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Review

Bis-Chalcones: Recent Reports of Their Diverse Applications in Biological and Material Sciences

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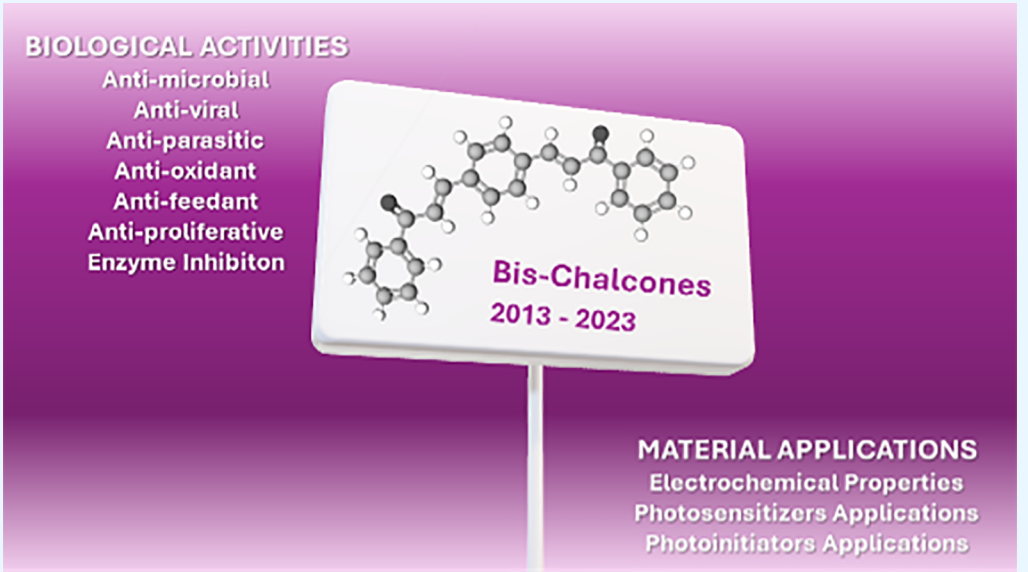

ABSTRACT: Originating from the basic chalcone structure, bis-chalcones are characterized by their dual α,β-unsaturated carbonyl systems and carry a range of biological activities that include antimicrobial, antiviral, antiparasitic, antioxidant, antiproliferative, and chemical reactivities that warrant a review to cover recent progress. Thus, this review presents the significant potential demonstrated by bis-chalcones in various biological applications. For example, compounds **2.3.1** showed excellent antiparasitic activity against leishmania with good selectivity index, and compounds **2.2.1**−**2.2.3** showed submicromolar activity against SupT1 cells. Compound **2.6.22** stood out in its antiproliferative activity against a panel of 60 different cell lines. Compounds **2.6.4** and **2.6.9** have been shown as submicromolar noncompetitive xanthine oxidase inhibitors. We also present their recent applications in material science, for example, as photosensitizers and photoinitiators, to showcase their broader potential for innovation in both medicinal chemistry and industrial applications.

1. INTRODUCTION

1.1. Background. The chalcone framework, consisting of an α, β-unsaturated carbonyl group with two aromatic rings[1] (Figure 1), is part of many naturally occurring secondary metabolites.[2] The framework has received significant attention in the organic and medicinal chemistry due to availability of various synthetic routes for their synthesis and diverse biological activities.[2−5]

Bis-chalcone is a distinct class of compounds containing two α,β-unsaturated carbonyl moieties compared to one such group in chalcones. These compounds have been gaining significant

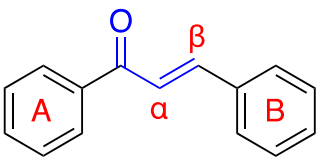

Figure 1. General structure of the chalcone.

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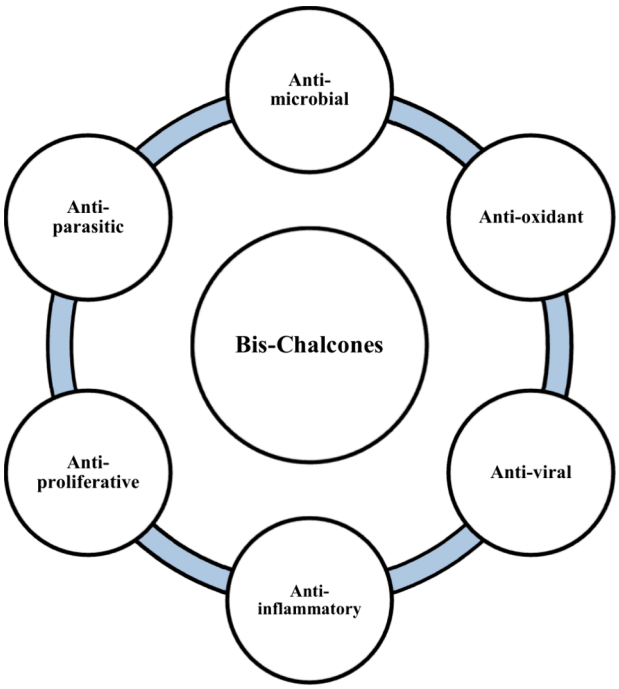

Figure 2. Biological properties of bis-chalcones.

attention in recent years due to their remarkably wide range of biological activities, including antioxidant properties,[6] anti-inflammatory,[7] antiproliferative,[8] anticancer,[9] antimicrobial,[10] antiparasitic,[11] and antifungal[10] activities (Figure 2). In materials sciences, bis-chalcones have carved a notable niche, owing to their multifaceted properties. Their application in 3D printing technologies,[12] as photoinitiators,[13] in electrochemistry,[14] their optical[15] properties, and fluorescence[16] has been gaining interest.

The broad spectrum of biological and material applications coupled with their adaptable chemical structure make bis-chalcones an interesting class to study. A detailed look into the recent reports can lead to identification of the opportunities that lie in the future for this scaffold for new therapeutics and applications. Thus, the present review is designed to offer a comprehensive outlook on the scaffold in both medicinal chemistry and materials science. This review focuses on bis-chalcones with general structures shown in Figure 3. During compilation of this review, we performed a literature search for published works between the year 2013 to 2023 using Google Scholar, and SciFinder. The search terms included "bis-chalcone", "bis-chalcone", "bischalcones", and "bichalcone" to obtain literature related to the promising therapeutic and material applications.

Table 1. Antimicrobial Activity of Bis-Chalcones 2.1.1−2.1.6 as Indicated by the Zone of Inhibition

	Zone of Inhibition (mm ± SD)			
	Antibacterial Activity			
Compounds	*E. coli*	*P. aeruginosa*	*S. aureus*	*S. enteritidis*
2.1.1	18.4 ± 0.1	19.8 ± 0.2	18.5 ± 0.1	18.2 ± 0.1
2.1.2	22.5 ± 0.2	19.1 ± 0.2	20.1 ± 0.3	19.0 ± 0.3
2.1.3	16.7 ± 0.3	14.7 ± 0.2	13.7 ± 0.1	15.4 ± 0.2
2.1.4	20.6 ± 0.3	20.1 ± 0.3	19.5 ± 0.2	18.6 ± 0.1
2.1.5	17.7 ± 0.3	16.9 ± 0.2	15.1 ± 0.2	16.0 ± 0.2
2.1.6	16.4 ± 0.1	15.0 ± 0.3	14.6 ± 0.3	17.4 ± 0.1

Table 2. Antimicrobial Activity of Bis-Chalcones 2.1.7−2.1.12 as Indicated by Zone of Inhibition

	Zone of Inhibition (mm)	
	Antibacterial Activity	
Compounds	*S. aureus*	*E. coli*
2.1.7	9	10
2.1.8	12	15
2.1.9	12	15
2.1.10	18	15
2.1.11	17	20
2.1.12	15	16
Ciprofloxacin	6.25	6.25
Quercetin	>100	>100

1.2. Synthesis of Bis-Chalcones. The synthetic strategies for producing bis-chalcones are based on the conventional approaches used to synthesize chalcones. Due to their novelty and increased complexity, bis-chalcones are often synthesized using the most reliable and straightforward procedures that were previously employed for chalcone synthesis. The synthetic routes used for the bis-chalcone synthesis have been nicely summarized by Pereira and co-workers.[17] Thus, we keep this section brief. Claisen−Schmidt condensation, Wittig reaction, Suzuki-coupling, and Mizoroki−Heck coupling reactions are the

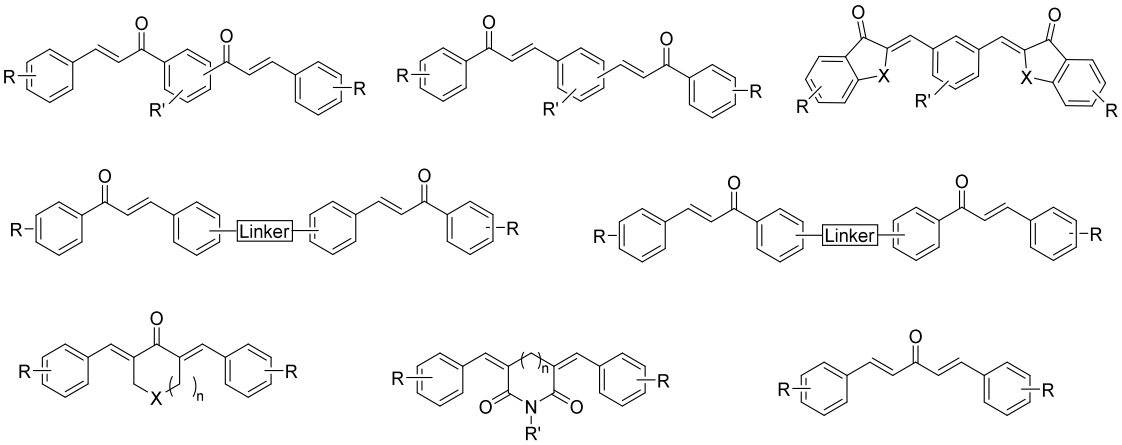

Figure 3. General structure of bis-chalcones covered in this article (X = CH_2, N, and O).

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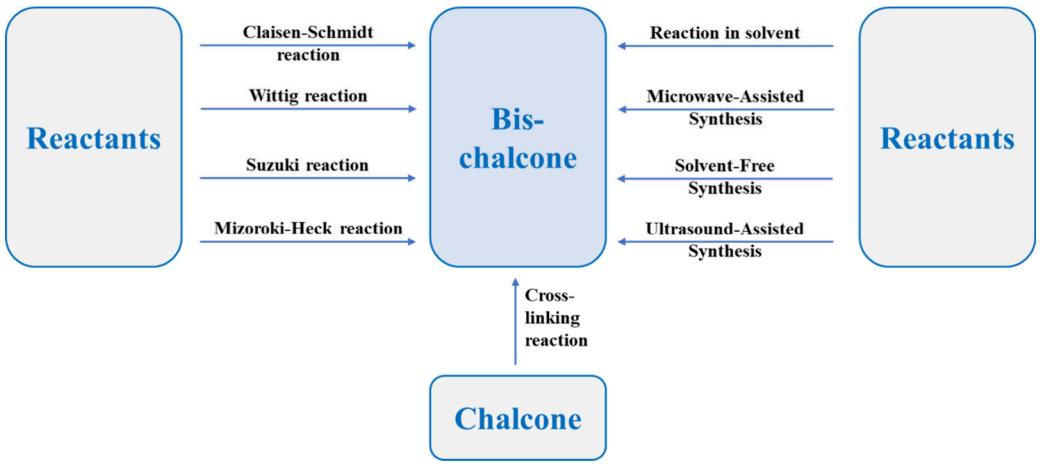

Figure 4. General routes and methods for bis-chalcone synthesis.

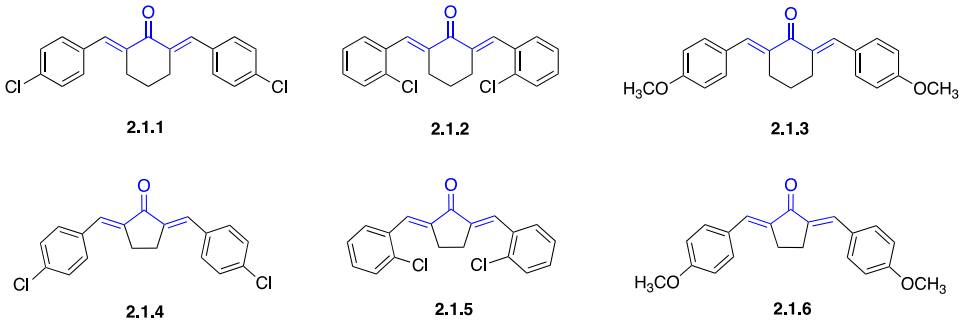

Figure 5. Series of bis-chalcones **2.1.1**−**2.1.6** tested by Kuttithodi et al. for antimicrobial activity.

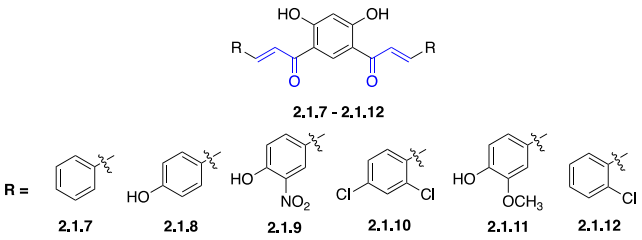

Figure 6. Chemical structures of bis-chalcones **2.1.7**−**2.1.12**.

Table 3. Antimicrobial Activity of Bis-Chalcones 2.1.13−2.1.18 as Indicated by Zone of Inhibition

	Zone of Inhibition (mm ± SD)			
	Antibacterial Activity[a]			Antifungal Activity[a]
Compounds	*S. aureus*	*E. coli*	*K. pneumonia*	*C. albicans*
2.1.13	12.3 ± 0.5	9 ± 0.1	NA	NA
2.1.14	NA	NA	NA	NA
2.1.15	NA	NA	NA	NA
2.1.16	15.6 ± 0.5	NA	NA	NA
2.1.17	NA	NA	NA	NA
2.1.18	NA	NA	NA	NA
Ampicillin	22 ± 0.1	-	-	-
Gentamicin	-	27 ± 0.5	25 ± 0.5	-
Amphotericin B	-	-	-	21 ± 0.5

[a]NA: non active.

common methods of the chalones synthesis, with Claisen−Schmidt condensation being the most commonly utilized synthetic route.[18,19] Linking the two individual chalcone units has also been reported in the literature.[20] The variations of the methods have included the use of Eaton's reagent as a catalyst,[21] solvent-free synthesis,[22−25] microwave-assisted synthesis,[26,27] and ultrasound-assisted synthesis[28,29] (Figure 4).

Table 4. Antimicrobial Activity of a Series of Bis-Chalcones (2.1.19−2.1.23) as Indicated by Zone of Inhibition

	Zone of Inhibition (mm)			
	Antibacterial Activity			
Compounds	*S. aureus*	*B. subtilis*	*E. coli*	*P. aeruginosa*
2.1.19	18	-	-	-
2.1.20	-	-	-	-
2.1.21	23	20	-	18
2.1.22	23	20	-	18
2.1.23	17	8	-	8
Gentamycin	23	20	22	21

2. BIOLOGICAL ACTIVITIES

2.1. Antimicrobial Activities. Kuttithodi et al.[30] prepared six bis-chalcones (Figure 5) through Claisen−Schmidt condensation. The antibacterial efficacy of the synthesized compounds was assessed against *E. coli*, *P. aeruginosa*, *S. aureus*, and *S. enteritidis* strains (Table 1) and the compounds showed good activity against the tested strains.

Alwan et al.[31] reported bis-chalcones synthesis by condensing diacetyl resorcinol (DAR) with different aldehydes in ethanol and NaOH (Figure 6). The compounds were examined for their antibacterial activity against *E. coli* and *S. aureus*. The data (Table 2) showed promising results for compounds **2.1.10** and **2.1.11**.

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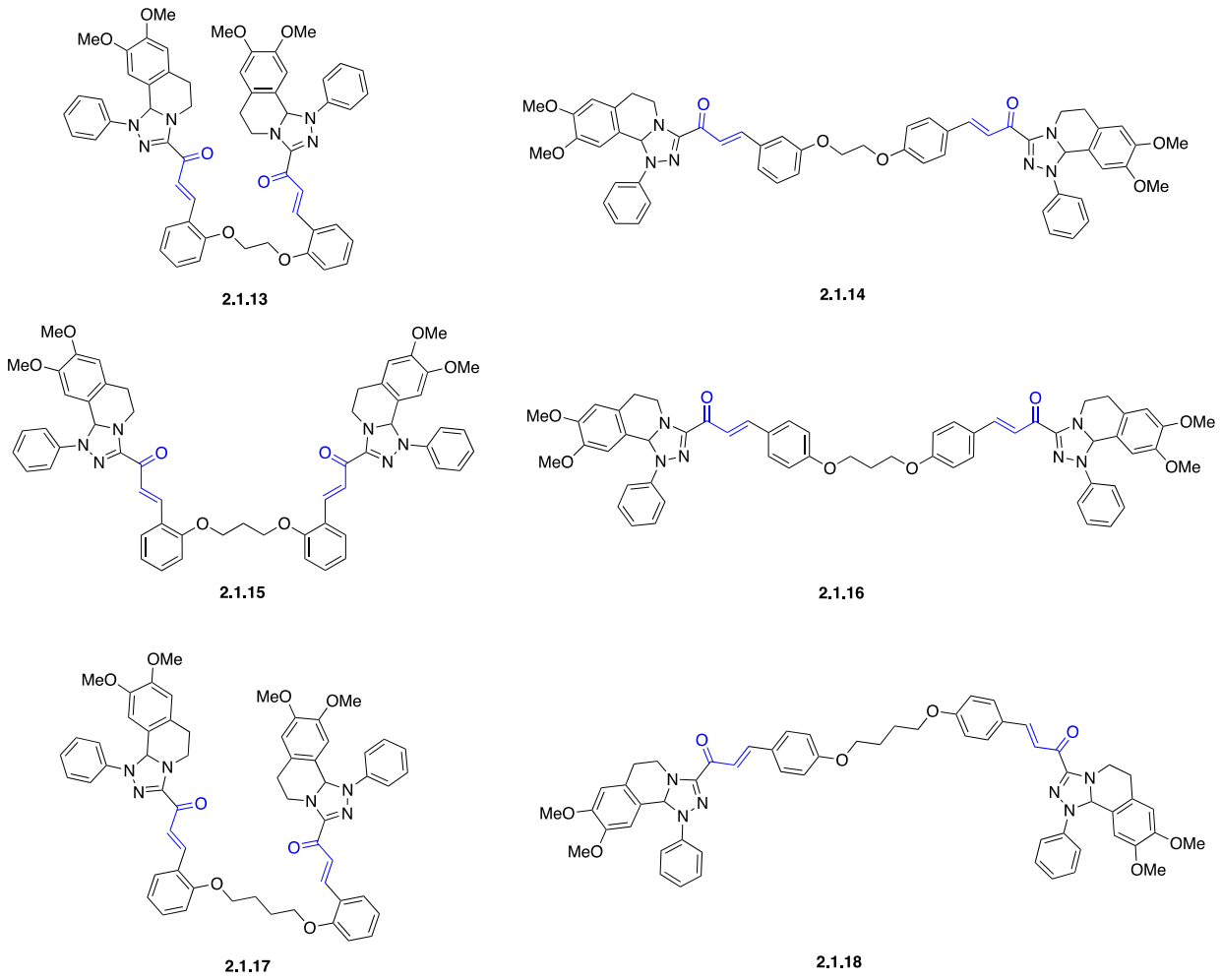

Figure 7. Chemical structures of bis-chalcones (**2.1.13**−**2.1.18**).

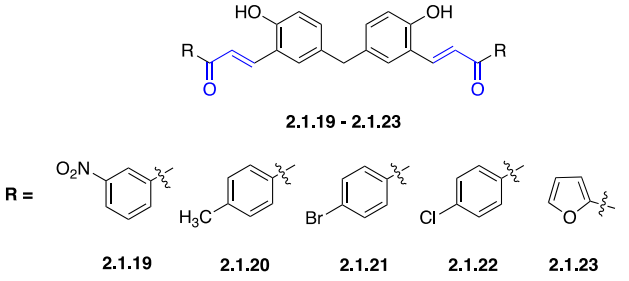

Figure 8. Series of bis-chalcones (**2.1.19**−**2.1.23**) tested by Tapeh et al. for antimicrobial activity.

Ibrahim et al.[32] reported the synthesis and antimicrobial properties of bis-chalcones containing [1,2,4]triazolo[3,4-*a*]-isoquinolines (Figure 7). Bis-chalcones were synthesized by reacting bis-aldehyde with [1,2,4] triazolo[3,4-*a*] isoquinoline in the presence of a KOH. The antibacterial activity of bis-chalcones was evaluated *in vitro* against *S. aureus*, *E. coli*, and *K. pneumonia* and antifungal activity was reported against *C. albicans* (Table 3). Bis-chalcones **2.1.13** and **2.1.16** exhibited good activity against *S. aureus*. Compound **2.1.13** was the only active compound against *E. coli*. These compounds did not show any activity against *K. pneumonia* and *C. albicans*.

Tala-Tapeh et al.[33] synthesized bis-chalcones **2.1.19**−**2.1.23** (Figure 8) via Claisen−Schmidt condensation of bis-aldehyde and various ketones in an alkaline solution. The antibacterial

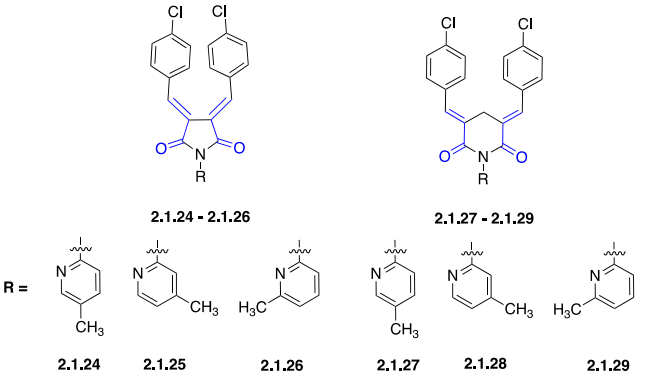

Figure 9. Series of bis-chalcones (**2.1.24**−**2.1.29**) tested by Chaudhari et al. for antimicrobial activity.

activity of bis-chalcones was reported against *S. aureus* and *B. subtilis*, and *E. coli* and *P. aeruginosa* (Table 4). Compounds **2.1.21** and **2.1.22** were the standout compounds in this analysis with good activities comparable to the control against *S. aureus, B. subtilis*, and *P. aeruginosa.* Considering the impact of halogen, it would be interesting to study these compounds with halogens at various positions and polyhalogenated compounds.

Chaudhari et al.[34] reported the synthesis of bis-chalcones (Figure 9) through the condensation of *N*-aryl succinimides and *p*-chlorobenzaldehyde in a neutral Al_2O_3 using microwave

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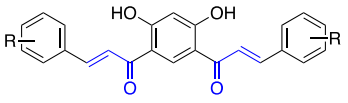
Table 5. Antimicrobial Activity of a Series of Bis-Chalcones (2.1.24−2.1.29) as Indicated by Zone of Inhibition

	Zone of Inhibition (mm ± SD)					
	Antibacterial Activity				Antifungal Activity	
Compounds	*S. aureus*	*B. subtilis*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*
2.1.24	15.92 ± 0.09	14.45 ± 0.10	25.99 ± 0.15	12.46 ± 0.09	20.10 ± 0.05	21.3 ± 0.13
2.1.25	-	7.90 ± 0.07	-	-	19.83 ± 0.16	20.3 ± 0.12
2.1.26	-	-	-	-	19.83 ± 0.05	20.2 ± 0.10
2.1.27	-	9.40 ± 0.04	-	-	20.27 ± 0.27	19.7 ± 0.17
2.1.28	-	8.69 ± 0.15	-	-	11.37 ± 0.34	10.2 ± 0.08
2.1.29	-	7.05 ± 0.05	-	-	20.14 ± 0.01	20.3 ± 0.07
Chloramphenicol	23.92 ± 0.17	28.43 ± 0.29	24.09 ± 0.10	14.39 ± 0.07	-	-
Amphotericin B	-	-	-	-	15.21 ± 0.15	11.8 ± 0.08

Table 6. Antimicrobial Activity of a Series of Bis-Chalcones (2.1.30−2.1.36) as Indicated by Zone of Inhibition[a]

	Minimum Inhibitory Concentration (mg/mL)				
	Antibacterial Activity			Antifungal Activity	
Compounds	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*
2.1.30	50	>100	50	50	>100
2.1.31	>100	-	50	50	>100
2.1.32	12.5	25	25	25	50
2.1.33	50	>100	>100	50	-
2.1.34	-	-	>100	>100	-
2.1.35	25	25	50	25	50
2.1.36	50	25	>100	50	>100
Ciprofloxacin	6.25	6.25	6.25	nt	nt
Griseofulvin	nt	nt	nt	6.25	6.25
Quercetin	>100	>100	nt	>100	nt

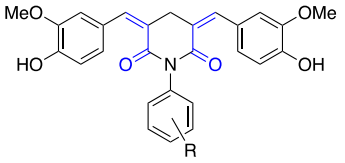
[a]"-" = insignificant activity; "nt" = not tested.



2.1.30 - 2.1.36

Compounds	R
2.1.30	4-Bromo
2.1.31	3-Nitro
2.1.32	2,6-Dichloro
2.1.33	2-Hydroxy
2.1.34	3-Methyl
2.1.35	4-Fluoro
2.1.36	4-Nitro

Figure 10. Series of bis-chalcones **2.1.30−2.1.36** tested by Husain et al. for antimicrobial activity.



2.1.37 - 2.1.46

Compounds	R
2.1.37	H
2.1.38	4-Br
2.1.39	4-Cl
2.1.40	4-CH_3
2.1.41	4-OMe
2.1.42	4-F
2.1.43	4-NO_2
2.1.44	Phenyl
2.1.45	3-Cl
2.1.46	2,4,5-Cl

Figure 11. Series of bis-chalcones **2.1.37−2.1.46** tested by Dhivare et al. for antimicrobial activity.

irradiation. The activity of these bis-chalcones was reported against Gram-positive bacteria *S. aureus* and *B. subtilis*, Gram-negative species *E. coli* and *P. aeruginosa* and fungi *C. albicans* and *A. niger* (Table 5). A subset of the compounds exhibited decent to good activity against Gram-positive bacteria and fungi. The study was limited to methyl pyridine and chlorophenyl derivatives and would have been interesting if other substitutions were also examined.

Husain et al.[35] synthesized bis-chalcones (Figure 10) through the condensation of 1,1′-(4,6-dihydroxy-1,3-phenylene)-diethanone with suitable aryl aldehydes using Claisen-Schmidt reaction conditions. The compounds were evaluated for their antibacterial activity against *S. aureus*, *E. coli*, and *P. aeruginosa* and for their antifungal activity against *C. albicans* and *A. niger* (Table 6). The bis-chalcones exhibited decent activity in antibacterial and antifungal assays, with compound **2.1.32** exhibiting better activity than the other derivatives.

Dhivare et al.[36] synthesized bis-chalcones (Figure 11) by combining *N*-phenyl glutarimide and 4-hydroxy-3-methoxy benzaldehyde by microwave assistance under solvent-free conditions. The compounds were then evaluated against *B. subtilis* and *E. coli* for Gram-positive and Gram-negative bacteria, respectively and were tested against *C. albicans* and *A. niger* strains for their antifungal properties (Table 7). Some of the compounds had decent antibacterial properties, and many showed good antifungal activities.

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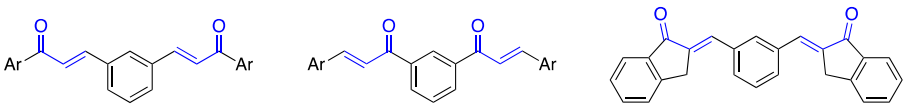
Table 7. Antimicrobial Activity of a Series of Bis-Chalcones 2.1.37−2.1.46 as Indicated by the Zone of Inhibition[a]

	Zone of Inhibition (mm ± SD)			
	Antibacterial Activity		Antifungal Activity	
Compounds	*B. subtilis*	*E. coli*	*C. albicans*	*A. niger*
2.1.37	-	-	16.31 ± 0.33	16.46 ± 0.27
2.1.38	-	2.33 ± 4.04	17.80 ± 0.16	17.36 ± 0.31
2.1.39	8.33 ± 0.57	8.33 ± 0.57	22.42 ± 0.39	21.69 ± 0.18
2.1.40	7.33 ± 0.57	4.66 ± 4.04	21.41 ± 0.25	19.50 ± 0.45
2.1.41	-	-	14.53 ± 0.41	16.56 ± 1.75
2.1.42	8.33 ± 0.57	8.33 ± 0.57	16.15 ± 0.22	18.57 ± 0.32
2.1.43	-	2.33 ± 4.04	20.43 ± 0.16	17.12 ± 0.12
2.1.44	-	-	19.04 ± 0.08	15.89 ± 1.72
2.1.45	-	-	17.71 ± 0.22	16.31 ± 0.22
2.1.46	7.66 ± 1.15	2.33 ± 4.04	19.94 ± 0.15	21.67 ± 0.48
Ampicillin	18.33 ± 0.57	18.33 ± 0.57	-	-
Amphotericin B	-	-	12.40 ± 0.43	10.45 ± 0.11

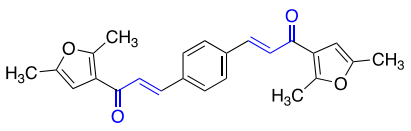
[a]"-" means no zone.



2.1.47 - 2.1.55 2.1.56 - 2.1.64 2.1.65

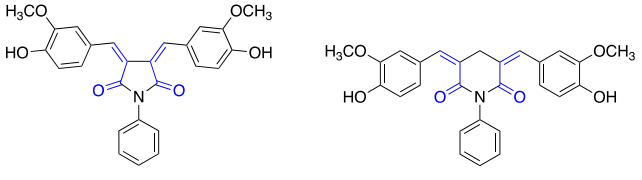
Compounds	R	Compounds	R
2.1.47	Phenyl	**2.1.56**	Phenyl
2.1.48	4-CH_3Ph	**2.1.57**	4-CH_3Ph
2.1.49	4-OCH_3Ph	**2.1.58**	4-OCH_3Ph
2.1.50	4-FPh	**2.1.59**	4-FPh
2.1.51	4-ClPh	**2.1.60**	4-ClPh
2.1.52	4-BrPh	**2.1.61**	4-BrPh
2.1.53	3,4-OCH_3Ph	**2.1.62**	3,4-OCH_3Ph
2.1.54	Furan-2-yl	**2.1.63**	Furan-2-yl
2.1.55	Thiophen-2-yl	**2.1.64**	Thiophen-2-yl

Figure 12. Series of bis-chalcones **2.1.47**−**2.1.65** tested by Tutar et al. for antimicrobial activity.



2.1.66

Figure 13. Chemical structure of bis-chalcone **2.1.66** tested by Asiri et al. for antimicrobial activity.



2.1.67 2.1.68

Figure 14. Chemical structures of bis-chalcones **2.1.67** and **2.1.68**.

Tutar et al.[37] synthesized 1,3-bis-chalcones (Figure 12) utilizing Claisen−Schmidt condensation and screened those for antibacterial and antifungal properties (Table 8). Many of these compounds showed activities that are comparable to those of the control for *B. subtilis* and *S. pyogenes*. However, the compounds were less active for the other tested organisms.

Asiri et al.[38] synthesized bis-chalcones by reacting 1-(2,5-dimethylfuran-3-yl)ethan-1-one with terephthalaldehyde under Claisen-Schmidt conditions. The antibacterial activity of **2.1.66** (Figure 13) was evaluated using the disc diffusion method on Gram-positive bacteria *S. aureus* (10.8 ± 0.3), *S. pyogenes* (10.2 ± 0.4) and Gram-negative bacteria *S. typhimurium* (10.6 ± 0.3) and *E. coli* (11.2 ± 0.4). Compound **2.1.66** displayed activities less than chloramphenicol but showed decent activity that shows the potential to further study this scaffold to develop a structure activity relationship.

Dhivarea et al.[39] reported the synthesis of bis-chalcones under solvent-free microwave conditions employing phenyl succinimide, glutarimide, and vanillin. The antibacterial activity of the compounds was assessed against the Gram-positive bacterium *B. subtilis* and the Gram-negative bacteria *E. coli*, and the antifungal activity was done against *C. albicans* and *A. niger* (Table 9). Compound **2.1.67** had better activity against *B. subtilis* and *E. coli*. In antifungal evaluation, bis-chalcones **2.1.67** showed activity comparable to that of the standard (Figure 14) against *C. albicans* and decent antibacterial activity. Compound **2.1.68**, on the other hand, showed slightly better antifungal activity as compared to the standard.

Nager et al.[40] reported the synthesis of two bis-chalcones compound **2.1.69** and its ruthenium III metal complex (**2.1.70**, Figure 15). The antifungal measurements showed that both compounds were potent against *F. equiseti* and enhanced the

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Table 8. Antimicrobial Activity of a Series of Bis-Chalcones 2.1.47−2.1.65

	Minimum Inhibitory Concentration (μg/mL)				
	Antibacterial Activity				Antifungal Activity
Compounds	*B. subtilis*	*S. pyogenes*	*P. aeruginosa*	*S. boydii*	*C. albicans*
2.1.47	100	200	200	400	400
2.1.48	100	400	400	400	400
2.1.49	100	400	400	400	400
2.1.50	100	200	400	400	400
2.1.51	400	200	200	200	200
2.1.52	400	50	200	200	400
2.1.53	100	100	200	400	200
2.1.54	200	50	200	200	200
2.1.55	100	100	200	400	100
2.1.56	100	200	400	200	400
2.1.57	100	400	400	400	400
2.1.58	200	400	400	400	400
2.1.59	200	400	400	400	200
2.1.60	200	50	200	400	200
2.1.61	100	50	200	400	200
2.1.62	200	100	200	200	200
2.1.63	100	100	400	200	100
2.1.64	100	50	200	400	200
2.1.65	100	100	200	400	200
P/T[a]	100	50	50	50	-
Fluconazole	-	-	-	-	12.5

[a]P/T: piperacillin/tazobactam (8:1).

Table 9. Antimicrobial Activity of Bis-Chalcones 2.1.67 and 2.1.68 as Indicated by the Zone of Inhibition

	Zone of Inhibition (mm ± SD)			
	Antibacterial Activity		Antifungal Activity	
Compounds	*B. subtilis*	*E. coli*	*C. albicans*	*A. niger*
2.1.67	8.33 ± 0.57	8.33 ± 0.57	11.94 ± 0.99	-
2.1.68	-	-	16.31 ± 0.33	16.46 ± 0.27
Ampicillin	24.33 ± 0.57	24.33 ± 0.57	-	-
Amphotericin B	-	-	12.40 ± 0.43	10.45 ± 0.11

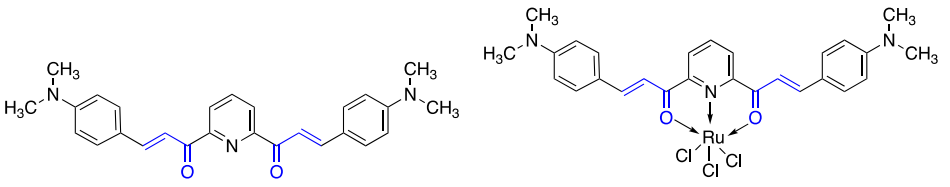

Figure 15. Chemical structures of bis-chalcones **2.1.69** and **2.1.70** and their antifungal activity against *F. equiseti* at 2 mM.

Table 10. Antimicrobial Activity of a Series of Bis-Chalcones 2.1.71−2.1.73

	Growth Inhibition (μg/mL)						
	Antibacterial Activity					Antifungal Activity	
Compounds	*S. Aureus*	*E. coli*	*K. pneumonia*	*P. aeruginosa*	*A. bacterbaumannii*	*C. lbicans*	*C. neoforman*
2.1.71	9.45	−0.75	2.79	1.40	40.56	7.25	−23.53
2.1.72	4.37	−4.51	−13.39	1.33	13.13	19.98	−8.44
2.1.73	10.87	1.55	16.16	6.80	5.80	11.79	3.00

vegetative growth of pepper plants, thus indicating a lack of phototoxicity in greenhouse conditions. Compound **2.1.69** completely inhibited the mycelial growth at 2 mM concentration followed by compound **2.1.70** (97.14%). The susceptibility of *F. equiseti* to **2.1.69** at 2 mM was equivalent to that of the positive control "Hattrick" at this dose.

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Table 11. Anti-biofilm Activity[a] of a Series of Bis-Chalcones 2.1.47−2.1.65

	Microorganism (μM ± SD)				
Compounds	*B. subtilis*	*S. pyogenes*	*P. aeruginosa*	*S. boydii*	*C. albicans*
2.1.47	90.6 ± 1.2	90.1 ± 0.4	28.9 ± 2.6	71.5 ± 0.5	32.5 ± 0.8
2.1.48	76.8 ± 4.9	90.7 ± 0.2	52.7 ± 0.2	80.7 ± 0.6	81.3 ± 0.7
2.1.49	93.6 ± 1.5	90.1 ± 0.4	77.9 ± 0.7	83.9 ± 0.2	71.5 ± 0.4
2.1.50	93.2 ± 1.3	81.9 ± 1.1	67.4 ± 1.1	85.7 ± 0.8	82.1 ± 0.6
2.1.51	96.2 ± 0.9	94.5 ± 0.1	67.6 ± 0.1	97.0 ± 0.6	95.1 ± 0.2
2.1.52	97.5 ± 0.3	76.6 ± 0.3	72.1 ± 0.5	96.4 ± 0.6	93.4 ± 0.2
2.1.53	93.8 ± 0.4	89.4 ± 0.4	78.3 ± 0.6	96.8 ± 0.3	93.2 ± 0.2
2.1.54	92.2 ± 0.2	90.8 ± 0.5	47.2 ± 0.3	86.3 ± 0.5	89.3 ± 0.1
2.1.55	94.1 ± 0.1	89.5 ± 0.8	70.9 ± 0.2	97.1 ± 0.2	46.9 ± 0.4
2.1.56	81.5 ± 2.5	83.7 ± 0.5	64.7 ± 1.2	87.4 ± 0.2	70.5 ± 0.4
2.1.57	88.3 ± 0.7	76.5 ± 0.3	2.7 ± 4.5	71.9 ± 1.2	0.5 ± 18.3
2.1.58	71.4 ± 3.3	81.4 ± 1.5	81.8 ± 0.3	55.1 ± 0.3	73.4 ± 1.8
2.1.59	84.7 ± 0.6	84.5 ± 0.3	24.8 ± 46.7	42.6 ± 0.7	83.4 ± 1.6
2.1.60	94.2 ± 0.2	87.4 ± 0.5	75.6 ± 0.4	97.1 ± 0.2	92.5 ± 0.3
2.1.61	95.6 ± 0.1	88.0 ± 0.3	86.0 ± 0.3	97.1 ± 0.2	89.6 ± 0.2
2.1.62	71.3 ± 2.4	46.9 ± 16.6	80.2 ± 1.2	60.8 ± 2.0	78.4 ± 0.4
2.1.63	93.7 ± 0.1	92.7 ± 0.5	80.3 ± 0.2	92.3 ± 0.2	89.0 ± 0.1
2.1.64	89.4 ± 0.1	46.0 ± 0.3	82.7 ± 0.6	96.8 ± 0.1	87.4 ± 0.2
2.1.65	89.4 ± 0.1	52.2 ± 0.4	79.8 ± 0.6	96.8 ± 0.3	89.8 ± 0.2

[a]Reduction in biofilm formation on MIC value (%)

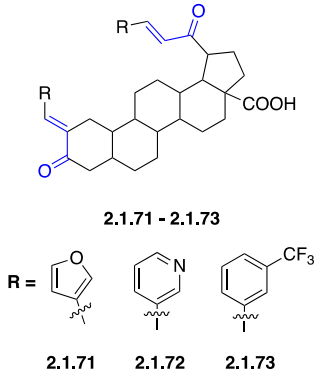
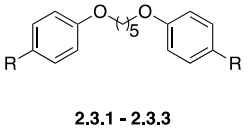


Figure 16. Series of bis-chalcones **2.1.71−2.1.73** tested by Khusnutdinova et al. for antimicrobial activity.

Khusnutdinova et al.[41] prepared the bis-chalcones (Figure 16), which were assessed against five bacterial strains, including Gram-negative *E. coli, K. pneumonia, A. baumannii,* and *P. aeruginosa,* and Gram-positive methicillin-resistant *S. aureus.* The fungicidal activity was assessed for *C. albicans* and *C.*

Table 12. Antiviral Activity of Bis-chalcone 2.1.72

	In Vitro Antiviral Activity				
	Human Cytomegalovirus (HCMV) (μM)				
Compounds	EC_{50}	EC_{90}	CC_{50}	SI_{50}	SI_{90}
2.1.72	>0.24	>0.24	0.86	<4	<4
Ganciclovir	0.40	0.88	>150.00	>377	>170



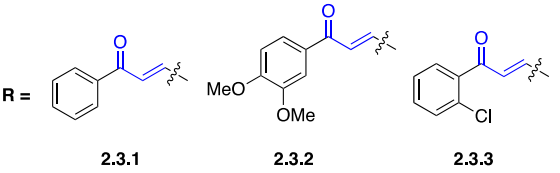


Figure 18. Series of bis-chalcones **2.3.1−2.3.3** tested by Tyagi et al. for antiparasitic activity.

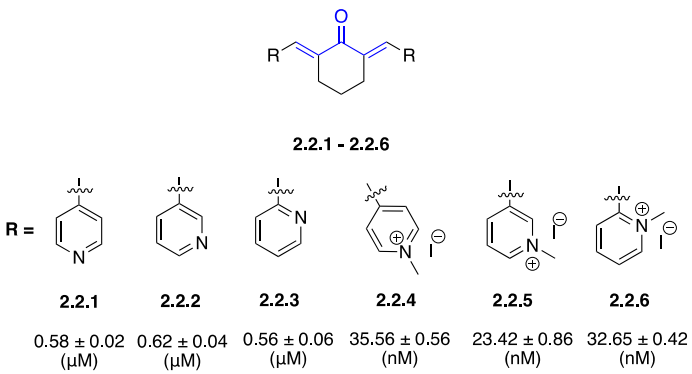


Figure 17. Series of bis-chalcones **2.2.1−2.2.6** tested by Kammari et al. for antiviral activity.

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Table 13. Anti-parasitic Activity[a] of a Series of Bis-Chalcones 2.3.1−2.3.3

Antileishmanial Activity			
Compounds	Antiamastigote activity IC_{50} (μM)	Cytotoxicity CC_{50} (μM)	Selectivity index (SI)
2.3.1	1.65	>400	>242.42
2.3.2	NI	ND	ND
2.3.3	NA	NA	NA
Pentamidine	20.43	52.70	2.58
Sodium stibo-gluconate	71.90	397.60	5.53
Miltefosine	12.5	3.2	0.25

[a]Selectivity index (SI) defined by the ratio CC_{50} (in KB cell lines)/IC_{50} (Intracellular leishmania amastigotes). "NI" no inhibition, "ND" not determine, "NA" not available.

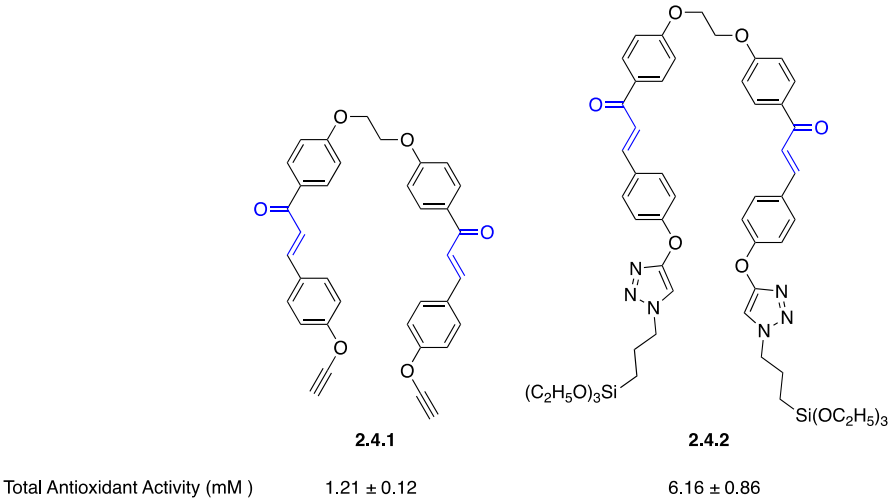
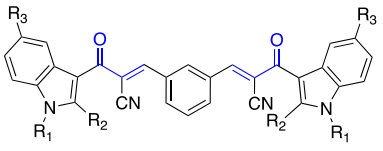


Figure 19. Chemical structures of bis-chalcones **2.4.1** and **2.4.2** tested by Singh et al. for antioxidant activity.



2.4.3 - 2.4.14

Compounds	R_1	R_2	R_3
2.4.3	H	H	H
2.4.4	H	CH_3	H
2.4.5	H	H	Br
2.4.6	H	H	OCH_3
2.4.7	H	H	CN
2.4.8	H	H	NO_2
2.4.9	CH_3	H	H
2.4.10	CH_3	CH_3	H
2.4.11	CH_3	H	Br
2.4.12	CH_3	H	OCH_3
2.4.13	CH_3	H	CN
2.4.14	CH_3	H	NO_2

Figure 20. Series of bis-chalcones **2.4.3**−**2.4.14** tested by Bhale et al. for antioxidant activity.

neoformans. However, these compounds did not show any significant potential in the assay (Table 10).

Tutar et al.[37] investigated the antibiofilm properties of several bis-chalcones (Figure 12) against *B. subtilis, S. pyogenes, P. aeruginosa, S. boydii*, and *C. albicans* using the microtiter plate method. Bis-chalcones inhibited the biofilm of *B. subtilis, S. pyogenes, P. aeruginosa, S. boydii*, and *C. albicans* at minimum inhibitory concentration (MIC) values ranging from 71.3 to 97.5 μM, 46.0 to 94.5 μM, 2.7 to 86.0 μM, 42.6 to 97.1 μM, and 0.5 to 95.1 μM, respectively (Table 11).

Table 14. Anti-parasitic Activity of a Series of Bis-Chalcones 2.1.1−2.1.6

Larvicidal Activity	
Compounds	LC_{50} (μg/mL)
2.1.1	45.27 ± 2.34
2.1.2	59.81 ± 2.09
2.1.3	99.04 ± 2.18
2.1.4	56.46 ± 3.07
2.1.5	89.22 ± 3.12
2.1.6	79.18 ± 2.69

2.2. Antiviral Activities. Khusnutdinova et al.[41] also tested bis-chalcones (Figure 16) for their antiviral activity against HCMV. Compound **2.1.72** exhibited activity against HCMV, with an EC_{50} value more than 0.24 μM and a SI_{50} value less than 4 (Table 12).

Kammari et al.[42] reported the anti-HIV activities of the various derivatives of bis-chalcone shown in Figure 17. These compounds showed a dose-dependent response to inhibiting HIV-1 replication. Water-soluble **2.2.4**−**2.2.6** had nanomolar activities and these compounds were more active than the DMSO-soluble compounds **2.2.1**−**2.2.3**. The study also demonstrated a strong correlation between the inhibition of TopoIIβKHIV-1 and its effectiveness against HIV-1.

2.3. Anti-parasitic Activities. Tyagi et al.[11] synthesized a series of new bis-chalcones (Figure 18) and assessed them for their capacity to inhibit the growth of leishmania parasites

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Table 15. Antioxidant Activity of a Series of Bis-chalcones 2.1.1−2.1.6

	Antioxidant Activity			
Compounds	DPPH (IC_{50} μg/mL)	ABTS (IC_{50} μg/mL)	Nitric oxide (IC_{50} μg/mL)	FRAP (EC_{50} μg/mL)
2.1.1	18.41 ± 1.45	18.63 ± 1.41	28.87 ± 1.49	1.35 ± 0.10
2.1.2	19.92 ± 1.52	21.57 ± 1.55	26.04 ± 1.61	5.24 ± 0.21
2.1.3	27.75 ± 2.50	26.47 ± 1.42	34.30 ± 2.55	12.40 ± 0.20
2.1.4	25.42 ± 1.39	22.18 ± 1.29	29.15 ± 1.72	4.34 ± 0.11
2.1.5	36.49 ± 1.55	42.10 ± 2.27	45.67 ± 3.04	15.61 ± 0.30
2.1.6	35.47 ± 1.64	46.17 ± 3.23	49.09 ± 3.11	16.20 ± 0.24

Table 16. Antioxidant Activity of a Series of Bis-Chalcones 2.4.3−2.4.14

	Antioxidant Activity			
	%age inhibition at 1 mM			
Compounds	DPPH	NO	SOR	H_2O_2
2.4.3	50.04	62.64	80.16	66.11
2.4.4	41.10	59.97	88.08	71.00
2.4.5	46.90	44.18	60.55	69.05
2.4.6	51.09	63.11	79.12	56.00
2.4.7	37.90	59.25	54.99	59.12
2.4.8	31.32	51.11	54.00	80.13
2.4.9	30.11	42.67	81.40	71.14
2.4.10	27.18	36.01	85.92	73.23
2.4.11	29.13	37.17	43.14	64.57
2.4.12	30.09	34.43	54.21	60.16
2.4.13	12.72	40.00	65.12	56.98
2.4.14	17.43	41.30	43.43	63.19
AA	40.78	42.63	87.05	79.42

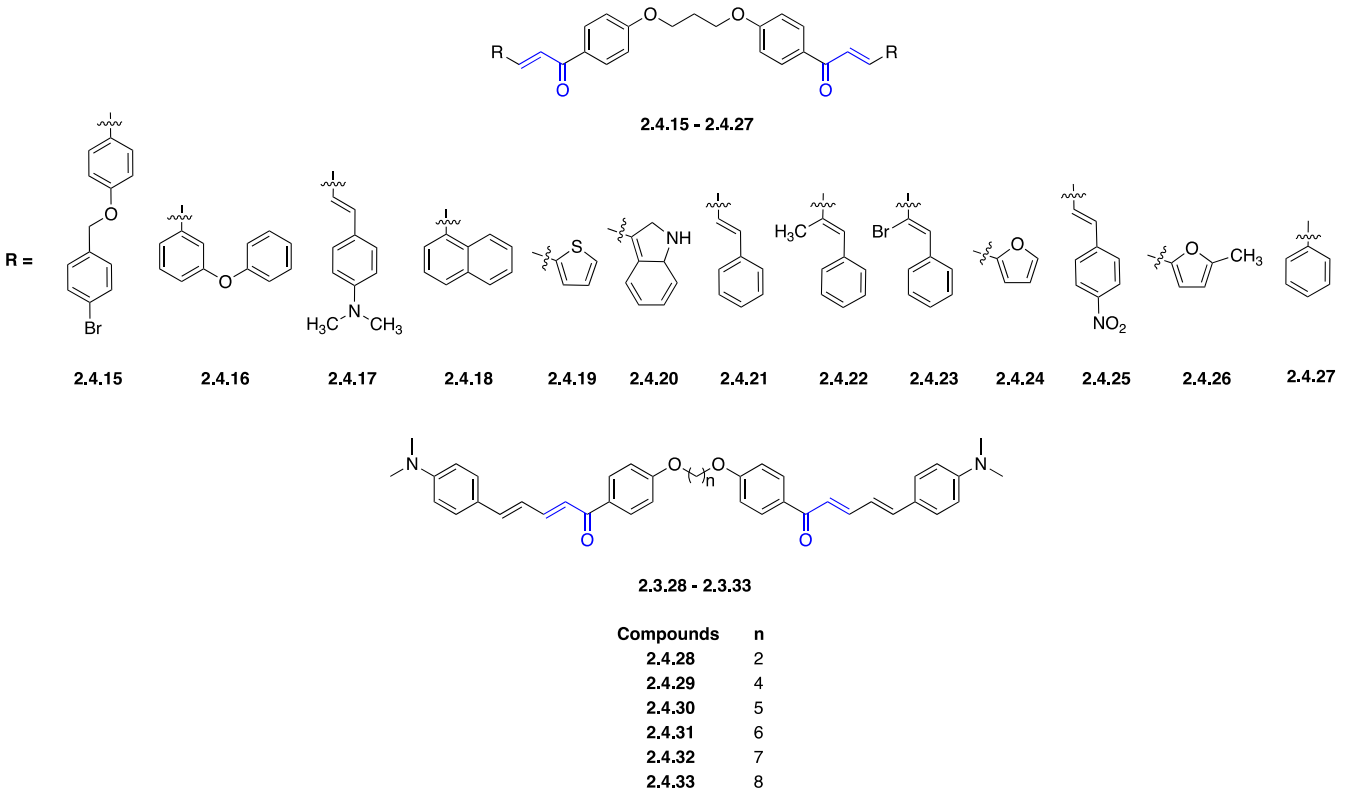

Figure 21. Series of bis-chalcones **2.4.15−2.4.33** tested by Liargkova et al. for antioxidant activity.

(Table 13). Compound **2.3.1** exhibited the best activity and selectivity index compared with the other bis-chalcones and standard compounds.

Kuttithodi et al.[30] also analyzed bis-chalcones (Figure 5) for larvicidal activities (Table 14). Compounds **2.1.1**, **2.1.2**, and

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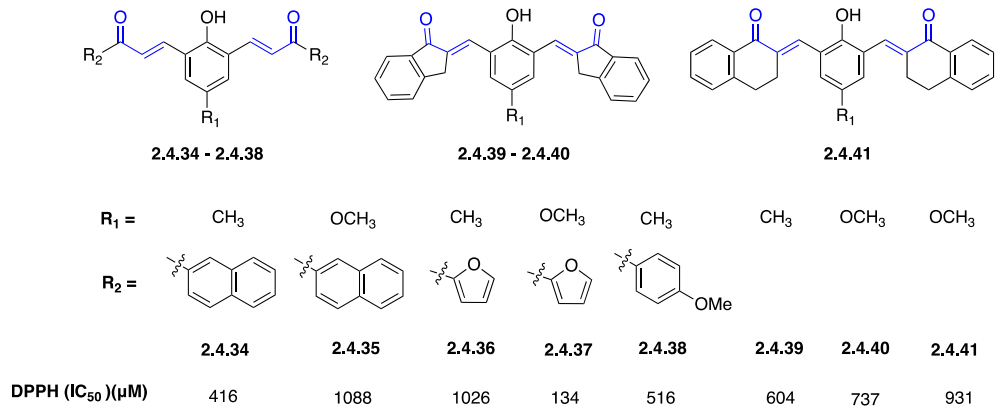


Figure 22. Structure and antioxidant activity of bis-chalcones **2.4.34**−**2.4.41**.

Table 17. Antioxidant Activity of Bis-Chalcones 2.1.69 and 2.1.70

Antioxidant Activity	
Compounds	DPPH (means ± SD)
2.1.69	51.91 ± 5.19%
2.1.70	72.62 ± 3.63%
Hattrick	6.23 ± 0.68%

Table 18. Antioxidant Activity[a] of a Series of Bis-Chalcones 2.4.15−**2.4.33**

Antioxidant Activity					
Compounds	Reducing Activity% 100 μM 20 min	Reducing Activity% 100 μM 60 min	ABTS• + Inhb. % @100 μM	AAPH% @100 μM	% Inhb. of Liposomes @100 μM
2.4.15	36	55	No	42	Nt
2.4.16	No	8	No	22	2
2.4.17	17	14	99	70	81
2.4.18	19	50	No	95	3
2.4.19	No	No	No	46	Nt
2.4.20	No	No	No	100	Nt
2.4.21	No	No	No	82	Nt
2.4.22	No	No	No	75	Nt
2.4.23	No	No	No	32	Nt
2.4.24	No	No	11	77	Nt
2.4.25	No	No	No	68	Nt
2.4.26	No	No	17	68	74
2.4.27	No	No	No	71	Nt
2.4.28	No	No	98	71	4
2.4.29	No	No	No	47	Nt
2.4.30	No	No	73	72	77
2.4.31	No	No	25	14	Nt
2.4.32	No	No	79	64	64
2.4.33	No	No	88	6	Nt
Trolox	Nt	Nt	96	93	69
Tacrine	Nt	Nt	88	Nt	Nt
NDGA	81	83	Nt	Nt	Nt

[a]"No" no activity under the reported experimental conditions. Means within each column differ significantly ($p < 0.05$); "Nt" not tested.

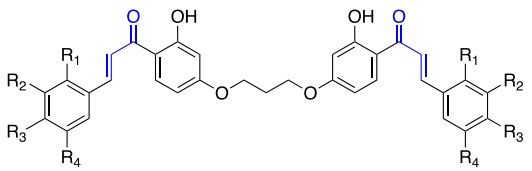
2.1.4 exhibited a more potent larvicidal effect among the synthesized bis-chalcones.

2.4. Antioxidant Activities. Singh et al.[43] reported the synthesis of a series of novel acetylenic bis-chalcones and chalcone functionalized 1,2,3-triazole allied bis-organosilanes through aldol condensation, followed by Cu(I) catalyzed click method. The compounds were examined by using a colorimetric technique. The TAA analysis demonstrated that both alkyne **2.4.1** and bis-organosilane **2.4.2** (Figure 19) exhibited antioxidant activity. The activity was attributed to the presence of a biologically active chalconyl bond, alkynyl moiety, and triazole rings in the compound. The bis-organosilane **2.4.2** showed better antioxidant activity compared to alkyne **2.4.1** and standard ascorbic acid (1.00 mM).

Kuttithodi et al.[30] also tested the bis-chalcones (Figure 5) for the antioxidant activity using FRAP assay and antiradical properties using DPPH, ABTS, and nitric oxide (Table 15). The bis-chalcones showed good antioxidant activity, particularly compound **2.1.1** and compound **2.1.2** exhibited better

Table 19. Anti-feedant Activity Bis-Chalcones 2.5.1−**2.5.8**

Anti-feedant Activity				
Compounds	FR_{50} Mean ± SD	Larval mortality (%)	Pupal mortality (%)	Malformed adults (%)
2.5.1	1.05 ± 0.13	20	15	75
2.5.2	0.93 ± 0.20	85	5	10
2.5.3	0.91 ± 0.18	40	20	40
2.5.4	1.06 ± 0.10	15	15	70
2.5.5	0.98 ± 0.13	60	10	30
2.5.6	0.93 ± 0.20	60	5	35
2.5.7	0.89 ± 0.16	55	20	25
2.5.8	0.91 ± 0.18	60	20	20



Compounds	R_1	R_2	R_3	R_4
2.5.1	Br	H	H	H
2.5.2	H	OH	H	H
2.5.3	H	Br	H	H
2.5.4	F	H	H	H
2.5.5	H	H	Br	H
2.5.6	H	H	OCH_3	H
2.5.7	H	OCH_3	OCH_3	OCH_3
2.5.8	H	F	H	H

Figure 23. Series of bis-chalcones **2.5.1**−**2.5.8** tested by Devi et al. for antifeedant activity.

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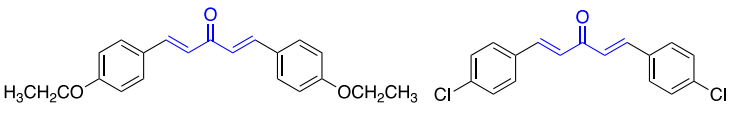
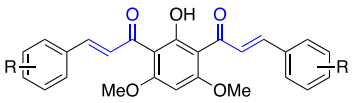


	2.6.1	2.6.2
Anti-Proliferative Activity HCT-116 cells (10 μM)	8.21 ± 4.32	85.03 ± 0.57

Figure 24. Chemical structures of bis-chalcones **2.6.1** and **2.6.2** tested by Oliveira et al. for antiproliferative activity.



2.6.3 - 2.6.10

Compounds	R
2.6.3	H
2.6.4	2-F
2.6.5	3-F
2.6.6	4-F
2.6.7	2,3-diF
2.6.8	2,4-diF
2.6.9	2,5-diF
2.6.10	3,4-diF

Figure 25. Series of bis-chalcones **2.6.3**−**2.6.10** tested by Burmaoglu et al. for antiproliferative activity.

Table 20. Anti-proliferative Activity of Bis-Chalcones 2.6.3−**2.6.10**

Anti-proliferative Activity		
Compounds	MCF-7 (IC_{50}) (μM)	Caco-2 (IC_{50}) (μM)
2.6.3	4.9	14.5
2.6.4	4.9	9.6
2.6.5	10.3	12.6
2.6.6	16.9	21.1
2.6.7	103.7	92.3
2.6.8	12.4	12.0
2.6.9	1.9	7.3
2.6.10	15.5	6.8
Cisplatin	139.7	102.0

Table 21. Anti-proliferative Activity of a Series of Bis-Chalcones 2.2.1−**2.2.6**

Anti-proliferative Activity	
Compounds	CC_{50} (Mean ± SD)
2.2.1	0.82 ± 0.044 μM
2.2.2	0.96 ± 0.032 μM
2.2.3	0.92 ± 0.056 μM
2.2.4	2.02 ± 0.068 mM
2.2.5	2.12 ± 0.086 mM
2.2.6	2.04 ± 0.042 mM
3-Phenylpyridine (control)	1.50 ± 0.029 mM

Table 22. Anti-proliferative Activity of a Series of Bis-Chalcones 2.1.13−**2.1.16**

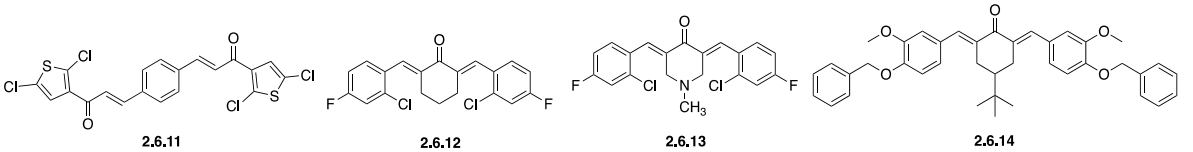
Anti-proliferative Activity				
	HCT116		HEPG2	
Compounds	% inhibition (100 μg/mL)	%inhibition (50 μg/mL)	%inhibition (100 μg/mL)	% inhibition (50 μg/mL)
2.1.13	43.49	25.65	44.13	33.15
2.1.14	11.6	10.2	24.5	0
2.1.15	34.12	0	32.46	7.9
2.1.16	75	33.9	71	12
2.1.17	27.2	25.2	48	13.01
2.1.18	68.4	67.45	32.67	29.1
Doxorubicin IC_{50} (μM)	22 ± 3.1		0.6 ± 0.1	

Table 23. Anti-proliferative Activity of a Series of Bis-Chalcones 2.1.7−**2.1.12**

Anti-proliferative Activity	
Compounds	IC_{50} (μg/mL)
2.1.7	1329.049
2.1.8	972.1166
2.1.9	933.6702
2.1.10	644.3925
2.1.11	-
2.1.12	1022.727

scavenging capabilities in DPPH, nitric oxide, and ABTS assays. Additionally, compound **2.1.1** stood out in the FRAP assay.

Bhale et al.[44] prepared new bis-chalcones (Figure 20) and evaluated their antioxidant activities to scavenge different reactive oxygen and nitrogen species, including DPPH, NO, SOR, and H_2O_2 radicals (Table 16). Most of the bis-chalcones showed decent to good antioxidant activity against DPPH and NO radicals. They also showed very good activity against SOR and H_2O_2 radicals. Compounds **2.4.3**, **2.4.4**, **2.4.5**, and **2.4.6** exhibited better DPPH free radical scavenging activity in comparison to the standard (ascorbic acid). Compounds **2.4.3**−**2.4.9** exhibited better NO free radical scavenging ability in comparison to that of the standard ascorbic acid. Compound **2.4.4** showed activity against the SOR radical that was comparable to the reference ascorbic acid. Compound **2.4.8** was comparable to the standard in scavenging H_2O_2 radicals.



	2.6.11	2.6.12	2.6.13	2.6.14
Anti-Proliferative Activity MCF-7 (IC_{50}) (μM)	35.5 ± 3.8	19.3 ± 0.7	4.4 ± 0.1	31.1 ± 1.3

Figure 26. Chemical structure of bis-chalcones **2.6.11**−**2.6.14** tested by Alidmat et al. for antiproliferative activity.

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Table 24. Anti-proliferative Activity of a Series of Bis-Chalcones 2.4.15−2.4.26

	L929 cells				
Compounds	1 μM Average (% PI) $\pm \sigma$	10 μM Average (% PI) $\pm \sigma$	20 μM Average (% PI) $\pm \sigma$	50 μM Average (% PI) $\pm \sigma$	100 μM Average (% PI) $\pm \sigma$
2.4.15	38.5 ± 6.9	49.5 ± 7.8	53.5 ± 0.71	74 ± 5.6	74 ± 5.6
2.4.16	17 ± 1.4	29 ± 4.2	43 ± 2.8	55 ± 4.2	55 ± 4.2
2.4.17	81 ± 0.8	90 ± 1	100 ± 0	100 ± 0	100 ± 0
2.4.18	29.5 ± 3.5	42 ± 4.6	46 ± 5.6	67 ± 9.2	67 ± 9.2
2.4.19	0.32 ± 0.45	0.97 ± 0.2	3.02 ± 1.36	7.26 ± 0.3	7.26 ± 0.3
2.4.20	1.12 ± 1.15	2.2 ± 1.66	1.16 ± 0.81	3.03 ± 0.02	3.03 ± 0.02
2.4.21	22.5 ± 11.64	28.73 ± 11.78	25.4 ± 8.42	28.84 ± 5.62	28.84 ± 5.62
2.4.22	35.72 ± 10.23	29.05 ± 9.62	35.69 ± 5.85	38.7 ± 4.96	38.7 ± 4.96
2.4.23	12.5 ± 10.31	15.88 ± 6.31	28.76 ± 2.74	29.53 ± 6.87	29.53 ± 6.87
2.4.24	18.10 ± 11.82	13.48 ± 10.36	25.93 ± 9.73	32.11 ± 9.38	32.11 ± 9.38
2.4.25	6.4 ± 0.4	19.07 ± 7.23	34.63 ± 0.31	64.53 ± 3.07	64.53 ± 3.07
2.4.26	13.22 ± 0.64	31.31 ± 4.84	53.79 ± 16.95	84.03 ± 2.25	84.03 ± 2.25

Table 25. Anti-proliferative Activity of a Series of Bis-Chalcones 2.1.1−2.1.6

	Anti-proliferative Activity IC_{50} (μg/mL)	
Compounds	MCF-7	MDA-MB-231
2.1.1	86.13 ± 3.45	128.66 ± 3.62
2.1.2	79.51 ± 2.85	97.64 ± 3.15
2.1.3	132.49 ± 3.71	160.54 ± 5.22
2.1.4	71.09 ± 2.34	89.62 ± 2.18
2.1.5	103.56 ± 2.48	141.05 ± 4.84
2.1.6	109.82 ± 4.10	155.32 ± 5.03

Nagar et al.[40] analyzed bis-chalcone **2.1.69** and its ruthenium metal complex **2.1.70** (Figure 15) for antioxidant properties using DPPH assay (Table 17). Both compounds **2.1.69** and **2.1.70** exhibited superior antioxidant ability compared with the control.

Liargkova et al.[8] synthesized bis-chalcones **2.4.15−2.4.33** (Figure 21) using Claisen−Schmidt route and reported antioxidant activity in various assays. In the ABTS inhibition assay, except for compounds **2.4.17**, **2.4.28**, **2.4.30**, **2.4.32**, and **2.4.33**, all the bis-chalcones exhibited low or no activity. The antioxidant activity of the bis-chalcones was also examined using liposome inhibition. The results (Table 18) demonstrated that compounds **2.4.17**, **2.4.26**, **2.4.30**, and **2.4.32** had very good activity.

Khazaei-Poul et al.[45] used a two-directional Claisen−Schmidt condensation of various ketones with benzaldehyde under alkaline conditions to report a series of bis-chalcones (Figure 22). In the DPPH assay, these compounds exhibited significant antioxidant activity compared to ascorbic acid. The compounds displayed very good IC_{50} values, better than those of the standard ascorbic acid (937 μM) in most cases, with **2.4.37** being the standout in the list.

2.5. Anti-feedant Activity. Devi et al.[46] documented the antifeedant properties of eight bis-chalcones (Figure 23) on *S. frugiperda* larvae. The antifeedant activity was determined by measuring the percentage of larvae in the control sample that consumed 50% of the diet using the FR factor. All the synthesized compounds showed significant efficacy as an antifeedant agent against *S. frugiperda*. The toxicity analysis (Table 19) indicated that bis-chalcones **2.5.2, 2.5.5, 2.5.6,** and **2.5.8** had a lethal effect on *S. frugiperda* during the early larval stages, with **2.5.2** being the most toxic (85%). Adult individuals experienced deformities and reduced size, resulting in premature death before egg-laying. The surviving larvae exhibited deformities and had a decline in growth, ultimately resulting in a mortality.

2.6. Anti-proliferative Activity. Oliveira et al.[47] synthesized two new bis-chalcones, **2.6.1** and **2.6.2** (Figure 24). Antiproliferative analysis on HCT-116 cells showed that compound **2.6.2** had a significant activity. Both compounds successfully passed the drug-likeness test, suggesting potential as an oral treatment, particularly for **2.6.2**, which effectively suppressed the proliferation of colon cancer cells. However, the study requires follow-up to quantify the structure activity relationship and evaluate the impact of various substitutions.

Burmaoglu et al.[48] reported the synthesis of fluoro substituted bis-chalcone (Figure 25) by Claisen−Schmidt condensation. The compounds were assessed for cytotoxicity on MCF-7 and Caco-2 cell lines using an MTT assay. All compounds exhibited significantly greater cytotoxicity compared to cisplatin against Caco-2 and MCF-7 cell lines (Table 20). Compound **2.6.9** was the most potent compound against the MCF-7 cell line. The findings in the Caco-2 cell line typically aligned with those observed in MCF-7. Furthermore, compounds **2.6.9** and **2.6.10** exhibited greater cytotoxicity in comparison to other com-

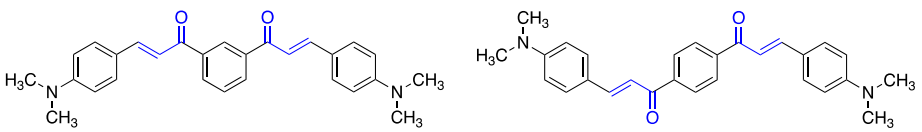

Figure 27. Chemical structures of bis-chalcones **2.6.15** and **2.6.16** tested by Zhou et al. for antiproliferative activity.

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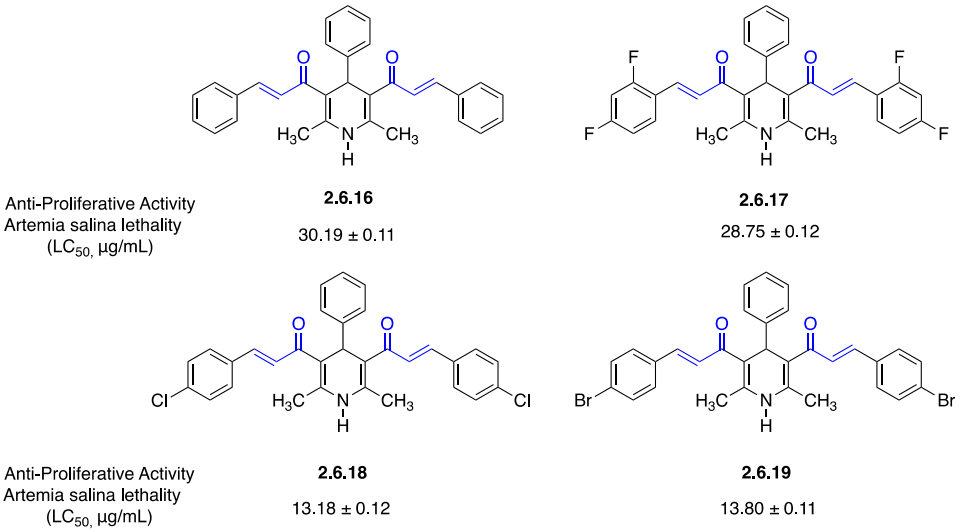
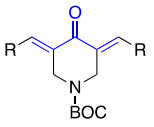


Figure 28. Series of bis-chalcones **2.6.16**−**2.6.19** tested by Ganesan et al. for antiproliferative activity.



2.6.20 - 2.6.29

Compounds	R
2.6.20	2,4-dimethylphenyl
2.6.21	4-methylphenyl
2.6.22	2- methylphenyl
2.6.23	3- methylphenyl
2.6.24	2- thiophenyl
2.6.25	2,5-dimethylphenyl
2.6.26	2,6-dimethylphenyl
2.6.27	2-furanyl
2.6.28	3-furanyl
2.6.29	2-fluorophenyl

Figure 29. Series of bis-chalcones **2.6.20**−**2.6.29** tested by Smith et al. for anticancer activity.

pounds. Authors also showed the binding mode of the bis-chalcones in the active site of xanthine oxidase.

Kammari et al.[42] reported the cytotoxicity of compounds (Figure 17) in SupT1 cells using MTT assay. The results (Table 21) showed compounds **2.2.1**−**2.2.3** to be more potent than compounds **2.2.4**−**2.2.6**.

Alidmat et al.[49] evaluated the cytotoxic effects of 13 bis-chalcone on the MCF-7 breast cancer cell line with compounds **2.6.13** showing IC_{50} values of 4.4 ± 0.1 μM (Figure 26). Some of the reported compounds were more potent than the standard (Tamoxifen IC_{50}: 17.9 ± 1.2 μM) The structure−activity relationship investigations indicated that bis-chalcone compounds containing *ortho*-chlorine and *para*-fluorine demonstrated better cytotoxic activity against the MCF-7 cell line in comparison with other compounds. Other active compounds included **2.6.11**, **2.6.12**, and **2.6.14** with compound **2.6.12** giving a value comparable to the standard.

Ibrahim et al.[32] evaluated the cytotoxicity of bis-chalcones on the HCT116 colon carcinoma cell line and the HepG2 hepatic carcinoma cell line. The data (Table 22) showed decent to good activity at 50 and 100 μg/mL (Figure 7).

Alwan et al.[31] evaluated bis-chalcones for their cytotoxicity against MCF-7 Cells using MTT assay. The median inhibitory concentration (IC_{50}) values (Table 23) suggested decent activities with compound **2.1.10** (Figure 6) being the more potent of the tested compounds.

Liargkova et al.[8] also assessed bis-chalcones (Figure 21) for their cytotoxicity against L929 mouse fibroblast using the propidium iodide (PI) fluorescence method. The results (Table 24) presented the cell survival values as a percentage of PI%. The

Table 26. Anticancer Activity of a Series of Bis-Chalcones 2.6.20−2.6.29 against Leukemia Cell Lines

	Anticancer Activity					
	Leukemia Cell Lines (% Growth)					
Compounds	CCRF-CCM	HL-60 (TB)	K-562	MOLT-4	RPMI-8226	SR
2.6.20	69.41	ND	64.33	77.61	24.86	ND
2.6.21	3.02	41.90	3.47	34.68	−25.84	−13.09
2.6.22	2.95	40.64	5.76	10.76	−23.71	8.93
2.6.23	8.66	90.16	5.44	51.77	−7.31	6.54
2.6.24	51.71	96.68	75.83	69.43	55.36	55.48
2.6.25	4.98	10.75	7.09	7.40	−24.42	0.12
2.6.26	107.49	103.62	108.81	115.13	100.39	100.57
2.6.27	83.45	98.46	100.54	94.99	71.54	80.60
2.6.28	16.54	87.59	29.29	76.14	−22.98	−8.41
2.6.29	88.11	101.29	103.74	94.82	86.12	95.61

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Table 27. Anticancer Activity of a Series of Bis-Chalcones 2.6.20−2.6.29 against NSCLC Cell Lines

	Anticancer Activity								
	NSCLC Cell Lines (% Growth)								
Comp.	A549/ATCC	EKVX	HOP-62	HOP-92	NCI-H226	NCI-H23	NCI-H322M	NCI-H460	NCI-H522
2.6.20	75.36	74.58	118.29	88.60	82.22	74.05	108.27	82.38	78.17
2.6.21	81.53	84.32	94.93	84.10	84.86	56.56	98.71	53.03	58.37
2.6.22	49.11	55.65	48.22	82.63	42.24	8.22	80.93	−38.31	20.79
2.6.23	97.38	93.43	96.91	87.32	99.58	92.68	95.75	110.44	63.79
2.6.24	86.90	99.50	89.01	82.24	93.12	96.25	94.33	105.24	79.50
2.6.25	80.53	82.80	93.42	91.33	88.96	49.71	93.86	45.31	46.07
2.6.26	94.80	104.74	90.79	92.03	100.83	88.63	95.51	107.65	81.85
2.6.27	95.89	113.70	95.85	104.10	105.55	94.05	100.42	105.61	76.42
2.6.28	101.66	102.16	93.91	100.47	98.33	99.11	87.70	106.54	78.83
2.6.29	114.82	96.22	106.68	89.13	98.51	105.90	97.10	102.87	84.89

Table 28. Anticancer Activity of a Series of Bis-Chalcones 2.6.20−2.6.29 against Colorectal Cancer Cell Lines

	Anticancer Activity						
	Colorectal Cancer Cell Lines (% Growth)						
Compounds	COLO 205	HCC-2998	HCT0116	HCT-15	HT29	KM12	SW-620
2.6.20	64.24	90.50	32.38	64.49	81.08	84.66	69.42
2.6.21	51.62	29.52	−44.37	1.94	−49.94	−16.00	5.21
2.6.22	−28.50	3.27	−53.94	1.66	−26.36	−32.80	5.37
2.6.23	114.72	103.13	11.21	76.20	46.48	74.12	7.71
2.6.24	116.54	106.19	63.47	85.13	86.36	97.21	84.52
2.6.25	30.89	52.19	−16.71	19.36	9.93	16.74	18.52
2.6.26	130.98	107.41	96.44	105.56	92.73	99.35	100.54
2.6.27	118.38	98.70	82.72	99.00	97.51	103.59	95.60
2.6.28	108.53	98.89	21.73	99.62	97.95	88.82	56.77
2.6.29	123.74	109.73	88.39	107.93	90.12	110.36	102.52

Table 29. Anticancer Activity of a Series of Bis-Chalcones 2.6.20−2.6.29 against CNS Cancer Cell Lines

	Anticancer Activity					
	CNS Cancer Cell Lines (% Growth)					
Compounds	SF-268	SF-295	SF-539	SNB-19	SNB-75	U251
2.6.20	87.04	ND	101.00	80.27	79.17	59.78
2.6.21	49.10	89.92	90.36	71.38	79.75	12.37
2.6.22	2.68	24.57	31.18	39.06	53.43	0.09
2.6.23	94.09	100.86	104.20	95.90	74.71	63.63
2.6.24	91.77	98.94	99.03	94.53	78.86	83.70
2.6.25	53.56	55.94	94.87	59.94	78.54	15.88
2.6.26	99.62	94.46	99.99	100.88	75.71	98.84
2.6.27	98.60	97.90	101.48	105.90	76.46	94.37
2.6.28	89.54	102.58	106.16	96.52	77.02	88.22
2.6.29	95.71	102.26	105.64	99.47	97.04	113.28

cytotoxicity was concentration dependent with bis-chalcones, and compounds **2.4.19** and **2.4.20** showed better activities.

Kuttithodi et al.[30] evaluated bis-chalcones (Figure 5) utilizing the MTT assay on two human breast cancer cell lines, MCF-7 and MDA-MB-231. The bis-chalcones exhibited more toxicity toward the MCF-7 cells than the MDA-MB-231 cells, as indicated by the IC_{50} values (Table 25). However, the values presented moderate activity.

Zhou et al.[16] assessed the cytotoxicity of bis-chalcone compounds on human nonsmall cell lung cancer cell line A549. The bis-chalcones (**2.6.15** and **2.6.16**, Figure 27) did not exhibit any significant activity.

Ganesan et al.[29] evaluated bis-chalcones (Figure 28) via Brine Shrimp Lethality Assay. Compounds **2.6.18** and **2.6.19** exhibited noteworthy LC_{50} values while compounds **2.6.16** and **2.6.17** had less activity.

Smith et al.[50] prepared a library of ten bis-chalcones (**2.6.20−2.6.29**) involving the reaction of *tert*-butyl 4-oxopiperidine-1-carboxylate with two equivalents of different aldehydes (Figure 29) and testing these on a panel of 60 different cell lines.

In the analysis of on six leukemia cell lines (Table 26), compounds **2.6.21**, **2.6.22**, and **2.6.25** exhibited substantial antiproliferative effects across all cell lines and showed only minimal cytotoxicity. The compounds were tested against nine cell lines of nonsmall cell lung cancer (

Table 27). Compound **2.6.22** had the highest inhibitory activity among the compounds. Seven distinct cell lines of colorectal cancer (Table 28) were used for the analysis, and compound **2.6.22** was the standout compound. Compound **2.6.22** had the highest inhibitory action among the tested compounds against CNS cancer cell lines (Table 29). Testing on nine melanoma cell lines (Table 30) suggested compound **2.6.25** to have better activity than other compounds. Analysis of the compounds against seven ovarian cancer cell lines (Table 31) showed compound **2.6.22** to have higher inhibitory potency among all the tested compounds. Eight kidney carcinoma cell lines (Table 32) were subjected to testing using these ten compounds, and the compound **2.6.22** was again the most promising compound displaying better activity than other compounds. Compound **2.6.22** stood out in the testing against two types of prostate cancer PC-3 and DU-145 cell lines (Table 33). Testing of compounds against six different forms of breast cancer (Table 34) showed that compound **2.6.22** exhibited the

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Table 30. Anticancer Activity of a Series of Bis-Chalcones 2.6.20−2.6.29 against Melanoma Cell Lines

	Anticancer Activity								
	Melanoma Cell Lines (% Growth)								
Comp.	LOX IMVI	MALME-3M	M14	MDA-MB-435	SK-MEL-2	SK-MEL-28	SK-MEL-5	UACC-257	UACC-62
2.6.20	77.57	105.06	81.96	101.57	99.17	92.36	84.55	87.69	67.24
2.6.21	−63.20	83.47	43.01	−44.36	83.77	87.26	78.86	79.36	56.47
2.6.22	−62.38	73.70	30.75	12.04	86.36	55.50	82.95	74.29	28.67
2.6.23	47.13	90.58	90.45	93.05	92.29	103.88	101.14	94.73	81.30
2.6.24	90.87	95.78	98.26	99.70	95.62	106.34	87.90	ND	66.74
2.6.25	0.93	67.73	20.10	−9.21	81.99	41.32	44.96	59.39	37.29
2.6.26	96.62	90.24	97.82	101.50	96.27	105.79	98.81	88.91	95.54
2.6.27	94.33	103.39	98.60	100.63	95.06	105.39	96.42	96.80	91.12
2.6.28	90.69	92.65	92.24	98.19	96.45	102.08	99.84	95.92	88.25
2.6.29	97.22	95.48	96.72	107.30	94.32	105.90	108.44	112.59	86.97

Table 31. Anticancer Activity of a Series of Bis-Chalcones 2.6.20−2.6.29 against Ovarian Cancer Cell Lines

	Anticancer Activity						
	Ovarian cancer Cell Lines (% Growth)						
Comp.	IGROV1	OVCAR-3	OVCAR-4	OVCAR-5	OVCAR-8	NCI/ADR-RES	SK-OV-3
2.6.20	95.63	70.01	68.41	104.67	84.67	100.06	89.66
2.6.21	69.30	7.18	65.45	111.98	25.02	76,25	104.21
2.6.22	25.99	039.91	−2.97	51.10	17.06	15.66	74.92
2.6.23	90.41	97.52	89.22	108.61	85.38	87.97	93.31
2.6.24	83.03	103.81	82.20	109.03	87.83	96.31	90.07
2.6.25	78.06	13.12	22.04	86.13	12.67	26.46	87.73
2.6.26	76.29	109.61	106.62	99.38	99.41	95.12	90.47
2.6.27	95.00	110.91	91.99	109.62	98.27	88.23	91.63
2.6.28	95.63	106.22	100.03	97.02	101.05	97.65	99.46
2.6.29	91.62	116.48	105.65	102.84	114.61	105.54	102.87

Table 32. Anticancer Activity of a Series of Bis-Chalcones 2.6.20−2.6.29 against Renal Cancer Cell Lines

	Anticancer Activity							
	Renal Cancer Cell Lines (% Growth)							
Comp.	786-0	A498	ACHN	CAKI-1	RXF393	SN12C	TK-10	UO-31
2.6.20	96.66	98.79	97.23	ND	98.01	84.42	113.36	79.04
2.6.21	56.51	67.64	20.29	61.05	99.38	60.65	87.01	66.93
2.6.22	25.81	84.81	−21.68	28.75	61.07	−6.85	30.31	31.91
2.6.23	94.60	93.90	83.87	73.53	128.16	95.35	96.08	69.02
2.6.24	81.36	81.92	97.17	67.23	ND	93.64	110.35	71.38
2.6.25	74.48	72.98	15.52	45.22	91.09	31.37	89.09	61.13
2.6.26	96.82	62.82	105.06	60.23	100.01	96.51	99.42	67.88
2.6.27	90.05	99.06	98.79	89.91	109.55	100.53	101.75	76.35
2.6.28	93.81	74.11	99.58	82.46	ND	97.82	94.78	74.19
2.6.29	98.38	72.73	105.07	73.73	ND	97.89	96.20	70.72

highest level of inhibitory action. Overall, compound **2.6.22** emerged as the most promising compound; however, there is need to further quantify the activity and considering the small library size, and it would be interesting to design an expansion involving more functionalization.

Alwi et al.[51] prepared **2.6.30** (Figure 30). The compound was shown to be more potent and more bioavailable than curcumin (Table 35). The cytotoxicity of **2.6.30** was assessed using an MTT assay.

Bhale et al.[44] also reported the anticancer activities of α-cyano substituted indolyl bis-chalcones (Figure 20) on the estrogen receptor-positive human breast cancer cell line MCF7 and normal Vero cell lines using the sulforhodamine B (SRB) assay (Table 36). The GI_{50}, TGI, and LC_{50}, were determined as part of the screening process. Compounds **2.4.3**, **2.4.5**, and **2.4.6** had stronger activity against the MCF-7 cell line. However, when these were tested against the normal Vero Monkey cell line, they showed moderate selectivity.

Alidmat et al.[52] evaluated the cytotoxicity of novel bis-chalcone compounds (Figure 31) against breast cancer cell lines (MCF-7) and normal breast cell lines (MCF-10A) (Table 37). Compounds **2.6.31** and **2.6.34** gave activities comparable to tamoxifen on MCF-7 cells after 48 h of exposure. In addition, it was shown that these compounds showed better selectivity toward MCF-7 cells.

Tamang et al.[53] synthesized a range of bis-chalcones known as diarylidenecyclopentanones (DACPs, Figure 32). The cytotoxicity of all of these compounds was assessed on HeLa cell lines

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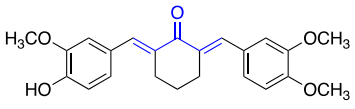
Table 33. Anticancer Activity of a Series of Bis-Chalcones 2.6.20−2.6.29 against Prostate Cancer Cell Lines

	Anticancer Activity	
	Prostate Cancer Cell Lines (% Growth)	
Compounds	PC-3	DU-145
2.6.20	52.05	95.62
2.6.21	29.93	38.73
2.6.22	21.91	9.09
2.6.23	89.01	105.75
2.6.24	74.74	107.21
2.6.25	46.61	37.69
2.6.26	85.73	107.99
2.6.27	100.61	107.61
2.6.28	89.50	109.29
2.6.29	87.27	118.60

Table 34. Anticancer Activity of a Series of Bis-Chalcones 2.6.20−2.6.29 against Breast Cancer Cell Lines

	Anticancer Activity					
	Breast Cancer Cell Lines (% Growth)					
Comp.	MCF7	MDA-MB-231/ATCC	HS 578T	BT-549	T-47D	MDA-MB-468
2.6.20	23.46	89.45	98.92	99.77	62.38	74.23
2.6.21	15.72	88.26	59.56	99.91	61.07	56.20
2.6.22	19.19	42.69	31.19	70.26	51.76	36.65
2.6.23	23.21	98.85	96.69	104.77	87.75	102.55
2.6.24	39.09	101.29	93.32	97.65	82.50	87.54
2.6.25	23.29	92.13	43.94	85.55	61.42	57.34
2.6.26	94.59	112.78	92.30	105.00	91.57	95.12
2.6.27	81.67	110.93	96.97	98.11	87.47	98.85
2.6.28	20.50	109.32	90.62	101.68	82.40	97.28
2.6.29	85.56	110.14	104.58	105.53	85.55	109.41



2.6.30

Figure 30. Chemical structure of bis-chalcone **2.6.30** tested by Alwi et al. for anticancer activity.

Table 35. Anticancer Activity of Bis-Chalcone 2.6.30 against Human Liver Cancer Cells and Noncancerous Mouse Fibroblast Cells

		Anticancer Activity	
		IC_{50} (μM)	
Compounds	Incubation time (hours)	HepG2	3T3
2.6.30	24	16.85 ± 2.49	5.50 ± 0.211
	48	4.97 ± 1.47	3.03 ± 0.413
	72	2.73 ± 0.759	3.05 ± 0.446
Curcumin	24	46.13 ± 0.254	35.32 ± 6.27
	48	26.30 ± 2.76	17.67 ± 1.88
	72	17.93 ± 1.97	18.37 ± 1.87

using the MTT assay (Table 38). Compounds **2.6.51**, **2.6.56**, and **2.6.57** exhibited significant cytotoxicity at the tested concentration with compound **2.6.51**, containing a 2-nitro group, being the better of the tested molecule.

Li et al.[54] prepared eight bis-chalcone (Figure 33) conjugates with a lysine linker using an alkylation procedure and assessed their potential for inhibiting cell growth of liver cancer (MHCC-97H), colorectal cancer (HCT116), and gastric cancer (TMK1) using the CCK-8 assay. The results (Table 39) indicated the derivative **2.6.63** displayed better activity against TMK1 and AGS. The *in vivo* antitumor investigation demonstrated that compound **2.6.63** successfully suppressed tumor growth in the TMK1-induced xenograft model, with no observable adverse effects. The mechanism by which **2.6.63** inhibits tumor growth was further examined by RNA-Seq sequencing in TMK1 cells, showing that it positively regulated the apoptotic signaling pathway. The induction of programmed cell death in cancer cells was shown using Annexin V staining, cleaved caspase, and Bax expression in TMK1 cells.

2.7. Enzyme Inhibitory Activities. Cai et al.[55] prepared six chalcones and 13 bis-chalcones and reported their ability to reverse the resistance of cancer cell lines that exhibit multidrug resistance (MDR) (Table 40, Figure 34). This study showed the effect of methoxy and hydroxy substitutions and the extended π system on the potencies of bis-chalcones, and some of the compounds showed single decimal micromolar activity. The authors, however, showed that a simple chalcone was more potent in reversal activities against both ABCG2- and ABCB1-mediated MDR and increased the accumulation of anticancer drugs in the cells overexpressing ABCG2 and ABCB1.

Burmaoglu et al.[48] synthesized bis-chalcones with fluoro substitutions (Figure 25) using Claisen−Schmidt condensation and reported inhibition of xanthine oxidase (XO) and growth-inhibitory effects on MCF-7 and Caco-2 human cancer cell lines. The experimental results (Table 41) showed that all compounds exhibited good inhibitory activity that was better or comparable to allopurinol. Investigation of the effects of eight compounds as XO inhibitors showed compound **2.6.4** had a noteworthy result followed by **2.6.9.** Furthermore, compounds **2.6.3**, **2.6.4**, **2.6.6**, and **2.6.9** exhibit noncompetitive inhibition, whereas compounds **2.6.5**, **2.6.7**, **2.6.8**, and **2.6.10** display competitive inhibition like allopurinol.

Kammari et al.[42] assessed bischalcones (Figure 17) for their ability to block the phosphorylation of serine residues in topo IIβ. Mouse antihuman Topo IIβ was employed for immunoprecipitation of Topo IIβ from the infected cells. The findings (Table 42) demonstrated that **2.2.4**, **2.2.5**, and **2.2.6** effectively suppressed serine phosphorylation in Topo IIβ. Compound **2.2.5** exhibited the most potent suppression of serine phosphorylation among the compounds followed closely by **2.2.6** and **2.2.4**.

Khusnutdinova et al.[41] tested bis-chalcones **2.1.71** and **2.1.73** (Figure 16) for their ability to inhibit the *a*-glucosidase using the enzyme from *S. cerevisiae* (Table 43). The platanic acid compounds containing furfurylidene **2.1.71** and trifluoromethylbenzylidene **2.1.73** fragments exhibited notable inhibitory characteristics, showing 97- and 52-fold more activity compared with the standard acarbose. The molecular modeling results revealed that compounds **2.1.71** and **2.1.73** bind specifically to allosteric site 1 of the enzyme.

Tutar et al.[37] analyzed 1,3-bis-chalcone derivatives **2.1.47−2.1.65** (Figure 12) for their ability to inhibit carbonic anhydrase (Table 44). Bis-chalcones exhibited nanomolar inhibitory activity against human carbonic anhydrase isoforms I and II. The chemicals efficiently suppressed the activity of hCA I and II, unlike acetazolamide.

Aliabadi et al.[6] assessed compounds **2.7.14−2.7.21** (Figure 35) for their ability to suppress the mushroom tyrosinase activity by a spectrophotometric test utilizing LDOPA as a substrate.

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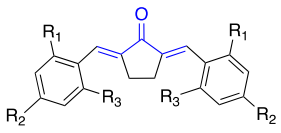
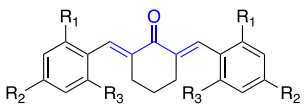
Table 36. Anticancer Activity of a Series of Bis-Chalcones 2.4.3−2.4.14 the Estrogen Receptor-Positive Human Breast Cancer Cell Line and Normal Vero Cell Lines

	Anticancer Activity					
	MCF-7 (μM)			Vero (normal) (μM)		
Compounds	LC_{50}	TGI	GI_{50}	LC_{50}	TGI	GI_{50}
2.4.3	>100	>100	11.7	>100	>100	65.1
2.4.4	>100	>100	47.2	>100	>100	>100
2.4.5	>100	>100	15.3	>100	>100	70.6
2.4.6	>100	>100	17.9	>100	>100	55.3
2.4.7	>100	>100	>100	>100	>100	>100
2.4.8	>100	>100	>100	>100	>100	>100
2.4.9	>100	>100	>100	>100	>100	95.2
2.4.10	>100	>100	79.1	>100	>100	>100
2.4.11	>100	>100	>100	>100	>100	>100
2.4.12	>100	>100	88.0	>100	>100	78.1
2.4.13	>100	>100	>100	>100	>100	>100
2.4.14	>100	>100	>100	>100	>100	>100
Adriamycin	100	11.0	<0.1	>100	10.0	<0.1



2.6.31 - 2.6.33

Compounds	R_1	R_2	R_3
2.6.31	Cl	H	H
2.6.32	Cl	H	Cl
2.6.33	F	H	Cl



2.6.34 - 2.6.36

Compounds	R_1	R_2	R_3
2.6.34	Cl	H	H
2.6.35	Cl	H	Cl
2.6.36	F	H	Cl

Figure 31. Series of bis-chalcones **2.6.30−2.6.35** tested by Alidmat et al. for anticancer activity.

Table 37. Anticancer Activity of a Series of Bis-Chalcones 2.6.31−2.6.36 against Breast Cancer Cell Lines

		Anticancer Activity IC_{50} (μM)		
Compounds	Incubation time (hours)	MCF-7	MCF-10A	Selective Index (IC_{50} in normal cells/IC_{50}in cancer cells) (μM)
2.6.31	24	9.5	87.5	9.21
	48	8	98.5	12.32
	72	7	78.2	11.17
2.6.32	24	14	100	7.14
	48	44	>100	-
	72	75.5	53	0.71
2.6.33	24	>100	>100	-
	48	>100	74	-
	72	24	26	1.08
2.6.34	24	14	100	7.14
	48	9.5	39	4.11
	72	21	24	1.14
2.6.35	24	>100	>100	-
	48	>100	>100	-
	72	>100	49.5	-
2.6.36	24	40	>100	-
	48	31.5	48.5	1.54
	72	23	33	1.43
Tamoxifen	48	9.3 ± 0.44	23.71 ± 0.99	2.54

Compounds **2.7.12, 2.7.16**, **2.7.18**, and **2.7.20** exhibited better activities that were comparable to the standard (kojic acid, 0.18 mM).

Winter et al.[56] reported symmetric bis-chalcones and the lead compounds **2.7.22** and **2.7.23** (Figure 36) were examined for their ability to hinder the removal of mitoxantrone from ABCG2-transfected HEK293 cells (Table 45). Compound **2.7.22**, exhibited selectivity toward ABCG2 over P-glycoprotein and MRP1. It appeared not to be transported by ABCG2 and displayed better activity in H460 and H23 cells.

Cai et al.[57] assessed bis-chalcones as inhibitors of *a*-glucosidase (Table 46), using 1-deoxynojirimycin as a positive control. Compounds containing two or four hydroxyl groups (Figure 34) and (Figure 37) exhibited superior inhibitory effects compared to 1-deoxynojirimycin, through a noncompetitive mechanism. Furthermore, the majority of hydroxy bis-chalcones demonstrated significant inhibitory effects on a-glucosidase in enzyme testing. The bis-chalcone **2.7.27** (Figure 37) had the most potent inhibitory action.

Bale et al.[58] reported the synthesis and α-amylase activity of bis-chalcones. These compounds showed a good α-amylase inhibitory activity comparable to the standard acarbose (1.04 ± 0.3) with compound **2.7.30** (Figure 38) as being relatively more potent among these compounds. Substituting 4/4′-OMe with 4/4′-SMe, as observed in compound **2.7.31**, led to a small decrease in inhibitory action. This drop could be attributed to the slightly lower polarity of compound **2.7.31** compared to compound **2.7.30**. The activity of compound **2.7.30** can also be compared to that of halogenated derivatives **2.7.28** and **2.7.29**, which had chlorine (Cl) and bromine (Br) substitutions at positions 4 and 4′, respectively. It was noted that these derivatives exhibited a similar inhibitory effect. Compound **2.7.32**, which possesses hydroxyl groups at positions 2 and 2′ and an ethoxy group at positions 3 and 3′, exhibited a decent inhibitory action.

3. MATERIAL APPLICATIONS

3.1. Electrochemical Properties. Maşlakci et al.[14] examined the electrochemical characteristics of two bis-chalcones (**3.1.1**) and (**3.1.2**, Figure 39) by cyclic voltammetry (CV), employing an indium tin oxide (ITO) as the working electrode. Repeated cyclic voltammogram measurements showed that these compounds had excellent long-term redox

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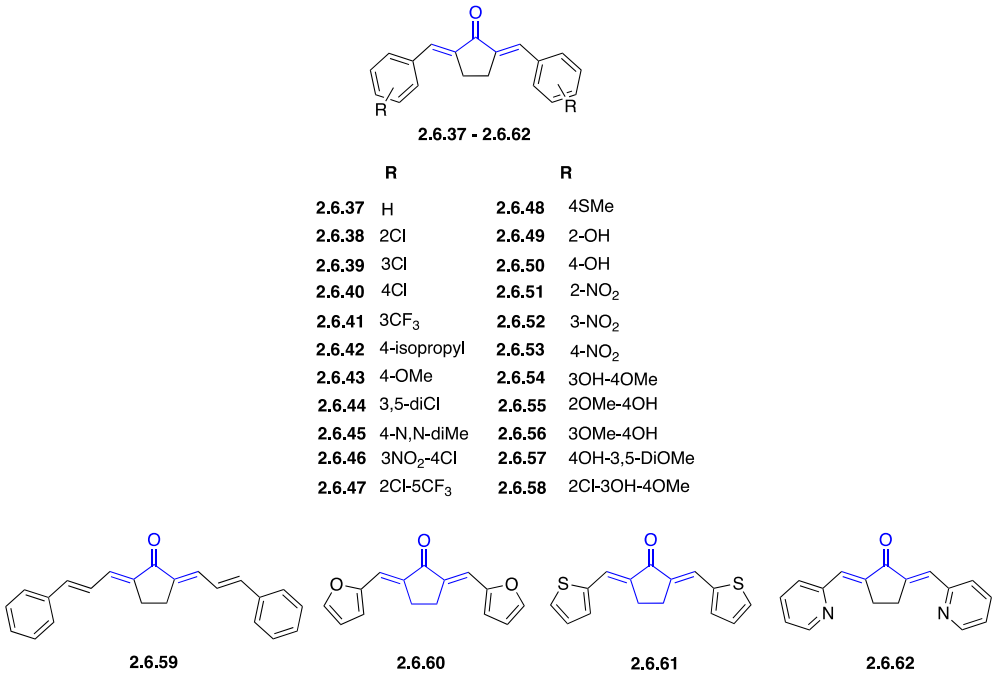

Figure 32. Chemical structures of bis-chalcones **2.6.37**−**2.6.62** tested by Tamang et al. for anticancer activity.

Table 38. Anticancer Activity of a Series Bis-Chalcones 2.6.37−**2.6.62 against HeLa Cells**

Anticancer Activity	
Compounds	HeLa Cells (10 μM)
2.6.37	91.27 ± 4.00
2.6.38	90.57 ± 6.66
2.6.39	81.70 ± 4.76
2.6.40	90.24 ± 5.89
2.6.41	82.05 ± 6.99
2.6.42	71.50 ± 4.14
2.6.43	84.83 ± 2.19
2.6.44	81.52 ± 1.01
2.6.45	69.44 ± 1.38
2.6.46	85.74 ± 4.28
2.6.47	76.83 ± 0.06
2.6.48	78.19 ± 0.20
2.6.49	86.26 ± 2.28
2.6.50	80.27 ± 7.34
2.6.51	33.39 ± 2.61
2.6.52	79.95 ± 6.25
2.6.53	90.73 ± 5.14
2.6.54	83.33 ± 8.81
2.6.55	89.39 ± 2.77
2.6.56	61.52 ± 7.64
2.6.57	56.17 ± 1.82
2.6.58	103.29 ± 4.34
2.6.59	73.97 ± 4.78
2.6.60	84.07 ± 2.71
2.6.61	73.10 ± 5.14
2.6.62	96.96 ± 5.08
5-fluorouracil	76.37 ± 4.04

stability. The oxidation peak for in the anodic region for the first cycle of the compounds appeared at t −0.20 V, −0.47 V. The presence of NO_2 group at *p*-position on the **3.1.2** led to increase of HOMO and LUMO energy gap (Table 47).

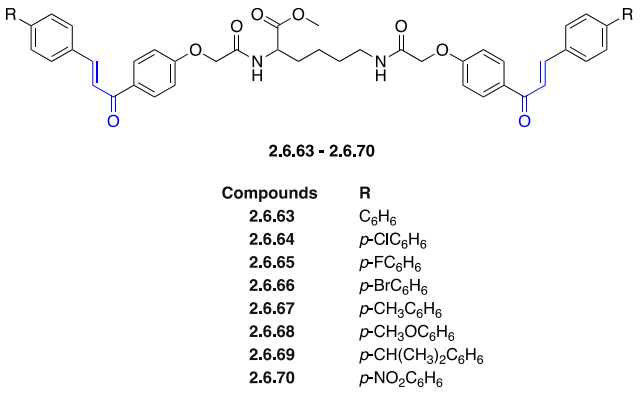

Figure 33. Series of bis-chalcones **2.6.63**−**2.6.70**.

3.2. Properties as Photosensitizers. Teo et al.[59] reported synthesis and the conversion efficiency of bis-chalcone in dye-sensitized solar cells. Six bis-chalcones **3.2.1**−**3.2.6** (Figure 40) were synthesized using a Claisen-Schmidt condensation and used as dyes in dye-sensitized solar cells (DSSCs) to assess their solar energy conversion efficiency (Table 48). Compound **3.2.2**, with hydroxy groups showed better efficiency than bis-chalcones.

Phan et al.[60] developed unsymmetrical bis-chalcones (Figure 41) incorporating electron-donating groups such as methoxy (OMe) or chloro (Cl). These compounds were utilized as dye sensitizers in dye-sensitized solar cells (DSSCs), employing fluorine-doped tin oxide (FTO) glass coated with titanium(IV) oxide (TiO_2) as the working electrode and indium tin oxide (ITO) glass coated with platinum as the counter electrode. The conversion efficiency and open circuit photovoltage (V_{oc}) of the DSSCs were assessed (Table 49), revealing that the bis-chalcone **3.2.9**, which contains a methoxy group, exhibited the higher conversion efficiency and V_{oc} value. Compound **3.2.8** exhibited a higher fill factor (FF), but the lowest solar circuit current

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Table 39. Anticancer Activity of a Series of Bis-Chalcones 2.6.63−2.6.70 against Various Cancer Cell Lines

	Anticancer Activity						
	IC_{50} (μM)						
Compounds	TMK1	97H	HCT116	GES1	MKN45	AGS	IM95
2.6.63	22.29	>100	35.44	65.66	>100	22.14	>100
2.6.64	62.30	>100	93.68	>100	>100	74.86	>100
2.6.65	58.34	>100	73.48	>100	>100	>100	86.18
2.6.66	>100	>100	>100	>100	>100	>100	>100
2.6.67	87.79	>100	>100	>100	>100	>100	>100
2.6.68	>100	>100	65.56	>100	>100	>100	>100
2.6.69	60.39	>100	35.18	>100	>100	>100	>100
2.6.70	60.07	>100	>100	>100	>100	>100	>100

Table 40. Cytotoxicity and Reversal Study of a Series of Bis-Chalcones 2.7.1−2.7.13

	Cytotoxicity and Reversal Study		
	S1	S1-M1-80	
Compounds	IC_{50} (μM)	IC_{50} (μM)	Concentration for reversal study (μM)
2.7.1	3.2 ± 0.8	4.0 ± 0.5	1
2.7.2	>100	>100	10
2.7.3	24.5 ± 6.9	>100	5
2.7.4	24.9 ± 2.4	30.0 ± 4.9	10
2.7.5	11.0 ± 0.3	35.7 ± 2.1	5
2.7.6	83.9 ± 7.6	>100	10
2.7.7	2.7 ± 0.9	3.5 ± 0.9	1
2.7.8	2.5 ± 0.4	4.5 ± 0.2	1
2.7.9	8.4 ± 0.07	8.6 ± 0.8	1
2.710	98.0 ± 0.6	>100	10
2.7.11	83.2 ± 3.4	>100	10
2.7.12	33.5 ± 8.2	39.1 ± 1.8	10
2.7.13	13.7 ± 0.1	19.1 ± 1.8	5

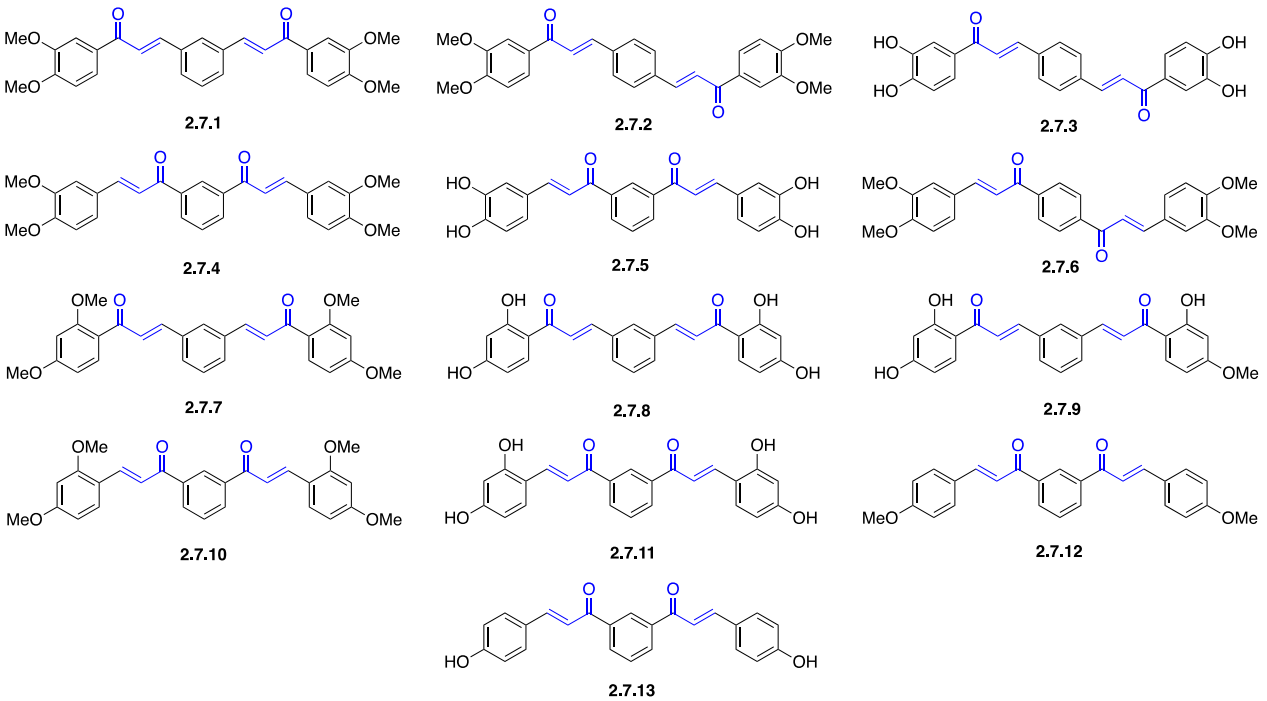

Figure 34. Chemical structure of bis-chalcones **2.7.1**−**2.7.13** tested by Cai et al. for cytotoxicity and reversal study.

density (J_{sc}) and lower conversion efficiency in comparison to compounds **3.2.7** and **3.2.9**.

3.3. Properties as Photoinitiators. Wu et al.[61] reported three novel oxime ester dyes (Figure 42) for radical visible photopolymerization by synthesizing photoleachable bis-

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Table 41. Xanthine Oxidase (XO) Inhibitory Activity of a Series of Bis-Chalcones 0.6.3−2.6.10

XO Inhibition Activity		
Compounds	IC_{50} (μM)	Type of Inhibition
2.6.3	2.010 ± 0.046	Noncompetitive
2.6.4	0.728 ± 0.009	Noncompetitive
2.6.5	6.058 ± 0.095	Competitive
2.6.6	3.592 ± 0.044	Noncompetitive
2.6.7	5.516 ± 0.077	Competitive
2.6.8	4.001 ± 0.089	Competitive
2.6.9	0.764 ± 0.008	Noncompetitive
2.6.10	3.995 ± 0.059	Competitive
Allopurinol	5.430 ± 0.029	Competitive

Table 42. Topoisomerase II Inhibitory Activity of a Series of Bis-Chalcones 2.2.1−2.2.6

Inhibition of TopoIIβK_{HIV-1}	
Compounds	IC_{50} (pM)
2.2.1	$4.4 \pm 0.33 \times 10^2$
2.2.2	$3.2 \pm 0.22 \times 10^2$
2.2.3	$5.5 \pm 0.26 \times 10^2$
2.2.4	1.5 ± 0.29
2.2.5	1.0 ± 0.24
2.2.6	1.4 ± 0.56
3-Phenylpyridine (Control)	$3.80 \pm 0.01 \times 10^2$

Table 43. *a*-Glucosidase Inhibitory Activity of a Series of Bis-Chalcones 2.1.71 and 2.1.73

Inhibition of α-Glucosidase	
Compounds	IC_{50} (μM)
2.1.71	1.76
2.1.73	3.3
Acarbose	170.00

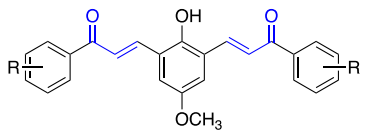
chalcone. These were D-π−A-π−A′ type radical visible photoinitiators (TAs) in which the 4-diethylamino group served as the donor, keto groups as the first acceptor, and the oxime ester as the second acceptor. These compounds demonstrated significant molar absorptivity values within the visible light spectrum (Table 50). Compound **3.3.2** showed very good photoinitiating capability and photobleaching characteristics, enabling it to effectively start the polymerization of acrylate columns.

Deng et al.[62] synthesized six photoinitiators based on bis-chalcone compounds (Figure 43) using the Claisen−Schmidt reaction and investigated the impact of various frameworks of polycyclic aromatic hydrocarbons and unsaturated groups on the maximum absorption wavelength, solubility, and migratory properties of the synthesized compounds (Table 51). The three-component system consisting of products, iodonium, and an amine exhibited rapid and efficient photopolymerization. In addition, compounds exhibit specific photobleaching characteristics, and the migration ratio decreased as unsaturated groups were introduced and the relative molecular weight increased.

Xu et al.[63] synthesized six bis-chalcones (Figure 44) and studied these as novel photoinitiators (Table 52). These compounds, when combined with an amine and an iodonium salt, can be used to initiate the free radical polymerization of acrylates. This polymerization process occurred when the compounds were exposed to LED irradiation at a wavelength

Table 44. Carbonic Anhydrase Inhibitory Activity of a Series of Bis-Chalcones 2.1.47−2.1.65

Carbonic anhydrase inhibition activity		
	IC_{50} (nM)	
Compounds	hCA I	hCA II
2.1.47	403.68	343.94
2.1.48	187.11	130.11
2.1.49	437.34	247.58
2.1.50	141.44	171.27
2.1.51	202.24	209.53
2.1.52	126.54	123.67
2.1.53	464.38	375.41
2.1.54	195.57	183.58
2.1.55	282.88	249.67
2.1.56	855.44	717.77
2.1.57	551.53	452.41
2.1.58	447.37	309.43
2.1.59	153.43	117.43
2.1.60	164.38	142.38
2.1.61	98.63	77.33
2.1.62	501.24	392.97
2.1.63	744.48	676.46
2.1.64	266.03	177.62
2.1.65	462.36	408.48
Acetazolamide	997.67	901.36



2.7.14 - 2.7.21

Compounds	R	Mushroom Tyrosinase Inhibition IC_{50} (mM)
2.7.14	4-F	0.2
2.7.15	4-OH	0.25
2.7.16	4-OMe	0.2
2.7.17	4-CH_3	0.26
2.7.18	4-I	0.21
2.7.19	4-Cl	0.62
2.7.20	3,4-OMe	0.21
2.7.21	3-Br	0.41

Figure 35. Series of bis-chalcones **2.7.14−2.7.21** tested by Aliabadi et al. for mushroom tyrosinase inhibitory activity.

of 405 nm. All of these compounds exhibited significant photoinitiating capabilities for the photopolymerization of acrylates conducted on thin samples in laminate. When evaluated as photoinitiators for thick samples, compounds **3.3.12** and **3.3.14** demonstrated better activity. Both were effective in facilitating the cationic polymerization of epoxides under LED light exposure at a wavelength of 405 nm, with the presence of an iodonium salt enhancing its performance.

Chen et al.[64] synthesized four distinct series of bis-chalcone compounds, using benzylpiperidinone, tetrahydrothiopyranone, pyridine, or biphenyl as the core elements. When these compounds are combined with an amine and an iodonium salt, these served as initiators for the free radical photopolymerization (FRP) of poly(ethylene glycol) diacrylate (PEG-diacrylate) and the cationic photopolymerization (CP) of 3,4-epoxycyclohexylmethyl-3,4-epoxycyclohexane carboxylate (EPOX). All the bis-chalcones exhibited good photoinitiation capabilities when subjected to LED irradiation at 375 nm

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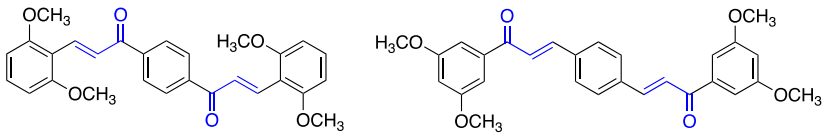


2.7.22 2.7.23

Figure 36. Chemical structures of bis-chalcones **2.7.22** and **2.7.23** tested by Winter et al. for ABCG2 inhibitory activity.

Table 45. ABCG2 Inhibitory Activity of Bis-Chalcones 2.7.22 and 2.7.23

Inhibition of ABCG2-Overexpressing Cancer Cells			
	EC_{50} (μM)		
Compounds	H460	H23	PANC-1
2.7.22	0.08 ± 0.01	0.22 ± 0.11	0.21 ± 0.18
2.7.23	1.63 ± 0.08	1.17 ± 0.71	0.21 ± 0.18

Table 46. α-Glucosidase Inhibitory Activity of a Series of Bis-Chalcones 2.7.24−2.7.27

α-Glucosidase Inhibitory Activities	
Compounds	IC_{50} (μM)
2.7.2	32.0%[a]
2.7.3	10.1 ± 1.7
2.7.4	16.0%[a]
2.7.5	6.5 ± 0.2
2.7.7	27.2%[a]
2.7.8	23.7 ± 0.3
2.710	55.2%[a]
2.7.11	5.5 ± 1.2
2.7.12	29%[a]
2.7.13	18.3 ± 0.7
2.7.24	27%[a]
2.7.25	66.9 ± 2.5
2.7.26	22.5 ± 3.2
2.7.27	1.0 ± 0.1
(1-Deoxynojirimycin) Positive Control	21.3 ± 8.7

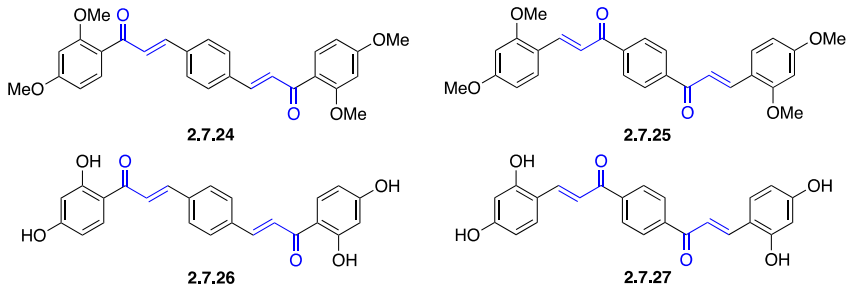
[a]The inhibition of the compounds at the concentration of 40 μM. The solubility of these methoxyl bis-chalcones in PBS are low.

compared to 405 nm for the photopolymerization of acrylates (Table 53). This can be attributed mostly to their exceptional light absorption qualities in the near-UV range. Pyridine-based bis-chalcones, specifically bis-chalcones **3.3.20** and **3.3.24** (Figure 45), had superior efficiency as photoinitiators in comparison with the other bis-chalcone series. Furthermore, all these compounds are also capable of facilitating the cationic polymerization of epoxides under LED light exposure at a wavelength of 375 nm, provided they are in the presence of an iodonium salt and an amine.

Xue et al.[65] developed dyes that had *N*-alkylated pyrrole (**3.3.26**), indole (**3.3.27**), and carbazole (**3.3.28**) groups (Figure 46). These dyes were then analyzed for the influence of the peripheral groups to initiate photochemical reactions (Table 54). These compounds exhibited a high light absorption in the wavelength range of 300−500 nm. The polymerization kinetics of a diacrylate monomer were studied using real-time FT-IR under 405/460 nm LED irradiation. The monomer was polymerized in the presence of either one-component C 3s or bimolecular C 3s/triethanolamine (TEOA). The polymerization profiles indicate that C 3s can initiate the polymerization process. Additionally, TEOA plays a substantial role in enhancing the initiation efficiency of **3.3.28**, whereas its impact on the acceleration effect is very minor for **3.3.26** and **3.3.27**. To understand these processes, a combination of photolysis, cyclic voltammetry, and theoretical calculations was employed. It was suggested that **3.3.26** and **3.3.27** tend to undergo photolysis via intramolecular hydrogen abstraction.

Xue et al.[66] prepared pyrrole-based compounds by combining *N*-methypyrrole-2-aldehyde with four ketones, resulting in the formation of **3.3.29**, **3.3.30**, **3.3.31**, and **3.3.32** (Figure 47). They examined the impact of the compounds on the photochemical and photophysical characteristics (Table 55) and showed that the ketone component had no impact on their absorption properties, but significantly altered their photophysical properties, particularly the quantum yield of fluorescence emission. The starting performance of these compounds in radical photopolymerization exhibited significant variation, with compound **3.3.29** having better performance.

Li et al.[67] produced a type II photoinitiator (**3.3.32**, Figure 48) containing furan rings. This photoinitiator possessed a significant molar extinction coefficient and exhibited absorption at long wavelengths (Table 56). The analysis of photopolymerization kinetics demonstrated that when present in low concentrations, it displayed a significantly elevated rate of polymerization and conversion. The UV−vis absorption and fluorescence spectrum indicated that compound **3.3.32** exhibited a significant red shift in the presence of poly(ethylene glycol)diacrylate (PEGDA) solution. These results in the



2.7.24 2.7.25 2.7.26 2.7.27

Figure 37. Chemical structures of bis-chalcones **2.7.24**−**2.7.27** tested by Cai et al. for *a*-glucosidase inhibitory activity.

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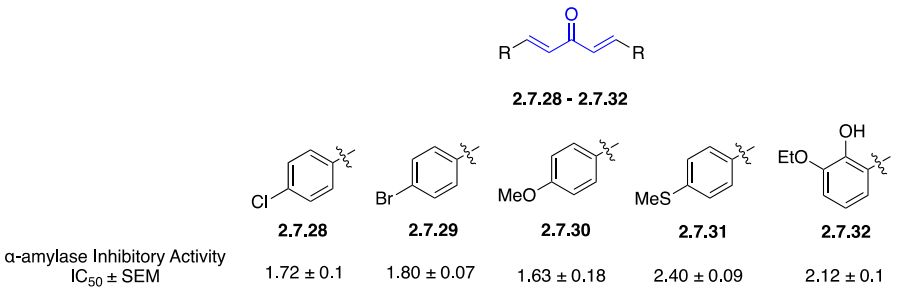


Figure 38. Chemical structure of bis-chalcone **2.7.28**−**2.7.32** tested by Bale et al. for α-amylase inhibitory activity.

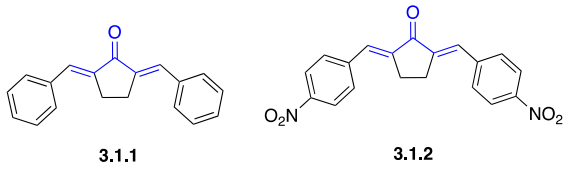


Figure 39. Chemical structures of bis-chalcones **3.1.1** and **3.1.2** tested by Maşlakci et al. for electrochemical properties.

Table 47. Electrochemical Properties of Bis-Chalcones 3.1.1 and 3.1.2

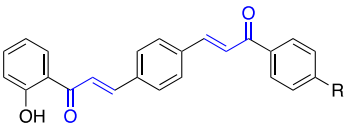
	Electrochemical Properties				
Compounds	E_{ox}^{onset} (V)	E_{red}^{onset} (V)	HOMO (eV)	LUMO (eV)	E_g^{elec} (eV)
3.1.1	1.6	−1.15	−5.83	−3.08	2.75
3.1.2	1.7	−1.23	−5.93	−3.0	2.93

extension of the light absorption region up to 500 nm, attributed to the formation of an exciplex between **3.3.32** and PEGDA. Furthermore, PEGDA was a good hydrogen donor for **3.3.32** when compared to the conventional co-initiator amine. The **3.3.32**/PEGDA photoinitiator system exhibited exceptional photobleaching capabilities, making it suitable for use in light-colored materials that undergo visible light photopolymerization. This system showed promise in applications like 3D photopolymerization printing materials that utilize long-wavelength LED lamps.

Xu et al.[68] synthesized 12 bis-chalcones with tertiary amines or anthracenes as peripheral substituents. The derivatives were specifically developed for the polymerization of di-(trimethylolpropane) tetraacrylate (TA), which is a tetrafunctional polyether acrylate. This polymerization process normally occurs under LED@405 nm irradiation and can be carried out in

Table 48. Power Conversion Efficiency of a Series of Bis-Chalcones 3.2.1−3.2.6

	Power Conversion Efficiency			
Compounds	V_{oc} (V)	J_{sc} (mA/cm^2)	Fill factor (%)	Efficiency (%)
3.2.1	0.410	0.144	50.649	0.030
3.2.2	0.460	0.225	51.604	0.054
3.2.3	0.440	0.150	48.570	0.032
3.2.4	0.370	0.193	43.970	0.032
3.2.5	0.361	0.144	41.620	0.022
3.2.6	0.390	0.182	49.423	0.035

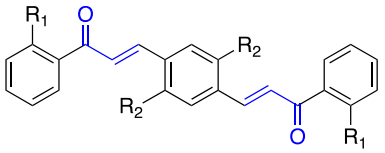


3.2.7 - 3.2.9

Compounds	R
3.2.7	H
3.2.8	Cl
3.2.9	OMe

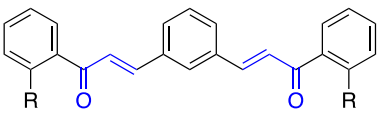
Figure 41. Series of bis-chalcones **3.2.7**−**3.2.9** tested by Phan et al. for power conversion efficiency.

both thin and thick film settings (Table 57). When combined with an amine or an iodonium salt (Iod), these compounds form distinct photoinitiating systems. Within these systems, the combination of **3.3.34**/amine/Iod achieves the highest conversion rates of acrylates in thick film applications (about 1.4 mm thickness), whereas the **3.3.44**/amine/Iod system is the most effective for converting acrylates in thin film applications (approximately 25 μm thickness). The photosensitivity of **3.3.34** and **3.3.44** (Figure 49) was analyzed through steady-state



3.2.1 - 3.2.4

Compounds	R_1	R_2
3.2.1	H	H
3.2.2	OH	H
3.2.3	H	OMe
3.2.4	OH	OMe



3.2.5 - 3.2.6

Compounds	R
3.2.5	H
3.2.6	OH

Figure 40. Series of bis-chalcones **3.2.1**−**3.2.6** investigated by Teo et al. for power conversion efficiency.

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Table 49. Power Conversion Efficiency of a Series of Bis-Chalcones 3.2.7−3.2.9

Power Conversion Efficiency						
Compounds	Electron Acceptor	Electron Donor	V_{oc} (V)	J_{sc} (mA/cm^2)	Fill Factor (%)	Efficiency (%)
3.2.7	OH	-	0.377	0.302	44.5	0.051 ± 0.001
3.2.8	OH	Cl	0.410	0.185	49.3	0.037 ± 0.000
3.2.9	OH	OMe	0.430	0.286	49.0	0.060 ± 0.001

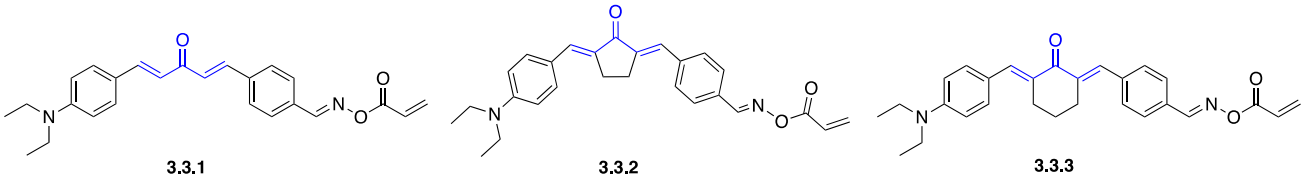

Figure 42. Chemical structures of bis-chalcones **3.3.1**, **3.3.2**, and **3.3.3**) tested by Wu et al. for photoinitiating properties.

Table 50. Photophysical Data of Bis-Chalcones 3.3.1, 3.3.2, and 3.3.3

Photophysical Data of TAs									
Comp.	λ_{max} (nm)	ε_{max} (M^{-1} cm^{-1})	ε_{455}(M^{-1} cm^{-1})	λ_{ex} (nm)	λ_{em} (nm)	E_{ox} (eV)	E_{red} (eV)	E_s (eV)	ΔG_{et} (eV)
3.3.1	437	33750	30450	411	533	0.70	−1.15	2.55	− 0.70
3.3.2	465	39530	37830	479	664	0.71	−1.21	2.67	− 0.75
3.3.3	436	29380	25830	425	633	0.72	−1.17	2.29	− 0.40

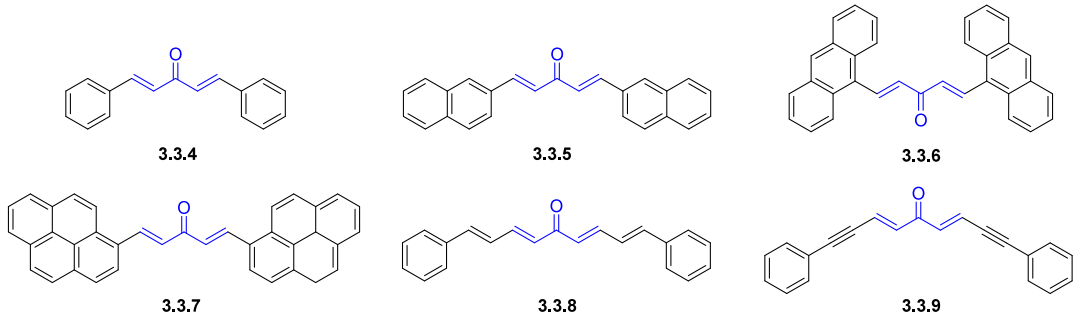

Figure 43. Series of bis-chalcones **3.3.4**−**3.3.9** tested by Deng et al. for photoinitiating properties.

Table 51. Photophysical Data of a Series of Bis-Chalcones 3.3.4−3.3.9

Photophysical Properties		
Compounds	λ_{max} (nm)	ε_{max} (M^{-1} cm^{-1})
3.3.4	300	11,778
3.3.5	340	37,102
3.3.6	390	12,687
3.3.7	442	45,695
3.3.8	370	50,000
3.3.9	395	55,770

Table 52. Light Absorption Properties of a Series of Bis-Chalcones 3.3.10−3.3.15

Light Absorption Properties			
Compounds	λ_{max} (nm)	ε_{max} (M^{-1}cm^{-1})	ε_{405nm} (M^{-1} cm^{-1})
3.3.10	368	29230	9740
3.3.11	365	25020	7980
3.3.12	370	34920	11690
3.3.13	368	34200	10130
3.3.14	372	31470	11950
3.3.15	370	29750	10280

photolysis and fluorescence quenching tests. A photocuring 3D printing method was employed for di(trimethylolpropane) tetraacrylate (TA), and both the **3.3.34** and **3.3.44** based photoinitiating systems were successfully utilized to produce macroscopic 3D designs, achieving remarkable spatial resolution. Subsequently, a photocuring 3D printing method was employed for di(trimethylolpropane) tetraacrylate (TA), and both **3.3.34** and **3.3.44**-based photoinitiating systems were successfully utilized to produce macroscopic 3D designs, achieving remarkable spatial resolution.

Chen et al.[69] developed 12 distinct bis-chalcone based dyes (Figure 50) using 2,5-diethylene-cyclopentan-1-one as a base and employed them as high-performance type II photoinitiators (Table 58). When used together with bis(4-*tert*-butylphenyl) iodonium hexafluorophosphate (Iod) and ethyl 4-dimethylamino-benzoate (EDB), their combination significantly improved the efficiency of free radical photopolymerization (FRP) of polyethylene glycol diacrylate (PEG-DA) as well as the cationic photopolymerization (CP) of 3,4-epoxycyclohexylmethyl-3,4-epoxycyclohexane carboxylate (EPOX) upon exposure to 405 nm wavelength LED light.

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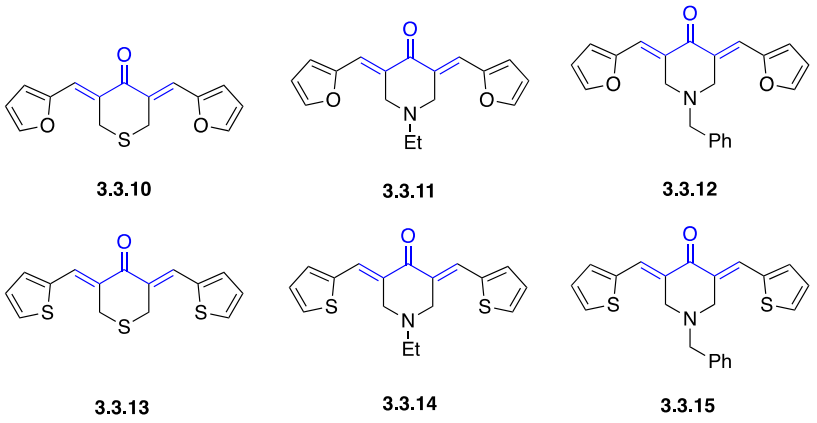

Figure 44. Series of bis-chalcones **3.3.10**−**3.3.15** tested by Xu et al. for photoinitiating properties.

Table 53. Light Absorption Properties of a Series of Bis-Chalcones 3.3.16−**3.3.25**

	Light Absorption Properties			
Compounds	λ_{max} [a] (nm)	ε_{max} (M^{-1} cm^{-1})	ε_{405nm} (M^{-1} cm^{-1})	ε_{375} nm (M^{-1} cm^{-1})
3.3.16	370 250 (sh)	21 900 19 900	12740	21800
3.3.17	380 253	28 200 19 100	19730	29000
3.3.18	332 511	18 200 4940	4420	5800
3.3.19	369 256	4980 4230	2550	4800
3.3.20	347 230 (sh)	23 100 25 300	6800	16500
3.3.21	364 253 (sh)	22 700 18 800	10070	21500
3.3.22	430 280	38 900 17 000	26420	8500
3.3.23	330 520	19 800 4200	2960	4000
3.3.24	370 256 (sh)	24 600 18 200	13670	24000
3.3.25	350	49 300	2220	24500

[a]sh means the shoulder of the absorption spectrum.

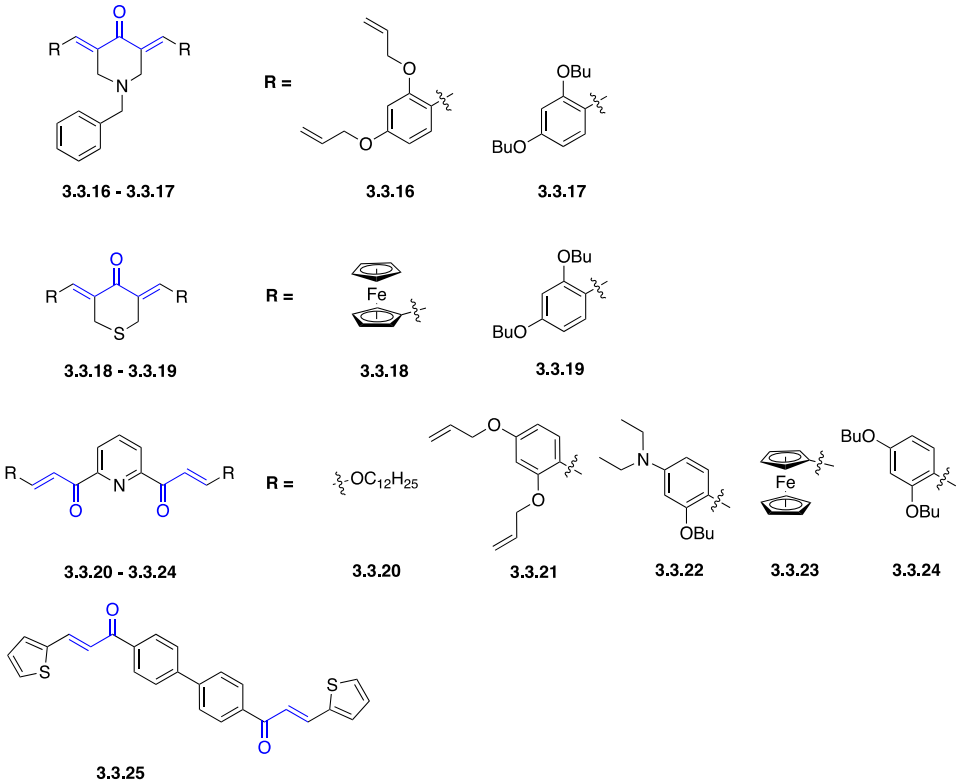

Figure 45. Chemical structures of bis-chalcones **3.3.16**−**3.3.25** tested by Chen et al. for photoinitiating properties.

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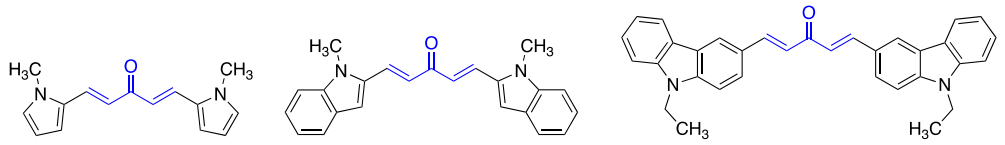

Figure 46. Series of bis-chalcones **3.3.26**−**3.3.28** tested by Xue et al. for photoinitiating properties.

Table 54. Photophysical Data of a Series of Bis-Chalcones 3.3.26−**3.3.28**

	Photophysical Data					
Compounds	λ_{max} (nm)	ε_{max} (M^{-1} cm^{-1})	ε_{405} (M^{-1} cm^{-1})	ε_{460} (M^{-1} cm^{-1})	λ_{em} (nm)	τ_{av}(ns)
3.3.26	414	43,300	42,200	6400	499	0.12
3.3.27	422	39,220	36,500	21,000	544	0.29
3.3.28	403	40,090	39,900	4300	511	0.67

Table 55. Photophysical Data of a Series of Bis-Chalcones 3.3.29−**3.3.32**

	Photophysical Data						
Comp.	λ_{max} (nm)	ε_{max} (M^{-1} cm^{-1})	ε_{405} (M^{-1} cm^{-1})	ε_{460} (M^{-1} cm^{-1})	λ_{em} (nm)	Φ_f	τ_{av} (ns)
3.3.29	414	43,300	42,200	6400	499	1.0	0.12
3.3.30	413	44100	42800	3100	498	0.12	0.62
3.3.31	415	46200	44500	2650	495	0.11	0.51
3.3.32	412	40400	39590	2660	497	0.07	1.17

Table 56. Light Absorption Properties of a Bis-Chalcone 3.3.32

	Light Absorption Properties				
Compounds	λ_{max} (nm)	ε_{max}(M^{-1} cm^{-1})	ε_{365}(M^{-1} cm^{-1})	ε_{385}(M^{-1} cm^{-1})	ε_{405}(M^{-1} cm^{-1})
3.3.32	373	38200	35100	32600	11800

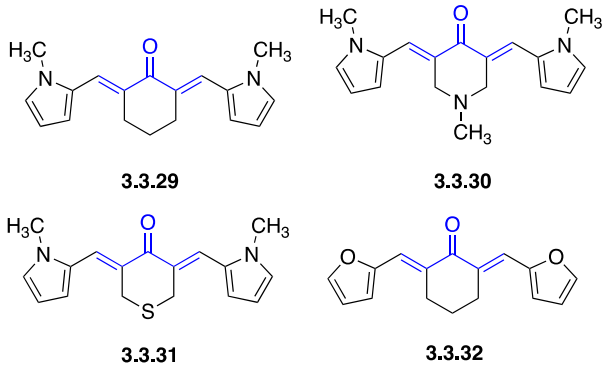

Figure 47. Series of bis-chalcones **3.3.29**−**3.3.32** tested by Xue et al. for photoinitiating properties.

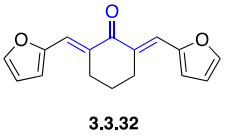

Figure 48. Chemical structure of bis-chalcone **3.3.32** tested by Li et al. for photoinitiating properties.

Table 57. Light Absorption Properties of a Series of Bis-Chalcones 3.3.33−**3.3.44**

	Light Absorption Properties		
Compounds	λ_{max} (nm)	ε_{max} (M^{-1} cm^{-1})	ε_{405} (M^{-1} cm^{-1})
3.3.33	430	41600	31900
3.3.34	430	45300	35000
3.3.35	431	49900	38400
3.3.36	430	40000	31900
3.3.37	436	49200	34200
3.3.38	440	43300	30000
3.3.39	250	81800	5400
3.3.40	250	113300	7400
3.3.41	250	149600	9900
3.3.42	250	178400	11500
3.3.43	250	175900	12000
3.3.44	250	129500	7800

4. CONCLUSION

Bis-chalcones have been shown to possess a wide range of applications. These compounds provide remarkable versatility yet flexibility for further SAR to optimize activity against various therapeutic targets. The derivatives have been reported with antimicrobial, antiviral, antioxidant, antiparasitic, antifeedant, antibiofilm, and antiproliferative activities and provide a nice starting point to improve the activity. Moreover, their roles in material science and other industries have been highlighted, showcasing their potential as organic dyes, photoinitiators, and electrochemical applications. Reactivity trends observed across different bis-chalcone compounds suggest an opportunity for further investigation, particularly in understanding the molecular foundations of their biological and material functions. Many of the current studies are phenotypic in nature, and while some studies have shown the mechanisms of action underlying the biological activities of bis-chalcones, comprehensive mechanistic insights remain sparse. This gap presents an opportunity for future research to delve into the molecular interactions and

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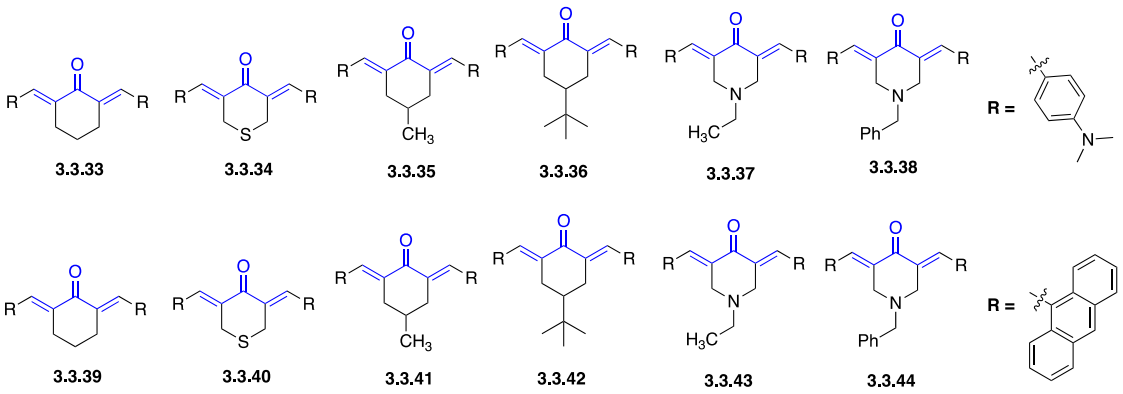

Figure 49. Chemical structures of bis-chalcones **3.3.33**−**3.3.44** tested by Xu et al. for photoinitiating properties.

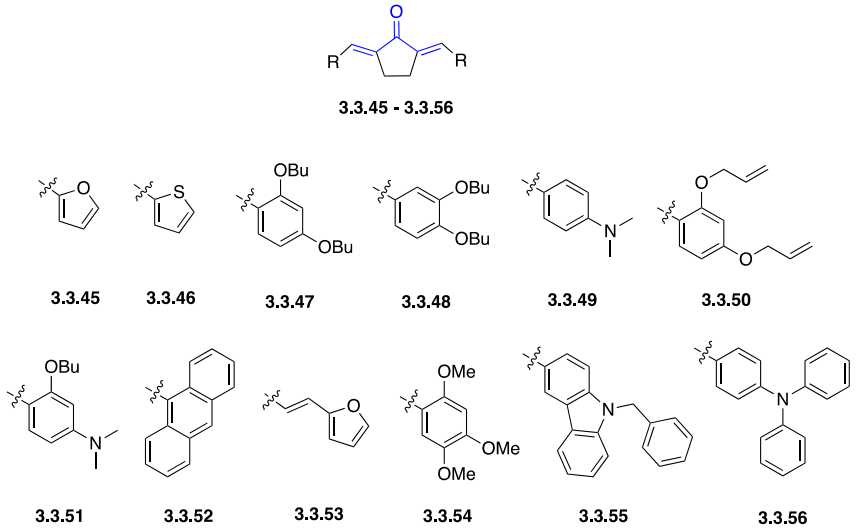

Figure 50. Chemical structures of bis-chalcones **3.3.45** and **3.3.56** tested by Chem et al. for photoinitiating properties.

Table 58. Light Absorption Properties of a Series of Bis-Chalcones 3.3.45−3.3.56

Light Absorption Properties				
Compounds	λ_{max} (nm)	ε_{max} (M^{-1} cm^{-1})	$\varepsilon_{@405nm}$ (M^{-1} cm^{-1})	$\varepsilon_{@407nm}$ (M^{-1} cm^{-1})
3.3.45	396	41,980	37050	270
3.3.46	392	40840	33590	110
3.3.47	400 274	41,770 69,250	41610	2720
3.3.48	399	42500	41580	1280
3.3.49	460 274	57,400 37,300	23700	53446
3.3.50	397	38150	36700	1710
3.3.51	485 278	65,670 22,680	16200	59370
3.3.52	418 268	6970 12890	6800	1600
3.3.53	428 283	61,130 15,340	50310	16540
3.3.54	427 280	42062 14160	32270	14380
3.3.55	421 236	36,350 46,810	30560	10160
3.3.56	460 298	47620 35060	25300	44400

pathways that confer bis-chalcones with their wide-ranging activities to understand the cellular targets that are being engaged by these compounds. Besides being phenotypic in nature, many studies just report a single data point of activity with no error margins. It would be interesting to have these activities repeated at least in duplicate to have more confidence in the reported activities. The studies often lack a comprehensive SAR, for example, some report the study of halogen substituted bis-chalcones, others report the activity of the methyl substituted bis-chalcones. The studies with a comprehensive set of substitutions are lacking. On a similar note, the impact of nonsymmetrical bis-chalcones on the activity remains to be seen. The study of the use of bis-chalcones as adjuvants is another untapped area of research. Lastly, determination of the toxicity and the tissue distribution of these compounds could open avenues of the preparation of liposomes and nanoparticles containing these compounds and study the delivery of the

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compounds to the target sites along with evaluation of the activity and cytotoxicity.

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L.S. conducted the literature review and wrote the initial draft; M.B.H contributed to the writeup of the draft, and R.S.Z.S and G.A.C. revised and updated the manuscript. All authors have read and agreed to the published version of the manuscript.

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