Curcumin and its derivatives as chemotherapeutic agents

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ABSTRACT

A popular Indian spice, turmeric (Curcuma longa) has been used for centuries in herbal medicines for the treatment of a variety of disorders such as rheumatism, diabetic ulcers, anorexia, cough and sinusitis. Curcumin (diferuloylmethane) is the main active constituent present in turmeric, responsible for its yellow color. It has been shown to possess significant anti-inflammatory, anti-oxidant, anti-carcinogenic, anti-mutagenic, anticoagulant and anti-infective effects. This review recapitulates and discusses recently published papers on the key chemotherapeutic potential of curcumin and its analogues. The promising activity revealed by these compounds chains their use and places them ahead as a potential drug candidate for the future studies. The review mainly emphasizes the highlighted studies, which provides the evidence of the ability of curcumin and its analogues to show significant anti-cancer and anti-microbial properties, thus encouraging those involved in the field of developing effective chemotherapeutic agents.

Keywords: Chemotherapeutic, anti-cancer, cytotoxicity, anti-microbial

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INTRODUCTION

From ancient times, plants have been an excellent source of therapeutic as well as chemotherapeutic agents such as *Garcinia mangostana* [1] and many more [2]. Curcumin [1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] is one of a natural polyphenolic yellow colored compound isolated from the rhizome of Curcuma longa Linn (turmeric) (family Zingiberaceae), which has been used for centuries as a dietary pigment, spice, and traditional medicine in India and China [3-5]. Diferuloylmethane known as curcuminoid is major constituent of curcumin (77 wt%); the other two curcuminoids are demethoxycurcumin (17 wt%) and bis-demethoxycurcumin (3 wt%) as shown in Figure 1 [6]. It is traditional drug used to treat various disorders such as anorexia, biliary complaints, cough, hepatic diseases, and sinusitis [7].

Curcumin is a hydrophobic polyphenol with two carbonyl groups and several studies have revealed extremely low water-solubility, low stability, rapid metabolism and poor absorption of this molecule due to the presence of two carbonyl atoms that severely reduces its bioavailability and consequently decreasing the health benefits related to this vital compound [8-10]. Hence to overcome this problem several monocarbonyl derivatives and drug delivery systems have also been discovered [11-13]. It is considered to be a safe phytochemical owing non-toxic, non-genotoxic, and non-teratogenic properties even at high doses [14].

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	R	R'
Curcumin	OCH$_3$	OCH$_3$
Demethoxy-curcumin	H	OCH$_3$
Bis-demethoxy-curcumin	H	H
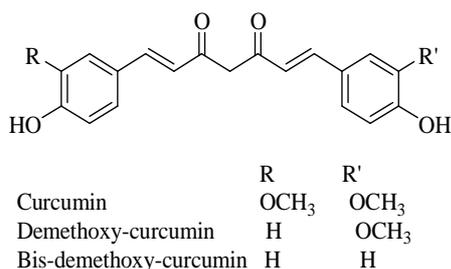
Figure 1 : Curcuminoids, the constituents of curcumin

Curcumin and its derivatives owns a broad spectrum of therapeutic activities viz., antibacterial [15], antifungal [16], antiviral [17], anti-HIV [18], anti-inflammatory [19], anti-Parkinson's [20], anti-Alzheimer's [21], anti-angiogenesis [22], free radical scavenging activity [23], antirheumatic [24], antimalarial [25], anticancer [26], antiprotozoan [27], antimutagenic [28], wound treatment [29], hepatoprotective activity [30], anti-leishmanial activity [31] and amyloid heart disease [32]. Recent reports have revealed that curcumin helps in decreasing total cholesterol and LDL cholesterol level in serum and increases the beneficial HDL cholesterol level [33].

It can been noticed that curcumin is entirely an active moiety possessing a large number of biological activities but the most widely studied and effective biological properties are discussed here in. Hence the chemotherapeutical potential of curcumin is demonstrated. The most common approaches in drug discovery with improved therapeutic effect is chemical modification of bioactive components and consequently methods that successfully minimize their side effects are the focus of much attention [34,35]. Thus there is a salient need of an article that that would describe the vital potential of curcumin analogues and, thus, the present article is a collection of various research works that supports the use of differently substituted curcumin derived molecules as potent anticancer and antimicrobial agents. This article would surely help the researchers aiming at the development/study of curcumin analogues as either antimicrobial or anticancer compounds.

1. Chemotherapeutic potential of various curcuminoids
2-1. Curcumin and its analogues acting as Anti-cancer :
Junko.I.*et al* synthesized fifty-eight curcumin analogues and evaluated for in vitro cytotoxicity against a panel of human tumor cell lines. The most potent analogue **1** (Figure 2) was evaluated against several cell lines, including HOS (bone cancer) and 1A9 (breast cancer), showed ED$_{50}$ values of 0.97 and <0.63 µg/mL, respectively [36].

Brian.K.A.*et al* synthesized symmetrical α,β-unsaturated and saturated ketones and screened for anti-cancer and anti-angiogenesis activities. The compounds **2** and **3** (Figure 2) exhibited a high degree of cytotoxicity in the NCI in vitro anti-cancer cell line screen. Analogues that were effective in the anti-cancer screens were also effective in in-vitro anti-angiogenesis assays [37].

Sabari.D.*et al* synthesized a new semicarbazone derivative of curcumin **4** (CRSC) (Figure 2) and examined for its antioxidant, anti-proliferative, and anti-radical activity and compared with those of curcumin (CR). The antioxidant activity was tested by their ability to inhibit radiation induced lipid peroxidation in rat liver microsomes. The anti-proliferative activity was tested by studying the in-vitro activity of CRSC against estrogen dependant breast cancer cell line MCF-7. The results suggested that the compounds are good candidates for the above three disorders mentioned [38].

Somepalli.V.*et al* synthesized a series of curcumin analogues. The antioxidant activity of these analogs was determined by superoxide free radical nitroblue tetrazolium and DPPH free radical scavenging methods and the polyhydroxycurcuminoids **5** (Figure 2) displayed excellent antioxidant activity. These analogs showed cytotoxicity to lymphocytes and promising tumor-reducing activity on Dalton's lymphoma ascites tumor cells [39].

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1

ED$_{50}$
HOS (bone cancer) = 0.97 µg/mL
1A9 (breast cancer) = <0.63 µg/mL

2
GI$_{50}$ = 1.2 µg/mL

3
GI$_{50}$ = 0.7 µg/mL

4   **5**
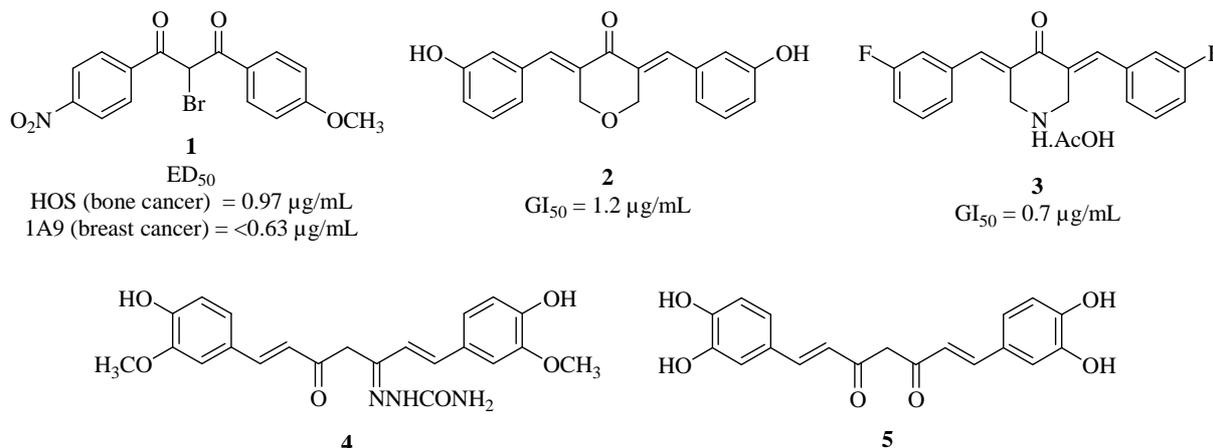
Figure 2. Curcumin Derivatives showing anti-cancer as well as anti-oxidant potential

Li.L.*et al* designed and synthesized 4-fluoro-4-ethoxycarbonylethyl curcumin and 4-ethoxycarbonylethylenyl curcumin. The two target compounds and their synthetic intermediates were evaluated for their inhibitory activity against androgen receptor transcription in LNCaP and PC-3 prostate cancer cell lines. One of the derivative **6** (Figure 3) was found to be the most potent anti-AR agent and is considered to be a promising drug candidate for the treatment of prostate cancer [40].

Ajit.P.Z.*et al* synthesized curcumin analogues using Knoevenagel condensation. Copper(II) conjugates of all synthesized ligands were prepared and structurally characterized as well as evaluated for their potential of inhibiting TNF-induced NF-κB activation and proliferation in human leukemic KBM-5 cells. A single compound **7** (Figure 3) showed more potency than curcumin [41].

6   **7**
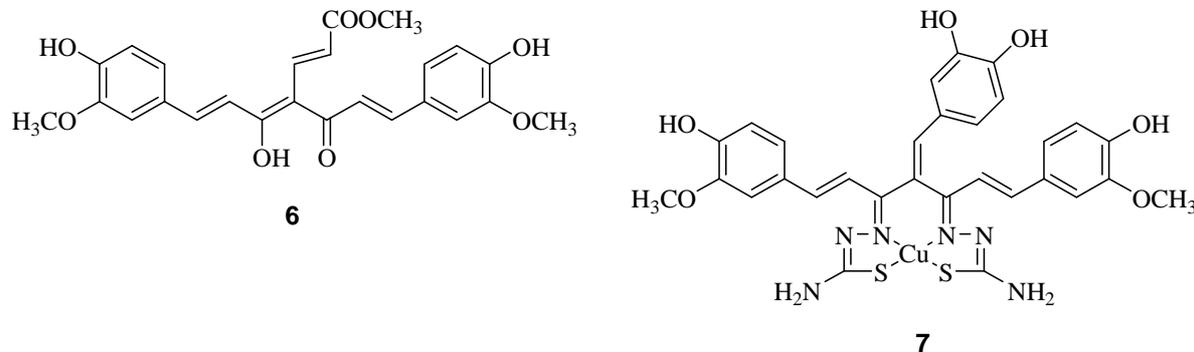
Figure 3. Curcumin derivatives utilized for prostate cancer and leukemia

Li.L.*et al* designed and synthesized over 40 new analogues classified into four series: monophenyl analogues, Series A (**8,9**) shown in Table 1, heterocycle containing analogues, Series B (**10,11**) shown in Figure 4, analogues bearing various substituents on the phenyl rings, Series C (**12,13**) shown in Table 2, and analogues with various linkers Series D (**14,15**) as shown in Table 3. The new compounds were tested for cytotoxicity against two human prostate cancer cell lines, androgen-dependent LNCaP and androgen-independent PC-3. Anti-androgenic activity was also evaluated in LNCaP cells and PC-3 cells transfected with wild-type androgen receptor. The compounds possessed potent cytotoxicity against both LNCaP and PC-3 cells, some were potent against LNCaP, and one solely against PC-3 as shown in Tables 1,2 and 3 [42].

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Table 1. Cytotoxicity of curcumin analogues (Series A) against LNCaP and PC-3 Human Prostate Cancer Cells
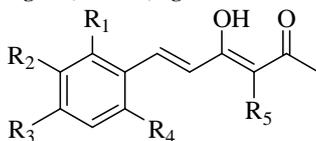
Compounds	R1	R2	R3	R4	R5	Cytotoxicity PC-3	IC$_{50}$ (µM) LNCap
8	H	OH	OMe	H	H	6.1	5.3
9	OMe	OMe	OMe	H	H	7.8	5.8

10
Cytotoxicity LNCaP = 7.3
IC$_{50}$ (µM) = 9.0

11
Cytotoxicity LNCaP = 6.3
IC$_{50}$ (µM) = 7.7
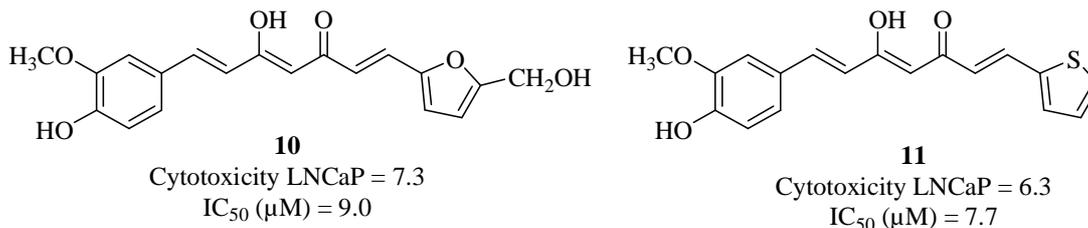
Figure 4. Curcumin analogues of Series B

Table 2. Cytotoxicity of curcumin analogues (Series C) against LNCaP and PC-3 Human Prostate Cancer Cells
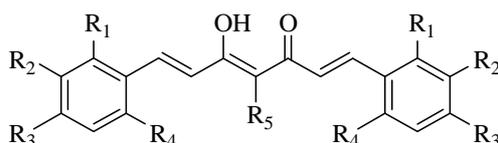
Compounds	R1	R2	R3	R4	R5	PC-3 IC$_{50}$ (µM)	LNCaP IC$_{50}$ (µM)
12	H	OMe	OMe	OMe	H	2.4	2.9
13	OMe	OMe	OMe	H	H	8.1	4.8

Table 3. Cytotoxicity of curcumin analogues (Series D) against LNCaP and PC-3 Human Prostate Cancer Cells
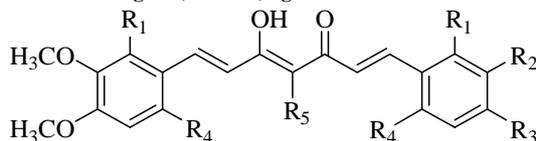
Compounds	R1	R2	R3	R4	R5	PC-3 IC$_{50}$ (µM)	LNCaP IC$_{50}$ (µM)
14	H	OH	OMe	H	H	5.5	4.8
15	H	OMe	OH	H	H	6	3.3

Dani.Y.*et al* synthesized a series of novel cyclic analogues of curcumin and analyzed for in vitro cytostatic activity. A number of these analogues were found to have significant anticancer activity against representative murine and human cancer cell lines during in vitro bioassays. Compound **16** (Figure 5) was found to be most potent [43].

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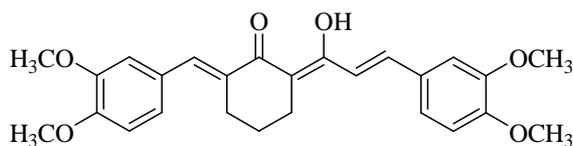
16
IC$_{50}$ (μM)
L1210 = 1.4 ± 0.3
Molt4C/8 = 1.2 ± 0.2
CEM = 1.3 ± 0.3

Figure 5. Cyclic curcumin analogue

Chandru.H.*et al* synthesized novel dienone cyclopropoxy curcumin analogs. Anti-angiogenic studies of the compounds demonstrated significant reduction of microvessel density (MVD) in the peritoneum wall sections of mice and induced avascular zone in CAM model. The study demonstrated that the tumor growth inhibitory effects of synthetic dienone cyclopropoxy curcumin analogue **17** (Figure 6) could be further mediated by promoting apoptosis and inhibiting tumor angiogenesis [44].

Ahmad.S.*et al* developed conjugates of curcumin to two differently sized poly(ethylene glycol) molecules in an attempt to overcome the low aqueous solubility of this natural product with cytotoxic activity against some human cancer cell lines. The soluble conjugate **18** (Figure 6) exhibited enhanced cytotoxicity as compared to that of the parent drug [45].

Daniele.S.*et al* synthesized a series of curcumin analogs. The cell growth inhibitory and apoptosis inducing effects of the new analogs were evaluated by in vitro assays in the hepatocellular carcinoma HA22T/VGH cells, as well as in the MCF-7 breast cancer cell line and in its multidrug resistant (MDR) variant MCF-7R. Increased antitumor activity on all cell lines was found with the isoxazole analog and especially with the benzyl oxime derivative **19** (Figure 6) [46].

Xu.Q.*et al* synthesized a series of curcumin derivatives. The inhibitory activities on thioredoxin reductase (TrxR) of all analogues were evaluated by DTNB assay in vitro. It was found that most of the analogues can inhibit TrxR in the low micromolar range; Structure-activity relationship analysis reveals that analogues with furan moiety have excellent inhibitory effect on TrxR in an irreversible manner. Compound **20** (Figure 6) was found to be the most potent furan ring containing curcumin analogue [47].

Shiv.K.D.*et al* synthesized and assessed the antimicrobial and anticancer (antiproliferative) activities of the monoesters of curcumin. The studies suggested that diester derivative of curcumin **21** (Figure 6) was found to be one of the most active than curcumin itself due to their increased solubility, slow metabolism and better cellular uptake [48].

Erika.F.*et al* synthesized curcumin derivatives in order to improve chemical properties of curcumin. The binding of glucose to curcumin reduces the cytotoxicity of the derivatives towards cisplatin (cDDP)-sensitive and –resistant human ovarian carcinoma cell lines, the compounds displayed a good selectivity since they are much less toxic against non-tumourigenic, Vero cells. The results showed an improvement of cDDP efficacy with higher selectivity towards cancer cells than non-cancer cells with the most potent compound **22** (Figure 6) [49].

Guang.L.*et al* developed a series of mono-carbonyl analogues of curcumin. The cytotoxic activities of mono-carbonyl analogues were evaluated in seven different tumor cell lines by MTT assay. The results suggest that the five-carbon linker-containing analogues of curcumin may be favorable for the curcumin based drug development both pharmacokinetically and pharmacologically such as compound **23** (Figure 6) [50].

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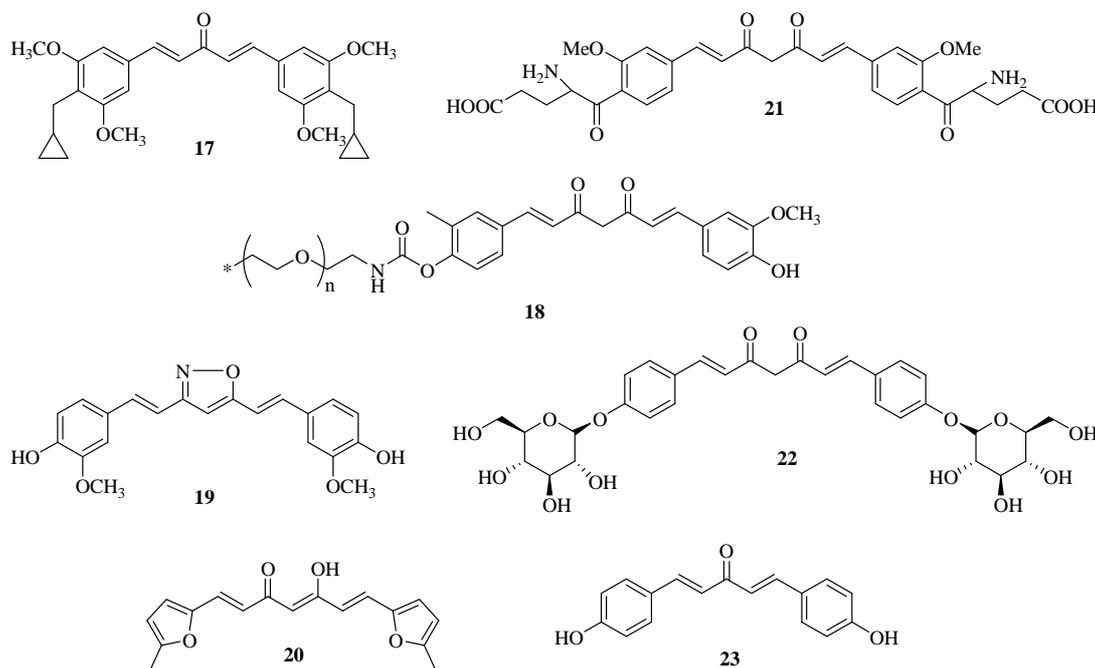
Figure 6. Curcumin derivatives acting as anti-cancer by various mechanisms

Alessandra.V.*et al* synthesized a new ionic Pd(II) complex **24** (Figure 7), [(bipy)Pd(Pcurc)][CF3SO3], with the metal center coordinated to two different chelating ligands, the pure curcumin (Pcurc) and the 4,4′-dinonyl-2,2′-bipyridine (bipy). The Pd(II) complex induces both cell growth inhibition and apoptosis of human prostate cancer cells, (LnCaP, PC3, and DU145) through the production of ROS and JNK phosphorylation associated with GSTp1 down regulation [51].
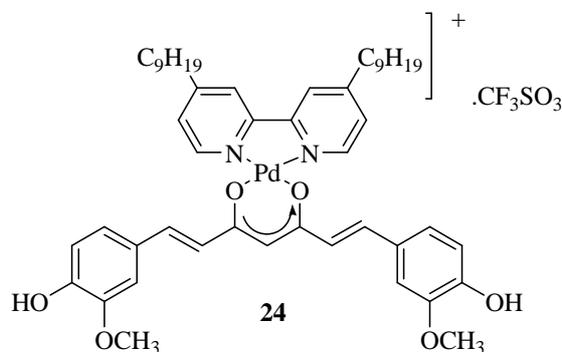
Figure 7. Pd(II) complex

Babasaheb.Y.*et al* designed and synthesized a series of 18 heterocyclic cyclohexanone analogues of curcumin and screened for their activity in both adherent and non-adherent cancer cell models. Cytotoxicity towards MBA-MB-231 breast cancer cells, as well as ability to inhibit NF-κB transactivation in non-adherent K562 leukemia cells was investigated. The compounds showed potent cytotoxicity towards MBA-MB-231, MDA-MB-468, and SkBr3 cell lines with EC_{50} values below 1 μM and inhibition of NF-κB activation below 7.5 μM. The lead drug candidate **25** (Figure 8) was also able to cause 43% of MDA-MB-231 cells to undergo apoptosis after 18 h [52].

Qin.Z.*et al.* synthesized a series of curcumin analogues with different substituents at the 4-position of the phenyl group and screened for in-vitro cytotoxicity against a panel of human cancer cell lines. The analogues provided good feedback as anti-cancer agents. The compounds **26**, **27** (Figure 8) exhibited selective and potent cytotoxic activity against human epidermoid carcinoma cell line A-431 and human glioblastoma cell line U-251, implying their specific potential in the chemoprevention and chemotherapy of skin cancer and glioma [53].

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Katsori.A.M.*et al* synthesized a series of novel curcumin analogues and tested in-vitro/in-vivo as potential multi-target agents. Their anti-proliferative and anti-inflammatory activities were studied. The derivatives were assessed for their anti-proliferative activity using three different human cancer cell lines. All the compounds exhibited significant growth inhibitory activity as compared to curcumin, against all three cancer cell lines but compound **28** (Figure 8) was the most potent with GI_{50} of 0.8 µM and 0.9 µM against MCF-7 and SF-268 respectively [54].
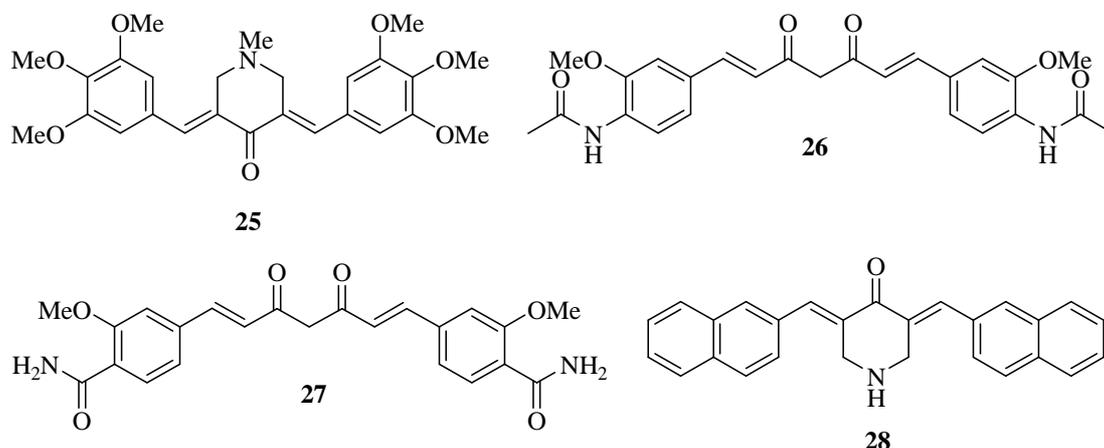
Figure 8. Curcumin derivatives as multi-target anti-cancer agents

Michael.W.A.*et al* prepared electron-rich pyrazole and isoxazole analogues and evaluated against two breast cancer cell lines, which resulted in the identification of several compounds that exhibit low micromolar to mid nanomolar anti-proliferative activity. The analogues were tested against MCF-7 (ER+) and SKBr-3 (ER-, HER2 overexpressing) breast cancer cell lines. The results indicate that compounds **29**, **30**, **31**, and **32** (Figure 9) represent the most potent analogues [55].

29
IC_{50} (µM)
MCF-7 = 1.07 ± 0.05
SKBR3 = 0.955 ± 0.145

30
IC_{50} (µM)
MCF-7 = 1.09 ± 0.03
SKBR3 = 1.02 ± 0.05

31
IC_{50} (µM)
MCF-7 = 0.512 ± 0.004
SKBR3 = 0.564 ± 0.020

32
IC_{50} (µM)
MCF-7 = 1.28 ± 0.14
SKBR3 = 1.96 ± 0.65
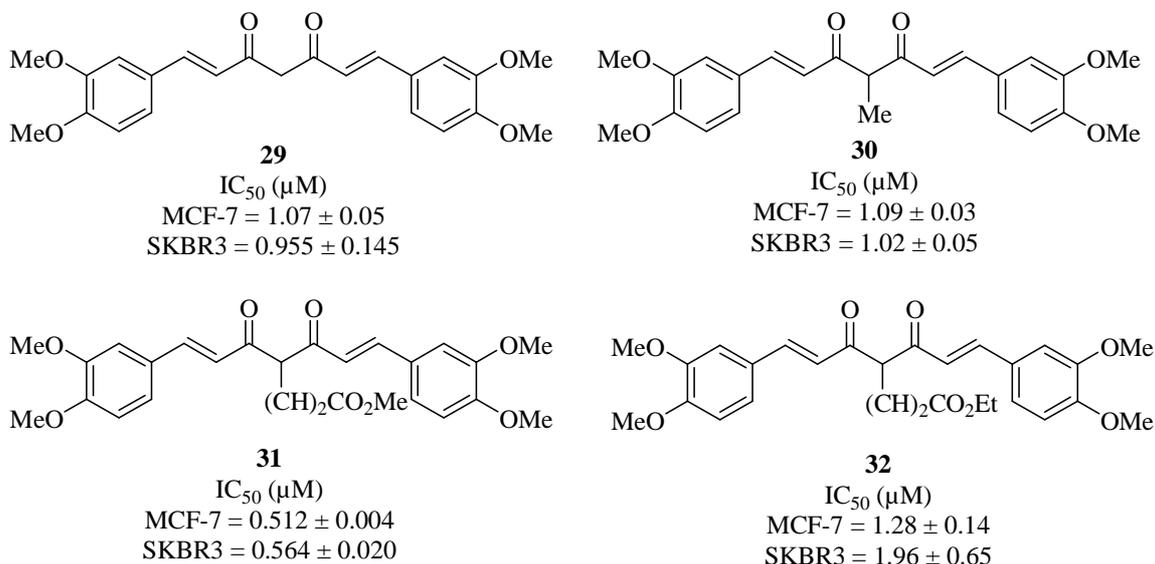
Figure 9. Pyrazole and isoxazole containing curcumin analogues

Minggui.Y.*et al* discovered a series of curcumin derivatives with high inhibitory activity against human GLO I (Glyoxalase I). Satisfactory agreement between experiment and theory suggested that comparative molecular similarity index analysis (CoMSIA) modeling exhibit much better correlation and predictive power. Inhibition constant (Ki) values of compounds **33, 34, 35, 36, 37** (Figure 10) to GLO I were found to be 4.600 µM, 2.600 µM, 3.200 µM, 3.600 µM and 3.600 µM, respectively [56].

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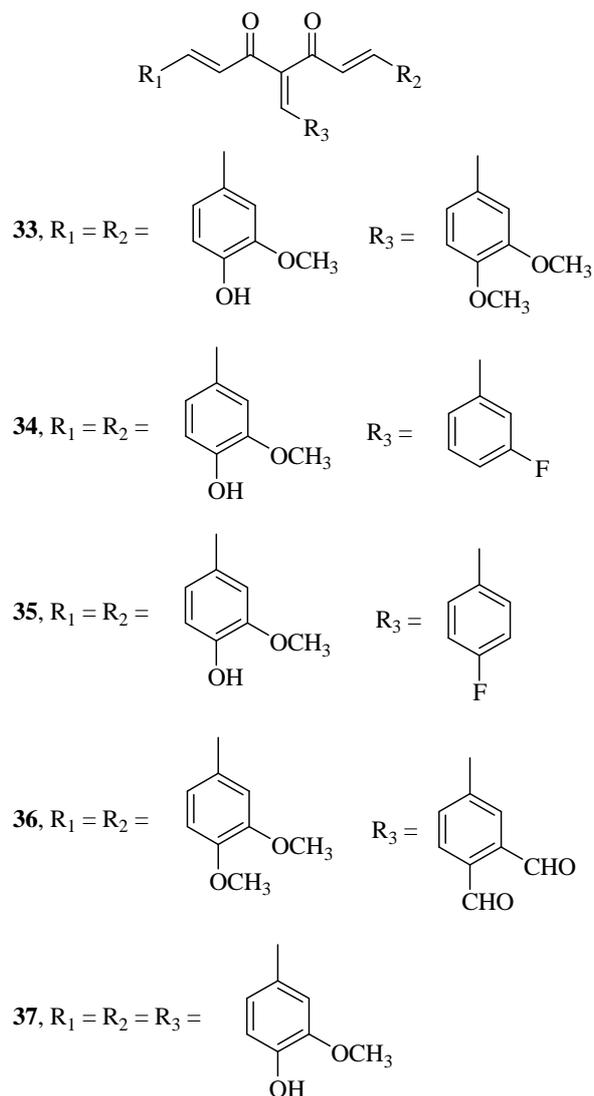
Figure 10. Curcuminoids active against Glyoxalase I

Erika.F.*et al* founded new curcumin analogues such as **38** (Figure 11) (ester and acid series) with the aim to improve the chemical stability in physiological conditions and potential anticancer activity. Cytotoxicity against different tumorigenic cell lines (human ovarian carcinoma cells – A2780, C13*, and A2780/CP, and human colon carcinoma cells HCT116 and LoVo) was tested. Most of ester derivatives show IC_{50} values lower than curcumin and exhibit selectivity against colon carcinoma cells [57].

Francesco.C.*et al* assessed the in vitro anti-proliferative activity of Ruthenium−Arene complex **39** (Figure 11) of curcumin on five tumor cell lines shows preference for the colon−rectal tumor HCT116, IC_{50} = 13.98 μM, followed by breast MCF7 (19.58 μM) and ovarian A2780 (23.38 μM) cell lines; human glioblastoma U-87 and lung carcinoma A549 were less sensitive [58].

Ho.B.W.*et al* synthesized a novel curcumin mimic library possessing variously substituted benzimidazole groups. The MTT assay of the cancer cells MCF-7, SH-SY5Y, HEP-G2, and H460 showed compound **40** with IC_{50} of 1.0 and 1.9 μM has a strong inhibitory effect on the growth of SH-SY5Y and Hep-G2 cells, respectively, and the other compound **41** with IC_{50} of 1.9 μM has a strong inhibitory effect on the growth of MCF-7 cancer cells (Figure 11) [59].

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Xingchuan.W.*et al* synthesized sixty one curcumin related compounds such as **42** (Figure 11) and evaluated for their anticancer activity toward cultured prostate cancer PC-3 cells, pancreas cancer Panc-1 cells and colon cancer HT-29 cells. Inhibitory effects of these compounds on the growth of PC-3, Panc-1 and HT-29 cells were determined by the MTT assay. The Compounds exhibited exceptionally potent inhibitory effects on the growth of cultured PC-3, Panc-1 and HT-29 cells. The IC_{50} for these compounds was lower than 1 µM in all three cell lines [60].

Yinglin.Z.*et al* designed and synthesized a series of new 4-arylidene curcumin analogues (4-arylidene-1,7-bisarylhepta-1,6-diene-3,5-diones) and found to be potent anti-proliferative agents against a panel of cancer cell lines at submicromolar to low micromolar concentrations by SRB assay. The compound **43** (Figure 11) showed IC_{50} of 0.13 ± 0.01, 0.28 ± 0.01, 0.43 ± 0.03, 0.48 ± 0.02, 0.20 ± 0.06 µM against a panel of cell lines viz A549, CNE2, SW480, MCF-7, HepG2 respectively and was found to be most potent [61].

Ban.F.R.*et al* synthesized a series of resveratrol derivatives possessing curcumin moiety and evaluated for their anti-proliferative activity against three cancer cell lines including murine melanoma B16-F10, human hepatoma HepG2 and human lung carcinoma A549. One compound **44** (Figure 11) displayed the most potent in vitro anti-proliferative activity against B16-F10 with IC_{50} value of 0.71 µg/mL and also exhibited good tubulin polymerization inhibitory activity with IC_{50} value of 1.45 µg/mL [62].

Qian.S.*et al* designed and synthesized 15 new curcumin analogues and evaluated for cytotoxicity against two human prostate cancer cell lines, androgen-dependent LNCaP and androgen-independent PC-3. One of the synthesized compound **45** (Figure 11) showed very good activity [63].
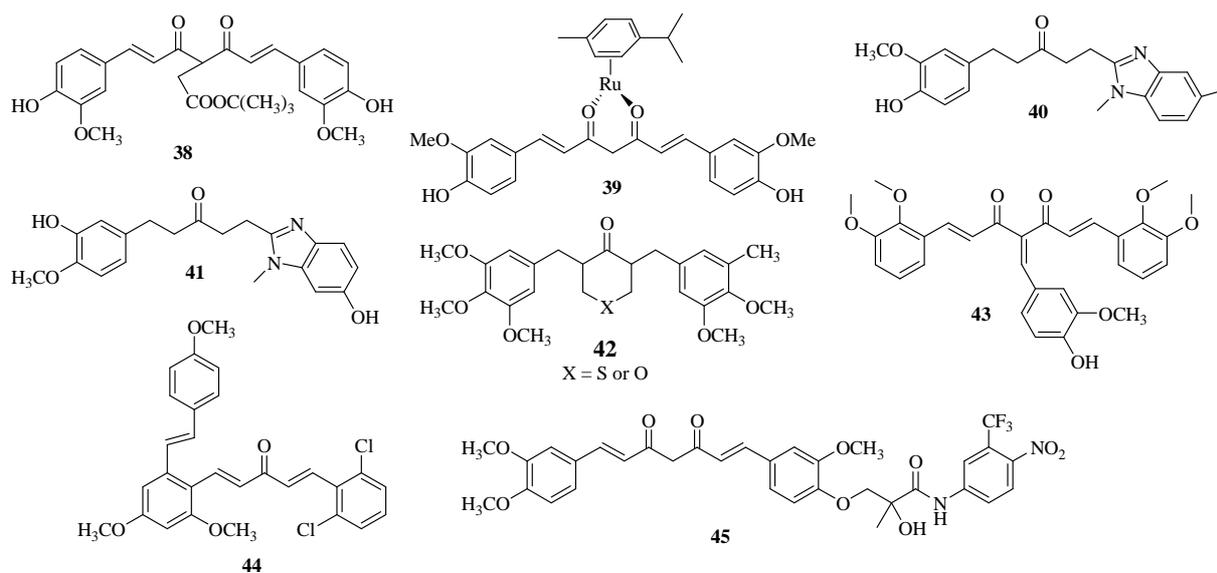
Figure 11. Cytotoxic curcumin analogs against various cancer cell lines

Sunny.M.*et al.* synthesized a series of novel monocarbonyl analogues of curcumin and tested for their activity against Molt4, HeLa, PC3, DU145 and KB cancer cell lines. The analogues **46** (Figure 12) showed potent cytotoxicity towards these cell lines with IC_{50} values below 1 µM, which is better than doxorubicin [64].

Xubin.F.*et al* designed and synthesized a series of dimethylaminomethyl substituted curcumin derivatives. All compounds particularly **47** and **48** (Figure 12) effectively inhibited HepG2, SGC-7901, A549 and HCT-116 tumor cell lines proliferation in MTT assay [65].

Tridib.K.G.*et al.* synthesized Copper(II) complexes [Cu(Fc-aa)(cur)] of curcumin (Hcur). The DNA photocleavage activity, photocytotoxicity and cellular localization in HeLa and MCF-7 cancer cells of the complex was studied. Acetylacetonate (acac) complexes [Cu(Fc-aa)(acac)] were prepared and used as controls. Complex **49** (Figure 12) showed high photocytotoxicity with low dark toxicity thus giving remarkable photodynamic effect [66].

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Yun.Y.X.*et al* designed and prepared type of novel α,β-unsaturated cyclohexanone analogous based on the curcumin core structure, have been discovered as potential EGFR inhibitors. These compounds exhibit potent anti-proliferative activity in two human tumor cell lines (Hep G2 and B16-F10). The compounds **50** and **51** (Figure 12) displayed the most potent EGFR inhibitory activity (IC_{50} = 0.43 μM and 1.54 μM, respectively) [67].

Shane.B.*et al* described the synthesis of analogues of curcumin, and their analysis in acting as nuclear receptor specific agonists. These studies may lead to the discovery of novel curcumin analogues such as **52** (Figure 12) that activate nuclear receptors, including RXR, RAR and VDR, resulting in similar health benefits as those for vitamins A and D, such as lowering the risk of epithelial and colon cancers [68].

Imran.A.*et al* prepared Knoevenagel's condensates and Schiff's bases of curcumin-I, purified and characterized. Hemolysis assays, cell line activities, DNA bindings and docking studies were carried out. The anticancer activities of the reported compounds might be due to their interactions with DNA. The results indicated the bright future of the reported compounds **53-60** (Figure 12) as anticancer agents [69].
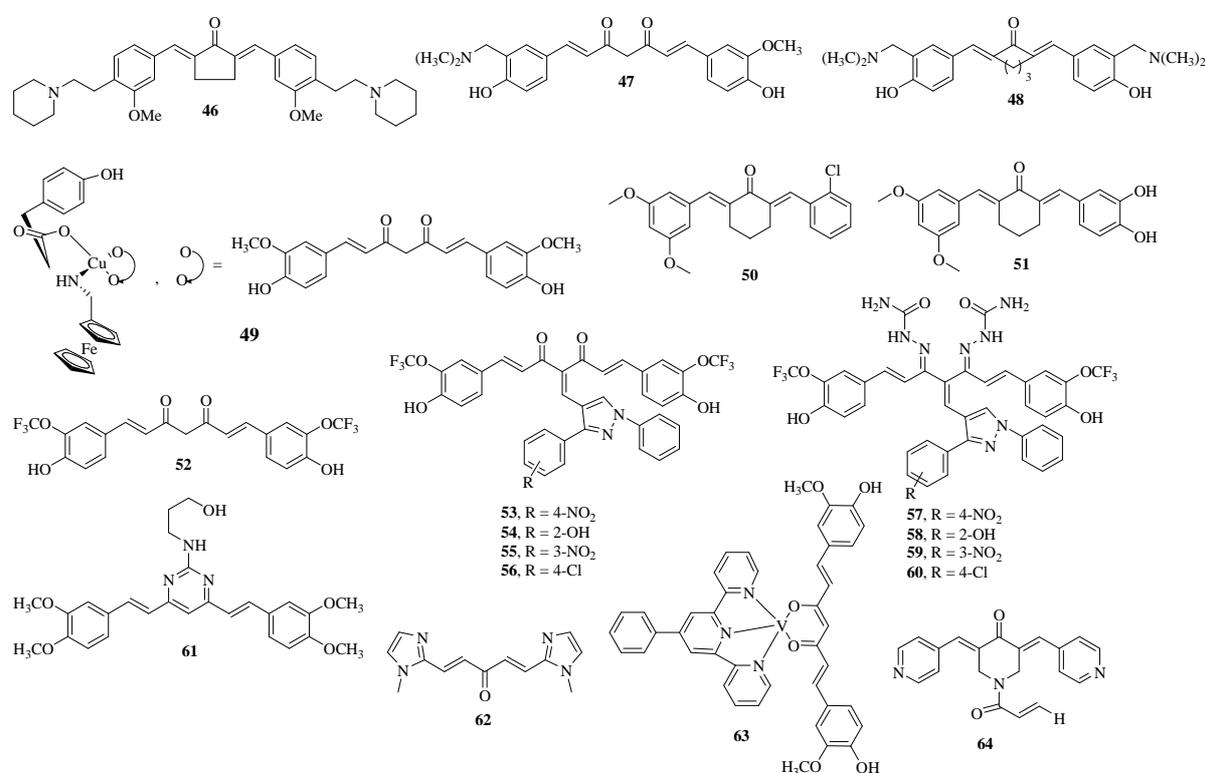
Figure 12. Curcumin based candidates as antineoplastic agents

Peiju.Q.*et al* designed and synthesized six novel pyrimidine-substituted curcumin analogues with or without a hydroxyl group. The cell viability tests indicated that IC_{50} of the analogue **61** (Figure 12) containing hydroxyl group were 3 to 8-fold lower than those of the analogues without hydroxyl group in two colon cancer cell lines tested [70]. Nawras.S.*et al* improved the potential of curcumin to treat advanced hormone-refractory prostate cancer, three series of heteroaromatic analogs (thirty two compounds) with different monoketone linkers have been synthesized and evaluated for cytotoxicity against two human androgen-independent prostate cancer cell lines (PC-3 and DU-145). All the analogs were found to be more potent than curcumin against PC-3 cells, and twenty one analogs were more cytotoxic towards DU-145 cells relative to curcumin with compound **62** (Figure 12) the most potent [71].

Babu.B.*et al* prepared Oxovanadium (IV) complexes. The compounds were characterized and their photo-induced DNA cleavage activity and photocytotoxicity in visible light studied. The complex **63** (Figure 12) showed photocytotoxicity in HeLa and Hep G2 cancer cells in visible light of 400-700 nm with low dark toxicity [72].

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Nawal.K.P.*et al* synthesized a series of eleven N-acryloyl/N-cinnamoyl-3,5-bis(pyridin-4-yl)methylene-4-piperidones as curcumin-based candidate antineoplastic agents. The cytostatic potency of these compounds was evaluated against three representative cell lines and all compounds were found to exhibit significant anti-cancer cell activity in vitro. The compounds **64** (Figure 12) was significantly more cytotoxic than melphalan and curcumin [73].

Xiaolin.L.*et al* prepared two ruthenium-arene complexes **65** and **66** (Figure 13) containing curcuminoid ligands, (η^6-cymene)Ru(curc)Cl. The complexes were evaluated for their in vitro anti-proliferative activities against Hela human cervical epithelioid cancer, as well as BEL-7404 and SMMC-7721 human liver cancer cell lines. The complexes showed good activity [74].

Ashutosh. P.*et al* synthesized the glucuronide metabolites of curcumin. The newly synthesized curcumin glucuronide compounds were tested and their anti-proliferative effects against KBM-5, Jurkat cell, U266, and A549 cell lines were reported. Curcumin mono-glucuronide **67** as well as di-glucuronide **68** (Figure 13) displayed no suppression of cell proliferation. [75].

David.J.S.*et al* performed synthesis of C5-curcumin-fatty acid (C5-Curc-FA) conjugates. It was found that C5-Curc-FA conjugates containing either decanoic acid or palmitic acid moieties were cytotoxic against colorectal adenocarcinoma cell (CCL-229) at IC_{50}s ranging from 22.5 to 56.1 µg/mL. The results strongly suggested that a decanoic acid moiety at the meta position in C5-Curc-FA conjugates as in compound **69** (Figure 13) is important for their anticancer activity effect [76].

Saiharish.R.*et al* synthesized curcumin–quinolone hybrids and their in vitro cytotoxicity was determined on a panel of representative cell lines (A549, MCF7, SKOV3 and H460) using MTT assay. The compounds showed very good anti-cancer activity. The most potent compound **70** (Figure 13), was analysed for its mode of action using various cell biology experiments. SKOV3 cells treated with compound **70** showed distorted cell morphology under phase contrast imaging and induction of apoptosis was confirmed by Annexin V/PE assay. [77].

Qiao-Hong.C.*et al* synthesized ten new hybrid molecules, 3-(1E,4E)-5-(1-alkyl-1H-imidazol-2-yl)-3-oxopenta-1,4-dien-1-yl)-4H-chromen-4-ones, **71** (Figure 13). The WST-1 cell proliferation assay showed that they have greater anti-proliferative potency than curcumin, quercetin and genistein on both androgen-dependent and androgen-independent human prostate cancer cells [78].

Lucas.N.S.*et al* synthesized novel functionalized quaternary ammonium curcuminoids. These molecules were found to be highly water soluble with increased cytotoxicity compared to native curcumin against three cancer cell lines MIAPaCa-2, MDA-MB-231, and 4T1. The compound **72** (Figure 13) has been found to exhibit good tumor growth inhibition as a single agent and also in combination with clinical pancreatic cancer drug gemcitabine. [79].

Said.M.B.*et al* synthesized curcumin analogues and their antioxidant activities were investigated by measuring their free radical scavenging capacities. The in vitro and in vivo antitumor activities of the synthesized compounds on Ehrlich ascites carcinoma (EAC) cell line were evaluated. 4-(4-Chlorophenyl)-2-(5-ethyl-7-(4-methoxybenzylidene)-3-(4-methoxyphenyl)-3,3a,4,5,6,7-hexahydro-2H-pyrazolo[4,3-c]pyridin-2-yl)thiazole, **73** (Figure 14) showed excellent antineoplastic activity in both in vitro and in vivo studies [80].

Qingyong.L.*et al* synthesized 12 asymmetric curcumin (CUR) analogues and 5 symmetric curcumin derivatives. The antioxidant activity of these derivatives were evaluated by radicals 1,1-diphenyl-2-picryl-hydrazyl (DPPH) assay, 2,2-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) assay, ROO*(TRAP) assay and O2$^-$* (NET) assay and anti-proliferative activities of these analogues were assessed against the human hepatoma cell line (SMMC-7721), the human breast cancer cell line (MCF-7) and the human prostate cancer cell lines (PC-3). Most of the asymmetric compounds such as **74** (Figure 14) showed stronger antioxidant activities than Vitamin C (Vc) [81].
Qiaoyou.W.*et al* designed and synthesized 37 novel long-chain alkoxylated MACs for anti-cancer evaluation. The MTS assay was used to determine the cytotoxicity of compounds in gastrointestinal cancer cells. The compounds showed strongest inhibition against gastric cancer cell proliferation. Compound **75** (Figure 14) showed strongest inhibition against gastric cancer cell proliferation and exhibited significant tumor inhibition in SGC7901-driven xenograft mouse model [82].

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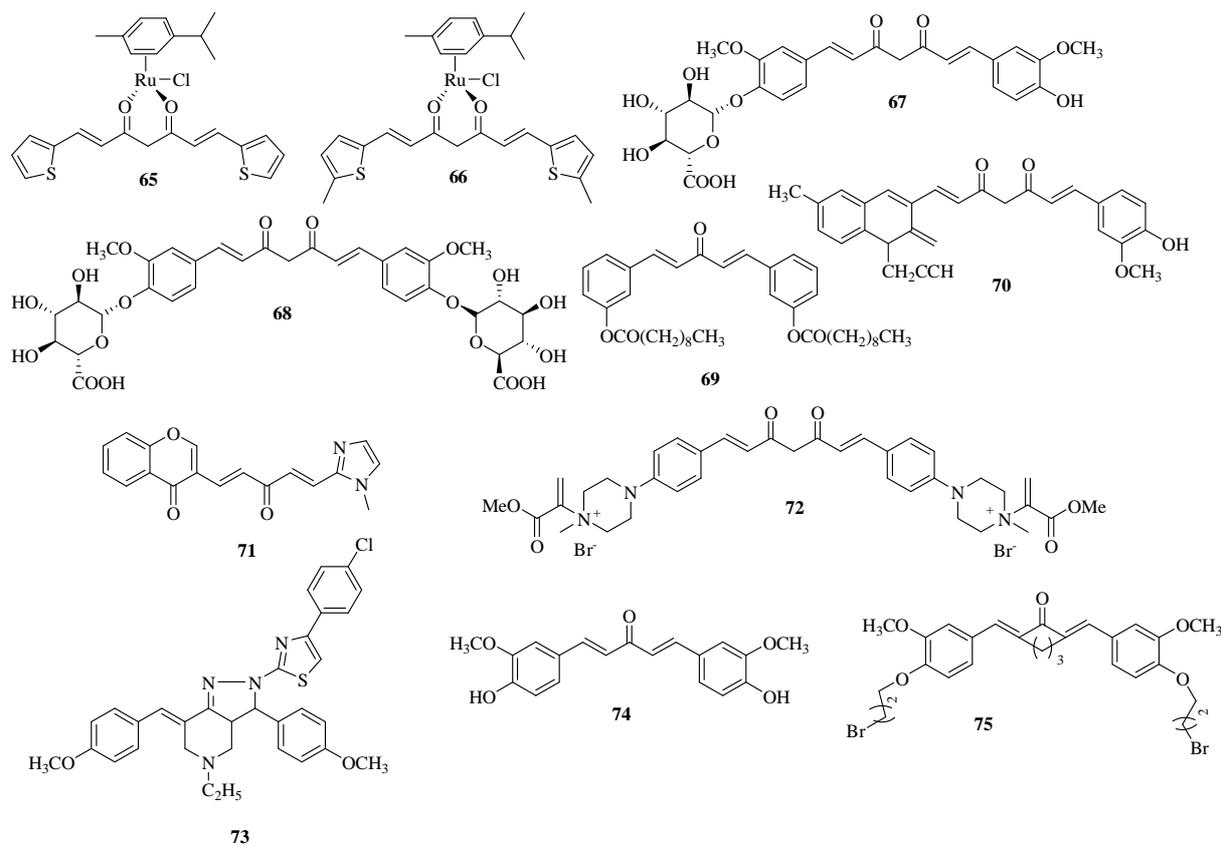
Figure 14. Curcuminoids acting against cancer cell proliferation

Amitabh.J.*et al* designed and synthesized 3,5-bis(arylmethylene)-1-(N-(ortho-substituted aryl)maleamoyl)-4-piperidones. Compounds were evaluated against human CD_4^+ T-lymphocyte Molt4/C8 and CEM cells as well as murine L1210 lymphocytic leukemia cells following a literature procedure [83]. The compounds **76-78** (Figure 15) were found to be most potent with their IC_{50} values given in Table 4 [84].
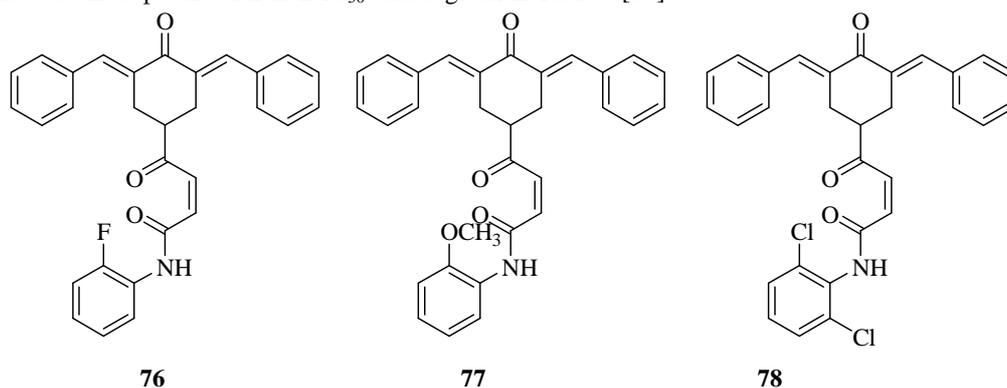
Figure 15. 3,5-bis(arylmethylene)-1-(N-(ortho-substituted aryl)maleamoyl)-4-piperidones

Table 4. IC_{50} values of most potent compounds against three cancer cell lines

Compounds	IC_{50} (µM)			SR[a]
	Molt 4/C8	CEM/0	L1210	
76	0.53 ± 0.18	0.48 ± 0.07	2.1 ± 0.3	4.9
77	0.43 ± 0.05	0.42 ± 0.01	1.7 ± 0.1	4.0
78	0.44 ± 0.06	0.40 ± 0.01	1.9 ± 0.1	4.8

[a] *SR indicates the selectivity ratio, that is, the ratio between the highest and lowest IC_{50} values of either the T-lymphocytes or murine leukemic cells*

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Sahil.S.*et al* prepared molecular hybrids of monocarbonyl curcumin and isatin tethered by triazole ring and evaluated for in vitro cytotoxicity against THP-1, COLO-205, HCT-116, A549, HeLa, CAKI-I, PC-3, MiaPaca-2 human cancer cell lines. The results revealed that the compounds showed a good range of IC_{50} values against THP-1, COLO-205, HCT-116 and PC-3 cell lines, while the other four cell lines among these were found to be almost resistant but compounds **79-82** (Figure 16) showed significant cytotoxicity by IC_{50} value ranging from 1.12–5.67 µM, 2.67–7.64 µM, 3.45–8.95 µM and 5.61–9.40 µM against HCT-116, THP-1, COLO- 205 and PC-3. These compounds were further evaluated for tubulin inhibition and the compound **79** was found to significantly inhibit the tubulin polymerization (IC_{50} = 1.2 µM against HCT-116) [85].
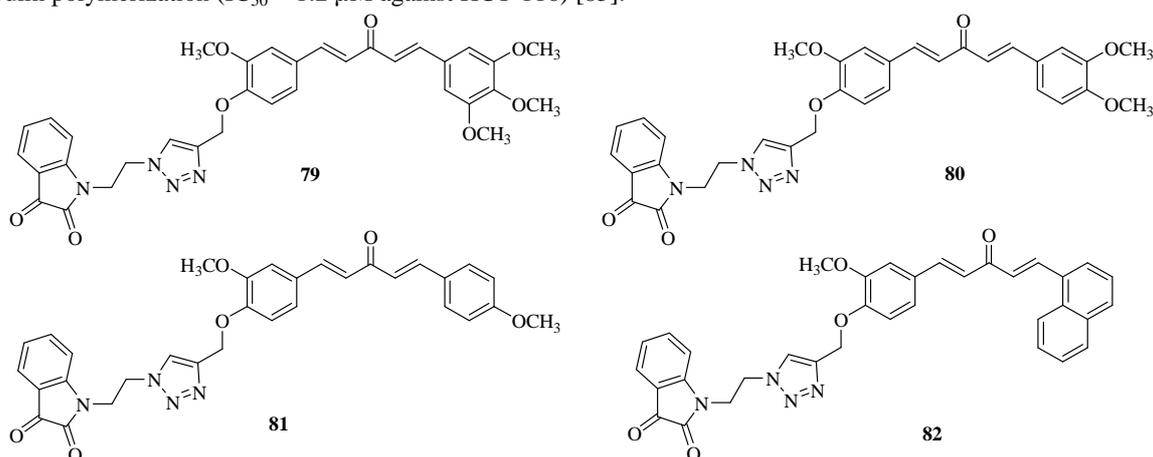
Figure 16. Molecular hybrids of monocarbonyl curcumin and isatin tethered by triazole ring

2-2. Structure Activity Relationship for curcumin and its analogues as Anti-cancer agents [86]**:**
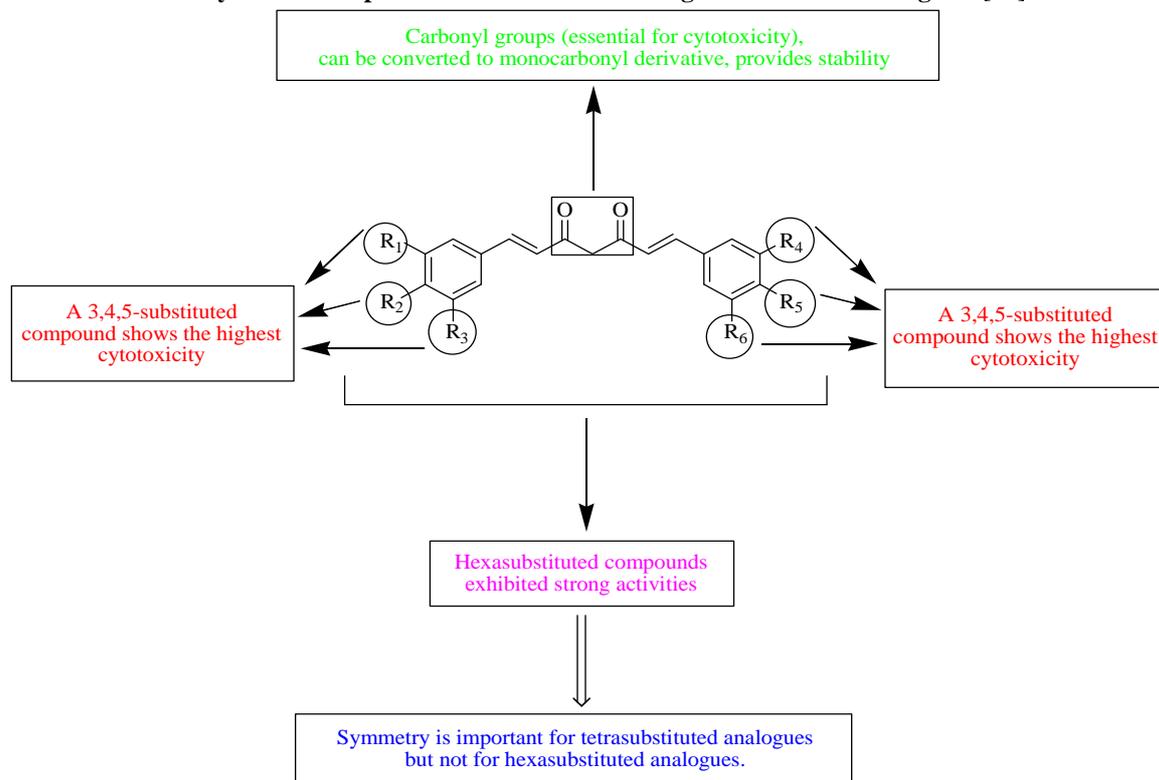
Figure 17. SAR for anti-cancer curcumin analogues

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2-3. Several curcumin analogues as Anti-microbial agents:
Satyendra.M.*et al* synthesized different curcumin bioconjugates viz. 4,4'-di-O-glycinoyl-curcumin **83**; 4,4'-di-O-D-alaninoylcurcumin **84**; 4,4'-di-O-(glycinoyl-di-N-piperoyl)-curcumin **85**; 4,4'-di-O-piperoyl curcumin **86**; curcumin-4,4'-di-O-b-D-glucopyranoside **87**; 4,4'-di-O-acetyl-curcumin **88** along with piperoyl glycine **89** (Figure 18). These bioconjugates were tested in vitro against different bacteria and fungi, were found to be effective. The 4,4'-di-O-(glycinoyl-di-N-piperoyl)-curcumin **85** and 4,4'-di-O-acetyl-curcumin **88** were found to be more effective than Cefepime, an antibacterial drug available in market, at the same concentration. The 4,4'-di-O-(glycinoyl-di-N-piperoyl)-curcumin **85** and 4,4'-di-O-piperoyl curcumin **86** had antifungal activity in vitro almost comparable with fluconazole, the most popular antifungal drug [87].

Ramendra.K.S.*et al* synthesized curcumin bioconjugates and tested for their antibacterial and antiviral activities. The conjugates **90** and **91** (Figure 18) have shown very promising antibacterial activity with MIC ranging between 0.09 and 0.67 µM against Gram-positive cocci and Gram-negative bacilli. The conjugates have also been screened for their antiviral activities against HSV, VSV, FIPV, PIV-3, RSV and FHV and the molecules **90**, **91** have also shown good results with EC_{50} 0.011 µM and 0.029 µM against VSV and FIPV/FHV, respectively [88].
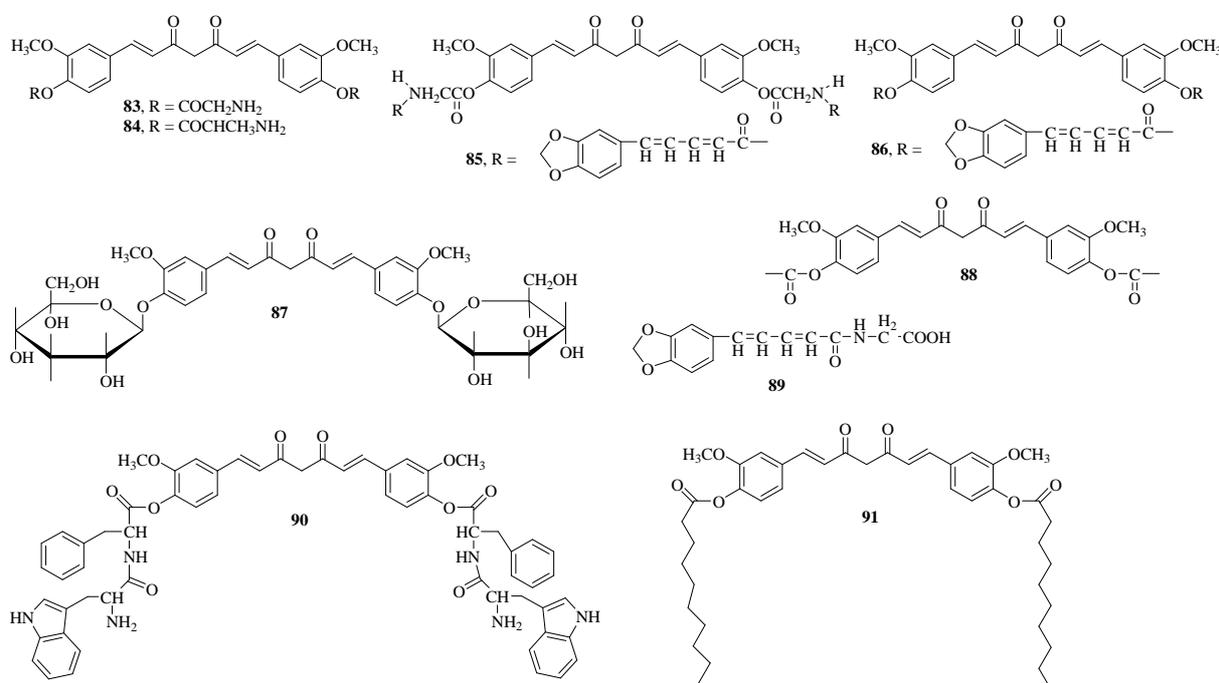
Figure 18. Curcumin bioconjugates as anti-microbial

Jaggi.L.*et al* synthesized 3,4-Dihydropyrimidinones of curcumin. The synthesized compounds were evaluated for their synergistic antimicrobial (antibacterial and antifungal) activity against bacteria and fungi. Zone of inhibition was measured by adopting disc diffusion method. Compounds **92-94** (Figure 19) with MIC of 40–80 were more active than curcumin (MIC 80), whereas remaining compounds showed moderate antibacterial activity.

The in vitro cytotoxicity of synthesized compounds against three human cancer lines Hep-G2, HCT-116 and QG-56 were also evaluated. All the compounds exhibited anticancer activity with IC_{50} values ranging from <12.5 to 100 µM/ml, while the positive control, adriamycin demonstrated the IC_{50} in the range of <2.5 to 5.0 µM/ml. [89].

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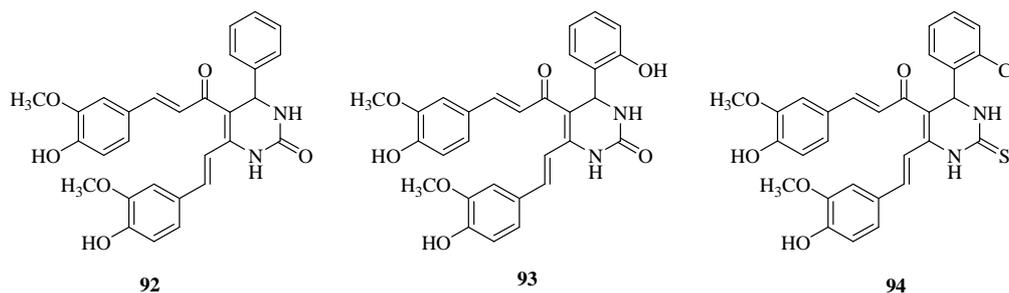
Figure 19. 3,4-Dihydropyrimidinones of curcumin

Pramod.K.S.*et al* provided an efficient procedure for synthesis of 4H-pyrimido[2,1-b]benzothiazole, pyrazole and benzylidene derivatives of curcumin. The synthesized compounds were evaluated for their antibacterial activity against gram-positive and gram-negative bacteria viz. *Staphylococcus aureus, Pseudomonas aeruginosa, Salmonella typhi, Escherichia coli, Bacillus cereus* and *Providencia rettgeri* and antifungal activity against fungi viz *Aspergillus niger, Aspergillus fumigates, Aspergillus flavus*. The results revealed that derivatives **95, 96** and **97** (Figure 20) were most potent and showed significant activity as anti-microbials [90].

Jaggi.L.*et al* prepared a series of curcumin derivatives with sulfonamides and evaluated for in-vitro antibacterial activity against selected medically important gram-(+) and gram-(-) bacterial species viz. Staphylococcus aureus, Bacillus cereus, Salmonella typhi, Pseudomonas aeruginosa and Escherichia coli, and antifungal activity against few pathogenic fungal species viz. Aspergillus niger, Aspergillus flavus, Trichoderma viride and Curvularia lunata. The cytotoxicity was determined by measuring IC_{50} values against human cell lines HeLa, Hep G-2, QG-56 and HCT-116. Among the compounds screened, **98-100** (Figure 20) showed the most potent biological activity against tested bacteria and fungi and higher cytotoxicity than curcumin [91].

David.J.S.*et al* synthesized C5-curcumin–2-hexadecynoic acid (C5-Curc–2-HDA, **101**) conjugate and tested for antibacterial activity against methicillin-resistant Staphylococcus aureus (MRSA) strains. The results revealed that compound **101** (Figure 20) was active against eight MRSA strains at MICs that range between 31.3 and 62.5 µg/ml. It was also found from the results that conjugation of 2-hexadecynoic acid to C5-curcumin enhanced its antibacterial activity [92].
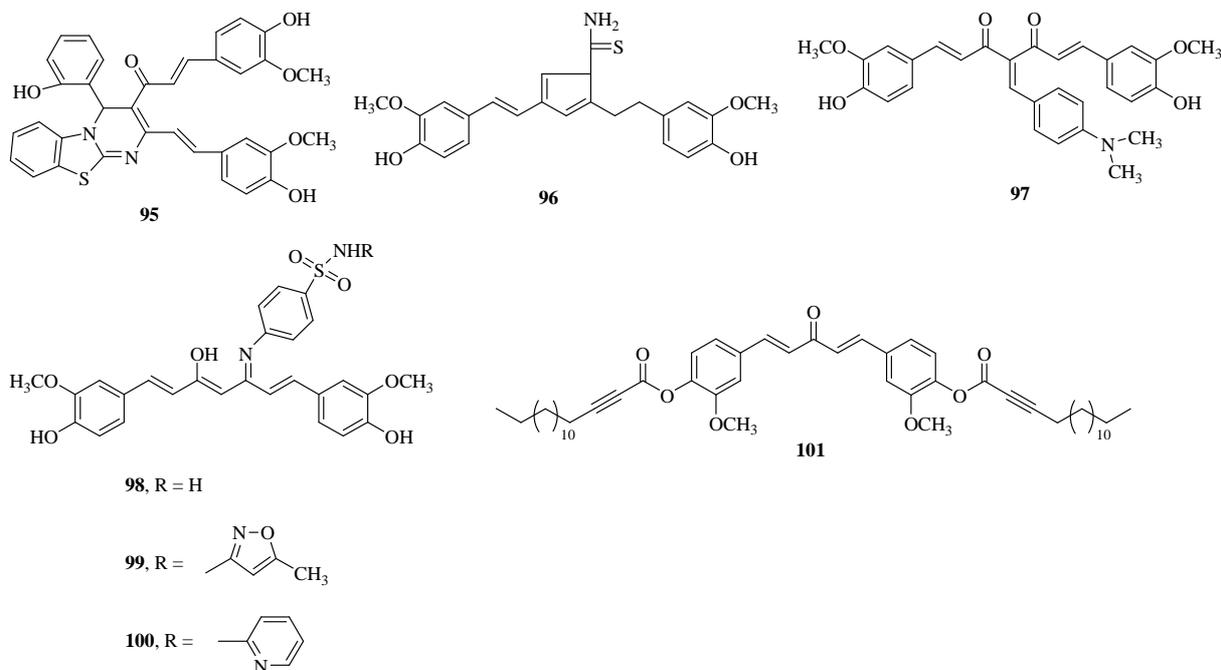
Figure 20. Several curcumin derivatives acting against microorganisms

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CONCLUSION

In short, the importance of curcumin and its analogues as anti-cancer and anti-microbial agents has been summarized. Studies suggested that the use of various analogues of curcumin have left a landmark in the field of search for new anticancer as well as anti-microbial agents. Based on the results and reports, it is suggested that the future trends must aim at the development of curcumin analogues as antimicrobial agents. On the other side, a lot of work has been done on the development of anticancer agents from curcumin which includes its monocarbonyl derivatives and hybrids etc., showed very good results. Its potential has been supported by the reports described in this article. Researchers must aim at the development of some new curcumin analogues with new and efficient substitutions, thus exploring this central and chief nucleus to a large extent.

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