Anti-Breast Cancer Properties of Curcumin Analogs

Subjects: Chemistry, Medicinal

Contributor: Abigail L. Flint , David W. Hansen , LaVauria D. Brown , Laura E. Stewart , Eduardo Ortiz , Siva S. Panda

Breast cancer (BC), the most common malignancy in women, results from significant alterations in genetic and epigenetic mechanisms that alter multiple signaling pathways in growth and malignant progression, leading to limited long-term survival. Curcumin (a natural yellow pigment), the principal ingredient in the spice turmeric, is well-documented for its diverse pharmacological properties including anti-cancer activity. However, its clinical application has been limited because of its low solubility, stability, and bioavailability. To overcome the limitation of curcumin, several modified curcumin conjugates and curcumin analogs were developed and studied for their anti-cancer properties.

curcumin curcumin mimic conjugates

1. Introduction

Breast cancer is the most prevalent form of the disease found in women and is the main cause of cancer-related deaths in women globally. As with many other human cancers, breast cancer is caused by major modifications in genetic and epigenetic processes, as well as the targeting of many signaling pathways in the process of development and malignant progression toward an incurable and fatal disease. It has been established that a higher risk of breast cancer is related to both an earlier age at the onset of menarche as well as a later age at the onset of menopause. In the United States, roughly one in eight women at some point in their lives will be diagnosed with invasive breast cancer. This accounts for around thirteen percent of all women who are diagnosed with breast cancer. Furthermore, the Centers for Disease Control and Prevention (CDC) report breast cancer claims the lives of over 42,000 American women and 500 men each year [1][2]. As a result of this, research has been carried out to discover and develop drugs that are capable of effectively treating this particularly aggressive form of cancer. There is current difficulty in creating an effective treatment option for cancer, due to most available medications lacking the needed potency to provide full protection against the disease. The process of producing a new drug is time-consuming, challenging, and expensive. Additionally, it is intricate, and there is a high degree of unpredictability regarding the effectiveness of the drug after development. The difficulty in targeting cancer stem cells (CSCs), related to the drug-resistant properties of cancer stem cells rendering them immune to anti-cancer drugs, the lack of cancer epigenetic profiling, and the lack of specificity of existing epi-drugs are some of the most encountered challenges associated with cancer treatment [3].

Natural products have been used as a significant source of medications for many years. As of today, around half of all pharmaceuticals are still produced with the assistance of natural components. Several key commercialized medications in the field of cancer treatment have been derived from natural sources by structurally altering existing compounds or by synthesizing novel compounds like natural components. Research on modern anti-cancer drugs continues to place a significant emphasis on the search for improved cytotoxic agents. Due to the enormous structural diversity of natural compounds and the bioactivity potential of these compounds, several products that have been isolated from plants, marine flora, and microorganisms can serve as “lead” compounds. The improvement of their therapeutic potential through molecular modification can be carried out due to the large structural diversity that natural compounds possess [4].

Curcumin (**Figure 1**) is an example of a naturally occurring substance that has shown promise in treating breast cancer. Curcumin, a polyphenolic compound that can be found in turmeric (*Curcumin longa*), has been the topic of breast cancer research for over the past two decades due to its potential anti-inflammatory and anti-cancer effects. It has been revealed that curcumin suppresses the growth, spread, and metastasis of several malignancies. Its capacity to suppress oncogenic molecules such as protein kinases, cytokines, transcription factors, and growth factors plays a significant role in mediating its anti-cancer actions. In addition to this, curcumin obstructs the expansion and dissemination of cancer cells by obstructing their passage through the various phases of the cell cycle and/or by inducing apoptosis in cancer cells. However, according to pharmacokinetic studies, curcumin has poor systemic bioavailability because it is rapidly metabolized in the liver, where it undergoes glucuronidation and sulfation before being eliminated in the stool. The attempts undertaken up until this point to slow curcumin’s rapid metabolism have been ineffective in most cases. Due to curcumin’s restricted bioavailability and quick metabolism, researchers have previously explored and are currently exploring novel synthetic curcumin analogs that have lower toxicity, yet increased effectiveness [5][6].

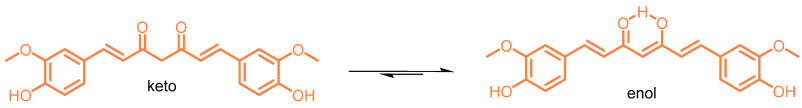


Figure 1. Keto-enol tautomeric forms of curcumin (CUR).

Curcumin scaffolds have been extensively explored and investigated including several analogs, conjugates, and mimics to reform their pharmacological potency and improve bioavailability [7][8][9][10][11]. The scaffold of curcumin has been broken down to identify the potential sites for structural modifications. The structure–activity relationship of the curcumin-based compounds indicates the key structural components/modifications responsible for a specific target (**Figure 2**). Curcumin itself has many pharmacological properties such as modulating signaling molecules, including cytokines, chemokines, transcription factors, adhesion molecules, microRNAs, tumor suppressor genes, etc. Structural modifications of curcumin have been advocated for improving its bioavailability, enhancing stability, and increasing potency. The modified curcumin could serve as the next generation of drug candidates for cancer therapy.

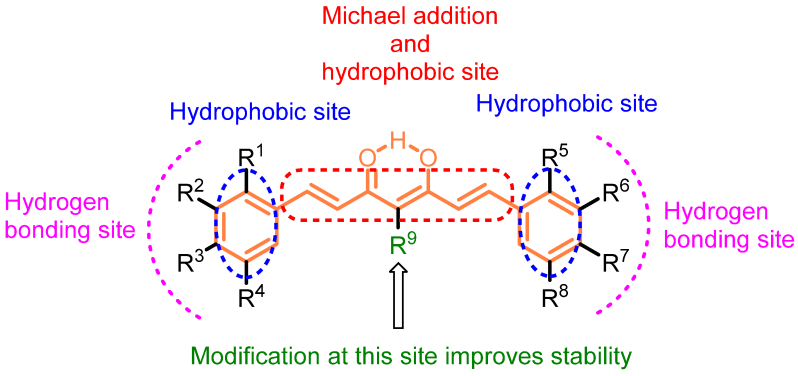
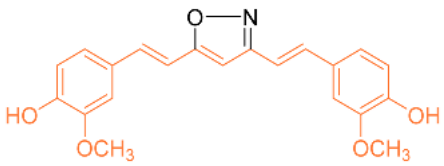


Figure 2. Structure of curcumin with indications of the important sites.

2. Anti-Breast Cancer Properties of Curcumin Analogs

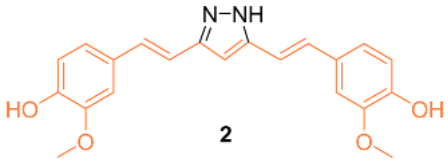
The isoxazole curcumin analog **1** was synthesized and the anti-cancer properties against the MCF-7 breast cancer cell line and its multidrug-resistant (MDR) version, MCF-7R, were compared with curcumin. After 72 h of treatment, the IC_{50} of curcumin was calculated from four separate experiments to be 29.3 ± 1.7 μM in MCF-7 and 26.2 ± 1.6 μM in MCF-7R, indicating that the cytotoxic activity of curcumin in the MDR breast cancer cell line is at least equivalent to, and perhaps slightly stronger than, its parental variant. In both the parental and MDR cell line, derivative **1** was more effective than curcumin with an IC_{50} of 13.1 ± 1.6 μM in MCF-7 and 12.0 ± 2.0 μM in MCF-7R. An MDR form of HL-60 leukemia also showed comparable outcomes. RT-PCR analyses in MCF-7 and MCF-7R cell lines revealed that curcumin and **1** caused early changes in the quantities of important gene transcripts, which were, nevertheless, primarily varied between the two cell lines. Overall, these results show that the expression of P-gp or the absence of ER in breast cancer cells does not impede the anti-cancer activities of either curcumin or **1**. Remarkably, the agents seemed to adjust their molecular actions in response to the different patterns of gene expression found in the MDR and the parental MCF-7 [12].



1

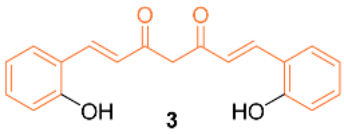
According to Wang et al., research was conducted on hydrazinocurcumin **2** (HC) to investigate its effectiveness against breast cancer cells, specifically in the cell lines MDA-MB-231 and MCF-7. After 72 h of treatment, dose-dependent suppression of tumor cell survival and proliferation was seen for the MDA-MB-231 and MCF-7 cell lines. The IC_{50} values for **2** were 3.37 μM and 2.57 μM, respectively, which were both significantly lower than those for curcumin (26.9 μM and 21.22 μM). Compared to curcumin, the results demonstrated that **2** was significantly more effective in suppressing cell viability in both cell lines tested. Apoptosis was induced in MDA-MB-231 and MCF-7 cells using FCM, and the influence of **2** and curcumin on this process was analyzed. At 10 μM, **2** significantly induced cells apoptosis (14% in MDA-MB-231 cells and 26% in MCF-7 cells), whereas at the same concentration, curcumin only induced 9% and 20% cell apoptosis in MDA-MB-231 and MCF-7 cells, respectively. The results showed that **2** caused an increase in the apoptotic rate of cells in a dose-dependent manner after a treatment

period of 48 h. In addition, the Western blot analysis demonstrated that **2** was much more effective than curcumin in suppressing the production of STAT3 protein in MDA-MB-231 and MCF-7 cells at the same concentration (10–20 μM). The data showed that **2** was more effective than curcumin at suppressing cell proliferation, losing colony formation, depressing cell migration and invasion, and inducing cell death via inhibiting STAT3 phosphorylation and downregulating an array of STAT3 downstream targets [13].



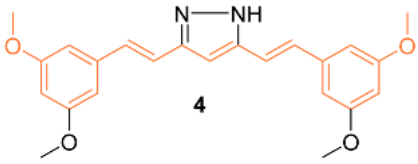
2

Mohankumar et al. studied the apoptotic mechanism of **3**, an *ortho*-hydroxy substituted analog of curcumin using an in vitro and in silico approach. In the study, it was found that **3** exhibited a greater potency in the modulation of selective apoptotic markers and inhibited MCF-7 at a dose level of 30 μM (equivalent dosage level to curcumin), and significantly regulated PI3k/Akt, both intrinsic and extrinsic apoptotic pathways, by inhibiting Bcl-2 and inducing p53, Bax, cytochrome c, Apaf-1, FasL, caspases-8, 9, 3, and PARP cleavage. mRNA expression studies for Bcl-2/Bax indicated increased efficiency with **3** compared to curcumin, while an in silico molecular docking study utilizing PI3K revealed that the docking of **8** was more potent than curcumin. Cells treated with **3** effectively induced apoptosis through ROS intermediates, as measured by 2′,7′-dichlorodihydrofluorescein diacetate (DCFH-DA). Results showed **3** induced apoptosis more effectively than curcumin, and this activity can be attributed to the presence of the hydroxyl group in the *ortho* position in the structure [14]. In addition, Western blotting indicated that compound **3** significantly downregulated the expression levels of NF-κB, p65, and c-Rel. In addition, src levels were significantly reduced in comparison to cells treated with curcumin. In silico docking studies were performed with the derivative and curcumin with NF-κB (PDB ID: 1NFK). The results indicated that the derivative displayed a stronger interaction with NF-κB compared to curcumin, with a Lidblock score of 109.814 while curcumin's was 95.696 [15].



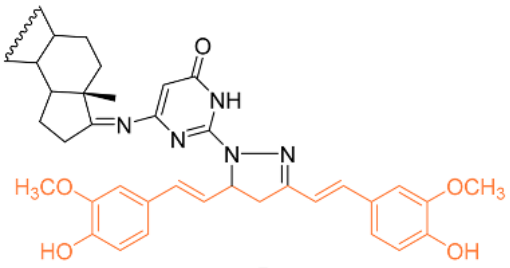
3

Lien et al. synthesized over 30 curcumin derivatives and published findings that a novel curcumin derivative (**4**) inhibits cell proliferation and drug resistance of HER2-overexpressing cancer cells. The mimic was tested in vitro on both the MCF-7 and MDA-MB-435 cell lines transfected with pSV2-*erbB2*. Results indicated that the derivative preferentially suppresses the growth of HER2-overexpressing cancer cells. Studies were also carried out to investigate if the derivative would sensitize HER2-overexpressing cancer cells to clinical drugs and it was found that overexpressing cells showed greater cytotoxic activity when the derivative was administered in combination with doxorubicin (DOX), etoposide, or taxol [16].



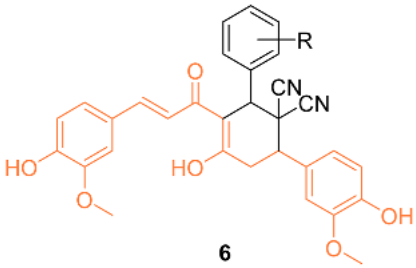
4

To understand the molecular hybridization impact and the integration of two drugs with different modes of action, affecting the same target, a variety of heterocyclic steroids and curcumin moieties were considered for the synthesis of hybrid conjugates and to determine their anti-cancer activity. The authors synthesized the hetero-steroid compounds and conducted in vitro studies of the cytotoxic effects against the MCF-7 breast cancer cell line. Of all compounds, **5** had the best cytotoxic activity against the MCF-7 cell line with an IC_{50} value of 18 μM. This compound is also promising as an anti-cancer compound having pro-apoptotic effects resulting in desired cell growth inhibition [17].

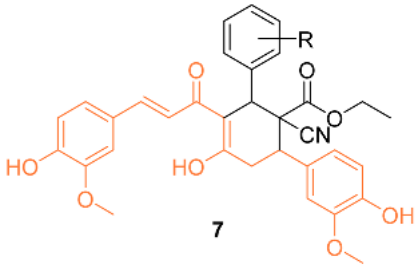


5

Bhuvaneswari et al. reported the biological evaluation and molecular docking of novel curcumin derivatives **6a**–**l** and **7a**–**k**. Firstly, in vitro cytotoxicity was tested against the MCF-7 breast cancer cell line. The IC_{50} for **6j** and **7i** were 15 µM and 10 µM, respectively. When the compounds were tested against normal HBL-100 cells, the cells were resistant to the compounds up to 50 µM doses, showing the compounds are selective and dose-dependent. Molecular docking studies were also conducted in PatchDock and suggested that these two compounds could be the starting point for designing new potent Bcl-2 anti-apoptotic protein inhibitors, with **7** having a geometrical score of 6028 and **6** with a score of 5962 compared to 4190 for curcumin (PDB: 1GJH) [18].



6

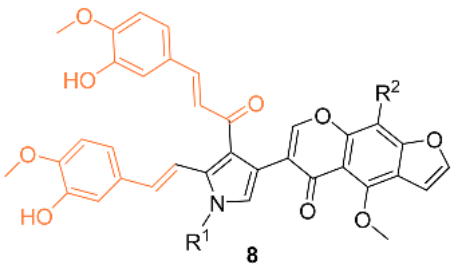


7

6a: R = H
6b: R = 2-Cl
6c: R = 4-Cl
6d: R= 2-F
6e: R = 4-NO_2
6f: R = 3-NO_2
6g: R = 2-NO_2
6h: R = 4-CH_3
6i: R = 4-OCH_3
6j: R = 3,4-OCH_3, OH
6k: R = 2,4-Cl
6l: R = 3-OH

7a: R = H
7b: R = 2-Cl
7c: R = 4-Cl
7d: R = 4-Br
7e: R = 2-F
7f: R = 4-NO_2
7g: R = 3-NO_2
7h: R = 2-NO_2
7i: R = 4-CH_3
7j: R = 4-OCH_3
7k: R = 2,4-Cl

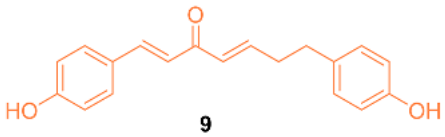
Nagwa et al. synthesized a set of curcumin derivatives **8a**–**g** and then experimented to determine the efficacy of the derivatives against breast cancer. Preliminary tests were conducted with normal MCF-10A cells and it was found that all derivatives had little cytotoxicity, with more than 85% cell viability. An MTT assay was performed with the derivatives against an MCF-7 breast cancer cell line. Compounds **8a** and **8c** were the most potent against the breast cancer cells, with an IC_{50} of 20 and 22 µg/mL, respectively. Pharmacokinetic (ADME) studies confirm that compounds **8a** and **8c** have good intestinal absorption and are non-carcinogenic [19].



8

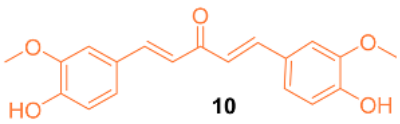
8a R^1 = 4-OHPh; R^2 = OCH_3
8b R^1 = 4-OCH_3Ph; R^2 = OCH_3
8c R^1 = 4-BrPh; R^2 = H
8d R^1 = CH_2Ph; R^2 = H
8e R^1 = 2,6-$(NO_2)_2$Ph, R^2 = OCH_3
8f R^1 = 2,6,-$(NO_2)_2$Ph; R^2 = H
8g R^1 = 4-OHPh; R^2 = H

Hong et al. reported the synthesis of and anti-cancer studies on the novel curcumin mimic (1*E*,4*E*)-1,7-bis(4-hydroxyphenyl) (hepta-1,4-dien-3-one) **9** isolated from mistletoe. It was first tested for in vitro cytotoxicity in which it showed activity in the micromolar range. Additionally, **9** showed a higher potency than cis-platinum against four human breast cancer cell lines (SKBR3, MDA-MB231, MCF-7, and MDA-MB453). The IC_{50} values for the breast cancer cell lines were significantly lower with **9** compared to cis-platinum. The cytotoxicity of **9** with normal cells was investigated with LO2 human liver cells, GES-1 human gastric epithelial cells, and BEAS-2B human lung epithelial cells. The results indicated that **9** had a little inhibitory effect on normal cells, with each group having a less than 5% inhibition rate, which is much lower than the rate on cancer cells at the same concentration, indicating **9** has a selectivity for the toxic effects of cancer cells rather than normal cells. In addition, in vivo data on the MCF-7 breast cancer model in mice suggest that **9** is more effective than cisplatin. The groups administered **9** had a stable weight for up to 9 days, while a clear weight loss was observed in the positive control group [20].



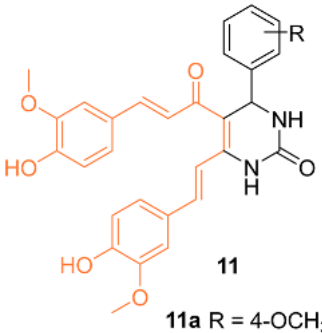
9

Shen et al. tested the efficacy of a curcumin analog **10** in breast cancer cells. The breast cancer cell lines MCF-7 and MDA-MB-231 were used to study the cell viability, cell migration, cell cycle, and apoptosis of this analog. It was shown that when the concentration of **10** was increased, there was a decrease in cell viability. In addition, **10** had an IC_{50} of 8.84 µM compared to curcumin with an IC_{50} of 16.85 µM against MCF-7 breast cancer cells. It was shown that **10** is a compound that activates the mitochondrial apoptosis pathway in breast cancer cells [21].



10

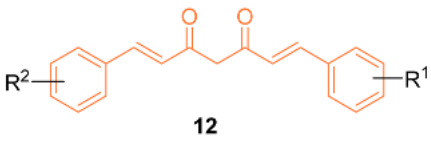
Sharma et al. synthesized 3,4-Dihydropyrimidin-2(1H)-one/thione curcumin analogs and, among them, compounds **11a**–**c** were submitted to the National Cancer Institute (NCI) to investigate activity against various cell lines, including the breast cancer cell lines MDA-MB-231 and HS 578T. At a concentration of 100 µM, compounds **11a**–**c** all displayed moderate activity, with compound **11a** being the most active. This is supported by a growth percent value (GP) of 55.45 for compound **11a** on MDA-MB-231 cells and a GP of 73.39 on HS 578T cells, while activities with a GP of 73.63 and 67.70 on MDA-MB-231 cells were found for compounds **11b** and **11c**, respectively. The authors believe compounds **11a**–**c** should be further studied to increase the moderate anti-cancer activity [22].



11

11a R = 4-OCH_3
11b R = 4-Cl
11c R = 3-OCH_3, 4-OH

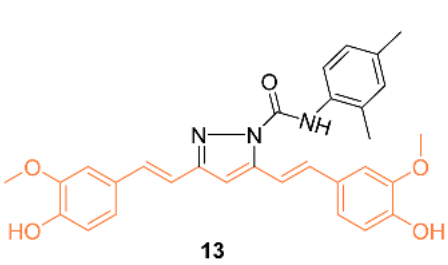
Zhang et al. reported on the synthesis and anti-cancer activity of ten curcumin mimics **12a**–**j**. Compound **12b** exhibited the best anti-cancer activity, with an IC_{50} value of 4.99 µM against MDA-MB-231 breast cancer cells compared to the 6.18 µM of cisplatin. In vivo data were obtained and were promising. However, in vivo testing was only carried out on H22 hepatic cells. Further testing is needed to evaluate if compound **12b** is a promising anti-breast cancer drug [23].



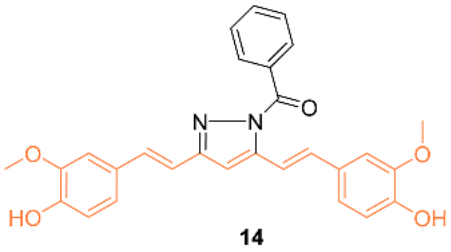
12

12a R_1 = 3-OCH_3, 4-OH; R_2 = 4-N(Ethyl)$_2$
12b R_1 = 4-OCH_3; R_2 = 4-N(Ethyl)$_2$
12c R_1 = 4-OH; R_2 = 4-N(Ethyl)$_2$
12d R_1 = 4-N(Ethyl)$_2$; R_2 = 4-N(Ethyl)$_2$
12e R_1 = 3-OCH_3, 4-OH; R_2 = 4-NO_2
12f R_1 = 4-OCH_3; R_2 = 4-NO_2
12g R_1 = 4-OH; R_2 = 4-NO_2
12h R_1 = 3-OCH_3, 4-OH; R_2 = 4-MeO
12i R_1 = 3-OCH_3, 4-OH; R_2 = H
12j R_1 = 4-OCH_3; R_2 = 4-OCH_3

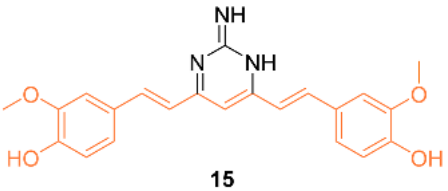
Considering the importance of pyrazole moiety, Ahsan et al. synthesized various curcumin analogs **13**–**15** containing a pyrazole or pyrimidine ring to target the epidermal growth factor receptor (EGFR) tyrosine kinase. Fourteen curcumin analogs with pyrazole or pyrimidine moieties were synthesized, with ten being evaluated amongst 60 different cell lines to observe anti-cancer effects. The activity was observed from various compounds, however, **13**–**15** displayed anti-cancer activity against various cell lines including MDA-MB-468. Compound **13** showed a cell promotion of −30.34%, compound **14** showed −31.86%, and compound **15** showed −35.04%. Ahsan et al. claim their curcumin analogs are promising and can be a therapeutic intervention in cancer treatment [24].



13



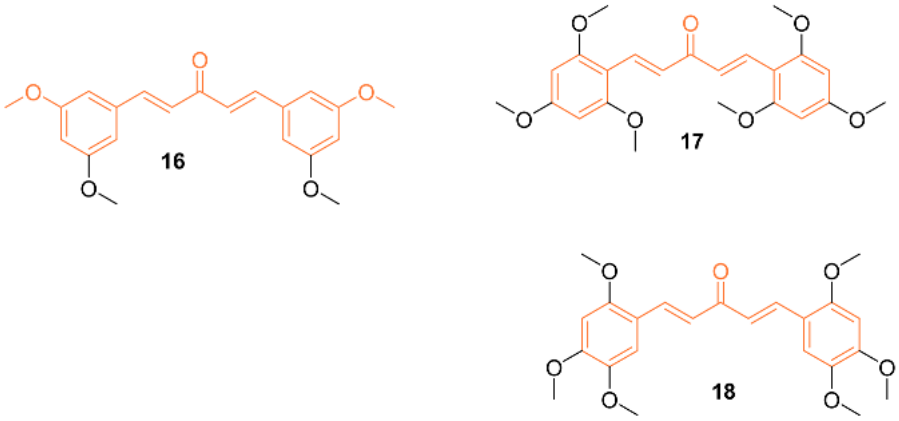
14



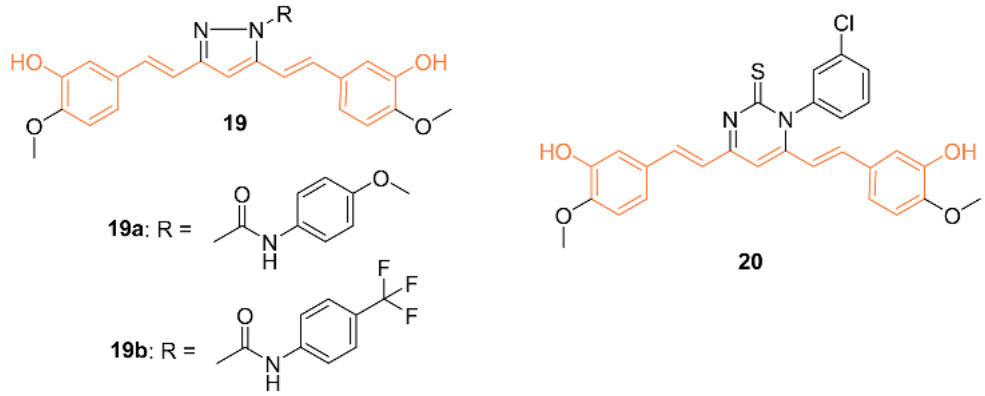
15

A set of twenty-four different analogs of curcumin containing pentadienone moiety were synthesized and examined for their anti-cancer properties against breast cancer cells (MCF-7 and MDA-MB-231). A dose-dependent suppression of tumor cell survival and proliferation was observed after 72 h of treatment with compounds **16**–**18**. The IC_{50} values for compound **16** were 2.7 ± 0.5 µM and 1.5 ± 0.1 µM for the cell lines MCF-7 and MDA-MB-231, respectively, which were 5-8 times lower than those for curcumin (21.5 ± 4.7 µM and 25.6 ± 4.8 µM). Furthermore, the IC_{50} values of compounds **17** (0.4 ± 0.1 µM and 0.6 ± 0.1 µM) and **18** (2.4 ± 1.0 µM and 2.4 ± 0.4 µM) were favorable for the MCF-7 and MDA-MB-231 cell lines, respectively. The non-malignant mammary epithelial cell line (MCF-10) demonstrated no toxicity from any of the three compounds. In comparison to curcumin, which did not exhibit any selectivity against cancer cell lines, it was discovered that compounds **16**–

18 displayed a selectivity ratio of at least fivefold or greater. Compound **17**, having IC_{50} values in the sub-micromolar range and a selectivity ratio greater than 25, was found to be the most potent analog. All three compounds, however, show promise as possible anti-tumor drug candidates for breast cancer [25].



Ali et al. synthesized curcumin analogs **19a**, **19b**, and **20** and tested them against several breast cancer lines to determine their anti-cancer effects. The compounds were docked against the epidermal growth factor receptor, which allowed for the determination of binding efficiency. All derivatives showed moderate inhibition of epidermal growth factor receptors. Compounds **19b** and **20** showed the most anti-cancer activity against BT-549 with GI_{50} values of 2.98 μM for 2 and 1.51 μM for 3 [26].



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