

Synthetic strategies in curcumin chemistry focused on anticancer applications

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Dedicated to Professor Jan Bergman on the occasion of his 80th birthday

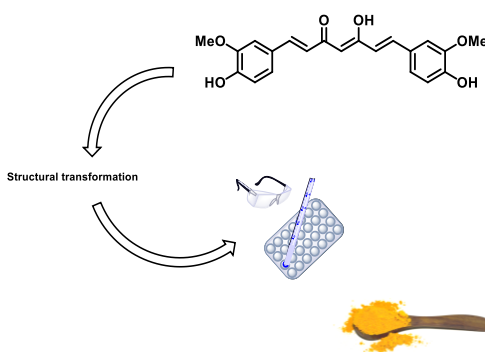
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Abstract

In spite of having received considerable interest as a potential anticancer agent over the past two decades, curcumin has not been developed into a sturdy drug candidate yet, mainly due to the challenges imposed by its rapidly metabolizable structure, leading to bioavailability and stability issues, and its aspecific activity. To circumvent these obstacles, chemical modification of the parent scaffold has been shown to involve an eligible approach for the construction of curcuminoids with improved properties. This review article provides a compilation of curcumin modifications and the effect thereof on the anticancer activity displayed by the resulting new analogs.



Keywords: Curcumin, Curcuminoids, Bioavailability, Cancer

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1. Introduction

Curcumin, a natural product extracted from the rhizomes of the turmeric plant *Curcuma longa*, has been commonly used as a food additive and a traditional medicine in South Asia. In addition, curcumin has been explored pharmacologically by many researchers, driven by the shedload of biological potential associated with this compound. The promising prospects of curcumin-based molecules have indeed attracted notable attention, especially in the field of oncology. However, curcuminoids exhibit propitious effects on inflammation, ageing, diabetes, and cardiovascular diseases, among other potential applications as well.¹⁻³ Despite this broad therapeutic window, most of the curcumin research is linked to anticancer activity. Malignant disorders represent a major health challenge accounting for more than 8 million deaths per year and therefore new therapeutic opportunities in that context are highly desirable. Curcumin-based studies within that framework include curcumin-mediated suppression of cell proliferation, reduction of tumor load and induction of apoptosis in various cancers, both *in vitro* and *in vivo*.⁴ The anticancer activity of curcumin is effective through several pathways such as an induction of p53-dependent apoptosis pathways in different cancer cells (colon, breast, bladder), and stimulation of both p53-dependent and p53-independent G2/M phase arrest has also been shown to exert inhibitory effects on cyclooxygenase COX-2 and proto-oncogene cyclin D1, mediated through the transcription factor NF- κ B and hence the restriction of tumor cell growth in colorectal cancer.⁵⁻⁸ The growth of malignant tumors has been observed to be restricted upon these mechanisms along with an inclusion of pro-apoptotic, antiproliferative, antioxidant and anti-inflammatory mechanisms.^{9,10} However, the lack of understanding of the mode of action coupled with other issues such as a low bioavailability leading to a poor absorption in the body still remains a huge obstacle in the development of curcumin-derived pharmaceuticals. Indeed, although curcumin has been amply shown to inhibit cancer cell proliferation, it is rapidly metabolized and systemically eliminated from the human body, and it suffers from chemical degradation in aqueous solutions.^{11,12} In contrast to other polyphenols, the degradation of curcumin is not related to its phenolic groups but is rather induced by hydrolysis of the labile β -diketo moiety. Unfortunately, these drawbacks imply a serious concern and hamper potential applications of curcumin in health care. In addition to bioavailability and stability issues, the mode of action of curcuminoids remains poorly understood; hence, they are often considered to be pan-assay interference compounds (PAINS)

showing rather unspecific activity across a range of assays.¹³ But it has been recently demonstrated that curcumin is able to block Kaposi's sarcoma associated herpesvirus replication and inhibits the pathogenic processes of cell invasion and angiogenesis predicting a potential application in treatment of viral infection and virus-related cancer and also suggesting that curcumin is not a PAINS but an inhibitor to APE1 redox function that affects many genes and pathways.¹⁴ Nevertheless, it might be possible to circumvent problems associated with low bioavailability, low stability and non-specific activity to a great extent through structural modifications of the basic curcumin framework. Curcumin contains a β -diketo moiety, two phenolic groups and two olefinic entities delivering a broad diversity of options for chemical modification of the curcumin scaffold. The curcumin framework has been utilized frequently for a variety of straightforward transformations, mainly focused on the synthesis of pyrazoles and isoxazoles,¹⁵⁻¹⁷ but the dearth of the investigation of an extensive range of transformations still provides opportunities for further exploration. For example, a recent study revealed improved water solubility, antioxidant effects and anti-proliferative activities upon replacement of the curcumin β -diketo moiety with a β -enaminone group.^{18,19} In addition to enaminone production, other synthetic transformations, such as replacement of the aromatic benzene rings by heteroaromatic scaffolds and simultaneous modification of the olefinic and diketo moieties, were also addressed as a part of this review to examine rather unapprised innovative classes of curcuminoids.

Despite many recent realizations in curcuminoid chemistry and biology, current contributions remain insufficient for the development of curcumin-based drugs, which has been acknowledged in a *J. Med. Chem.* Perspective, calling upon the curcumin chemistry community to move towards more out-of-the-box approaches.²⁰ The present review article has the intention to outline the state-of-the-art and to provide anchor points to guide future synthetic endeavors in this field of research.

2. Chemical Structure and Biological Interest of Curcuminoids

Curcumin (diferuloylmethane) is a polyphenolic compound that can be isolated from different sources, e.g., the roots of the plants *Curcuma longa*, *Curcuma zedoaria*, and *Curcuma aromati*. The major curcuminoids present in turmeric are bisdemethoxycurcumin **2**, demethoxycurcumin **3** and the later identified cyclocurcumin **4**.²¹ The main components of commercially available curcumin samples are approximately 77% curcumin **1**, 17% demethoxycurcumin (DMC), and 3% bisdemethoxycurcumin (BDMC) (Figure 1).^{22,23} Curcuminoids are a class of natural compounds found in turmeric responsible for imparting a yellow color to it, but are not essentially limited to diferuloylmethane (curcumin), demethoxycurcumin and bisdemethoxycurcumin. Turmeric has initially been put forward as a food spice used as an essential ingredient of curries and as a part of Asian cuisine, primarily for the flavor and the color, and has also been used to cure a variety of inflammation-related health problems by Asians since long.^{24,25} The scope of the research to seek new potential anticancer agents stems from the toxicity, virtually inefficiency, and expense of the existing ones, thus rendering them far out of reach for a large number of population groups. Curcumin has been shown to have a potentially strong therapeutic profile against a variety of cancers and a promising ability to suppress transformation, proliferation, and metastasis of tumors based on research in the past few decades with no considerably muddling side effects often associated with traditional medications like nausea, vomiting, diarrhea or even liver failure.^{22,26,27} Curcumin has also been noted for its rather high tolerance levels with doses of 12 grams per day being both safe and efficacious.²⁸ To that end, its use as a regular dietary supplement in some parts of Asia might therefore be one of the contributing factors for the lower incidence of cancer in those regions compared to the western world.²⁹

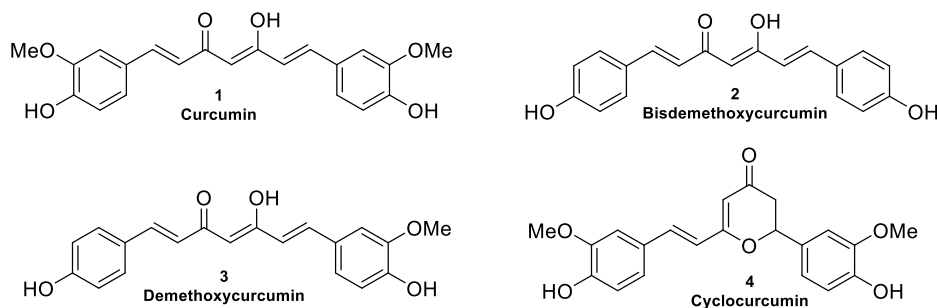


Figure 1. Chemical structure of curcuminoids **1-4**.

Chemically speaking, curcumin is a bis- α , β -unsaturated β -diketone that exhibits keto-enol tautomerism, with the enol tautomer as the predominant form in solution based on NMR studies at pH 3-9.³⁰ The planarity of the enol form allows for intramolecular hydrogen bonding (which leads to a more stable structure). However, the compound is more stable in acidic conditions and rapidly degrades at either natural or alkaline pH (Figure 2).^{11,20,31} There have been attempts to improve the stability of **1** through synthetic manipulations, including encapsulation strategies,^{32,33} removal or protection of oxidation sites,³⁴ and derivatization of the diketone moiety.^{35,36}

An example of the effect of structural modifications of the curcumin scaffold comprises of the significantly different antioxidant, antitumor, and anti-inflammatory activities of compounds **1-3** through only the introduction of a methoxy substituent. Till date, there has been no clear correlation between the physicochemical and molecular properties of the three curcuminoids and their biological activities, but there are reports that provide clues to map the groups responsible for a given biological activity within the curcuminoid series. Most studies suggest that curcumin **1** is the best radical scavenger and antioxidant among the three, followed by compounds **3** and **2** in decreasing order of potential, which is explicable in terms of *O*-methoxy substitutions: intramolecular hydrogen bonding between the phenolic hydroxy and methoxy groups (in **1** and **3**) influences the O–H bond energy, subsequently easing the H-atom abstraction by free radicals, and thus the absence of this methoxy group in the compound **2** renders it as the weakest radical scavenger.³⁷

Despite great advances in curcuminoid research, there are still several challenges to be addressed, such as understanding the mode of action of curcumin and improving its low bioavailability due to its poor solubility and fast metabolism. Curcumin has also been observed (via HPLC-MS) to degrade into vanillin, ferulic acid, and feruloylmethane under different conditions.^{11,38} Thus, for the foreseeable future, further research shall most likely focus on overcoming these disadvantages through encapsulations/nanoparticles,³⁹⁻⁶² combination effects with piperine to enhance the bioactivity/bioavailability⁶³⁻⁷³ and – of particular interest to this overview – structural modifications.^{7,22,23,74,75}

In this literature review, the general synthetic route towards curcumin and optimization thereof is discussed, since that approach forms the basis for further derivatization. An overview of the oncological applications of curcumin(oids) has been dispensed, followed by a discussion of the structural modifications to the curcumin scaffold that have been performed as a strategy to improve its pharmacokinetic profile.

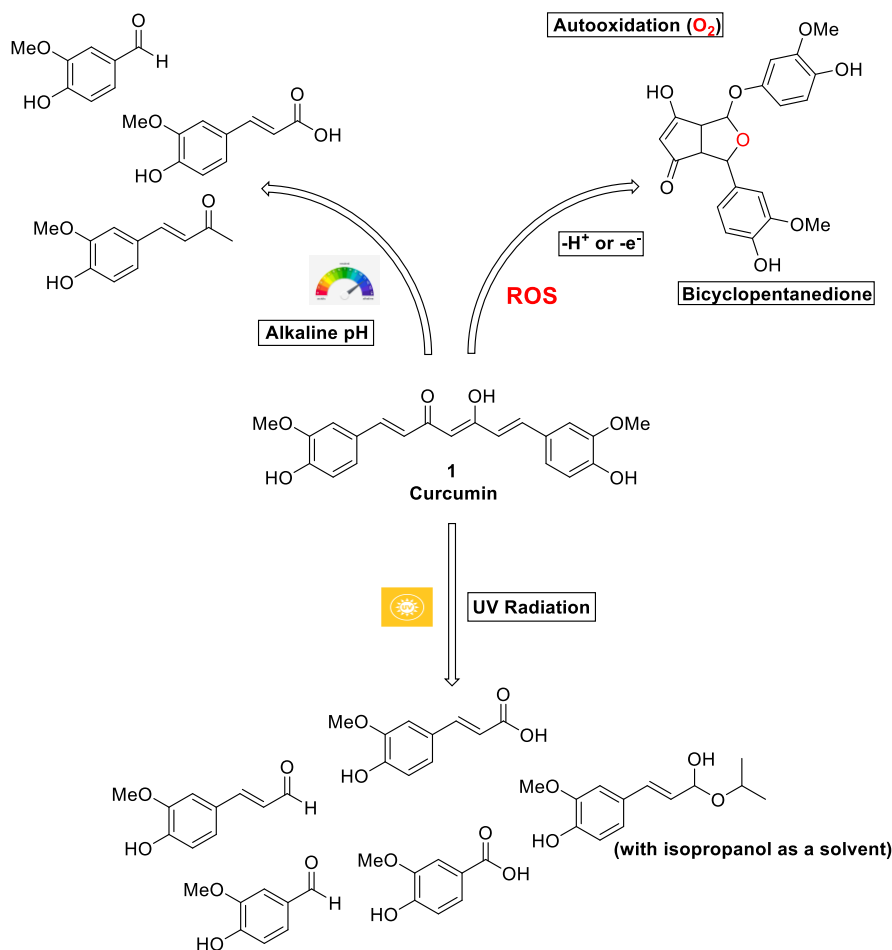


Figure 2. Possible major degradation pathways of curcumin **1**.

3. General Synthetic Routes to Curcumin and its Analogs

The general synthetic strategy towards curcumin and its derivatives involves the condensation of substituted benzaldehydes with acetylacetone (Figure 3).^{76,77} The synthesis of curcumin **1** under variable reaction conditions such as solvent systems, complexing agents, temperature, time and amount of H₂O scavenger, has been studied in detail in order to achieve an optimized process. For the synthesis of curcumin **1**, acetylacetone and 4-hydroxy-3-methoxybenzaldehyde (vanillin) were used in a theoretically stoichiometric ratio (1:2). Boric oxide was used as a complexing agent to protect the C3 of acetylacetone from Knoevenagel condensation. Solvent selection was also an important factor in the optimization process to obtain the appropriate solubility for the reactants, intermediates and products. Various solvents were screened, including dimethylformamide (DMF), ethyl acetate (EtOAc), 1,4-dioxane, acetonitrile (MeCN) and toluene (Table 1). Furthermore, it is critical to select a basic catalyst that ideally only deprotonates the methyl groups of acetylacetone (in all chosen solvents), because a stronger base can also deprotonate the phenolic OH group, which might result in the deactivation of vanillin and thus prevent the condensation reaction. The base *n*-butylamine (*n*-BuNH₂) was identified as the most appropriate catalyst. Catalyst loading was performed slowly up to 40% (volume) of acetylacetone.^{76,78}

The reaction was carried out under anhydrous conditions by using high purity solvents, as water molecules could bind to the diketone complex (i.e., complex of acetylacetone and boron, Figure 3) and reduce the yield.

However, water is also produced when the diketone complex and curcumin are formed. Therefore, tributyl borate ($n\text{-BuO}$)₃B was incorporated as a water scavenger in order to bind to H₂O molecules produced during the reaction. Varying ratios of ($n\text{-BuO}$)₃B were tested to find the optimal amount.⁷⁶⁻⁷⁸ Another parameter influencing the reaction between the diketone complex and vanillin is the temperature. Below 40°C, the reaction rate was too slow to get a workable yield, so higher temperature conditions had to be procured. In that respect, the reaction conditions were altered by varying the solvents at different temperatures (Table 1), with n -butylamine as a catalyst and ($n\text{-BuO}$)₃B as a water scavenger (if any). First the reaction between acetylacetone and vanillin with a molar ratio of 1:2, respectively, was carried out at 60°C in DMF. The complexing agent (B₂O₃) was added at an equivalent molar ratio to acetylacetone without any water scavenger. After 12 h, only a 6% yield was obtained. No significant improvement in yield was observed upon repetition with a water scavenger.⁷⁸

Subsequently, other solvents were utilized with varying reaction parameters, including amount of water scavenger ($n\text{-BuO}$)₃B and catalyst ($n\text{-BuNH}_2$ or other bases), time and temperature. In ethyl acetate, an increased amount of ($n\text{-BuO}$)₃B did improve the yield significantly from 21% to 43%. In the presence of acetonitrile and dioxane, almost identical yields were obtained. Using toluene as a solvent resulted in very low yields, even at higher temperatures. Ethyl acetate (EtOAc) was found to give the most significant improvement in yield due to better solubility of the reactants, intermediates and products, delivering the highest yield (89%) at 80°C (Table 1, bold) with a 2:1 ratio of ($n\text{-BuO}$)₃B and B₂O₃ to acetylacetone-vanillin solution.⁷⁶

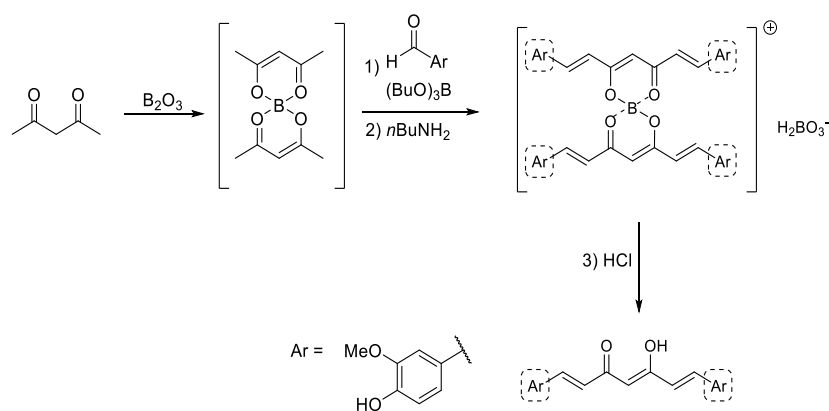


Figure 3. General synthetic route to curcumin **1**.

Table 1. Parameter variation for curcumin synthesis^{76,78}

Solvent	H ₂ O scavenger	Ratio ($n\text{BuO}$) ₃ B:B ₂ O ₃	Temp. (°C)	Time (h)	Yield (%)
DMF	-	-	60	12	6
DMF	($n\text{-BuO}$) ₃ B	2:1	80	12	15
EtOAc	-	-	60	4	21
EtOAc	($n\text{-BuO}$) ₃ B	2:1	60	4	43
EtOAc	($n\text{-BuO}$)₃B	2:1	80	4	89
Dioxane	($n\text{-BuO}$) ₃ B	2:1	60	12	20
MeCN	($n\text{-BuO}$) ₃ B	2:1	60	12	18
Toluene	($n\text{-BuO}$) ₃ B	2:1	60	12	3
Toluene	($n\text{-BuO}$) ₃ B	2:1	80	12	6

4. Curcumin against Cancer

Cancer involves the dysregulation of multiple cellular pathways that normally regulate cell proliferation. The annual global incidence of cancer is expected to increase from 14.1 million new cases in 2012, with 8.2 million deaths to nearly 25 million new cases in 2032.⁷⁹ Most drugs currently available for the treatment of cancer have limited potential because they are either very toxic, highly inefficient, or too expensive for the majority to afford. Treatments without these disadvantages are constantly being sought for, with curcumin presenting itself as a potential scaffold for future studies. To an advantage, curcumin has been consumed as a dietary supplement for centuries and is considered to be pharmacologically safe.²⁵

Accumulating evidence suggests that curcumin has a diverse range of molecular targets, which supports the notion that it influences numerous biochemical and molecular cascades. Among its molecular targets are transcription factors, growth factors and their receptors, cytokines, enzymes, and genes regulating cell proliferation and apoptosis. Extensive investigation suggests that curcumin has therapeutic potential in the treatment of various disorders (Scheme 1) as it is known to reduce blood cholesterol,⁸⁰⁻⁸⁵ prevent low-density lipoprotein oxidation,⁸⁶⁻⁸⁸ inhibit platelet aggregation,^{89,90} suppress thrombosis^{91,92} and myocardial infarction,⁹³⁻⁹⁶ suppress symptoms associated with type II diabetes,⁹⁷⁻¹⁰⁴ rheumatoid arthritis,¹⁰⁵⁻¹⁰⁹ multiple sclerosis¹¹⁰ and Alzheimer's disease,¹¹¹⁻¹¹⁵ inhibits HIV replication,¹¹⁶⁻¹²⁴ enhance wound healing,¹²⁵⁻¹³⁰ protect against liver injury,¹³¹⁻¹³⁸ prevent cataract formation,¹³⁹⁻¹⁴¹ protect from pulmonary toxicity and fibrosis, has therapeutic effects in leishmaniasis,¹⁴²⁻¹⁴⁴ and has anti-atherosclerotic activity.¹⁴⁵⁻¹⁴⁷ Most importantly, there is extensive literature suggesting that curcumin has potential in the prevention and treatment of various cancers, including colorectal cancer,^{148,149} pancreatic cancer,¹⁵⁰ breast cancer,^{70,151} prostate cancer,¹⁵² multiple myeloma,¹⁵¹ lung cancer and oral cancer.¹⁵¹ The ability of curcumin to target multiple pathways makes it an extremely potent anticancer agent. Despite having multiple pharmacological effects and being safe in phase-I clinical evaluations (even at high doses of 12 g/day),²⁸ curcumin has poor *in vivo* bioavailability, as demonstrated by its low serum levels and limited tissue distribution.^{12,153-155} It has been found that curcumin can be mostly metabolized in liver (hepatocyte cells) and intestine,¹⁵⁶ through both conjugation and reduction pathways in humans and rodents. Curcumin given orally undergoes conjugation, resulting in curcumin glucuronide and sulfates on hydroxy positions on the curcumin scaffold (Figure 5). Curcumin administered intraperitoneally or systemically undergoes reduction to generate tetrahydrocurcumin (THC, **5**), hexahydrocurcumin (HHC, **6**) and octahydrocurcumin (OHC, **7**) (Figure 4 and Scheme 2).^{157,158} It has been suggested by a study conducted for evaluation of tetrahydrocurcumin **5** as an anticancer agent relative to curcumin and a standard anticancer drug 5-fluorouracil (5-FU) employing three ESCC cell lines TE-1, TE-8 and KY-5 that further investigation of tetrahydrocurcumin in combination with standard treatments should be considered particularly for chemo-resistant ESCC because of the observed significant suppression of TE-1 cell proliferation with 5-FU in combination with tetrahydrocurcumin in contrast to no significant repression with 5-FU alone at the same dosage.¹⁵⁹ Tetrahydrocurcumin **5** has also been gaining research interest because of a better water solubility, anti-oxidative activity and chemical stability than curcumin. The revelation from many *in vitro* and *in vivo* studies that it brings into play regarding anti-cancer effects through diverse mechanisms such as xenobiotic detoxification, metastasis, proliferation, inflammation, oxidative stress and programmed cell death gives an idea that its utility is yet to be extensively evaluated as only a few oral bioavailability and pharmacokinetic studies have been performed so far.¹⁶⁰

Recently a nanoparticle-based administration of curcumin resulted in a 27-fold increase of blood levels in humans compared to that of curcumin powder indicating a promising therapeutic strategy for tackling bioavailability issues.¹⁶¹ Moreover, the comparisons between orally administered and intravenously (IV)

administered routes have been illustrated in Scheme 2 in order to provide a clear understanding of the different ways of administering curcumin and show its metabolism throughout Phases I and II on gut microbiota/liver.

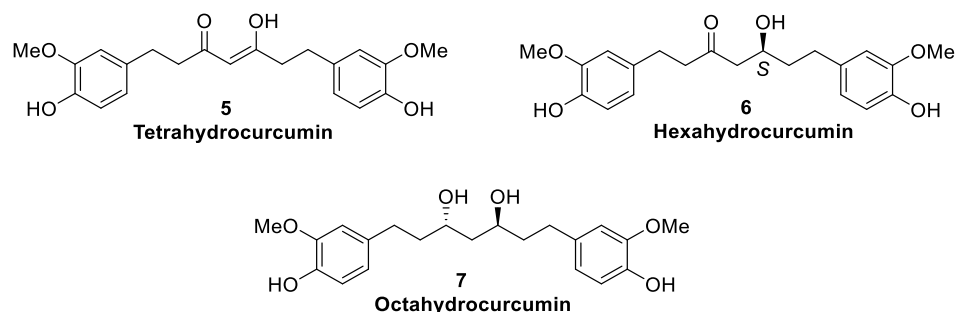


Figure 4. Metabolization of curcumin through reduction pathways provides analogs **5-7**.

Although the multicomponent nature of curcumin is well documented, it is not always clear as to which structures exist in a particular preparation. Herein the term *curcumin* will often be used interchangeably with *curcuminoids* unless a distinction is specifically made. Many studies with *in vitro* experiments use synthetic, pure curcumin while most *in vivo* studies and clinical trials use a mixture of curcuminoids.²⁰ In many scientific and medicinal circles, the extensive reported effects of curcumin have marked it as an imminent breakthrough therapy for complex diseases that are thought to require potent but nonselective remedies. Unfortunately, the uncritical enthusiasm for its potential benefits often disregards its dark side (poor bioavailability and fast metabolism).¹⁶² This eagerness could lead to an overly-optimistic interpretation of results, and consequently, compounds could be misidentified as a *hit* for drug development. As a matter of fact, neither curcumin nor its known analogs appear to possess the properties required for good drug candidates, i.e., chemical stability, high water solubility, potency, selectivity, high bioavailability, broad tissue distribution and stable metabolism. In that respect, the key challenge in curcumin research involves the elimination of these undesirable properties through structural modification and careful biological evaluation of novel types of curcuminoids, hopefully obtaining good candidates for an anticancer drug in the process.

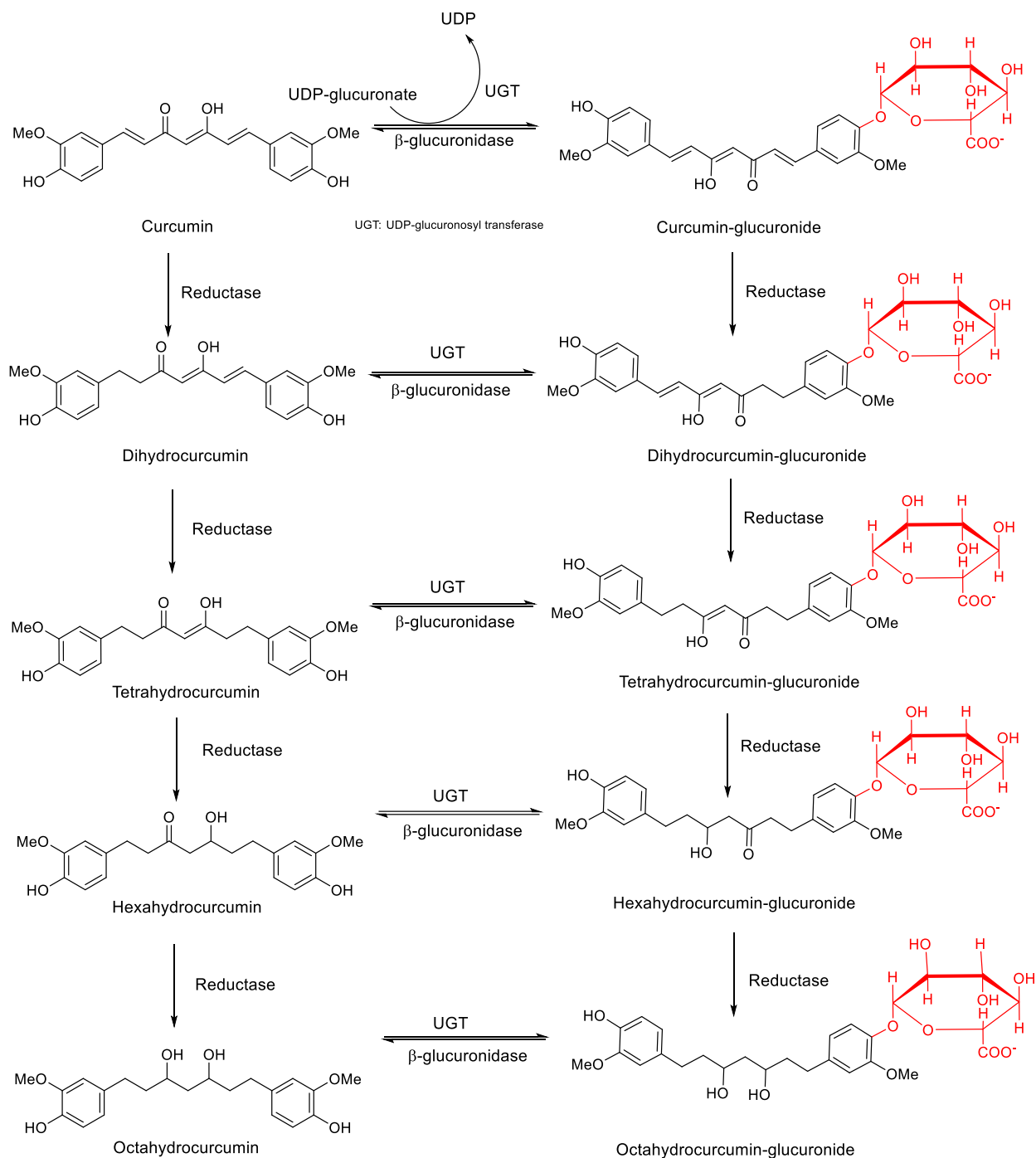
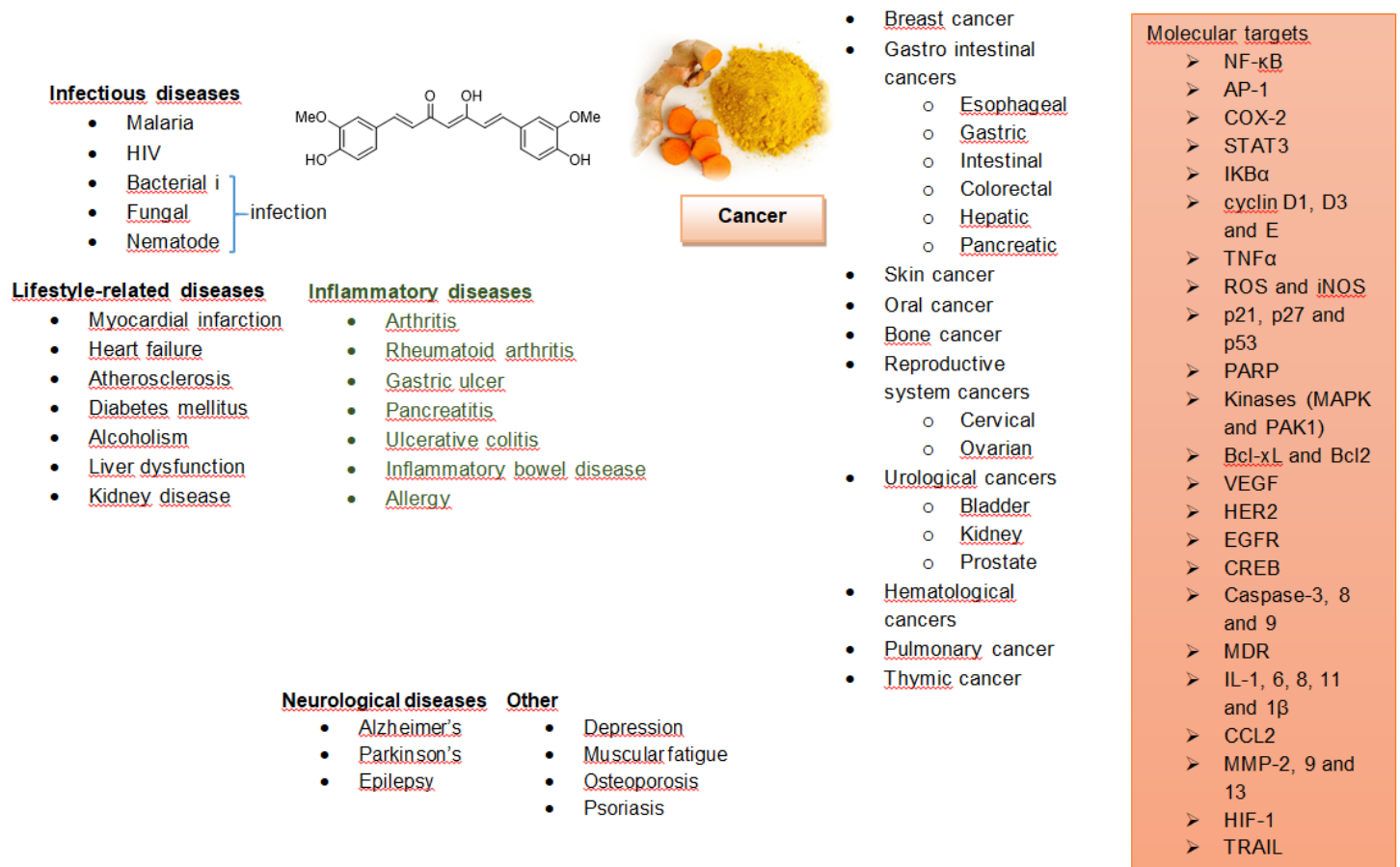
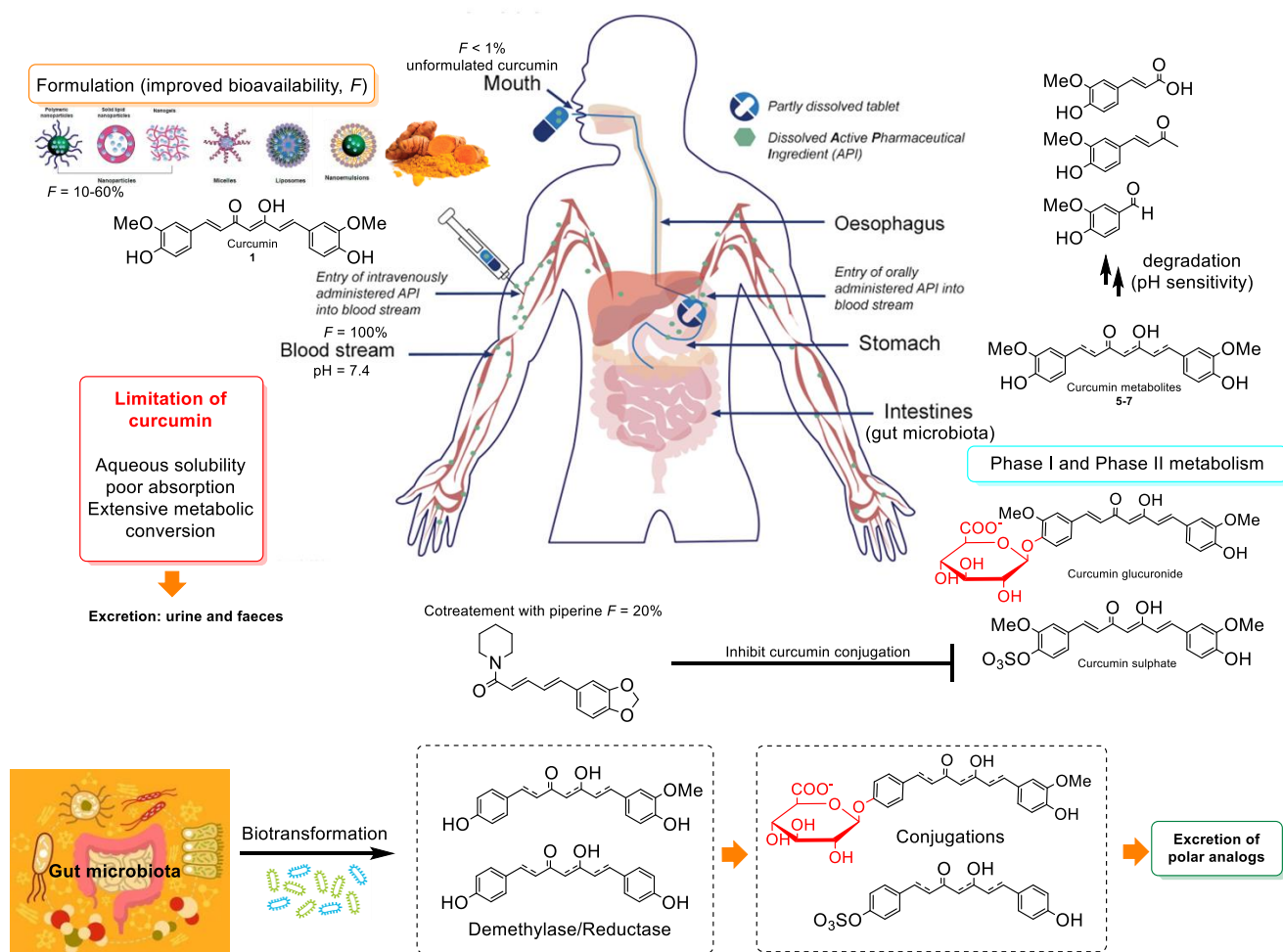


Figure 5. Phase I and phase II (glucuronidation) metabolism of curcumin via UGT enzyme.^{163,164}



Scheme 1. General illustration of the biological effects of curcumin.



Scheme 2. An illustration of potential delivery systems (oral administration vs IV routes)¹⁵⁶ to enhance curcumin bioavailability (F) via either formulations^{41,43,59,61,62} or piperine^{66,69,71} and metabolic conversion/detoxification (Phase I and II metabolism) in either intestine (gut microbiota)¹⁶⁵⁻¹⁷⁰ or liver.^{156, 171,172,173}

5. Structural Modification

The rapid degradation of curcumin brings about many challenges while investigating its biological influences (both *in vitro* and *in vivo*), which could be overcome through chemical modification strategies. Curcumin is a symmetrical diferuloylmethane, consisting of a methoxy group and a hydroxy group on its aromatic rings, a heptadiene with two Michael acceptors, and a β -diketone moiety. These groups are often modified in the hope of creating structural homologs with improved bioactivity and/or bioavailability compared to the original structure. Generally, an aldehyde (usually vanillin) and acetylacetone form the building blocks of curcumin. A wide variety of curcumin analogs can be synthesized by using different aldehydes as well as acetylacetone derivatives,^{119,174-192} including C3-substituted acetylacetone or acetylcycloalkanones (Figure 6).^{193,194}

A structure-activity relationship (SAR) study of symmetrical curcuminoids showed that the feruloyl (aromatic) moiety plays a critical role in various biological functions. As previously mentioned, curcumin is stable at an acidic pH, and its instability at a pH above 6.5 (i.e. physiological conditions) is most likely due to the active methylene group and the β -diketone moiety. This suggests that the deletion or modification of the β -diketone

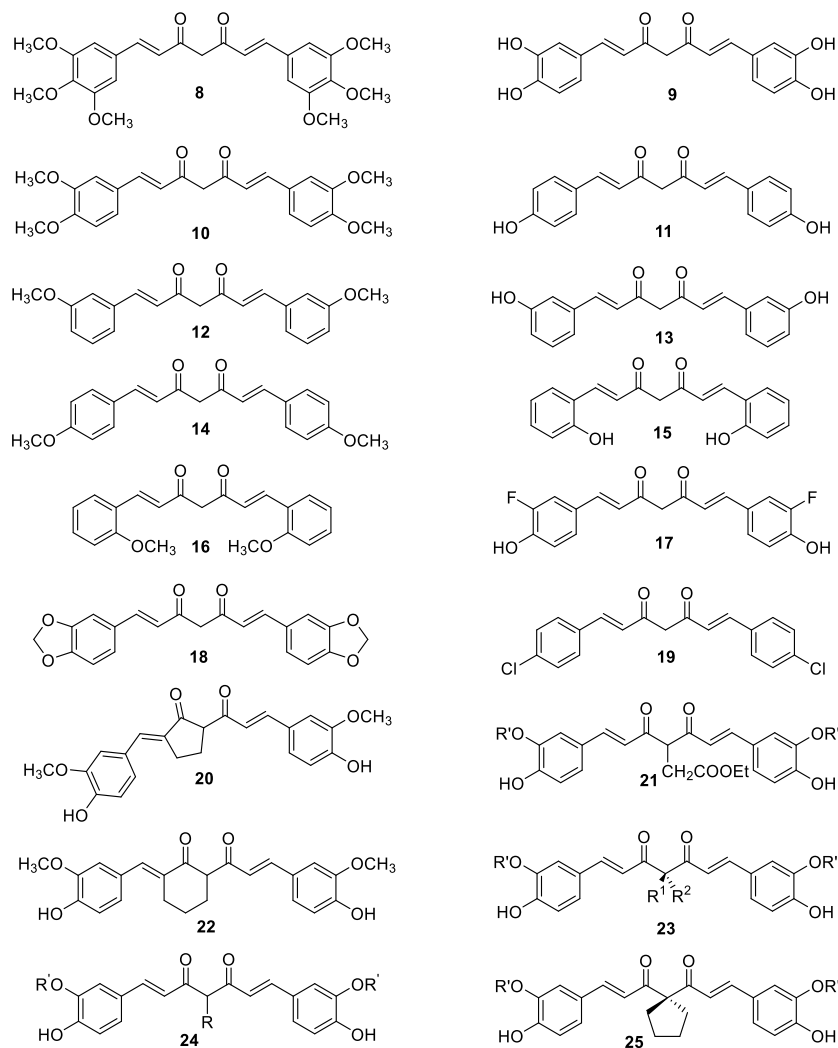
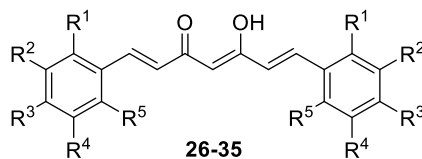


Figure 6. Curcuminoid analogs **8-25**.

5.1. Changes in aromatic ring substitutions

The antioxidant activity of curcumin **1** is not only due to its phenolic groups but also the *ortho*-methoxy functionality. Thus, it is anticipated that modifications of the substituents on the aromatic moiety will affect antioxidant activity. As mentioned earlier, the *ortho*-methoxy group can form an intramolecular hydrogen bond with the phenolic hydrogen, facilitating H-atom abstraction from the *ortho*-methoxy phenols. The scavenging activity significantly decreased in the order THC (18.7 μM , **5**) > HHC (21.6 μM , **6**) = OHC (23.6 μM , **7**) > Trolox (31.1 μM) \geq curcumin (35.1 μM , **1**) > DMC (53.4 μM , **3**) \gg BDMC (> 200 μM , **2**).³⁷ However, an increased number of hydroxy groups on the aromatic moiety (e.g. polyhydroxy-curcuminoid **26**, Scheme 4) showed interesting antioxidant properties.¹⁹⁷ Non-phenolic analogs **27-31** were either less active or inactive as antioxidants. It has been suggested that the steric crowding at *ortho* positions in compounds **32-34** (Scheme 4) contributes to a facile transfer of hydrogen atoms by stabilizing the phenoxy radical and preventing the phenolic group from forming a hydrogen bond with the medium, but when the R^2 and R^4 groups were replaced with bulkier *tert*-butyl groups ($\text{C}(\text{Me})_3$, **35**), antioxidant activity was reduced significantly due to the absence of a hydroxy group compared to **26**.^{198,199}



Compound	R ¹	R ²	R ³	R ⁴	R ⁵
26	H	OH	OH	OH	H
27	H	OMe	OMe	H	H
28	H	OMe	OMe	OMe	H
29	OMe	OMe	OMe	H	H
30	H	OMe	OMe	H	OMe
31	H	H	OMe	H	H
32	H	OMe	OH	OMe	H
33	H	OCH ₂ Me	OH	H	H
34	H	Me	OH	Me	H
35	H	C(Me) ₃	OCOMe	C(Me) ₃	H

Scheme 4. Chemical structures of curcuminoid analogs with aromatic ring substitutions **26-35**.

5.2. Changes in β -diketone moiety

5.2.1 Pyrazole and isoxazole analogs. The enol form of curcumin in solution was found to be responsible for its rapid degradation, and hence, to inflate the firmness of the structure, a number of analogs has been synthesized in which the diketone moiety was replaced by an isoxazole or pyrazole group. Interestingly, compounds **36** and **37** showed better free radical scavenging activity than curcumin with an IC₅₀(μ M) value for inhibition of proliferation of the A549 cells upon treatment with **37** being 3.70 ± 0.16 compared to the value of 11.0 ± 0.59 for curcumin **1** in RAW 264.7 cells (Figure 7).²⁰⁰ Synthesis, characterization and testing of *in vitro* anticancer activity of a novel series of curcumin analogs to explore potential therapeutics established compound **38**, which exhibited the best activity among several compounds tested and may be transformed further into a potential therapeutic.²⁰⁰ A number of click diarylpentane curcuminoids and their pyrazole derivatives has been synthesized, and this class of compounds validates as novel types of antimiotic agents, recognizing the pyrazole adduct **39** as a promising lead.²⁰⁰ Curcumin analogs of benzyloxime and the isoxazole and pyrazole substitutes demonstrated amplification in the antitumor activity both in the parental and in MDR MCF-7 cells.²⁰⁰

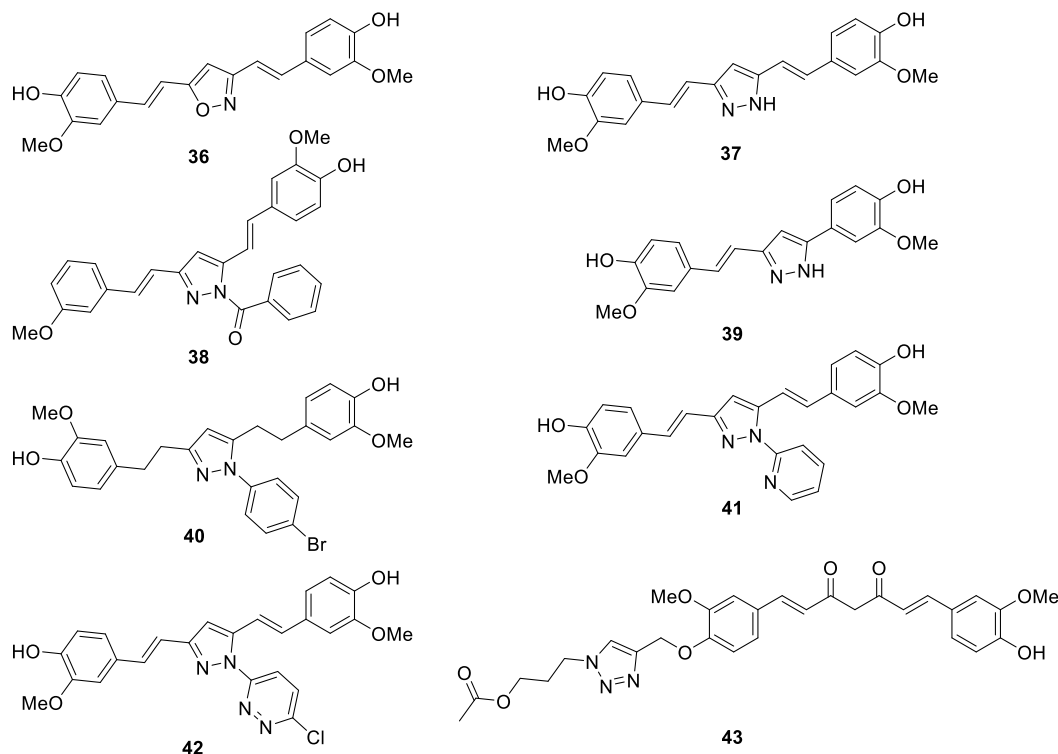
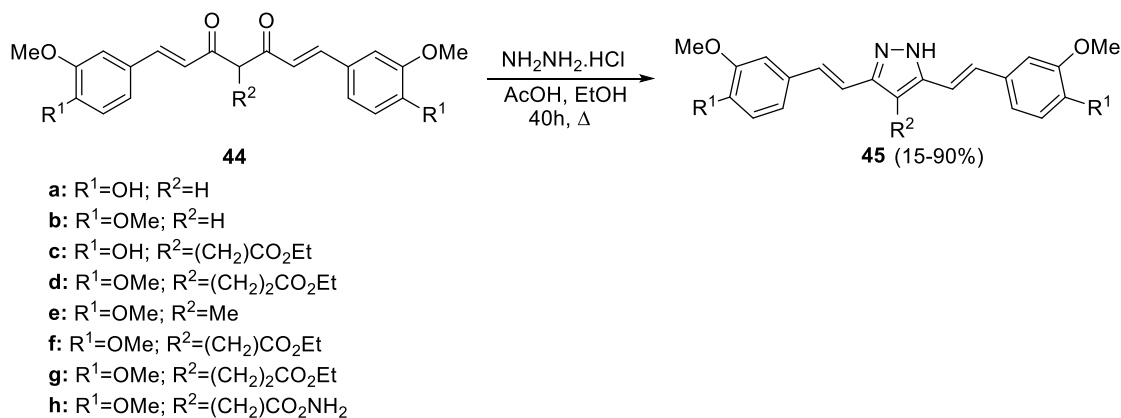


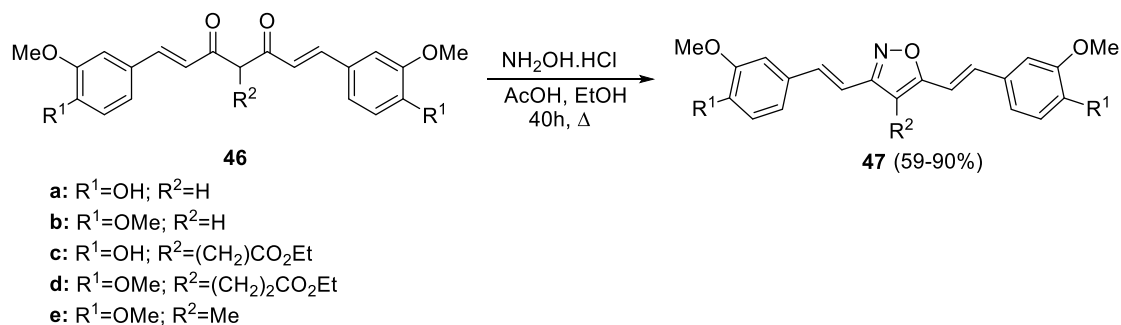
Figure 7. Structures of synthesized curcumin isoxazoles, pyrazoles and their analogs **36-43**.

Isoxazole and pyrazole derivatives were shown to be less prone to nucleophilic benzyl mercaptan addition than curcumin itself and demonstrated a better cell growth inhibition and pro-apoptotic effect in liver cancer HA22T/VGH cells as well as other tumor cells.²⁰⁰ A series of new pyrazole derivatives of THC, a major metabolite of curcumin, has shown to exhibit excellent anticancer activity against MCF-7 cell lines with good IC_{50} values.²⁰⁰ 4-Bromophenyl derivative **40** at the pyrazole moiety was the most effective and inhibited the growth of all three tested cell lines with IC_{50} values of 8.0 μ M (A549), 9.8 μ M (HeLa) and 5.8 μ M (MCF-7).²⁰⁰ Other pyrazole and triazole curcumin analogs have been synthesized and shown to exhibit activity at the micromolar range against head and neck cancer, among which compounds **42** and **43** demonstrated potent cytotoxicity values against HNSCC cell lines. Interestingly, compounds **41** and **42** appeared to have a pronounced effect on pSTAT3 phosphorylation with compound **42** being the first reported click chemistry curcumin analog showing good cytotoxic activity. Disruption of pFAK and pAKT phosphorylation signaling is shown with compound **43**.²⁰⁰ A number of pyrazole derivatives of penta-1,4-dien-3-one compounds containing a substituted pyrazole were synthesized and some of those showed significant antiproliferative activity against HepG2 cell lines with an IC_{50} value of 0.10-5.05 μ M compared to a value of 16.20 μ M for Sorafenib.²⁰⁰ Pyrazole **45** and isoxazole **47** analogs of curcumin **1** were produced with different substituents on the active methylene group. For the synthesis of pyrazole derivatives **45**, diketo derivatives **44** were prepared and reacted in an acid-catalyzed condensation reaction with 1.2 equivalents of hydrazine hydrochloride ($NH_2NH_2 \cdot HCl$) in absolute ethanol under reflux for forty hours (Scheme 5).²⁰¹ Likewise, isoxazole derivatives **47** were prepared from compounds **46** using hydroxylamine hydrochloride ($NH_2OH \cdot HCl$) (Scheme 6). Reported yields were generally high, ranging from 58% to 90%, with only compound **45g** having a very low yield of 15%.



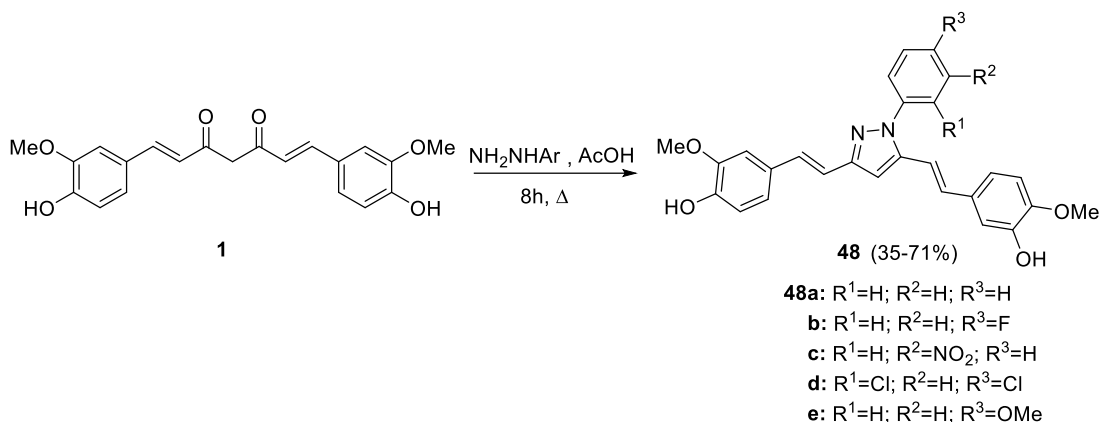
Scheme 5. Knorr pyrazole synthesis of pyrazole curcuminoids **45**.

In a study on the investigation of curcumin analogs as antimalarial agents, some new pyrazole derivatives (**48a-e**) containing an *N*-phenyl group were prepared (Scheme 7).²⁰² For their synthesis, curcumin **1** was dissolved in glacial acetic acid and reacted with 1.25 equivalents of the appropriate hydrazine under reflux. Phenylhydrazine, 4-fluorophenylhydrazine, 3-nitrophenylhydrazine, 2,4-dichlorophenylhydrazine and 4-methoxyphenylhydrazine were used to produce the corresponding compounds **48a-e**, respectively. In contrast to previous reactions, low to good yields (35-71%, Scheme 6) were obtained after a reaction time of 8 hours.²⁰² Additionally, analogs **45a** and **47a** were also evaluated for antimalarial activity against *Plasmodium falciparum* in this study.

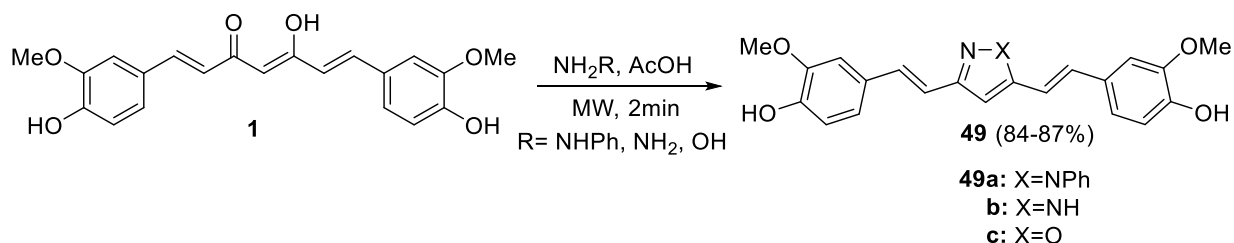


Scheme 6. Synthesis of isoxazole curcuminoids via Paal-Knorr chemistry **47**.

These molecules were prepared using a similar procedure as mentioned previously. The study reported good antimalarial activity exerted by compounds **45a** and **48c**, with respective IC₅₀ values of 0.48 ± 0.04 μM and 0.87 ± 0.07 μM, which is a higher potency compared to curcumin **1** (3.25 ± 0.6 μM).²⁰²



Scheme 7. Synthesis of *N*-arylpyrazole analogs **48**.

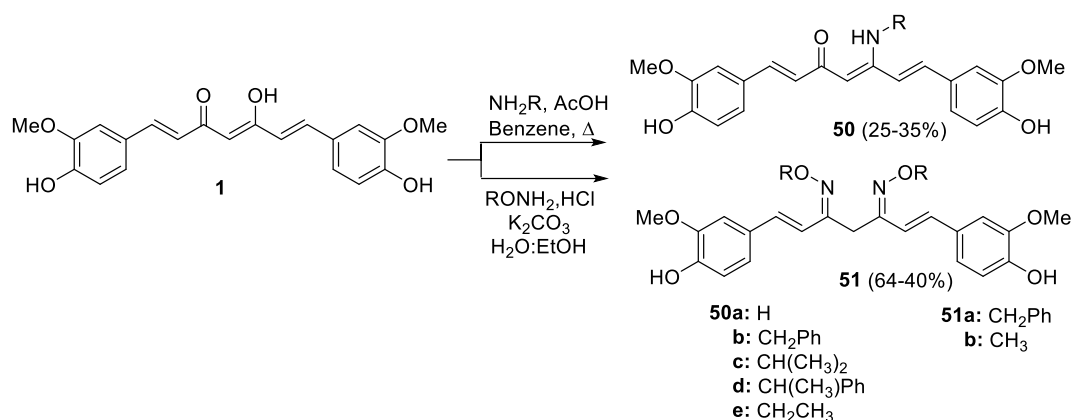


Scheme 8. Synthesis of pyrazole and isoxazole curcuminoids **49** via microwave irradiation.

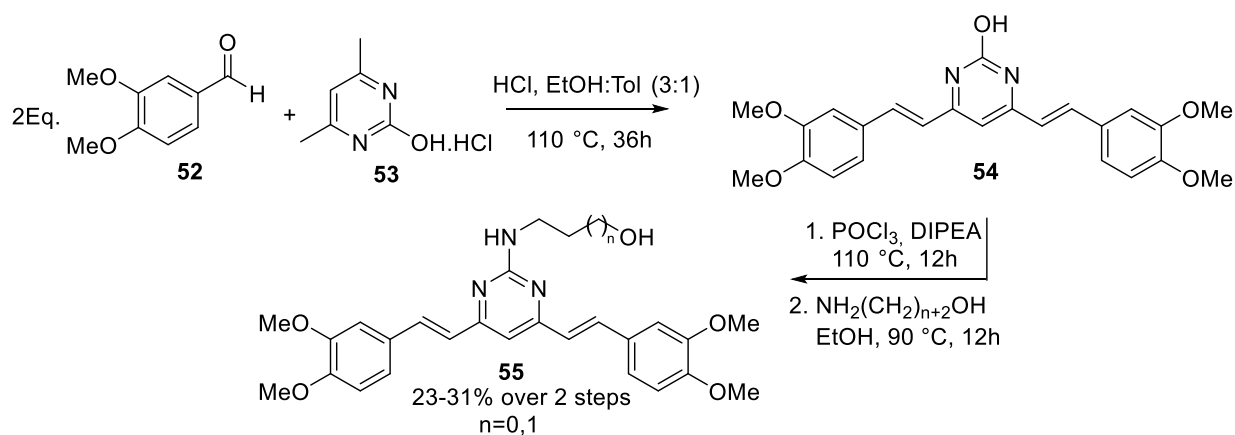
Modifications to the conventional synthesis procedure are also possible; for instance, three of the previously discussed isoxazole and pyrazole analogs have been synthesized with the assistance of microwave irradiation (Scheme 8).²⁰³ Compounds **49a-c** correspond to **48a**, **45a**, and **47a**. They were produced by reacting an equivalent amount of curcumin **1** and hydrazine (phenylhydrazine, hydrazine hydrate, and hydroxylamine hydrochloride, respectively) in 2 mL of glacial acetic acid for two minutes while being subjected to microwave irradiation. In a modified procedure, three more isoxazole/pyrazole analogs (**49a-c**) of curcumin **1** were prepared using microwave irradiation.²⁰³ This short procedure resulted in very high yields (84-87%). Compared to the duration of conventional reactions which could last from 8 to 40 hours, microwave irradiation seems to hold a remarkable potential in curcumin synthesis.²⁰¹⁻²⁰³

Isoxazole analogs of curcumin exhibited antiproliferative and cell death effects in MCF-7R comparable to those achieved in MCF-7 and cause minor changes in NF-κB or STAT3 activation.²⁰⁰ 4,4'-(1*E*,1'*E*)-2,2'-[1-(3-chlorophenyl)-1*H*-pyrazole-3,5-diyl]bis(ethene-2,1-diyl) bis(2-methoxyphenol) showed a high degree of cytotoxicity and cell proliferation inhibition against cancer cells and can be selected for further *in vitro* and *in vivo* investigations.²⁰⁰ Isoxazole analogs of curcumin exhibited significantly improved *in vitro* drug-like properties including solubility, metabolic stability, cell permeability and lack of nonspecific cytotoxicity when compared with curcumin.²⁰⁰

5.2.2. β-enaminones. Also β-enaminone analogs (**50a-e**) have been prepared in low yields (25-35%) by adding the appropriate primary amine to a mixture of curcumin **1** and acetic acid (Scheme 9). Any water formed during the reaction was removed via the Dean-Stark setup.²⁰⁴ Dioxime analogs **51a-b** were prepared by adding a solution of curcumin **1** and two equivalents of *O*-methyl or *O*-benzylhydroxylamine hydrochloride in 25% water-ethanol (1:3) to a solution of potassium carbonate in water (Scheme 9).²⁰⁴ The mixture was then heated under reflux for 25 minutes. Compounds **50a** and **50b** were obtained in 40% and 34% yield, respectively.

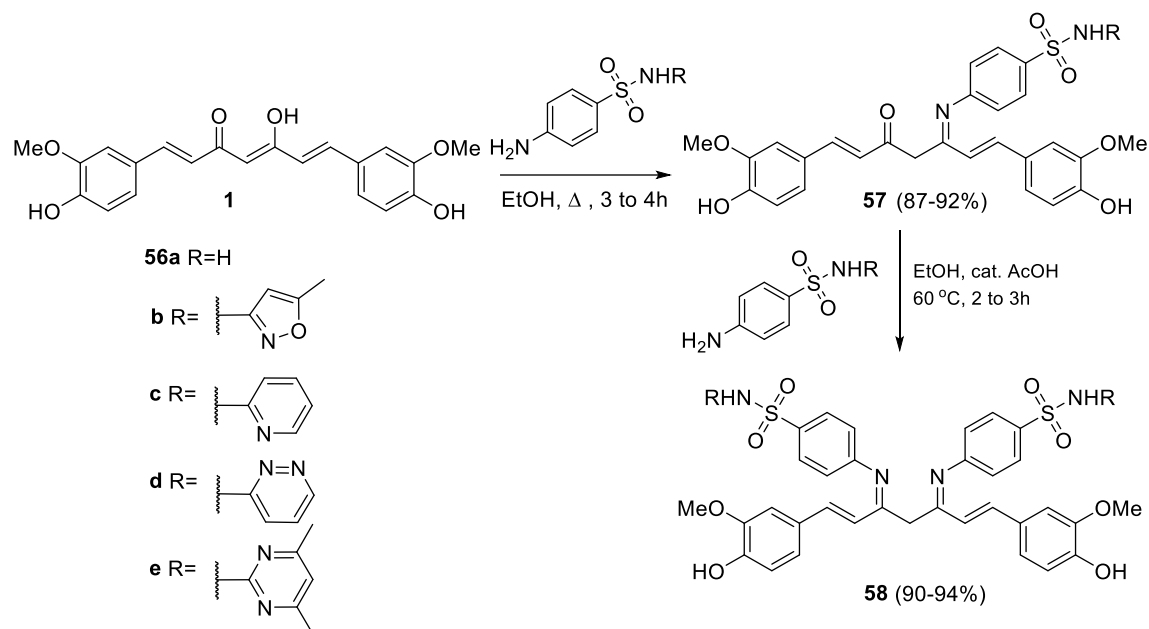


Scheme 9. Synthesis of mono/di-β-enaminone analogs **50** and **51**.



Scheme 10. Synthesis of pyrimidine-substituted curcumin analogs **55**.

For the synthesis of compounds **55**, two equivalents of 3,4-dimethoxybenzaldehyde **52** were reacted with 4,6-dimethyl-2-hydroxypyrimidine hydrochloride **53** in a solvent mixture of toluene and ethanol (1:3) with HCl as the catalyst. The obtained product **54** was then combined with diisopropylethylamine (DIPEA) in an excess of phosphoryl chloride (POCl₃) at reflux temperature. Here, the hydroxy group of **54** is substituted by a chlorine (not shown), and this intermediate can in turn react with a selected primary amine in EtOH to form the desired products **55** (Scheme 10).²⁰⁵ These compounds have been shown to be active and promote apoptosis against colon cancer (HTC116 cell line), which was consistent with the multiple functions of EGFR signaling pathways. Sulfonamide-containing curcuminoids **57** and **58** can be synthesized from imination with sulfanilamides in ethanol (Scheme 11).²⁰⁶ When acetic acid is added as the catalyst, compound **57** can react with sulfanilamide again and result in **58**. These curcumins showed interesting antibacterial properties (against *Staphylococcus aureus*, *Bacillus cereus*, *Salmonella typhi*, *Pseudomonas aeruginosa*, *Escherichia coli*: MIC = 20-80 μM) and antifungal activities (against *Aspergillus niger*, *Aspergillus flavus*, *Curvularia lunata*, *Trichoderma viride*: MIC = 40-80 μM), as well as moderate cytotoxicity (IC₅₀ values = 25-50 μM/mL against HeLa, HepG2, QG-56 and HCT116 cell lines).



Scheme 11. Synthesis of new derivatives of curcumin containing sulfonamides **57** and **58**.

5.2.3. Monocarbonyl analogs of Curcumin (MACs). To contend with research on traditional curcumin, the chemical class of curcumin monocarbonyl analogs has evolved bearing biological properties similar or superior to curcumin itself, furnishing a 10-20 fold potency gain for a number of cancer cell lines and cellular proteins and better pharmacokinetic profiles in mice, as well as higher tumor regression in cancer xenografts *in vivo* than curcumin.²⁰⁷ As the instability of curcumin stems from the methylene group and β -diketone moiety, the absence of the β -diketone moiety in monocarbonyl analogs may help enhance its stability. These analogs can be symmetrical, non-symmetrical or cyclic. An example class is made up by replacing the central 1,3-diketo structure by a piperidone skeleton **59** and **60** (Figure 8). This class is characterized by a better stability and easier synthesis compared to that of curcumin **1**.^{208,209}

Compound **59** has been shown to have good anti-inflammatory activity.^{188,189} A more remarkable analog is compound **60**, better known as EF24,²¹⁰⁻²¹⁴ which has been reported to work more effectively against several cancer cell lines than the regularly used chemotherapeutic drug Cisplatin®. In the field of anti-angiogenesis, the potency of compound **60** approaches the level of the drug TNP-470, an analog of Fumagillin.^{208,215} Further research on piperidone analogs furnished compound **65** that was even more powerful, synthesized by reaction of 2-chlorobenzaldehyde **62** and 4-piperidone hydrochloride **63** in glacial acetic acid (Scheme 12).²¹⁶ The reagents undergo a Claisen-Schmidt condensation, and compound **64** is formed. Finally, **64** is reacted with maleic anhydride in the presence of triethylamine (Et_3N) to obtain the desired compound **65** in a yield of 94%.

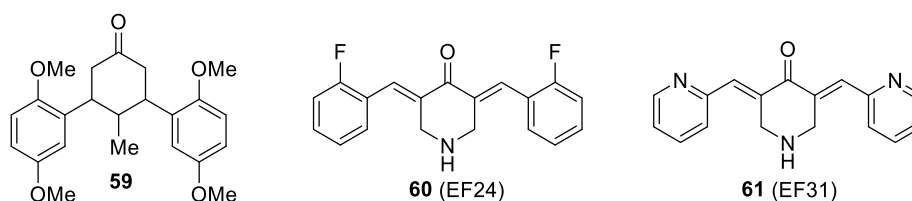
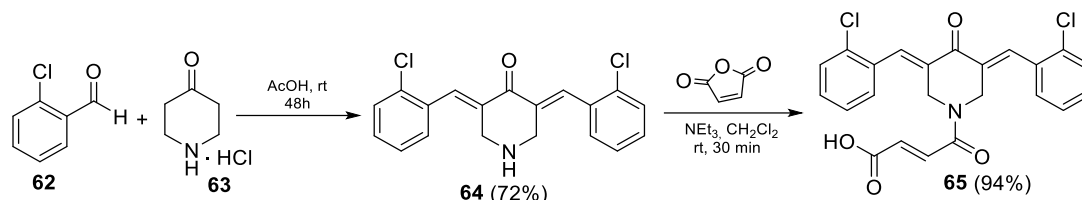


Figure 8. Monocarbonyl curcuminoids **59-61**.^{163,164,204,207}



Scheme 12. Synthetic approach towards 3,5-bis(2-chlorobenzylidene)-4-piperidones **64** and synthesis of *N*-acyl derivatives of 3,5-bis(2-chlorobenzylidene)-4-piperidone **65**.

MAC curcumin analogs are often assessed in phenotypic assays such as proliferation and angiogenesis by investigators in cancer studies. One of the MACs, EF31 (**61**, Figure 8) has shown to be able to block 22 of 50 cancer-related kinases by a recent modest kinase screen.²⁰⁷ In addition to other techniques, glycosylation is also known to significantly alter the properties of small molecules and therefore concerns a frequently applied modification of drug-like compounds. For example, glycosylation can enhance water solubility and the stability and/or bioactivity of target structures. In that respect, the glycosylation of curcumin has been explored intensively in the literature, e.g. culminating in efficient biocatalytic methodologies to efficiently produce curcumin (di)glucoside.²¹⁷

A series of symmetric piperidones **66-89** (Figures 9 and 10) has been synthesized to evaluate cytotoxic effects using murine P388 and L1210 cells as well as human Molt4/C8 and CEM T lymphocytes, amongst which the average value for the *N*-acroyl analogs **75-81** being 1.8 μ M for the four cell lines while the *N*-unsubstituted compounds **82-88** furnished a higher average of 44 μ M, for which the electronic parameters were deemed the most important factor influencing cytotoxicity.²⁰⁷

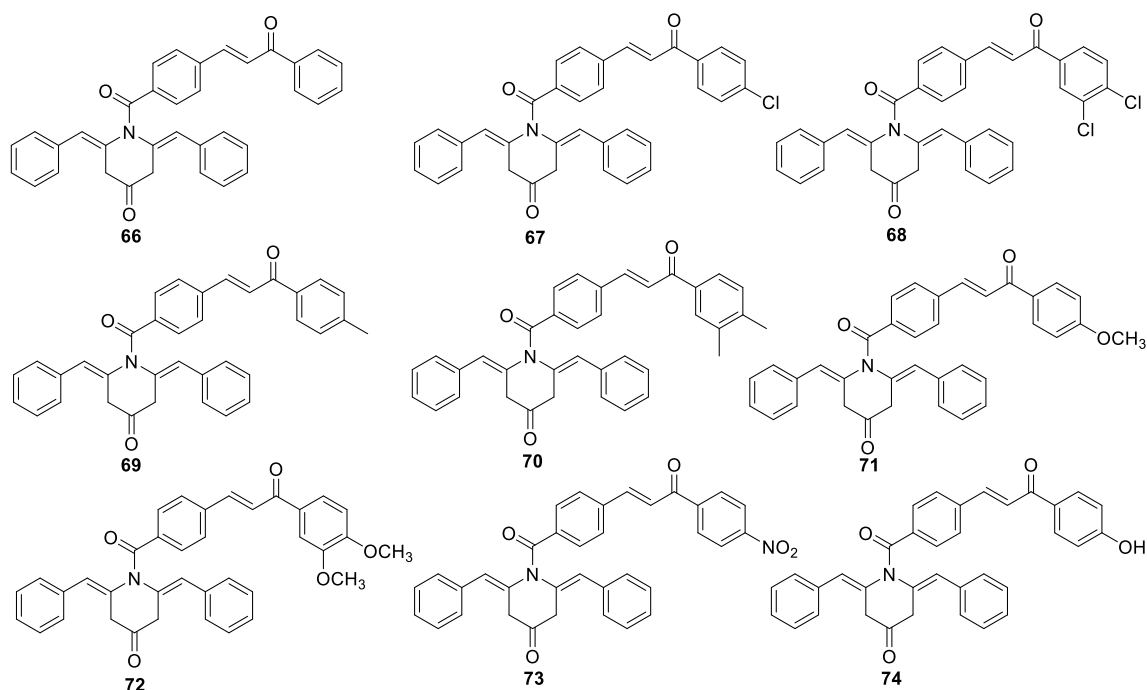


Figure 9. Structures of anticancer MACs **66-74**.

Another series of MACs **89-97** (Figure 10) was produced and tested for anti-proliferation and anti-angiogenic activity. Analogs **60** (EF24), **91**, **92** and **93** showed cytotoxicity better than cisplatin being effective in anti-

proliferation assays as well as efficacious in anti-angiogenesis assays.²⁰⁷ The data suggest that (i) the symmetrical α,β -unsaturated ketone moiety installed shows a superior anticancer activity compared to the β -diketone structure of curcumin; (ii) *ortho*-substitution on aromatic rings (**91-93**, Figure 10) increases the activity compared to the *meta*- or *para*-substitutions (**95, 96**, Figure 10) being a little less active; and (iii) a heteroatom in the cyclic ketone (**92, 93** and **97**, Figure 10) generally results in improved anticancer and anti-angiogenic activity. Compound **90** was further investigated and found to decrease cell viability of lung cancer cells, and an interesting observation was made in context of its anti-hypoxia inducible factor(HIF)-1 activity compared to curcumin: while curcumin inhibited HIF-1 α gene transcription, **90** inhibited HIF-1 α post-transcriptionally, and also curcumin brings out microtubule stabilization in cells, whereas **90** has no effect.²⁰⁷

Symmetrical 1,5-diarylpentanediones **98-102** (Figure 11) were produced, synthesized and tested against cell growth of colon cancer cells. The compound **99** was determined to exhibit a four times higher potency than curcumin with an IC₅₀ value of 2 μ M compared to a value of 8 μ M for curcumin.²⁰⁷ Compounds **103-106** were evaluated by means of anti-proliferation and anti-angiogenic assays. Anti-angiogenic activity was demonstrated by considerable reduction of micro vessel density in peritoneum wall sections in Ehrlich ascites tumor mouse models. The two aromatic regions were interpreted to be critical for potential drug-protein interactions from the study.²⁰⁷

Among the aromatic enone and dienone analogs **107-115** showing cell proliferation upon being screened in an *in vitro* anti-angiogenic assay, **111** and **114** were found to be particularly potent, indicating the importance of heterocyclic substitution. The same group subsequently came up with generated derivatives with variation in the substitution pattern of benzene rings or fusion characteristics, systems **116-119** being the most important, which are structurally tetralones introducing rigidity in the molecule. The 2-naphthyl analog **117** exhibited the best anti-angiogenic activity, 85% at 1 μ g/mL in the sequence **117**>**118**>**116**>**119**.²⁰⁷

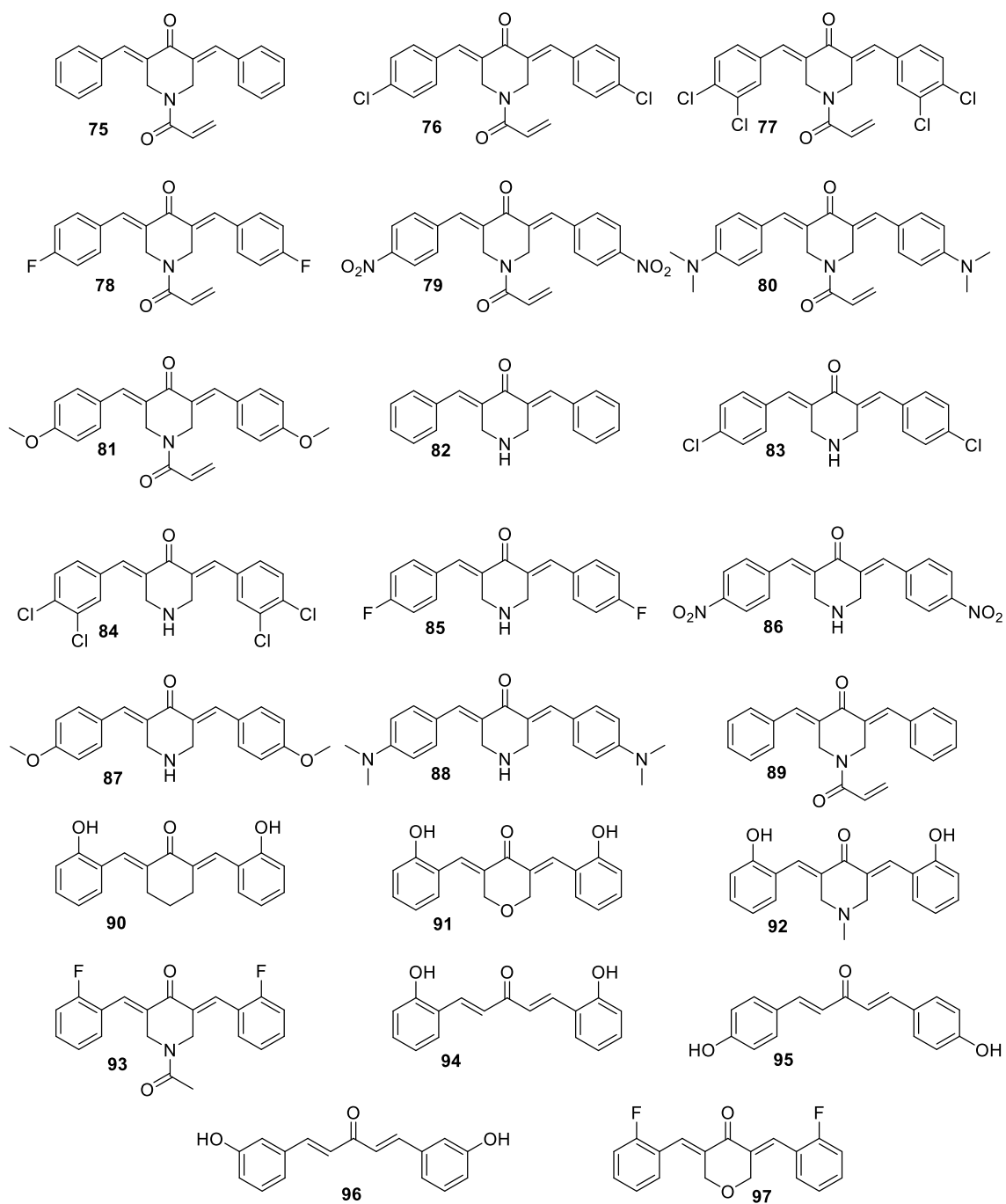


Figure 10. Structures of anticancer MACs 75-97.

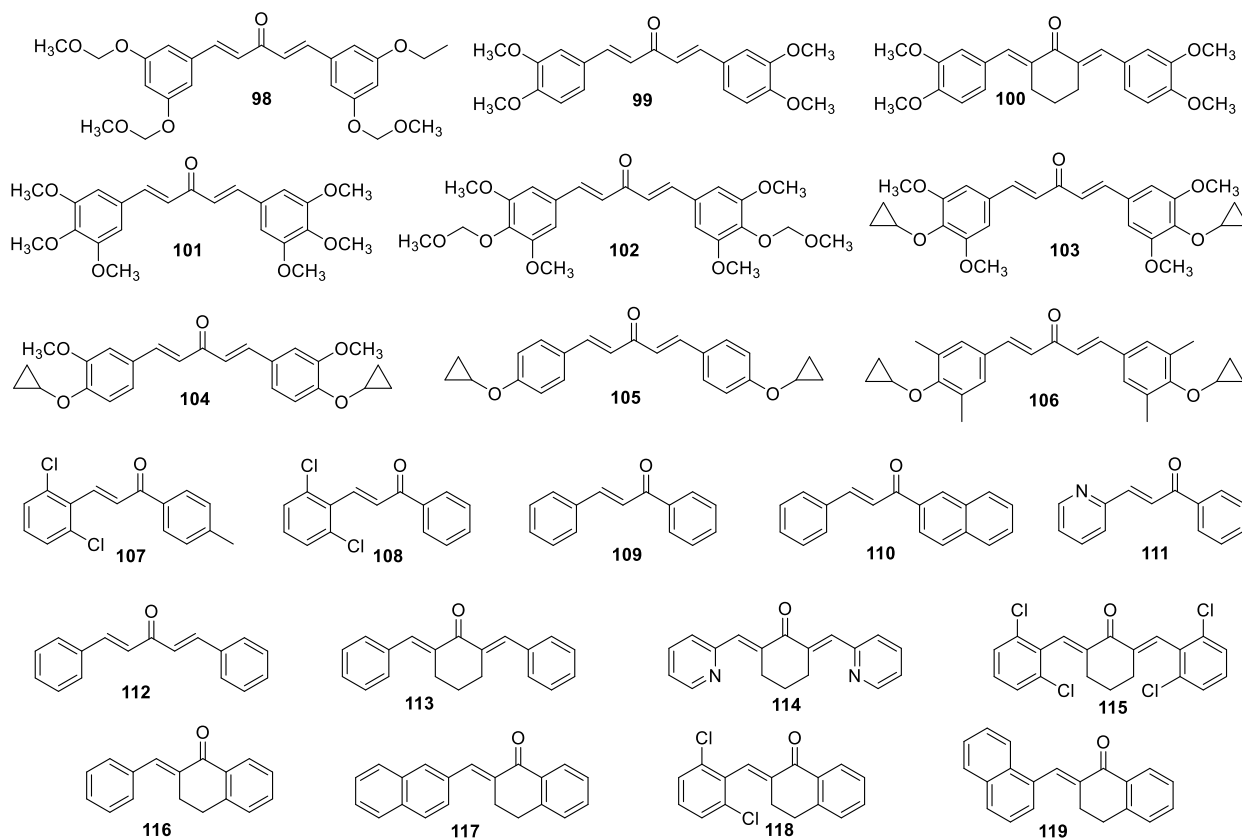


Figure 11. Structures of anticancer MACs 98-119.

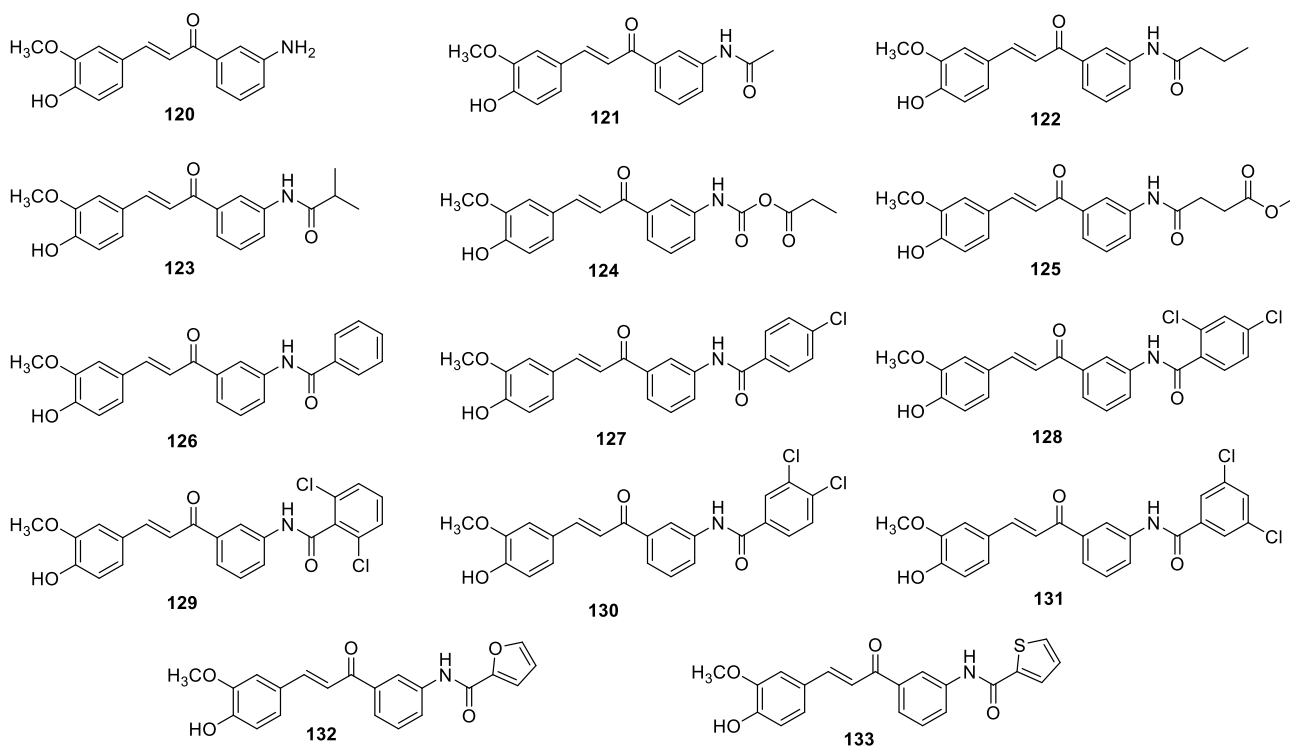


Figure 12. Structures of anticancer MACs 120-133.

A series of non-symmetrical MAC chalcones was conceived by coupling substituted phenyl amides with the terminal curcumin styrene unit with *m*-OMe and *p*-OH substitution, giving rise to structures **120-133** (Figure 12). The particular importance of non-symmetrical phenyl alkyl amides coupled with heteroaromatic moieties is suggested by the potent anti-angiogenic activity of **129**, **130**, **132** and **133** due to *in vitro* growth inhibition of human umbilical vein endothelial cells (HUVEC).²⁰⁷

A series of highly polar MACs **134-149** (Figure 13) was synthesized by replacement of the keto-enol functionality by a substituted piperidone, and the compounds **141-149** were found to be significantly more potent than the control agent Melphalan in inhibition of leukemia and colon cancer cell lines in human Molt 4/C8 cells and CEM T-lymphocytes, but compounds **134-140** lost activity. The change in potential can be attributed to the geometric disposition of the double bond configuration within the framework of piperidone substituents.

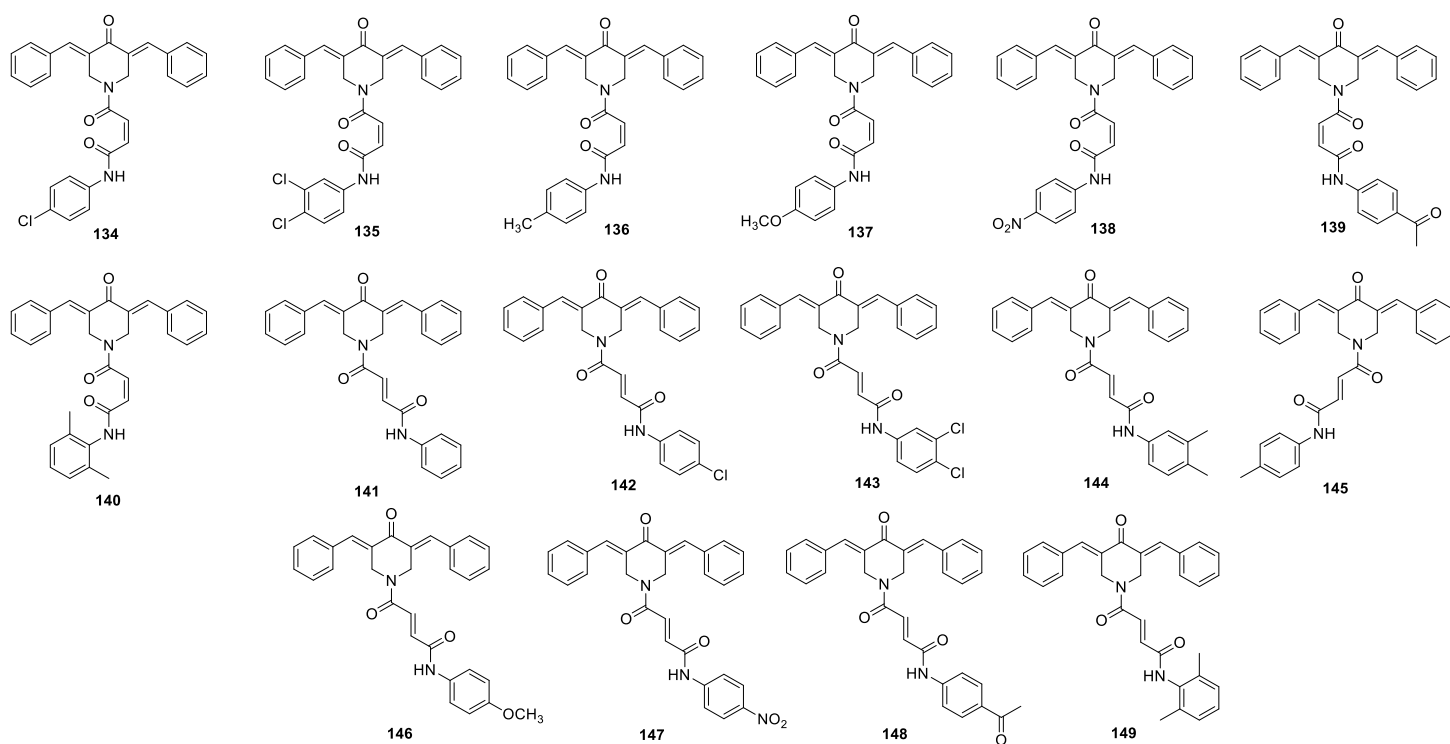


Figure 13. Structures of anticancer MACs **134-149**.

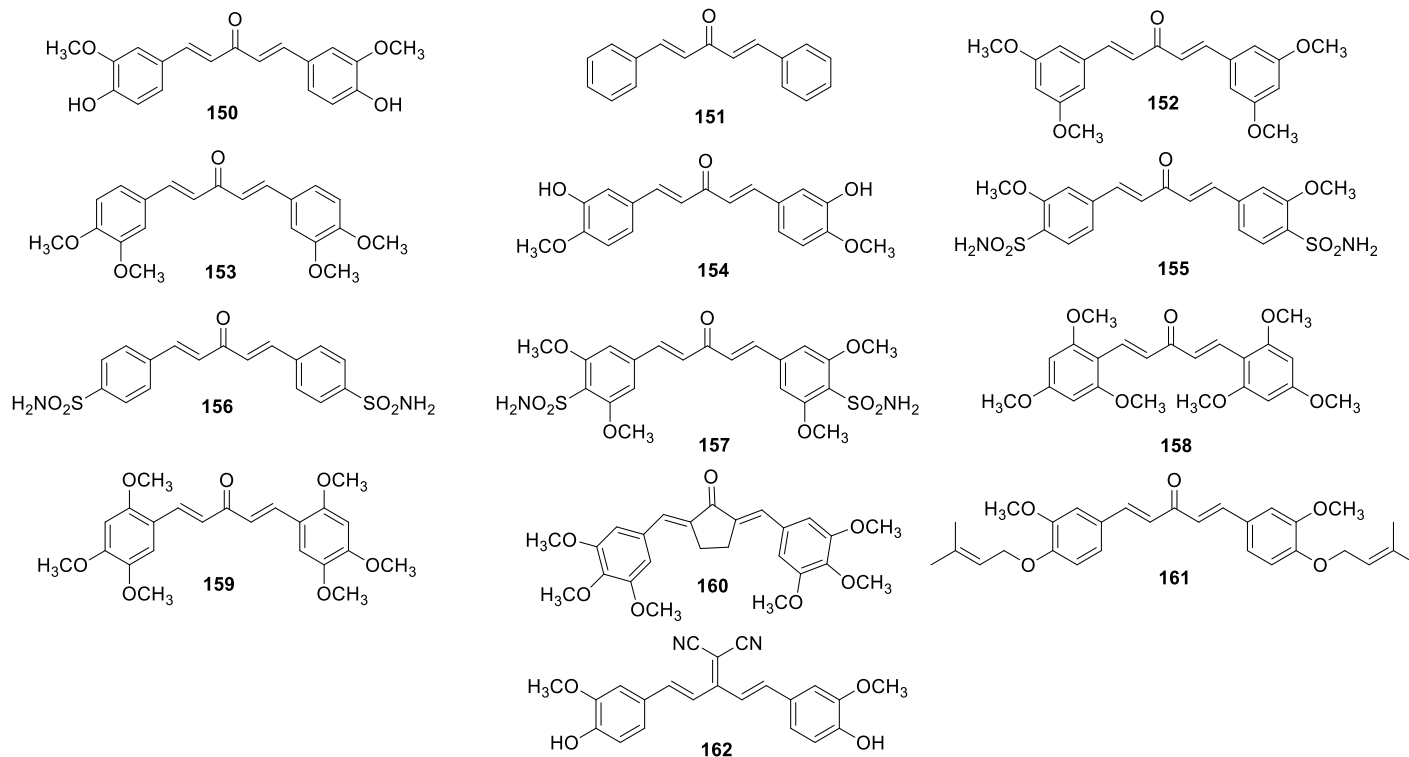


Figure 14. Structures of anticancer MACs **150-162**.

A collection of largely acyclic MACs **150-162** (Figure 14) has been synthesized, and their antitumor activity was tested by blocking the proliferation of prostate and breast cancer cells, out of which compound **158** bearing three methoxy groups was found particularly active with an IC_{50} within the μM range.²⁰⁷ The compounds **163-175** (Figure 15) were reported to be cytotoxic to the human colon cancer cell line HCT-116.²⁰⁷ This study highlighted the structural motifs for bis(arylmethylidene)acetone and 3-oxo-1,4-pentadiene and the dress of substitution being important for maintaining high levels of cell cytotoxicity. Structurally similar compounds **176** and **177** were presented to induce tumor cell apoptosis by activating the stress mechanism of endoplasmic reticulum by another group and have been reported to be under preclinical study for non-small cell lung cancer.²⁰⁷ Compounds **178** and **179** also inhibited phosphorylation of STAT3 in breast and prostate cancer cells. Another series of novel 3,5-bis(arylidene)-4-piperidone based symmetrical MACs was screened for their potential anticancer activity, with compounds **180** and **181** showing inhibition against many human cell lines.

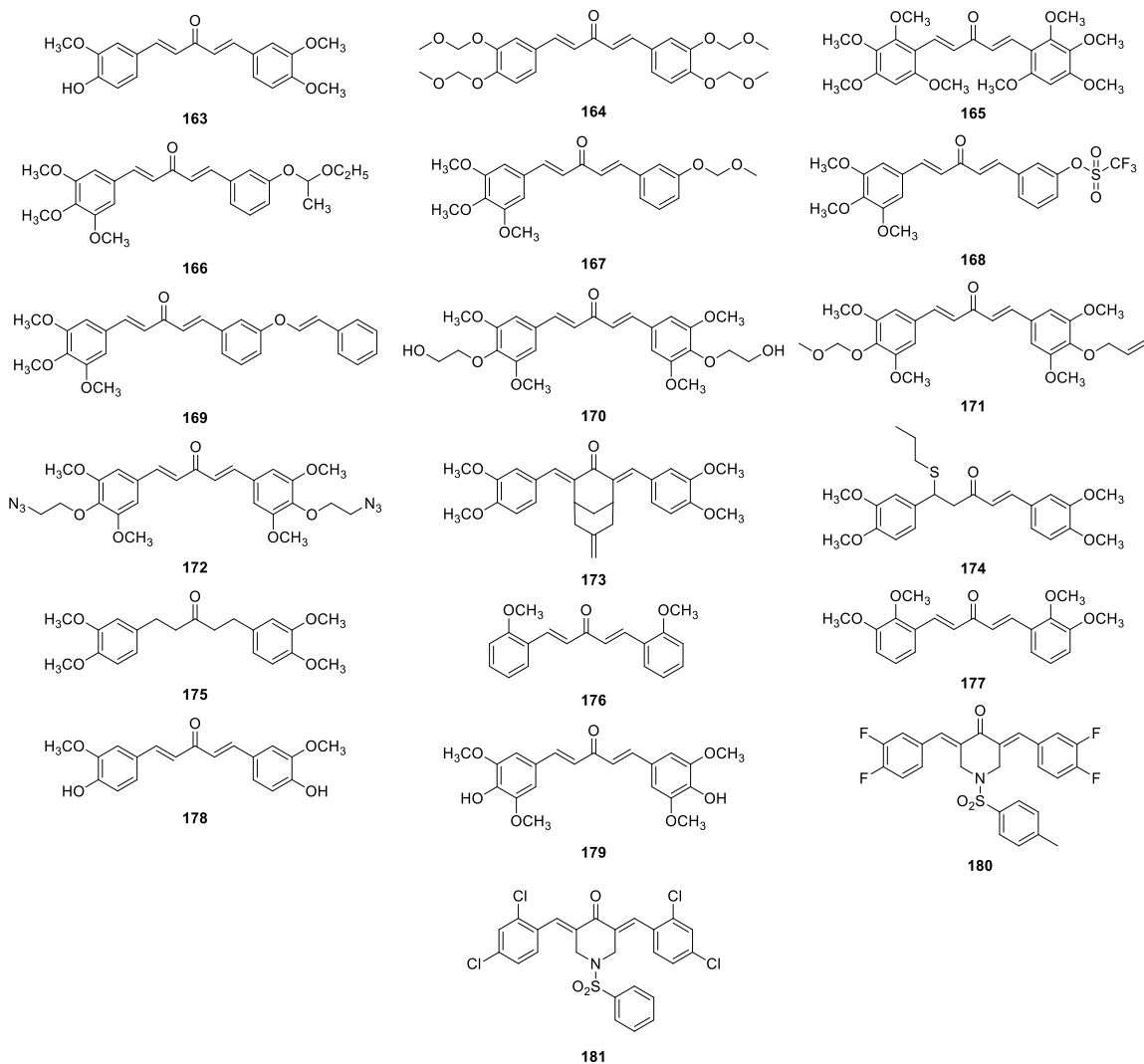


Figure 15. Structures of anticancer MACs 163-181.

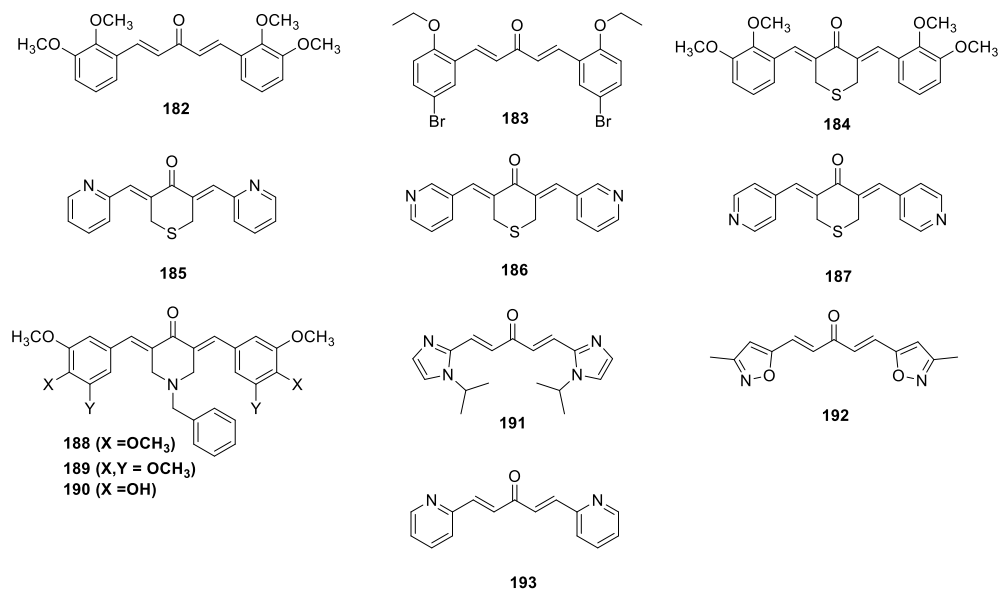


Figure 16. Structures of anticancer MACs 182-193.

More recently, compound **182** (Figure 16) has been determined to elicit an anti-angiogenic activity by suppressing the downstream protein kinase activation of vascular endothelial growth factor (VEGF) via decreasing phosphorylation of AKT and p38. Compound **183** was also reported to display an antitumor effect in the MTT cell proliferation assay using a H460 non-small cell lung cancer cell line.²⁰⁷ A Guangzhou-New Jersey collaboration reported an *in vitro* activity for two series of analogs, thiopyran-4-ones **184-187** and the benzyl piperidones **188-190** (Figure 16). The thiopyranones were shown to deliver suppressive IC₅₀ values < 1 μM upon testing in an MTT proliferation assay against prostate PC-3, HT-29 colon and Panc-1 cancer cell lines. In a parallel study with benzyl piperidones **188-190**, PC-3, pancreas BxPC-2, HT-29, and H1299 lung cancer cell lines were probed with growth inhibition, MTT and trypan blue exclusion assays and the compounds were found to be active with IC₅₀ values < 2 μM.²⁰⁷ Structures **191-193** (as nitrogen-containing heterocyclic derivatives) were reported to furnish anti-prostate cytotoxicity IC₅₀ values of 50-390 nM and no toxicity against MCF-10A normal mammary epithelial cells.

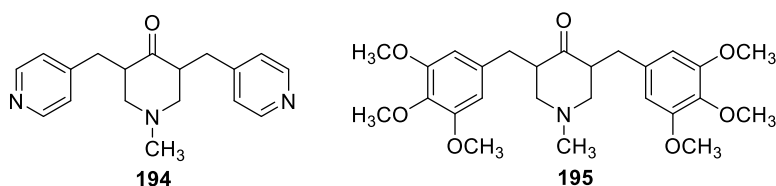
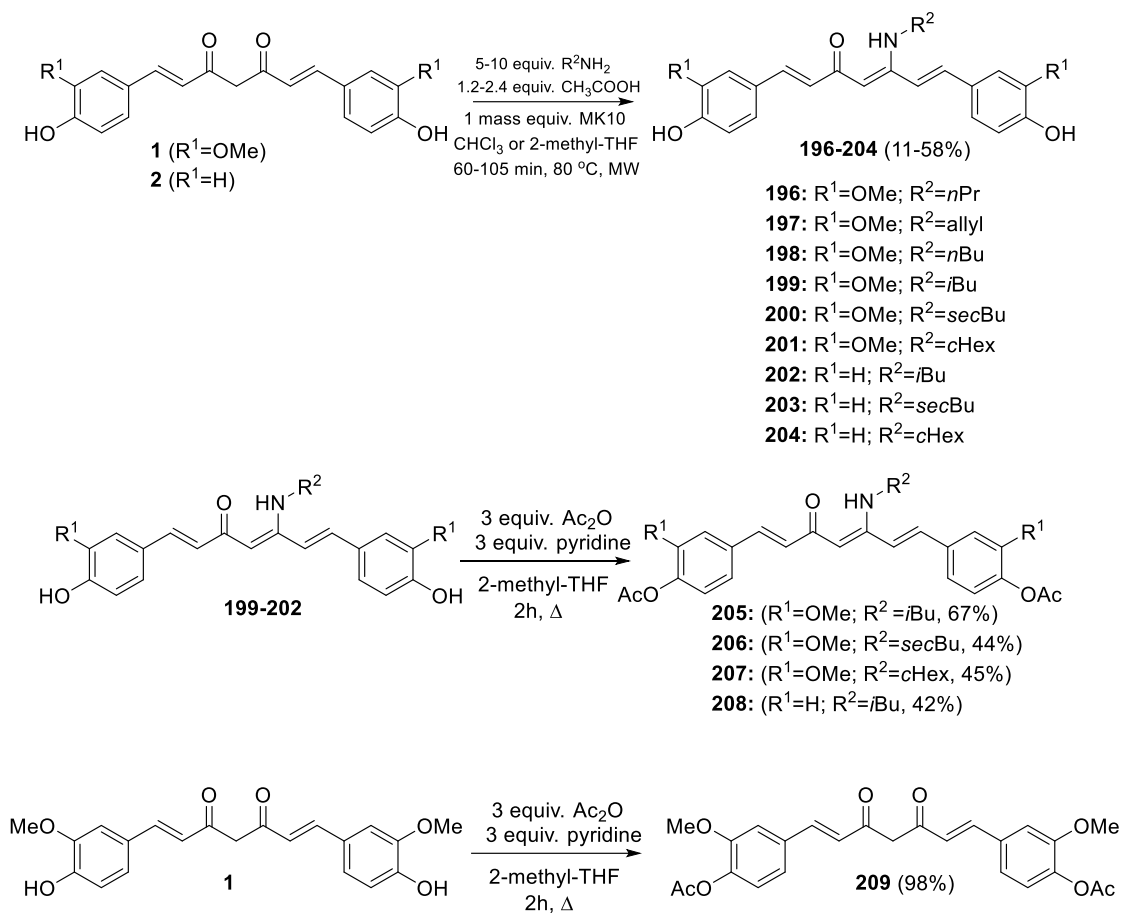


Figure 17. Structures of anticancer MACs **194-195**.

Finally, two piperidines **194** and **195** (Figure 17) displayed inhibition of the κB activation complemented by substantial toxicity towards MBA-MB-231, MDA-MB-468 and SkBr3 breast cancer cell lines; models for triple cancer. Against the MBA-MB-231 cell line, the EC₅₀ values are submicromolar at 0.8 and 0.3, respectively, while they cause apoptosis in 40%-45% of the SKBr3 and MDA-MB-231 cells.²⁰⁷

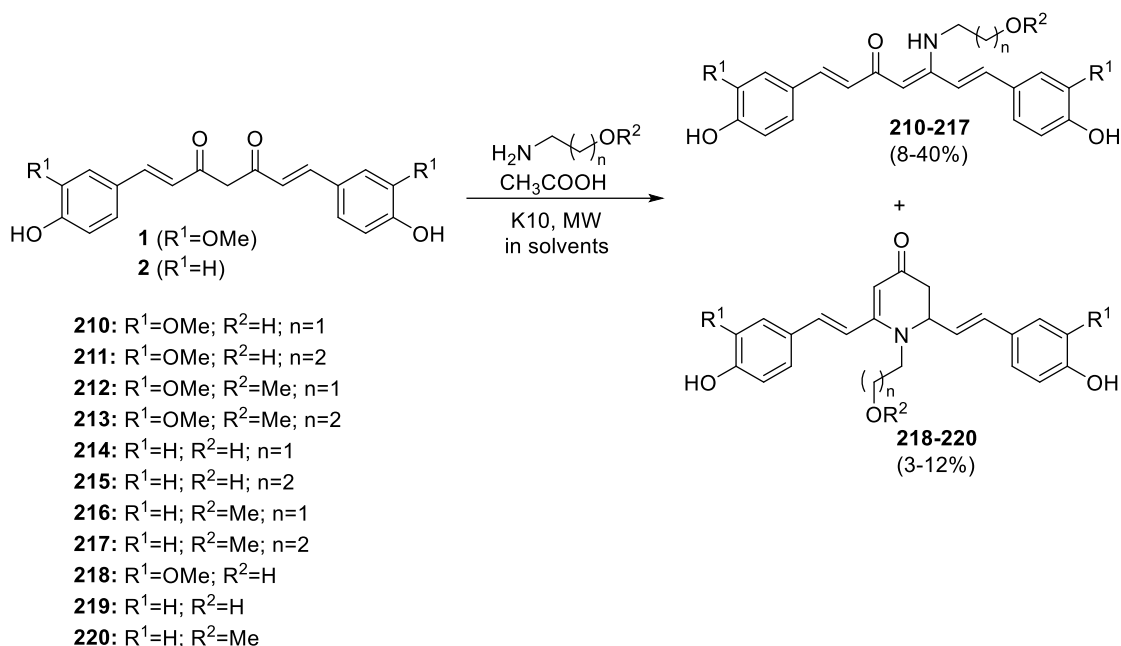
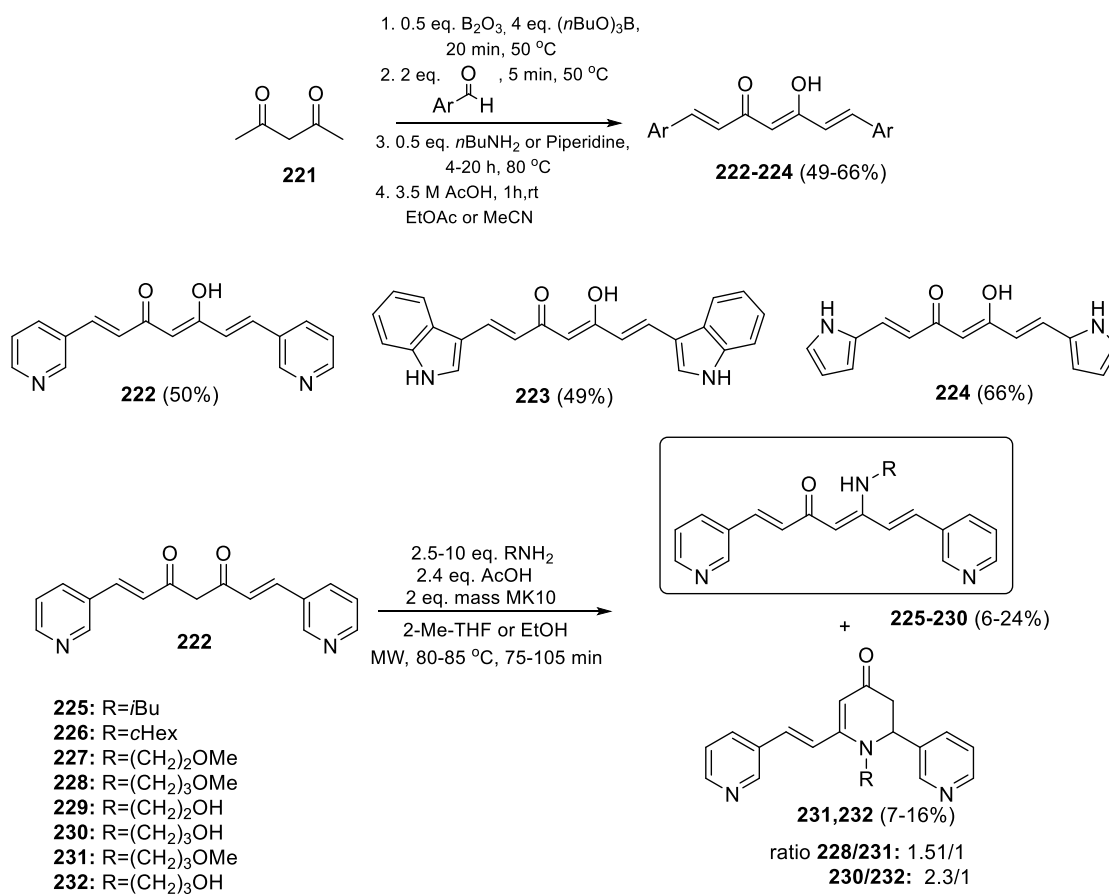
5.3. Modification of both the aromatic rings and the β-diketone moiety

A part of the recent research in our lab has intensively focussed on the synthesis and evaluation of novel curcuminoids and their evaluation as anticancer agents. In view of the problem of low bioavailability being associated partly with the labile β-diketo structure, thirteen N-alkyl enaminones **196-208** (and bis-acetylated curcumin **209**) were synthesized starting from curcumin **1** and bisdemethoxycurcumin **2** using montmorillonite K10 clay and microwave irradiation (Scheme 13), and a number of nitrogen derivatives showed promising effects upon characterization in terms of solubility, chemical antioxidant properties and in screening assays for cell toxicity, growth and oxidative stress using CHO-K1, EA.hy926, HT-29 and Caco-2 cell lines. It was concluded that the cellular responses are strongly increased by N-analogs, and all the compounds appeared to induce no toxicity effects on differentiated intestinal cells.¹⁸



Scheme 13. Synthesis of β -enaminones **196-208** and bis-acetylated curcumin **209**.

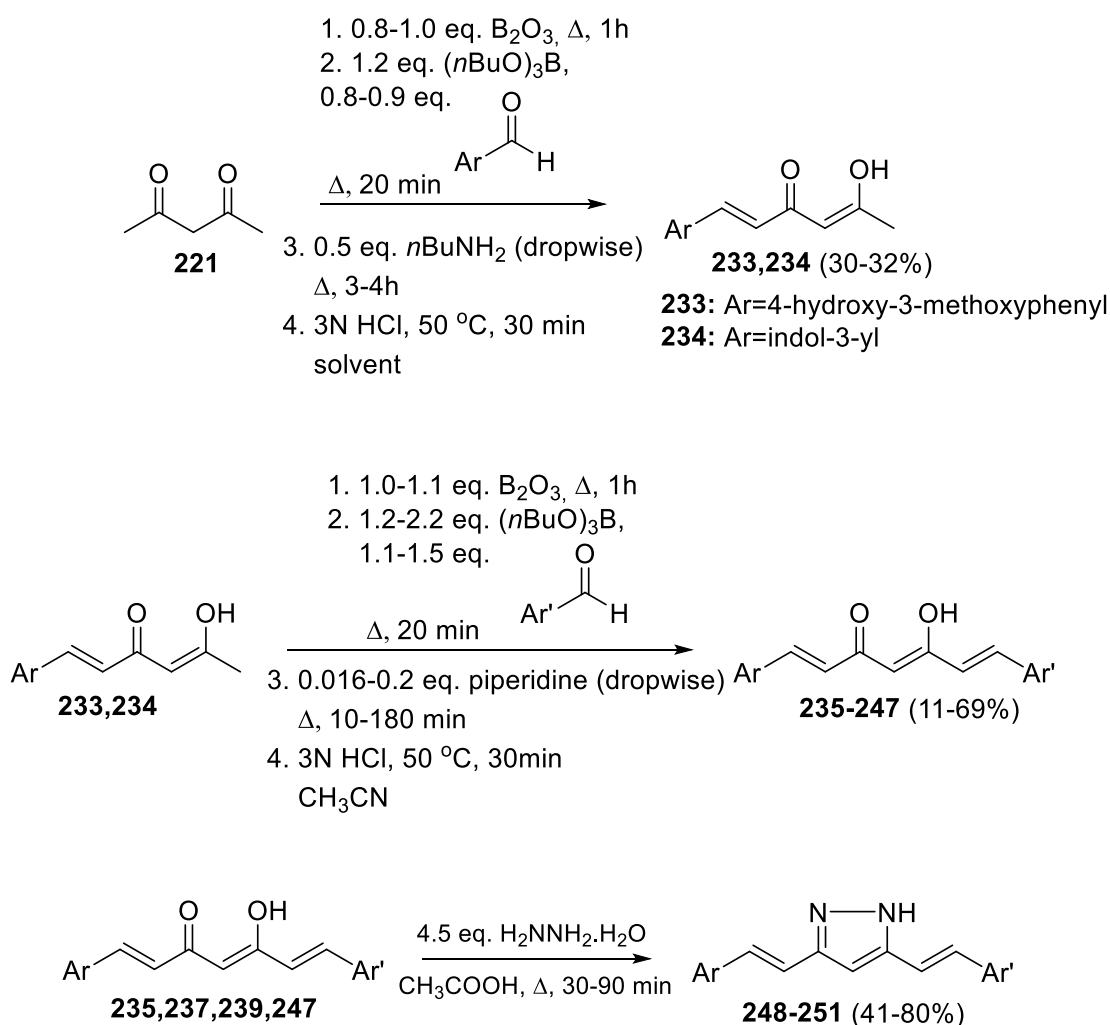
New analogs **210-217** (Scheme 14) were then prepared in continuation of this work using more polar amines with an aim of improving water solubility without altering the biological activity of the resulting curcuminoids, again starting from curcumin **1** and bisdemethoxycurcumin **2** and employing different solvents to minimize the formation of side products **218-220**. The resulting β -enaminones displayed activities better than or comparable to curcumin, and water solubility was also found to be improved significantly.¹⁹

Scheme 14. Synthesis of β -enaminones **210-220**.Scheme 15. Synthesis of β -enaminones **222-232**.

Another set of pyridine-, indole- and pyrrole-based curcumin analogs **222-232** was synthesized with the objective of addressing the bioavailability and improvement of biological activity of curcumin (Scheme 15).²¹⁸

All of these symmetrical aza-heteroaromatic curcuminoids showed better water solubility profiles in comparison to curcumin and bisdemethoxycurcumin.

A set of non-symmetrical curcuminoids **235-252** (Figure 18) containing both a phenolic group and an azaheteroaromatic scaffold was further prepared in continuation of this work in order to combine good solubility, antioxidant potential and cytotoxic properties in a single molecule (Scheme 16).²¹⁹ **252** was synthesized to compare its activity with **247** and **251**, which both contain a thiophen-2-yl moiety. All the derivatives displayed a better water solubility than curcumin and higher IC₅₀ values for non-carcinogenic cells than carcinogenic cell lines, implying that they might be less harmful toward healthy cells. The study concluded that the preservation of the 4-hydroxy-3-methoxyphenyl moiety may provide interesting properties when combined with different azaheteroaromatics.



Scheme 16. Synthesis of β-enaminones **235-251**.

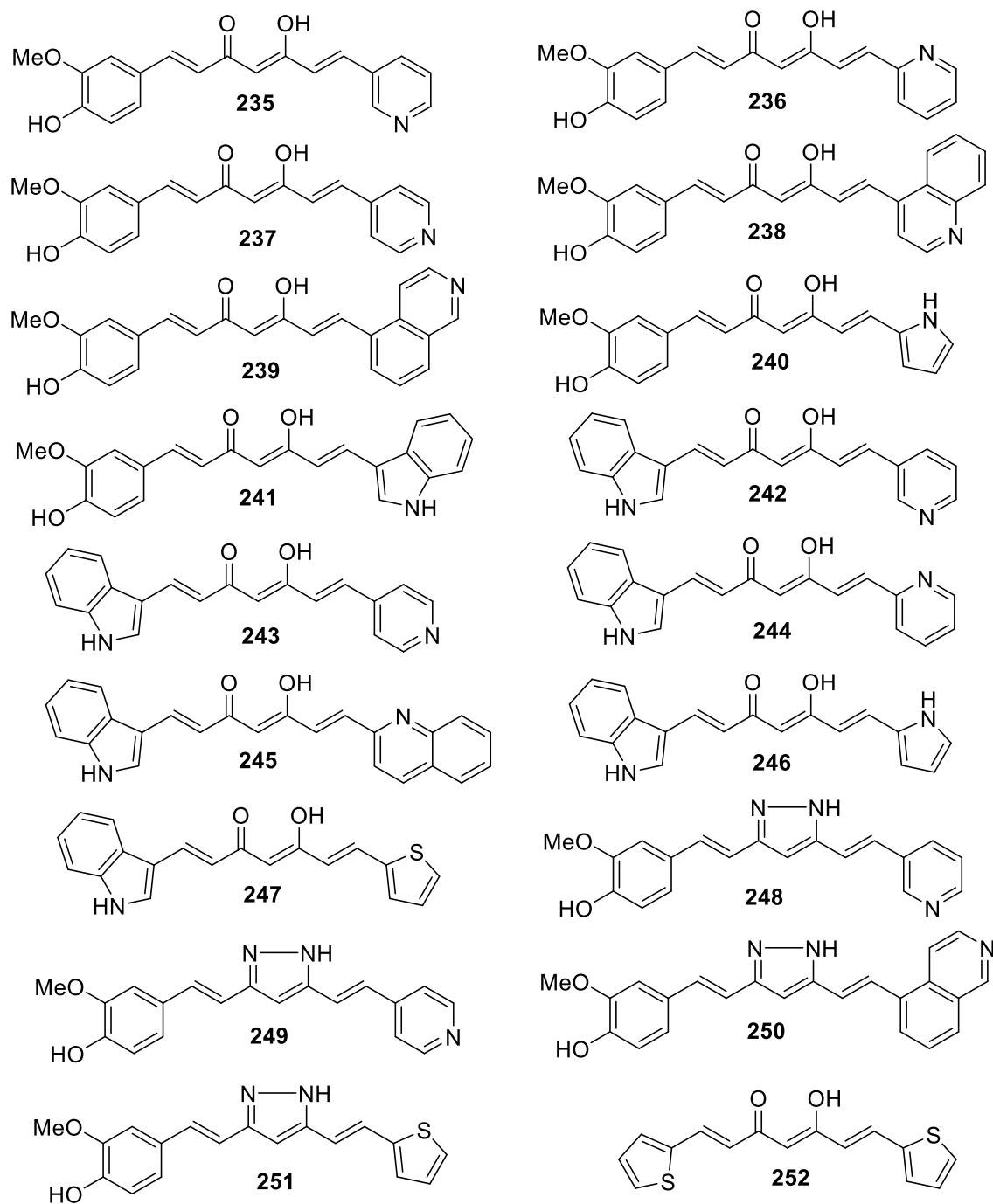
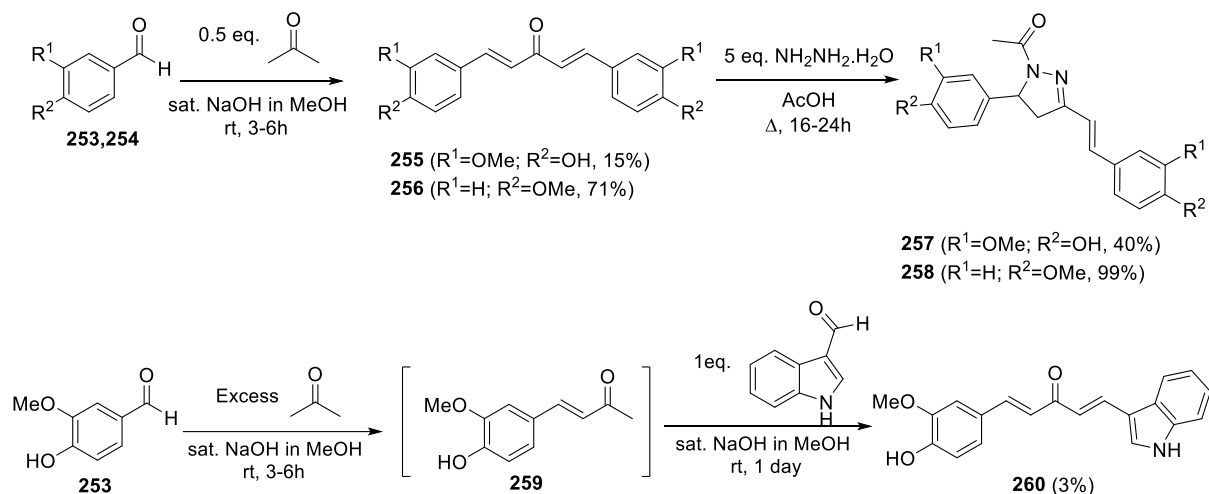


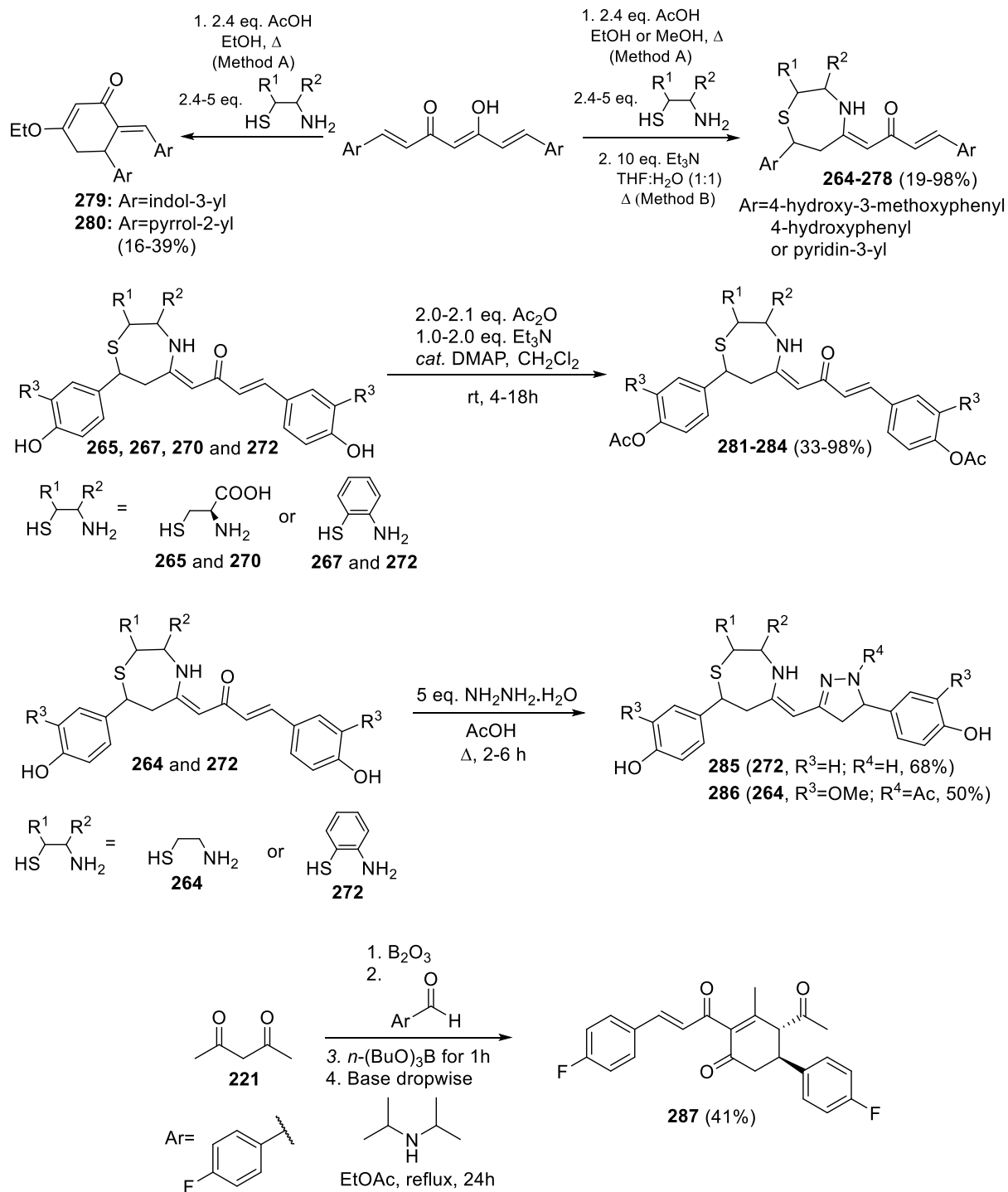
Figure 18. Structures of curcuminoids **235-252**.

Another small set of monocarbonyl analogs of curcumin **255-260** was also synthesized (Scheme 17) and evaluated for cytotoxicity. In particular, bis-3-methoxy-4-hydroxy- and bis-4-methoxyphenyl-substituted monocarbonyls were synthesized and transformed into three-dimensional *N*-acetylpyrazoline derivatives.²²⁰ Preliminary cytotoxic evaluation revealed significant effects for 4-hydroxy (pyrazoline) monocarbonyl curcuminoid **257**, and non-phenolic variants displayed rather poor activity.



Scheme 17. Synthesis of β -enaminones **255-260**.

Deviating from the classical flat curcuminoid framework, an unexplored modification has been investigated recently, in which novel out-of-plane 1,4-thiazepane-based curcuminoids **264-287** (Figure 19) were prepared (Scheme 18), and the impact of this modification was examined on their biological activity.²²¹ Thiazepane analogs **264-278** were generated from starting materials curcumin **1** and bisdemethoxycurcumin **2** or the pyridin-3-yl analog of curcumin, compounds **281-284** were prepared via *O*-acetylation from derivatives of series **264-278**, and unprecedented thiazepine-pyrazoline curcuminoids **285** and **286** were constructed via an extension of enone structural modification of analogs **264** and **272**. Arylmethylidene-substituted cyclohexenones **279** and **280**, based on substrates indol-3-yl and pyrrol-2-yl curcuminoids, were selectively produced using ethanol as the solvent. Furthermore, fluorophenyl-containing cyclohexanone **287** was synthesized for the first time by changing *n*-butylamine to di-isopropylamine, which stimulated the attack of a second molecule of acetylacetone. The synthesized derivatives **266-268**, **272-273**, **277-278**, **279**, **285** and **287** displayed a better antiproliferative activity compared to the parent compounds **1** and **2**, and in some cases a better activity than Doxorubicin, an established anticancer drug. The cell protectivity tests were conducted with derivatives **264-265**, **269-270**, **275-276** and a better cytoprotection than curcumin **1** and a comparable cytoprotective capacity as that of ascorbic acid and Trolox was observed. Because of their three-dimensional architecture, generally culminating in a better druglikeness, and their promising cytotoxic properties, these thiazepane-based curcuminoids can be considered as an innovative scaffold for further elaborations *en route* to the development of curcumin-based anticancer drugs.

Scheme 18. Synthesis of curcuminoids **264-287**.

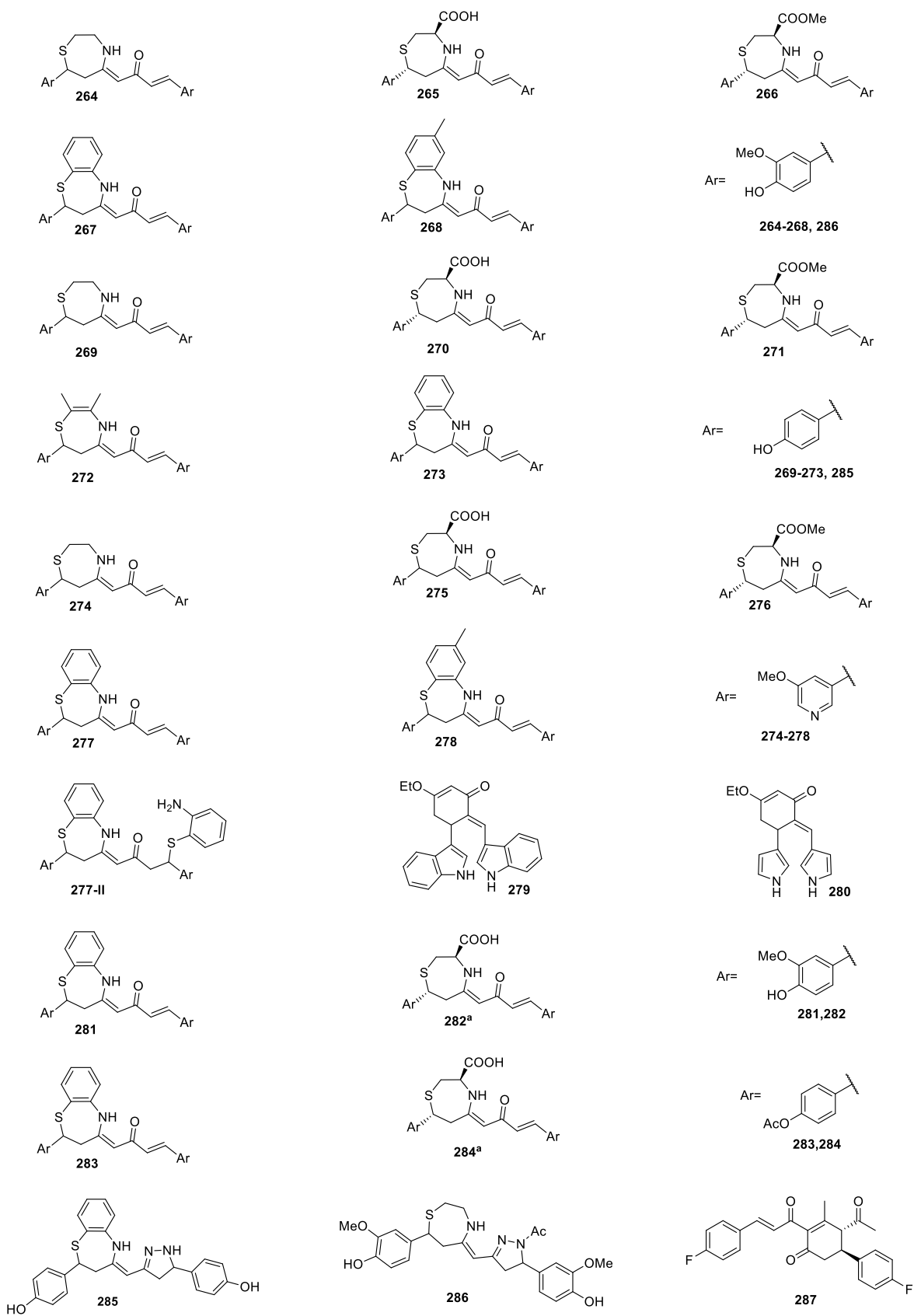


Figure 19. Structures of curcuminoids **264-287**.

Conclusions

Despite its celebrated pharmacological profile, limitations associated with the natural product curcumin, such as structural instability, low solubility and aspecific activity, have incited medicinal chemists to pursue the construction of new derivatives. In this short literature overview, the synthesis and biological assessment of selected curcumin analogs is discussed, some of them demonstrating superior activities as compared to the parent curcumin scaffold. It is clear that this field has witnessed major efforts related to pyrazole and isoxazole curcuminoid synthesis, culminating in interesting new structures in terms of stability, solubility and/or activity, although it is expected that more innovative approaches will be required to also address the problem of non-specific biological interactions. In particular, the search for curcuminoids bearing a higher sp^3 fraction, exemplified by the recently discovered thiazepane curcuminoid framework, could provide a breath of fresh air in this field by developing stable three-dimensional structures with a better druglike profile, without compromising the pronounced bioactivity of the mother molecule.

Acknowledgements

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References

1. Shehzad A.; Lee J.; Lee Y. S. *BioFactors* **2013**, *39*, 56-68.
<https://doi.org/10.1002/biof.1068>
2. Shen L. R.; Parnell L. D.; Ordovas J. M.; Lai C. Q. *BioFactors* **2013**, *39*, 133-140.
<https://doi.org/10.1002/biof.1086>
3. He Y.; Yue Y.; Zheng X.; Zhang K.; Chen S.; Du Z. *Molecules* **2015**, *20*, 9183-9213.
<https://doi.org/10.3390/molecules20059183>
4. Kunnumakkara A. B.; Anand P.; Aggarwal B. B. *Cancer lett.* **2008**, *269*, 199-225.
<https://doi.org/10.1016/j.canlet.2008.03.009>
5. Choudhuri T.; Pal S.; Das T.; Sa G. J. *Biol. Chem.* **2005**, *280*, 20059-20068.
<https://doi.org/10.1074/jbc.M410670200>
6. Goel A.; Jhurani S.; Aggarwal B. B. *Mol. Nutr. Food Res.* **2008**, *52*, 1010-1030.
<https://doi.org/10.1002/mnfr.200700354>
7. Johnson J. J.; Mukhtar H. *Cancer lett.* **2007**, *255*, 170-181.
<https://doi.org/10.1016/j.canlet.2007.03.005>
8. Villegas I.; Sanchez-Fidalgo S.; Alarcon de la Lastra C. *Mol. Nutr. Food Res.* **2008**, *52*, 1040-1061.
<https://doi.org/10.1002/mnfr.200700280>
9. Aggarwal B. B.; Kumar A.; Bharti A. C. *Anticancer Res.* **2003**, *23*, 363-398.
10. Sarkar F. H.; Li Y.; Wang Z.; Padhye S. *Curr. Pharm. Des.* **2010**, *16*, 1801-1812.
<https://doi.org/10.2174/138161210791208956>
11. Wang Y. J.; Pan M. H.; Cheng A. L.; Lin L. I.; Ho Y. S.; Hsieh C. Y.; Lin J. K. *J. Pharm. Biomed. Anal.* **1997**, *15*, 1867-1876.

- [https://doi.org/10.1016/S0731-7085\(96\)02024-9](https://doi.org/10.1016/S0731-7085(96)02024-9)
12. Anand P.; Kunnumakkara A. B.; Newman R. A.; Aggarwal B. B. *Mol. Pharm.* **2007**, *4*, 807-818.
<https://doi.org/10.1021/mp700113r>
 13. Baell J. B.; Holloway G. A. *J. Med. Chem.* **2010**, *53*, 2719-2740.
<https://doi.org/10.1021/jm901137j>
 14. Li H.; Zhong C.; Wang Q.; Chen W.; Yuan Y. *Antiviral Res.* **2019**, *167*, 98-103.
<https://doi.org/10.1016/j.antiviral.2019.04.011>
 15. Narlawar R.; Pickhardt M.; Leuchtenberger S.; Baumann K.; Krause S.; Dyrks T.; Weggen S.; Mandelkow E.; Schmidt B. *ChemMedChem* **2008**, *3*, 165-172.
<https://doi.org/10.1002/cmdc.200700218>
 16. Wang Y.-L.; Huang W.; Chen S.; Chen S.-Q.; Wang S.-F. *J. Chin. Pharm.* **2011**, *20*, 235-244.
 17. Ahsan N.; Mishra S.; Jain M. K.; Surolia A.; Gupta S. *Sci. Rep.* **2015**, *5*, 9862.
<https://doi.org/10.1038/srep09862>
 18. De Vreese R.; Grootaert C.; D'hoore S.; Theppawong A.; Van Damme S.; Van Bogaert M.; Van Camp J.; D'hooghe M. *Eur. J. Med. Chem* **2016**, *123*, 727-736.
<https://doi.org/10.1016/j.ejmech.2016.07.017>
 19. Theppawong A.; De Vreese R.; Vannecke L.; Grootaert C.; Van Camp J.; D'hooghe M. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 5650-5656.
<https://doi.org/10.1016/j.bmcl.2016.10.068>
 20. Nelson K. M.; Dahlin J. L.; Bisson J.; Graham J.; Pauli G. F.; Walters M. A. *J. Med. Chem.* **2017**, *60*, 1620-1637.
<https://doi.org/10.1021/acs.jmedchem.6b00975>
 21. Kiuchi F.; Goto Y.; Sugimoto N.; Akao N.; Kondo K.; Tsuda Y. *Chem. Pharm. Bull.* **1993**, *41*, 1640-1643.
<https://doi.org/10.1248/cpb.41.1640>
 22. Shishodia S.; Chaturvedi M. M.; Aggarwal B. B. *Curr. Probl. Cancer* **2007**, *31*, 243-305.
<https://doi.org/10.1016/j.currprobcancer.2007.04.001>
 23. Anand P.; Thomas S. G.; Kunnumakkara A. B.; Sundaram C.; Harikumar K. B.; Sung B.; Tharakan S. T.; Misra K.; Priyadarsini I. K.; Rajasekharan K. N.; Aggarwal B. B. *Biochem. Pharmacol.* **2008**, *76*, 1590-1611.
<https://doi.org/10.1016/j.bcp.2008.08.008>
 24. Govindarajan V. S. *Crit. Rev. Food Sci. Nutr.* **1980**, *12*, 199-301.
<https://doi.org/10.1080/10408398009527278>
 25. Ammon H. P.; Wahl M. A. *Planta Med.* **1991**, *57*, 1-7.
<https://doi.org/10.1055/s-2006-960004>
 26. Burish T. G.; Jenkins R. A. *Health Psychol. Open* **1992**, *11*, 17-23.
<https://doi.org/10.1037/0278-6133.11.1.17>
 27. Lee W. M. *N. Engl. J. Med.* **1993**, *329*, 1862-1872.
<https://doi.org/10.1056/NEJM199312163292508>
 28. Lao C. D.; Ruffin M. T. T.; Normolle D.; Heath D. D.; Murray S. I.; Bailey J. M.; Boggs M. E.; Crowell J.; Rock C. L.; Brenner D. E. *BMC Complement. Altern. Med.* **2006**, *6*, 10.
<https://doi.org/10.1186/1472-6882-6-10>
 29. Dorai T.; Aggarwal B. B. *Cancer Lett.* **2004**, *215*, 129-140.
<https://doi.org/10.1016/j.canlet.2004.07.013>
 30. Payton F.; Sandusky P.; Alworth W. L. *J. Nat. Prod.* **2007**, *70*, 143-146.
<https://doi.org/10.1021/np060263s>

31. Jagannathan R.; Abraham P. M.; Poddar P. J. *Phys. Chem. B* **2012**, *116*, 14533-14540.
<https://doi.org/10.1021/jp3050516>
32. Ghosh M.; Singh A. T. K.; Xu W.; Sulchek T.; Gordon L. I.; Ryan R. O. *Nanomedicine* **2011**, *7*, 162-167.
<https://doi.org/10.1016/j.nano.2010.08.002>
33. Sun M.; Su X.; Ding B.; He X.; Liu X.; Yu A.; Lou H.; Zhai G. *Nanomedicine* **2012**, *7*, 1085-1100.
<https://doi.org/10.2217/nnm.12.80>
34. Tamvakopoulos C.; Dimas K.; Sofianos Z.; Hatziantoniou S.; Han Z.; Liu Z.; Wyche J.; Pantazis P. *Clin. Cancer Res.* **2007**, *13*, 1269-1277.
<https://doi.org/10.1158/1078-0432.CCR-06-1839>
35. Robinson T. P.; Hubbard R. B.; Ehlers T. J.; Arbiser J. L.; Goldsmith D. J.; Bowen J. P. *Bioorg. Med. Chem.* **2005**, *13*, 4007-4013.
<https://doi.org/10.1016/j.bmc.2005.03.054>
36. Liang G.; Shao L.; Wang Y.; Zhao C.; Chu Y.; Xiao J.; Zhao Y.; Li X.; Yang S. *Bioorg. Med. Chem.* **2009**, *17*, 2623-2631.
<https://doi.org/10.1016/j.bmc.2008.10.044>
37. Somparn P.; Phisalaphong C.; Nakornchai S.; Unchern S.; Morales N. P. *Biol. Pharm. Bull.* **2007**, *30*, 74-78.
<https://doi.org/10.1248/bpb.30.74>
38. Shen L.; Ji H.F. *Trends. Mol. Med.* **2012**, *18*, 138-144.
<https://doi.org/10.1016/j.molmed.2012.01.004>
39. Bisht S.; Feldmann G.; Soni S.; Ravi R.; Karikar C.; Maitra A.; Maitra A. *J. Nanobiotechnology* **2007**, *5*, 3.
<https://doi.org/10.1186/1477-3155-5-3>
40. Gupta V.; Aseh A.; Ríos C. N.; Aggarwal B. B.; Mathur A. B. *Int. J. Nanomedicine* **2009**, *4*, 115-122.
<https://doi.org/10.2147/IJN.S5581>
41. Prajakta D.; Ratnesh J.; Chandan K.; Suresh S.; Grace S.; Meera V.; Vandana P. *J. Biomed. Nanotechnol.* **2009**, *5*, 445-455.
<https://doi.org/10.1166/jbn.2009.1038>
42. Bisht S.; Mizuma M.; Feldmann G.; Ottenhof N. A.; Hong S.M.; Pramanik D.; Chenna V.; Karikari C.; Sharma R.; Goggins M. G.; Rudek M. A.; Ravi R.; Maitra A.; Maitra A. *Mol. Cancer Ther.* **2010**, *9*, 2255-2264.
<https://doi.org/10.1158/1535-7163.MCT-10-0172>
43. Das R. K.; Kasoju N.; Bora U. *Nanomedicine* **2010**, *6*, 153-160.
<https://doi.org/10.1016/j.nano.2009.05.009>
44. Duan J.; Zhang Y.; Han S.; Chen Y.; Li B.; Liao M.; Chen W.; Deng X.; Zhao J.; Huang B. *Int. J. Pharm.* **2010**, *400*, 211-220.
<https://doi.org/10.1016/j.ijpharm.2010.08.033>
45. Mulik R. S.; Mönkkönen J.; Juvonen R. O.; Mahadik K. R.; Paradkar A. R. *Int. J. Pharm.* **2010**, *398*, 190-203.
<https://doi.org/10.1016/j.ijpharm.2010.07.021>
46. Yallapu M. M.; Gupta B. K.; Jaggi M.; Chauhan S. C. *J. Colloid Interface Sci.* **2010**, *351*, 19-29.
<https://doi.org/10.1016/j.icis.2010.05.022>
47. Yallapu M. M.; Maher D. M.; Sundram V.; Bell M. C. Jaggi M.; Chauhan S. C. *J. Ovarian Res.* **2010**, *3*, 11.
<https://doi.org/10.1186/1757-2215-3-11>
48. Yen F.-L.; Wu T.-H.; Tzeng C.-W.; Lin L.-T.; Lin C.-C. *J. Agric. Food Chem.* **2010**, *58*, 7376-7382.
<https://doi.org/10.1021/jf100135h>
49. Jithan A. V.; Madhavi K.; Madhavi M.; Prabhakar K. *Int. J. Pharm. Investig.* **2011**, *1*, 119-125.

- <https://doi.org/10.4103/2230-973X.82432>
50. Kakkar V.; Singh S.; Singla D.; Kaur I. P. *Mol. Nutr. Food Res.* **2011**, *55*, 495-503.
<https://doi.org/10.1002/mnfr.201000310>
51. Kim T. H.; Jiang H. H.; Youn Y. S.; Park C. W.; Tak K. K.; Lee S.; Kim H.; Jon S.; Chen X.; Lee K. C. *Int. J. Pharm.* **2011**, *403*, 285-291.
<https://doi.org/10.1016/j.ijpharm.2010.10.041>
52. Sanoj Rejinold N.; Muthunarayanan M.; Divyarani V. V.; Sreerekha P. R.; Chennazhi K. P.; Nair S. V.; Tamura H.; Jayakumar R. *J. Colloid Interface Sci.* **2011**, *360*, 39-51.
<https://doi.org/10.1016/j.icis.2011.04.006>
53. Dev S.; Prabhakaran P.; Filgueira L.; Iyer K. S.; Raston C. L. *Nanoscale* **2012**, *4*, 2575-2579.
<https://doi.org/10.1039/C2NR11502F>
54. Kakran M.; Sahoo N. G.; Tan I.-L.; Li J. *Nanopart. Res.* **2012**, *14*, 757.
<https://doi.org/10.1007/s11051-012-0757-0>
55. Liu J.; Xu L.; Liu C.; Zhang D.; Wang S.; Deng Z.; Lou W.; Xu H.; Bai Q.; Ma J. *Carbohydr. Polym.* **2012**, *90*, 16-22.
<https://doi.org/10.1016/j.carbpol.2012.04.036>
56. Kazemi-Lomedasht F.; Rami A.; Zarghami N. *Adv. Pharm. Bull.* **2013**, *3*, 127-130.
57. Phuong T. H.; Tuan Q. D.; Thu T. M. T.; Hong H. T. T.; Hoai N. N.; Xuan P. N.; Minh N. T. T.; Quoc T. P.; Hong T. P. T.; Kim O. V. T.; Mai H. L. *Chem. Lett.* **2013**, *42*, 255-257.
58. Yallapu M. M.; Ebeling M. C.; Jaggi M.; Chauhan S. C. *Curr. Drug Metab.* **2013**, *14*, 504-515.
<https://doi.org/10.2174/1389200211314040012>
59. Yen F.-L.; Tsai M.-H.; Yang C.-M.; Liang C.-J.; Lin C.-C.; Chiang Y.-C.; Lee H.-C.; Ko H.-H.; Lee C.-W. *PLoS One* **2013**, *8*, e63845.
<https://doi.org/10.1371/journal.pone.0063845>
60. Ding Q.; Niu T.; Yang Y.; Guo Q.; Luo F.; Qian Z. *J. Biomed. Nanotechnol.* **2014**, *10*, 632-641.
<https://doi.org/10.1166/jbn.2014.1829>
61. Zhang J.; Li S.; An F.-F.; Liu J.; Jin S.; Zhang J.-C.; Wang P. C.; Zhang X.; Lee C.-S.; Liang X.-J. *Nanoscale* **2015**, *7*, 13503-13510.
<https://doi.org/10.1039/C5NR03259H>
62. Zhao Z.; Xie M.; Li Y.; Chen A.; Li G.; Zhang J.; Hu H.; Wang X.; Li S. *Int. J. Nanomedicine* **2015**, *10*, 3171-3181.
<https://doi.org/10.2147/IJN.S80434>
63. Shoba G.; Joy D.; Joseph T.; Majeed M.; Rajendran R.; Srinivas P. S. S. R. *Planta Med.* **1998**, *64*, 353-356.
<https://doi.org/10.1055/s-2006-957450>
64. Shaikh J.; Ankola D. D.; Beniwal V.; Singh D.; M. N. V. R. Kumar *Eur. J. Pharm. Sci.* **2009**, *37*, 223-230.
<https://doi.org/10.1016/j.ejps.2009.02.019>
65. Sehgal A.; Kumar M.; Jain M.; Dhawan D. K. *Food Chem. Toxicol.* **2011**, *49*, 3002-3006.
<https://doi.org/10.1016/j.fct.2011.07.058>
66. Sehgal A.; Kumar M.; Jain M.; Dhawan D. K. *Hum. Exp. Toxicol.* **2012**, *31*, 473-482.
<https://doi.org/10.1177/0960327111421943>
67. Rinwa P.; Kumar A. *Brain Res.* **2012**, *1488*, 38-50.
<https://doi.org/10.1016/j.brainres.2012.10.002>
68. Ramakrishna Rao R.; Platel K.; Srinivasan K. *Food / Nahrung* **2003**, *47*, 408-412.
<https://doi.org/10.1002/food.200390091>

69. Moorthi C.; Kathiresan K. *J. Medical Hypotheses and Ideas* **2013**, *7*, 15-20.
<https://doi.org/10.1016/j.imhi.2012.10.005>
70. Kakarala M.; Brenner D. E.; Korkaya H.; Cheng C.; Tazi K.; Ginestier C.; Liu S.; Dontu G.; Wicha M. S. *Breast Cancer Res. Tr.* **2010**, *122*, 777-785.
<https://doi.org/10.1007/s10549-009-0612-x>
71. Gulseren I.; Guri A.; Corredig M. *Food Funct.* **2014**, *5*, 1218-1223.
<https://doi.org/10.1039/c3fo60554j>
72. Bhutani M. K.; Bishnoi M.; Kulkarni S. K. *Pharmacol. Biochem. Behav.* **2009**, *92*, 39-43.
<https://doi.org/10.1016/j.pbb.2008.10.007>
73. Balakrishnan S.; Vellaichamy L.; Menon V. P.; Manoharan S. *Toxicol. Mech. Method* **2008**, *18*, 691-696.
<https://doi.org/10.1080/15376510701781520>
74. Anand P.; Sundaram C.; Jhurani S.; Kunnumakkara A. B.; Aggarwal B. B. *Cancer Lett.* **2008**, *267*, 133-164.
<https://doi.org/10.1016/j.canlet.2008.03.025>
75. Shehzad A.; Wahid F.; Lee Y. S. *Arch. Pharm.* **2010**, *343*, 489-499.
<https://doi.org/10.1002/ardp.200900319>
76. Pabon H. J. J. *Recl. Trav. Chim. Pays-Bas* **1964**, *83*, 379-386.
<https://doi.org/10.1002/recl.19640830407>
77. Pedersen U.; Rasmussen P. B.; Lawesson S.-O. *Justus Liebigs Ann. Chem.* **1985**, *1985*, 1557-1569.
<https://doi.org/10.1002/jlac.198519850805>
78. Ahmed M.; Abdul Qadir M.; Imtiaz Shafiq M.; Muddassar M.; Hameed A.; Nadeem Arshad M.; Asiri A. M. *Acta Pharm.* **2017**, *67*, 385-395.
<https://doi.org/10.1515/acph-2017-0023>
79. McGuire S. *Adv. Nutr.* **2016**, *7*, 418-419.
<https://doi.org/10.3945/an.116.012211>
80. Rao D. S.; Sekhara N. C.; Satyanarayana M. N.; Srinivasan M. *J. Nutr.* **1970**, *100*, 1307-1315.
<https://doi.org/10.1093/in/100.11.1307>
81. Patil T. N.; Srinivasan M. *Indian J. Exp. Biol.* **1971**, *9*, 167-169.
82. Keshavarz K. *Poult. Sci.* **1976**, *55*, 1077-1083.
<https://doi.org/10.3382/ps.0551077>
83. Hussain M. S.; Chandrasekhara N. *Indian J. Med. Res.* **1992**, *96*, 288-291.
84. Soni K. B.; Kuttan R. *Indian J. Physiol. Pharmacol.* **1992**, *36*, 273-275.
85. Asai A.; Miyazawa T. *J. Nutr.* **2001**, *131*, 2932-2935.
<https://doi.org/10.1093/in/131.11.2932>
86. Ramirez-Tortosa M. C.; Mesa M. D.; Aguilera M. C.; Quiles J. L.; Baro L.; Ramirez-Tortosa C. L.; Martinez-Victoria E.; Gil A. *Atherosclerosis* **1999**, *147*, 371-378.
[https://doi.org/10.1016/S0021-9150\(99\)00207-5](https://doi.org/10.1016/S0021-9150(99)00207-5)
87. Naidu K. A.; Thippeswamy N. B. *Mol. Cell. Biochem.* **2002**, *229*, 19-23.
<https://doi.org/10.1023/A:1017930708099>
88. Patro B. S.; Rele S.; Chintalwar G. J.; Chattopadhyay S.; Adhikari S.; Mukherjee T. **2002**, *3*, 364-370.
[https://doi.org/10.1002/1439-7633\(20020402\)3:4<364::AID-CBIC364>3.0.CO;2-S](https://doi.org/10.1002/1439-7633(20020402)3:4<364::AID-CBIC364>3.0.CO;2-S)
89. Srivastava R.; Puri V.; Srimal R. C.; Dhawan B. N. *Arzneimittel-Forsch.* **1986**, *36*, 715-717.
90. Srivastava K. C.; Bordia A.; Verma S. K. *Prostag. Leukotr. Ess.* **1995**, *52*, 223-227.
[https://doi.org/10.1016/0952-3278\(95\)90040-3](https://doi.org/10.1016/0952-3278(95)90040-3)
91. Srivastava R.; Dikshit M.; Srimal R. C.; Dhawan B. N. *Thromb. Res.* **1985**, *40*, 413-417.

- [https://doi.org/10.1016/0049-3848\(85\)90276-2](https://doi.org/10.1016/0049-3848(85)90276-2)
92. Kim D. C.; Ku S. K.; Bae J. S. *BMB Rep.* **2012**, *45*, 221-226.
<https://doi.org/10.5483/BMBRep.2012.45.4.221>
93. Dikshit M.; Rastogi LShukla.; R., Srimal R. C. *Indian J. Med. Res.* **1995**, *101*, 31-35.
94. Nirmala C.; Puvanakrishnan R. *Mol. Cell. Biochem.* **1996**, *159*, 85-93.
<https://doi.org/10.1007/BF00420910>
95. Nirmala C.; Puvanakrishnan R. *Biochem. Pharmacol.* **1996**, *51*, 47-51.
[https://doi.org/10.1016/0006-2952\(95\)02118-3](https://doi.org/10.1016/0006-2952(95)02118-3)
96. Venkatesan N. *Br. J. Pharmacol.* **1998**, *124*, 425-427.
<https://doi.org/10.1038/sj.bjp.0701877>
97. Srinivasan M. *Indian J. Med. Sci.* **1972**, *26*, 269-270.
<https://doi.org/10.1136/jech.26.4.269>
98. Babu P. S.; Srinivasan K. *Mol. Cell. Biochem.* **1995**, *152*, 13-21.
99. Babu P. S.; Srinivasan K. *Mol. Cell. Biochem.* **1997**, *166*, 169-175.
<https://doi.org/10.1023/A:1006819605211>
100. Suresh Babu P.; Srinivasan K. *Mol. Cell. Biochem.* **1998**, *181*, 87-96.
<https://doi.org/10.1023/A:1006821828706>
101. Arun N.; Nalini N. *Plant Foods Hum. Nutr.* **2002**, *57*, 41-52.
<https://doi.org/10.1023/A:1013106527829>
102. Nishiyama T.; Mae T.; Kishida H.; Tsukagawa M.; Mimaki Y.; Kuroda M.; Sashida Y.; Takahashi K.; Kawada T.; Nakagawa K.; Kitahara M. *J. Agric. Food Chem.* **2005**, *53*, 959-963.
<https://doi.org/10.1021/jf0483873>
103. Pari L.; Murugan P.; *Ren. Fail.* **2007**, *29*, 881-889.
<https://doi.org/10.1080/08860220701540326>
104. Chuengsamarn S.; Rattanamongkolgul S.; Luechapudiporn R.; Phisalaphong C.; Jirawatnotai S. *Diabetes Care* **2012**, *35*, 2121-2127.
<https://doi.org/10.2337/dc12-0116>
105. Deodhar S. D.; Sethi R.; Srimal R. C. *Indian J. Med. Res.* **1980**, *71*, 632-634.
106. Khanna D.; Sethi G.; Ahn K. S.; Pandey M. K.; Kunnumakkara A. B.; Sung B.; Aggarwal A.; Aggarwal B. B. *Curr. Opin. Pharmacol.* **2007**, *7*, 344-351.
<https://doi.org/10.1016/j.coph.2007.03.002>
107. Banji D.; Pinnapureddy J.; Banji O. J. F.; Kumar A. R.; Reddy K. N. *Indian J. Pharm.* **2011**, *43*, 546-550.
<https://doi.org/10.4103/0253-7613.84970>
108. Huang G.; Xu Z.; Huang Y.; Duan X.; Gong W.; Zhang Y.; Fan J.; He F. *J. Clin. Immunol.* **2013**, *33*, 550-557.
<https://doi.org/10.1007/s10875-012-9839-0>
109. Daily J. W.; Yang M.; Park S. *J. Med. Food* **2016**, *19*, 717-729.
<https://doi.org/10.1089/jmf.2016.3705>
110. Natarajan C.; Bright J. J. *J. Immunol.* **2002**, *168*, 6506-6513.
<https://doi.org/10.4049/jimmunol.168.12.6506>
111. Frautschy S. A.; Hu W.; Kim P.; Miller S. A.; Chu T.; Harris-White M. E.; Cole G. M. *Neurobiol. Aging* **2001**, *22*, 993-1005.
[https://doi.org/10.1016/S0197-4580\(01\)00300-1](https://doi.org/10.1016/S0197-4580(01)00300-1)
112. Lim G. P.; Chu T.; Yang F.; Beech W.; Frautschy S. A.; Cole G. M. *J. Neurosci.* **2001**, *21*, 8370-8377.
<https://doi.org/10.1523/JNEUROSCI.21-21-08370.2001>

113. Hamaguchi T.; Ono K.; Yamada M. *CNS Neurosci. Ther.* **2010**, *16*, 285-297.
<https://doi.org/10.1111/j.1755-5949.2010.00147.x>
114. Ringman J. M.; Frautschy S. A.; Teng E.; Begum A. N.; Bardens J.; Beigi M.; Gylys K. H.; Badmaev V.; Heath D. D.; Apostolova L. G.; Porter V.; Vanek Z.; Marshall G. A.; Hellemann G.; Sugar C.; Masterman D. L.; Montine T. J.; Cummings J. L.; Cole G. M. *Alzheimers Res Ther* **2012**, *4*, 43.
<https://doi.org/10.1186/alzrt146>
115. Tang M.; Taghibiglou C. J. *Alzheimers Dis. : JAD* **2017**, *58*, 1003-1016.
<https://doi.org/10.3233/JAD-170188>
116. Li C. J.; Zhang L. J.; Dezube B. J.; Crumpacker C. S.; Pardee A. B. *PNAS* **1993**, *90*, 1839-1842.
<https://doi.org/10.1073/pnas.90.5.1839>
117. Sui Z.; Salto R.; Li J.; Craik C.; Ortiz de Montellano P. R. *Bioorg. Med. Chem.* **1993**, *1*, 415-422.
[https://doi.org/10.1016/S0968-0896\(00\)82152-5](https://doi.org/10.1016/S0968-0896(00)82152-5)
118. Jordan W. C.; Drew C. R. *J. Natl. Med. Assoc.* **1996**, *88*, 333.
119. Mazumder A.; Neamati N.; Sunder S.; Schulz J.; Pertz H.; Eich E.; Pommier Y. *J. Med. Chem.* **1997**, *40*, 3057-3063.
<https://doi.org/10.1021/jm970190x>
120. Barthelemy S.; Vergnes L.; Moynier M.; Guyot D.; Labidalle S.; Bahraoui E. *Res. Virol.* **1998**, *149*, 43-52.
[https://doi.org/10.1016/S0923-2516\(97\)86899-9](https://doi.org/10.1016/S0923-2516(97)86899-9)
121. De Clercq E. *Med. Res. Rev.* **2000**, *20*, 323-349.
[https://doi.org/10.1002/1098-1128\(200009\)20:5<323::AID-MED1>3.0.CO;2-A](https://doi.org/10.1002/1098-1128(200009)20:5<323::AID-MED1>3.0.CO;2-A)
122. Riva D. A.; Fernández-Larrosa P. N.; Dolcini G. L.; Martínez-Peralta L. A.; Coulombié F. C.; Mersich S. E. *Arch. Virol.* **2008**, *153*, 561-565.
<https://doi.org/10.1007/s00705-007-0023-4>
123. Prasad S.; Tyagi A. K. *Food Funct* **2015**, *6*, 3412-3419.
<https://doi.org/10.1039/C5FO00485C>
124. Ali A.; Banerjea A. C. *Sci. Rep.* **2016**, *6*, 27539.
<https://doi.org/10.1038/srep27539>
125. Sidhu G. S.; Singh A. K.; Thaloor D.; Banaudha K. K.; Patnaik G. K.; Srimal R. C.; Maheshwari R. K. *Wound Repair Regen.* **1998**, *6*, 167-177.
<https://doi.org/10.1046/j.1524-475X.1998.60211.x>
126. Sidhu G. S.; Mani H.; Gaddipati J. P.; Singh A. K.; Seth P.; Banaudha K. K.; Patnaik G. K.; Maheshwari R. K. *Wound Repair Regen.* **1999**, *7*, 362-374.
<https://doi.org/10.1046/j.1524-475X.1999.00362.x>
127. Phan T. T.; See P.; Lee S. T.; Chan S. Y. *J. Trauma* **2001**, *51*, 927-931.
<https://doi.org/10.1097/00005373-200111000-00017>
128. Gopinath D.; Ahmed M. R.; Gomathi K.; Chitra K.; Sehgal P. K.; Jayakumar R. *Biomaterials* **2004**, *25*, 1911-1917.
[https://doi.org/10.1016/S0142-9612\(03\)00625-2](https://doi.org/10.1016/S0142-9612(03)00625-2)
129. Panchatcharam M.; Miriyala S.; Gayathri V. S.; Suguna L. *Mol. Cell. Biochem.* **2006**, *290*, 87-96.
<https://doi.org/10.1007/s11010-006-9170-2>
130. Mohanty C.; Sahoo S. K. *Drug Discov. Today* **2017**, *22*, 1582-1592.
<https://doi.org/10.1016/j.drudis.2017.07.001>
131. Morikawa T.; Matsuda H.; Ninomiya K.; Yoshikawa M. *Biol. Pharm. Bull.* **2002**, *25*, 627-631.
<https://doi.org/10.1248/bpb.25.627>

132. Nanji A. A.; Jokelainen K.; Tipoe G. L.; Rahemtulla A.; Thomas P.; Dannenberg A. J. *Am. J. Physiol-Gastrointest. Liver Physiol.* **2003**, *284*, G321-G327.
<https://doi.org/10.1152/ajpgi.00230.2002>
133. Farombi E. O.; Shrotriya S.; Na H. K.; Kim S. H.; Surh Y. J. *Food Chem. Toxicol.* **2008**, *46*, 1279-1287.
<https://doi.org/10.1016/j.fct.2007.09.095>
134. Wu S. J.; Lin Y. H.; Chu C. C.; Tsai Y. H.; Chao J. C. *J. Med. Food* **2008**, *11*, 224-229.
<https://doi.org/10.1089/jmf.2007.555>
135. Rivera-Espinoza Y., Muriel P. *Liver Int.* **2009**, *29*, 1457-1466.
<https://doi.org/10.1111/j.1478-3231.2009.02086.x>
136. Yun S. S.; Kim S. P.; Kang M. Y.; Nam S. H. *Biotechnol. Lett.* **2010**, *32*, 209-214.
<https://doi.org/10.1007/s10529-009-0153-8>
137. Tu C.-T.; Han B.; Yao Q.-Y., Zhang Y.-A.; Liu H.-C.; Zhang S.-C. *Int. Immunopharmacol.* **2012**, *12*, 151-157.
<https://doi.org/10.1016/j.intimp.2011.11.005>
138. Vera-Ramirez L.; Perez-Lopez P.; Varela-Lopez A.; Ramirez-Tortosa M.; Battino M.; Quiles J. L. *BioFactors* **2013**, *39*, 88-100.
<https://doi.org/10.1002/biof.1057>
139. Awasthi S.; Srivatava S. K.; Piper J. T.; Singhal S. S.; Chaubey M.; Awasthi Y. C. *Am J. Clin. Nutr.* **1996**, *64*, 761-766.
<https://doi.org/10.1093/ajcn/64.5.761>
140. Manikandan R.; Thiagarajan R.; Beulaja S.; Chindhu S.; Mariammal K.; Sudhandiran G.; Arumugam M. *Chem. Biol. Interact.* **2009**, *181*, 202-209.
<https://doi.org/10.1016/j.cbi.2009.05.011>
141. Manikandan R.; Thiagarajan R.; Beulaja S.; Sudhandiran G.; Arumugam M. *Free Radic. Biol. Med.* **2010**, *48*, 483-492.
<https://doi.org/10.1016/j.freeradbiomed.2009.11.011>
142. Saleheen D.; Ali S. A.; Ashfaq K.; Siddiqui A. A.; Agha A.; Yasinzai M. M. *Biol. Pharm. Bull.* **2002**, *25*, 386-389.
<https://doi.org/10.1248/bpb.25.386>
143. Chan M. M.; Adapala N. S.; Fong D. *Parasitol. Res.* **2005**, *96*, 49-56.
<https://doi.org/10.1007/s00436-005-1323-9>
144. Adapala N.; Chan M. M. *Lab. Invest.* **2008**, *88*, 1329-1339.
<https://doi.org/10.1038/labinvest.2008.90>
145. Huei-Chen H.; Tong-Rong J.; Sheau-Farn Y. *Eur. J. Pharmacol.* **1992**, *221*, 381-384.
[https://doi.org/10.1016/0014-2999\(92\)90727-L](https://doi.org/10.1016/0014-2999(92)90727-L)
146. Chen H.-W.; Huang H.-C. *Br. J. Pharmacol.* **1998**, *124*, 1029-1040.
<https://doi.org/10.1038/sj.bjp.0701914>
147. Sahebkar A. *Nat. Prod. Res.* **2015**, *29*, 491-492.
<https://doi.org/10.1080/14786419.2014.956212>
148. Carroll R. E.; Benya R. V.; Turgeon D. K.; Vareed S.; Neuman M.; Rodriguez L.; Kakarala M.; Carpenter P. M.; McLaren C.; Meyskens Jr F. L.; Brenner D. E. *Cancer Prev. Res.* **2011**, *4*, 354-364.
<https://doi.org/10.1158/1940-6207.CAPR-10-0098>
149. He Z.-Y.; Shi C.-B.; Wen H.; Li F.-L.; Wang B.-L.; Wang J. *Cancer Invest.* **2011**, *29*, 208-213.
<https://doi.org/10.3109/07357907.2010.550592>
150. Durgaprasad S.; Pai C.G.; Vasanthkumar; Alvres J.F.; Namitha S. *Indian J. Med. Res.* **2005**, *122*, 315-318.

151. Gupta S. C.; Kismali G.; Aggarwal B. B. *BioFactors* **2013**, *39*, 2-13.
<https://doi.org/10.1002/biof.1079>
152. Ide H.; Tokiwa S.; Sakamaki K.; Nishio K.; Isotani S.; Muto S.; Hama T.; Masuda H.; Horie S. *The Prostate* **2010**, *70*, 1127-1133.
<https://doi.org/10.1002/biof.1079>
153. Sharma R. A.; Gescher A. J.; Steward W. P. *Eur. J. Cancer* **2005**, *41*, 1955-1968.
<https://doi.org/10.1016/j.ejca.2005.05.009>
154. Goel A.; Kunnumakkara A. B.; Aggarwal B. B. *Biochem. Pharmacol.* **2008**, *75*, 787-809.
<https://doi.org/10.1016/j.bcp.2007.08.016>
155. Aggarwal B. B.; Sung B. *Trends Pharmacol. Sci.* **2009**, *30*, 85-94.
<https://doi.org/10.1016/j.tips.2008.11.002>
156. Prasad S.; Tyagi A. K.; Aggarwal B. B. *Cancer Res. Treat.* **2014**, *46*, 2-18.
<https://doi.org/10.4143/crt.2014.46.1.2>
157. Ireson C. R.; Jones D. J.; Orr S.; Coughtrie M. W.; Boocock D. J.; Williams M. L.; Farmer P. B.; Steward W. P.; Gescher A. J. *Cancer Epidemiol Biomarkers Prev* **2002**, *11*, 105-111.
158. Garcea G.; Berry D. P.; Jones D. J.; Singh R.; Dennison A. R.; Farmer P. B.; Sharma R. A.; Steward W. P.; Gescher A. J. *Cancer Epidemiol Biomarkers Prev* **2005**, *14*, 120-125.
159. Pendleton E.G.; Jamasbi R.J.; Geusz M.E. *Anticancer Agents Med Chem* **2019**, *19*, 1012-1020.
<https://doi.org/10.2174/1871520619666190116141448>
160. Lai C.-S.; Ho C.-T.; Pan M.-H. *Biomolecules* **2020**, *10*, 831.
<https://doi.org/10.3390/biom10060831>
161. Sasaki H.; Sunagawa Y.; Takahashi K.; Imaizumi A.; Fukuda H.; Hashimoto T.; Wada H.; Katanasaka Y.; Kakeya H.; Fujita M.; Hasegawa K.; Morimoto T. *Biol. Pharm. Bull.* **2011**, *34*, 660-665.
<https://doi.org/10.1248/bpb.34.660>
162. Burgos-Moron E.; Calderon-Montano J. M.; Salvador J.; Robles A.; Lopez-Lazaro M. *Int. J. Cancer* **2010**, *126*, 1771-1775.
163. Pan M. H.; Huang T. M.; Lin J. K. *Drug Metab. Dispos.* **1999**, *27*, 486-494.
164. Hoehle S. I.; Pfeiffer E.; Sólyom A. M.; Metzler M. *J. Agric. Food Chem.* **2006**, *54*, 756-764.
<https://doi.org/10.1021/jf058146a>
165. Dempe J. S.; Scheerle R. K.; Pfeiffer E.; Metzler M. *Mol. Nutr. Food Res.* **2013**, *57*, 1543-1549.
<https://doi.org/10.1002/mnfr.201200113>
166. Swanson H. I. *Drug Metab. Dispos.* **2015**, *43*, 1499-1504.
<https://doi.org/10.1124/dmd.115.065714>
167. An C.-Y.; Sun Z.-Z.; Shen L.; Ji H.-F. *Food Nutr. Res.* **2017**, *61*, 1412814.
<https://doi.org/10.1080/16546628.2017.1412814>
168. Burapan S.; Kim M.; Han J. *J. Agric. Food Chem.* **2017**, *65*, 3305-3310.
<https://doi.org/10.1021/acs.jafc.7b00943>
169. Frank J.; Schiborr C.; Kocher A.; Meins J.; Behnam D.; Schubert-Zsilavec M.; Abdel-Tawab M. *Plant Foods Hum. Nutr.* **2017**, *72*, 48-53.
<https://doi.org/10.1007/s11130-016-0587-9>
170. Peterson C. T.; Vaughn A. R.; Sharma V.; Chopra D.; Mills P. J.; Peterson S. N.; Sivamani R. K. *J. Evid.-Based Integr. Med.* **2018**, *23*, 1-8.
<https://doi.org/10.1177/2515690X18790725>

171. Tranchida F.; Rakotoniaina Z.; Shintu L.; Tchiakpe L.; Deyris V.; Yemloul M.; Stocker P.; Vidal N.; Rimet O.; Hiol A.; Caldarelli S. *Sci. Rep.* **2017**, *7*, 5880-5880.
<https://doi.org/10.1038/s41598-017-06220-0>
172. Farzaei M. H.; Zobeiri M.; Parvizi F.; El-Senduny F. F.; Marmouzi I.; Coy-Barrera E.; Naseri R.; Nabavi S. M.; Rahimi R.; Abdollahi M. *Nutrients* **2018**, *10*, 855.
<https://doi.org/10.3390/nu10070855>
173. Toden S.; Goel A. *J. Restor. Med.* **2017**, *6*, 27-36.
<https://doi.org/10.14200/jrm.2017.6.0101>
174. Nurfina A. N.; Reksohadiprodjo M. S.; Timmerman H.; Jenie U. A.; Sugiyanto D.; van der Goot H. *Eur. J. Med. Chem.* **1997**, *32*, 321-328.
[https://doi.org/10.1016/S0223-5234\(97\)89084-8](https://doi.org/10.1016/S0223-5234(97)89084-8)
175. Sardjiman S. S.; Reksohadiprodjo M. S.; Hakim L.; Van Der Goot H.; Timmerman H. *Eur. J. Med. Chem.* **1997**, *32*, 625-630.
[https://doi.org/10.1016/S0223-5234\(97\)83288-6](https://doi.org/10.1016/S0223-5234(97)83288-6)
176. Venkatesan P.; Rao M. N. A. *J. Pharm. Pharmacol.* **2000**, *52*, 1123-1128.
<https://doi.org/10.1211/0022357001774886>
177. Hahm E. R.; Cheon G.; Lee J.; Kim B.; Park C.; Yang C. H. *Cancer Lett* **2002**, *184*, 89-96.
[https://doi.org/10.1016/S0304-3835\(02\)00170-2](https://doi.org/10.1016/S0304-3835(02)00170-2)
178. Ishida J.; Ohtsu H.; Tachibana Y.; Nakanishi Y.; Bastow K. F.; Nagai M.; Wang H.-K.; Itokawa H.; Lee K.-H. *Bioorg. Med. Chem.* **2002**, *10*, 3481-3487.
[https://doi.org/10.1016/S0968-0896\(02\)00249-3](https://doi.org/10.1016/S0968-0896(02)00249-3)
179. Ohtsu H.; Xiao Z.; Ishida J.; Nagai M.; Wang H.; Itokawa H.; Su C.; Shih C.; Chiang T.; Chang E. *J. Med. Chem.* **2002**, *45*, 5037-5042.
<https://doi.org/10.1021/jm020200g>
180. Srivivasan A.; Menon V. P.; Periaswamy V.; Rajasekaran K. N. *J. Pharm. Pharm. Sci.* **2003**, *6*, 327-333.
181. Hahm E. R.; Gho Y. S.; Park S.; Park C.; Kim K. W.; Yang C. H. *Biochem. Biophys. Res. Commun.* **2004**, *321*, 337-344.
<https://doi.org/10.1016/j.bbrc.2004.06.119>
182. Ligeret H.; Barthelemy S.; Bouchard Doulikas G.; Carrupt P. A.; Tillement J. P.; Labidalle S.; Morin D. *FEBS Lett.* **2004**, *569*, 37-42.
<https://doi.org/10.1016/j.febslet.2004.05.032>
183. Rukkumani R.; Aruna K.; Varma P. S.; Rajasekaran K. N.; Menon V. P. *J. Pharm. Pharm. Sci.* **2004**, *7*, 274-283.
<https://doi.org/10.1089/jmf.2004.7.456>
184. Weber W. M.; Hunsaker L. A.; Abcouwer S. F.; Deck L. M.; Vander Jagt D. L. *Bioorg. Med. Chem.* **2005**, *13*, 3811-3820.
<https://doi.org/10.1016/j.bmc.2005.03.035>
185. Chen W.-F.; Deng S.-L.; Zhou B.; Yang L.; Liu Z.-L. *Free Radic. Biol. Med.* **2006**, *40*, 526-535.
<https://doi.org/10.1016/j.freeradbiomed.2005.09.008>
186. Jankun J.; Aleem A. M.; Malgorzewicz S.; Szkudlarek M.; Zawodszky M. I.; Dewitt D. L.; Feig M.; Selman S. H.; Skrzypczak-Jankun E. *Mol. Cancer Ther.* **2006**, *5*, 1371-1382.
<https://doi.org/10.1158/1535-7163.MCT-06-0021>
187. Lin L.; Shi Q.; Nyarko A. K.; Bastow K. F.; Wu C.-C.; Su C.-Y.; Shih C. C. Y.; K.-H. Lee *J. Med. Chem.* **2006**, *49*, 3963-3972.

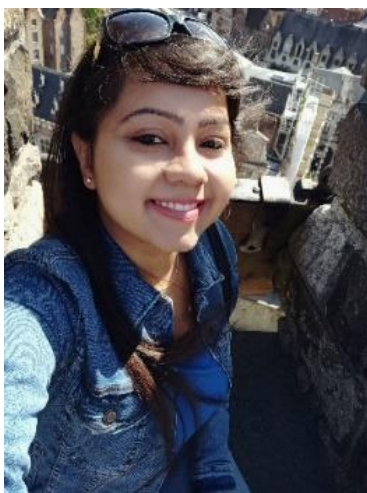
- <https://doi.org/10.1021/jm051043z>
188. Weber W. M.; Hunsaker L. A.; Gonzales A. M.; Heynekamp J. J.; Orlando R. A.; Deck L. M.; Vander Jagt D. L. *Biochem. Pharmacol.* **2006**, *72*, 928-940.
<https://doi.org/10.1016/j.bcp.2006.07.007>
189. Weber W. M.; Hunsaker L. A.; Roybal C. N.; Bobrovnikova-Marjon E. V.; Abcouwer S. F.; Royer R. E.; Deck L. M.; Vander Jagt D. L. *Bioorg. Med. Chem.* **2006**, *14*, 2450-2461.
<https://doi.org/10.1016/j.bmc.2005.11.035>
190. Wei Q. Y.; Chen W. F.; Zhou B.; Yang L.; Liu Z. L. *Biochim. Biophys. Acta* **2006**, *1760*, 70-77.
<https://doi.org/10.1016/j.bbagen.2005.09.008>
191. Costi, R.; Di Santo R.; Artico M.; Miele G.; Valentini P.; Novellino E.; Cereseto A. *J. Med. Chem.* **2007**, *50*, 1973-1977.
<https://doi.org/10.1021/jm060943s>
192. Handler N.; Jaeger W.; Puschacher H.; Leisser K.; Erker T. *Chem. Pharm. Bull.* **2007**, *55*, 64-71.
<https://doi.org/10.1248/cpb.55.64>
193. Nichols C.E.; Youssef D.; Harris R.G.; Jha A. *Arkivoc* **2006**, *13*, 64-72.
<https://doi.org/10.3998/ark.5550190.0007.d07>
194. Youssef D.; Nichols C.; Cameron T.; Balzarini J.; De Clercq E.; Jha A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5624-5629.
<https://doi.org/10.1016/j.bmcl.2007.07.079>
195. Ding L.; Ma S.; Lou H.; Sun L.; Ji M. *Molecules* **2015**, *20*, 21501-21514.
<https://doi.org/10.3390/molecules201219772>
196. Wang J.; Xiong T.; Zhou J.; He H.; Wu D.; Du X.; Li X.; Xu B. *Nano Res.* **2018**, *11*, 3453-3461.
<https://doi.org/10.1007/s12274-018-1994-z>
197. Deng S.-L.; Chen W.-F.; Zhou B.; Yang L.; Liu Z.-L. *Food Chem.* **2006**, *98*, 112-119.
<https://doi.org/10.1016/j.foodchem.2005.05.063>
198. Zhang Q.; Fu Y.; Wang H. W.; Gong T.; Qin Y.; Zhang Z. R. *Chin. Chem. Lett.* **2008**, *19*, 281-285.
<https://doi.org/10.1016/j.ccllet.2007.12.035>
199. Bairwa K.; Grover J.; Kania M.; Jachak S. M. *RSC Adv.* **2014**, *4*, 13946-13978.
<https://doi.org/10.1039/c4ra00227j>
200. Mishra S.; Patel S.; Halpani C.G. *Chem. Biodiversity* **2019**, *16*, e1800366 and references cited therein.
201. Amolins M. W.; Peterson L. B.; Blagg B. S. *Bioorg. Med. Chem.* **2009**, *17*, 360-367.
<https://doi.org/10.1016/j.bmc.2008.10.057>
202. Mishra S.; Karmodiya K.; Surolia N.; Surolia A. *Bioorg. Med. Chem.* **2008**, *16*, 2894-2902.
<https://doi.org/10.1016/j.bmc.2007.12.054>
203. Mayadevi M.; Sherin D. R.; Keerthi V. S.; Rajasekharan K. N.; Omkumar R. V. *Bioorg. Med. Chem.* **2012**, *20*, 6040-6047.
<https://doi.org/10.1016/j.bmc.2012.08.029>
204. Simoni D.; Rizzi M.; Rondanin R.; Baruchello R.; Marchetti P.; Invidiata F. P.; Labbozzetta M.; Poma P.; Carina V.; Notarbartolo M.; Alaimo A.; D'Alessandro N. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 845-849.
<https://doi.org/10.1016/j.bmcl.2007.11.021>
205. Qiu P.; Xu L.; Gao L.; Zhang M.; Wang S.; Tong S.; Sun Y.; Zhang L.; Jiang T. *Bioorg. Med. Chem.* **2013**, *21*, 5012-5020.
<https://doi.org/10.1016/j.bmc.2013.06.053>
206. Lal J.; Gupta S. K.; Thavaselvam D.; Agarwal D. D. *Eur. J. Med. Chem.* **2013**, *64*, 579-588.

- <https://doi.org/10.1016/j.eimech.2013.03.012>
207. Shetty S.; Kim Y. J.; Shim H.; Snyder J. P. *Molecules* **2015**, *20*, 249-292 and references cited therein.
<https://doi.org/10.3390/molecules20010249>
208. Yin S.; Zheng X.; Yao X.; Wang Y.; Liao D. *J. Cancer Ther.* **2013**, *4*, 113-123.
<https://doi.org/10.4236/jct.2013.41016>
209. Zhao C.; Liu Z.; Liang G. *Curr. Pharm. Des.* **2013**, *19*, 2114-2135.
<https://doi.org/10.2174/1381612811319110012>
210. Adams B. K.; Cai J.; Armstrong J.; Herold M.; Lu Y. J.; Sun A.; Snyder J. P.; Liotta D. C.; Jones D. P.; Shoji M. *Anticancer drugs* **2005**, *16*, 263-275.
<https://doi.org/10.1097/00001813-200503000-00005>
211. Thomas S. L.; Zhong D.; Zhou W.; Malik S.; Liotta D.; Snyder J. P.; Hamel E.; Giannakakou P. *Cell Cycle* **2008**, *7*, 2409-2417.
<https://doi.org/10.4161/cc.6410>
212. Tan X.; Sidell N.; Mancini A.; Huang R. P.; Shenming W.; Horowitz I. R.; Liotta D. C.; Taylor R. N.; Wieser F. *Reprod. Sci.* **2010**, *17*, 931-940.
<https://doi.org/10.1177/1933719110374239>
213. He G.; Feng C.; Vinothkumar R.; Chen W.; Dai X.; Chen X.; Ye Q.; Qiu C.; Zhou H.; Wang Y.; Liang G.; Xie Y.; Wu W. *Cancer Chemoth. Pharm.* **2016**, *78*, 1151-1161.
<https://doi.org/10.1007/s00280-016-3172-x>
214. Bertazza L.; Sensi F.; Cavedon E.; Watutantrige-Fernando S.; Censi S.; Manso J.; Vianello F.; Casal Ide E.; Iacobone M.; Pezzani R.; Mian C.; Barollo S. *Endocrinology* **2018**, *159*, 2348-2360.
<https://doi.org/10.1210/en.2018-00124>
215. Adams B. K.; Ferstl E. M.; Davis M. C.; Herold M.; Kurtkaya S.; Camalier R. F.; Hollingshead M. G.; Kaur G.; Sausville E. A.; Rickles F. R.; Snyder J. P.; Liotta D. C.; Shoji M. *Bioorg. Med. Chem.* **2004**, *12*, 3871-3883.
<https://doi.org/10.1016/j.bmc.2004.05.006>
216. Lagisetty P.; Vilekar P.; Sahoo K.; Anant S.; Awasthi V. *Bioorg. Med. Chem.* **2010**, *18*, 6109-6120.
<https://doi.org/10.1016/j.bmc.2010.06.055>
217. Dewitte G.; Walmagh M.; Diricks M.; Lepak A.; Gutmann A.; Nidetzky B.; Desmet T. *J. Biotechnol.* **2016**, *233*, 49-55.
<https://doi.org/10.1016/j.jbiotec.2016.06.034>
218. Theppawong A.; Van de Walle T.; Grootaert C.; Bultinck M.; Desmet T.; Van Camp J.; D'hooghe M. *ChemistryOpen* **2018**, *7*, 381-392.
<https://doi.org/10.1002/open.201800029>
219. Theppawong A.; Van de Walle T.; Grootaert C.; Van Hecke K.; Catry N.; Desmet T.; Van Camp J.; D'hooghe M. *ChemistryOpen* **2019**, *8*, 236-247.
<https://doi.org/10.1002/open.201800287>
220. Van de Walle T.; Theppawong A.; Grootaert C.; De Jonghe S.; Persoons L.; Daelemans D.; Van Hecke K.; Van Camp J.; D'hooghe M. *Montash. Chem.* **2019**, *150*, 2045-2051.
<https://doi.org/10.1007/s00706-019-02516-1>
221. Theppawong A.; Van de Walle T.; Van Hecke K.; Grootaert C.; Van Camp J.; D'hooghe M. *Chem. Eur. J.* **2019**, *25*, 12583-12600.
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Authors' Biographies



Atiruj Theppawong was born in Chiang Mai, Thailand in 1989. He obtained his Bachelor's degree (Hon.) in Biochemistry and Biotechnology at Chiang Mai University, Thailand and Master's degree in Chemical Biology from Chulabhorn Graduate Institute, Thailand. He started his PhD under the supervision of Prof. Matthias D'hooghe at the SynBioC Research Group (Department of Green Chemistry and Technology, Faculty of Bioscience Engineering, Ghent University) in 2015, in collaboration with the group of Prof. John Van Camp. He obtained his PhD degree in Applied Biological Sciences: Chemistry and Bioprocess Technology in 2019 with research work mainly focused on synthesis of curcuminoid analogs and their anticancer evaluation.



Gurkirat Kaur was born in Abohar, Punjab, India in 1996. She received her diploma for B.Sc.(HS)-Chemistry and M.Sc.(HS)-Chemistry, both from Guru Nanak Dev University, Amritsar, Punjab, India in 2016 and 2018 respectively. She is currently pursuing a sandwich PhD at the SynBioC Research Group, Department of Green Chemistry and Technology (Faculty of Bioscience Engineering, Ghent University) with Prof. Matthias D'hooghe as the promoter and Prof. Vipin Kumar as the co-promoter. The major component of her research interest comprises of the synthesis of β -lactam based bioactive compounds.



Vipin Kumar is presently working as an Assistant Professor in the Department of Chemistry, Guru Nanak Dev University, Amritsar. He obtained his PhD with Prof. Mohinder P Mahajan, in the Department of Applied Chemistry, GNDU. In 2007, he moved to the University of Cape Town (UCT), South Africa, to pursue his postdoctoral studies with Prof. Kelly Chibale. In 2015, he was awarded a research fellowship from Carl Tryggers research foundation, Sweden, to carry out research at University of Umea, Sweden. His research interests include the development of diverse synthetic protocols for synthesis of novel molecular frameworks targeting tropical infections. Dr. Kumar is author of >110 publications in international journals with an H-index of 28.



John Van Camp was born in Deurne, Belgium, in 1965. He received his Master's diploma in 1989 (Master of Science in Bioscience Engineering: Chemistry) and his PhD degree in 1996 (Doctor in Applied Biological Sciences: Chemistry), both from Ghent University, Belgium, with Prof. A. Huyghebaert as promoter. In 1996, he became post-doctoral assistant at the Department of Food Technology, Safety and Health, Ghent University, and in 1997-1998 he performed a postdoctoral stay of 6 months at the "Bundesanstalt für Milchforschung, Institut für Physiologie und Biochemie der Ernährung", Kiel, Germany, where he worked on endothelial cell culture models. In October 2001, he was promoted to Associate Professor at the Department of Food technology, Safety and Health (Faculty of Bioscience Engineering, Ghent University), and where he was promoted to full Professor in 2014. He has a main interest in designing advanced cell (co-)culture models to study bioavailability and bioactivity of nutrients and bioactive components in the context of cardiovascular diseases, satiety, and cancer (<https://www.ugent.be/bw/foodscience/en/research>). As bioactive food expert, PI Van Camp has over 210 A1-publications (H-index 43). He was participant in the European Nutrition Leadership Programme (ENLP) in human nutrition science in Europe. June, 15th-21st, 2000, in Luxembourg,

NZO-VLAG visiting Professor 2006 at Wageningen University (September, 26-29th, 2006), and FRANCQUI National chair holder 2015-2016 at UCL (Université Catholique De Louvain, Faculté des Bioingénieurs). He is (co-) promotor of 26 PhD's at the Faculty of Bioscience Engineering, Ghent University, and one of the organizers of the 2nd Food Chemistry Conference in Seville (E), 17 September – 19 September 2019.



Matthias D'hooghe was born in Kortrijk, Belgium, in 1978. He received his Master's diploma in 2001 (Master of Science in Bioscience Engineering: Chemistry) and his PhD degree in 2006 (Doctor in Applied Biological Sciences: Chemistry), both from Ghent University, Belgium, with Prof. N. De Kimpe as promotor. In 2007, he became postdoctoral assistant at the Department of Green Chemistry and Technology, Ghent University, and in 2009 he performed a short postdoctoral stay with Prof. D. Vogt at Eindhoven University of Technology (The Netherlands) in the field of homogeneous catalysis. In October 2010, he was promoted to Professor (Research Professor) at the Department of Green Chemistry and Technology (Faculty of Bioscience Engineering, Ghent University), and he was granted tenure in 2015. His main research interests include the chemistry of small-ring azaheterocycles, with a special focus on aziridines, azetidines and β -lactams, and the synthesis of different classes of bioactive heterocyclic compounds at the SynBioC Research Group (<http://www.synbioc.ugent.be>). Prof. D'hooghe is the author of >160 publications in international journals (H-index 31) and was elected as a laureate of the DSM Science & Technology Awards 2007, finalist of the European Young Chemist Award 2012 and recipient of the Thieme Chemistry Journal Award 2013. He organized and chaired the international Bioheterocycles 2019 conference and became a Bioheterocycles International Scientific Committee member in June 2019.

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