and ee values (Table 3). For example, in 2005, a cinchona alkaloid derived chiral bifunctional thiourea organocatalyst (12, Scheme 14) was used in the Michael addition of nitroalkanes to chalcones, and *R*-22 was obtained,¹⁹⁴ while catalyst 23 was used to give *S*-22.¹⁹⁵ In 2010, Du and co-workers reported a class of squaramide-based organocatalysts, among which squaramides 24 and 25 showed excellent catalytic activity to obtain the desired *R* or *S* enantiomers, respectively, with high yields and excellent enantioselectivities (94–95% ee).¹⁹⁶ The above conditions could achieve high ee and yields, although the reaction time was long. R-22 could also be obtained by per-6-ABCD (mentioned in section 5.1.1) with 100% conversion in 24 h but only 68.5% ee.¹⁷⁴

5.1.5. Other Michael Additions of Chalcones.—Xu and co-workers prepared a series of *R*-aromatic amine–chalcones (26, Scheme 17) using phenylamine (28) and silicon-based Lewis acid (TMSX)–cinchonine (9) cocatalysts under solventfree conditions with high enantioselectivity (>99%) and conversion (>99%).¹⁹⁷ In 2013, Liang et al. reported another example of β -aminoketones (27), which were prepared by the reaction of chalcones with a combination of NBS and DBU with high yields (>80%).¹⁹⁸ Cinchona alkaloids are commonly used in the aza-Michael addition reaction. For example, the addition of azlactones to chalcone derivatives have been achieved (29) using malononitrile and a cinchona alkaloid (30).¹⁹⁹ Wang and co-workers developed a method for the addition of cyclopentanone to chalcone by a simple and commercially available system of chiral 1,2-diaminocyclohexanes (32 and 33) and hexanedioic acid to obtain 31. Their method exhibited good yields (up to 92%) and excellent enantioselectivities (up to 99% ee). It also solved the problem of the low reactivity and high steric hindrance of chalcone substrates in the organocatalytic asymmetric Michael addition reactions in comparison to simple ketones.¹⁹⁹

Shibata and co-workers developed a method of using Cu/Zn complex catalyzed alkylation at the α,β -unsaturated position (compound 34). *S*-34 was obtained by (*S*)-6,6'-SPINOLPHOS (35), while *R*-34 was prepared with (*S*)-4,4'-SPINOLPHOS (36), both of which had over 90% ee.²⁰⁰ The *R*-isomer was also synthesized using Cu(OTf)₂ and aminohydroxyphosphine (37), with 98% ee.²⁰¹ The copper-catalyzed asymmetric conjugate addition of diethylzinc to chalcones has been extended using [2.2]paracyclophane-derived monodentate phosphoramidite (38) as a ligand, with a 98% yield and 95% ee.²⁰² Compared with those required under other conditions,²⁰¹ the loadings of the catalyst (1 mol %) and ligand (1.2 mol %) have been found to be extremely low.²⁰²

5.2. Cases of Chalcone-Involving Cascade Reactions

It is becoming popular to construct multiple stereocenters in a single step using organocatalyzed cascade reactions.^{203–207} Chalcone is a very important type of starting material that could undergo enantioselective Michael addition involving cascade reactions, such as the Michael–Mannich reaction or Michael–Michael addition.^{208,209}

As mentioned in section 5.1, C–S bond formation is important in organic chemistry for chiral sulfur-containing bioactive compounds. A three-component intermolecular Michael–Mannich domino reaction (Scheme 18) using chalcone (*39*) as the Michael acceptor with catalyst *41* and Cs₂CO₃ has been shown to result in the formation of *40* in high yield (>74%), diastereoselectivity (dr, >95:5), and ee (>95%).²¹⁰

An asymmetric oxa-Michael–Michael cascade reaction (Scheme 19) between *trans*-nitrostyrene (*43*) and 2-hydroxychalcones (*42*) with the use of the same catalyst (*24*) as in the nitroalkanes' Michael addition (Table 4) has recently been employed to obtain chiral chroman derivatives with excellent enantioselectivities (up to 99%) and good yields (up to 95%) and diastereoselectivities (up to 5:1).²¹¹ This reaction has also been used to synthesize 2-CF₃ chromanes. β -CF₃-nitroalkenes instead of *trans*-nitrostyrene (*43*) have been used for the squaramide (*24*) catalyzed cascade reaction with *42* to yield CF₃-containing heterocyclic compounds (*44*) bearing three contiguous stereogenic centers with satisfactory qualities.²¹²

Azetidines are a class of important frameworks because of their remarkable medicinal and biological activities.^{213,214} In 2010, Fan and co-workers reported a facile stereoselective synthesis (Scheme 20) of highly functionalized azetidines (*47*) from a novel [2 + 2]-cycloaddition of 2-aminomalonates (*46*) to chalcones (*45*) under grind-promoted, solvent-free, and PhIO/Bu₄NI mediated oxidative cyclization conditions. Twenty-two derivatives were obtained in good yields (46–75%).²¹⁵

As shown in Scheme 21, an asymmetric cross-cascade reaction of different α,β -unsaturated ketones can be catalyzed by a bulky primary amine salt (*51*). Twenty-one compounds (*50*) have been formed with excellent enantioselectivity (92–99% ee) and diastereoselectivity (>30:1 dr).²¹⁶ The method has also been extended to construct spirocyclic compounds using cyclic enones containing exocyclic double bonds (*49*).²¹⁶

Nair and co-workers reported another case of the construction of four contiguous stereocenters in a stereoselective manner (Scheme 22).²¹⁷ Methyl-hydroxycyclopantanecarboxylate (*54*) was prepared in a one-pot operation by the nucleophilic heterocyclic carbene (NHC) (*55*) catalyzed annulation of an enal (*52*) with chalcones (*53*) in methanol. Although the reaction yields were decent (59–70%), there were considerable amounts of byproducts (17–33%).

5.3. Epoxidation and Aziridination of Chalcones

Epoxides and aziridines are extremely important intermediates existing in many natural products.^{218–222} Great efforts have been put forth for chalcones' epoxidation (*56*) and aziridination (*57*) (Scheme 23) for the enhancement of not only the yield but also the ee

value. Several types of catalysts, such as PTC and peptide-type catalysts, have been used to obtain the highly enantioselective compounds.

In 1976, Wynberg and co-workers first utilized the cinchona alkaloid derived quaternary ammonium salt as a PTC to catalyze the epoxidation of chalcone (Table 4, entry 1).²²³ The ee value was initially not very good (25% ee), but it was a great success in that period of time, encouraging scientists to explore better conditions for epoxidation. In 1998, Arai and co-workers discovered that the substituents on the phenyl ring of the *N*-benzyl unit of quaternary ammonium salt catalysts were of great importance in the asymmetric induction, among which *p*-iodophenyl gave the products with the highest yields (>95%) and ee (>84%) (Table 4, entry 2–4).^{224,225} In 1999, Corey and co-workers further developed a PTC catalyst, where the C-9 hydroxyl was substituted by benzyl ethers. The new catalyst was demonstrated to give a remarkably high enantioselective (98.5% ee) product using KOCl as the oxidant (Table 4, entry 5).²²⁶ In addition to cinchona alkaloid derived quaternary ammonium salts, binaphthyl has also been applied as a PTC. For example, Maruoka and co-workers used binaphthyl-based spiro quaternary ammonium salts (*19*) to catalyze the epoxidation of chalcones (Table 4, entry 6).²²⁷ The epoxidation product was obtained in a 99% yield and 96% ee using catalyst *19* and NaOCl as the oxidant reagent. A urea–guanidinium salt was shown to be an effective catalyst for epoxidation, where the functional groups were suggested to contribute cooperatively by interacting with guanidine–hydrogen peroxide (H₂O₂) and urea–enones, giving the epoxidation products in a 99% yield and 91% ee (Table 4, entry 7).²²⁸ β -Amino alcohol catalysts, such as α,α -diphenyl-L-prolinol, are effective for the epoxidation, giving epoxidated chalcones under *tert*-butyl hydroperoxide (TBHP) conditions at a 90% yield and 91% ee (Table 4, entry 8).²²⁹ In addition to prolinols, several other types of amino alcohols have also been examined, demonstrating that four- and six-membered ring catalysts are less effective than the corresponding prolinol catalysts (structures not shown).²³⁰ Chiral amine salt catalysts are another class of catalysts for the epoxidation of chalcones. Although such catalysts are very useful for ketones, the epoxidation of chalcones has only been achieved for up to 84% yield using TBHP (Table 4, entries 9–11).²³¹

Peptide-type catalysts are another type of reagents for chalcone's epoxidation. A polypeptide-catalyzed asymmetric epoxidation of (E)-chalcone using H₂O₂–NaOH in a toluene–water system was first reported by Juliá and co-workers in 1980.²³² Using a poly-L-alanine after the further optimization of the length from 5 to 30, the epoxidation of chalcone was highly effective, and the product was provided in a 96% yield and 96% ee (Table 4, entry 12).²³³ Subsequently, the reaction solvent and the catalyst can be replaced by CCl₄ and poly-L-leucine, respectively. Comparable results have been achieved for chalcone with poly-L-leucine (85% yield and 93% ee) (Table 4, entry 13). Moreover, poly-D-leucine results in the optical isomer of the epoxide at a 98% yield and 93% ee (Table 5, entry 14).²³⁴ Considering the insolubility of the polypeptide catalyst in toluene and water, a triphasic reaction system has also been used. Roberts and co-workers developed a nonaqueous phase method, where the aqueous H₂O₂–NaOH was replaced by urea–H₂O₂ (UHP) and DBU. The chalcones were efficiently epoxidized with immobilized poly-L-leucine (CLAMPS-PLL) under this biphasic condition with a 85% yield and 95% ee (Table 4, entry 15).²³⁵ Polypeptides containing unnatural amino acids have also been applied for the epoxidation of

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chalcones. For example, an epoxide has been obtained in a 99% yield and 98% ee using a cyclic α,α -disubstituted amino acid catalyst (Table 4, entry 16) with a UHP–DBU–THF system.²³⁶

For the asymmetric aziridination of chalcones, the progress is relatively slow. As shown in Table 5, a base and *O*-mesitylenesulfonylhydroxylamine (MSH) or *O*-(diphenylphosphinyl)hydroxylamine (DppONH₂) as the NHtransfer agents are effective for the aziridination of chalcones, giving products with good yields (64–90%) and moderate ee values (37–56%).^{237–239}

In this section, some examples of the epoxidation and aziridination of chalcones are provided. For details on this topic, it is advised to refer to a well-reviewed paper by Shi et al. in 2014.²⁴⁰

6. MEDICINAL ASPECTS OF CHALCONES

6.1. Overview of Biological Activities

Chalcones exhibit a broad spectrum of biological activities, probably due to their small structures and Michael acceptor features, which make them tolerant to different biological molecules and allow them to readily or reactively bind with them. The biological activities of chalcones include anticancer activity, cancer-preventative effects, anti-inflammatory activity, antibacterial activity, antituberculosis activity, antidiabetic activity, antioxidant activity, antimicrobial activity, antiviral activity, antimalarial activity, neuroprotective effects, and others.^{1–5,8,10,12–14,18,21,22,241–251} As presented in Table 1, even a single chalcone compound can exhibit several types of bioactivities. For example, isoliquiritigenin (Table 1, entry 1) has at least anticancer, cancer-chemopreventive, antioxidant, and anti-inflammatory activities. Xanthohumol (Table 1, entry 17) also exhibits anti-HIV-1, antibacterial, and anticancer activities. In addition to these therapeutic potentials, the side effects have also been evaluated. Recently, Xing et al. found a hepatotoxic risk for one type of chalcone, which needs to be more thoroughly investigated.²⁵² Flavokawains A (58) and B (59) (Figure 4), two chalcone derivatives isolated from kava kava, a natural source of great human health relevance, exhibit hepatotoxic synergism with acetaminophen, demonstrating and characterizing the hepatotoxic risk of kava. Another study reported that flavokawain A could significantly inhibit cytochrome P450 isotypes (CYP1A2,CYP2D1,CYP2C6, and CYP3A2), providing the mechanistic insights of the hepatic adverse side effect of flavokawain A and kava extracts.²⁵³ These studies have provided valuable information for the future development of *in vivo* chalcone studies and have contributed to the progress of chalcone-based drug discovery.

6.2. Representative Mechanisms of Action of Chalcones

Tremendous effort has been devoted to characterizing the mechanisms of action of these chalcone compounds. Their multitarget and broad-spectrum biological activities have been reviewed in previous papers.^{1–5,7–22,241} Nevertheless, there is not enough convincing evidence to support some of these molecular targets.^{1,254} In this section, the representative

mechanisms of action of chalcones reported in recent years are summarized, and the targets predicted by computational modeling are detailed in section 7.1.

6.2.1. Michael Acceptor Related Mechanisms.

6.2.1.1. I κ B Kinases (IKKs).: I κ B kinases (IKKs) are one of the key regulators of the nuclear factor kappa B (NF- κ B) pathway, which is recognized as the central mediator of immune responses and inflammation.²⁵⁵ Intervening with the NF- κ B through IKK inhibition is expected to suppress the NF- κ B protein translocation to the nucleus, which is considered to be a promising strategy for disease treatment, especially against inflammation and inflammation-related cancer.^{256,257} Mechanistically, cysteine 179 of IKK β has been shown to be of great importance to IKK inhibition, indicating a covalent-reactive site for biological processes.

As mentioned in section 5.1, the Michael acceptors of chalcones could be covalently modified by proteins, which is one of the major mechanisms of their therapeutic potentials.⁸⁵ The chalcones demonstrate NF- κ B inhibitory activity by the covalent modification of the IKK proteins via the α,β -unsaturated ketone with the Michael-type activity.¹⁷³ For example, Pandey et al. reported that butein (Table 1, entry 2)²⁵⁸ inhibited IKK β in biochemical- and cell-based assays. Additionally, isoliquiritigenin (Table 1, entry 1),^{259,260} flavokawain A (58) and B (59),²⁶¹ licochalcone A (Table 1, entry 27),⁵² and xanthohumol (Table 1, entry 17)⁴³ all have anti-inflammatory and anticancer activities, where the dual activities might result from inhibiting IKK β by the covalent modification of cysteine 179.^{174,175} DK-139 (60, Figure 5) has been found to induce an anti-inflammatory effect on microglial cells by inhibiting the Akt/I κ B kinase (IKK) and nuclear translocation of the NF- κ B signaling pathway.²⁶² In 2009, 3hydroxy-4,3',4',5'-tetramethoxychalcone (61) was reported to exhibit potent anticancer activity in vitro and in vivo that correlated with its NF- κ B inhibitory activity. Compound 61 has also been proposed to react with the cysteines of IKK β , with an inhibition of 46% at 10 μ M.¹⁶⁴ A subsequent study of its mechanism of action showed that this compound killed different cancer cells through a JNK-mediated autophagy pathway that triggers c-IAP.²⁶³ The combination of this compound with TNF-related apoptosis-inducing ligand (TRAIL) or cisplatin significantly increases its cytotoxicity in lung cancer cells. It has been demonstrated that the synergistic effect is the result of the suppression of the expression of the cellular FLICE (FADD-like IL-1 β -converting enzyme)-inhibitory protein large (c-FLIP_L) and cellular inhibitor of apoptosis proteins (c-IAPs), which cooperatively activate autophagy.^{264,265} Toll-like receptor 4 (TLR4) and a coreceptor, myeloid differentiation 2 (MD2), have been reported to regulate the downstream signal transduction, such as MAPK phosphorylation and NF- κ B activation. Compound 62 has been demonstrated to have MD2 inhibitory activity leading to antiinflammatory effects in an LPS-induced acute lung injury (ALI) model.²⁶⁶

6.2.1.2. Thioredoxin Reductase (TrxR).: Thioredoxin (Trx) is one of the major biological antioxidants regulating the cellular redox balance. This enzyme system, consisting of thioredoxin reductase (TrxR) with selenocysteine, is overexpressed in many human tumors and is recognized as a potential target for cancer therapy.^{267,268} Gan et al. reported that chalcones 63 and 64 showed cellular TrxR inhibitory activity in a panel of Michael acceptor-

type pharmacophores (Figure 6). MS analysis demonstrated that the most potent chalcone derivative (*64*) covalently modified TrxR at the selenocysteine residue U498.¹⁶² In 2015, Zhang et al. reported a series of chalcone analogues based on xanthohumol (Table 1, entry 17). Among them, compound *65* displayed good cytotoxicity against HeLa cells ($IC_{50} = 1.4 \mu M$), selective inhibition of TrxR, and induction of cell apoptosis. Mechanistically, the U498C mutation of TrxR was performed to support the covalent mechanism. As a result, this compound could significantly decrease the cellular thiol level and induce the expression of reactive oxygen species (ROS).²⁶⁹

6.2.1.3. Keap1-Nrf2-ARE Pathway: Nuclear factor erythroid 2 related factor 2 (Nrf2) is key to inducing the phase II enzymes and antioxidant enzymes that prevent the oxidative stress,²⁷⁰ which could cause cancer, diabetes, Alzheimer's disease, arteriosclerosis, and inflammation.^{271–279} Under unstressed conditions, Nrf2 remains at a low cellular concentration and is negatively regulated by another cellular component, namely, Kelch-like ECH-associated protein 1 (Keap1).²⁸⁰ Upon exposure to oxidative stress, Keap1 is deactivated such that Nrf2 escapes from the Keap1-mediated degradation and translocates into the nucleus to transcriptionally activate the ARE-dependent antioxidant genes. Electrophilic agents have been reported to induce Nrf2 through the covalent modification of the Keap1 cysteines, resulting in a conformational change that facilitates the process of Nrf2 escaping from the Keap1–Nrf2 interaction.^{281,282} Kumar et al. reported a novel trifluoromethylchalcone (*66*, Figure 7) as a potent activator of Nrf2 using in vitro and in vivo models.²⁸³ The potency of the chalcone in human lung epithelial cells was measured by the expression of Nrf2-dependent antioxidant genes, such as glutamate–cysteine ligase modifier subunit (GCLM), NADPH:quinone oxidoreductase 1 (NQO1), and heme oxygenase 1 (HO-1). In the small intestine of mice, the GCLM and NQO1 after treatment were 6-fold and 10-fold higher, respectively, compared with the vehicle. A subsequent study developed a similar series of heterocyclic chalcone-based Nrf2 activators (e.g., *67*) with increased aqueous solubility and oral bioavailability and enhanced in vivo efficacy.²⁸⁴ However, whether these chalcones covalently modify the cysteines of Keap1 has not been characterized. Furoxanyl chalcone (*68*) is a heterocycle containing compound that translocated Nrf2 and significantly induced the activities of phase II enzymes in the liver.²⁸⁵ 2',4',6'-Tris(methoxymethoxy) chalcone (*69*) has been reported to induce the expression of heme oxygenase 1 (HO1).²⁸⁶ Natural products, e.g., licochalcone²⁸⁷ and xanthohumol,²⁸⁸ can also induce phase II enzymes and activate Nrf2 in cells. A recent study with a chalcone-based probe confirmed that the probe was covalently bound with the cysteines of Keap1 in AREc32 reporter cells (for mdetails, see section 7.2.2.1).²⁸⁹

6.2.2. Other Mechanisms or Targets of Chalcones Validated by in Vivo Models.

6.2.2.1. Microtubule Formation: Microtubules, ubiquitous dynamic polymers of α - and β -tubulin heterodimers, are in a highly dynamic polymerization–depolymerization process in cells.^{1,290–292} Numerous synthetic (Figure 8) and natural chalcones (Table 1) have been reported to exhibit antimicrotubule activities.

Millepachine (Table 1, entry 32), first isolated from *Millettia pachycarpa*, induces cell cycle arrest and apoptosis in human hepatocarcinoma cells in vitro and in vivo.⁵⁴ With the aim of enhancing the antiproliferative activity of millepachine, Yang and co-workers developed an amino-substituent millepachine derivative (*70*) exhibiting excellent anticancer activity against a panel of drug sensitive cancer cell lines and multidrug-resistant cancer cells. Several studies using microtubule dynamics and competitive assays have provided support that this compound inhibits tubulin polymerization by binding at the colchicine site.^{293–295} In addition to simple chalcones, chalcones with fused structures (*71–73, 76*) have also exhibited antimicrotubule and cytotoxicity effects. Bu et al. synthesized a novel *o*-aryl chalcone (*74*) by the Suzuki–Claisen–Schmidt reaction. This chalcone showed potent cytotoxicity against several multidrugresistant cancer cell lines (paclitaxel-resistant human ovarian carcinoma cells, vincristine-resistant human ileocecum carcinoma cells, and doxorubicin-resistant human breast carcinoma cells) in an extremely low nanomolar range. A target determination assay indicated that the chalcone was bound to tubulin at the colchicine site and induced mitosis and arrested cells at the G2/M phase,²⁹⁶ which is a key feature of antimicrotubule agents.²⁹⁷ Compound *75* suppressed approximately 50% of the growth of A549 tumor xenografts without an apparent loss of body weight in nude mice.^{296,290} An indole–chalcone (*76*), namely, IPP51, induced prometaphase arrest and the subsequent apoptosis of bladder cancer cells and showed a significant inhibition of tumor growth without a great loss in body weight. Biochemically, this compound inhibited tubulin polymerization and competed for colchicine binding to soluble tubulin.²⁹⁸

Very recently, Liekens et al. reported a landmark investigation of a series of newly designed chalcones, namely, TUB091 (*77*) and TUB092 (*78*).²⁹⁹ TUB092 was soaked in the crystals of a protein complex comprising $\alpha\beta$ -tubulin (T2) dimers, a stathmin-like protein RB3 (R), and tubulin tyrosine ligase (TTL). The high-resolution cocrystal structure (2.4 Å) provided the first insight into a chalcone compound binding with tubulin (PDB entry 5JVD). The chalcone bound with tubulin at the colchicine binding site (Figure 9): (a) the 1,3benzodioxole ring of TUB092 located in the hydrophobic pocket formed by the side chains of β -tubulin residues; (b) a water-mediated hydrogen bond to the backbone carbonyl and amide of Gly237 and Cys241 was formed; (c) the carbonyl of the α,β -unsaturated ketone generated a hydrogen bond with Asp251; (d) another two water-mediated hydrogen bonds were formed by the backbone carbonyls of Thr179 and Asn349 with the hydroxyl and methoxy groups. A subsequent solubility optimization identified a prodrug (TUB099, *79*) with an L-LysL-Pro dipeptide, showing a 1954-fold better solubility (31 mg/ mL in PBS) than TUB091 (0.016 mg/mL in PBS). TUB099 also inhibited primary tumor growth and spontaneous metastasis in mice (iv injection, 10 mg/kg, 5 days) with 90% or higher inhibition.

6.2.2. Receptor Tyrosine Kinase Inhibitory Activities.: Receptor tyrosine kinases (RTKs), including the epidermal growth factor receptor (EGFR) and the vascular endothelial growth factor receptor (VEGFR), are cell-signaling effectors responsible for cancer development.³⁰⁰ Isoliquiritigenin (Table 1, entry 1) exhibits EGFR inhibitory activity and in vivo antitumor efficacy against a mutant EGFR-expressing xenograft mouse model.²⁸ This compound has also been found to inhibit the VEGFR enzymatic activity and VGEF-induced

angiogenesis in vivo.²⁹ Yang et al. reported that natural butein (Table 1, entry 2) inhibited EGFR in the micromolar range. A competitive biochemical assay showed that the compound potentially bound to the ATP-binding pocket.^{30,31} In 2013, Limper et al. reported that xanthoangelol (Table 1, entry 18) could inhibit EGFR in enzymatic assays.⁴⁵

6.2.2.3. Aldose Reductase Inhibitory Activities.: Aldose reductase (ALR2) catalyzes the conversion of glucose to sorbitol, which is the first step in the polyol pathway of glucose metabolism.^{301,302} Isoliquiritigenin and butein have also exhibited ALR2 inhibitory activities in biochemical assays and inhibited sorbitol accumulation in vivo.^{303–305} Iwata et al. optimized isoliquiritigenin to obtain compound *80* (Figure 10), which showed nanomolar inhibitory activity and 100-fold potency compared to that of isoliquiritigenin.³⁰⁶

6.2.2.4. Cyclooxygenase Inhibitory Activities.: Cyclooxygenase (COX), a target gene of NF- κ B, is thought to be involved in the pathology of cancer and inflammation.^{307,308} Broussochalcone A (Table 1, entry 16) has been demonstrated to inhibit COX activity. Synthetic compound *81* has been designed as a dual inhibitor of COX and 5-lipoxygenase (5LOX), exhibiting both mechanisms of action in vivo.³⁰⁹ Ozdemir and co-workers reported a class of indole–chalcones (*82*) showing potent COX inhibitory activity as well as in vivo anti-inflammatory activity.³¹⁰ The *N*-arylpyrazole of celecoxib has been hybridized into chalcone, where compound *83* selectively inhibits COX-2 activity with good in vivo efficacy.³¹¹

6.2.3. Other Mechanisms of Action.—Chalcones have also been characterized to act on many other cell signaling pathways, such as JAK/STAT,³¹² ROS/MAPK,³¹³ and p38.³¹⁴ However, these topics are not covered in this review because not enough evidence has been provided to support them as the direct target(s) for chalcones. More discussion about the chalcones’ target identification strategies will be presented in section 7.

6.3. Hybrid Chalcones

Molecular hybridization is a strategy used for the design of new chemical entities by the fusion of two different chemotypes. This is an alternative to combination chemotherapy, where two or more drugs of different mechanisms of action are combined for the treatment.^{315,316} However, the simple combination chemotherapy has a high risk of drug–drug interaction.^{15,317} Chalcones are recognized as a privileged scaffold for the incorporation of different molecules or pharmacophores with various activities. The synthesis of these hybrids or conjugations typically uses the classical condensation or the synthesis methods discussed above (section 4) to build the chalcone core. In addition to the biological activities for multitargeting mechanisms, hybrid molecules are also selected for other reasons, such as improving the solubility and oral bioavailability. Two approaches, the construction of ketone or aldehyde hybrids and linkage with chalcones, are detailed below.

6.3.1. Fused Hybrids.—Fused chalcones are easily achieved by the Claisen–Schmidt condensation process using fused aldehydes or ketones (Scheme 24). Based on this strategy, several fused chalcones (Figures 11–15) have been developed with various biological activities.

6.3.1.1. Boron-Containing Chalcones.: Chalcone–benzoxaborole (*84*), prepared from the intermediates 6-formylbenzoxaborole and the corresponding ketone, has recently been found to inhibit *Trypanosoma brucei* growth and possess antitrypanosomal activity (Figure 11).³¹⁸ Boronic–chalcone (*85*) was described early in 2002 as a fluorescent probe for the detection of fluorides.³¹⁹ Boronic–chalcone exhibits not only fluorescent properties but also other biological activity. Compound *85* has been reported as an antitumor agent targeting MDM2 oncoprotein.³²⁰ Compound *86* can induce antitumor activity against malignant glioma cell lines both in vitro and in vivo.³²¹ Compound *87* exhibits potent anticancer activity (HCT116 cells, IC₅₀ = 3.9 μM) together with proteasome inhibitory activity.³²²

6.3.1.2. Coumarin–Chalcones.: Coumarin–chalcones are another interesting class of hybrids (Figure 12), which hybridize a six-member ring at the 1,6-positions (*88*),^{323–325} 4,5-positions (*89*), or 2,3-positions (*90*)³²⁶ of the chalcone’s aldehyde side or the 2',3'-positions (*91*)³²⁷ of the chalcone’s ketone side. The hybrids (*89–91*) are easy to synthesize through the traditional Claisen–Schmidt condensation using fused aldehydes or ketones. The preparation is completely different for the 1,6-position fused coumarin–chalcone (*88*), where a one-pot Knoevenagel condensation can be applied using a substituted salicylaldehyde, a β-ketoester, and piperidine in ethanol.^{323,328,329}

Compound *88* has been reported to possess antioxidant activity.³²³ The electrochemical properties of coumarin–chalcones are better than those of the reference compounds quercetin and catechin, and they also exhibit a high radical scavenging capacity. The compounds have also presented good cytoprotective effects against H₂O₂- and ONOO[–]-induced cell death but low cytotoxicity against BAEC cells. Another study provided more evidence on the radical-scavenging property of the hybrids.³³⁰ Chalcone–coumarin derivatives also possess antitumor activity that significantly inhibited in vitro and in vivo tumor growth.^{325,326} Compound *88* has been reported to show antibacterial activity for the treatment of tenacibaculosis in fish.³²⁴ A biscoumarin–chalcone hybrid (*90*) exhibited good in vitro anti-inflammatory and moderate protective activity in carrageenan-induced paw edema in albino rats (33%).³³¹ Compound *91* has been demonstrated to have excellent cytotoxic activity against paclitaxel-resistant cancer cells.³²⁷ The Hence, derivatives containing the π-conjugated potential chromophore system and spectroscopic and photophysical properties of a coumarinyl chalcone (*92*) have also been evaluated.³³² Similar to the fluorescent properties of chalcones, these properties are extremely sensitive to the polarity of the solvent (see section 3).

6.3.1.3. Indole–Chalcones.: Indole is a scaffold that commonly appears in natural products and synthesized compounds due to its broad spectrum of biological activity.^{333,334} To date, at least two types of indole–chalcone hybrids (*93–95*, Figure 13) have been developed with their biological activities evaluated.^{295,310,335–337} Sashidhara et al. obtained indole–chalcone fibrates based on indole and coumarin–chalcone fibrate, and they exhibited potent in vitro antioxidant and significant in vivo antidiabetic effects.³³⁶ The architecture of compound *93* has also been evaluated in cancer cells. 3-(5-Methoxy-2-methyl-1H-indol-3-yl)-1-(4-pyridinyl)-2-propen-1-one (*94*, MOMIPP) exhibits methionine-inducing activity at submicromolar concentrations. A 6-azido MOMIPP was

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designed by a photolabeling strategy for target identification. However, no pull-down experiment has been performed, and the exact binding target(s) is not well understood.³³⁷ This scaffold has been found to possess in vitro and in vivo anti-inflammatory activity nonselectively targeting COX-1 and COX-2.³³⁶ Unlike the scaffold of compound 93, compound 95, another type of indole–chalcone, has been synthesized from indole-5-carboxaldehyde.^{295,335} This indole–chalcone labeled with ¹²⁵I can be used in β -amyloid imaging probes for detecting Alzheimer’s disease (AD), targeting A β _{1–42} aggregates with high affinity ($K_i = 1.97$ antglioma activity by the activation of the Bax/mitochondrial/caspase-9 pathway and the inhibition of the p53-MDM2 pathway.^{338,339} Loch-Neckel et al. reported a further investigation of the mechanism of an analogue (97).³³⁸ In vitro and in vivo, it could inhibit glioma cell growth and induce mitochondrial apoptosis in U87-MG glioma cells via the inhibition of MDM2.

6.3.1.5. Other Fused Hybrid Chalcones.: Several hybrids besides those discussed above have also been reported to exhibit potent anticancer activities (Figure 15). For example, β -carboline–chalcone (98) exhibits significant DNA binding interaction and DNA stabilization.³⁴⁰ Imidazothiazole–chalcone (99) exhibits promising cytotoxicity with a microtubuledestabilizing mechanism and could compete with colchicine.^{15,341} Anthraquinone–chalcone (100) shows high cytotoxicity in HeLa cells.^{342,343} The compound induces the activity of caspase-3 and caspase-8 in HeLa cells and has shown potent inhibition of MMP-2 secretion.

6.3.2. Hybrids Using Linkages.—Using linkers is another common method to connect chalcones with other active compounds (Figures 16–21). The use of a direct connection like an amide, diol, or ester linkage or the use of a triazole via click chemistry are the most convenient strategies. These hybrids typically retain or enhance the biological properties of the parent chalcones. In this section, representative hybrids using a linker are discussed.

6.3.2.1. Using an Amide as a Linker.: A series of α -bromoacryloylamido chalcones (Figure 16) have been obtained by the hybridization of an α -bromoacryloyl moiety and the α,β -unsaturated ketone system of the chalcone framework, where they might covalently react with the targets.³⁴⁴ Compounds 101 and 102 exhibit the highest activity against tumor cell growth ($IC_{50} < 1 \mu\text{M}$) and 10–100-fold increases in potency compared with the corresponding amide derivatives. The mechanism of action has only been preliminarily studied, and the compounds appear to induce apoptosis mediated by the involvement of the mitochondria and the activation of caspase- 3. Dithiocarbamate–chalcones using an amide as the linker (103) exhibited excellent growth inhibition against SK-N-SH cells, with an IC_{50} value of $2.03 \mu\text{M}$, but are nontoxic to normal cells (GES-1, $>64 \mu\text{M}$), mechanistically inducing apoptosis and arresting the cell cycle at the G0/G1 phase.³⁴⁵

6.3.2.2. Using a Diol as a Linker.: A diol linker is one of the most widely utilized strategies to connect pharmacophores in medicinal chemistry.³⁴⁶ Several chalcone hybrids have been successfully designed and synthesized using this method (Figure 17). The 1,4-dihydropyridyl group is an important pharmacophore that has been introduced into hybrid molecules.⁸¹ The 1,4-dihydropyridyl–chalcones (104) can be synthesized in glycol and

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showed significant vasorelaxant activities, but no mechanism of action or binding target(s) has been reported.³⁴⁷ Pyrrolobenzodiazepine–chalcone (*105*) can be prepared by employing a solid-phase synthetic protocol via an intramolecular aza-Wittig reductive cyclization. This compound shows promising anticancer activities in an NCI-60 panel and exhibited a significant DNA-binding affinity as determined by thermal denaturation studies.^{348,349} Recently, a series of novel dihydroartemisinin (DHA)–chalcones connected by a diol have been reported.³⁵⁰ Compound *106* exhibits an IC₅₀ value of 0.3 μM in cytotoxicity, which is similar to that of the standard therapy (doxorubicin, IC₅₀ = 0.3 μM), and a 6-fold increase in activity compared to that of DHA.

6.3.2.3. Using an Ester or Ether as a Linker: Using an ester or ether is a simple strategy to connect different pharmacophores by directly reacting with the hydroxyl groups of the chalcone (Figure 18). For example, chalcone–amidobenzothiazole conjugates (*107* and *108*) have been shown to exhibit potent activities against different cancer cell lines in the range 0.85–3.3 μM and induced cell cycle arrest at the G2/M phase.³⁵¹ A chalcone–platinum(II) complex (*109*) has been found to exhibit an excellent antitumor effect against a panel of 21 cancer cell lines, similar to the activity of its parent chalcone but different in long-term treatment and slightly different in the mechanism of apoptosis induction.³⁵² This hybrid containing a cisplatin moiety shows promising activity, although no *in vivo* data has been published. Metronidazole is an FDA-approved drug for trichomoniasis, and resistance usually occurs in metronidazole treated *Trichomonas vaginalis*.³⁵³ A metronidazole–chalcone hybrid (*110*) has been reported to be active against not only metronidazole-susceptible but also metronidazole-resistant *T. vaginalis*.³⁵⁴

6.3.2.4. Using 1,2,3-Triazole as a Linker: Using a click reaction to achieve 1,2,3-triazole-linked chalcone hybrids (Figure 19) is an efficient strategy to connect two pharmacophores due to the mild reaction conditions and the triazole’s varied biological activities.³⁵⁵ This type of chalcone has typically been synthesized using an azido-chalcone and an alkyne compound, enabling the use of either an ether linker or a propargyloxychalcone and an azide compound.

Coumarin–chalcone can be hybridized by a 1,2,3-triazole ring at different positions (*111a* and *111b*), exhibiting both anticancer and antimarial activities.³⁵⁶ The hybrids exhibit better cytotoxicity against HepG2 cells than etoposide and extremely low toxicity toward the normal cells. The binding targets have been predicted to be tubulin and falcipain-2 by molecular docking, although no validation has been published. Chibale et al. reported a series of chalcone–dienone hybrid compounds containing aminoquinoline or nucleoside templates.³⁵⁷ They were hybridized into chalcone molecules to improve the biological activities, solubility, and/or oral bioavailability. Among them, chloroquine–chalcone (*112*) was found to be the most potent, showing antimarial activities with submicromolar IC₅₀ values against the D10, Dd2, and W2 strains of *Plasmodium falciparum*. A preliminary mechanistic study showed that the compounds decently inhibited β-hematin formation. However, the β-hematin inhibition and *in vitro* antimarial potency are not well-correlated (see section 6.3.2.5).

Liu et al. designed and synthesized 24 matrine–1*H*-1,2,3triazole–chalcone conjugates using propargyloxychalcone and a 13-azido matrine with an excellent yield by a Michael addition reaction between sophocarpine and excess trimethylsilyl azide in the presence of acetic acid at ambient temperature. The conjugated compound *113* exhibited more potent anticancer activity than 5-fluorouracil against four human cancer cell lines and low cytotoxicity to NIH3T3 normal cells. Moreover, a synergistic effect was observed after hybridization, as compound *113* showed better antiproliferative activity against A549 compared with matrine alone or a simple combination of chalcone and matrine. Nevertheless, the most important characteristic of the hybrid was its favorable safety profile in vivo. The compound was found to have an excellent antitumor efficacy (89.6% tumor growth inhibition) in the A549 xenograft nude mouse model (10.0 mg/kg/day, 20 days, iv) without any apparent loss of body weight.³⁵⁸

β -Lactam has been recognized to be an evergreen bioactive scaffold with not only the antimicrobial activity of naturally occurring bicyclic penicillin and cephalosporin but also various other biological activities.³⁵⁹ Kumar et al. hybridized the lactam scaffold into chalcones with a click reaction.³⁶⁰ Thirteen β -lactam–triazole–chalcones were designed and synthesized. The most potent compound (*114*) exhibited high cytotoxicity against lung (A549) and leukemia (THP-1) cancer cells, with IC₅₀ values < 1 μ M. However, the anticancer activities of the other hybrids were not remarkable.

6.3.2.5. Other Linkers: Chalcone–benzothiazole (*115*)³⁶¹ and chloroquine–chalcone (*116*)³⁶² have been conjugated to hydrazine at different sites of chalcones (Figure 20). Compound *115* shows antifilarial activity selectively targeting *Brugia malayi* thymidylate kinase (BnTMK). Compound *116* is a hybrid connecting on the α -position of the chalcone and exhibiting antimalarial activity. Notably, it has high efficacy against both chloroquine-susceptible (3D7) and chloroquineresistant (K1) strains of *P. falciparum* in the nanomolar range, which is probably due to the inhibition of β -hematin formation.

Another chloroquine–chalcone hybrid connected by piperazine can be optimized from the chloroquine–triazole–chalcone (*112*) to address the poor solubility.³⁶³ The chloroquine–piperazine–chalcone (*117*) was designed by the in silico and in vitro prediction of the physical chemistry and ADME properties using different linkers. The in vitro antiplasmodial activities against the D10, Dd2, and W2 strains of *P. falciparum* of compound *117* have been demonstrated to be 10-fold lower than that of the triazole hybrid (*112*). The strength of this piperazine–chalcone is its excellent solubility under acidic conditions (pH 2.0, >100 μ g/mL), although there is no such increase for the triazole compound *112* under the same conditions (pH 2.0, <1.6 μ g/mL). Mechanistically, this compound exhibits greater potency in the β -hematin inhibition assay than compound *112*, which is identified to be a primary in vitro mechanism of action.

Combretastatin A-4 is an attractive microtubule-targeting natural product from the bark of *Combretum caffrum*.³⁶⁴ Kamal et al. reported a series of imidazolone–chalcone hybrids to mimic the combretastatin A-4 scaffold and evaluated them for anticancer activities against a panel of 53 human tumor cell lines derived from nine different cancer types (leukemia, nonsmall cell lung, colon, CNS, renal, prostate, ovarian, breast, and melanoma).³⁶⁵

Compound *118* showed good anticancer activity, with GI₅₀ values ranging from 1.26 to 10.5 μM and arresting cells at the G2/M phase.

Stilbene derivatives, such as stilbenoids and chalcones, are naturally present in plants and share most of their biosynthetic pathways (see section 4.1).³⁶⁶ These two compounds have been hybridized (*119*) using a Claisen–Schmidt–Knoevenagel–Heck approach and evaluated for their antiplasmodial activity, inhibiting 50% of *P. falciparum* at a concentration of 2.2 μM , in contrast to the 32.5 μM concentration required in the case of the simple mixing of equimolar stilbene and chalcone.³⁶⁷ The mechanism is not well understood, although it has only been characterized to cause chromatin condensation, DNA fragmentation, and the loss of mitochondrial membrane potentials in *P. falciparum*.

Several other hybrids have also been reported to possess promising biological activities. Recently, anthraquinone–chalcone (*120*) has been shown to have high cytotoxicity toward HeLa cells but low toxicity to normal cells.³⁶⁸ Mondhe and co-workers reported a novel quinazolinone chalcone derivative (*121*) as a potential anticancer agent inducing mitochondrial-dependent apoptosis and inhibiting the PI3K/ Akt/mTOR signaling pathway.³⁶⁹ Hybrid *122*, in which indole is directly connected to the chalcone scaffold, showed potent inhibitory activity against vascular cell adhesion molecule-1 and significant anti-inflammatory effects in a mouse model.³⁷⁰ Sulfonamide chalcones (*123*) exhibited good in vitro antifilarial activities against the human lymphatic filarial parasite *B. malayi* by affecting the folate pathway.³⁷¹

A combination of photodynamic therapy (PDT) and vascular-disrupting agents (VDAs) is a creative approach that attempts to mitigate their limits (for their respective limits, refer to ref 372). It has been reported that chalcones with VDA properties can covalently bind to phthalocyanine with PDT properties to achieve phthalocyanine–chalcone conjugates (Figure 21, *124* and *125*).^{372,373} Compound *124* was first designed and obtained by the condensation of tetrahydroxylated nonperipherally substituted Zn(II) phthalocyanine and isocyanate chalcone.³⁷² Compound *125* has been designed to address the deficiency of being too hydrophobic for biological explorations.³⁷³ This monochalcone–phthalocyanine has been synthesized and characterized to show an improved vascular targeting activity due to the incorporation of a cleavable bond (highlighted in red) selectively releasing chalcone at the tumor tissue and the capability to generate singlet oxygen. This example provides a promising strategy for the treatment of solid tumors by combining a photosensitizer and a VDA into one molecule.

7. TARGET IDENTIFICATION

The identification and confirmation of the molecular target(s) of bioactive compounds, especially natural products, is often a decisive step in pharmaceutical research.³⁷⁴ Researchers have devoted tremendous efforts in exploring the direct binding target(s) using different strategies. This section presents the most frequently employed experimental approaches for target identification, such as in silico methods and activity-based protein profiling (ABPP). Several representative examples illustrating the state of the art will be provided.

7.1. Computational Strategy

In silico methods such as quantitative structure–activity relationships (QSARs), molecular docking, and virtual screening have been widely used in the target research of natural and synthetic chalcones (Figures 22 and 23).

Ducki et al. predicted tubulin to be the target of chalcone due to the similarity between chalcone and the β -tubulin inhibitor combretastatin A4 (CA4). A 5D-QSAR model was used to conclude that the methyl group at the α -position made a sizable difference in the preferred conformation from *s-cis* (126) to *trans* (127) for tubulin binding. This theory explains the high potency of α -methyl chalcone (K562, $IC_{50} = 0.21$ nM; tubulin, $IC_{50} = 0.46$ μ M).^{375,376} In 1992, MDL-27048 (128) was the first chalcone found to have antimitotic activity.³⁷⁷ This compound was bound to tubulin at the colchicine-binding site and inhibited tubulin polymerization.³⁷⁸ Based on a proposed binding model for MDL-27048,^{377,378} a virtual screening of 9720 natural compounds was carried out. Compound 129 has been found to show good inhibitory activity of tubulin polymerization.³⁷⁹ Compounds 107 and 130–136 (Figure 22) have been designed and synthesized in later medicinal chemistry work. These compounds were originally predicted to bind to tubulin at the colchicine-binding site, which has been confirmed via *in vitro* competition binding assays.^{298,351,380–384} Very recently, a series of novel indole–chalcone derivatives were synthesized and evaluated for their antiproliferative activity.⁷⁶ Among these indole–chalcones, compound 133 has exhibited IC_{50} values of 3–9 nM against six cancer cell lines, similar activities against resistant cancer cells, and low toxicity toward normal human cells. Molecular docking and mechanistic studies have demonstrated that this compound could bind to the colchicine-binding site, inhibit tubulin polymerization with an IC_{50} of 2.68 μ M, arrest the cell cycle at the G2/M phase, induce apoptosis, and decrease the mitochondrial membrane potential (MMP). Moreover, this compound and its phosphate salt 134 with better water solubility have been shown to exhibit 66 and 70% *in vivo* antitumor inhibitory rates (ip, 30 mg/kg), respectively, without any apparent loss of body weight.

Molecular docking has also been applied to predict the binding mode and explain the phenotypic activity of EGFR,³⁸⁵ aurora kinase,³⁸⁶ anaplastic lymphoma kinase (ALK) enzyme,³⁸⁷ the estrogen receptor (ER β),³⁸⁷ and *Torpedo californica* AChE (TcAChE)³⁸⁸ with their corresponding chalcones (137–141, Figure 23). The advantage of the computational strategy is the convenience of predicting the binding target(s) of chalcones before the biological validation. However, the binding site and binding specificity need validation.

The technique of activity-based proteome profiling (ABPP) in the direct target identification of bioactive chalcones is discussed in section 7.2.^{389–395}

7.2. Activity-Based Protein Profiling Strategy

Although the ABPP strategy has been widely used for natural products^{396,397} and synthetic molecules,^{398,399} its application to chalcone and its analogues has not been widely published. In this review, representative cases including the probe design reported recently are summarized.

7.2.1. Overview of the Activity-Based Probes.—An activity-based probe (ABP) is the prerequisite to perform ABPP. The probe possesses the specific reactivity and structural characteristics of the active sites, which can be covalently bound with the receptor through its tag. Thus, the ABPs require three basic components to achieve this goal: a reactive group, a binding or affinity core, and a receptor tag, such as a fluorophore for the detection, enrichment, and identification of the target protein(s).³⁹⁹ Additionally, a linker is typically designed by the incorporation of a functional group to avoid steric hindrance between the ABPs and their target proteins.³⁷⁴ Currently, ABPs are generally classified into three types: (a) electrophilic probes, such as an α,β -unsaturated moiety that could selectively modify the nucleophilic residues in the active sites of the target protein(s);^{400–411} (b) photoaffinity probes that create a covalent bond with the protein through activation by UV irradiation;^{393,412–418} and (c) clickable probes that could introduce different receptor tags *in situ*.^{419–422} For the chalcone's target identification, the design of the chalcone probes adopts one of the above strategies or a combination of them to obtain a multifunctional probe to identify their targets successfully.^{25,101,289,374,423} For more information on the development of small-molecule probes, several recent reviews are available.^{374,399}

7.2.2. Case Studies.

7.2.2.1. Target Identification by Click Chemistry.: 4-Hydroxyderricin (*142*), isolated from *Angelica keiskei*,⁴²⁴ has attracted great interest due to its antibacterial activity.^{42,425–427} It is hypothesized that the α,β -unsaturated double bond in the compound is a Michael acceptor that potentially captures nucleophiles, such as cysteines. This is likely the main mechanism for its high activity against *Staphylococcus aureus*. After establishing the structure–activity relationship (SAR) of 4-hydroxyderricin,^{425,426} an ABP (*143*) was designed and synthesized for the target identification via a chemical proteomics approach (Scheme 25).⁴²³ *S. aureus* NCTC 8325 cell lysates were incubated with *143* in a concentration gradient ranging from 5 to 100 μM and subsequently reacted with Rh-biotin-N₃ through click chemistry. The bound proteins were enriched and isolated with avidin–agarose beads, followed by SDS–PAGE and Coomassie staining. Although more than one band was observed, the most prominent hit exhibiting the strongest labeling intensities in a dose–response manner was a protein with a molecular mass of approximately 50 kDa. Mass spectrometry revealed that this bound protein was seryl-tRNA synthetase (STS), with five cysteines. Probe *143* also effectively inhibited the catalytic activity of STS in a dose–response manner, and the STS protein was competitively labeled by the parent compound *142*. A further special-site mutation experiment showed that more than one cysteine was involved in the binding. Unfortunately, the exact binding details are still unclear and cocrystallization could shed more light on this.

Recently, a similar target study on the natural product xanthohumol (Scheme 26) has been published.²⁸⁹ Structurally, xanthohumol (Table 1, entry 17) is very similar to 4hydroxyderricin (*142*). Interestingly, this compound has attracted much attention due to its potential as a cancer chemopreventive agent.^{428–430} Based on the same principles as the Michael addition and click chemistry, xanthohumol was designed with an alkyne handle connecting propylene glycol as a short linker to obtain its ABP (*145*). Through copper(I)catalyzed azide–alkyne cycloaddition, the direct target of *145* in AREc32 reporter

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cells was confirmed to be the Keap1 protein and several newly identified target proteins, including glucose-6-phosphate dehydrogenase (G6PDH), which were demonstrated to be inhibited by the xanthohumol-based ABPP at low micromolar concentrations.

7.2.2.2. Target Identification by Photoaffinity Labeling (PAL).: The above two cases used the Michael acceptor of chalcones that is a weak electrophile and may not reach all the thiols.⁴³¹ Based on this theory, these two probes might selectively target specific proteins due to their steric hindrance and noncovalent binding feature. Nevertheless, the nonspecific binding is a key problem that cannot be ignored in target research using the ABPP approach. The cells or lysates are generally exposed to a high concentration of the immobilized probe that might label the specific target(s) and the nonspecific ones. These binders will increase the complexity of the mass spectrometry. Thus, the high affinity of the probe with some negative controls is deemed more desirable for successful target identification. Studies conducted in the authors' lab have recently involved the development of a library of chalcones (data unpublished), showing a sharp SAR in their cellular cytotoxicity and leading to the design of structurally similar cytotoxic and noncytotoxic chalcones as chemical probes. Among them, compound 147 with an α -methyl group exhibited excellent antitumor activity ($IC_{50} = 0.4 \mu M$). The high potency due to its conformational change can be explained by the theory of Ducki et al.^{101,375} However, the electron-donating methyl group and the induced conformational changes decrease the activity of the intrinsic electrophile. For the consideration of this question, three trifunctional probes¹⁰¹ (148–150, Scheme 27) with an azide that could be photoactivated by UV irradiation^{432–435} and an alkyne coupled by copper(I)-catalyzed Huisgen [3 + 2] cycloaddition (click chemistry)^{355,436} to a biotin-azide were designed. A significant cytotoxicity SAR was obtained, and chemical proteomics was performed. One 52-kDa protein was clearly labeled by compound 148, but not the noncytotoxic chalcones (149 and 150). The other nonspecific binders were also eliminated by the negative controls. The 52kDa protein was isolated by the subsequent streptavidin–biotin-based target enrichment. A mass spectrometry analysis unambiguously identified the target protein as β -tubulin. This finding was confirmed by biochemical and cell cycle assays. MSbased peptide quantitation revealed that compound 148 might modify the peptide N337–K350 (NSSYFVEWIPNNVK) near the colchicine-binding site. Although this study did not discover new targets for chalcone's cytotoxicity, the findings provided solid evidence for the computational study predicting tubulin as chalcone's target (see section 7.1) and matched well with the first cocrystallization of chalcone derivatives with tubulin (see section 6.2.2.1). To the best of our knowledge, this is the first time PAL chalcone probes have been used to explore chalcone's direct cellular targets. More importantly, chalcone can be developed as a privileged structure instead of a promiscuous one.¹⁰¹

7.2.2.3. Target Identification by Stable Isotope Labeling with Amino Acids in Cell Culture (SILAC).: For SILAC-based target identification,^{437,438} the cells are cultured under either normal conditions or conditions to incorporate isotope-labeled, such as ^{13}C and ^{15}N , essential amino acids.^{438,439} Piperlongumine (152, Scheme 28A), a natural product from *Piper longum* L., is structurally similar to chalcone in that it can selectively kill cancer cells with increasing cellular ROS levels.^{25,440–442} Specific piperlongumine–protein interactions have been identified using the SILAC methodology and a piperlongumine bead (153).

Glutathione S-transferase 1 (GSTP1) or carbonyl reductase 1 (CBR1) has been identified to be the cellular target contributing to piperlongumine-induced ROS. Some other indirect targets have also been proposed.²⁵ However, the knockdown of GSTP1 or CBR1 does not affect the ROS levels or apoptosis in cancer cells, raising the uncertainty of them being the essential targets.²⁵ Recently, Liang et al. reported that the selenocysteine-containing antioxidant enzyme TrxR1 might be a primary binding target of the piperlongumine.⁴⁴³ Subsequent studies have revealed that the lactam is critical for the cytotoxicity due to its much stronger electrophile property than that of the α,β -unsaturated double bond,⁴⁴¹ allowing it to react with thiols of the target protein(s). Thus, using ABPP and the design of ABPs (154 and 155) might be a promising future direction as the strategy for target identification (Scheme 28B).

8. CONCLUSIONS AND PERSPECTIVES

Privileged structures have been widely used as an effective strategy in medicinal chemistry for drug discovery. The strengths of this strategy are as follows: (1) they can quickly provide structurally novel chemotypes by modifying the central core structure and/or introducing the side chains of the existing active compounds; (2) synthetically, well-established protocols are typically established to allow quick expansion of the amount of derivatives for biological uses; (3) they are the core molecular frameworks, providing useful ligands for multiple targets by rational structural optimization.^{444–453} Chalcone is a common scaffold found in many naturally occurring compounds, especially plant-derived natural products. In addition, many chalcone derivatives have been prepared due to their convenient synthesis. Chalcone is regarded as a privileged structure of great practical interests because these natural and synthetic chalcone derivatives have shown numerous interesting biological activities with clinical potential against various diseases. Chalcone has attracted considerable research interest in multiple disciplines, with over 1300 peer-reviewed publications during the past five years. The research topics include the isolation of novel chalcone derivatives, the development of new synthetic methodologies, the evaluation of biological properties, and the exploration of the mechanism of action including target identification. New evidence has emerged to support chalcone being a privileged template instead of a promiscuous structure. Research on the development of an activity-based photoactive probe approach to identify the direct cellular targets of chalcone-based compounds conducted in the authors' lab has provided unambiguous evidence for tubulin being the direct cellular target responsible for chalcone's cytotoxicity. Moreover, the first cocrystallization (PDB entry 5JVD) of a chalcone derivative with tubulin has recently been published. In the future, with these promising advances, chalcone-based science is expected to be applied in drug discovery. Nevertheless many challenges remain, with two listed as follows:

1. In organic chemistry, numerous efforts have been made in the methodology development of chalcones' synthesis and Michael and olefin moiety applications. However, the synthesis needs to be optimized because the reaction conditions and yields using the commonly accepted approach vary depending on the starting materials. The chemical methodologies of chalcone-based natural products with multiple chiral centers and diversity-oriented organic synthesis using a chalcone scaffold to make a biological compound library need to be extended.

2. In medicinal chemistry, various chalcones and chalconemimics have been isolated for biological uses. Because chalcones represent a very simple scaffold, it is easy to elucidate the structure, although novel structures are not easy to identify. Nevertheless, the natural chalcones as well as their biological uses will still attract great interest in the future. Synthetic analogues need to be designed for further SAR study and to determine their particular properties (e.g., fluorescence) in biological applications. Given the poor solubility of most chalcone compounds, the *in vivo* efficacy has not reached the expected levels in preclinical evaluations. Thus, the optimization of the physicochemical properties will be one of the most important research directions of chalcone-based compounds. For the targets of chalcone compounds, several proposed targets must be verified. Activity-based protein profiling is a powerful approach for target identification that must be determined on a case-by-case basis due to the properties of chalcone molecules. It is encouraging that the first cocrystal structure of chalcone with the cytotoxicity target tubulin has been published, providing the insights of structure-based information for further optimization. More cocrystallizations are also needed in the structural biology of chalcone analogues with their direct binding target(s), which will guide the further optimization for medicinal chemists to rationalize the bioactivity of interest and the side effects such as hepatotoxicity *in vivo*.

These questions will no doubt attract further interest in the coming years. It is also expected that novel chalcone-based drugs will be discovered using modern drug discovery strategies and new chemical sources. In addition, more studies on the chalcone moiety in other areas not mentioned in this review are also expected.

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Biographies

Chunlin Zhuang is currently a lecturer at the School of Pharmacy, Second Military Medical University, China. He received his Ph.D. in medicinal chemistry from the research group of Prof. Wannian Zhang in 2014. In 2012, he was sponsored by the China Scholarship Council’s Ph.D. Abroad Training Plan to work under the supervision of Prof. Chengguo Xing at the University of Minnesota. His research interests are mainly focused on the target identification of natural products and structure-based drug design.

Wen Zhang received his Ph.D. from the Institute of Materia Medica, Chinese Academy of Sciences, in 2005. He moved to Istituto di Chimica Biomolecolare—CNR (Italy) as a visiting researcher in 2006 and completed postdoctoral work at Universität Paderborn (Germany) in 2007. He joined the faculty of the Second Military Medical University and was nominated as a full professor in 2008. He has held a joint professorship with Tongji

University since 2013. His research interests focus on the discovery and potential target screening of functional molecules from marine invertebrates and associated microorganisms, which have resulted in more than 60 scientific articles.

Chunquan Sheng received his bachelor's degree in pharmacy (2000) and Ph.D. in medicinal chemistry (2005) from the Second Military Medical University and then joined the Department of Medicinal Chemistry, School of Pharmacy, in 2005 as a faculty member. Currently, he is a professor and Director of the Department of Medicinal Chemistry. His research interests include the structurebased design and synthesis of drug-like molecules with an emphasis on the small molecule inhibitors of protein–protein interactions and multitargeting drugs.

Wannian Zhang received his bachelor's degree in pharmacy (1968) and M.S. degree in medicinal chemistry (1981) from the Second Military Medical University. He worked as a professor of Medicinal Chemistry from 1992 and was Director of the Department of Medicinal Chemistry, School of Pharmacy, Second Military Medical University, from 1992 to 1994. From 1994 to 2001, he served as Dean of the School of Pharmacy. Currently, Prof. Zhang is Chief of the State's Key Discipline of Medicinal Chemistry, Second Military Medical University. He has held a joint professorship with Ningxia Medical University and served as Dean of the School of Pharmacy since 2011. His research interests are mainly focused on antifungal and antitumor drug design and development. He has published more than 100 scientific articles and developed four compounds that have been certificated by the CFDA.

Chengguo Xing received his bachelor's degree from Dalian University of Technology (1996) and Ph.D. in organic chemistry from Arizona State University (2001). He joined Harvard University working with Prof. Andrew G. Myers as a postdoctoral associate in 2001 and the University of Minnesota as a faculty member in 2003. Currently, he is a professor and the Frank A. Duckworth Eminent Scholar Chair in Drug Research and Development at the University of Florida. His research interests are mainly in isolating, identifying, designing, and synthesizing biologically active small molecules, employing such candidates as probes to tackle fundamental health-related biological questions and diseases and evaluating their clinical potentials in clinically relevant animal models.

Zhenyuan Miao is currently an associate professor at the School of Pharmacy, Second Military Medical University, China. He received his Ph.D. degree in medicinal chemistry from the research group of Prof. Wannian Zhang in 2006. In 2015, he joined the research group of Prof. Gunda I. Georg as a visiting scholar. His research interests are mainly focused on the medicinal chemistry aspects of natural products, small molecule inhibitors of protein–protein interactions, and fluorinecontaining drug discovery.

ABBREVIATIONS

4-TsNH₂	p-toluenesulfonamide
5-LOX	5-lipoxygenase

99mTc	technetium-99m
ABP	activity-based probe
ABPP	activity-based proteome profiling
AD	Alzheimer's disease
AgNO₃ ,	silver nitrate
ALK	anaplastic lymphoma kinase
ALR2	aldose reductase
AlCl₃	aluminum chloride
ARE	antioxidant response element
BnTMK	Brugia malayi thymidylate kinase
BF₃-Et₂O	boron trifluoride–etherate
CA4	combretastatin A4
c-FLIP_L	cellular FLICE-inhibitory protein large
CHI	chalcone isomerase
CHR	chalcone reductase
CHS	chalcone synthase
c-IAP	cellular inhibitor of apoptosis protein
CO	carbon monoxide
COX	cyclooxygenase
CTMAB	cetyltrimethylammonium bromide
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DHA	dihydroartemisinin
DME	1,2-dimethoxyethane
Dr	diastereoselectivity
ee	enantiomeric excess
EGFR	epidermal growth factor receptor
ERβ	estrogen receptor
FER	fluorescence–environment relationship
FLICE	FADD-like IL-1 β -converting enzyme

G6PDH	glucose-6-phosphate dehydrogenase
GCLM	glutamate–cysteine ligase modifier subunit
GSTP1	glutathione S-transferase 1
hH3R	human histamine H3 receptors
HO-1	heme oxygenase-1
H₂O₂	hydrogen peroxide
IKK	IκB kinase
K₂CO₃	potassium carbonate
LiHDMS	lithium bis(trimethylsilyl)amide
mESC	mouse embryonic stem cells
MMP	mitochondrial membrane potential
MOMIPP	3-(5-methoxy-2-methyl-1H-indol-3-yl)-1-(4-pyridinyl)-2-propen-1-one
Na₂S₂O₈	sodium thiosulfate
NBS	N-bromosuccinimide
NF-κB	nuclear factor kappa B
NHC	nucleophilic heterocyclic carbene
NQO1	NADPH:quinone oxidoreductase 1
Nrf2	nuclear factor erythroid 2-related factor 2
PAL	photoaffinity labeling
PDT	photodynamic therapy
per-6-ABCD	heptakis(6-amino-6-deoxy)-β-cyclodextrin
PKS	polyketide synthase
PSC	pluripotent stem cells
PTC	phase-transfer catalyst
p-TsOH	p-toluenesulfonic acid
QSAR	quantitative structure–activity relationship
ROS	reactive oxygen species
RTK	receptor tyrosine kinase

TrxR	thioredoxin reductase
SAR	structure–activity relationship
SFR	structure–fluorescence relationship
SILAC	stable isotope labeling with amino acids in cell culture
STS	seryl-tRNA synthetase
TBAB	tetrabutylammonium bromide
t-BuOK	potassium tert-butoxide
TcAChE	Torpedo californica AChE
TEA	triethylamine
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
THF	tetrahydrofuran
TRAIL	TNF-related apoptosis-inducing ligand
UHP	urea–H ₂ O ₂
VDA	vascular-disrupting agent

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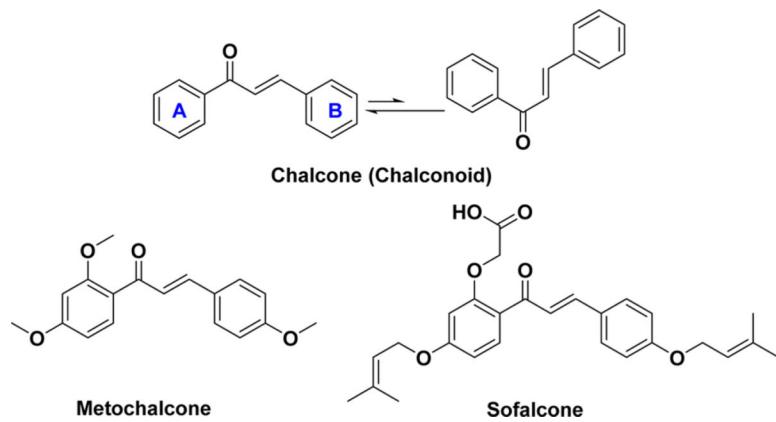


Figure 1.

Structures of chalcone and two clinically approved chalconebased drugs.

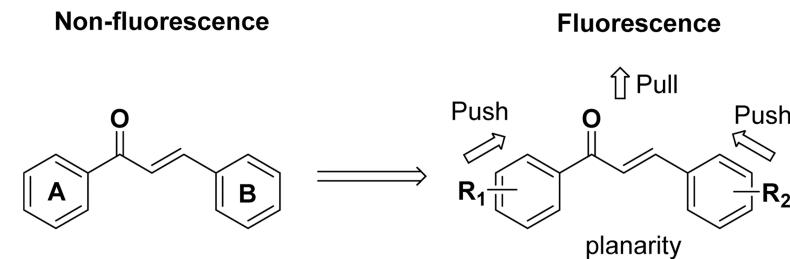


Figure 2.

Electron push–pull pairs for fluorescent chalcones.

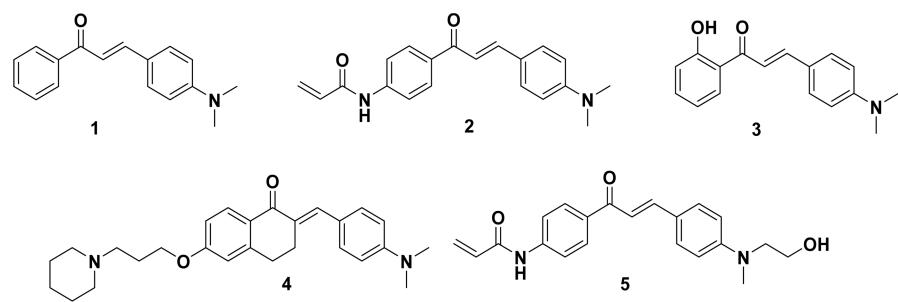


Figure 3.
Representative fluorescent chalcones.

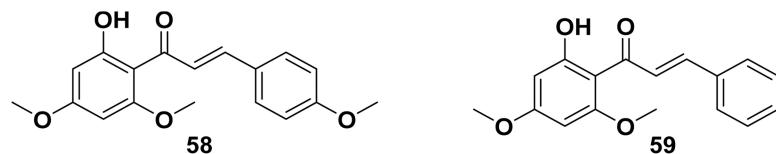


Figure 4.
Flavokawains A (58) and B (59).

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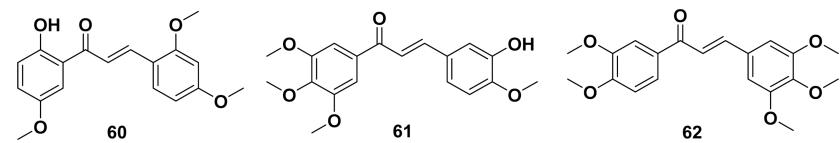


Figure 5.
Structures of chalcones as NF-κB inhibitors.

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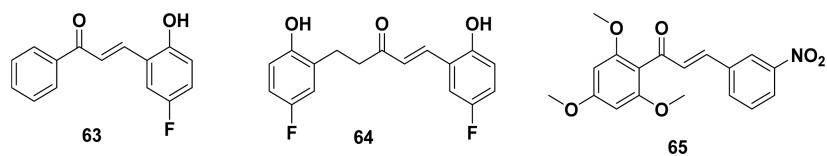


Figure 6.
Structures of chalcones as TrxR inhibitors

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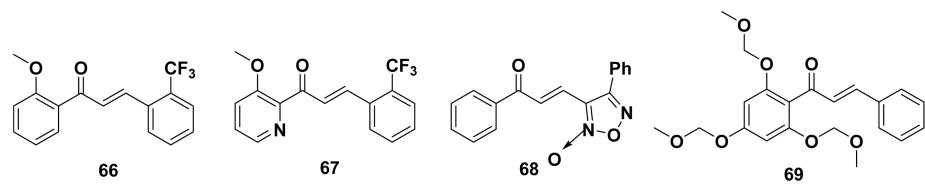


Figure 7.
Structures of chalcones as Nrf2 activators

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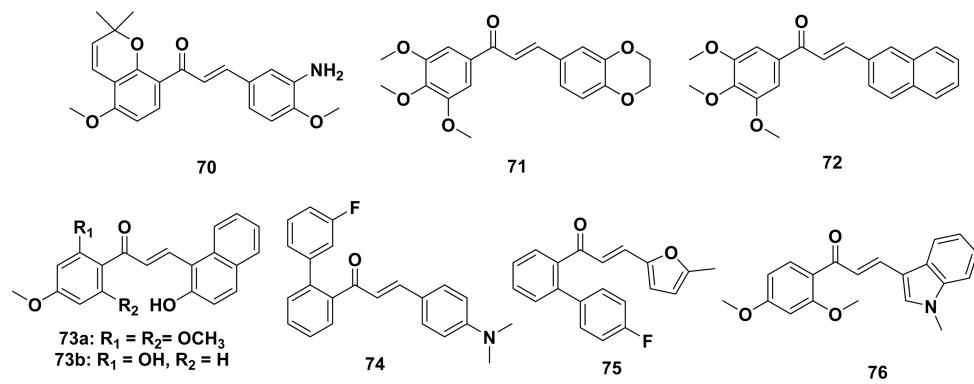


Figure 8.
Representative antimicrotubule chalcones.

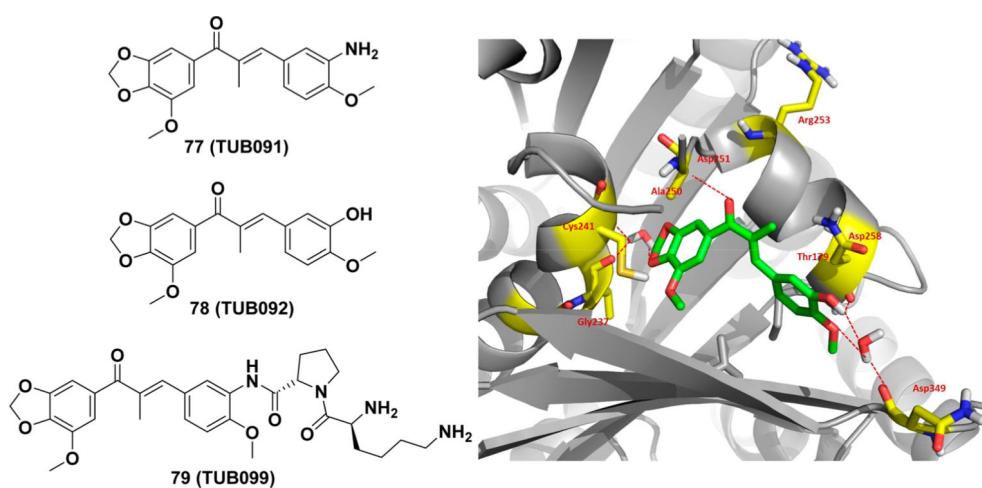


Figure 9.

Structures of TUB chalcones and cocrystal structure of TUB092 with tubulin [generated using PyMol (<http://www.pymol.org/>)].

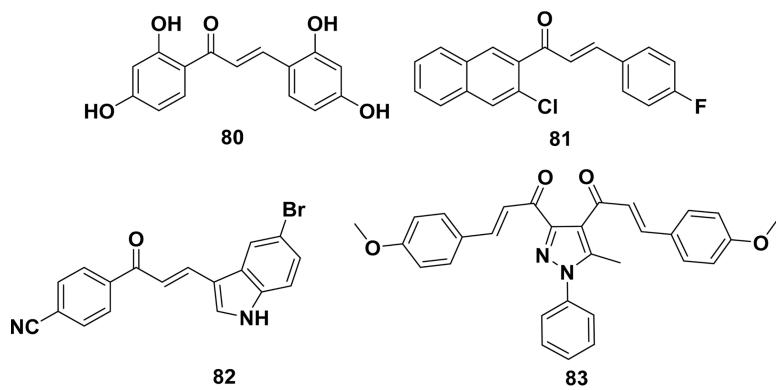


Figure 10.

Structures of chalcones as ALR2 and COX inhibitors.

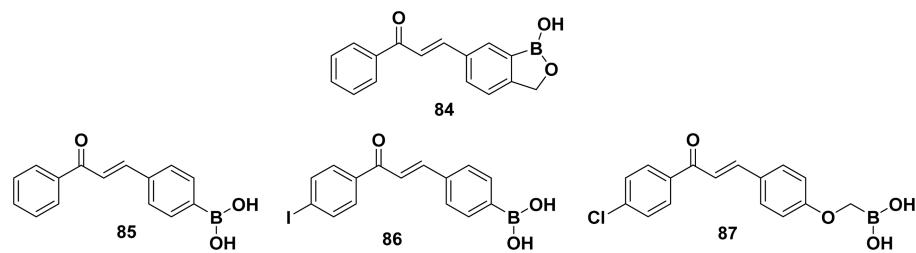


Figure 11.
Structures of boron-containing chalcones.

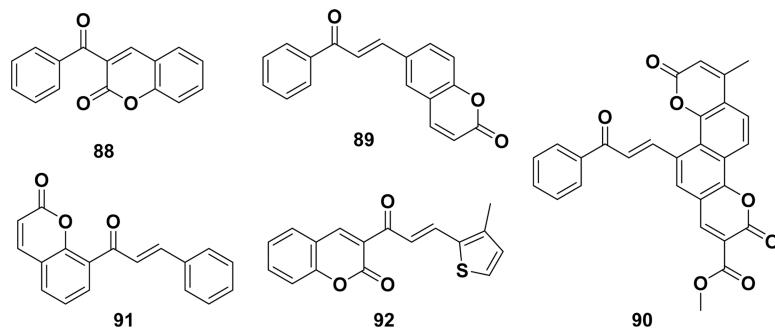


Figure 12.
Structures of coumarin–chalcones

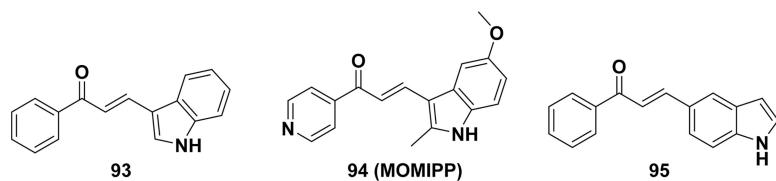


Figure 13.
Structures of indole–chalcones.

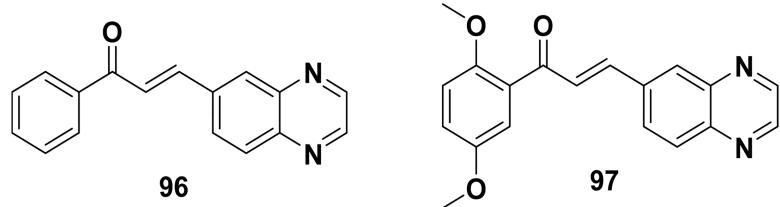


Figure 14.
Structures of chalcone–quinoxalines

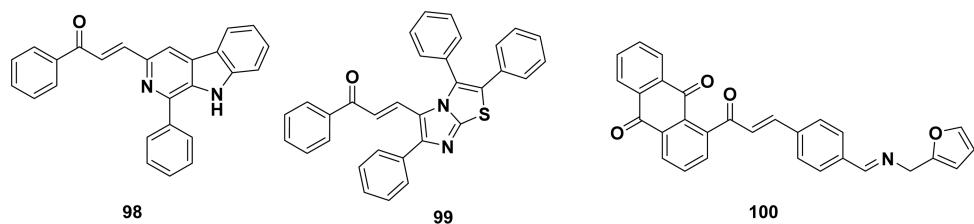


Figure 15.
Other representative fused chalcone hybrids

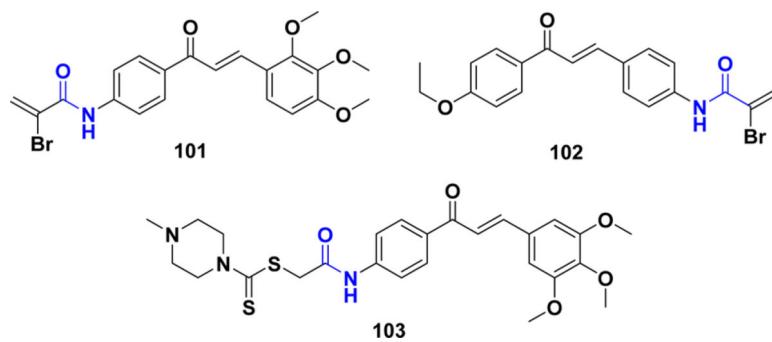


Figure 16.
Amide-linked chalcones

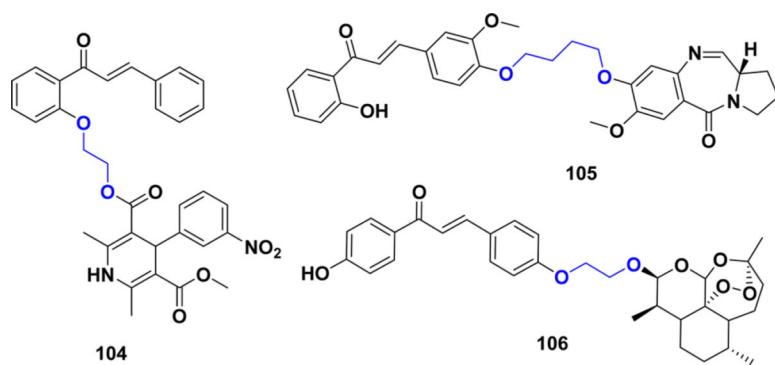


Figure 17.
Diol-linked chalcones

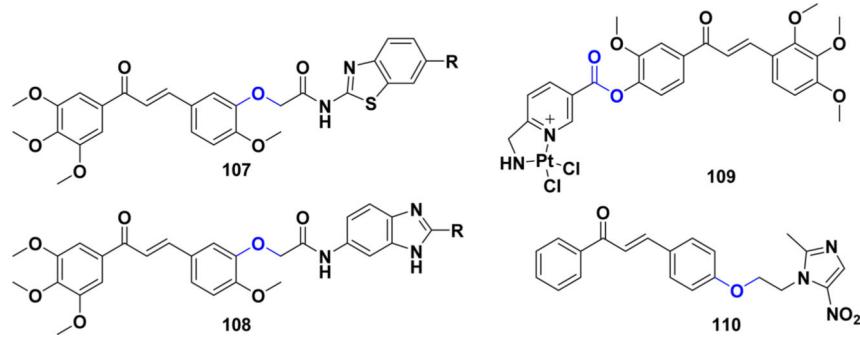


Figure 18.
Ester- or ether-linked chalcones

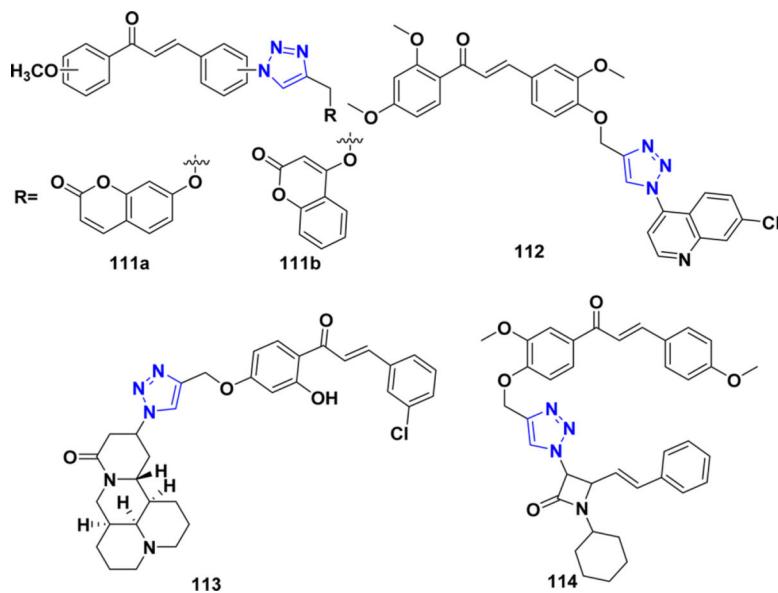
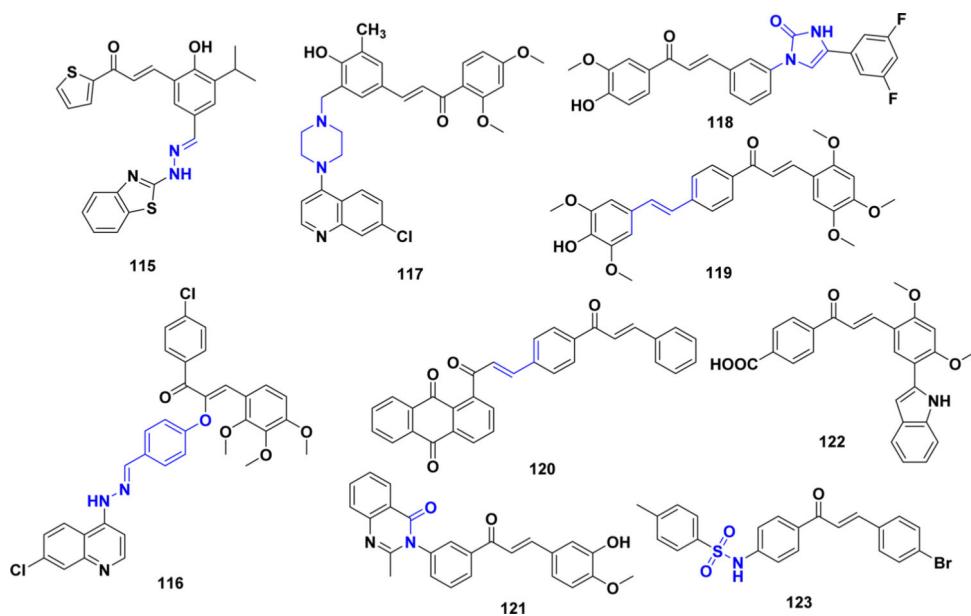


Figure 19.
1,2,3-Triazole linked chalcones

**Figure 20.**

Other representative linked chalcones.

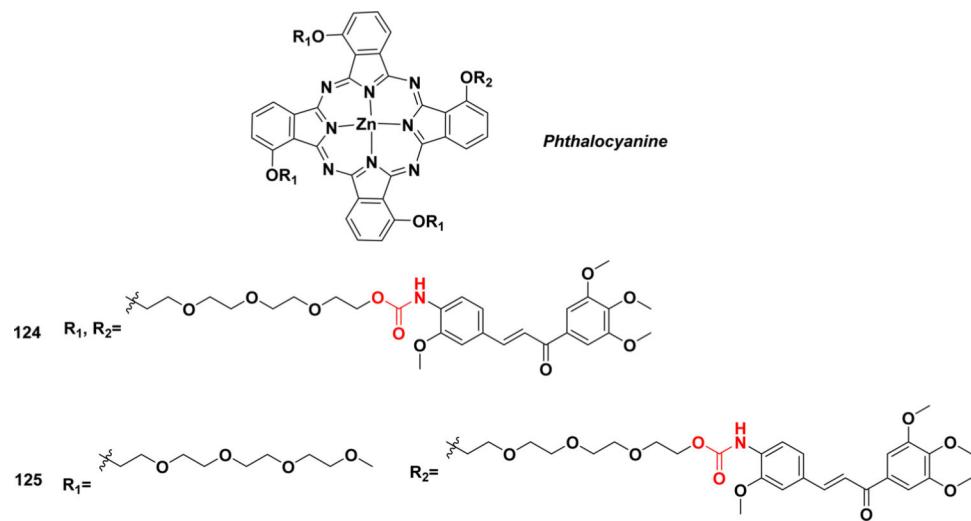


Figure 21.
Phthalocyanine–chalcone conjugates

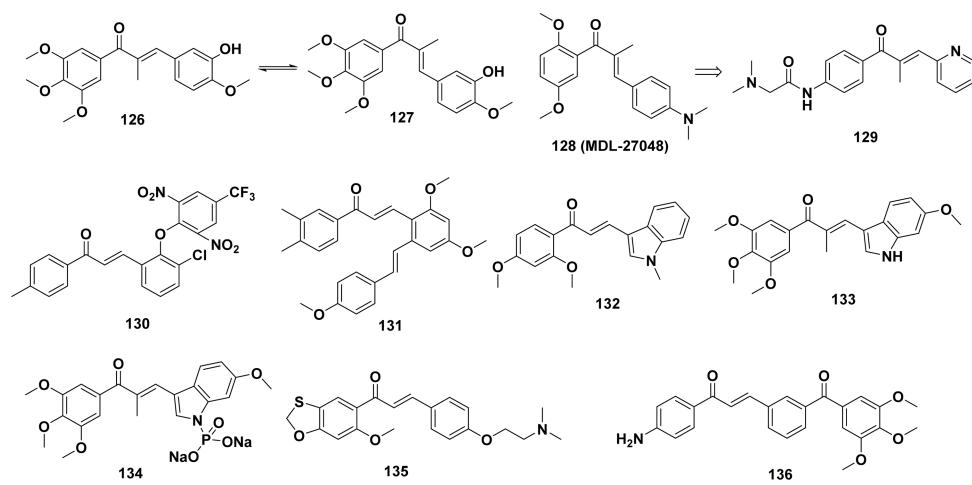


Figure 22.
Chalcones targeting tubulin predicted by computational strategy.

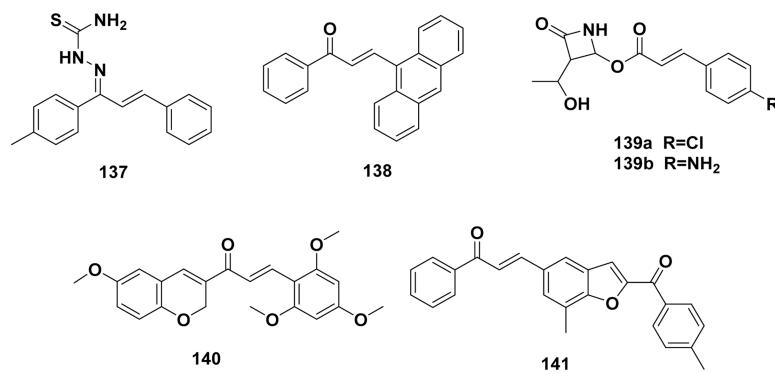
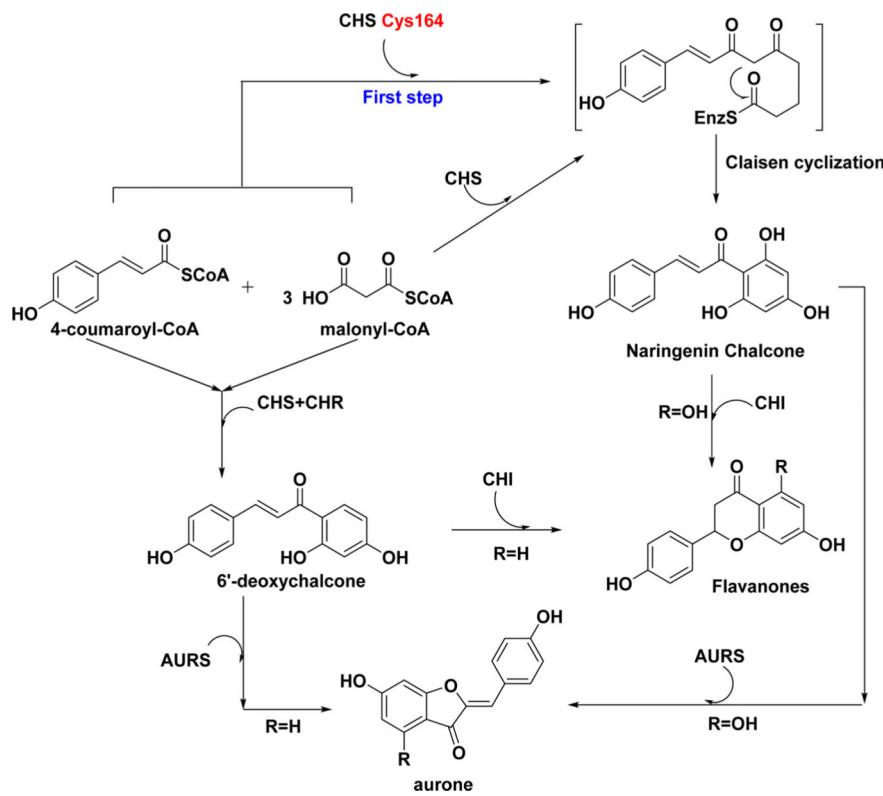
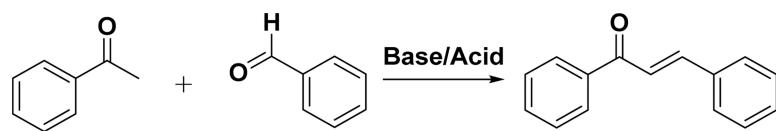


Figure 23.

Other representative chalcones for target identification by computational strategy.

**Scheme 1.**

Biosynthesis of Chalcones and Downstream Pathways



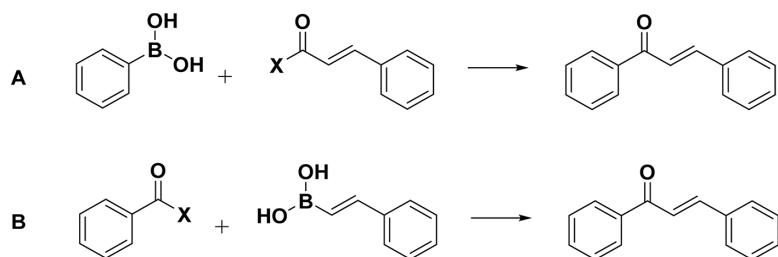
Scheme 2.
Claisen–Schmidt Condensation of Chalcone

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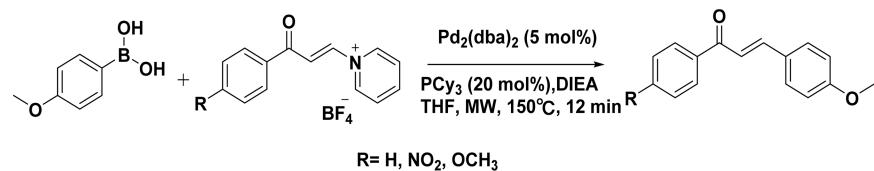
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Scheme 3.
Suzuki Coupling for Chalcone Synthesis



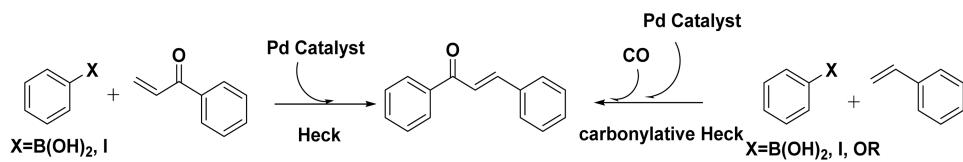
Scheme 4.
Suzuki–Miyaura Coupling for Chalcone Synthesis

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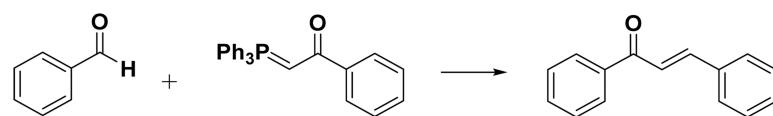
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Scheme 5.

Heck Coupling and Carbonylative Heck Coupling for Chalcone Synthesis



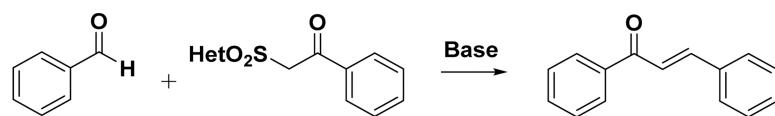
Scheme 6.
Wittig Reaction for Chalcone Synthesis

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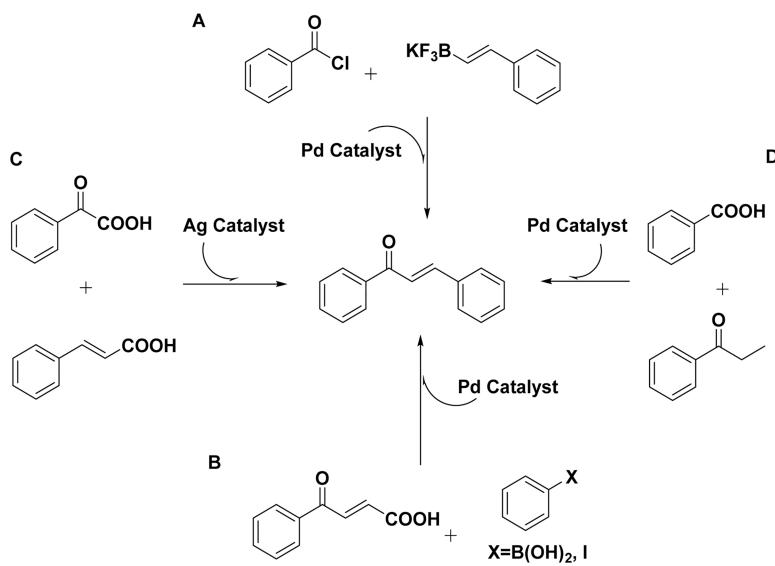
Scheme 7.
Julia–Kocienski Olefination for Chalcone Synthesis

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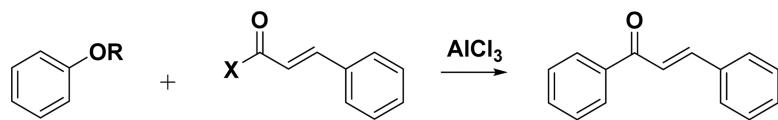
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Scheme 8.
Other Cross-Couplings for Chalcone Synthesis



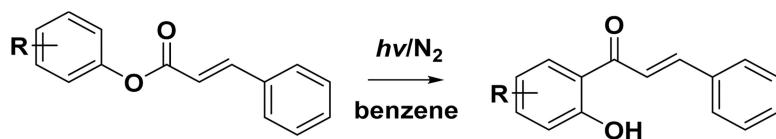
Scheme 9.
Friedel–Crafts Acylation for Chalcone Synthesis

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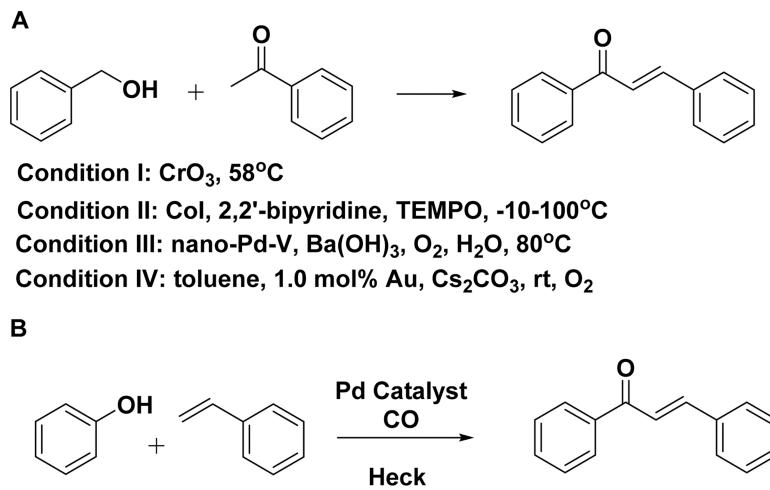
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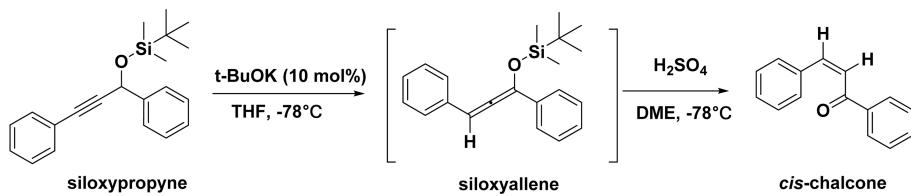


Scheme 10.

Photo-Fries Rearrangement for Chalcone Synthesis



Scheme 11.
One-Pot Synthesis of Chalcones



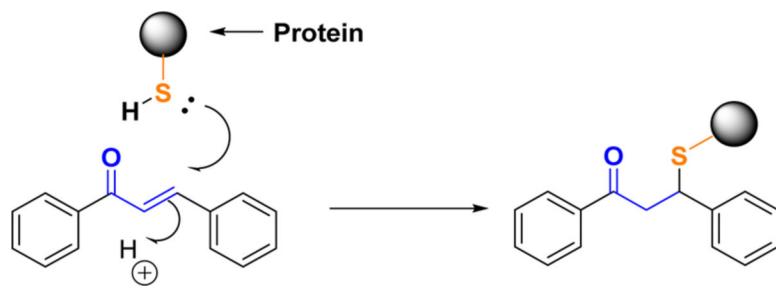
Scheme 12.
Synthesis of *cis*-Chalcones

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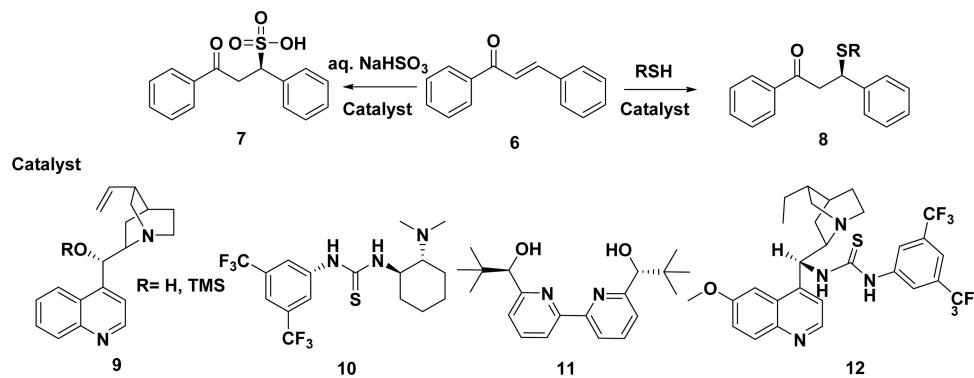
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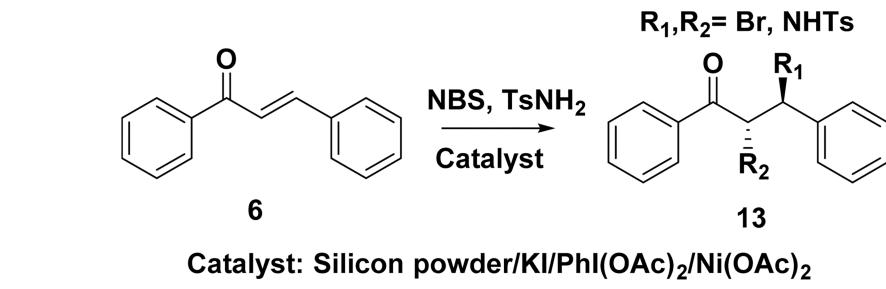
Scheme 13.

Michael Addition of a Chalcone with Cysteine

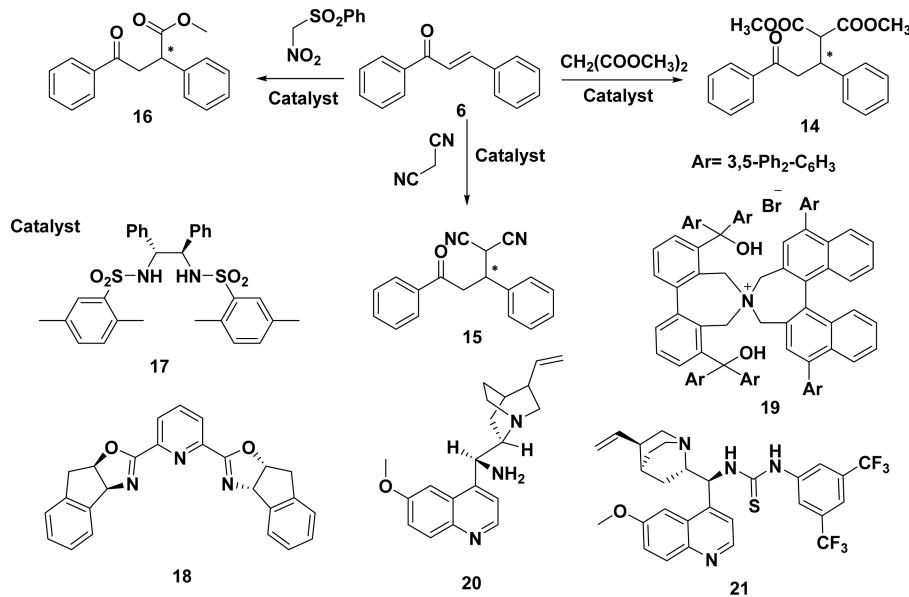


Scheme 14.

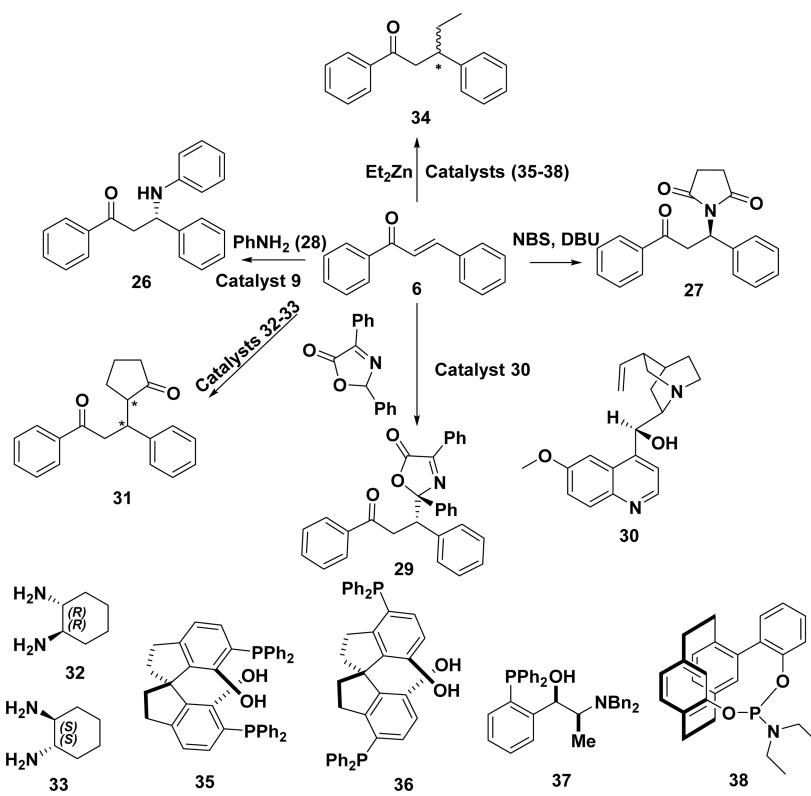
Sulfa-Michael Addition of Chalcones



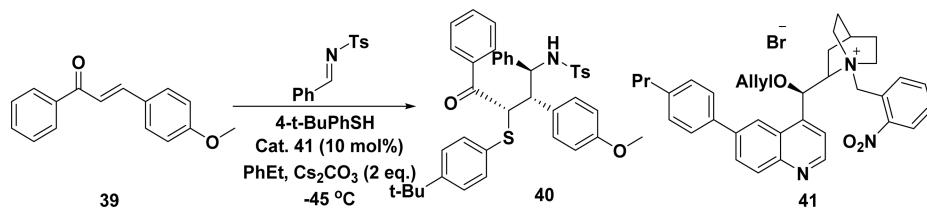
Scheme 15.
Aminohalogenation of Chalcones

**Scheme 16.**

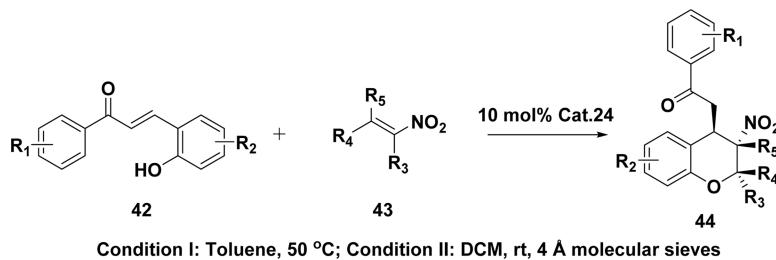
Asymmetric Michael Addition of Malonates/Malononitriles to Chalcones



Scheme 17.
Other Michael Additions of Malonates to Chalcones



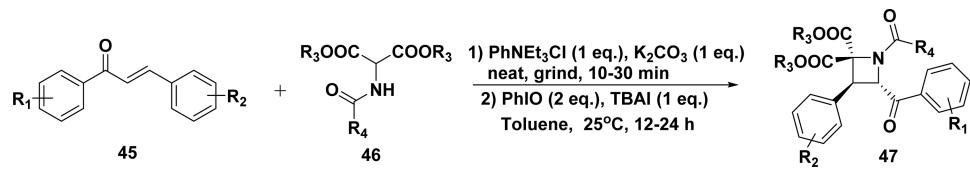
Scheme 18.
Michael–Mannich Domino Reaction



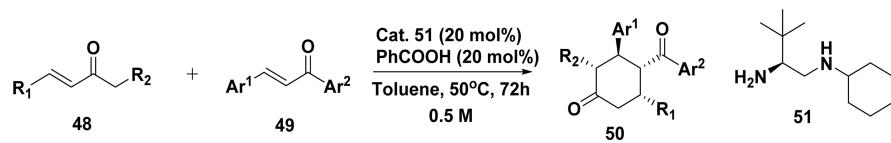
Condition I: Toluene, 50 °C; Condition II: DCM, rt, 4 Å molecular sieves

Scheme 19.

Asymmetric Oxa-Michael–Michael Addition of *trans*-Nitrostyrene (43) to 2-Hydroxychalcones

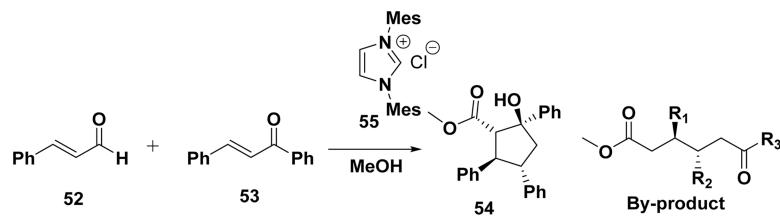
**Scheme 20.**

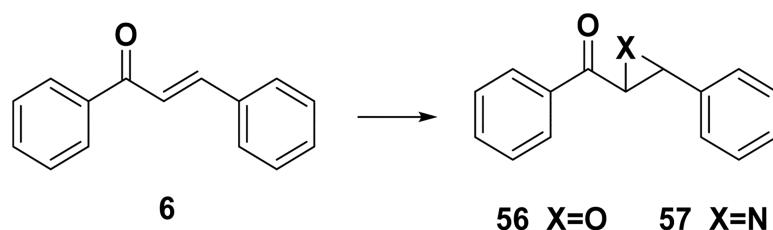
[2 + 2]-Cycloaddition of 2-Aminomalonates to Chalcones



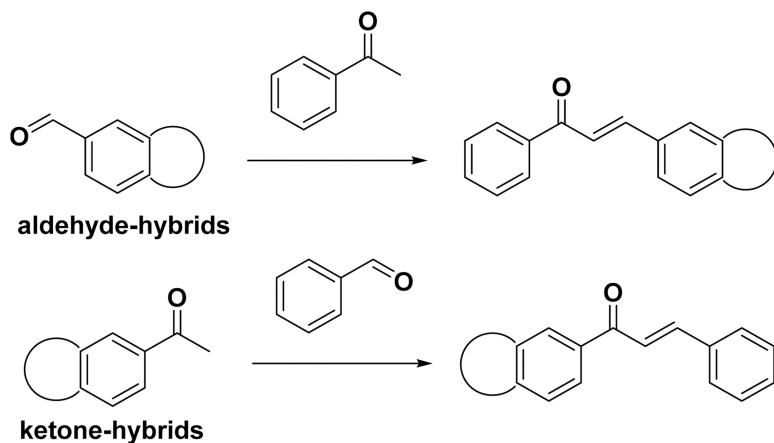
Scheme 21.

Enantioselective Cross-Reactions of Different Enones: Synthesis of Cyclohexanone

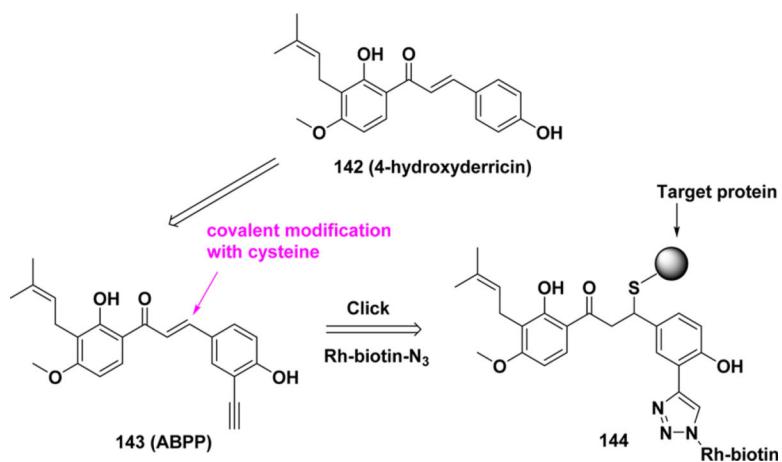
**Scheme 22.**Annulation of *p*-Methoxycinnamaldehyde with Chalcones



Scheme 23.
Epoxidation and Aziridination of Chalcones

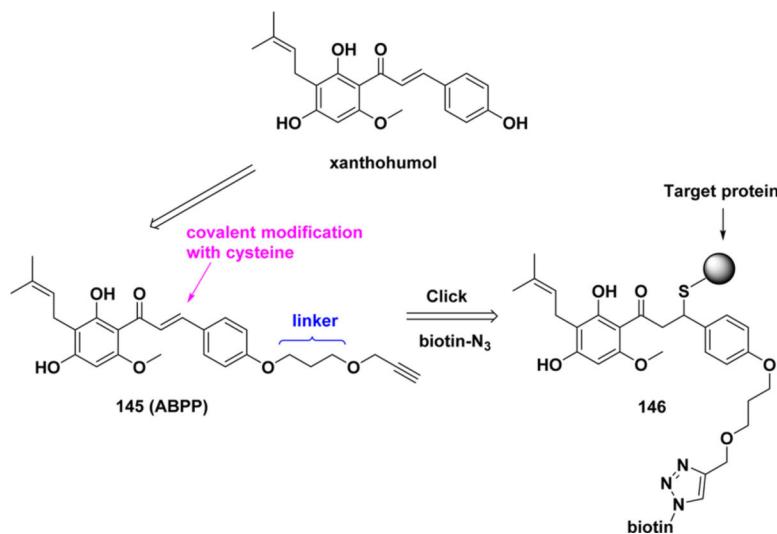


Scheme 24.
Synthetic Strategy of Fused Chalcone Hybrids



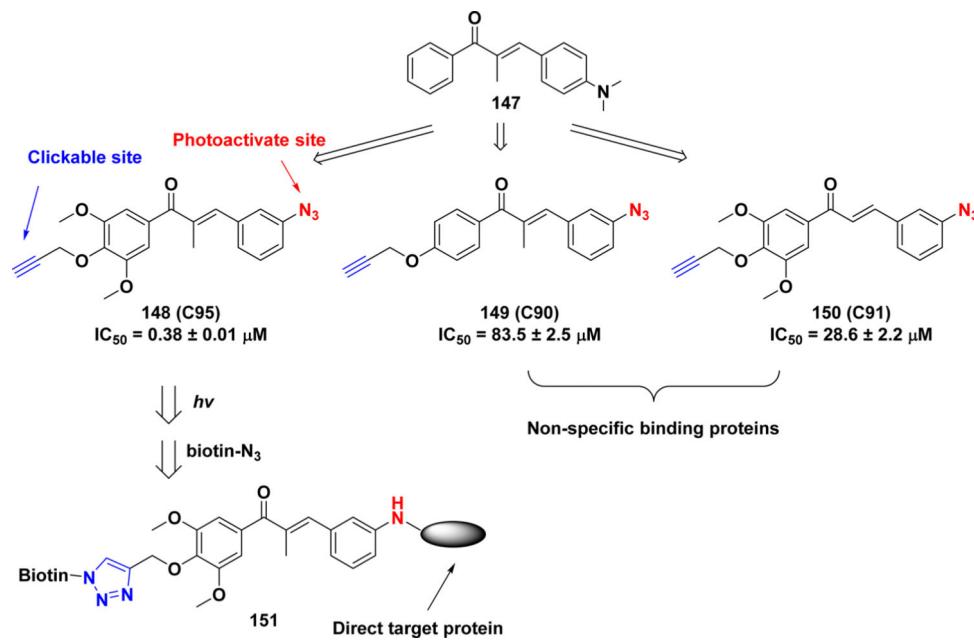
Scheme 25.

Structural Formula of 4-Hydroxyderricin and the ABPP

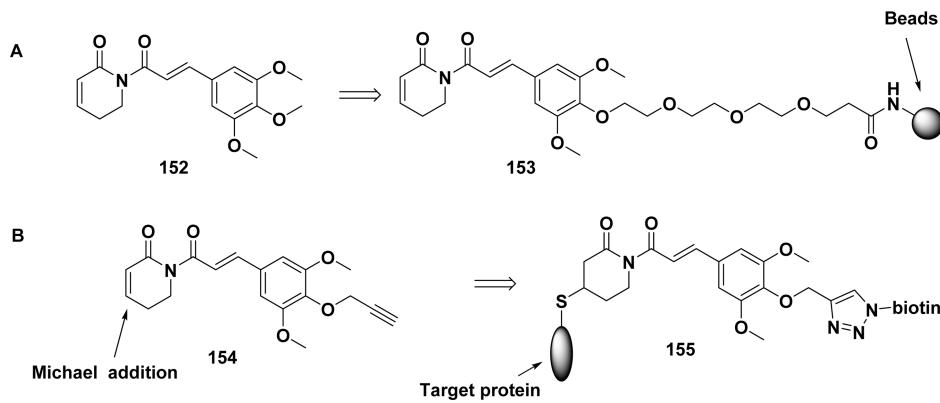


Scheme 26.

Structural Formula of Xanthohumol and the ABPP



Scheme 27.
Structural Formula of PAL Chalcones



Scheme 28.
Structural Formula of Piperlongumine and Proposed Strategy

Representative Chalcones from Natural Sources²⁷⁻⁶⁶**Table 1.**

Entry	Name	Structure	Activity	Natural Source
<i>Classical chalcones</i>				
1	isoliquiritinigen ²⁷⁻²⁹		Anti-cancer Cancer chemopreventive Anti-oxidant Anti-inflammation	<i>Nepalese propolis</i>
2	butein ^{30,31}		Anti-cancer Anti-inflammation	<i>Rhus verniciflua</i>
3	cardamonin ³²			<i>Piper aduncum L.</i>
4	sappanchalcone ^{33,34}			<i>Sappan Lignum</i>
5	3-deoxysappanchalcone ³³		Anti-inflammation	
6	isoavachalcone ^{35,36}		Anti-oxidant α -Glucosidase inhibitory activity Cancer chemopreventive Anti-cancer Anti-bacterial Anti-fungal	<i>Psoralea corylifolia (Leguminosae)</i> <i>Kadsura amanoana</i>
7	bavachalcone ³⁷		Anti-bacterial	<i>Psoralea corylifolia</i>
8	<i>a</i> _{jejuchalcone A} ³⁸			<i>Apis mellifera</i>
9	<i>a</i> _{jejuchalcone B} ³⁸		ND ^b	

Entry	Name	Structure	Activity	Natural Source
<i>Classical chalcones</i>				
10	<i>a</i> -jejuchalcone C ³⁸			
11	<i>a</i> -jejuchalcone D ³⁸			
12	<i>a</i> -jejuchalcone E ³⁸			
13	<i>a</i> -jejuchalcone F ³⁸			
14	<i>a</i> (\pm)-jejuchalcone G ³⁸		Cytotoxicity	<i>Machilus pomifera</i>
15	morachalcone A ³⁹			
16	broussochalcone A ⁴⁰		Protein kinase C inhibitor	<i>Broussonetia papyrifera</i>
17	xanthohumol ⁴¹⁻⁴³		Anti-HIV-1 Anti-bacterial Anti-cancer	<i>Hops Humulus lupulus/Angelica keiskei/Kaidzumi</i>
18	xanthoangelol ⁴⁴⁻⁴⁵		Anti-cancer	<i>Angelica keiskei/Poria coryli/olia</i>
19	gemichalcone C ⁴⁶		ND	<i>Hypericum geminiflorum</i>
20	isogemichalcones B ⁴⁷		Cytotoxicity	<i>Hypericum Geminiflorum</i>

Entry	Name	Structure	Activity	Natural Source
<i>Classical chalcones</i>				
21	isogemichalcones C ⁴⁸		Cytotoxicity	<i>Broussonetia papyrifera</i>
22	spinochalcone A ⁴⁹		Cytotoxicity	<i>Aeschynomene fascicularis</i>
23	spinochalcone C ⁴⁹		ND	<i>Aeschynomene fascicularis</i>
24	candidachalcone ⁵⁰		Estrogenic activity	<i>Tephrosia Candida</i>
25	4'-O-methylbavachalcone ³⁵		α -Glucosidase inhibitory activity	<i>Psoralea corylifolia</i>
26	isobavachromene ³⁵		α - Glucosidase inhibitory activity	<i>Psoralea corylifolia</i>
27	licochalcone A ^{51,52}		Anti-inflammation Anti-cancer	<i>Glycyrrhiza inflata</i>
28	oxyphyllumchalcone A ²⁶			
29	oxyphyllumchalcone B ²⁶		Cytotoxicity	<i>Desmodium oxyphyllum</i>

Entry	Name	Structure	Activity	Natural Source
<i>Classical chalcones</i>				
30	oxyphyllunchalcone c ²⁶			
31	pinostrobin chalcone ⁵³		Cytotoxicity	<i>Alpinia mutica</i>
32	<i>a</i> -millepachine ⁵⁴		Anticancer	<i>Millettia pachycarpa</i>
33	<i>a</i> , ⁴ , ² , ⁴ '-trihydroxy- ³ '-[^(2E,5E) -7-methoxy- ^{3,7} -dimethyl- ^{2,5} -octadienyl]- ² -octenyl]chalcone ⁵⁵			
34	<i>a</i> , ⁴ , ² , ⁴ ', ⁴ '-trihydroxy- ³ '-[^(2E) -6'-hydroxy- ⁷ -methoxy- ^{3,7} -dimethyl- ² -octenyl]chalcone ⁵⁵			
35	<i>a</i> , ⁴ , ² , ⁴ ', ⁴ '-trihydroxy- ³ '-[^(2E) -3'-methyl- ⁵ -(1,3-dioxolan-2-yl)- ² -pentenyl]chalcone ⁵⁵			<i>Angelica keiskei</i> <i>Koidzumi</i> (aerial parts)
36	<i>a</i> , ² ', ³ ', ⁴ '-furano-4-hydroxy- ⁴ '-methoxychalcone ⁵⁵			
37	<i>a</i> (^{\pm})-4-hydroxy- ² , ³ \pm- ^{(2,3} -dihydro- ² -methoxyfuran)- ⁴ \pm- ⁽² -methoxychalcone ⁵⁵			
38	<i>a</i> (⁻)-rubrichalcolactone ⁵⁶		ND	<i>Cryptocarya rubra</i>

Entry	Name	Structure	Activity	Natural Source
<i>Classical chalcones</i>				
39	rhuschalcone I ²³			
40	rhuschalcone III ²³		Cytotoxicity	<i>Rhus pyroides</i>
41	rhuschalcone IV ²³			
42	rhuschalcone V ²³			
43	verbenachalcone ⁵⁷		Enhancement of nerve growth factor-mediated neurite outgrowth	<i>Verbena littoralis</i>
44	^a heminchalcone A ²⁴			<i>Flemingia philippinensis</i>
45	^a heminchalcone B ²⁴		Tyrosinase inhibitor	

Entry	Name	Structure	Activity	Natural Source
<i>Classical chalcones</i>				
46	<i>a</i> -Flemiphilippone B ⁵⁸		Anti-proliferative activity Apoptosis-inducing property	<i>Flemingia philippinensis</i>
47	<i>a</i> -Flemiphilippone C ⁵⁸		Anti-proliferative activity Apoptosis-inducing property	<i>Flemingia philippinensis</i>
48	elastichalcone A ⁵⁹		ND	<i>Artocarpus elasticus</i>
49	elastichalcone B ⁵⁹		Free radical scavenging inhibitory activity	<i>Artocarpus elasticus</i>
50	elatadihydروchalcone ⁶⁰		Anti-plasmoidal	<i>Tephrosia elata</i>
51	chinendihydrochalcone ⁶¹		Anti-fungal and cytotoxicity	<i>Desmos chinensis</i> (stem barks)
<i>Chalcone mimics/Fused chalcones</i>				
52	<i>a</i> -cinnamoyl-4-hydroxy-3-methoxycyclohex-2-enone ⁶²		Nitric oxide production inhibitory activity	<i>Nepalese propolis</i>
53	schefflerichalcone ⁶³		Non-toxic	<i>Uvaria scheffleri</i>

Entry	Name	Structure	Activity	Natural Source
<i>Classical chalcones</i>				
54	^a tunicatachalcone ⁶⁴		ND	<i>Tephrosia tunicata</i> (roots)
55	^a kamalachalcone E ⁶⁵		Anti-fungal	<i>Mallotus philippensis</i>
56	^a oxyfadichalcone A ²⁶			
57	^a oxyfadichalcone B ²⁶		ND	<i>Oxytropis falcata</i>
58	^a oxyfadichalcone C ²⁶			
59	^a nardoaristolone A ⁶⁶		Protective effects on H2O2-induced myocardial injury	<i>Nardostachys chinensis</i>

^aFirst report of the isolation of chalcone from a natural source.

^bThe biological activities have not been determined in the references (ND = not determined).

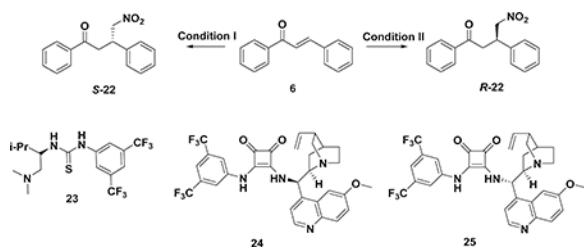
Table 2.

Cases of Claisen–Schmidt Condensation for the Synthesis of Chalcones

Entry	Catalyst	Solvent	Reaction	Ref
1	NaOH	ethanol		98
2	NaOH KOH	methanol ethanol		55,56,99
3	Piperazine	methanol ethanol		100
4	Ca(OH) ₂ Ba(OH) ₂ Sr(OH) ₂	aprotic solvent		101
5	LiHDMS	THF		102
6	NaNO ₃ (LiNO ₃)/natural phosphates	methanol		6,103
7	HCl	ethanol		107
8	AlCl ₃	carbon disulfide		107
9	BF ₃ –Et ₂ O	dioxane		105,110
10	SOCl ₂	ethanol		454
11	p-TsOH	acetic acid		109
12	NaOH	/		113
13	KF-Al ₂ O ₃	/		115
14	CaO	/		114
15	TBAB	inorganic alkaline solution		119
16	hydrotalcite	[dbmin]BF ₄		120

Table 3.

Michael Addition of Nitroalkanes to Chalcones



entry	condition I		condition II		ee (%)	yield (%)	ref
	catalyst	temp, time	catalyst	temp, time			
1	10 mol % cat. 23	50 °C, 72 h	—	—	95	100	195
2	—	—	10 mol % cat. 12	toluene, 25 °C, 110 h	96	94	194
3	10 mol % cat. 24	ClCH ₂ CH ₂ Cl, 80 °C, 72 h	—	—	94	97	196
4	—	—	5 mol % cat. 25	ClCH ₂ CH ₂ Cl, 80 °C, 72 h	95	99	196
5	—	—	100 mol % cat. per-6-ABCD	H ₂ O, room temp, 24 h	68.5	100	174

Table 4.

Asymmetric Epoxidation of Chalcones

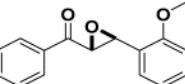
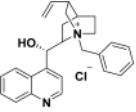
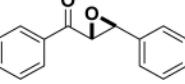
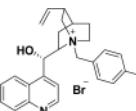
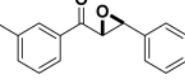
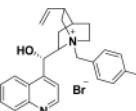
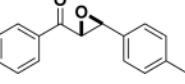
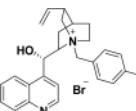
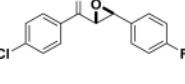
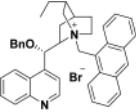
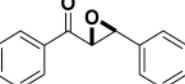
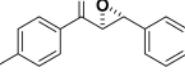
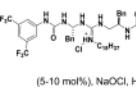
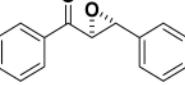
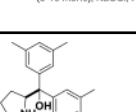
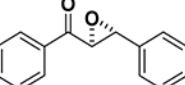
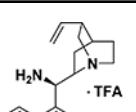
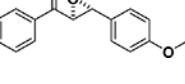
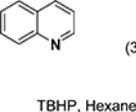
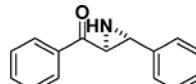
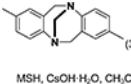
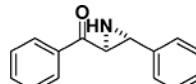
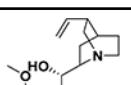
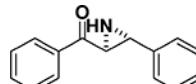
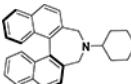
Entry	Structure	Catalyst/ Solvent	Yield %	<i>ee</i> (Major) %	Refs
1		 (2.5 mol%) NaOH, 30% H ₂ O ₂ , Toluene	/	25%	223
2		 (5 mol%)	97%	84%	
3		 (5 mol%)	100%	92%	224, 225
4		 (5 mol%)	95%	89%	
5		 (10 mol%) aq KOCl, Toluene, -40°C	94%	98.5%	226
6		Cat. 14 (3 mol%), aq NaOCl, Toluene, 0°C	99%	96%	227
7		 (5-10 mol%), NaOCl, H ₂ O ₂	99%	94%	228
8		 (10-30 mol%), TBHP	90%	91%	229
9		 (30 mol%)	75%	69.2%	
10		 TBHP, Hexane, rt	62%	84%	231

Table 5.

Asymmetric Aziridination of Chalcones

1		 (30-100 mol%) MSH, CsOH H ₂ O, CH ₃ CN, CH ₂ Cl ₂	90%	55%	237
2		 (105 mol%) DppONH ₂ , NaH, <i>i</i> -PrOH, CH ₂ Cl ₂	64%	55%	238
3		 (105 mol%) DppONH ₂ , NaH, CH ₂ Cl ₂	70%	37%	239