RECENT ADVANCES IN C-5 CURCUMINOIDS: DERIVATIVES AND THEIR PHARMACOLOGICAL INTERVENTIONS.

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Abstract

Curcumin (Diferuloylmethane) a phenolic compound, an active component of turmeric, has been extensively explored for its wide range of biological activities due it its nontoxic nature even at high concentrations. It has been reported to demonstrate anti-inflammatory, antimalarial, anti-oxidant, anti osteoporosis, anti-bacterial, anti-fungal, anti-cancerous properties. This compound has excellent therapeutic potential but the facts which constrains its use as a therapeutic agent include poor stability in vivo, low bioavailability and high rate of metabolism. In vivo studies established the fact that curcumin gets degraded into inactive metabolites. Many modifications have been done in curcumin to improve drawbacks of natural curcumin among which one approach is to modify 7 carbon spacer (C-7) diketone moiety by 5 carbon spacer (C-5) moiety and preparing its open chain, homocyclic and heterocyclic analogues to study its implications on biological activities. The promising biological activities of such derivatives prompted medicinal chemists to further explore the possible modification in thrust to get lead molecule for further studies. The various modifications included symmetrical and unsymmetrical C-5 analogues. The modification was also done by preparing acyclic as well as cyclic analogues of C-5 curcumin including homocyclic and heterocyclic analogues. Promising and diverse biological activities of these derivatives further encouraged medicinal chemists to explore the molecule and elicit the therapeutic potential of molecules obtained. In current review exhaustive study of various methods to obtain such curcuminoids are reported along with the biological activity data of revamped molecules.

Keywords: C-5 Curcuminoids, therapeutic potential, anti-cancer, anti-inflammatory.

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Introduction

A primary yellow-orange coloured natural polyphenol called diferuloylmethane, known widely as curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), is a constituent found in the rhizome of *Curcuma longa Linn* which is grown in tropical climatic regions.

Figure 1: Dried Turmeric in which Curcumin is present

Curcumin is soluble in organic solvents like methanol, dimethyl sulfoxide, acetone, ethanol etc. Curcumin decomposes in organic solvents when exposed to light[1–3]. It has a melting temperature of 183°C and a molecular mass of 368.37g. [4]. Due to its antimutagenic, anticancer, antibacterial, and anti-inflammatory qualities, turmeric has a longstanding experience of utilisation as a medicine in Asian nations. Turmeric's active ingredients are the flavonoid curcumin (diferuloylmethane) and a variety of volatile oils such as turmerone, atlantone, and zingiberene.[5]. Curcumin (77%), demethoxycurcumin (17%), and bisdemethoxycurcumin (3%), collectively known as curcuminoids, are the three main components of commercial Curcumin (Figure 1)[6].

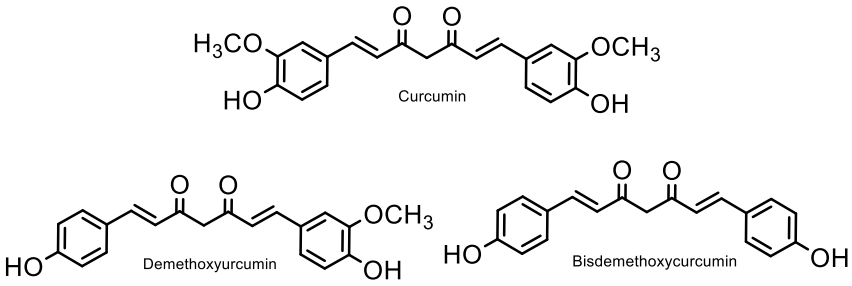


Figure 2: Various available forms of curcumin

In solution, curcumin exists as tautomer which are an enol and a keto form which is further solution acidity dependent (Figure 2) [7]. In neutral and acidic environments, keto predominates, whereas enol occurs in alkaline media. Resonance-assisted hydrogen bonding stabilises the enol form [8,9].

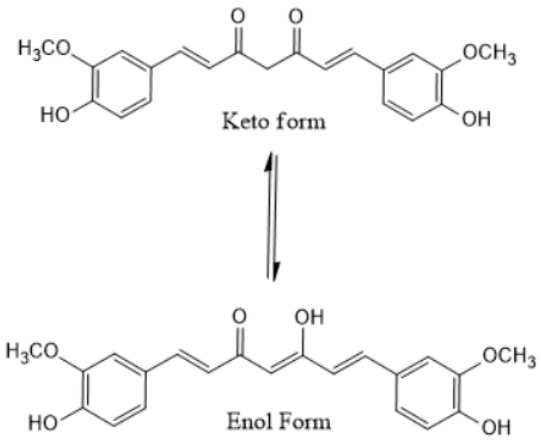


Figure 3: Keto-Enol tautomerism in Curcumin

Curcumin has three varied pK_a values, according to reports. The first two values i.e., 7.8, 8.5 are derived from the two -OH groups that are phenolic in nature, and the third value i.e., 9.0 is derived from the enolic proton. Curcumin has an octanol-water partition coefficient of 3.29 [10–13]. Rapid hydrolytic degradation of the compound occurs while dissociating at pH which is higher than 7. The major breakdown products have previously been reported as ferulic acid, feruloyl methane, and vanillin, with the latter being a subsequent degradation product created by feruloyl methane hydrolysis. The outstanding therapeutic effectiveness of curcumin has been related to its low toxicity profile, and it has been established that curcumin is non-toxic even at large oral dosages of 12 g/day [14]. Despite its safety profile & desirable biological properties, curcumin has not been approved as a therapeutic agent due to poor bioavailability. Curcumin's uses are circumscribed owing to its low solubility in water, that leads to poor bioavailability, quick excretion from the body post expeditious metabolism into inactive metabolites [15] and poor systemic and oral bioavailability [16][17]. Curcumin's β-diketone functionality is well known as an aldo-keto reductase precursor in the liver, which could

be among one of the explanations for curcumin's fast catabolism in vivo [18,19]. Furthermore, curcumin forms a complex with several targets, including albumin [20] and is thus seldom detected unbound/free in vivo. Another impediment is curcumin's limited cellular absorption due to its hydrophobic nature. Curcumin has a proclivity to infiltrate the cellular membrane and bind to the lipid membranes' fatty acyl chains through hydrogen bonding and hydrophobic interactions, leading to decreased curcumin availability within the cytoplasm [21,22].Various groups of researchers took these aspects into consideration and created five carbon enone mimics of curcumin (C-5 curcuminoids) having 1,5-diaryl-3-oxo-1,4-pentadienyl pharmacophore to replace seven carbon enone moiety (C-7 curcuminoids) in the hopes of retaining its activity while enhancing bioavailability [23–25]. When compared to curcumin and other C7-curcuminoids, C5-curcuminoids and their analogues have a stronger pharmacological profile, including enhanced bioavailability, high potency, and improved metabolic stability [26–29]. The results demonstrated that analogues with a 5-carbon spacer can significantly boost the biological activity of curcumin analogues [30]. Curcumin mono-carbonyl analogues (MAC) carry the potential anti-invasive chemotypes, cure to Alzheimer's disease [31], antibacterial [32], anti-inflammatory [33], anticancer [34], anti-obesity [35], antileishmanial [36], antioxidant [37], anti-tubulin activities [38], proinflammatory and lipoxygenase cytokines [39], topoisomerase-II alpha inhibitors [40] and antiparasitic [41] activities. Several of the mono-carbonyl curcumin analogues are said to have a superior pharmacokinetic profile & improved in vivo stability [42]. Concept of designing hybrid molecules for better efficacy is being adopted by medicinal chemists for drug discovery [43–50].

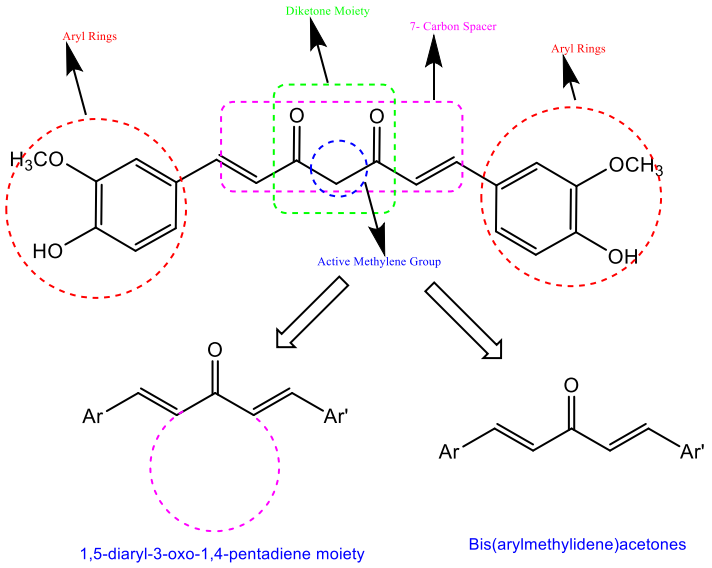


Figure 4: Sites for modification in Curcumin and modified analogues

Cancer targeting C-5 curcuminoids

The typical, healthy body's 37.2 trillion cells coexist in a complex yet co-ordinated relationship through which they control one another's growth. Healthy and normal cells only multiply when prompted to do so by neighbouring cells. This continuous collaboration ensures that each tissue retains the dimensions and structure required by the body. Mammalian cells typically multiply and spread via a process referred to as cell division to generate new cells when the demand is made by the human body. New cells take the place of the cells that die due to age or injury. Cancer is a medical condition that arises when certain cells in the body multiply rapidly and spread to other places of the body. In reality, the term "cancer" refers to more than 100 different types of the illness. Cancer may appear in almost any region of the human body. Damaged or abnormal cells grow and multiply when this well-ordered machinery breaks down. These cells can join to form tissue lumps which are called tumours. Tumours may be benign or malignant i.e., it could either be cancerous or not. Although a healthy body kills the cells with damaged DNA before they become malignant then also almost every tissue in the body has the potential to become cancerous. Every cancer has distinct characteristics. Our bodies' capability to accomplish this task declines as we grow old which further contributes to the

increased risk of cancer later in life. Each patient's cancer has a unique set of genetic changes. As the cancer advances, other changes will occur. Distinct cells within the given tumour may have genetic changes that are poles apart. Cancer is one of the most lethal diseases in modern history, claiming the lives of many people each year. In 2020, approximately 0.0193 billion new cancer cases emerged globally out of which 0.0181 billion cases were there excluding skin cancer of non-melanoma cells and over 0.01 billion cancer deaths were reported out of which 0.0099 billion were there excluding skin cancer that is non-melanoma. With a projected 11.7% of all new cases, female breast cancer became the most frequently diagnosed malignancy (2.3 million). It was further followed by 10% colorectal cancer cases, 11.4% cases of lung cancer, 5.6% cases of stomach cancer & 7.3% cases of prostate cancer. With 0.0018 billion deaths the primary cancer-causing factor is lung cancer mortality, then 9.4% of cancer cases related to colorectal, 8.3% liver cancer cases, 7.7% stomach cancer cases, and 6.9% female breast cancer cases. In accordance with a recent assessment issued by the NCRP which stands for National Cancer Registry Programme, the number of cancer cases is expected to rise to 15.7 lakh by 2025 as compared to 13.9 lakh in 2020, which makes it a surge of almost 20%.

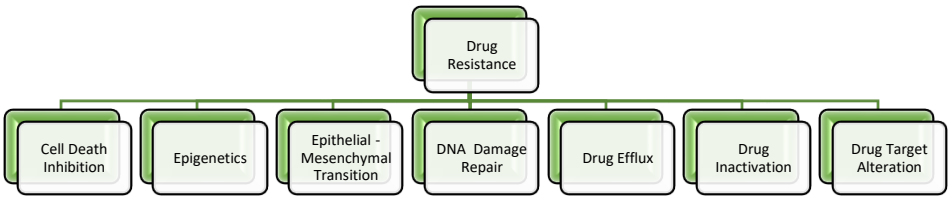


Figure 5: Cancer cell activities causing drug resistance.

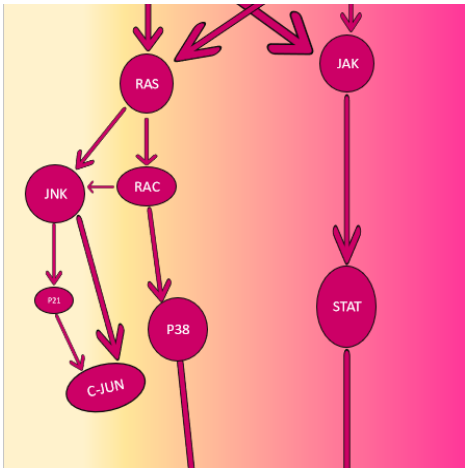


Figure 6: Mechanism of action of anti-cancer drugs

Anthwal et al. synthesised C-5 curcumin analogues with general structure 1 and did variations in nucleus of C-5 curcumin by replacing -H atom with methoxy group along with which benzylamide derivatives and substituted aromatic amide were employed in amido-ether linker. Investigators examined their cytotoxicity on colorectal cancer (HCT116) and chronic myeloid leukaemia cell lines (KBM5). When curcumin analogues were combined with derivatives of benzylamide, the produced molecule with -OCH_3 substitution in the C-5 curcumin core as well as the aromatic ring displayed significant activity. It showed 83.63 ± 0.34 % growth inhibition in chronic myeloid leukaemia (KBM5) and 57.96 ± 0.24% growth inhibition in cancer cell lines of colon (HCT116) at 5 μM. Curcumin analogues with aromatic amides molecules and chloro substituents at 4 and 3 positions, correspondingly, demonstrated greater cytotoxicity than curcumin in two cancer cell lines under study. The molecule containing the -OCH_3 group on the C-5 curcumin has been reported to be the most active. A molecule having a -OCH3 group on the C5 curcumin ring that was substituted by -CH3 groups at the 2 and 6-position in aromatic ring of amide generated promising results [51] .

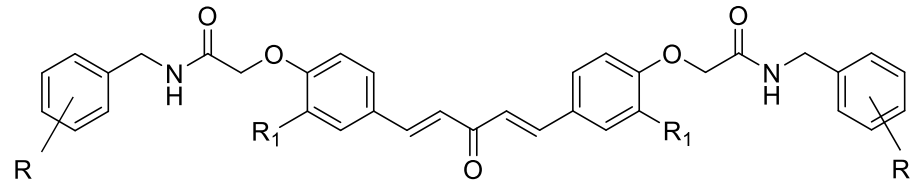


Figure 7: Curcumin analogues showing growth inhibition in KBM5 and HCT116 cell lines

Monocarbonyl analogues of curcumin 2 and 3 that Sanabria-Ríos et al. synthesised have a immediate cytotoxic effect on CCL-229 (colon cancer) cells & impede their dose-dependent in vitro proliferation. Three compounds were the most effective conjugates against CCL-229 out of the ten C-5-Cur-FA (C-5-curcumin-fatty acid) examined, with IC_{50} values that ranged from 56.1 to 22.5 µg/mL. The ability of C-5-Cur-FA to fight cancer rises when fatty acyl chain's carbon atom count decreases. C-5-Cur-FA conjugates with cyclohexanone moiety had lower antitumor efficacy against CCL-229 cells. The introduction of the -OMe group in a C-5-Cur-FA compound demonstrates anti-cancer properties and influences its anti-cancer activity against CCL-229. The addition of -OMe group at position that is para in curcuminoids in combination with chain length of 16 carbon fatty acids moieties improves their anticancer efficacy. The para location of the methoxy group reduces its antitumor action. The fatty acid moiety plays a major role in C-5-Cur-FA conjugates anticancer action against colorectal cancer cells [52]. According to Singh et al., conjugating fatty acids to C-5 curcumin is intended to improve half-life, enhance lipophilicity, improve cellular uptake, and lowers metabolism rate by carboxyesterase within the cell, ensuring low toxicity and high bioavailability as fatty acids are naturally occurring constituents of cell membranes. The inclusion of a fatty acid moiety in curcumin, as well as the removal of a -C=O group, diminishes the cytotoxicity of C-5-Cur-FA moiety when applied to PBMC (peripheral blood mononuclear cells)[53].

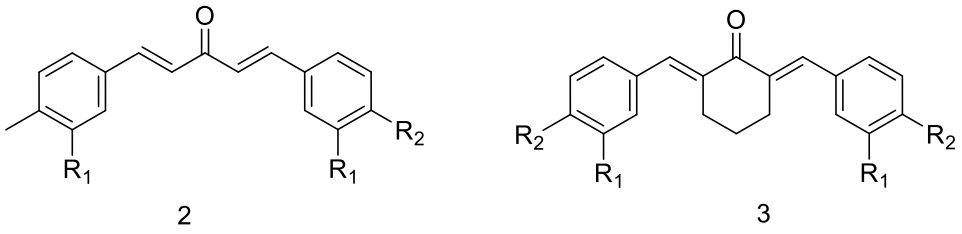
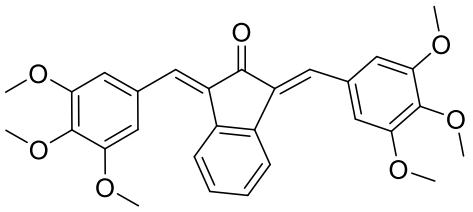


Figure 8: Monocarbonyl curcumin analogues with cytotoxic effect on CCL-229

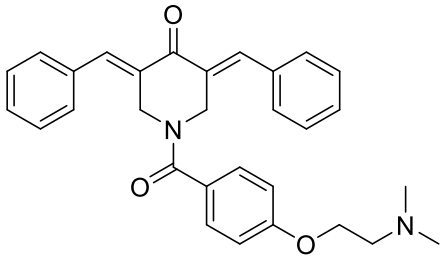
According to the study results, presence -OMe moiety in the aromatic ring of the 2-Indanone is responsible for the cytotoxic effect. A curcumin derivative called IND-4 showed strong cytotoxicity against all types of cell lines and revealed that curcumin was outperformed by IND-4 in terms of anti-proliferative and cytotoxicity activities by 20 folds. Zhou et al. discovered that a curcumin derivative incorporating 2-Indanone effectively demonstrated potent activity against BxPC-3 cells (cancer of pancreas), PC-3 cells (cancer of prostate), HT-29 cells (cancer of colon), RWPE-1 cells (epithelium cells in the human prostate that are not cancerous) and H1299 cell (lung cancer). Moreover, research found that more interaction between a curcumin derivative and the DNA of cancer cells via decreased steric hindrance demonstrated excellent anticancer activity [54].



IND-4

Figure 9: IND-4 effectively used against BxPC-3 cells, PC-3 cells, HT-29 cells, RWPE-1 cells and H1299 cells

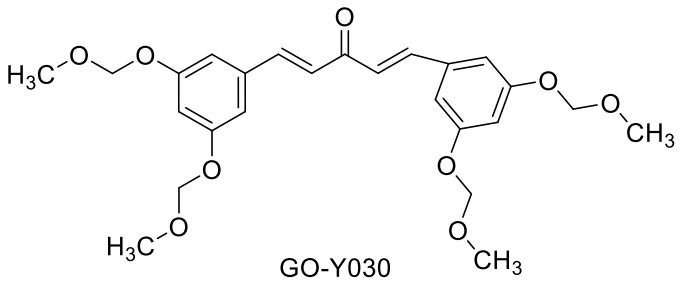
Helal et al. investigated the anti-proliferative effect of curcumin versus 5-Fluorouracil analogues (3,5-bis(benzylidene)-4-piperidone analogue), against HCT116 (colorectal cancer cells). By interfering with mitochondrial functioning, 3,5-bis (benzylidene)-4-piperidone analogues demonstrated remarkable capacity to inhibit proliferation by decreasing oxygen consumption and increasing ROS production. Das et al. carefully examined the effects of dimeric 3, 5-bis(arylidene)-4-piperidones, one of the derivatives of curcumin, on HT29 and HCT116 cell lines and compared them to curcumin and 5-fluorouracil. The study established the fact that curcumin analogues had IC_{50} values in the nanomolar to sub-micromolar range, and amidic carbonyl groups contributed considerably to its cytotoxic effect. Nevertheless, it has been proposed that inserting an electron withdrawing group that is strong in nature within the aryl rings might improve the efficiency of the curcumin counterpart.[55,56]



(3*E*,5*E*)-3,5-dibenzylidene-1-(4-(2-(dimethylamino)ethoxy)benzoyl)piperidin-4-one

Figure 10: Mono-carbonyl analogue of curcumin with potential against HT29 and HCT116 cancer cell lines

Lin et al. examined a novel curcumin analogue (GO-Y030) that enhanced apoptosis efficacy by suppressing STAT3 phosphorylation by starting caspase-3 and PARP cleavages, lowering cell viability, and preventing tumoursphere development. Furthermore, the findings indicated that the STAT3 derivative that is targeted give potential apoptosis in colorectal cancer cell lines. [57].



GO-Y030

Figure 11: Structure of curcumin analogue GO-Y030

A piperidone linkage has been substituted for the di-carbonyl group of curcumin in generic structure 4 which was further found to be endowed with anticancer action .The GI_{50} of compound with a benzyl moiety has been demonstrated to be closer to 10^{-3} M against every types of cancer cells tested[58].Adams et al. developed and synthesised new curcumin derivatives based on curcumin's structure, with compound EF24 being the most efficient in triggering apoptosis in human cancer cells from the prostate and breast among 100 produced analogues. The thorough investigation indicated that EF24 serves as Michael's acceptor, producing cell cycle halt by mitochondrial membrane ruptures. H4073 was produced when a fluorine atom was placed in the para position with improved anti-ovarian cancer cell activity [59]. EF31 performed marginally superior than EF24,

where the aryl moiety connected to the core ring in EF24 was substituted with a pyridine nucleus. In Tu212 SCC, (Squamous cell cancer) cells, the in vitro cytotoxic effects of EF31 and EF24 compounds were determined to be 7μM & 8μM, respectively [60]. UBS 109 was produced as a result of the central piperidon-4-one ring in EF31 being N-methylated. When pancreatic cancer cell lines were examined for their ability to inhibit angiogenesis, it was discovered to adversely influence NF-κB causing the DNMT-1 gene to be down-regulated (DNA methyltransferase-1). In pancreatic cancer, the important cell proliferation regulator DNMT-1 is overexpressed. Head and neck SCC cancers have also been treated with UBS 109 [61,62]. In ovarian cancer cell lines, EF-31 inhibits NF-κB activity[63,64]. A variety of N-acylated or alkylated 3,5-bis(arylidene)-4-piperidones (DAP were synthesized using Claisen Schmidt condensation of piperidin-4-one with the appropriate aldehyde. Studies were done on the cytotoxic effects of the compounds generated as well as their preference for the MCF-7 lines of cancer cells and A2780 over both healthy and normal cell lines. DAP derivatives have been discovered as strong curcumin equivalents that fight cancer. HO3867 outperformed the other derivatives created and was selected to be the key molecule for future investigation. [65]. By its antioxidant effect, this derivative has been shown to reduce the expression of STAT3 in malignant cells whilst safeguarding healthy cells.

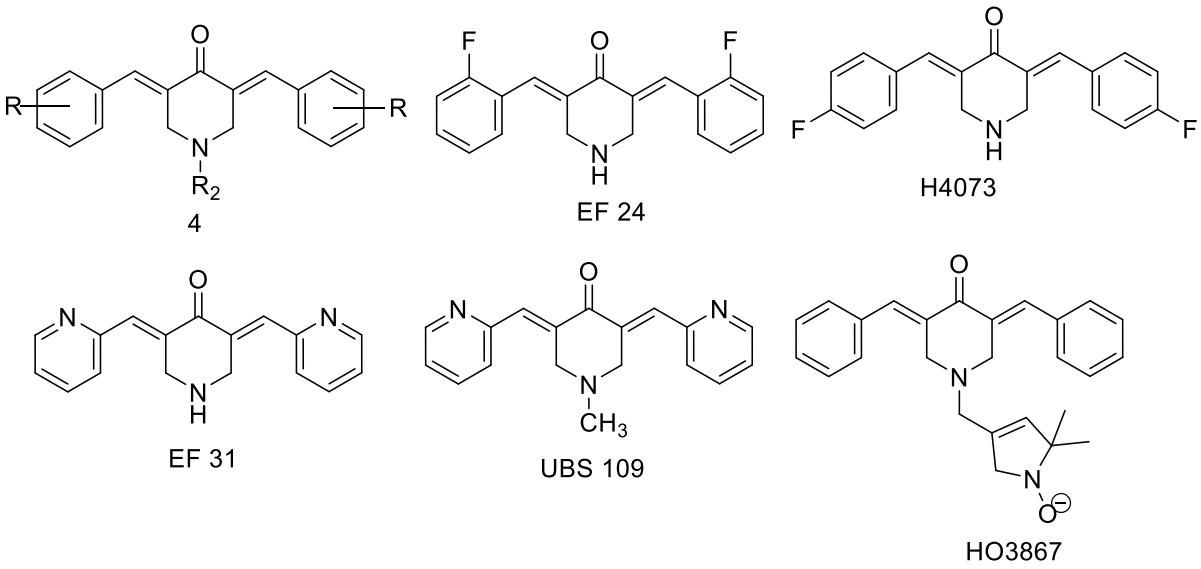


Figure 12: Cyclic curcumin analogues with potent biological activities

The most active compound 5 with pyridine rings linked by an acetone linker exhibited cytotoxicity against a variety of cancer cell types[66]. The anticancer properties of diarylpentanoid analogues were examined in cancer cell lines of liver by Xiao et al. The most effective compound, GL 63 i.e. (1E,4E)-1,5-bis(2-bromophenyl)penta-1,4-dien-3-one, suppressed cells of hepatocellular cancer at a concentration significantly lower than curcumin. [67]. Further research on the function of GL63 in ovarian cancer by Qu et al. revealed that it exhibited cytotoxic effects that vary with dosage on the HO8910 cell line.[68]. GL63 also inhibits the JAK2/STAT3 signalling mechanism. Tumour development was inhibited in wistar rats and mice experiments[69,70]. As compared to the parent medicine(curcumin), compound 6 has showed considerable inactivation of DU145 and PC-3 prostate cancer cell lines [71] .By shifting the compound's hydroxyl group from position 3 to position 2, another potent molecule 7 was created, with EC_{50} values of 1.03±0.5 μM & 2.6±0.9 μM in CaSki & HeLa cell lines, correspondingly[72]. A comprehensive analysis of the way that synthesized diarylpentanoid analogues work, specifically 1,5-bis(2,3-dimethoxyphenyl)penta-1,4-dien-3-one 8 revealed that stimulation of the stress signalling mechanism in the endoplasmic reticulum is critical in demonstrating cytotoxic activity [73]. A novel diarylpentanoid analogue of curcumin 9 exerts anti-neoplastic actions in non-small cell cells of lung cancer through an ER stress-mediated pathway [74].In contrast to earlier research that indicated symmetry to be a crucial factor in identifying anti-cancer activity, Zhang et al. discovered WZ35, an asymmetric curcumin derivative that was earlier synthesized and shown to be 9.5 times as powerful than curcumin [75].

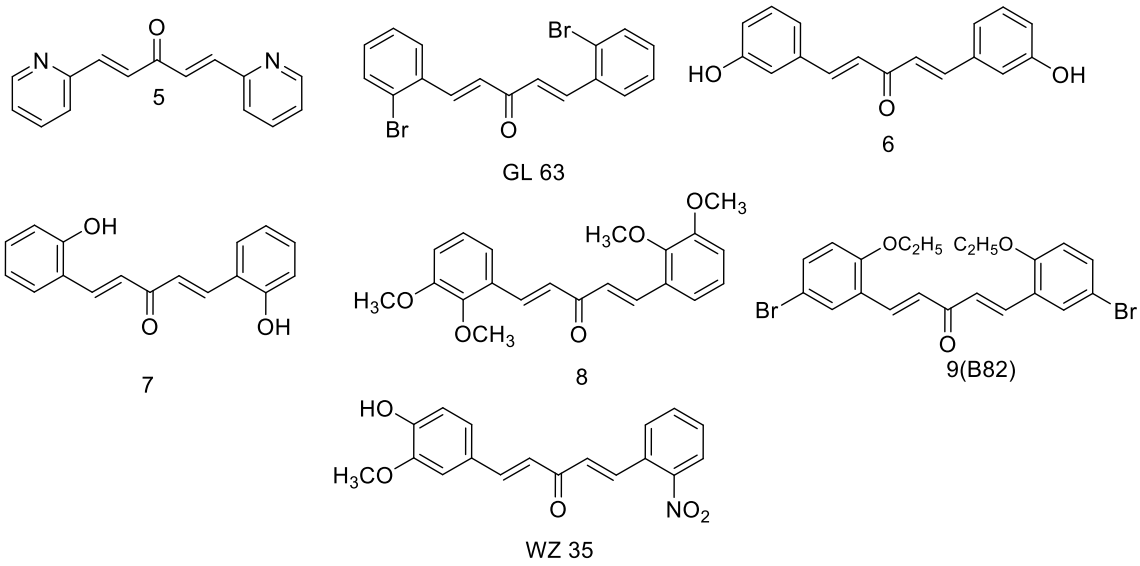


Figure 13: Acyclic curcumin analogues showing anticancer activity

When PGV-0 and PGV-1 were combined, they displayed increased sensitivity to MCF-7 cells that were resistant to doxorubicin [76] .In MDA-MB-231 breast cancer cells, RL91 showed excellent outcomes with an EC_{50} value of 1.10 µM. Its derivative triggered apoptosis by suppressing the cell cycle at G2/M [77]. Yadav et al. went on to synthesis a variety of compounds and put them to the test in ER-negative cell lines of breast cancer, Compound 10 explains substantial cytotoxic effects on MBA-MB-231 cell lines with EC_{50} value equivalent to 3.2 µM [78]. This compound has also been found to exhibit anticancer properties in human prostate cancer cells, although through mechanism of oxidative stress[79]. It was shown that curcumin alone was not as effective as the other analogues used in the study, but also compound 11 was also effective in inhibiting the NF-κB driven pathway. [80]. The most effective derivative, synthesised compound 12 demonstrates IC_{50} values 117, 46 and 72fold higher than curcumin moiety against growing colon, pancreatic, and prostate cancer cells, respectively [81]. In HeLa cells, the cyclohexanone-based new compound 13 had an IC_{50} of 0.64 µM, that was significantly lesser than that of the well-known anticancer agent doxorubicin[82] .Using terminal phenol and benzimidazole moieties as well as a cyclohexanone linker, another new asymmetric curcumin derivative, IHCH, displayed effective proliferation-resistant in lung cancer cells (A549) at 40 µM. [83] .

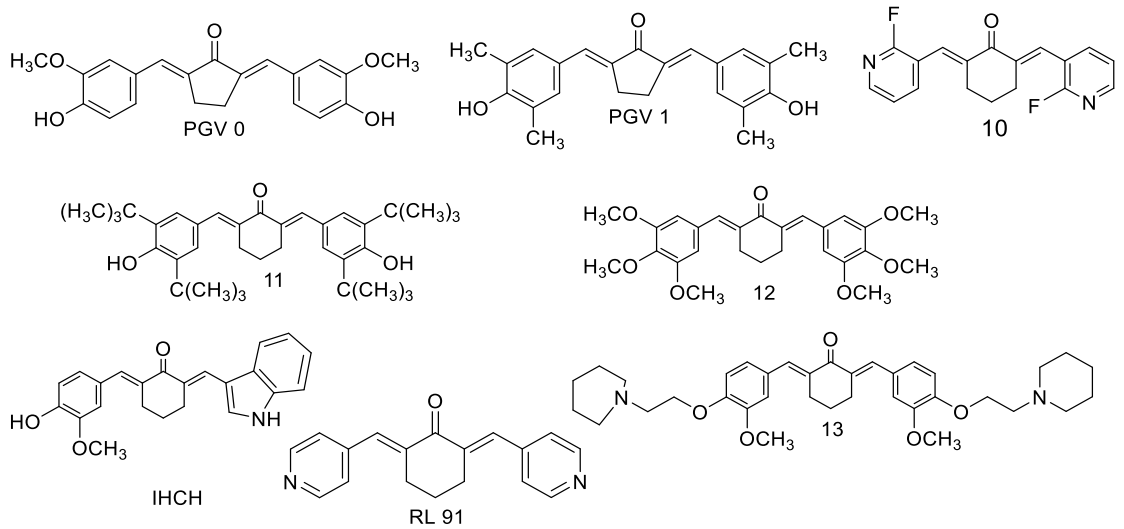


Figure 14: Cyclic curcuminoids with anticancer activity

The G2/M stage of colorectal and breast cancer cells' cell cycles is retarded by an analogue of curcumin known as PAC i.e., 5-Bis-(4-hydroxy-3-methoxybenzylidene)-N-methyl-4-piperidone. In two varieties of mentioned cells and the mouse model, it reduces tumour development and

prevents the transition of epithelial cells to mesenchymal cells[84,85].

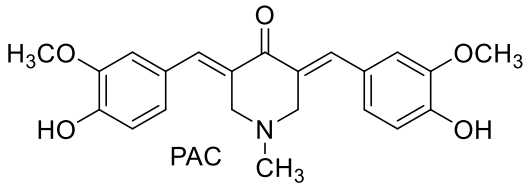


Figure 15: PAC retards G2/M stage cell cycles of colorectal and breast cancer cells

For pancreatic, colorectal, breast, neck and head squamous cell cancer lines, FLLL12 and FLLL11 are curcumin analogues that exhibit comparable behaviour. They particularly trigger the apoptosis-inducing process through caspase-3 and PARP cleavage by activating the apoptotic signalling system[86].

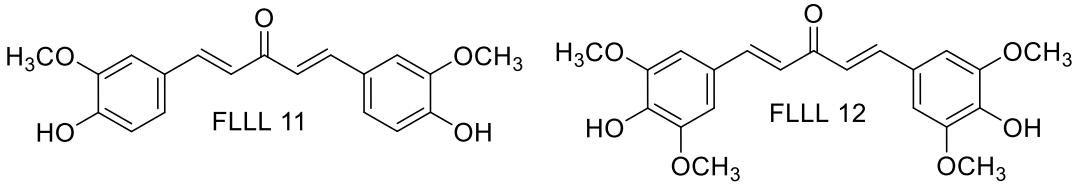


Figure 16: Compounds used against pancreatic, colorectal, breast, neck and head squamous cell cancer lines

To assess the cytotoxicity of the comparable ruthenium arene compounds 15a-b and 16a-b and the organic MAC entities 14a-b, the MTT assay was performed using the human acute lymphoblastic cell line MOLT-4[87]. It was discovered that the anticancer efficacy of the ruthenium and MAC analogues, which comprised of the cyclopentanone moiety in their structural motif, rose by an order of magnitude as more organo-ruthenium centres were linked to the ligand [88]. IC_{50} values for a set of ruthenium and MAC compounds that use cyclohexanone as a linker are comparable throughout all complexes and similar to that discovered for the reference medication cisplatin in terms of magnitude. According to earlier studies, comparable compounds with the cyclopentanone structural motif had less inhibitory effect on the proliferation of cancer cell lines and the androgen receptor than organic MACs with cyclohexanone linkers. These results concur with those of our investigation[89–91].

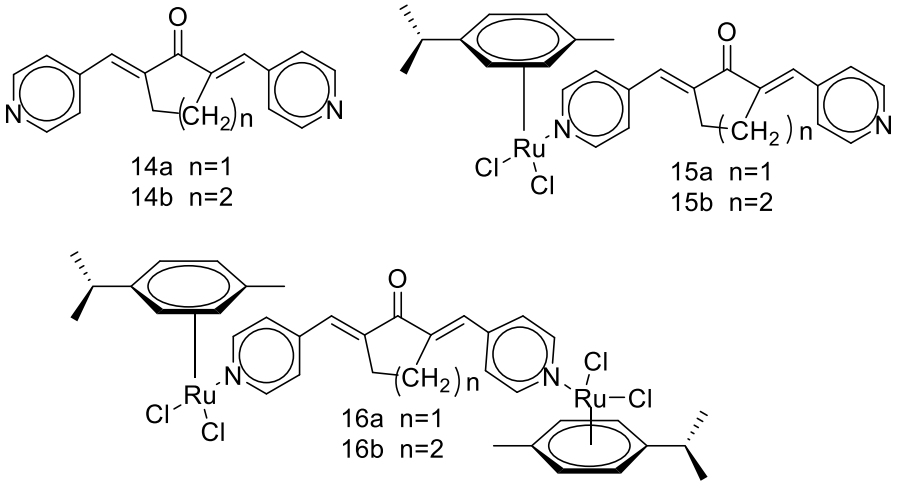
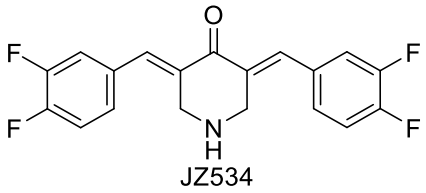


Figure 17: Ruthenium and MAC derivatives with potent anti-cancer activity

The anticancer effects of a newly synthesised curcumin analogue (JZ534) on lung cancer cell lines have been studied. By suppressing growth, causing apoptosis, & increasing the expression of proteins associated with apoptosis, including caspase 3, Bax, and p53, it demonstrated strong anti-lung cancer action. Moreover, at the same dose, JZ534 had greater anticancer efficacy than curcumin[92].



JZ534

Figure 18: MAC demonstrating strong potential against lung cancer cells

By examining how the novel curcumin analogues RL121 and RL118 affected DU145 and PC3 cells, Chen and colleagues discovered that they have a strong cytotoxic impact on the CRPC. Both analogues were shown to trigger apoptosis, raise the proportion of cells in the G2/M cell cycle stage, and suppress nuclear factor production, according to their findings[93]. The most effective test substances were the symmetrical hexamethoxy-diarylpentadienones (17 and 18), which had IC_{50} values of 3.4 ± 0.1 and 1.9 ± 0.1μM and were 11- and 20- fold more powerful than curcumin, respectively when tested for have a strong cytotoxic impact on the CRPC using the SRB assay [94]

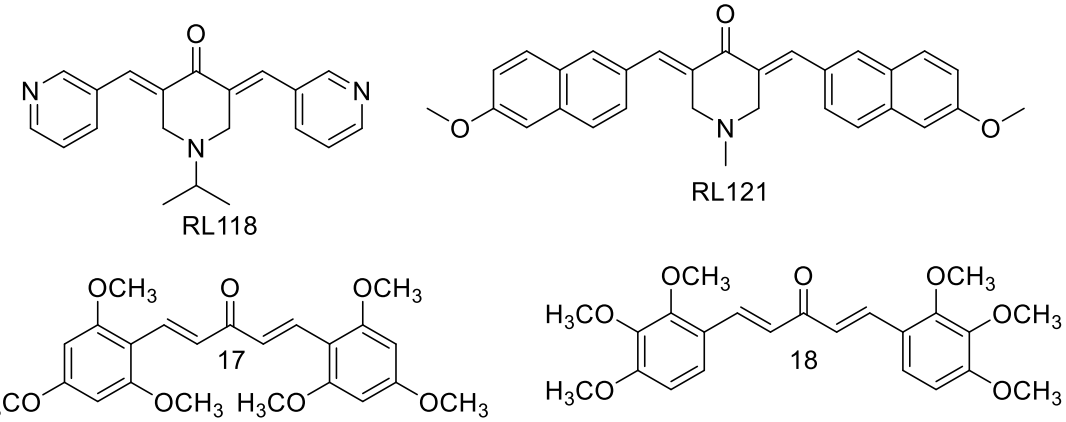


Figure 19: Compounds having strong cytotoxic impact on the CRPC

It was discovered that Far Upstream Element-Binding Protein 2/KH-type Splicing Regulatory Protein which is the nuclear protein, binds to GO-Y086. The c-Myc protein, which is necessary for cellular growth, is prevented from being produced by it through covalent binding to Cys 500 of FUBP2 [95].

Independent research group studied activity of compound 19 on A2780, an ovarian cancer cell line, and CP70, its cisplatin-resistant mutant. Compound 19 effectively and dose-dependently inhibited cell growth in CP70 cells during the course of the 24-hour treatment period. The findings showed that 19 is more effective than cisplatin-sensitive cancer cell lines in preventing ovarian cancer cell line proliferation. By using flow cytometry, it is also more successful in causing apoptosis in CP70 cells[96].

One significant mono-carbonyl curcumin analogue, 1- (4-hydroxy-3-methoxyphenyl)-5-(nitrophenyl) penta-1, 4-dien3-one (20) exhibited effective anticancer properties in vivo as well as in vitro investigations on cell lines associated with colon cancer. In a mouse model using CT26 xenografts, it exhibited very remarkable efficacy in preventing tumour development. Its anticancer activity was ascribed to the activation of cell apoptosis caused by endoplasmic reticulum (ER) stress, suggesting that it induces the production of ROS and could serve as a beneficial method for treating colon cancers [97].

The benzylidine cyclohexanone analogues 21 with moieties that are non-polar in nature, including propoxy, ethoxy, methoxy and alkoxy groups were evaluated on animal models of the tumours to see how effectively they inhibited esophageal

squamous cell carcinoma (KYSE30) and gastric adenocarcinoma (AGS). These compounds were synthesised in the presence of ethyl alcohol and hydrochloric (HCl) gas by reacting cyclohexanone with aromatic aldehydes in the appropriate ratios. In vitro tests on cancer cells from the stomach and oesophagus, on comparison with curcumin, all synthesised substances exhibited improved activity, greater effectiveness in inducing apoptosis, and G1 cell cycle arrest. After 48 hours of incubation, the bispropoxy analogue 21a was found to be 17 times more hazardous than curcumin [98].

To ascertain the efficacy of the potent drugs used to treat CNS cancers, the synthesised cyclic C5-curcuminoids' carcinogenic consequences were examined on neuroblastoma and astrocytoma cells. Neuroblastoma cells responded three times more favourably to 22 and 23. IC_{50} for 24 was 0.26 µM on astrocytoma cells, while 19b was 0.26 µM on neuroblastoma cells. The current cytotoxicity tests validate our previous observation that the p-position of benzylidene rings containing a halogen atom or atoms increased cytotoxicity when compared to alkyl or alkyloxy[99].

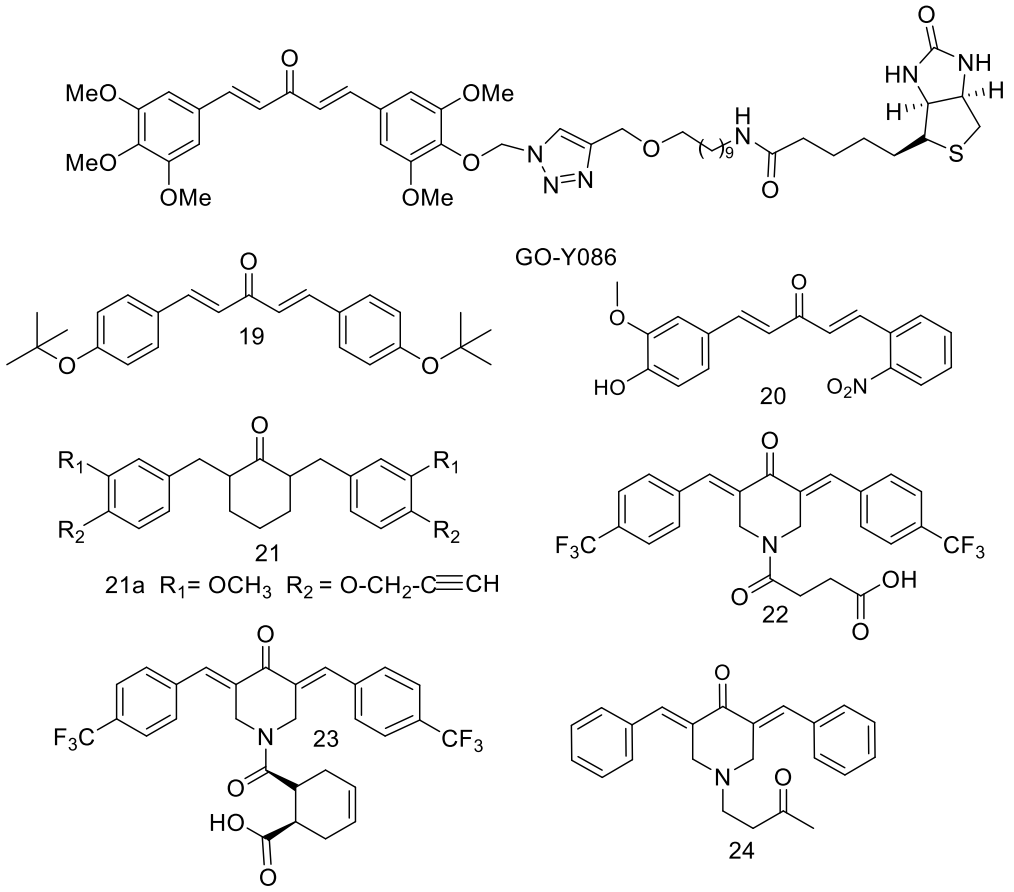
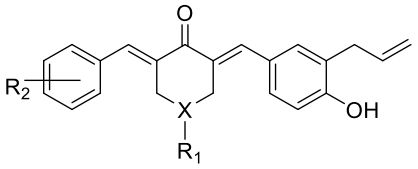


Figure 20: Structures of compound GO-Y086 and other MACs

Allylated MACs were developed as a unique molecularly targeted treatment for bile duct cancer (cholangiocarcinoma). Against RBE human cholangiocarcinoma cell line, the most of produced molecules demonstrated promising antiproliferative activity, and of all the compounds, 25b showed the strongest & significant anti-cancer activity with IC_{50} values of 8.9 µM against REB,9.3 µM against QBC-939,8.7 µM against HUCCA. These data indicated that allylated MACs hold considerable possibilities for the development of novel anticancer drugs. Over 24 h, the four compounds 25a,25b and 25c inhibited RBE cell growth the most, with IC_{50} values of 8.1,15.0 & 14.4 µM correspondingly. With IC_{50} values of 8.9 , 8.7 and 9.3 µM, respectively, 24-hour treatment with 25b significantly promoted for bile duct cancer cell death in RBE, HUCCA, QBC939 values were much lower than those of 5-FU [5-Fluorouracil], a chemotherapy drug used to treat cholangio-carcinoma. Meanwhile, the IC_{50} values demonstrate that compound 25b exhibits very minor cytotoxic effects in the healthy cell lines HIBEC (IC_{50} = 9.5 µM) & HL7702 (IC_{50} = 9.7 µM) when particularly in comparison to its anticancer capacity against cholangiocarcinoma cell lines, indicating its potential as an anti-cancer

medication. This research demonstrated that the cell development inhibition caused by 25b was affiliated with the activation of G2/M phase arrest. Importantly, 25b at a concentration of 10 μM dramatically increased cell apoptosis after 24 hours of treatment in RBE, QBC939 and HUCCA cells than in curcumin at a dosage of 20 μM. Cell apoptosis was detected using fluorescence-activated cell sorting and the Annexin V/PI protocol [100].



25a X=S R_1= c-Pr R_2 =3-allyl, 4-OH
25b X=O R_2 =3-allyl, 4-OH
25c X=N R_1= c-Pr R_2 =3-allyl, 4-OH

Figure 21: Allylated MAC targeted on treatment of bile duct cancer

Without having any discernible effects on parental cells, compound 28 was more effective than CUR at blocking BCRP-mediated efflux of probe substrates. All of these compounds effectively restored BCRP-mediated resistance to anticancer medicines. While BCRP-transfected cells were as vulnerable to their antiproliferative effects as parental cells, it does not appear that 26 or 27 are transported chemicals. Instead, they both reduced BCRP activity in a non-cell line and non-substrate-specific way. The reduction of BCRP activity by 26, 27, and 28 was verified in membrane vesicle uptake experiments, suggesting that they directly reduced BCRP activity without the need for intracellular conversion process to an active metabolite (Caffeic acid, for example, is an ABC transporter inhibitor)[101]. Analogue 27 could potentially be able to overcome opposition to cancer treatments effluxed via a variety of transporters since it inhibits MRP1 and MRP5. Furthermore, the former is efficacious against colorectal, pancreatic and prostate cancer cells, the analogues 27 and 28 were antiproliferative in TNBC cell lines [102–106].

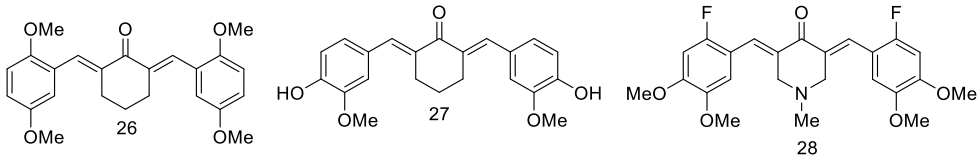
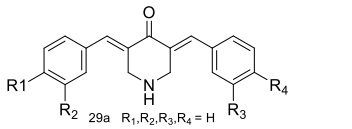
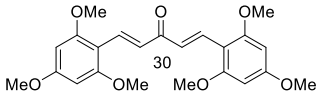


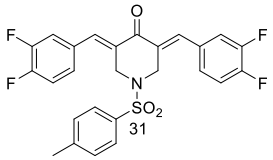
Figure 22: MAC derivatives active against BCRP

N-substituted compounds 29a-g had significantly greater average IC_{50} values equivalent to 44 μM. Consequently, the cytotoxicity of this class of drugs is much greater in N-substituted counterparts, and the SAR favourably corresponds with the size of the aryl substituents. For 29a-g, electronic characteristics were judged the most relevant factor impacting cytotoxicity [107]. Compound 30, which is adorned with 3 OMe groups at ortho and para locations of the terminal rings, is very appealing, with an IC_{50} of 106 μM, equivalent to an inhibitory efficacy more than 50 times that of curcumin. Among the molecules reported, 31 and 32 inhibited numerous human tumour cell lines significantly. According to investigations on the COLO 205 cell line's mechanism, compound 31 activates caspases 9 and 8, as well as effector caspase 3, to varying degrees. This indicates occurrence of an apoptotic process together with the DNA fragmentation. Compound 32 causes caspase 3 activation, DNA fragmentation and annexin positivity, as predicted. Caspase 8 is activated, but not caspase 9, which points to an extrinsic apoptotic mechanism [108].



29a R_1,R_2,R_3,R_4 = H
29b R_1,R_4= Cl, R_2,R_3= H
29c R_1,R_2,R_3,R_4 = Cl
29d R_1,R_4= F, R_2,R_3= H
29e R_1,R_4= NO_2, R_2,R_3= H
29f R_1,R_4= OCH_3, R_2,R_3= H
29g R_1 = $N(CH_3)_2$, R_4= $NH(CH_3)$, R_2,R_3= H





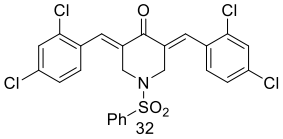


Figure 23: MAC with diverse anticancer activity

Compound 33(IC_{50} = 0.82 µM) with a trimethoxy phenyl ring as was nearly three times more active than 34 (IC_{50} = 2.34 µM), with a dimethoxy phenyl ring, the 2nd most powerful hybrid against the THP-1 cell line. The cytotoxicity data for these created hybrids, revealed an intriguing SAR: (i) the location of the naphthyl ring, which acted as a stand-in for the dimethoxy substituted phenyl ring (ii) a greater number of -OMe substituents, such as monomethoxy phenyl<dimethoxy phenyl< trimethoxy phenyl, on the phenyl ring resulted in a stronger effect. (iii) the activity profile was enhanced by replacing the unsubstituted phenyl ring with a heteroaryl ring, such thiophene or furan iv) it was shown that the cytotoxicity of hybrids with a monomethoxy substituted phenyl ring as Ring X was equivalent to that of the hybrid with a heteroaryl ring substituted. (v) The cytotoxic potential is greatly increased when a methoxy substituted phenyl ring is used. The favoured form of phenyl is trimethoxy phenyl, which is favoured above dimethoxy phenyl. These other forms include naphthyl, monomethoxy phenyl, furan, thiophene, and lastly phenyl. In addition, the length of the carbon-bridge between the coumarin moiety and triazole ring has a substantial impact on the activity. When the carbon-bridge chain length increases, cytotoxicity significantly decreases. With an IC_{50} value of 1.55 µM, compound 33 containing trimethoxy phenyl ring also has the highest anti-tubulin action. 33 also markedly reduced tubulin polymerization, with an IC_{50} value equal to 2.88 µM. Docking studies show that 32 fits well at the junction of 1/2 tubulin subunits and is maintained by numerous electrostatic interactions. D-R interactions involved residues from both subunits (1 and 2). The trimethoxy-phenyl ring is positioned in a cavity produced by the polar residues leu242, Ala991, Pro721, and Arg22 (a nonpolar residues). In this case, the Arg22's -NH function (donor of H-bonds) interacts with methoxy group (-O: H=bond acceptor; d=2.995). The aromatic phenyl ring (ring X) has three methoxy groups (-OCH3) that provide the inhibitor 32 a special combination of polarity and hydrophobicity. Via interactions with dispersion and van der Waals, this functional group greatly boosts inhibitor protein binding [109]. Combretastatin, podophyllotoxin and colchicine are all tubulin inhibitors that include the trimethoxy-phenyl group. As a consequence, 32's increased activity may be ascribed to trimethoxy-phenyl group's presence.[110]

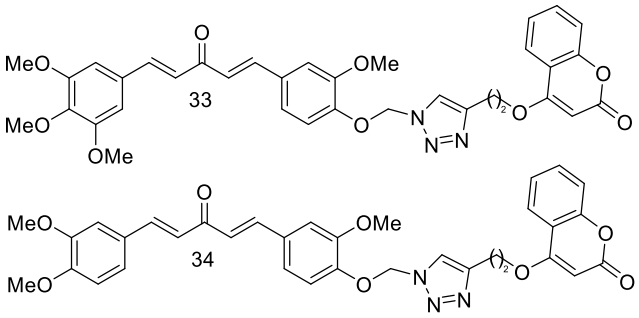


Figure 24: Potent MACs used on THP-1 cell line

Compounds 35a, 35c, 35d, 35g, and 35h were very toxic (LC_{50} > 30-100 µg/mL), whereas 35e and 35i were extremely toxic (LC_{50} 30 µg/mL)[111,112]. The vast majority of the chemicals synthesised exhibited cytotoxic action against HeLa cell lines, with IC_{50} values ranging from 40.65 to 95.55 µM. In contrast to HeLa cell lines, all produced compounds had stronger cytotoxic action on Vero cell lines with IC_{50} values in the range of 3.94-16.15 µM). Because of this, the selectivity index of the produced compounds was below one, indicating that they were more harmful to normal cells than to cervical cancer cells. The majority of AMACs (35f-35j) diethylamine mannich base derivatives displayed somewhat better & greater cytotoxic activity than the parent chemicals (35a–35e) against Hela cell lines. Compounds 35f-35i had IC_{50} values that were between of 3.94-7.28 µM to Vero cell lines. The MTT test findings revealed that 35a has noncytotoxic sort of action when used on MCF7 cell lines as they had IC_{50} value greater than 100 µM, but IC_{50} values for analogues 35b–35e and 35j ranged from 7.86 to 35.88 µM, indicating cytotoxicity. According to the results, on comparison with HeLa cell lines, MCF7 cells are more susceptible to the cytotoxic effects of the compound produced. Compound 35b, with a SI of 1.96 and an IC_{50} equal to 7.86 µM , was the most cytotoxic and selective against MCF7 cell lines among the synthetic compounds studied. The compound's cytotoxic activity was somewhat

higher than that of cisplatin and curcumin (IC_{50} value: 7.86 µM) (IC_{50} values 10.47 and 12.85 µM, respectively). Nonetheless, as compared to doxorubicin, which has an IC value of 2.94 µM, the cytotoxicity was quite low. Also, compared to curcumin and cisplatin , which had SI values of 1.96, 3.00, and 6.61, respectively, the compounds' selectivity index (SI) to Vero and MCF7 was lower. Safer chemicals have high SI number. Moreover, the most advantageous modification for a compound's cytotoxic activity was found to be a mild electron-donating substitution at the 4-position.[113,114] The research indicates that the electron-withdrawing substitution at position 4 decreased cytotoxic activity. The outcome is distinct from that of the electron-withdrawing substitution at position 2, which increases cytotoxic activity. [114].

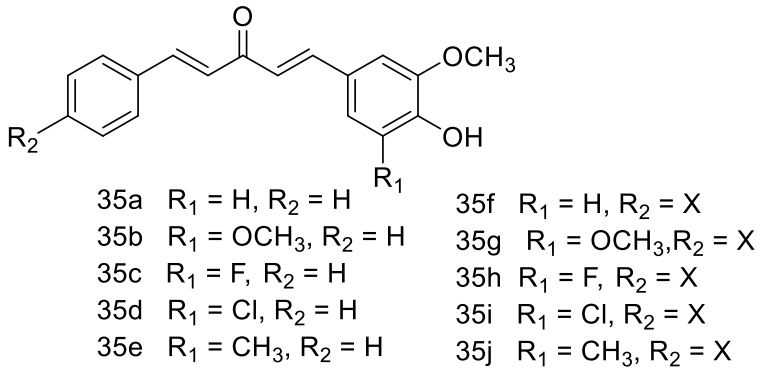


Figure 25: Compounds having stronger cytotoxic action on Vero and MCF7 cell lines.

Mono-carbonyl curcumin analogues targeting inflammation

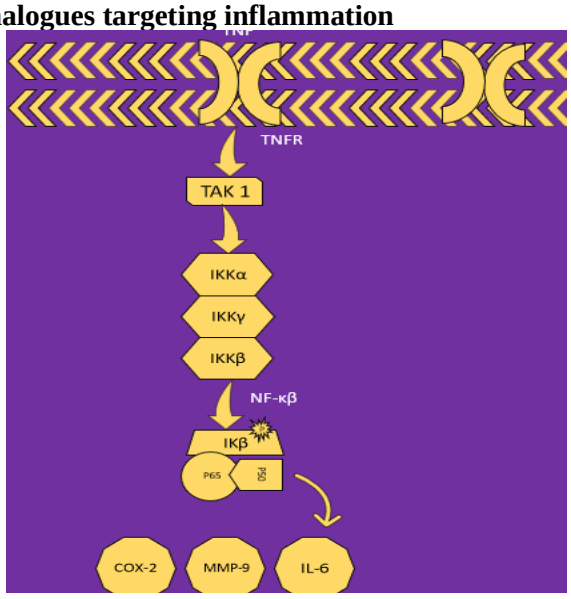


Figure 26: Mechanism through which anti-inflammatory drugs work

Cyclovalone(36a), along with three of its analogues (39b, 37a-b) possessing a linker between the two phenyl rings that is either cyclohexanone or cyclopentanone, exhibited anti-inflammatory action by inhibiting cyclooxygenase. Curcumin was outperformed by analogues 36b, 37a-b in terms of potency. The fact that analogues 36b and 37b were di-methylated and were thus more effective than analogues 1a and 2a, respectively, shows the addition of methyl groups to the phenyl rings were added to increase activity against inflammation. By substituting the cyclopentanone in 37a, and cyclohexanone in 36a , the inhibitory efficacy of cyclooxygenase was enhanced.

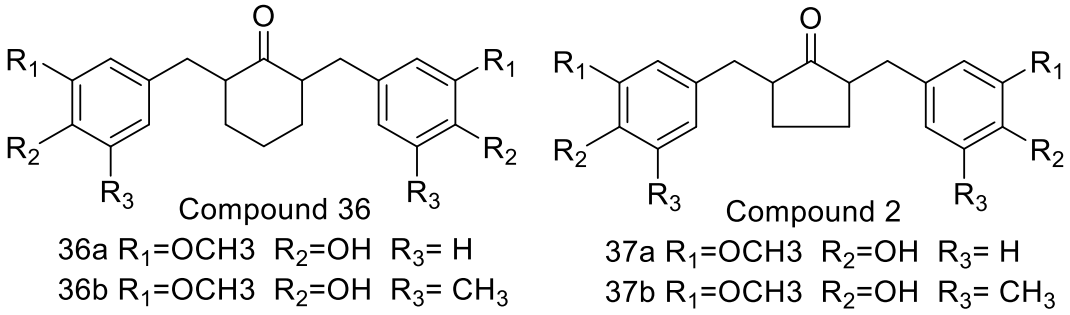


Figure 27: Compounds exhibiting anti-inflammatory action by inhibiting cyclooxygenase

As compared to the LPS control, compound 38a-e had the largest inhibitory effects on LPS-induced IL-6 production, with respective inhibitory rates of 98%, 96%, 90%, 90%, and 89%. The anti-inflammatory efficacy seems to be increased by benzene rings having electron-withdrawing halogen substituent. Halogenated compounds 38f-jcontaining benzene rings in the 2-position shown excellent action. The methoxyl group is always in favour of the actions that reduce inflammation. With IC_{50} values < 5 μM,38a,38c,38k,38d,38e show excellent dose-dependent suppression of LPS-induced IL-6 release. The most active compound is compound 38d, and its IC50 is less than 1 μM. This finding further supports the idea that MCACs containing piperid-4-one have anti-inflammatory properties. Compound 38d appears to have anti-inflammatory effects in part through blocking the NF-κB and ERK pathways, whereas compound 38e inhibits inflammatory cytokines while also inactivating NF-κB, ERK, and JNK. Yet, it's possible that NF-κB/MAPKs are not necessary for the bioactivities of 38a and 38c. Compounds 38a,38c,38k,38d,38e inhibited IL-6 expression after exposure to LPS in a dose-dependent manner, and pre - treatment with 38d and 38e extended life in a mouse model of acute inflammation brought on by LPS[115].

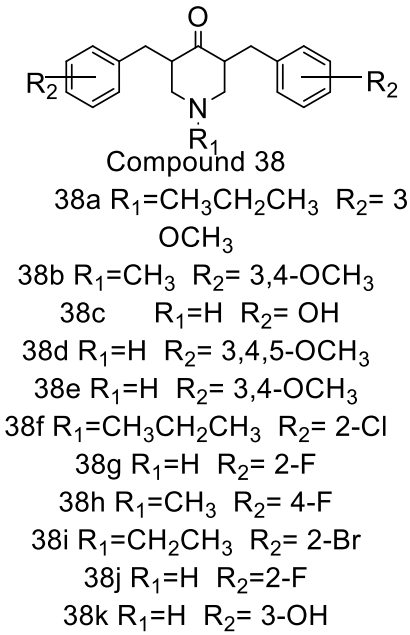
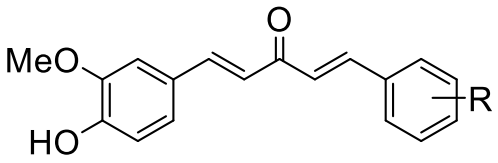


Figure 28: Curcumin mono-carbonyl analogues with 4-piperidone as anti-inflammatory drugs

By the induction of cytokine expression and release, macrophage activation by the bacterial endotoxin (LPS) results the induction of an inflammatory response. The effectiveness of curcumin and 32 semi-conservative MACs to prevent TNF-α release in mouse RAW 264.7 macrophages was tested earlier. Macrophages were exposed to the compounds for 2 hours at a concentration of 10 μM before being activated with LPS for 22 hours. TNF-α level in the medium were measured using the enzyme-linked immunosorbent assay (ELISA), and cytokine levels were restored to baseline using cell protein concentrations extracted from growth plates.

According to preliminary screening, curcumin has less potent anti-inflammatory properties than most MACs that are semi-conservative at a concentration of 10 μM. 39a-d in particular almost totally blocked the release of TNF- α. 4d decreased the IκB-α degradation brought on by LPS in a dose-dependent approach. By raising the compound's concentration, the quantity of P65 dropped in the nucleus (P65N) but rose in the cytoplasm (P65C). NF-κB capacity to bind the DNA in the nucleus of stimulated- LPS RAW264.7 cells that had been pre-treated with a variable dose of 39d was also discovered by EMSA test. 39d substantially and dose-dependently reduced NF-ability to bind to DNA. Our findings show that compound 39d inhibits LPS-induced NF-κB activation, which may contribute to its anti-inflammatory effects. According to reports, sepsis has been linked to LPS, a representative endotoxin, as a major cause. The evidence indicates that 39d has anti-inflammatory properties in vivo. The six active substances 39e-h as well as 39d shown considerable suppression on inflammatory gene expression in addition to dose-dependent reduction on TNF- α and IL6 production. The NF-κB pathway was shown to be involved in the most effective compound's anti-inflammatory action, 39d, and pretreatment with 39d might increase the survival rate in a mouse model of acute inflammation brought on by LPS. This finding suggests that MACs that are semi-conservative might be used as possible therapeutics for inflammatory disorders that are causing acute inflammation [116].



Compound 39
39a R= 2-Br , 5-F
39b R=2,5-Br
39c R=2-F, 4-OCH_3
39d R= 2-NO2
39e R= 3-Br, 5-OCH_3
39f R= 2,4,5-OCH_3
39g R= 2,4,6-CH_3

Figure 29: MACs' showing signs of anti-inflammation in macrophages of RAW 264.7

Investigations were also conducted on mono-carbonyl curcumin derivatives with allyl moieties at the phenolic rings. The anti-inflammatory capabilities of mono-carbonyl curcumin analogues were improved by adding allyl or prenyl groups. Most of them suppress the production of TNF- and IL-6, especially IL-6, which is stimulated by LPS. Compound 5a, the most effective molecule, displayed significant resistance to LPS-induced death in infected mice. Quantitative Structure Activity Relationship analysis revealed that asymmetric analogues outperformed their symmetric counterparts in terms of anti-inflammatory activity. Compound 5b (containing cyclopentanone moiety) demonstrated efficient defence against LPS-induced mortality. The symmetric and asymmetric allylated analogues (6 and 7) that include a piperidone fragment were developed using it as a lead molecule. By treating 3-allyl4-hydroxybenzaldehyde with substituted piperidones in HCl gas as a catalyst, the symmetric analogues (6) were created. The findings indicated that compound 7a was the most effective substance as it had a significant reducing effect on the Wet/Dry ratio in the lungs and protein concentration in bronchoalveolar lavage fluid. Moreover, it resulted in the suppression of several inflammatory cytokines in Beas-2B cells following a challenge with lipopolysaccharide (LPS), including, IL-1b, IL-6, VCAM-1 and TNF-α [117].

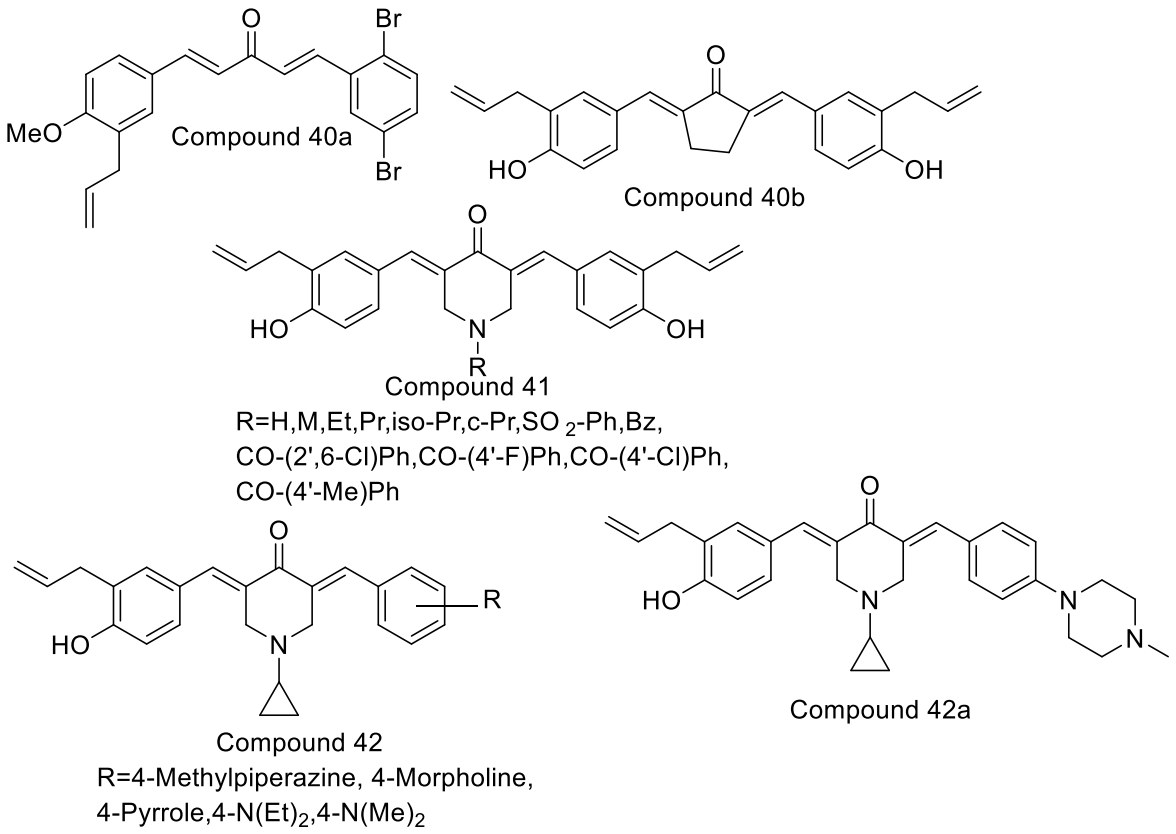


Figure 30: Curcumin derivatives with anti-inflammatory activity

The capacity of curcumin and its 33 synthetic counterparts to prevent the production of IL-6 and TNF-α from LPS-activated RAW 264.7 murine macrophages already examined [118]. The study revealed that curcumin can potentially reduce the production of IL-6 and TNF-α at 10mM dose of LPS. IL-6 and TNF-α expression induced by LPS were decreased by curcumin around 35.6% and 75.7%, respectively. The majority of the 33 substances evaluated decreased TNF- α and IL-6 expression caused by LPS to varying degrees. The top curcumin (35.6%) was outperformed by compounds MK1, MK4, OK3, M52, and M56 in terms of their capacity to suppress LPS-induced TNF-α expression. TNF- α production was inhibited by compounds NK2, MK3, MK4, N52, N57, M57, M58, O51, O55, and O59 in a 20-35.6% range. As compared to the LPS-treated control, the substituted amino-containing analogues MK1-3 demonstrated a 50% reduction of IL-6. M57 also demonstrated 51.1% IL-6 suppression, while derivatives M56 & M58 showed effectiveness against IL-6 release equivalent to that of curcumin. Moreover, IL-6 expression was inhibited by more than 30% by compounds NK4, MK4, N55, and M52 on comparison with LPS control. Particularly, compounds NK1 and M56 were more effective in inhibiting IL-6 and TNF-α expression induced by LPS than curcumin at the same dose. As compared to the LPS control, NK1 had the highest inhibitory impact on LPS-induced IL-6 and TNF-α production with inhibitory rates of 92.7 and 67.5%%, respectively. Several research teams have experimented with chemical alterations as well as the manufacture of curcumin analogues to determine the SAR conclusion and improved leads for the treatment of inflammatory illnesses. Few considerably powerful mimics, however, were discovered to be in the latter stages of pharmacological development. 33 mono-carbonyl analogues were also created concurrently, and their capacity to suppress the production of TNF-α and IL-6 was assessed. It has been noted previously that compared to cyclopentanone-derived N-class and cyclohexanone-derived O-class counterparts, acetone-derived M-class analogues are more efficient. particularly when it comes to inhibiting LPS-induced IL-6 expression. This finding suggests that the structure of a 5-carbonyl linker may be involved in such activities. Nonetheless, it was asserted that NK1 showed the greatest resistance to LPS-induced IL-6 release[118].

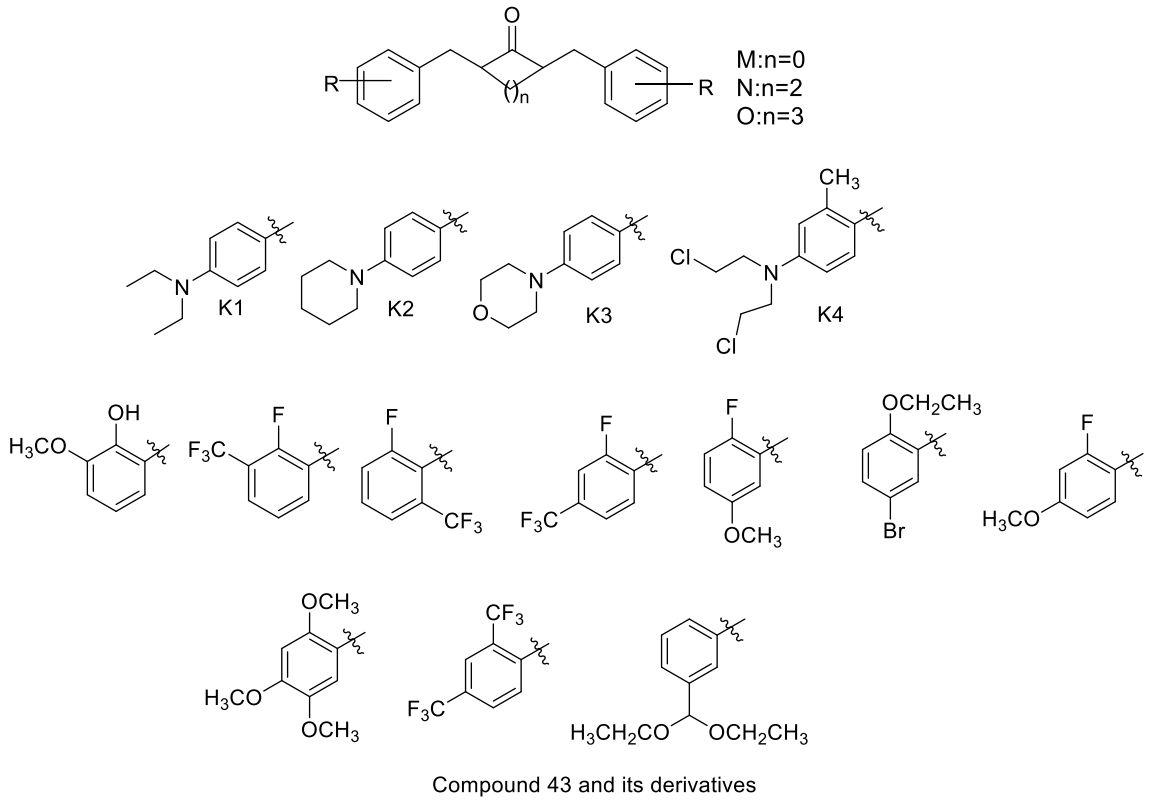
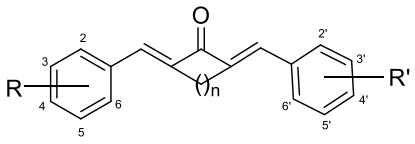


Figure 31: Structure of MAC exhibiting ant-inflammatory activities

The majority of the synthesised compounds had more inhibitory efficacy than curcumin, and all of them had IL-6 suppression with inhibition ratios ranging within 20-95%. Yet, due to their very modest activity, it is challenging to examine the SAR of mono-carbonyl analogues of curcumin connected to TNF-α inhibition. In comparison to symmetric analogues (series 44), the asymmetric MACs (series 45) often shown more action against IL-6 production. The analogues in series 44 that include cyclopentane or cyclohexane, such as 44c-e, were less potent than their acetone derivative counterparts, 44a and 44b. The most active compound was compound 44b which has an ortho positional 4-hydroxyl group on the 5-allyl moiety. Its inhibition ratio was 96.4%. As a result, it may be concluded that the -OH in this position is advantageous for anti-inflammatory function. Comparing the asymmetric MACs 45a and 45b led to a similar conclusion. In comparison to curcumin, compounds 44b, 45c, 45d, and 45e showed a higher suppression of IL-6 and TNF-α. Notably, with rates of inhibition of 91.1% and 67.5%, respectively, on LPS-induced IL-6 and TNF-α production, 45c had strongest impact [119].



44a R= 4-O-prenyl	R'= 4'-O-prenyl	n=0
44b R= 4-OH,5-allyl	R'= 4'-OH,5-allyl	n=0
44c R= 4-OH,5-allyl	R'= 4'-OH,5-allyl	n=2
44d R= 4-O-prenyl,5-OMe	R'= 4'-O-prenyl,5-OMe	n=2
44e R= 4-O-prenyl	R'= 4'-O-prenyl,	n=3
45a R= 4-OH,5-allyl	R'= 3',4'-OMe	n=0
45b R= 4-OMe,5-allyl	R'= 3',4'-OMe	n=0
45c R= 4-OMe,5-allyl	R'= 2',5'-Br	n=0
45d R= 4-OMe,5-allyl	R'= 2'-Br,5'-F	n=0
45c R= 4-OMe,5-allyl	R'= 2',4',5'-OMe	n=0

Figure 32: Prenylated and allylated mono-carbonyl derivative of curcumin as anti-inflammatory agents

Many illnesses, including cancer, diabetes, cardiovascular disease, and neurological disorders all include inflammation as a major contributor to their aetiology. NF-κB plays a significant part in the signal transduction pathways that are implicated in inflammatory disorders, in addition to other mediators. As a result, it is believed that NF- represents a possible therapeutic target for many illnesses. A number of researches have confirmed that curcumin significantly suppresses NF-, which has an anti-inflammatory impact. Several inflammatory cytokines like IL-8, TNF, IL-6, IL-1, interferon, and certain other chemokines are downregulated by curcumin, according to previous research. After synthesising a curcumin analogue (DM1) and assessing its impact on inflammatory mediators, Paulino and colleagues discovered that this analogue has the capacity to inhibit iNOS and COX2 [120].

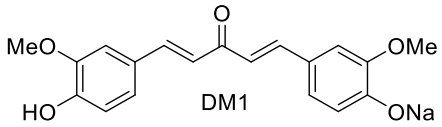


Figure 33: Analogue of curcumin with strong anti-inflammatory properties

Analogues showing anti-oxidant properties

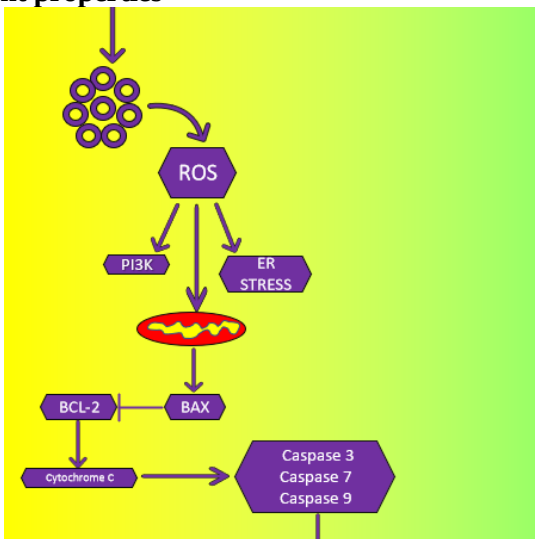


Figure 34: Mechanism through which anti-oxidant drugs work

There is widespread agreement about the significance of oxidation in human body and food. In order to survive, cells require an oxidative metabolism. This dependency has the unintended side effect of producing oxidative alterations are brought on by reactive oxygen species such free radicals. When there are too many free radicals, they can overpower preventive enzymes like peroxidase, superoxide dismutase and catalase and cause damaging and deadly cellular consequences like apoptosis by oxidising DNA, enzymes, cellular proteins, and membrane lipids, which stops cells from respiring. Any molecule that, in low levels as comparison to the oxidizable substrate, considerably slows down or stops that substrate from oxidation. is considered an antioxidant. Quenchers of secondary oxidation products, inactivators of peroxides, reactive oxygen species, free radical scavengers, metal ion chelators, inhibitors of pro-oxidative enzymes and singlet oxygen quenchers are a few examples of antioxidants that work to prevent the oxidation processes through a variety of actions and mechanisms. They may typically be categorised into primary and secondary antioxidants based on how they function. They may typically be categorised into main and secondary antioxidants based on how they function. Primary antioxidants, like certain phenolic substances and tocopherols, prevent the chain reaction of oxidation by acting as free radical acceptors or hydrogen donors and by generating more stable radicals. Synthetic compounds such as butylated hydroxyanisole and butylated hydroxytoluene as well as, natural substances such as flavonoids and phenolic acids, comprise the principal anti-oxidant category. Secondary antioxidants inhibit or slow oxidation by decreasing oxidation promoters such as pro-oxidative enzymes, metal ions, singlet oxygen, and other oxidants. Antioxidant enzyme cofactors such as Se and coenzyme Q_{10} and metal chelators such as ethylenediaminetetraacetic acid (EDTA)

are frequently included in the secondary antioxidant group. Redox processes enable reducing agents, also known as oxygen scavengers, to diminish lipid peroxides and associated oxidants. Certain secondary antioxidants, like ascorbic acid, can refill hydrogen atoms in primary antioxidants to renew them. This prevents the loss of vital primary antioxidants. Some secondary antioxidants either help hydroperoxides convert into non-radical species or absorb UV radiation or to shield fatty acids from UV-induced photooxidation. Different antioxidants operate as mechanisms for protecting against the effects of excessive oxidation, and it is well known that antioxidant activity must be assessed. Antioxidant activity cannot be tested directly, but rather by the antioxidant's ability to regulate the degree of oxidation. Techniques are quite diverse. Some procedures require a discrete oxidation phase followed by assessment of the result, such as linoleic acid oxidation followed by diene conjugation determination. In some cases, there is no apparent demarcation between the procedure's multiple stages. A substrate, an oxidant and an initiator, intermediates, and end products are all characteristics of oxidation, and measuring any of these may be used to determine antioxidant activity. For assessing antioxidant activity in vitro, the DPPH technique is most widely employed, while LPO was shown to be the most used *in vivo* antioxidant test.

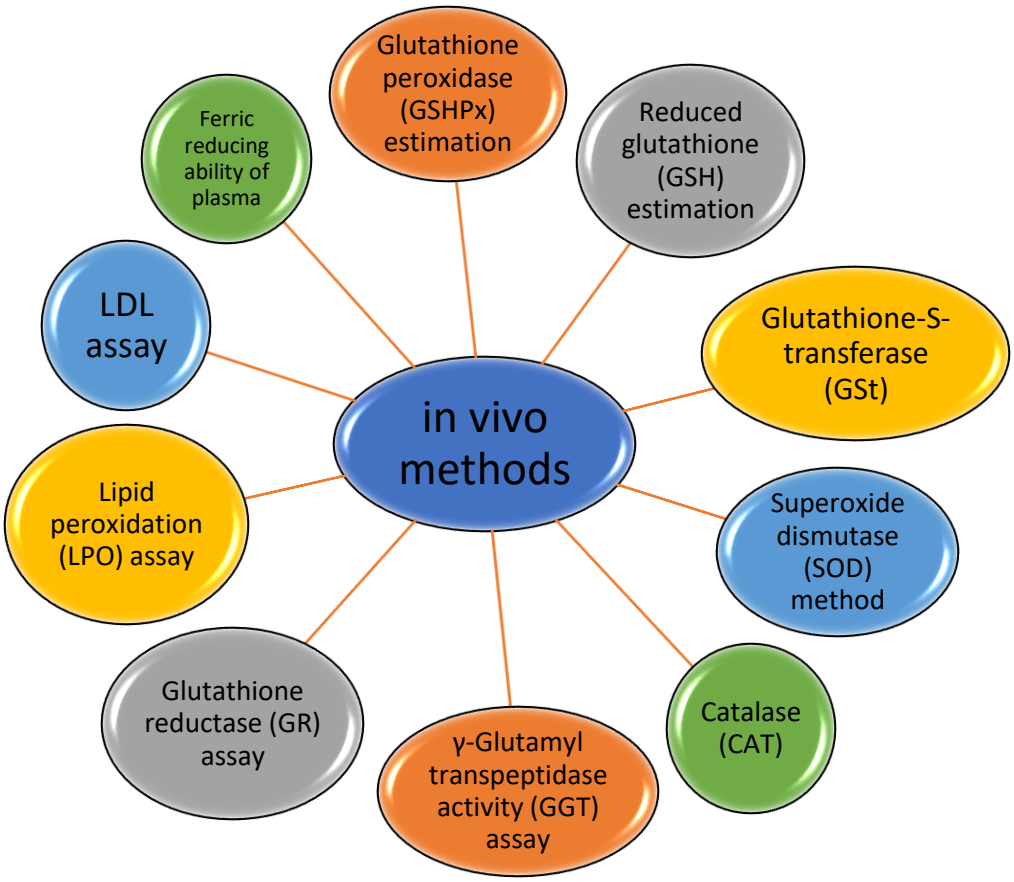


Figure 35: Various *in-vivo* methods used for antioxidant assessment

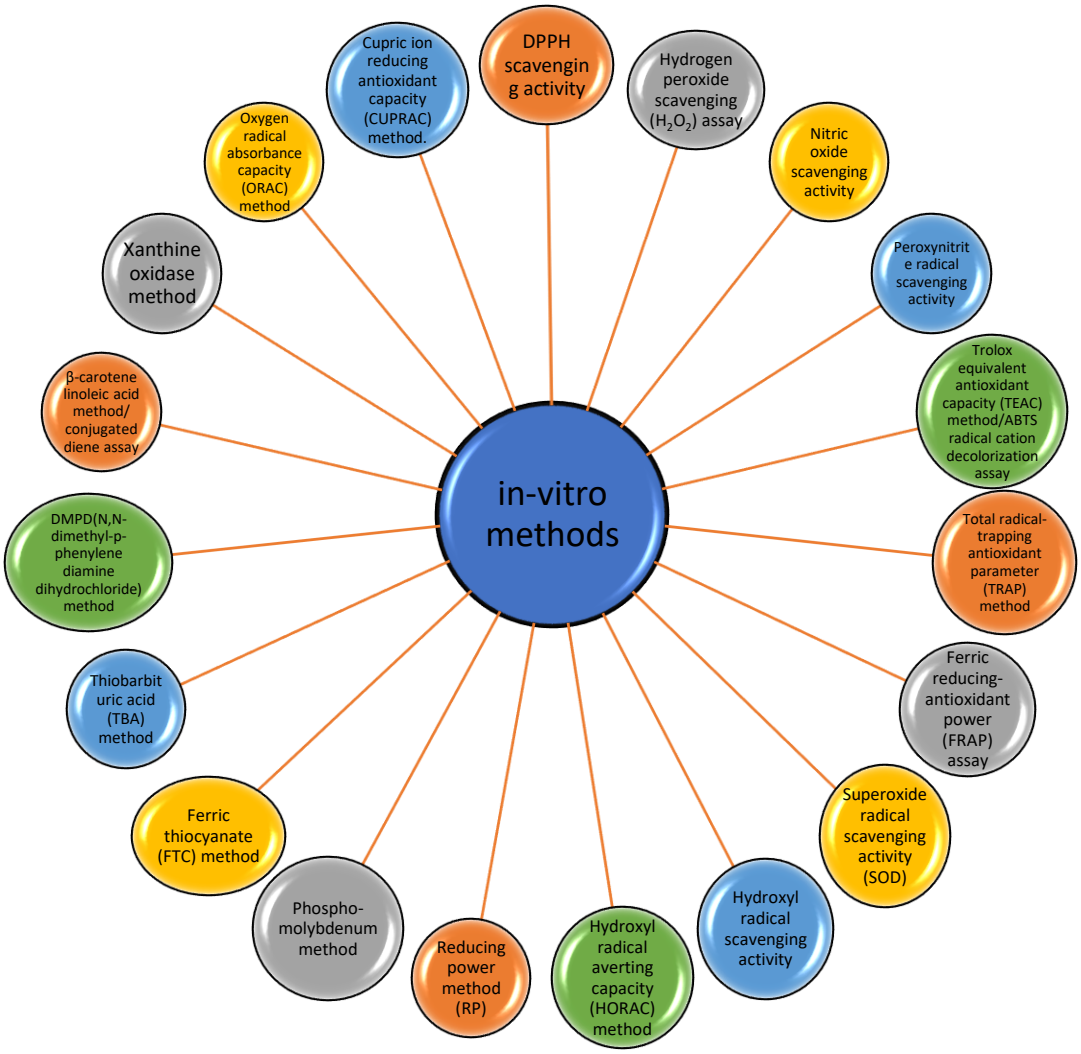


Figure 36: 19 *in-vitro* methods used for antioxidant assessment

The in-vitro radical scavenging ability of all produced analogues (46a-i, 47a-c and 48a-d) was assessed using the DPPH radical scavenging test. DPPH stands for 1, 1-diphenyl-2-picrylhydrazyl. BHT was employed as a positive reference for antioxidant activity with IC_{50} value of 16.47±0.18 µg/ml. These findings imply that the mono-carbonyl curcumin nucleus in the produced analogues contributed to the radical scavenging function via resonance. As compared to conventional BHT, all produced MACs had antioxidant efficacy that was either 2-3-fold higher or similar. Compounds 46e (IC_{50} = 05.39± 0.14 µg/ml) and 47b (IC_{50} = 06.37± 0.55 µg/ml) have three times the antioxidant potential of conventional BHT. Compounds 1h (IC_{50} = 07.44±0.16 µg/ml), 47a (IC_{50} = 08.92± 0.18 µg/ml), 47c(IC_{50} = 09.62 ± 0.76 µg/ml)and 48b(IC_{50}= 09.66±0.53 µg/ml) have two times the antioxidant potential. Additionally, structural activity data demonstrated that -Cl(chloro) modification on the quinoline scaffold significantly increases antioxidant activity as shown in compound 46e, which has one less chloro substitution than compound 46a. It was shown that replacement at position 7 of the quinoline scaffold had a greater influence on antioxidant potential than other places, additionally as seen by IC_{50} values; open chain linkers such as acetone show a potential increase in activity, followed by cyclopentanone, cyclohexanone, and N-methyl piperidone spacer [121].

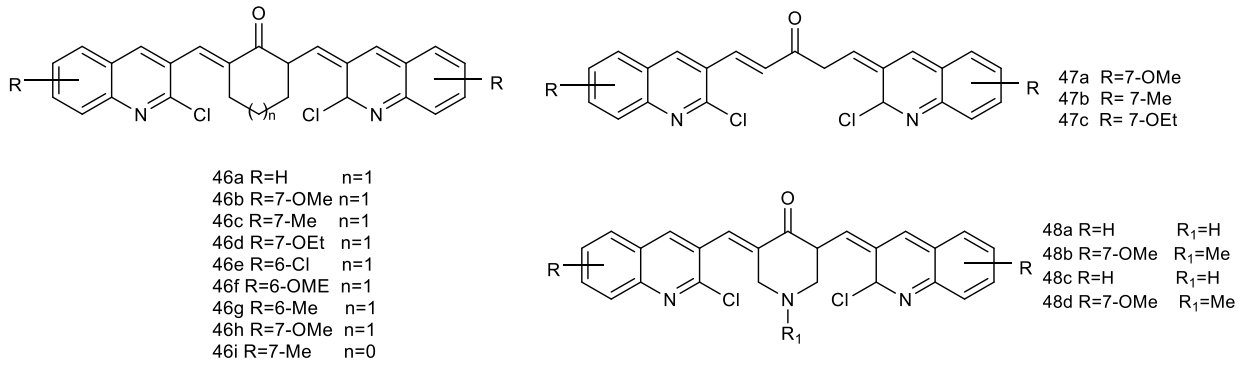


Figure 37: Monocarbonyl curcumin analogues derived from quinoline as potential antioxidant agents

Comparing compounds 49a,49b,50a and 50b to the standard antioxidant ascorbic acid reveals probable IC_{50} values for each of the compounds. DPPH radical scavenging activity was used to assess the antioxidant activity of each and every synthesised molecule. The IC_{50} value of 49a,49b,50a and 50b are 5.9± 0.1 µg/ml, 4.1±0.1 µg/ml,5.5±0.1 µg/ml and 7.7±0.05 µg/ml respectively. As compared to ascorbic acid, a commonly used medication, Analogs of mono-carbonyl curcumin were produced using cyclic linkers such N-methyl piperidone and cycloheptanone have superior radical scavenging efficacy. The IC_{50} value of ascorbic acid is 0.009±0.002 µg/ml. Moreover, compared to acyclic linkers like acetone, mono-carbonyl curcumin analogues with cyclic linkers have increased activity [122].

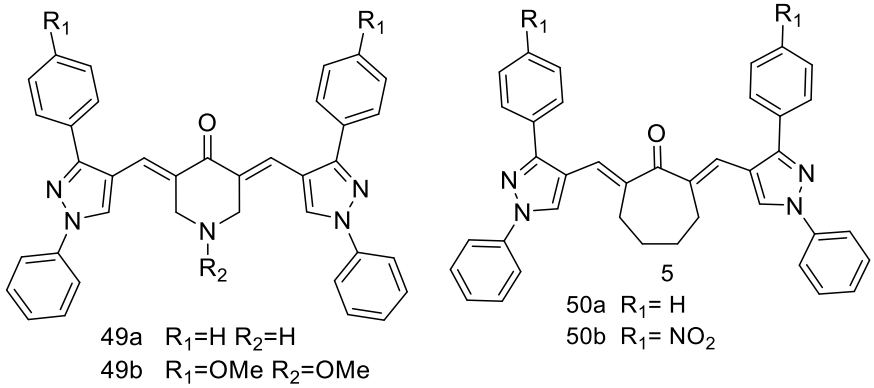


Figure 38: Cyclic linker-containing mono-carbonyl curcumin analogues

Diarylpentanoid analogues of curcumin were evaluated by Bukhari et al. for their ability to prevent the generation of reactive ROS. Isolated PMNs and human whole blood were used in the chemiluminescence experiment. It was noted that compounds 51a and 51b, with IC_{50} values ranging from 4.2 to 6.2 mol, strongly inhibited both intracellular and extracellular ROS generation at 12.5 µg/ml. As a result, the study demonstrated that a 2-methyl-4 aniline substituent was required to stop the generation of intracellular and extracellular ROS[123].

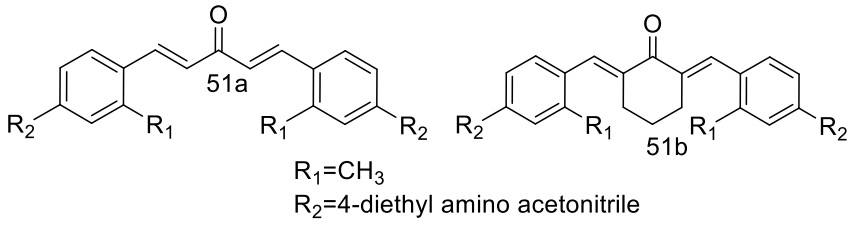


Figure 39: Curcumin mono-carbonyl analogues with diarylpentanoid moiety

C-5 curcuminoids 52a and 52b, with corresponding IC_{50} values of 53.29± 2.13µg/mL and 82.43 ±2.17 µg/ml, had the greatest reaction against DPPH free radicals in the in-vitro antioxidant testing when compared tocopherol which had an IC_{50} value of 9.16 ±1.14 µg/mL. Corresponding to this, in the ABTS (Azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) experiment,

52b had a much higher antioxidant response with an IC_{50} value of 70.21±1.26 µg/mL than the reference medication tocopherol, which had an IC_{50} of 13.18 ±1.16 µg/mL. In an in vitro test, these substances demonstrated strong antioxidant activity. Methoxy (-OCH_3) and hydroxyl (-OH) substituted derivatives were shown to have antioxidant properties, according to research [124]. The methoxy substituted group in the derivatives of mono-carbonyl curcumin showed a considerable antioxidant activity, which was in line with published findings [125,126].

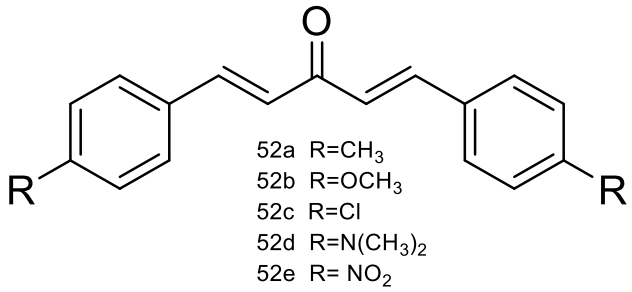


Figure 40: Mono-carbonyl curcumin that displayed anti-oxidant properties and had methoxy group and chlorine as substituents

In an attempt to discover novel substances with potent antioxidant action, several curcumin derivatives have been produced during the past 20 years. Three types of curcumin analogues(53a-c) were produced by Shang and colleagues, and their antioxidant efficacy was compared to that of curcumin. They discovered that the antioxidant activity of compounds with O-dimethoxy-phenoxyl and O-diphenoxyl groups was substantially greater than that of compounds without these groups. They came to the additional conclusion that the scavenging capabilities require the 7-carbon spacer, and that lowering the carbon to 5 atoms significantly decreased the act of scavenging. They added that the lipid solubility that comes from adding more carbon atoms was crucial for the antioxidant action[127].

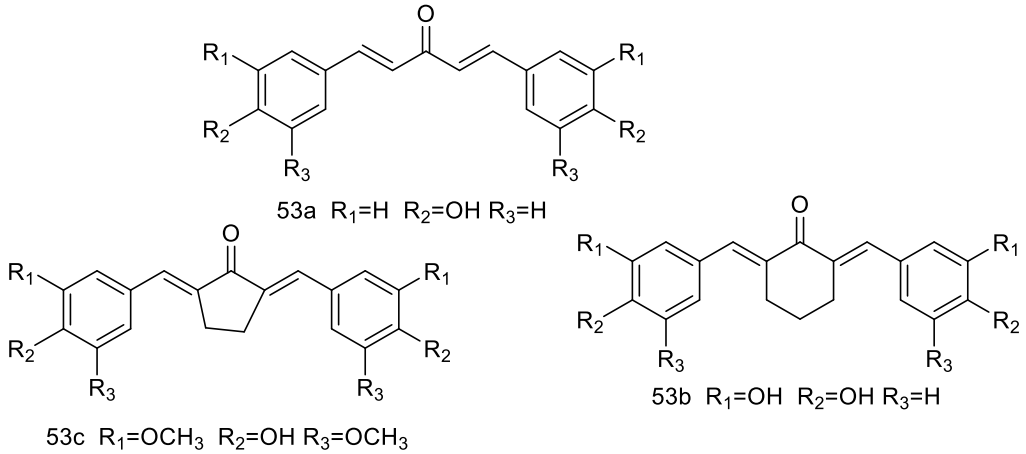


Figure 41: Curcumin analogues with O-dimethoxy-phenoxyl and O-diphenoxyl groups

Gallic acid was used as a reference molecule to measure the DPPH free radical scavenging activity of all the produced compounds' in vitro antioxidant activities. With an IC_{50} of less than 50 µg/mL, a handful of the compounds (54a, 54c-54f, and 56e) demonstrated strong antioxidant activity. A thorough examination of the structure activity relationship (SAR) investigations of the symmetrical C5-curuminoids (54a-g) set showed that the antioxidant activity often decreased as the alkyl chain length increased from 2 to 3. Most of the compounds there in unsymmetrical C5-curcuminoid set (55, 56a-f) had IC_{50} values more than 50 µg/mL, suggesting that they were less efficient at promoting antioxidant activity than symmetrical C5–curcuminoids (54a-g). Nevertheless, neither of the tested compounds were found to be as efficient as gallic acid, which was utilised as a reference in this assay (IC_{50} = 15.43 µg/mL)[128]

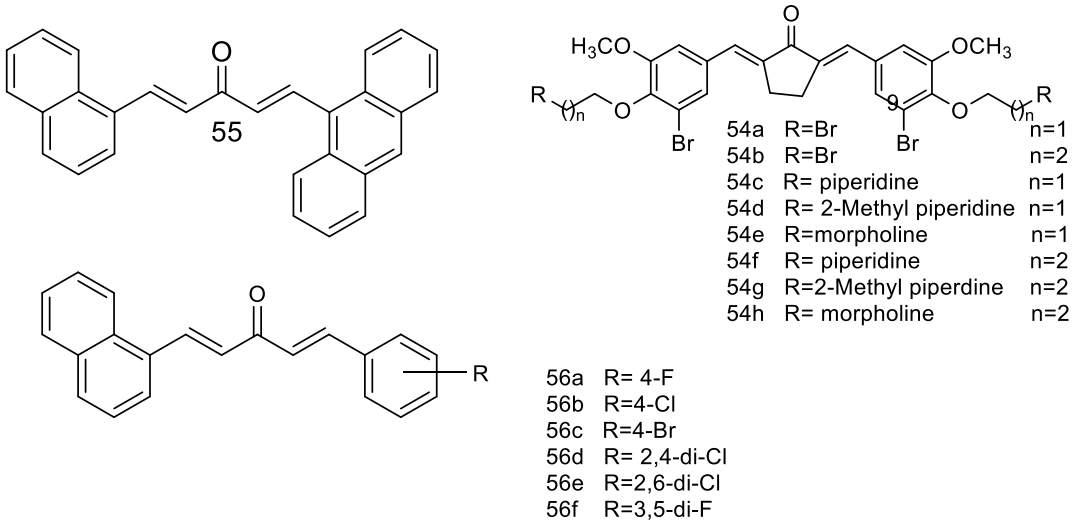


Figure 42: Symmetrical and unsymmetrical C5-curcuminoid promoting antioxidant activity

It makes sense to use a powerful antioxidant to combat oxidative stress caused by Alzheimer's disease (AD). The antioxidant properties of compound 57 and curcumin were investigated in an initial study [129]. The compound 57 has its IUPAC name as (2E,6E)-2,6-Bis(3,5-dimethoxybenzylidene) cyclohexanone. The substance exhibits more stability and improved anti-oxidative activity in vitro than curcumin. The endogenous antioxidant enzyme activity was found to protect PC12 cell lines, a prototype for neurological cells under Aβ oxidative stress, from H_2O_2 injury by searching for oxygen species that are reactive, preventing cells from being damaged by cytotoxicity induced from H_2O_2, and preventing cells from dying. [130].

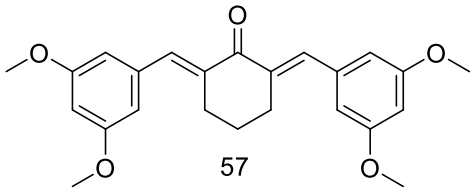


Figure 43: A powerful antioxidant to combat oxidative stress caused by Alzheimer's disease

Dinkova-Kostova et al. developed mono-carbonyl analogues of curcumin (58a-f) and evaluated the results of quinine reductase inhibition and free radical eradication in their hunt for the new antioxidant [131,132]. According to the results, the analogues with the -OH in the ortho position of the benzene ring were able to both remove superoxide from the system as well as strongly limit the activity of quinine reductase. Compounds 58d and 58e, for example, boosted their activity by 3 - 200 times more than analogue 58a-c and 58f, which did not include a hydroxyl in the ortho position [133].

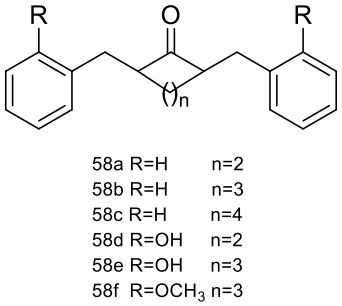


Figure 44: Mono-carbonyl analogue with and without the -OH in the ortho position of the benzene ring

Anti-microbial property displaying Mono-carbonyl Analogues of Curcumin

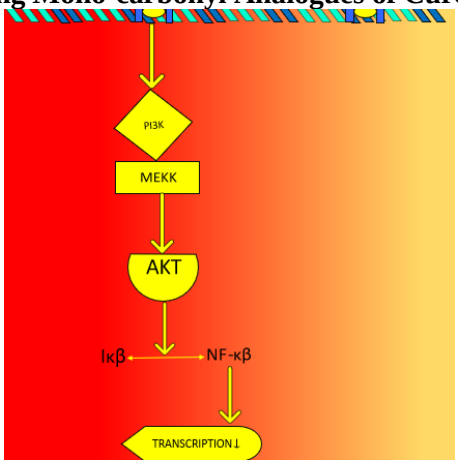


Figure 45: Mechanism through which anti-microbial drugs work

The in-vitro antifungal efficacy of each synthesised analogue of mono-carbonyl curcumin with 2-chloroquinoline was evaluated. Five distinct fungus strains, including, NCIM 1332 (*Fusarium oxysporum*), NCIM 3471 (*Candida albicans*), NCIM 1196 (*Aspergillus niger*), NCIM 576 (*Cryptococcus neoformans*) and NCIM 539 (*Aspergillus flavus*) were used to test the antifungal efficacy of produced analogues. Miconazole was employed as a reference to compare antifungal activity. As a solvent reference, dimethyl sulfoxide was employed. Several of the newly synthesised compounds were discovered to have superior antifungal action when compared to the conventional medication miconazole. According to the antifungal data information, the majority of the synthesised compounds demonstrated promising antifungal ability against all fungal strains. In particular, compounds 59 and 60 were found to be most effective when tested against all of the fungal strains under investigation, demonstrating the broad spectrum of activity of these analogues against the majority of fungal strains. The structure activity relationship demonstrated that the usage of cyclopentanone and acetone spacers results in a significant increased activity when compared to the miconazole (positive control). Additionally, piperidone and N-methyl piperidone spacers boost activity by a factor of two to three. The quinoline scaffold's electron donor groups were changed, perhaps increasing the antifungal potency.as shown by MIC values. A comparison of the fungicidal capability of newly synthesised curcumin analogues with the positive reference miconazole clearly shows that most of the produced MACs have 2-3 times greater potential than regular miconazole[121].

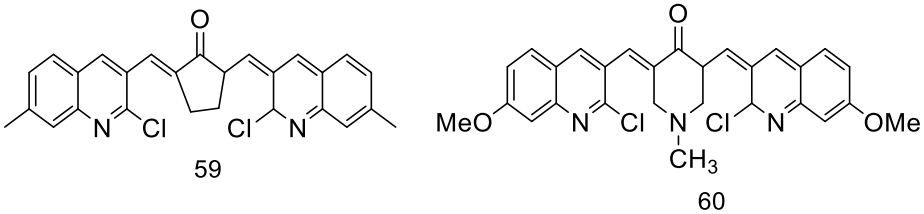


Figure 46: 2-chloroquinoline mono-carbonyl curcumin analogue possessing anti-fungal properties

The most common non-viral sexually transmitted infection, trichomoniasis, is brought on by the protozoan *Trichomonas vaginalis*. Curcumin analogues were tested for anti- *Trichomonas vaginalis* action using MIC and IC_{50}. The anti-*Trichomonas vaginalis* activity was determined by treating $2.6x10^5$ trophozoites/mL with the derivatives of curcumin, first at 10^{-4} M and then diluted in dimethyl sulfoxide. 3 controls were used: one containing 0.6% Dimethyl sulfoxide (for solubilization), and one containing just trophozoites, one containing 100 µM of (metronidazole). The IC_{50} and MIC values against *Trichomonas vaginalis* were determined using curcumin analogues at various concentrations ranging from 6.25- $3x10^2$µM. After being incubated at the appropriate MIC for 96 hours, the vitality of the trophozoites was assessed under a light microscope. Analysis of growth were performed at 96, 72, 48, 24, 12, 6, and 1 hour. The experiment to determine the IC_{50} and MIC values against *Trichomonas vaginalis* revealed that

compounds 62, 61b and 61a had the best anti-*Trichomonas vaginalis* action at concentrations (MIC value) of 0.000 2 M**,** 9×10^{-5} M & **8**$\times10^{-5}$ M**,** respectively. Derivatives 61a and 61b had an IC_{50} value equivalent to 5×10^{-5} M, whereas 62 had an IC_{50} value equivalent to 7×10^{-5} M [134].

Three most powerful curcuminoids (63a-c), demonstrated MIC values that lie in the range of 8-32 mg/mL against *E. coli* ATCC 25922, 4 mg/mL against Methicillin Resistant of *Staphylococcus aureus* (MRSA) and 2 mg/mL against Methicillin Sensitive *Staphylococcus aureus* (MSSA). These molecules (63a–c) were most effective active compounds and had an azepan-1-yl moiety present at the locations of the chain that are terminal and linked to the aromatic rings. Compared to its counterparts, due to large ring size of the azepan-1-yl moiety at the terminal position and their non-polar nature, curcuminoids may have a stronger antibacterial effect. These curcuminoids were tested against clinically isolated strains of MRSA & *Escherichia coli* demonstrated robust action against the selected 6 clinical variants of MRSA tested, with MICs ranging from 4 to 16 mg/mL. Also, the outcomes against clinical *E. coli* variations were quite positive with MIC values ranging from 16 to 32 mg/mL[135].

High antibacterial activity was demonstrated by curcuminoid analogue 64, which had the lowest MIC value of 8-16 µg/mL against clinical isolates of MRSA, 16 µg/mL against MRSA and 8 µg/mL against MSSA. In less than 4 hours, it completely eliminated staphylococcal cells (5 x 10^5 CFU/mL)[136].

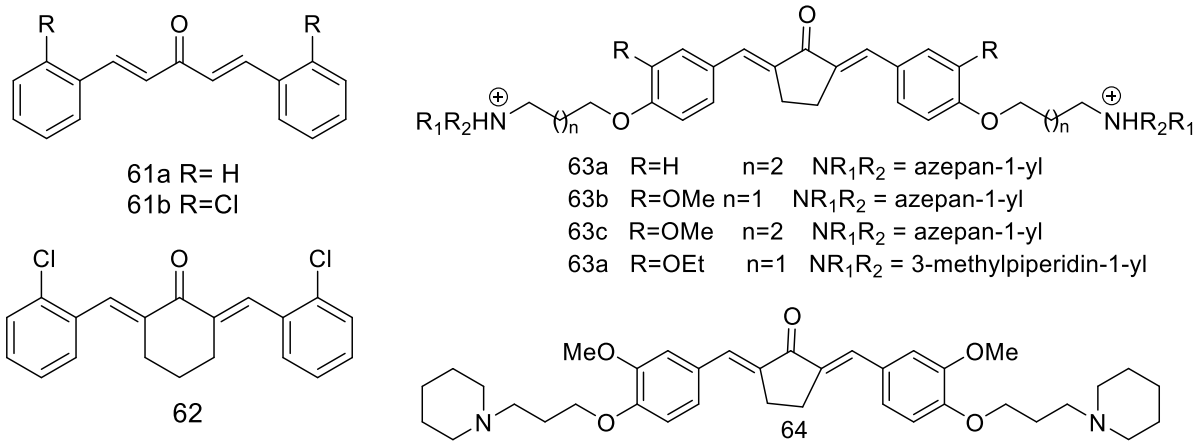


Figure 47: Mono-carbonyl analogue with potent anti-bacterial properties

The antibacterial ability of the produced hybrids was tested against two strains of human pathogenic bacteria, both gram-negative and gram positive. Gram-negative bacteria taken were *Escherichia coli* and *Pseudomonas aeruginosa* and Gram-positive taken were *Enterococcus faecalis* and *Staphylococcus aureus*. The most susceptible and resistant bacterial strains were *S. aureus* and *E. coli*. respectively, to the synthetic molecules. Hybrids having the highest antibacterial activity across all strains and the greatest effectiveness were 65 and 66 with *S. aureus* showing the greatest activity. The inhibition zones for 66 and 65 were 31and 29 mm, respectively, and the MICs were 6.25 µg/mL and 12.50 µg/mL, correspondingly. Coumarin/isatin and triazole molecule connected by a 2-carbon alkyl chain. seems to be well tolerated, according to the structure-activity relationship. Para-methoxy substitution in curcumin-coumarin hybrids on curcumin ring, chloro substitution on para position in curcumin-isatin and bromo substitution on isatin's fifth position are the most appropriate for anti-bacterial action. In S. aureus, dihydrofolate is reduced to tetrahydrofolate by the enzyme DHFR (Dihydrofolate Reductase) using NADPH., which is involved in the processes that produce intracellular purines (guanine and adenine). When DHFR is completely inhibited, *S. aureus* cannot replicate its DNA and dies. As a result, with regard to S. aureus in particular, DHFR is a well-validated target for the creation of antibacterial drugs. The interactions of the most powerful drugs (65 and 66) with the DHFR enzyme of *S. aureus* were studied using molecular modelling [137]. To highlight their ability to inhibit DHFR, many of the docking contacts between 65 and 66 and *S. aureus* DHFR active site is simplified. According to the overall binding behaviour of compounds 65 and 66, which involves interactions with binding site residues, both substances are quite well stabilised by a number of electrostatic interactions and fit comfortably inside the cavity [138].

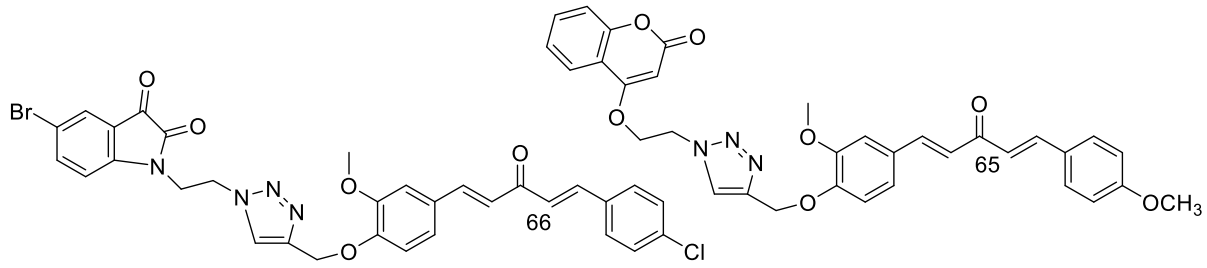


Figure 48: Mono-carbonyl derivatives with high potential against pathogenic bacteria

Using agar diffusion technique, the antibacterial activity of novel compounds was examined against, *E. coli*, *Vibrio cholera*, *S. aureus* and *Salmonella typhi* [139]. When the substances were examined for antibacterial potential, compound 67b outperformed curcumin in its ability to combat *S. typhi* and *V. cholera*. The 2-hydroxy-3, 5-dichloro-phenylsulfonamide derivatives (67-c) all shown promising action against *S. typhi* and *V. cholera* [140].

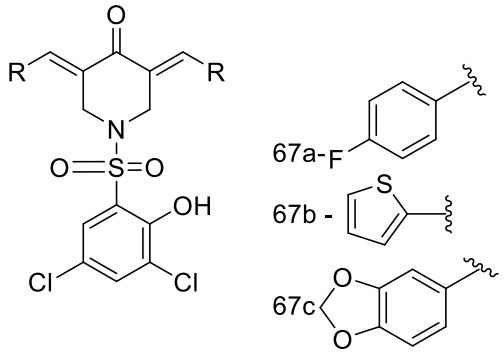


Figure 49: 2-hydroxy-3, 5-dichloro-phenylsulfonamide derivatives of curcumin possessing anti-bacterial properties

Several compounds (68, 69, and 70) shown considerable bactericidal activity when used in vitro to combat *Staphylococcus aureus* and *Pseudomonas aeruginosa* [128].

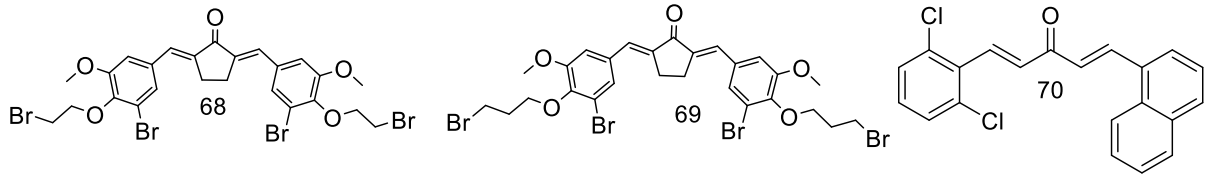


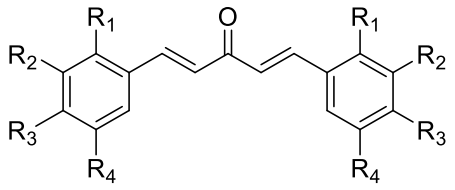
Figure 50: Mono-carbonyl analogues displaying anti-bacterial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa*

Gram-positive bacteria which include *Staphylococcus epidermidis*, *Micrococcus luteus*, *Staphylococcus aureus*, and *Staphylococcus saprophyticus* and gram-negative bacteria such as *Escherichia coli*, *Enterococus* sp. & *Enterobacter cloacae* were chosen. For contrast, a standard anti-bacterial drug, ampicillin, was tested under comparable circumstances. Of the phenolic compounds, 1,4-pentadiene-3-one analogues (71a-b) had strong activity against 4 bacterial strains that were gram positive. Majority of mono-carbonyl curcumin derivatives were effective against the ampicillin-resistant Gram-negative *E. cloacae*. and heterocycle or long-chain substituent' were shown to improve the activity of curcumin analogues[141].

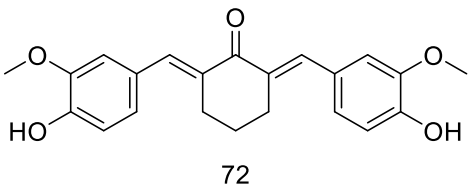
According to antimicrobial test findings, Gram-positive bacteria like *Bacillus cereus* and *Bacillus subtilis* were impacted by compound 72 and 73. The MIC values of compounds 72 and 73, which have an antibacterial effect, were computed and were found to be 9.76 µg/mL and 19.53 µg/mL, respectively, against *B. subtilis* and 625 µg/ml and 1250 µg/ml for *B. cereus*. After evaluating the antibacterial properties, it can be shown that these compounds have some structural traits. Two domains are included inside two aromatic or Michael acceptor and two cyclotriphosphazene

rings, with aromatic rings contained within unsaturated C=C bonds bordering the carbonyl groups. 72 and 73 may obtain antibacterial properties as a result of these qualities. This is expected to influence the antibacterial activity of the chemical [142,143].

Compound 74 displayed significant activity against *E. faecalis*, *P. aeruginosa*, *Acinetobacter baumannii*, MRSA, MSSA, *Staphylococcus epidermidis*, and *Mycobacterium tuberculosis* (125 µg/mL≥MIC≥0.9µg/mL) demonstrating that substituting -OH at meta position by replacing -OMe enhanced the range of potency and action . Furthermore, a comparison of compound 74 MIC/MBC values against *MRSA* (MIC/MBC = 15.6 µg/mL) & MSSA (MIC/MBC = 125 µg/mL) demonstrated that the resistant strain was more susceptible to being impacted by chemical 74. The major cause of TB is *M. tuberculosis* [144]. On A549 cells and MRC-5, compound 74 has been less hazardous (IC_{50} 79.4 µmol/L and 87.6 µmol/L, respectively). Also, compound 74 posed around 120 & 50 times less of a threat to MRC-5 and A549 cells than doxorubicin did. The selectivity indices (SI) of selected medications were determined as the ratio of the IC_{50} and MIC values against *A. baumannii* and *M. tuberculosis* to evaluate the effects on eukaryotic and prokaryotic cells. Compound 74 was more selective as comprehended by looking at the SI values that ranged from 5.4 to 15.6. Candidates for novel antitubercular drugs, according to Orme and colleagues, must have a SI value of 10. Since it possesses higher SI values, compound 74 appears to be more effective against tuberculosis. MRC-5 and A549 cells' SI values for compound 74 were 15.6 and 14.2, respectively [145,146].



71a R_1=H R_2=H R_3=OH R_4=H
71b R_1=H R_2=OCH_3 R_3=OH R_4=H



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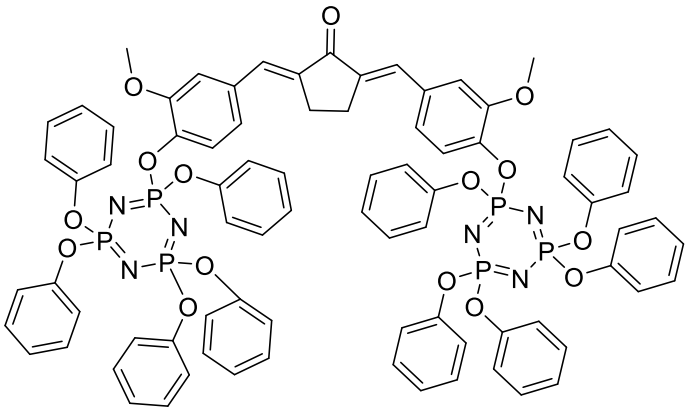

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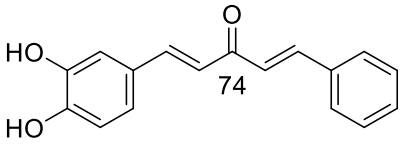
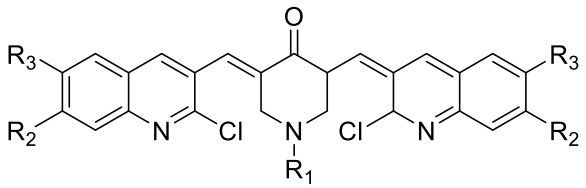


Figure 51: Compounds with potent activity against diverse pathogenic bacteria.

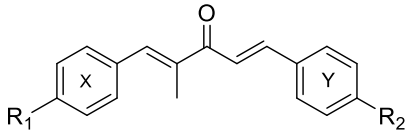
An effective series of new mono-carbonyl curcumin analogues based on quinolines was created, and its antimycobacterial activity against MTB and *M. bovis* BCG was tested in vitro with a better selectivity for the latter. Compounds 75a–d from this study was the most effective against *M. bovis* BCG, with MIC90 values in the range 2.7 - 9.4 µg/mL. With a MIC90 value of 7.8 µg/mL, 75d is the most potent against MTB of all the substances examined [147].



75a R_1=H R_2= OMe R_3=H
75b R_1=H R_2= H R_3=F
75c R_1=Me R_2=H R_3=H
75d R_1=Me R_2= OMe R_3=H

Figure 52: Quinoline based mono-carbonyl curcumin analogues with antibacterial activity

Compound 76b was the only one in the preliminary screening that could stop the proliferation of microbiological indicator strains, *S. aureus* and *E. coli*. It had MIC values of 250 µg/mL and 500 µg/mL, respectively. For gram-positive bacteria, compound 76a had MIC value 62.5 µg/mL and proved to be a good inhibitor. As compared to the positive control, ciprofloxacin, compounds 76a had MIC value 62.5 µg/mL and 76b had MIC value equivalent to 250 µg/mL for *S. aureus* had reduced MIC values. Upon considering structure, it can be seen that 76a has one para -OMe substitution in aromatic ring X while 76b has 2 N, N-dimethyl substitutions at para positions in both ring X and Y. Compound 76a was determined to be the most effective against gram positive, gram negative, and fungal bacteria. Moreover, the chemical 76a exhibited good bioactivity against *Candida albicans*, *Candida krusei*, *Staphylococcus aureus*, and *Staphylococcus saprophyticus*. Compound 76b displayed the same antibacterial properties as compound 76a. Two available electron-donating substituent's, according to the study's findings, exhibited strong activity of inhibition even stronger than ciprofloxacin. The size and length of the side chains, as well as the presence of non-polar or polar hydrophilic groups, are additional parameters that can affect the activity of the chalcone compounds. It is interesting that the polar character of several chemicals, which prevented membrane penetration, is connected to the limited antibacterial action [148].

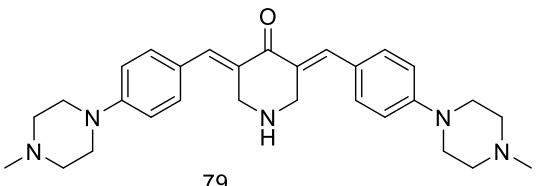


76a R_1=OMe R_2=H
76b R_1,R_2=$N(CH_3)_2$

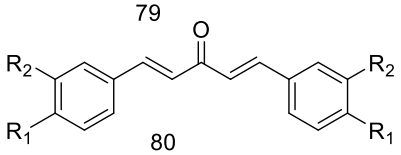
Figure 53: Mono-carbonyl analogue of curcumin displaying anti-bacterial activity against several bacterial strains

Alzheimer's disease (AD) is a neurodegenerative brain illness that has no effective treatment. Its origin and pathophysiology are still unknown, despite the fact that it developed as a result of several different circumstances rather than a singular cause. Aggregation of extracellular amyloid plaques is the main pathogenic characteristic found in AD. A growing body of evidence suggests that biometals like iron have a role in the deposition and generation of ROS, as well as the extensive oxidative damage seen in the brains of Alzheimer's disease patients. Subsequent analysis indicated that the derivative 79 performed better than the studied curcumin derivatives, and these results strongly advised that 79's structure be optimised further to generate more effective multifunctional anti-Alzheimer medicines [149]. Chen and colleagues produced and tested a number of curcumin derivatives for their usefulness in the treatment of Alzheimer's disease. These compounds outperformed curcumin in terms of inhibitory efficacy. They also outperformed the reference substance Trolox as antioxidants, metal chelators (iron and copper), and suppressors of metal-induced aggregation. Subsequent analysis indicated that the derivative1 performed better than the studied curcumin derivatives, and these results strongly advised that 79's structure be optimised further in order to generate more effective multifunctional anti-Alzheimer medicines [149][150]. Aiming to aid in the early identification of Alzheimer's disease, 1,5-diphenyl-1,4-pentadien-3-one analogues (80, 81) were created to be tested as imaging agents for the detection of β-amyloid (αβ) plaques in the brain (AD). The investigations showed a strong propensity for these derivatives to bind to αβ plaques, and compound 81a was shown to visibly stain ab plaques in sections of AD brain. The biodistribution test revealed radioiodinated ligand 3a had good clearance from the brain and high brain uptake [151].

Miscellaneous

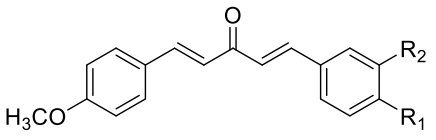


79



80

R_1=OH,OCH_3 , R_2= H,OCH_3



R_1 = OH,NO_2,NH_2,F,Br,I,$N(CH_3)_2$,OCF_3
R_2= H,OCH_3
81a R_1=H R_2=I

Figure 54: Mono-carbonyl analogue of curcumin displaying activity against Alzheimer's disease

Certain curcumin mono-carbonyl analogues were investigated for their antimalarial efficacy against *Plasmodium falciparum* strains that were CQ-resistant (W2 clone) and CQ-sensitive (D6 clone). As compared to the conventional medicine chloroquine, compounds 82a-f (in which the amine probe is linked through ethylene/butylene linker with cyclopentanone ring) showed the most action against the CQ-resistant strain of *P. falciparum* (IC_{50} values ranging from 0.37-0.63 µM) (CQ). These compounds also showed moderate to excellent activity against *P. falciparum* isolates that were susceptible to CQ, with IC_{50} values that ranged from 0.35-0.69 µM. As none of the chemicals were hazardous to Vero cells, this indicates that they are all suitable for use with mammalian cells [152].

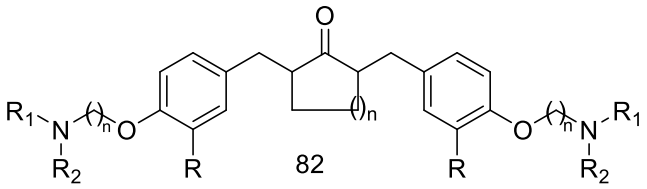


Figure 55: Mono-carbonyl analogue of curcumin with activity against *P. falciparum*

To test the validity of these findings, a few drugs were used to prevent Tat-induced HIV LTR transactivation in HeLa Tat-Luc cells, in which the HIV-1 Tat protein directly activates the Human immunodeficiency virus-1 (HIV-1) LTR. The most effective substance was the C5-analogue 83 (IC_{50} = 4.7 µM). These findings gave justification for further research into curcuminoids' ability to suppress HIV-1. The pNL4-3 HIV-1 clone pseudotyped with the vesicular stomatitis virus (VSV) envelope was used to infect Jurkat cells, bypassing the cells' normal mode of HIV-1 entrance and enabling strong HIV-1 replication [153].

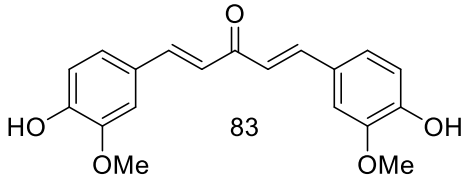
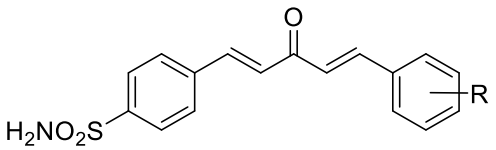


Figure 56: MAC used against HIV-1

For the treatment of glaucoma, a number of medications containing sulfonamide moieties were utilised as inhibitors of CA (carbonic anhydrase) isozyme II. Sulfonamide analogues of curcumin (Compound 84) were created and tested for their ability to inhibit CA against the following four isoforms: hCA I (involved in some eye diseases), II (a drug target for treating glaucoma), IX (a drug target for treating cancer), and XII (antiglaucoma and anticancer drug target). 4-Sulfamoyl benzaldehyde and chalcones. Based on the biological tests, compound 6a exhibited higher selectivity against the hCA II isoform than the hCA IX and hCA XII isoforms (by about a factor of 9), and compound 84b demonstrated greater selectivity (by about 3 and 70 times, correspondingly) against the hCA II isoform than the hCA IX and hCA XII isoforms[154].



84a R=2,4-di-OCH_3
84b R=3,4-di-OCH_3

Figure 57: MAC used as anti-glaucoma drug

Conclusion

This literature raises the prospect that curcumin's mono-carbonyl equivalents could be used as

therapeutic treatments for a range of ailments. The potential for the many synthetic MACs to be developed into medicines is encouraging. A methodology for restructuring curcumin molecule into mono-carbonyl analogues was done via synthetic routes in order to facilitate a positive change in its medicinal capacity. This was accomplished by inserting various types of substituents into different locations. When each moiety was inserted in a different location of the skeleton of the mono-carbonyl analogue of curcumin, it revealed a distinct type of property. The foregoing discussion included several more qualities in addition to the anti-cancerous, anti-inflammatory, and anti-microbial ones. Against a number of human tumour cell lines, analogues created for anti-cancer purposes significantly inhibited growth. There were various analogues of the mono-carbonyl curcumin family that were more active than the actual curcumin. The MAC's created particularly for inflammations were used to suppress several pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β, which are involved in the pathological pain (inflammation) process. The synthesised MAC's demonstrated bactericidal action against both Gram-negative & Gram-positive bacteria based on the MBC, ZOI (zone of inhibition), and MIC values. Based on the synthesised analogues' antimicrobial activity, the isolates' growth is inhibited in a specific zone. Curcumin analogues' antioxidant capabilities and activities have been investigated in various in-vitro and in-vivo experimental models. The findings of the current study have demonstrated that they are effective antioxidants in addition to curcumin. The C5 curcumin analogues were discovered to be genuine chemicals/drugs in treating a variety of ailments due to its excellent antioxidant and anti-inflammatory effects. Various beneficial properties of the synthesised symmetric as well as asymmetric mono-carbonyl analogues are attributed to be due to structural changes such as structure's inclusion of various functional groups, alteration in the length of carbon chain, changes in ring size, presence/absence of heterocyclic rings etc.

References

1. Tønnesen, H.H.; Karlsen, J.; van Henegouwen, G.B. Studies on Curcumin and Curcuminoids. VIII. Photochemical Stability of Curcumin. *Z Lebensm Unters Forsch* **1986**, *183*, 116–122, doi:10.1007/BF01041928.
2. Tønnesen, H.H.; Karlsen, J. Studies on Curcumin and Curcuminoids. VI. Kinetics of Curcumin Degradation in Aqueous Solution. *Z Lebensm Unters Forsch* **1985**, *180*, 402–404, doi:10.1007/BF01027775.
3. Tønnesen, H.H.; Karlsen, J. Studies on Curcumin and Curcuminoids. *Zeitschrift für Lebensmittel-Untersuchung und Forschung 1985 180:2* **1985**, *180*, 132–134, doi:10.1007/BF01042637.
4. Joe, B.; Vijaykumar, M.; Lokesh, B.R. Biological Properties of Curcumin-Cellular and Molecular Mechanisms of Action. *Crit Rev Food Sci Nutr* **2004**, *44*, 97–111, doi:10.1080/10408690490424702.
5. Akram, M.; Mohiuddin, E.; Asif, M. Curcuma Longa and Curcumin: A Review Article New Process of Sea Water Dessalination Using Solar Radiation View Project.
6. Chainani-Wu, N. Safety and Anti-Inflammatory Activity of Curcumin: A Component of Tumeric (Curcuma Longa). *J Altern Complement Med* **2003**, *9*, 161–168, doi:10.1089/107555303321223035.
7. Payton, F.; Sandusky, P.; Alworth, W.L. NMR Study of the Solution Structure of Curcumin. *J Nat Prod* **2007**, *70*, 143–146, doi:10.1021/NP060263S.
8. Parimita, S.P.; Ramshankar, Y.V.; Suresh, S.; Row, T.N.G. Redetermination of Curcumin: (1E,4Z,6E)-5-Hydroxy-1,7-Bis(4-Hydroxy-3-Methoxy-Phenyl)Hepta-1,4,6-Trien-3-One. *Acta Crystallogr Sect E Struct Rep Online* **2007**, *63*, o860–o862, doi:10.1107/S160053680700222X/BI2146ISUP2.HKL.
9. Anand, P.; Kunnumakkara, A.B.; Newman, R.A.; Aggarwal, B.B. Bioavailability of Curcumin: Problems and Promises. *Mol Pharm* **2007**, *4*, 807–818, doi:10.1021/MP700113R/ASSET/IMAGES/MEDIUM/MP-2007-00113R_0003.GIF.
10. Shen, L.; Ji, H.F. Theoretical Study on Physicochemical Properties of Curcumin. *Spectrochim Acta A Mol Biomol Spectrosc* **2007**, *67*, 619–623, doi:10.1016/J.SAA.2006.08.018.
11. Shen, L.; Ji, H.F. Theoretical Study on Physicochemical Properties of Curcumin. *Spectrochim Acta A Mol Biomol Spectrosc* **2007**, *67*, 619–623, doi:10.1016/J.SAA.2006.08.018.

12. Bernabé-Pineda, M.; Ramírez-Silva, M.T.; Romero-Romo, M.; González-Vergara, E.; Rojas-Hernández, A. Determination of Acidity Constants of Curcumin in Aqueous Solution and Apparent Rate Constant of Its Decomposition. *Spectrochim Acta A Mol Biomol Spectrosc* **2004**, *60*, 1091–1097, doi:10.1016/S1386-1425(03)00342-1.

13. Bernabé-Pineda, M.; Ramírez-Silva, M.T.; Romero-Romo, M.; González-Vergara, E.; Rojas-Hernández, A. Determination of Acidity Constants of Curcumin in Aqueous Solution and Apparent Rate Constant of Its Decomposition. *Spectrochim Acta A Mol Biomol Spectrosc* **2004**, *60*, 1091–1097, doi:10.1016/S1386-1425(03)00342-1.

14. Goel, A.; Kunnumakkara, A.B.; Aggarwal, B.B. Curcumin as "Curecumin": From Kitchen to Clinic. *Biochem Pharmacol* **2008**, *75*, 787–809, doi:10.1016/J.BCP.2007.08.016.

15. Anand, P.; Kunnumakkara, A.B.; Newman, R.A.; Aggarwal, B.B. Bioavailability of Curcumin: Problems and Promises. *Mol Pharm* **2007**, *4*, 807–818, doi:10.1021/MP700113R/ASSET/IMAGES/MEDIUM/MP-2007-00113R_0003.GIF.

16. Nagahama, K.; Utsumi, T.; Kumano, T.; Maekawa, S.; Oyama, N.; Kawakami, J. Discovery of a New Function of Curcumin Which Enhances Its Anticancer Therapeutic Potency. *Sci Rep* **2016**, *6*, doi:10.1038/SREP30962.

17. Wahlström, B.; Blennow, G. A Study on the Fate of Curcumin in the Rat. *Acta Pharmacol Toxicol (Copenh)* **1978**, *43*, 86–92, doi:10.1111/J.1600-0773.1978.TB02240.X.

18. Rosemond, M.J.C.; st. John-Williams, L.; Yamaguchi, T.; Fujishita, T.; Walsh, J.S. Enzymology of a Carbonyl Reduction Clearance Pathway for the HIV Integrase Inhibitor, S-1360: Role of Human Liver Cytosolic Aldo-Keto Reductases. *Chem Biol Interact* **2004**, *147*, 129–139, doi:10.1016/j.cbi.2003.12.001.

19. Wang, Y.J.; Pan, M.H.; Cheng, A.L.; Lin, L.I.; Ho, Y.S.; Hsieh, C.Y.; Lin, J.K. Stability of Curcumin in Buffer Solutions and Characterization of Its Degradation Products. *J Pharm Biomed Anal* **1997**, *15*, 1867–1876, doi:10.1016/S0731-7085(96)02024-9.

20. Gupta, S.C.; Prasad, S.; Kim, J.H.; Patchva, S.; Webb, L.J.; Priyadarsini, I.K.; Aggarwal, B.B. Multitargeting by Curcumin as Revealed by Molecular Interaction Studies. *Nat Prod Rep* **2011**, *28*, 1937–1955, doi:10.1039/C1NP00051A.

21. Tsukamoto, M.; Kuroda, K.; Ramamoorthy, A.; Yasuhara, K. Modulation of Raft Domains in a Lipid Bilayer by Boundary-Active Curcumin. *Chem Commun (Camb)* **2014**, *50*, 3427–3430, doi:10.1039/C3CC47738J.

22. Barry, J.; Fritz, M.; Brender, J.R.; Smith, P.E.S.; Lee, D.K.; Ramamoorthy, A. Determining the Effects of Lipophilic Drugs on Membrane Structure by Solid-State NMR Spectroscopy: The Case of the Antioxidant Curcumin. *J Am Chem Soc* **2009**, *131*, 4490–4498, doi:10.1021/JA809217U.

23. Robinson, T.P.; Ehlers, T.; Hubbard IV, R.B.; Bai, X.; Arbiser, J.L.; Goldsmith, D.J.; Bowen, J.P. Design, Synthesis, and Biological Evaluation of Angiogenesis Inhibitors: Aromatic Enone and Dienone Analogues of Curcumin. *Bioorg Med Chem Lett* **2003**, *13*, 115–117, doi:10.1016/S0960-894X(02)00832-6.

24. Ohtsu, H.; Xiao, Z.; Ishida, J.; Nagai, M.; Wang, H.K.; Itokawa, H.; Su, C.Y.; Shih, C.; Chiang, T.; Chang, E.; et al. Antitumor Agents. 217. Curcumin Analogues as Novel Androgen Receptor Antagonists with Potential as Anti-Prostate Cancer Agents. *J Med Chem* **2002**, *45*, 5037–5042, doi:10.1021/JM020200G/ASSET/IMAGES/MEDIUM/JM020200GN00001.GIF.

25. Thakur, A.; Manohar, S.; Vélez Gerena, C.E.; Zayas, B.; Kumar, V.; Malhotra, S. v.; Rawat, D.S. Novel 3,5-Bis(Arylidiene)-4-Piperidone Based Monocarbonyl Analogs of Curcumin: Anticancer Activity Evaluation and Mode of Action Study. *Medchemcomm* **2014**, *5*, 576–586, doi:10.1039/C3MD00399J.

26. Simoni, E.; Bergamini, C.; Fato, R.; Tarozzi, A.; Bains, S.; Motterlini, R.; Cavalli, A.; Bolognesi, M.L.; Minarini, A.; Hrelia, P.; et al. Polyamine Conjugation of Curcumin Analogues toward the Discovery of Mitochondria-Directed Neuroprotective Agents. *J Med Chem* **2010**, *53*, 7264–7268, doi:10.1021/JM100637K/SUPPL_FILE/JM100637K_SI_001.PDF.

27. Manohar, S.; Thakur, A.; Bhatia, R.; Walia, S.; Ponnan, P.; Diwan, &; Rawat, S. Antibacterial and Antioxidant Activity Evaluation of Novel Symmetrical and Unsymmetrical C5-Curcuminoids. *IJC-B Vol.54B(10) [October 2015]* **2015**, *54*, 1235–1246.

28. Tan, K.L.; Ali, A.; Du, Y.; Fu, H.; Jin, H.X.; Chin, T.M.; Khan, M.; Go, M.L. Synthesis and Evaluation of Bisbenzylidenedioxotetrahydrothiopranones as Activators of Endoplasmic Reticulum (ER) Stress Signaling Pathways and Apoptotic Cell Death in Acute Promyelocytic Leukemic Cells. *J Med Chem* **2014**, *57*, 5904–5918, doi:10.1021/JM401352A/SUPPL_FILE/JM401352A_SI_001.PDF.

29. Manohar, S.; Khan, S.I.; Kandi, S.K.; Raj, K.; Sun, G.; Yang, X.; Calderon Molina, A.D.; Ni, N.; Wang, B.; Rawat, D.S. Synthesis, Antimalarial Activity and Cytotoxic Potential of New Monocarbonyl Analogues of Curcumin. *Bioorg Med Chem Lett* **2013**, *23*, 112–116, doi:10.1016/J.BMCL.2012.11.004.

30. Zhang, Y.; Zhao, C.; He, W.; Wang, Z.; Fang, Q.; Xiao, B.; Liu, Z.; Liang, G.; Yang, S. Discovery and Evaluation of Asymmetrical Monocarbonyl Analogs of Curcumin as Anti-Inflammatory Agents. *Drug Des Devel Ther* **2014**, *8*, 373, doi:10.2147/DDDT.S58168.

31. Bukhari, S.N.A.; Jantan, I.; Masand, V.H.; Mahajan, D.T.; Sher, M.; Naeem-Ul-Hassan, M.; Amjad, M.W. Synthesis of α, β-Unsaturated Carbonyl Based Compounds as Acetylcholinesterase and Butyrylcholinesterase Inhibitors: Characterization, Molecular Modeling, QSAR Studies and Effect against Amyloid β-Induced Cytotoxicity. *Eur J Med Chem* **2014**, *83*, 355–365, doi:10.1016/J.EJMECH.2014.06.034.

32. Liang, G.; Yang, S.; Jiang, L.; Zhao, Y.; Shao, L.; Xiao, J.; Ye, F.; Li, Y.; Li, X. Synthesis and Anti-Bacterial Properties of Mono-Carbonyl Analogues of Curcumin. *Chem Pharm Bull (Tokyo)* **2008**, *56*, 162–167, doi:10.1248/CPB.56.162.

33. Liang, G.; Li, X.; Chen, L.; Yang, S.; Wu, X.; Studer, E.; Gurley, E.; Hylemon, P.B.; Ye, F.; Li, Y.; et al. Synthesis and Anti-Inflammatory Activities of Mono-Carbonyl Analogues of Curcumin. *Bioorg Med Chem Lett* **2008**, *18*, 1525–1529, doi:10.1016/J.BMCL.2007.12.068.

34. Baldwin, P.R.; Reeves, A.Z.; Powell, K.R.; Napier, R.J.; Swimm, A.I.; Sun, A.; Giesler, K.; Bommarius, B.; Shinnick, T.M.; Snyder, J.P.; et al. Monocarbonyl Analogs of Curcumin Inhibit Growth of Antibiotic Sensitive and Resistant Strains of Mycobacterium Tuberculosis. *Eur J Med Chem* **2015**, *92*, 693, doi:10.1016/J.EJMECH.2015.01.020.

35. Buduma, K.; Chinde, S.; Dommati, A.K.; Sharma, P.; Shukla, A.; Srinivas, K.V.N.S.; Arigari, N.K.; Khan, F.; Tiwari, A.K.; Grover, P.; et al. Synthesis and Evaluation of Anticancer and Antiobesity Activity of 1-Ethoxy Carbonyl-3,5-Bis (3′-Indolyl Methylene)-4-Pyperidone Analogs. *Bioorg Med Chem Lett* **2016**, *26*, 1633–1638, doi:10.1016/J.BMCL.2016.01.073.

36. Tiwari, A.; Kumar, S.; Shivahare, R.; Kant, P.; Gupta, S.; Suryawanshi, S.N. Chemotherapy of Leishmaniasis Part XIII: Design and Synthesis of Novel Heteroretinoid-Bisbenzylidine Ketone Hybrids as Antileishmanial Agents. *Bioorg Med Chem Lett* **2015**, *25*, 410–413, doi:10.1016/J.BMCL.2014.09.078.

37. Kálai, T.; Kuppusamy, M.L.; Balog, M.; Selvendiran, K.; Rivera, B.K.; Kuppusamy, P.; Hideg, K. Synthesis of N-Substituted 3,5-Bis(Arylidene)-4-Piperidones with High Antitumor and Antioxidant Activity. *J Med Chem* **2011**, *54*, 5414–5421, doi:10.1021/JM200353F/SUPPL_FILE/JM200353F_SI_001.PDF.

38. Singh, H.; Kumar, M.; Nepali, K.; Gupta, M.K.; Saxena, A.K.; Sharma, S.; Bedi, P.M.S. Triazole Tethered C5-Curcuminoid-Coumarin Based Molecular Hybrids as Novel Antitubulin Agents: Design, Synthesis, Biological Investigation and Docking Studies. *Eur J Med Chem* **2016**, *116*, 102–115, doi:10.1016/J.EJMECH.2016.03.050.

39. Bukhari, S.N.A.; Lauro, G.; Jantan, I.; Bifulco, G.; Amjad, M.W. Pharmacological Evaluation and Docking Studies of α,β-Unsaturated Carbonyl Based Synthetic Compounds as Inhibitors of Secretory Phospholipase A2, Cyclooxygenases, Lipoxygenase and Proinflammatory Cytokines. *Bioorg Med Chem* **2014**, *22*,

4151–4161, doi:10.1016/J.BMC.2014.05.052.

40. Jha, A.; Duffield, K.M.; Ness, M.R.; Ravoori, S.; Andrews, G.; Bhullar, K.S.; Rupasinghe, H.P.V.; Balzarini, J. Curcumin-Inspired Cytotoxic 3,5-Bis(Arylmethylene)-1-(N-(Ortho-Substituted Aryl)Maleamoyl)-4-Piperidones: A Novel Group of Topoisomerase II Alpha Inhibitors. *Bioorg Med Chem* **2015**, *23*, 6404–6417, doi:10.1016/J.BMC.2015.08.023.

41. Braga, S.F.P.; Alves, É.V.P.; Ferreira, R.S.; Fradico, J.R.B.; Lage, P.S.; Duarte, M.C.; Ribeiro, T.G.; Júnior, P.A.S.; Romanha, A.J.; Tonini, M.L.; et al. Synthesis and Evaluation of the Antiparasitic Activity of Bis-(Arylmethylidene) Cycloalkanones. *Eur J Med Chem* **2014**, *71*, 282–289, doi:10.1016/J.EJMECH.2013.11.011.

42. Liang, G.; Shao, L.; Wang, Y.; Zhao, C.; Chu, Y.; Xiao, J.; Zhao, Y.; Li, X.; Yang, S. Exploration and Synthesis of Curcumin Analogues with Improved Structural Stability Both in Vitro and in Vivo as Cytotoxic Agents. *Bioorg Med Chem* **2009**, *17*, 2623–2631, doi:10.1016/j.bmc.2008.10.044.

43. Uniyal, A.; Gairolla, J.; Saini, A.; Rana, D.; Anthwal, A. Designing And In Silico Screening Of Novel Umbelliferone-Imines for Anti-HIV And Anti-Cancer Activities. *J Pharm Negat Results* **2022**, *13*, 3542–3546, doi:10.47750/PNR.2022.13.S08.437.

44. Anthwal, A.; Singh, K.; S.M. Rawat, M.; K. Tyagi, A.; Haque, A.; Ali, I.; S. Rawat, D. Synthesis of 4-Piperidone Based Curcuminoids with Anti-Inflammatory and Anti-Proliferation Potential in Human Cancer Cell Lines. *Anticancer Agents Med Chem* **2016**, *16*, 841–851, doi:10.2174/1871520616666160201151206.

45. Kothiyal, S.C.; Anthwal, A. Evaluation of In Vivo and In Vitro Anti-Diabetic Activity of Roylea Cinerea Nutraceutical Potential of Wild Edible Fruits View Project Isolated Chemical Compound and Their Antidibetic Activity View Project. *Article in International Journal of Pharmaceutical Sciences Review and Research* **2015**, *32*, 210–213.

46. Thakur, B.K.; Anthwal, A.; Rawat, D.S.; Rawat, B.; Rashmi; Rawat, M. A Review on Genus Alseodaphne: Phytochemistry and Pharmacology. *Mini Rev Org Chem* **2012**, *9*, 433–445, doi:10.2174/157019312804699429.

47. (PDF) Synthesis, Antibacterial Screening and Theoretical Molecular Properties Prediction of Hydantoin-Chalcone Conjugates Available online: https://www.researchgate.net/publication/265165250_Synthesis_antibacterial_screening_and_theoretical_molecular_properties_prediction_of_hydantoin-chalcone_conjugates (accessed on 9 May 2023).

48. Anthwal, A.; Thakur, B.K.; Rawat, M.S.M.; Rawat, D.S.; Tyagi, A.K.; Aggarwal, B.B. Synthesis, Characterization and In Vitro Anticancer Activity of C-5 Curcumin Analogues with Potential to Inhibit TNF-α-Induced NF-KB Activation. *Biomed Res Int* **2014**, *2014*, doi:10.1155/2014/524161.

49. Anthwal, A.; Singh, K.; Rawat, M.S.M.; Tyagi, A.K.; Aggarwal, B.B.; Rawat, D.S. C5-Curcuminoid-Dithiocarbamate Based Molecular Hybrids: Synthesis and Anti-Inflammatory and Anti-Cancer Activity Evaluation. *RSC Adv* **2014**, *4*, 28756–28764, doi:10.1039/C4RA03655G.

50. Anthwal, A.; Rajesh, U.C.; Rawat, M.S.M.; Kushwaha, B.; Maikhuri, J.P.; Sharma, V.L.; Gupta, G.; Rawat, D.S. Novel Metronidazole-Chalcone Conjugates with Potential to Counter Drug Resistance in Trichomonas Vaginalis. *Eur J Med Chem* **2014**, *79*, 89–94, doi:10.1016/J.EJMECH.2014.03.076.

51. Anthwal, A.; Thakur, B.K.; Rawat, M.S.M.; Rawat, D.S.; Tyagi, A.K.; Aggarwal, B.B. Synthesis, Characterization and in Vitro Anticancer Activity of C-5 Curcumin Analogues with Potential to Inhibit TNF-α-Induced NF-KB Activation. *Biomed Res Int* **2014**, *2014*, doi:10.1155/2014/524161.

52. Sanabria-Ríos, D.J.; Rivera-Torres, Y.; Rosario, J.; Ríos, C.; Gutierrez, R.; Carballeira, N.M.; Vélez, C.; Zayas, B.; Álvarez-Colón, F.; Ortiz-Soto, G.; et al. Synthesis of Novel C5-Curcuminoid-Fatty Acid Conjugates and Mechanistic Investigation of Their Anticancer Activity. *Bioorg Med Chem Lett* **2015**, *25*, 2174–2180, doi:10.1016/J.BMCL.2015.03.065.

53. Singh, R.K.; Rai, D.; Yadav, D.; Bhargava, A.; Balzarini, J.; de Clercq, E. Synthesis, Antibacterial and Antiviral Properties of Curcumin Bioconjugates Bearing Dipeptide,

Fatty Acids and Folic Acid. *Eur J Med Chem* **2010**, *45*, 1078–1086, doi:10.1016/J.EJMECH.2009.12.002.

54. Zhou, D.; Ding, N.; Zhao, S.; Li, D.; van Doren, J.; Qian, Y.; Wei, X.; Zheng, X. Synthesis and Evaluation of Curcumin-Related Compounds Containing Inden-2-One for Their Effects on Human Cancer Cells. *Biol Pharm Bull* **2014**, *37*, 1977–1981, doi:10.1248/BPB.B14-00477.

55. Helal, M.; Das, U.; Bandy, B.; Islam, A.; Nazarali, A.J.; Dimmock, J.R. Mitochondrial Dysfunction Contributes to the Cytotoxicity of Some 3,5-Bis(Benzylidene)-4-Piperidone Derivatives in Colon HCT-116 Cells. *Bioorg Med Chem Lett* **2013**, *23*, 1075–1078, doi:10.1016/J.BMCL.2012.12.016.

56. Das, S.; Das, U.; Michel, D.; Gorecki, D.K.J.; Dimmock, J.R. Novel 3,5-Bis(Arylidene)-4-Piperidone Dimers: Potent Cytotoxins against Colon Cancer Cells. *Eur J Med Chem* **2013**, *64*, 321–328, doi:10.1016/J.EJMECH.2013.03.055.

57. Lin, L.; Liu, Y.; Li, H.; Li, P.K.; Fuchs, J.; Shibata, H.; Iwabuchi, Y.; Lin, J. Targeting Colon Cancer Stem Cells Using a New Curcumin Analogue, GO-Y030. *Br J Cancer* **2011**, *105*, 212, doi:10.1038/BJC.2011.200.

58. Katsori, A.M.; Chatzopoulou, M.; Dimas, K.; Kontogiorgis, C.; Patsilinakos, A.; Trangas, T.; Hadjipavlou-Litina, D. Curcumin Analogues as Possible Anti-Proliferative & Anti-Inflammatory Agents. *Eur J Med Chem* **2011**, *46*, 2722–2735, doi:10.1016/J.EJMECH.2011.03.060.

59. Selvendiran, K.; Kuppusamy, M.L.; Bratasz, A.; Tong, L.; Rivera, B.K.; Rink, C.; Sen, C.K.; Kálai, T.; Hideg, K.; Kuppusamy, P. Inhibition of Vascular Smooth-Muscle Cell Proliferation and Arterial Restenosis by HO-3867, a Novel Synthetic Curcuminoid, through Up-Regulation of PTEN Expression. *Journal of Pharmacology and Experimental Therapeutics* **2009**, *329*, 959–966, doi:10.1124/JPET.108.150367.

60. Zhu, S.; Moore, T.W.; Lin, X.; Morii, N.; Mancini, A.; Howard, R.B.; Culver, D.; Arrendale, R.F.; Reddy, P.; Evers, T.J.; et al. Synthetic Curcumin Analog EF31 Inhibits the Growth of Head and Neck Squamous Cell Carcinoma Xenografts. *Integrative Biology* **2012**, *4*, 633–640, doi:10.1039/C2IB20007D.

61. Nagaraju, G.P.; Zhu, S.; Wen, J.; Farris, A.B.; Adsay, V.N.; Diaz, R.; Snyder, J.P.; Mamoru, S.; El-Rayes, B.F. Novel Synthetic Curcumin Analogues EF31 and UBS109 Are Potent DNA Hypomethylating Agents in Pancreatic Cancer. *Cancer Lett* **2013**, *341*, 195–203, doi:10.1016/J.CANLET.2013.08.002.

62. Nagaraju, G.P.; Zhu, S.; Ko, J.E.; Ashritha, N.; Kandimalla, R.; Snyder, J.P.; Shoji, M.; El-Rayes, B.F. Antiangiogenic Effects of a Novel Synthetic Curcumin Analogue in Pancreatic Cancer. *Cancer Lett* **2015**, *357*, 557–565, doi:10.1016/J.CANLET.2014.12.007.

63. Hurtado, M.; Sankpal, U.T.; Ranjan, A.; Maram, R.; Vishwanatha, J.K.; Nagaraju, G.P.; El-Rayes, B.F.; Basha, R. Investigational Agents to Enhance the Efficacy of Chemotherapy or Radiation in Pancreatic Cancer. *Crit Rev Oncol Hematol* **2018**, *126*, 201–207, doi:10.1016/J.CRITREVONC.2018.03.016.

64. Nagaraju, G.P.; Zhu, S.; Wen, J.; Farris, A.B.; Adsay, V.N.; Diaz, R.; Snyder, J.P.; Mamoru, S.; El-Rayes, B.F. Novel Synthetic Curcumin Analogues EF31 and UBS109 Are Potent DNA Hypomethylating Agents in Pancreatic Cancer. *Cancer Lett* **2013**, *341*, 195–203, doi:10.1016/J.CANLET.2013.08.002.

65. Kálai, T.; Kuppusamy, M.L.; Balog, M.; Selvendiran, K.; Rivera, B.K.; Kuppusamy, P.; Hideg, K. Synthesis of N-Substituted 3,5-Bis(Arylidene)-4-Piperidones with High Antitumor and Antioxidant Activity. *J Med Chem* **2011**, *54*, 5414–5421, doi:10.1021/JM200353F/SUPPL_FILE/JM200353F_SI_001.PDF.

66. Samaan, N.; Zhong, Q.; Fernandez, J.; Chen, G.; Hussain, A.M.; Zheng, S.; Wang, G.; Chen, Q.H. Design, Synthesis, and Evaluation of Novel Heteroaromatic Analogs of Curcumin as Anti-Cancer Agents. *Eur J Med Chem* **2014**, *75*, 123–131, doi:10.1016/J.EJMECH.2014.01.041.

67. Xiao, J.; Chu, Y.; Hu, K.; Wan, J.; Huang, Y.; Jiang, C.; Liang, G.; Li, X. Synthesis and Biological Analysis of a New Curcumin Analogue for Enhanced Anti-Tumor Activity in HepG 2 Cells. *Oncol Rep* **2010**, *23*, 1435–1441, doi:10.3892/OR_00000781.

68. Qu, W.; Xiao, J.; Zhang, H.; Chen, Q.; Wang, Z.; Shi, H.; Gong, L.; Chen, J.; Liu, Y.; Cao, R.; et al. B19, a Novel Monocarbonyl Analogue of Curcumin, Induces Human Ovarian Cancer Cell Apoptosis via Activation of Endoplasmic Reticulum Stress and the Autophagy Signaling Pathway. *Int J Biol Sci* **2013**, *9*, 766, doi:10.7150/IJBS.5711.

69. Pan, Y.; Xiao, J.; Liang, G.; Wang, M.; Wang, D.; Wang, S.; Yang, H. A New Curcumin Analogue Exhibits Enhanced Antitumor Activity in Nasopharyngeal Carcinoma. *Oncol Rep* **2013**, *30*, 239–245, doi:10.3892/OR.2013.2457/HTML.

70. Zhao, J.A.; Sang, M.X.; Geng, C.Z.; Wang, S.J.; Shan, B.E. A Novel Curcumin Analogue Is a Potent Chemotherapy Candidate for Human Hepatocellular Carcinoma. *Oncol Lett* **2016**, *12*, 4252–4262, doi:10.3892/OL.2016.5126/HTML.

71. Luo, C.; Li, Y.; Zhou, B.; Yang, L.; Li, H.; Feng, Z.; Li, Y.; Long, J.; Liu, J. A Monocarbonyl Analogue of Curcumin, 1,5-Bis(3-Hydroxyphenyl)-1,4-Pentadiene-3-One (Ca 37), Exhibits Potent Growth Suppressive Activity and Enhances the Inhibitory Effect of Curcumin on Human Prostate Cancer Cells. *Apoptosis 2013 19:3* **2013**, *19*, 542–553, doi:10.1007/S10495-013-0947-Y.

72. Paulraj, F.; Abas, F.; Lajis, N.H.; Othman, I.; Hassan, S.S.; Naidu, R. The Curcumin Analogue 1,5-Bis(2-Hydroxyphenyl)-1,4-Pentadiene-3-One Induces Apoptosis and Downregulates E6 and E7 Oncogene Expression in HPV16 and HPV18-Infected Cervical Cancer Cells. *Molecules 2015, Vol. 20, Pages 11830-11860* **2015**, *20*, 11830–11860, doi:10.3390/MOLECULES200711830.

73. Xiao, J.; Wang, Y.; Peng, J.; Guo, L.; Hu, J.; Cao, M.; Zhang, X.; Zhang, H.; Wang, Z.; Li, X.; et al. A Synthetic Compound, 1,5-Bis(2-Methoxyphenyl)Penta- 1,4-Dien-3-One (B63), Induces Apoptosis and Activates Endoplasmic Reticulum Stress in Non-Small Cell Lung Cancer Cells. *Int J Cancer* **2012**, *131*, 1455–1465, doi:10.1002/IJC.27406.

74. Liu, Z.; Sun, Y.; Ren, L.; Huang, Y.; Cai, Y.; Weng, Q.; Shen, X.; Li, X.; Liang, G.; Wang, Y. Evaluation of a Curcumin Analog as an Anti-Cancer Agent Inducing ER Stress-Mediated Apoptosis in Non-Small Cell Lung Cancer Cells. *BMC Cancer* **2013**, *13*, 1–9, doi:10.1186/1471-2407-13-494/FIGURES/4.

75. Zhang, X.; Chen, M.; Zou, P.; Kanchana, K.; Weng, Q.; Chen, W.; Zhong, P.; Ji, J.; Zhou, H.; He, L.; et al. Curcumin Analog WZ35 Induced Cell Death via ROS-Dependent ER Stress and G2/M Cell Cycle Arrest in Human Prostate Cancer Cells. *BMC Cancer* **2015**, *15*, 1–11, doi:10.1186/S12885-015-1851-3/FIGURES/5.

76. Dewi Pamungkas Putri, D.; Fitriasari, A.; Husnaa, U.; Purnomo, H. Curcumin Analogues Enhance Sensitivity of Resistant MCF-7 Cells to Doxorubicin Asian Pac. *Asian Paciic Journal of Cancer Prevention* **2014**, *15*, 179–184, doi:10.7314/APJCP.2014.15.1.179.

77. Somers-Edgar, T.J.; Taurin, S.; Larsen, L.; Chandramouli, A.; Nelson, M.A.; Rosengren, R.J. Mechanisms for the Activity of Heterocyclic Cyclohexanone Curcumin Derivatives in Estrogen Receptor Negative Human Breast Cancer Cell Lines. *Invest New Drugs* **2011**, *29*, 87–97, doi:10.1007/S10637-009-9339-0/METRICS.

78. Yadav, B.; Taurin, S.; Rosengren, R.J.; Schumacher, M.; Diederich, M.; Somers-Edgar, T.J.; Larsen, L. Synthesis and Cytotoxic Potential of Heterocyclic Cyclohexanone Analogues of Curcumin. *Bioorg Med Chem* **2010**, *18*, 6701–6707, doi:10.1016/J.BMC.2010.07.063.

79. Fajardo, A.M.; MacKenzie, D.A.; Ji, M.; Deck, L.M.; Jagt, D.L.V.; Thompson, T.A.; Bisoffi, M. The Curcumin Analog Ca27 Down-Regulates Androgen Receptor through an Oxidative Stress Mediated Mechanism in Human Prostate Cancer Cells. *Prostate* **2012**, *72*, 612–625, doi:10.1002/PROS.21464.

80. Wei, X.; Du, Z.Y.; Cui, X.X.; Verano, M.; Mo, R.Q.; Tang, Z.K.; Conney, A.H.; Zheng, X.; Zhang, K. Effects of Cyclohexanone Analogues of Curcumin on Growth, Apoptosis and NF-KB Activity in PC-3 Human Prostate Cancer Cells. *Oncol Lett* **2012**, *4*, 279–284, doi:10.3892/OL.2012.710/HTML.

81. Wei, X.; Du, Z.Y.; Zheng, X.; Cui, X.X.; Conney, A.H.; Zhang, K. Synthesis and Evaluation of Curcumin-Related Compounds for Anticancer Activity. *Eur J Med Chem*

2012, *53*, 235–245, doi:10.1016/J.EJMECH.2012.04.005.

82. Manohar, S.; Khan, S.I.; Kandi, S.K.; Raj, K.; Sun, G.; Yang, X.; Calderon Molina, A.D.; Ni, N.; Wang, B.; Rawat, D.S. Synthesis, Antimalarial Activity and Cytotoxic Potential of New Monocarbonyl Analogues of Curcumin. *Bioorg Med Chem Lett* **2013**, *23*, 112–116, doi:10.1016/J.BMCL.2012.11.004.

83. Zuo, Y.; Huang, J.; Zhou, B.; Wang, S.; Shao, W.; Zhu, C.; Lin, L.; Wen, G.; Wang, H.; Du, J.; et al. Synthesis, Cytotoxicity of New 4-Arylidene Curcumin Analogues and Their Multi-Functions in Inhibition of Both NF-KB and Akt Signalling. *Eur J Med Chem* **2012**, *55*, 346–357, doi:10.1016/J.EJMECH.2012.07.039.

84. Al-Qasem, A.; Al-Howail, H.A.; Al-Swailem, M.; Al-Mazrou, A.; Al-Otaibi, B.; Al-Jammaz, I.; Al-Khalaf, H.H.; Aboussekhra, A. PAC Exhibits Potent Anti-Colon Cancer Properties through Targeting Cyclin D1 and Suppressing Epithelial-to-Mesenchymal Transition. *Mol Carcinog* **2016**, *55*, 233–244, doi:10.1002/MC.22271.

85. Al-Howail, H.A.; Hakami, H.A.; Al-Otaibi, B.; Al-Mazrou, A.; Daghestani, M.H.; Al-Jammaz, I.; Al-Khalaf, H.H.; Aboussekhra, A. PAC Down-Regulates Estrogen Receptor Alpha and Suppresses Epithelial-to-Mesenchymal Transition in Breast Cancer Cells. *BMC Cancer* **2016**, *16*, 1–11, doi:10.1186/S12885-016-2583-8/FIGURES/7.

86. Cen, L.; Hutzen, B.; Ball, S.; DeAngelis, S.; Chen, C.L.; Fuchs, J.R.; Li, C.; Li, P.K.; Lin, J. New Structural Analogues of Curcumin Exhibit Potent Growth Suppressive Activity in Human Colorectal Carcinoma Cells. *BMC Cancer* **2009**, *9*, 1–8, doi:10.1186/1471-2407-9-99/FIGURES/3.

87. Bi, J.; Pay, T.; Wong, Z.X.; Khong, Y.Y.; Kueh, M.X.; Ng, K.J.; Lee, P.P.F.; Tan, Y.L.K. Ruthenium Arene Complexes with Mono-Carbonyl Analogues of Curcumin as Pendant or Bridging Ligands: Synthesis, Anti-Cancer Activity and Interaction with Quadruplex DNA. *Polyhedron* **2019**, *171*, 396–402, doi:10.1016/J.POLY.2019.07.034.

88. Kandioller, W.; Balsano, E.; Meier, S.M.; Jungwirth, U.; Göschl, S.; Roller, A.; Jakupec, M.A.; Berger, W.; Keppler, B.K.; Hartinger, C.G. Organometallic Anticancer Complexes of Lapachol: Metal Centre-Dependent Formation of Reactive Oxygen Species and Correlation with Cytotoxicity. *Chemical Communications* **2013**, *49*, 3348–3350, doi:10.1039/C3CC40432C.

89. Zhou, D.Y.; Zhao, S.Q.; Du, Z.Y.; Zheng, X.; Zhang, K. Pyridine Analogues of Curcumin Exhibit High Activity for Inhibiting CWR-22Rv1 Human Prostate Cancer Cell Growth and Androgen Receptor Activation. *Oncol Lett* **2016**, *11*, 4160–4166, doi:10.3892/OL.2016.4536/HTML.

90. Zhou, D.Y.; Ding, N.; van Doren, J.; Wei, X.C.; Du, Z.Y.; Conney, A.H.; Zhang, K.; Zheng, X. Effects of Curcumin Analogues for Inhibiting Human Prostate Cancer Cells and the Growth of Human PC-3 Prostate Xenografts in Immunodeficient Mice. *Biol Pharm Bull* **2014**, *37*, 1029–1034, doi:10.1248/BPB.B14-00044.

91. Caruso, F.; Pettinari, R.; Rossi, M.; Monti, E.; Gariboldi, M.B.; Marchetti, F.; Pettinari, C.; Caruso, A.; Ramani, M. v.; Subbaraju, G. v. The in Vitro Antitumor Activity of Arene-Ruthenium(II) Curcuminoid Complexes Improves When Decreasing Curcumin Polarity. *J Inorg Biochem* **2016**, *162*, 44–51, doi:10.1016/J.JINORGBIO.2016.06.002.

92. Wu, J.; Cai, Z.; Wei, X.; Chen, M.; Ying, S.; Shi, L.; Xu, R.A.; He, F.; Liang, G.; Zhang, X. Anti-Lung Cancer Activity of the Curcumin Analog JZ534 in Vitro. *Biomed Res Int* **2015**, *2015*, doi:10.1155/2015/504529.

93. Chen, S.; Nimick, M.; Cridge, A.G.; Hawkins, B.C.; Rosengren, R.J. Anticancer Potential of Novel Curcumin Analogs towards Castrate-Resistant Prostate Cancer. *Int J Oncol* **2018**, *52*, 579–588, doi:10.3892/IJO.2017.4207.

94. Li, Y.; Zhang, L.P.; Dai, F.; Yan, W.J.; Wang, H.B.; Tu, Z.S.; Zhou, B. Hexamethoxylated Monocarbonyl Analogues of Curcumin Cause G2/M Cell Cycle Arrest in NCI-H460 Cells via Michael Acceptor-Dependent Redox Intervention. *J Agric Food Chem* **2015**, *63*, 7731–7742, doi:10.1021/ACS.JAFC.5B02011/ASSET/IMAGES/MEDIUM/JF-2015-02011E_0003.GIF.

95. Yamakoshi, H.; Kanoh, N.; Kudo, C.; Sato, A.; Ueda, K.; Muroi, M.; Kon, S.; Satake, M.; Ohori, H.; Ishioka, C.; et al. KSRP/FUBP2 Is a Binding Protein of GO-Y086, a Cytotoxic Curcumin Analogue. *ACS Med Chem Lett* **2010**, *1*, 273–276, doi:10.1021/ML1000454/SUPPL_FILE/ML1000454_SI_001.PDF.

96. Liang, G.; Shao, L.; Wang, Y.; Zhao, C.; Chu, Y.; Xiao, J.; Zhao, Y.; Li, X.; Yang, S. Exploration and Synthesis of Curcumin Analogues with Improved Structural Stability Both in Vitro and in Vivo as Cytotoxic Agents. *Bioorg Med Chem* **2009**, *17*, 2623–2631, doi:10.1016/J.BMC.2008.10.044.

97. Zhang, J.; Feng, Z.; Wang, C.; Zhou, H.; Liu, W.; Kanchana, K.; Dai, X.; Zou, P.; Gu, J.; Cai, L.; et al. Curcumin Derivative WZ35 Efficiently Suppresses Colon Cancer Progression through Inducing ROS Production and ER Stress-Dependent Apoptosis. *Am J Cancer Res* **2017**, *7*, 275.

98. Alibeiki, F.; Jafari, N.; Karimi, M.; Hadi, &; Dogaheh, P. Potent Anti-Cancer Effects of Less Polar Curcumin Analogues on Gastric Adenocarcinoma and Esophageal Squamous Cell Carcinoma Cells OPEN., doi:10.1038/s41598-017-02666-4.

99. Huber, I.; Pandur, E.; Sipos, K.; Barna, L.; Harazin, A.; Deli, M.A.; Tyukodi, L.; Gulyás-Fekete, G.; Kulcsár, G.; Rozmer, Z. Novel Cyclic C5-Curcuminoids Penetrating the Blood-Brain Barrier: Design, Synthesis and Antiproliferative Activity against Astrocytoma and Neuroblastoma Cells. *European Journal of Pharmaceutical Sciences* **2022**, *173*, 106184, doi:10.1016/J.EJPS.2022.106184.

100. Qiu, C.; Hu, Y.; Wu, K.; Yang, K.; Wang, N.; Ma, Y.; Zhu, H.; Zhang, Y.; Zhou, Y.; Chen, C.; et al. Synthesis and Biological Evaluation of Allylated Mono-Carbonyl Analogues of Curcumin (MACs) as Anti-Cancer Agents for Cholangiocarcinoma. *Bioorg Med Chem Lett* **2016**, *26*, 5971–5976, doi:10.1016/J.BMCL.2016.10.080.

101. Wortelboer, H.M.; Usta, M.; van Zanden, J.J.; van Bladeren, P.J.; Rietjens, I.M.C.M.; Cnubben, N.H.P. Inhibition of Multidrug Resistance Proteins MRP1 and MRP2 by a Series of α,β-Unsaturated Carbonyl Compounds. *Biochem Pharmacol* **2005**, *69*, 1879–1890, doi:10.1016/J.BCP.2005.04.001.

102. Yamada, A.; Ishikawa, T.; Ota, I.; Kimura, M.; Shimizu, D.; Tanabe, M.; Chishima, T.; Sasaki, T.; Ichikawa, Y.; Morita, S.; et al. High Expression of ATP-Binding Cassette Transporter ABCC11 in Breast Tumors Is Associated with Aggressive Subtypes and Low Disease-Free Survival. *Breast Cancer Res Treat* **2013**, *137*, 773–782, doi:10.1007/S10549-012-2398-5/METRICS.

103. Overexpression of Wild-Type Breast Cancer Resistance Protein Mediates Methotrexate Resistance1 | Cancer Research | American Association for Cancer Research Available online: https://aacrjournals.org/cancerres/article/62/17/5035/509045/Overexpression-of-Wild-Type-Breast-Cancer (accessed on 28 February 2023).

104. Bakos, E.; Evers, R.; Calenda, G.; Tusnády, G.E.; Szakács, G.; Váradi, A.; Sarkadi, B. Characterization of the Amino-Terminal Regions in the Human Multidrug Resistance Protein (MRP1). *J Cell Sci* **2000**, *113*, 4451–4461, doi:10.1242/JCS.113.24.4451.

105. Britton, K.M.; Eyre, R.; Harvey, I.J.; Stemke-Hale, K.; Browell, D.; Lennard, T.W.J.; Meeson, A.P. Breast Cancer, Side Population Cells and ABCG2 Expression. *Cancer Lett* **2012**, *323*, 97–105, doi:10.1016/J.CANLET.2012.03.041.

106. Joensuu, H.; Gligorov, J. Adjuvant Treatments for Triple-Negative Breast Cancers. *Annals of Oncology* **2012**, *23*, vi40–vi45, doi:10.1093/ANNONC/MDS194.

107. Thakur, A.; Manohar, S.; Vélez Gerena, C.E.; Zayas, B.; Kumar, V.; Malhotra, S. v.; Rawat, D.S. Novel 3,5-Bis(Arylidiene)-4-Piperidone Based Monocarbonyl Analogs of Curcumin: Anticancer Activity Evaluation and Mode of Action Study. *Medchemcomm* **2014**, *5*, 576–586, doi:10.1039/C3MD00399J.

108. Fuchs, J.R.; Pandit, B.; Bhasin, D.; Etter, J.P.; Regan, N.; Abdelhamid, D.; Li, C.; Lin, J.; Li, P.K. Structure–Activity Relationship Studies of Curcumin Analogues. *Bioorg Med Chem Lett* **2009**, *19*, 2065–2069, doi:10.1016/J.BMCL.2009.01.104.

109. Kumar, S.; Mehndiratta, S.; Nepali, K.; Gupta, M.K.; Koul, S.; Sharma, P.R.; Saxena,

A.K.; Dhar, K.L. Novel Indole-Bearing Combretastatin Analogues as Tubulin Polymerization Inhibitors. *Organic and Medicinal Chemistry Letters 2013 3:1* **2013**, *3*, 1–13, doi:10.1186/2191-2858-3-3.

110. Singh, H.; Kumar, M.; Nepali, K.; Gupta, M.K.; Saxena, A.K.; Sharma, S.; Bedi, P.M.S. Triazole Tethered C5-Curcuminoid-Coumarin Based Molecular Hybrids as Novel Antitubulin Agents: Design, Synthesis, Biological Investigation and Docking Studies. *Eur J Med Chem* **2016**, *116*, 102–115, doi:10.1016/J.EJMECH.2016.03.050.

111. Badisa, R.B.; Darling-Reed, S.F.; Joseph, P.; Cooperwood, J.S.; Latinwo, L.M.; Goodman, C.B. Selective Cytotoxic Activities of Two Novel Synthetic Drugs on Human Breast Carcinoma MCF-7 Cells. *Anticancer Res* **2009**, *29*, 2993–2996.

112. Detection and Isolation of Bioactive Natural Products. *Bioactive Natural Products* **2007**, 25–90, doi:10.1201/9781420006889-6.

113. Liang, G.; Shao, L.; Wang, Y.; Zhao, C.; Chu, Y.; Xiao, J.; Zhao, Y.; Li, X.; Yang, S. Exploration and Synthesis of Curcumin Analogues with Improved Structural Stability Both in Vitro and in Vivo as Cytotoxic Agents. *Bioorg Med Chem* **2009**, *17*, 2623–2631, doi:10.1016/J.BMC.2008.10.044.

114. Li, Q.; Chen, J.; Luo, S.; Xu, J.; Huang, Q.; Liu, T. Synthesis and Assessment of the Antioxidant and Antitumor Properties of Asymmetric Curcumin Analogues. *Eur J Med Chem* **2015**, *93*, 461–469, doi:10.1016/J.EJMECH.2015.02.005.

115. Wu, J.; Zhang, Y.; Cai, Y.; Wang, J.; Weng, B.; Tang, Q.; Chen, X.; Pan, Z.; Liang, G.; Yang, S. Discovery and Evaluation of Piperid-4-One-Containing Mono-Carbonyl Analogs of Curcumin as Anti-Inflammatory Agents. *Bioorg Med Chem* **2013**, *21*, 3058–3065, doi:10.1016/J.BMC.2013.03.057.

116. Wang, Z.; Zou, P.; Li, C.; He, W.; Xiao, B.; Fang, Q.; Chen, W.; Zheng, S.; Zhao, Y.; Cai, Y.; et al. Synthesis and Biological Evaluation of Novel Semi-Conservative Monocarbonyl Analogs of Curcumin as Anti-Inflammatory Agents. *Medchemcomm* **2015**, *6*, 1328–1339, doi:10.1039/C5MD00114E.

117. Noureddin, S.A.; El-Shishtawy, R.M.; Al-Footy, K.O. Curcumin Analogues and Their Hybrid Molecules as Multifunctional Drugs. *Eur J Med Chem* **2019**, *182*, 111631, doi:10.1016/J.EJMECH.2019.111631.

118. Zhao, C.; Cai, Y.; He, X.; Li, J.; Zhang, L.; Wu, J.; Zhao, Y.; Yang, S.; Li, X.; Li, W.; et al. Synthesis and Anti-Inflammatory Evaluation of Novel Mono-Carbonyl Analogues of Curcumin in LPS-Stimulated RAW 264.7 Macrophages. *Eur J Med Chem* **2010**, *45*, 5773–5780, doi:10.1016/J.EJMECH.2010.09.037.

119. Liu, Z.; Tang, L.; Zou, P.; Zhang, Y.; Wang, Z.; Fang, Q.; Jiang, L.; Chen, G.; Xu, Z.; Zhang, H.; et al. Synthesis and Biological Evaluation of Allylated and Prenylated Mono-Carbonyl Analogs of Curcumin as Anti-Inflammatory Agents. *Eur J Med Chem* **2014**, *74*, 671–682, doi:10.1016/J.EJMECH.2013.10.061.

120. Oglah, M.K.; Fakri Mustafa, Y.; Kahtan Bashir, M.; Jasim, M.H.; Mustafa, Y.F. Curcumin and Its Derivatives: A Review of Their Biological Activities. *Systematic Review Pharmacy* **2020**, *11*, 2020, doi:10.5530/srp.2020.3.60.

121. Nagargoje, A.A.; Akolkar, S. V.; Siddiqui, M.M.; Subhedar, D.D.; Sangshetti, J.N.; Khedkar, V.M.; Shingate, B.B. Quinoline Based Monocarbonyl Curcumin Analogs as Potential Antifungal and Antioxidant Agents: Synthesis, Bioevaluation and Molecular Docking Study. *Chem Biodivers* **2020**, *17*, e1900624, doi:10.1002/CBDV.201900624.

122. Nagargoje, A.A.; Akolkar, S. v.; Siddiqui, M.M.; Bagade, A. v.; Kodam, K.M.; Sangshetti, J.N.; Damale, M.G.; Shingate, B.B. Synthesis and Evaluation of Pyrazole-Incorporated Monocarbonyl Curcumin Analogues as Antiproliferative and Antioxidant Agents. *Journal of the Chinese Chemical Society* **2019**, *66*, 1658–1665, doi:10.1002/JCCS.201800405.

123. Bukhari, S.N.A.; Jantan, I.; Kumolosasi, E.; Jasamai, M. Immunomodulatory Effects of Diarylpentanoid Analogues of Curcumin. *Medicinal Chemistry Research* **2015**, *24*, 3405–3411, doi:10.1007/S00044-015-1387-8/METRICS.

124. Zafar, R.; Ullah, H.; Zahoor, M.; Sadiq, A. Isolation of Bioactive Compounds from Bergenia Ciliata (Haw.) Sternb Rhizome and Their Antioxidant and Anticholinesterase

Activities. *BMC Complement Altern Med* **2019**, *19*, 1–13, doi:10.1186/S12906-019-2679-1/TABLES/6.

125. Bhullar, K.S.; Jha, A.; Youssef, D.; Rupasinghe, H.P.V. Curcumin and Its Carbocyclic Analogs: Structure-Activity in Relation to Antioxidant and Selected Biological Properties. *Molecules 2013, Vol. 18, Pages 5389-5404* **2013**, *18*, 5389–5404, doi:10.3390/MOLECULES18055389.

126. 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.; et al. Biological Activities of Curcumin and Its Analogues (Congeners) Made by Man and Mother Nature. *Biochem Pharmacol* **2008**, *76*, 1590–1611, doi:10.1016/J.BCP.2008.08.008.

127. Shang, Y.J.; Jin, X.L.; Shang, X.L.; Tang, J.J.; Liu, G.Y.; Dai, F.; Qian, Y.P.; Fan, G.J.; Liu, Q.; Zhou, B. Antioxidant Capacity of Curcumin-Directed Analogues: Structure–Activity Relationship and Influence of Microenvironment. *Food Chem* **2010**, *119*, 1435–1442, doi:10.1016/J.FOODCHEM.2009.09.024.

128. Manohar, S.; Thakur, A.; Bhatia, R.; Walia, S.; Ponnan, P.; Rawat, D.S. Antibacterial and Antioxidant Activity Evaluation of Novel Symmetrical and Unsymmetrical C5-Curcuminoids. *IJC-B Vol.54B(10) [October 2015]* **2015**.

129. Ao, G.Z.; Chu, X.J.; Ji, Y.Y.; Wang, J.W. Antioxidant Properties and PC12 Cell Protective Effects of a Novel Curcumin Analogue (2E,6E)-2,6-Bis(3,5-Dimethoxybenzylidene)Cyclohexanone (MCH). *International Journal of Molecular Sciences 2014, Vol. 15, Pages 3970-3988* **2014**, *15*, 3970–3988, doi:10.3390/IJMS15033970.

130. Shetty, D.; Kim, Y.J.; Shim, H.; Snyder, J.P. Eliminating the Heart from the Curcumin Molecule: Monocarbonyl Curcumin Mimics (MACs). *Molecules 2015, Vol. 20, Pages 249-292* **2014**, *20*, 249–292, doi:10.3390/MOLECULES20010249.

131. Dinkova-Kostova, A.T.; Abeygunawardana, C.; Talalay, P. Chemoprotective Properties of Phenylpropenoids, Bis(Benzylidene)Cycloalkanones, and Related Michael Reaction Acceptors: Correlation of Potencies as Phase 2 Enzyme Inducers and Radical Scavengers†. *J Med Chem* **1998**, *41*, 5287–5296, doi:10.1021/JM980424S.

132. Dinkova-Kostova, A.T.; Talalay, P. Relation of Structure of Curcumin Analogs to Their Potencies as Inducers of Phase 2 Detoxification Enzymes. *Carcinogenesis* **1999**, *20*, 911–914, doi:10.1093/CARCIN/20.5.911.

133. Zhao, C.; Liu, Z.; Liang, G. Promising Curcumin-Based Drug Design: Mono-Carbonyl Analogues of Curcumin (MACs). *Curr Pharm Des* **2013**, *19*, 2114–2135, doi:10.2174/138161213805289282.

134. Carapina da Silva, C.; Pacheco, B.S.; das Neves, R.N.; Dié Alves, M.S.; Sena-Lopes, Â.; Moura, S.; Borsuk, S.; de Pereira, C.M.P. Antiparasitic Activity of Synthetic Curcumin Monocarbonyl Analogues against Trichomonas Vaginalis. *Biomedicine & Pharmacotherapy* **2019**, *111*, 367–377, doi:10.1016/J.BIOPHA.2018.12.058.

135. Gagandeep; Kumar, P.; Kandi, S.K.; Mukhopadhyay, K.; Rawat, D.S. Synthesis of Novel Monocarbonyl Curcuminoids, Evaluation of Their Efficacy against MRSA, Including Ex Vivo Infection Model and Their Mechanistic Studies. *Eur J Med Chem* **2020**, *195*, 112276, doi:10.1016/J.EJMECH.2020.112276.

136.Kumar, P.; Kandi, S.K.; Manohar, S.; Mukhopadhyay, K.; Rawat, D.S. Monocarbonyl Curcuminoids with Improved Stability as Antibacterial Agents against Staphylococcus Aureus and Their Mechanistic Studies. *ACS Omega* **2019**, *4*, 675–687, doi:10.1021/ACSOMEGA.8B02625/ASSET/IMAGES/MEDIUM/AO-2018-02625Y_M002.GIF.

137. Kobayashi, M.; Kinjo, T.; Koseki, Y.; Bourne, C.R.; Barrow, W.W.; Aoki, S. Identification of Novel Potential Antibiotics against Staphylococcus Using Structure-Based Drug Screening Targeting Dihydrofolate Reductase. *J Chem Inf Model* **2014**, *54*, 1242–1253, doi:10.1021/CI400686D/SUPPL_FILE/CI400686D_SI_001.PDF.

138. Singh, A.; Singh, J.V.; Rana, A.; Bhagat, K.; Gulati, H.K.; Kumar, R.; Salwan, R.; Bhagat,

K.; Kaur, G.; Singh, N.; et al. Monocarbonyl Curcumin Based Molecular Hybrids as Potent Antibacterial Agents. *ACS Omega* **2019**, *4*, S1–S50, doi:10.1021/ACSOMEGA.9B01109/SUPPL_FILE/AO9B01109_SI_001.PDF.

139. Barry, A.; Hoeprich, P.; Saubolle, M. The Antimicrobic Susceptibility Test : Principles and Practices. *Ann Intern Med* **1976**, *87*, 388, doi:10.7326/0003-4819-87-3-388_1.

140. Synthesis and Biological Evaluation of Some Curcumin Analogs and Their Derivatives Available online: https://www.researchgate.net/publication/297772385_Synthesis_and_biological_evaluation_of_some_curcumin_analogs_and_their_derivatives (accessed on 8 March 2023).

141. Liang, G.; Yang, S.; Jiang, L.; Zhao, Y.; Shao, L.; Xiao, J.; Ye, F.; Li, Y.; Li, X. Synthesis and Anti-Bacterial Properties of Mono-Carbonyl Analogues of Curcumin. *Chem Pharm Bull (Tokyo)* **2008**, *56*, 162–167, doi:10.1248/CPB.56.162.

142. Baldwin, P.R.; Reeves, A.Z.; Powell, K.R.; Napier, R.J.; Swimm, A.I.; Sun, A.; Giesler, K.; Bommarius, B.; Shinnick, T.M.; Snyder, J.P.; et al. Monocarbonyl Analogs of Curcumin Inhibit Growth of Antibiotic Sensitive and Resistant Strains of Mycobacterium Tuberculosis. *Eur J Med Chem* **2015**, *92*, 693–699, doi:10.1016/J.EJMECH.2015.01.020.

143. Gül Şeker, M.; Akbal, T.; Atilla, D.; Avşar, N.; İbişoğlu, H. Synthesis and Antimicrobial Effects of Cyclotriphosphazenes Containing Monocarbonyl Curcumin Analogs. **2018**, doi:10.12991/jrp.2018.95.

144. Koch, A.; Cox, H.; Mizrahi, V. Drug-Resistant Tuberculosis: Challenges and Opportunities for Diagnosis and Treatment. *Curr Opin Pharmacol* **2018**, *42*, 7–15, doi:10.1016/J.COPH.2018.05.013.

145. Orme, I. Search for New Drugs for Treatment of Tuberculosis. *Antimicrob Agents Chemother* **2001**, *45*, 1943, doi:10.1128/AAC.45.7.1943-1946.2001.

146. Polaquini, C.R.; Marques, B.C.; Ayusso, G.M.; Morão, L.G.; Sardi, J.C.O.; Campos, D.L.; Silva, I.C.; Cavalca, L.B.; Scheffers, D.J.; Rosalen, P.L.; et al. Antibacterial Activity of a New Monocarbonyl Analog of Curcumin MAC 4 Is Associated with Divisome Disruption. *Bioorg Chem* **2021**, *109*, 104668, doi:10.1016/J.BIOORG.2021.104668.

147. Subhedar, D.D.; Shaikh, M.H.; Nawale, L.; Sarkar, D.; Khedkar, V.M.; Shingate, B.B. Quinolidene Based Monocarbonyl Curcumin Analogues as Promising Antimycobacterial Agents: Synthesis and Molecular Docking Study. *Bioorg Med Chem Lett* **2017**, *27*, 922–928, doi:10.1016/j.bmcl.2017.01.004.

148. Ud Din, Z.; Serrano, N.F.G.; Ademi, K.; Sousa, C.P.; Deflon, V.M.; Maia, P.I. da S.; Rodrigues-Filho, E. Crystal Structures, in-Silico Study and Anti-Microbial Potential of Synthetic Monocarbonyl Curcuminoids. *J Mol Struct* **2017**, *1144*, 529–534, doi:10.1016/J.MOLSTRUC.2017.05.061.

149. Chen, S.Y.; Chen, Y.; Li, Y.P.; Chen, S.H.; Tan, J.H.; Ou, T.M.; Gu, L.Q.; Huang, Z.S. Design, Synthesis, and Biological Evaluation of Curcumin Analogues as Multifunctional Agents for the Treatment of Alzheimer's Disease. *Bioorg Med Chem* **2011**, *19*, 5596–5604, doi:10.1016/J.BMC.2011.07.033.

150. Oglah, M.K.; Fakri Mustafa, Y.; Kahtan Bashir, M.; Jasim, M.H.; Mustafa, Y.F. Curcumin and Its Derivatives: A Review of Their Biological Activities. *Systematic Review Pharmacy* **2020**, *11*, 2020, doi:10.5530/srp.2020.3.60.

151. Gan, C.; Hu, J.; Nan, D.D.; Wang, S.; Li, H. Synthesis and Biological Evaluation of Curcumin Analogs as β-Amyloid Imaging Agents. *https://doi.org/10.4155/fmc-2017-0079* **2017**, *9*, 1587–1596, doi:10.4155/FMC-2017-0079.

152. Manohar, S.; Khan, S.I.; Kandi, S.K.; Raj, K.; Sun, G.; Yang, X.; Calderon Molina, A.D.; Ni, N.; Wang, B.; Rawat, D.S. Synthesis, Antimalarial Activity and Cytotoxic Potential of New Monocarbonyl Analogues of Curcumin. *Bioorg Med Chem Lett* **2013**, *23*, 112–116, doi:10.1016/J.BMCL.2012.11.004.

153. Minassi, A.; Sánchez-Duffhues, G.; Collado, J.A.; Muñoz, E.; Appendino, G. Dissecting the Pharmacophore of Curcumin. Which Structural Element Is Critical for Which Action? *J Nat Prod* **2013**, *76*, 1105–1112, doi:10.1021/NP400148E/SUPPL_FILE/NP400148E_SI_001.PDF.

154. Ramya, P.V.S.; Angapelly, S.; Angeli, A.; Digwal, C.S.; Arifuddin, M.; Babu, B.N.; Supuran, C.T.; Kamal, A. Discovery of Curcumin Inspired Sulfonamide Derivatives as a New Class of Carbonic Anhydrase Isoforms I, II, IX, and XII Inhibitors. *https://doi.org/10.1080/14756366.2017.1380638* **2017**, *32*, 1274–1281, doi:10.1080/14756366.2017.1380638.