REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Curcumin Mimics: An Overview

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Abstract

Curcumin is a natural product which is isolated from *curcuma longa*, it was used for several centuries as an anti-inflammatory agent in traditional medicine. Curcumin has several activities including anti-inflammatory, antioxidant, antibacterial and anticancer activity. However, bioavailability, stability and selectivity problems associated with curcumin limited their use; that is why a great effort was done to develop curcumin mimics that overcome these problems. In this review, we will illustrate some different biological activities of curcumin mimetics.

Keywords: Curcumin, Anti-cancer, Anti-inflammatory, Curcumin mimetics.

1. Introduction

Curcumin (diferuloylmethane) is a dietary natural product dienones which was extracted from rhizome of curcuma longa (turmeric). It was extracted for the first time in 1870 as yellow spice (Golden spice) (Tomeh et al., 2019). Lampe and Milobedzka were the first to report the preparation of curcumin in 1913 however, Pabon develop a simple and effective technique for the preparation that is adapted to date (Lampe and Milobedzka, 2006).Curcumin possess diferuloylmethane core and two phenolic aromatic rings connected through conjugated aliphatic chain and β-diketones (Khwaja et al., 2018). The diketones in curcumin structure are in keto-enol form which is stabilized by hydrogen bond (Kazakova et al., 2022) [Figure1]. In addition to its proper safety, curcumin has several biological activities including anticancer, antioxidant, anti-inflammatory and antihypertension (Zhou et al., 2014). Despite these advantages, its use as therapeutic agent is limited due to its low bioavailability, low stability, and selectivity. Curcumin low water solubility results in low oral bioavailability and its hydrophobicity results in low availability in cytoplasm (curcumin tends to penetrate into the cell membrane and bind to its fatty acyl chains through hydrogen bond and hydrophobic interactions) (Teiten et al., 2014). An explanation of low curcumin stability is believed to be due to active methylene between the two β-diketone. Another problem was the low selectivity which is due to several curcumin targets (Barry et al., 2009). To minimize these drawbacks and improve the therapeutic use of curcumin there are two ways, the first one is using different delivery systems to improve its physicochemical properties including ligand targeting, composition formula and surface chemistry. The second is making

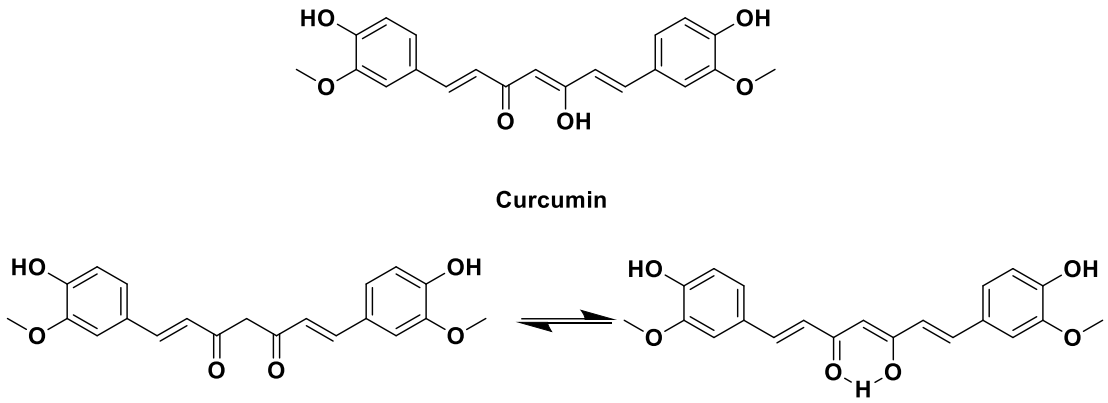


Figure .1 keto-enol form of Curcumin

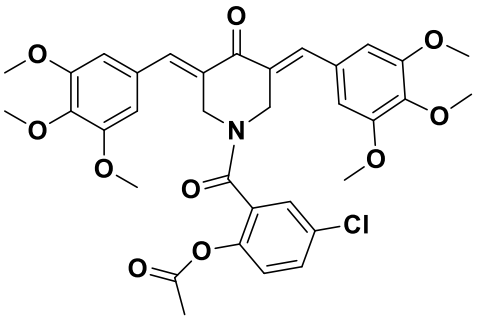
several structural modifications on curcumin to enhance its bioavailability selectivity and stability (Gupta et *al.*, 2017). Several changes in curcumin involve the replacement of diketones with one ketone group to improve the solubility and keeping the olefinic double bond which were found to be essential for the activity (Tomeh et al., 2019, Zhou et al., 2014, Fawzy et *al.*, 2019).

2. Biological Activities of Curcumin Analogues.

2.1. Anti-cancer activity.

In 2021, Srour *et al* synthesized a series of aspirin-curcumin mimic conjugates and tested them for their anticancer activity against HCT166 cell line (colon cancer cell line) and MCF7 cell line (breast cancer cell line). Among the tested compounds **(1)** and **(2)** exhibited anticancer activity against HCT116 cell line of 12.9 and 9.8-fold more than sunitinib and activity against MCF7 cell line of 1.19 and 1.12-fold more than 5-fluorouracil, respectively (Srour et al., 2021).

In 2019, Fawzy *et al* synthesized a series of 3,5-Bis (arylidene)-*N*-substituted-4-oxo-piperidine-1-carboxamides as curcumin mimics in a facile pathway through reaction of 3,5-bis (arylidene)-4-piperidones with the appropriate isocyanate in the presence of triethylamine. *In vitro* MTT assay of the new synthesized analogs against HCT 166 cell line (colon cancer cell), MCF7 (breast cancer cell) and A431 cell line (squamous skin cancer) revealed anti-proliferative property with potency higher than 5-fluorouracil. Also, the synthesized compounds exhibited promising inhibitory activity against DNA topoisomerase IIα and safe anti-proliferative profile against non-cancer RBE1(human immortalized retinal pigment epithelial cell line) that prove their selectivity. Among these compounds **(3-9)** had IC_{50} range (0.56-0.70 µm) against HCT 166 cell line and compound **(9)** had IC_{50} 0.64 µm of against A431 cell line (Fawzy et al., 2019).



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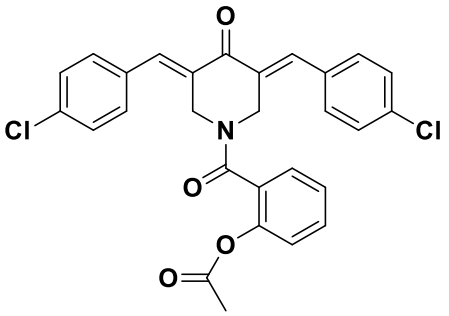

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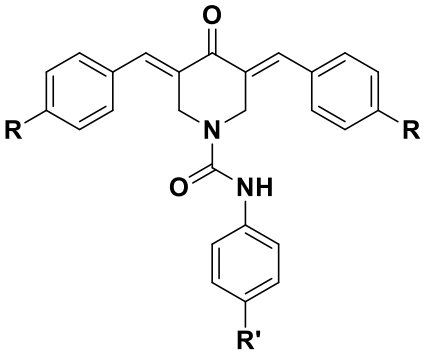
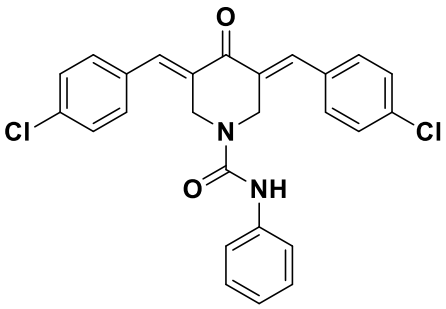


3, R=F, R'= H
4, R= F, R'= Cl
5, R=F, R'= C_2H_5
6, R=F, R'= $CH_2C_6H_5$
7, R= F, R'= OMe



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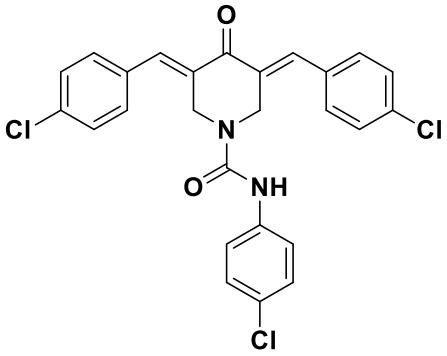

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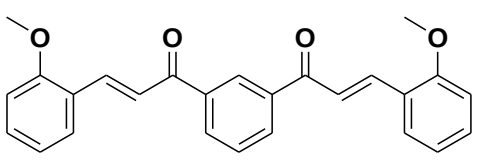
In 2018, Khwaja *et al* synthesized curcumin mimics with additional phenyl ring bridge in conjugation and tested them for their antiproliferative activity against A549 cell line (lung cancer), MCF7 cell line (breast cancer), DLD1 cell line (colorectal cancer) and A431 cell line (epidermoid cancer). Compound **(10)** exerted a potent cytotoxicity against A431 cell line with IC_{50} 1.5 µm and DLD1 cell line with IC_{50} 6.9 µm. Also, it destabilized polymerization process (polymerization of tubulin to microtubule) at IC_{50} 4.68 µm (Khwaja et al., 2018).

In 2018, Ramya *et al*., prepared series of curcumin inspired mimics and tested them for their cytotoxic activity against Hela cell line (cervical cancer), HGC-27 cell line (Gastric cancer), NCI- H460 (lung cancer), DU-145 and PC-3 cell line (prostate cancer) and 4T1 cell line (mouse breast cancer). Compound **(11)** was the most active candidate and inhibited the cancer cell growth at IC_{50} range 1.7-2.7 µm. Moreover, it exhibited cytotoxic activity on PC-3, HCG27 and Hela cell line of IC_{50} 2.11±0.27µm, 2.21±0.25µm and 2.53±0.01 µm respectively. In addition, compound **(11)** was found to be two times more selective to PC-3 and safe on RWPE-1 (normal human prostate). The assay of this compound as tubulin polymerization inhibitors revealed that it inhibited tubulin polymerization with IC_{50} 8.44±0.13 µm (Ramya et al., 2018).



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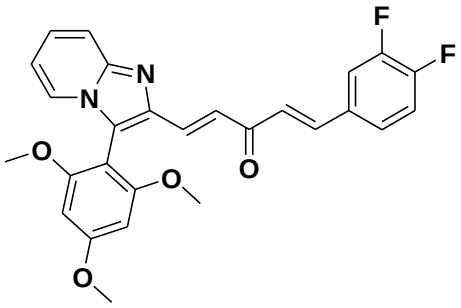

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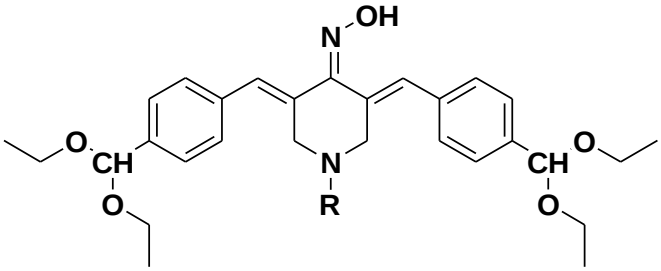

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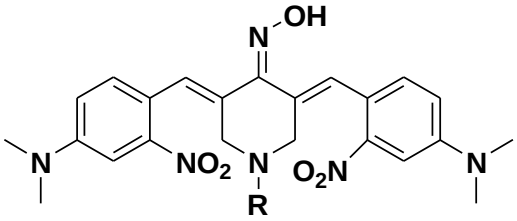
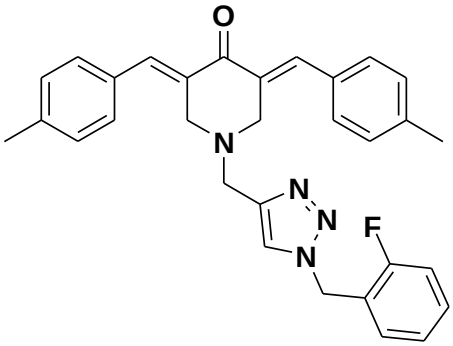
14, R= CH_3



13, R= H
15, R= CH_3



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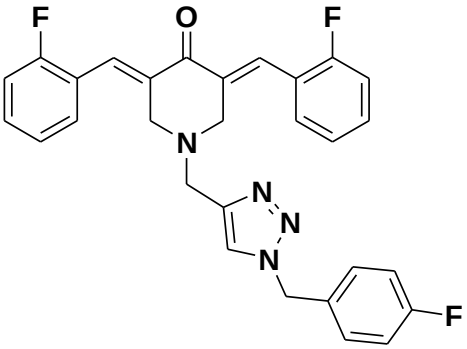

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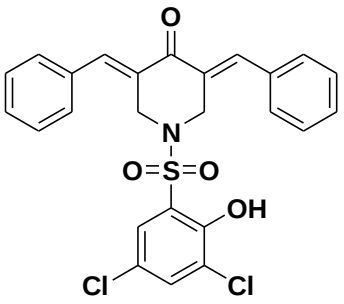
In 2017, Qin *et al* described the preparation of a series of oximes **(12-15)** that were based on curcumin and tested them against MCF-7 (breast cancer cell line), HT29 (colon cancer cell line), PC-3 (prostate cancer cell line), A-549 (epithelial cancer cell line), PaCa-2 (pancreatic carcinoma cell line), H460 (lung cancer cell line) and Panc-1 (pancreases' cancer cell line). Compounds **(12)** and **(13)** exhibited the highest IC_{50} that were comparable to reference drug erlotinib. The effect of the synthesized oximes on EGFR and tubulin polymerase revealed that compounds **(14)** and **(15)** inhibited both enzymes however the inhibition of compound **(14)** against EGFR was at IC_{50} (0.05 ± 0.0.2 µm) which was the same against erlotinib while compound **(15)** inhibited the same enzyme at IC_{50} (0.04 ± 0.01 µm) which was less than the reference drug erlotinib (Qin et al., 2017).

In 2016, Mandalapu *et al* synthesized a series of mono carbonyl derivatives of curcumin 1,2,3 triazoles and measured their anticancer activity. Out of these, compound **(16)** had the most significant activity against PC-3 and DU-145 cell lines (prostatic cancer cells) with IC_{50} 8.8µm and 9.5µm respectively, while compound **(17)** had significant activity against MCF 7, MDA-MB 231 cell lines (breast cancer cells) and 4T1 cell lines (muse mammary cell) with IC_{50} 6 µm, 10 µm and 6.4 µm respectively. The activity of these compounds was attributed to arrest the progression of cell cycle and induced apoptosis by the inhibition of Akt phosphorylation in prostate and breast cancer cells (Mandalapu et al., 2016).

2.2. Anti-bacterial activity.

In 2016, Singaram *et al*. described the preparation of curcumin analogues and tested them for their anti-bacterial activity against *Salmonella enterica*, *Vibrio cholera*, *Escherichia coli*, *Staphylococcus aureus.* Compound **(18)** had the highest zone of inhibition 22, 18, 15 and 21 mm against the tested bacteria, respectively which were comparable to the value of Ciprofloxacin (25,23, 22, and 22 mm) against the same bacteria. The same compound **(18)** had inhibition zone 26 mm against fungi *Aspergillus niger* that was higher than reference drug Fluconazole (25 mm) and inhibition zone of (24 mm) against *Aspergillus fumigates* that was comparable to Fluconazole (26 mm) (Singaram et al., 2016).



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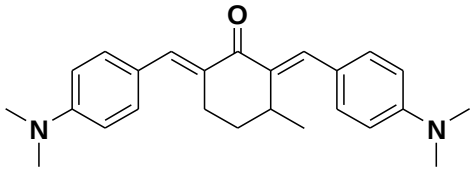
In 2012, Hawas *et al.* described the synthesis of curcumin analogues and tested them for their antimicrobial activity. The result revealed that compound **(19)** had inhibition zone 1.15, 1.95 and 1.85 cm against Gram-positive bacteria (*Bacillus subtilis*, *Bacillus aureus* and *Staphylococcus aureus*),respectively while compound **(20)** showed inhibition zone of 0.70 cm against tested Gram-negative bacteria (*Escherichia coli*) and compound **(21)** had inhibition zone 2.10 cm against Fungi (*Aspergillus niger*) these results were comparable to standard drugs Ampicillin and Chloramphenicol (Hawas et al., 2012).



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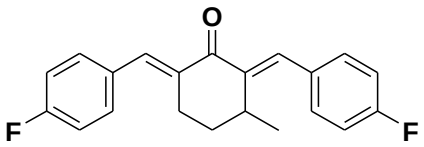

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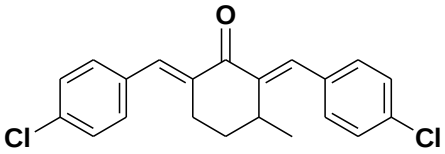

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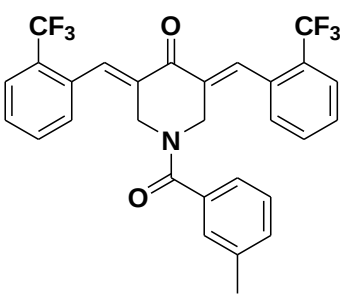
2.3. Anti-inflammatory activity.

In 2017, Xie *et al* prepared a total of 24 *N*-substituted-3,5-bis-(2-(trifluoromethyl) benzylidene) piperidin-4-one derivatives as curcumin analogues and the anti-inflammatory activity of these compounds were evaluated. The result revealed that compounds **(22)** and **(23)** displayed potent anti-inflammatory activity by the inhibition of LPS-stimulated TNFα,IL-6, IL-1β, PGE2. The oral and intravenous administration of these compounds significantly decreased paw edema inflammation in rats that was induced by carrageenan. The pharmacokinetic of compound **(22)** revealed that it had oral bioavailability better than curcumin (Xie et al., 2017).

In 2013, Wu *et al.* prepared a series of piperid-4-one-containing mono-carbonyl analogues of curcumin and their inhibitory effects against IL-6 production were evaluated in lipopolysaccharide (LPS)-stimulated macrophages. The result revealed that compounds **(24-28)** exhibited IC_{50} values under 5 μm. Moreover, compounds **(27)** and **(28)** dose-dependently prevented LPS-induced NF-kB and ERK activation. Finally, pretreatment with compounds **(27)** and **(28)** significantly protected the C57B/L6 mice from LPS-induced septic death (Wu et al., 2013).



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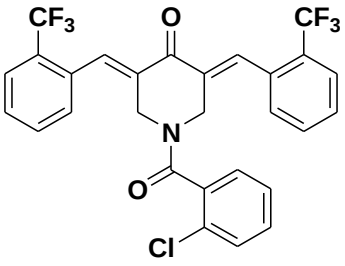

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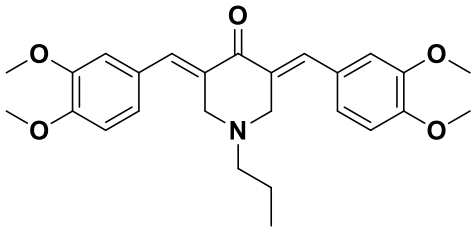

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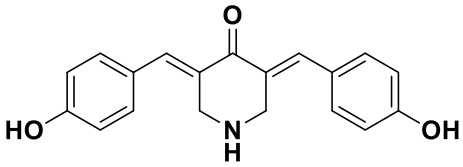

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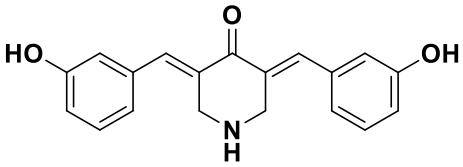

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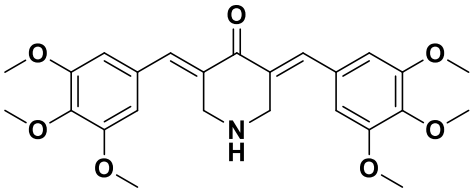

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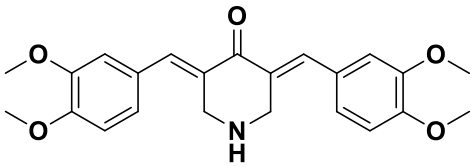

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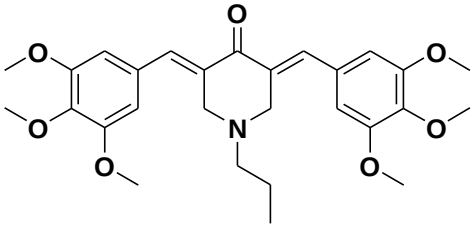
2.4. Anti-hypertension activity.

In 2016, Zhuang *et al*. described the preparation of curcumin inspired analogues and evaluated them for their antihypertension activity. These analogues were able to reduce hypertension *in vitro* through ACE inhibition and vasodilatation of artery. The potentiation of NO donor activity was suggested to be responsible for vasodilation mechanism. Compound **(29)** was the most active analogue and resisted metabolic deactivation in mice resulting in better bioavailability than curcumin. (Zhuang et al., 2016)



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3. Conclusion

Curcumin is a natural compound that has a wide range of biological activities including anti-inflammatory, anti-hypertension, antibacterial and anticancer but its low water solubility and selectivity make its use as therapeutic agent difficult. This review showed some of changes that can enhance the desired activity and eliminate undesired characters. It also illustrates some curcumin analogues that were obtained through changes on curcumin structure and have better anti-inflammatory, antihypertension, antibacterial, and anticancer activity than curcumin and even better than the reference drug.

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