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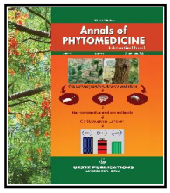

Review Article : Open Access

# 1, 3-diketo curcumin scaffolds: A gateway to profuse bioactive heterocycles

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**Abstract**

Curcumin (1,7-bis(4-hydroxy 3-methoxy phenyl)-1,6-heptadione-3,5-dione), also known as diferuloyl methane, is a polyphenolic compound with a 1,3-diketo moiety at its core. Natural curcumin's therapeutic application is limited due to its low bioavailability and instability. Many chemical modifications to the curcumin framework have been documented, either to improve bioavailability or to develop novel therapeutic candidates. The modification of curcumin's 1,3-diketone group by heterocycles such as pyrazole, isoxazole, pyrimidine, and other heterocycles is the subject of current review. Overall, the current review focus on the modification of curcumin's chemical structure, which resulted in important derivatives with enhanced pharmacokinetic characteristics and biological activities.

## 1. Introduction

Curcumin indicated as 01 is a yellow-orange phenolic compound derived from the turmeric plant (*Curcuma longa* L.) that has anti-inflammatory (Farhood *et al.*, 2019), antioxidant (Jakubczyk *et al.*, 2020), antibacterial (Zheng *et al.*, 2020), antiangiogenic (Shakeri *et al.*, 2019), anticancer (Shaikh *et al.*, 2021; Taha *et al.*, 2019) and antiproliferative properties in cancer cell lines (Baldi *et al.*, 2020; Tomeh *et al.*, 2019). Its use as a therapeutic agent is limited by its exceedingly low oral bioavailability (Hassanzadeh *et al.*, 2020; Sabet *et al.*, 2021). In a reducing chemical environment, curcumin loses its activity instantly (Yewle *et al.*, 2019). It also exists in solution as a tautomeric combination of keto and enol forms, with the enol form being responsible for the compound's rapid breakdown (Figure 1). The curcumin and quercetin mixture has hepatoprotective efficacy, according to antioxidant parameters and histopathological tests (Yadav *et al.*, 2021). Many recent studies have focused on synthesising various curcumin analogues to be effective in their actions such as antioxidants, antiproliferative and anti-inflammatory drugs to improve bioavailability and target selectivity (Ali, 2020; Kumar *et al.*, 2016; Lakey-Beitia *et al.*, 2017; Mohamed *et al.*, 2017; Noureddin *et al.*, 2019; Padhye *et al.*, 2010; Teiten *et al.*, 2014).

Many traditional and modern methods have been used for extraction and isolation of curcumin. The traditional extraction methods involve Maceration and Soxhlet extraction whereas ultrasound, microwave and enzyme assisted extractions are the most common methods. Tripathy and his team have mentioed the rhizome of the turmeric plant has been used to extract curcumin.The extraction of curcuminoids from *C. longa* using 69% ethanol, 21:1 liquid: solid ratio with a yield of 28.97 mg/g rhizomes powder has been mentioned (Tripathy *et al.*, 2021).

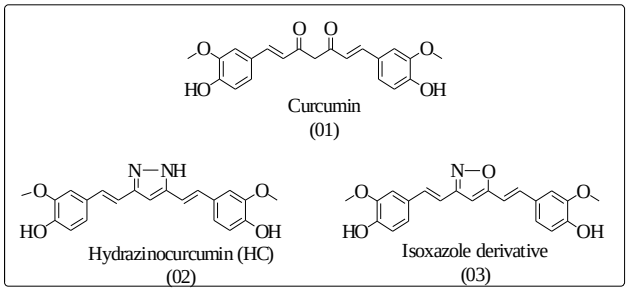


**Figure 1: Structures of curcumin 01 and its pyrazole 02 and isoxazole 03 derivative.**

Many research papers and earlier reports available on curcumin (Padhye *et al.*, 2010). Conversion of curcumin into heterocyclic derivatives showed promising biologically activities (Borik *et al.*, 2018; Martinez-Cifuentes *et al.*, 2015; Nabil *et al.*, 2018). Heterocycles play a vital role in biological processes (Rodrigues *et al.*, 2021; Desai *et al.*, 2021). The 1,3-diketone moiety of curcumin has been converted to oxime, heterocylic derivatives such pyrazole, isoxazole, and pyrimidine, diazepine, and other chemicals. It was discovered that isoxazole and pyrazole-modified curcumins were exceptionally stable at physiological pH and reducing conditions, and that they killed cancer cells under serum-depleted condition (Chakraborti *et al.*, 2013). When compared to the parent compound curcumin, the substitution of a heterocyclic ring for the 1,3-diketone

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group resulted in a significant increase in potency and a wide spectrum of biological activity. The modification of the 1,3-diketone group by heterocyclic groups is the theme of this review article. Recent advancements on heterocyclic curcumin analogues as a superior and favourable scaffold in medicinal chemistry were highlighted in this study.

## 2. Modification of curcumin as five membered heterocyclic analogues

Curcumin can be converted to its pyrazole 02 or isoxazole 03 analogues (Figure 1) by refluxing with hydrazine or hydroxylamine hydrochloride. Several curcumin derivatives with pyrazole or isoxazole groups were developed based on these studies and exhibited various biological activities (Zhang *et al.*, 2019). Curcumin's keto-enol moiety was converted to a pyrazole or isoxazole derivative, which boosted cytotoxicity against numerous cell types. Nitrogen substituted pyrazole rings in curcumin analogues have shown greater efficacy than curcumin.

### 2.1 Curcumin pyrazole and isoxazole analogues as anticancer and antiproliferative agents

Hydrazinocurcumin 02 is a synthetic pyrazole derivative of curcumin (Figure 1). It has antitumor properties and observed to slowdown the tumour growth in several malignancies. Hydrazin curcumin 02 showing more favourable pharmacological characteristics than curcumin, inhibited signal transducer and activator of transcription 3 (STAT3) and had a potent suppressive effect on the carcinogenicity of breast cancer cells. It showed $IC_{50}$ values of 3.37 µM for MDA-MB-231 and 5.26 µM for MCF-7 breast cancer cells by MTT assay (Wang *et al.*, 2012).

Marti-Centelles and his team studied the cytotoxicity compound 02 in three tumour cell lines (HT-29, MCF-7, and HeLa) as well as one non-malignant human cell line (HEK-293). It was cytotoxic at low concentrations with $IC_{50}$ values ranging from 0.72 to 11.1 µM. Compound 02 was more active than curcumin against all cell lines tested (Marti-Centelles *et al.*, 2016).

Compound 02 also suppressed the proliferation of hepatocellular carcinoma (HCC) cells and caused them to apoptosis. Hepatocellular carcinoma cells were induced to apoptosis by 02 *via* the p38 MAPK pathway. It was observed that 40 µM of 02 exhibited the best pro-apoptotic effect in HCC cells. *In vivo* experiments showed that compound 02 inhibited tumour growth more efficiently than 5-fluorouracil (5-FU) *via* the p38 MAPK pathway. Thus, 02 can exert antioncogenic and proapoptotic effects in HCC through activation of p38 MAPK signalling (He *et al.*, 2021).

In HA22T/VGH liver cancer cells and other tumour cell types, hydrazinocurcumin 02 and its isoxazole analogue 03 showed higher cell growth inhibition and stronger proapoptotic effects than curcumin. Growth inhibition analysis in HA22T/VGH cells showed $IC_{50}$ values (means ± SE) of 17.4 ± 1.2, 2.47 ± 0.6 and 12.8 ± 1.5 µM for curcumin 01, 02 and 03, respectively. Compounds 02 and 03, unlike curcumin, did not sensitise HA22T/VGH cells to cisplatin treatment, an outcome that was likely due to interactions with thiol groups of bionucleophile. As a result, the chemo-sensitization potential of 02 and 03 is reduced (Labbozzetta *et al.*, 2009).

In a male Sprague Dawley (SD) rat model, Zhou and his team investigated the effects of 02 on diethylnitrosamine (DEN)-induced hepatocarcinogenesis. The study showed that DEN caused serious histological and immunohistochemical changes in liver tissues, with levels of liver marker enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), γ-glutamyltransferase (GGT), and total bilirubin level (TBL) significantly increasing. Compound 02 effectively inhibited hepatocarcinogenesis produced by DEN. Significant differences between the groups were found using PCNA immunohistochemistry. Together, these findings revealed that curcumin and 02 may help to prevent cancer (Zhao *et al.*, 2014).

The anticancer effects of curcumin 01 and its isoxazole derivative 03 were unaffected by several gene expression alterations in a multidrug resistant (MDR) model of the MCF-7 breast cancer cell line. Curcumin and 03 had similar antitumor efficacy in the MDR cell line and the parent MCF-7 cell line. In MCF-7R cells, isoxazole 03 induced minimal changes in NF-κB, STAT3 expression and had antiproliferative and cell death effects comparable to those seen in MCF-7 cells (Poma *et al.*, 2007).

Isoxazole and pyrazole derivatives were also investigated for their cytotoxicity in human MCF-7 breast carcinoma cells. A concentration of 10 µM after 48 h showed inhibition of 38 ± 2%, 42 ± 5% and 28 ± 4% for 02, 03 and curcumin, respectively. These results indicated that 02 and 03 exhibited higher cytotoxicity compared to curcumin in these cancer cells (Priyadarsini *et al.*, 2020).

The cell growth inhibitory and apoptosis inducing effects of isoxazolederivative 03 were assessed by *in vitro* analysis both in hepatocellular cancer HA22T/VGH cells and in MCF-7 breast cancer cells as well as its MDR variant MCF-7R. Isoxazole derivative 03 showed increased antitumor activity against all cell lines and inhibited constitutive NF-κB activation. Cell growth inhibitory effects of the 03 evaluated after treatment for 72 h by MTS assays revealed $IC_{50}$ values of 12.8 ± 1.5 µM, 13.1 ± 1.6 µM and 12.0 ± 2.0 µM for HA22T/VGH, MCF-7 and MCF-7R cells, respectively (Simoni *et al.*, 2008).

Hydrazinocurcumin 02 and its bulky acid derivative hydrazinobenzoylcurcumin 04 were identified as *in vivo* inhibitors of angiogenesis (Figure 2). Compound 02 has a non-cytotoxic inhibitory effect against bovine aortic endothelial cells BAECs with an $IC_{50}$ of 0.52 mM, which was 30-fold higher than curcumin. With an $IC_{50}$ of 0.93 mM, compound 04 showed improved anti-proliferative efficacy against BAECs. Compound 04, on the other hand, was less active than 02 in terms of activity (Shim *et al.*, 2002).

Zhou and all team reported that 04 decreased human A549 non-small lung epithelial carcinoma cell proliferation *via* induction of autophagy. Inhibitory rate of 80 µM concentration of 04 on the *via* ability of A549 cells reached 76.68 ± 5.81% after 24 h (Zhou *et al.*, 2014). The effect of compound 04 on AMP activated protein kinase (AMPK) signalling was investigated further to check the role of 04 in autophagy of A549 cells. 04 activated AMPK signalling and induced AMPK-mediated autophagy, which played an important role for the inhibition of A549 cells by 04 (Zhou *et al.*, 2015). The connection between autophagy and apoptosis induced by HBC was distinguished. It was discovered that autophagy and apoptosis in 04 treated A549 cells could be mutually transformed, which was the first report on the connection between autophagy and apoptosis induced by

curcumin analogues. This will enable us to learn more about curcumin and its derivatives' anticarcinogenic mechanisms (Zhou *et al.*, 2015).

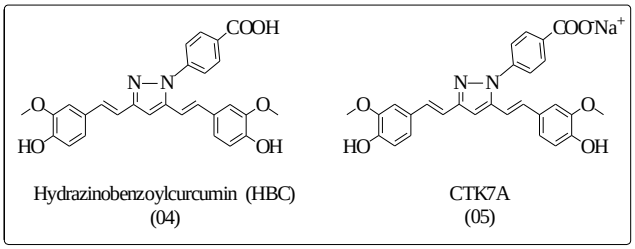


**Figure 2: Structures of curcumin pyrazole derivatives 04 and 05.**

Wu and his team reported that compound 04 inhibited androgen receptor activity and growth of castration-resistant prostate cancer in mice. Compound 04 bound exclusively to CaM, inhibited androgen receptor (AR) activity and suppressed the proliferation of both androgen-sensitive and castration-resistant AR-positive prostate cancer cells. The growth of castration-resistant prostate cancer tumors was inhibited by 04. These observations demonstrate that 04 is an effective compound in the treatment of castration-resistant prostate cancer (Wu *et al.*, 2015).

By inhibiting the histone acetyltransferase (HAT) activity of p300, the water-soluble hydrazinocurcumin derivative 05 (Figure 2) significantly inhibited oral tumour growth in a xenograft mice model. It was discovered that compound 05 inhibits HAT p300/CBP and PCAF, and so inhibits histone acetylation in the biological system, at least in part, through p300 autoacetylation inhibition. Compound 05 was innocuous to the mice after intraperitoneal administration (Arif *et al.*, 2010).

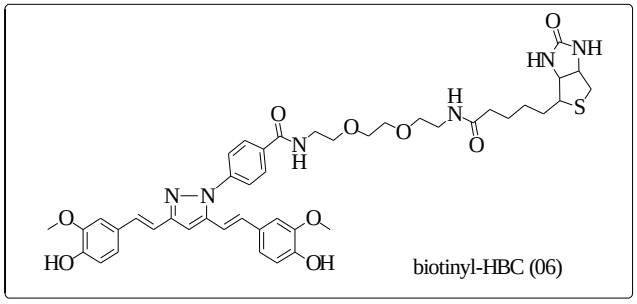


**Figure 3: Structure of a biotinylatedpyrazole derivative 06.**

Shim and his team synthesized the biotinylated derivative 06 as a molecular probe for target identification of $Ca^{2+}$/CaM (Figure 3). Compound 06 inhibited the proliferation of the HCT15 colon cancer cells with an $IC_{50}$ value of 42 µM, which is 2-fold less potent than that of the parent compound but still biologically active. It was concluded that these pyrazole derivatives inhibited the cell cycle progression of colon cancer cells through antagonizing $Ca^{2+}$/calmodulin functions (Shim *et al.*, 2004).

Fadda and his team developed pyrazole analogues 02, 07-10 (Figure 4). They tested their cytotoxicities both *in vitro* and *in vivo* against ehrlich ascites carcinoma (EAC). The cytotoxicity against EAC was enhanced when the ketoenol moiety was converted to the equivalent pyrazole. In this study, the compounds 02 and 08 were found to be the most active analogues (Fadda *et al.*, 2010).

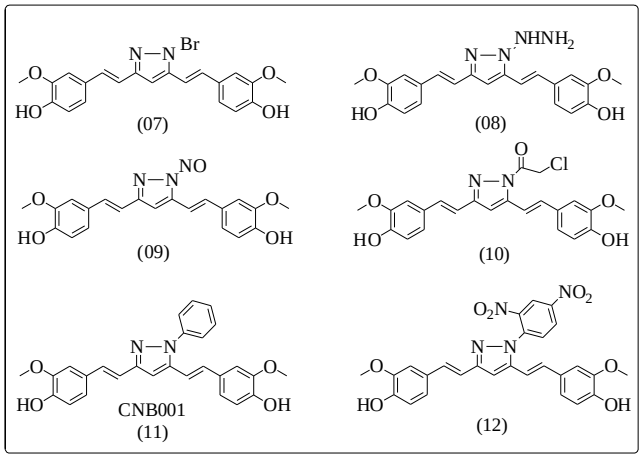


**Figure 4: Structures of pyrazole derivatives 07-12.**

The cytotoxicities of isoxazole and pyrazole curcumin analogues 02, 03, 11 and 12 against five human cancer cell lines were investigated against U-251 MG, glioblastoma; PC-3, human prostatic; HCT-15, human colorectal; K562, human chronic myelogenousleukemia; and SKLU-1. Some of the derivatives were more potent than curcumin against HCT-15 and K562 cells, with compound 11 having the highest $IC_{50}$ values of 5.0 ± 0.4 µM and 4.5 ± 0.2 µM in HCT-15 and K562 cells, respectively (Lozada-García *et al.*, 2017). Jordan and his team reported the synthesis and evaluation of pyrazole curcumin analogues 13-17 (Figure 5) for the treatment of head and neck cancer.The test compounds were sensitive to CAL27 and UMSCC-74A head and neck cancer cells at micromolar doses. Compound 15 was found to have significant cytotoxic effect against HNSCC cell lines. They showed increased cytotoxicity of compounds 15 and 17against CAL27 oral carcinoma cancer cell line compared to other compounds (Jordan *et al.*, 2018).

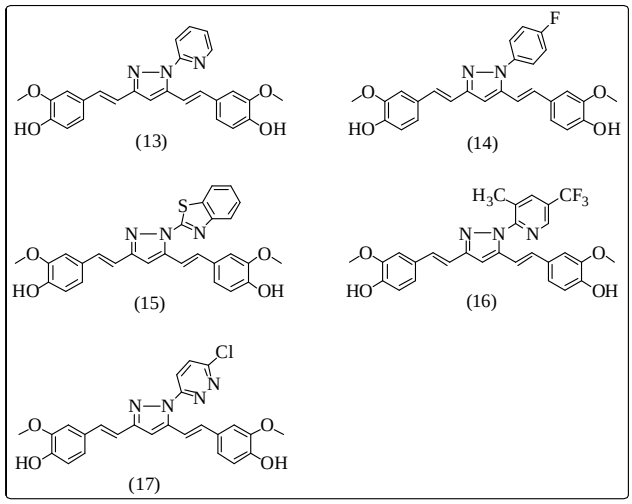


**Figure 5: Structures of pyrazole derivatives 13-17.**

Lien and his team synthesized a series of curcumin derivatives 02, 04, 12, 18-27 which were evaluated for their efficiency to degrade HER2 overexpressing cancer cells (Figure 6). All these compounds inhibit proliferation and clinical drug resistance of HER2-overexpressing cancer cells. Most of them showed significant cytotoxicity to SKOV3 cells which overexpressed HER2. Pyrazole

derivative 02 inhibited the expression of HER2 stronger than curcumin. The $IC_{50}$ value of compound 02 was 20 µM (Lien *et al.*, 2015).

The anticancer properties of pyrazole derivatives 11, 12, 22, 26 and 28 (Figure 7) were investigated using the MTT assay on various cancer cell lines. The analogues had significant $IC_{50}$ values ranging from 25.22 to 85.21 µM and inhibited proliferation in MCF-7, HeLa and K562 cell lines. Compound 22 demonstrated a high level of cytotoxicity and cell proliferation inhibition in cancer cells while having minimal growth inhibitory effects in normal cells (Puneeth *et al.*, 2016).

MTT assays were used to investigate the cytotoxicity of compounds 12, 29-31(Figure 7) against the cell lines Hep-G2, HCT-116 and QG-56. Compound 31 exhibited greater antiproliferative properties, with $IC_{50}$ values of 6.25 µM for Hep-G2 and HCT-116 and 12.5 µM for QG-56.42, according to the structure-activity relationship (Sahu *et al.*, 2016).

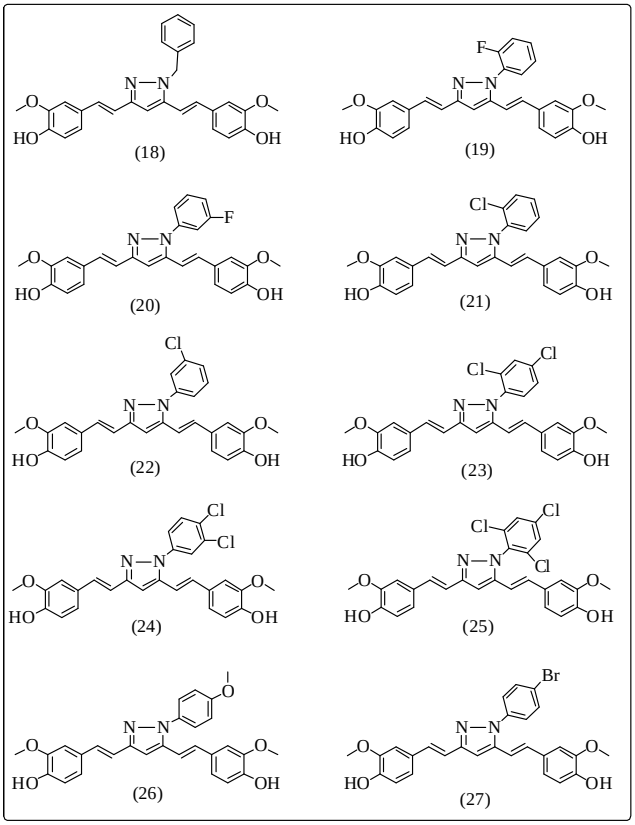


**Figure 6: Structures of pyrazole derivatives** 18-27.

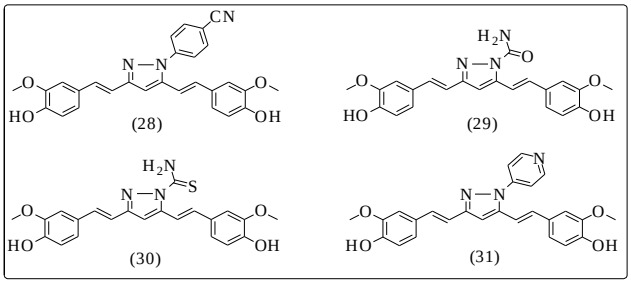


**Figure 7: Structures of pyrazole derivatives** 28-31.

Ahsan and his team produced a series of curcumin pyrazole derivatives 29, 32-41(Figure 8) and tested their antiproliferative activity on 60 cell lines including colon cancer, leukaemia, non-small cell lung cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, and breast cancer. All the test compounds had antiproliferative action across a wide range of cancer cell lines. The leukaemia cell lines produced the best results, with $IC_{50}$ values ranging from 0.0912 to 0.365 µM. Compound 29 was the most active of the series, with $GI_{50}$ values ranging from 0.0912 to 2.36 µM. It demonstrated unique activity on roughly 42 cell lines and was the most active of the series (Ahsan *et al.*, 2015).

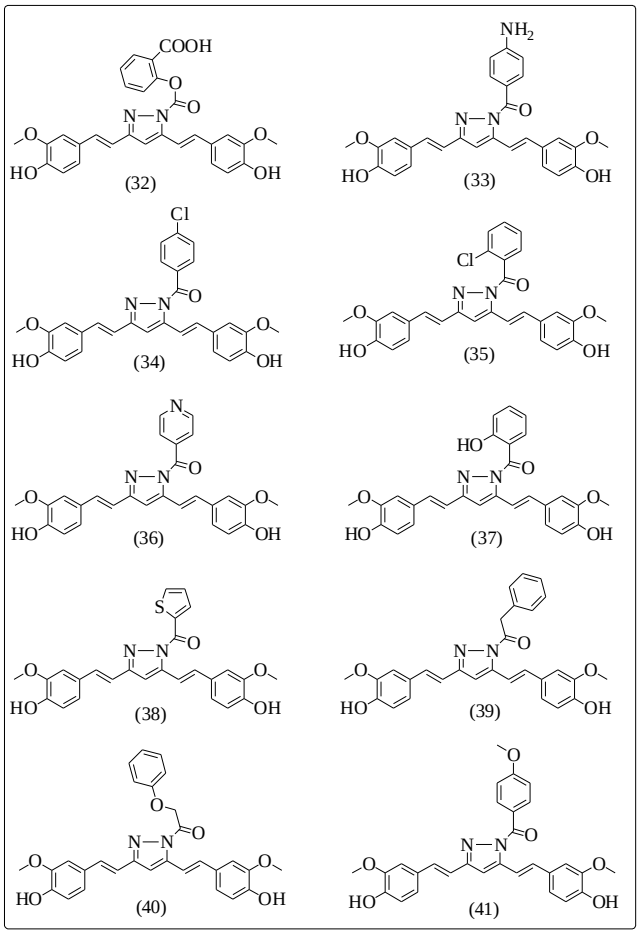


**Figure 8: Structures of pyrazole derivatives** 32-41.

Curcumin analogues 42-46 were tested *in vitro* against leukaemia, non-small cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer and breast cancer cell lines (Figure 9). In a single dose assay (drug concentration 10 µM), analogues 42-46 demonstrated promising anticancer efficacy, with mean percent growth inhibition ranging from 112.2 to 40.1 %. In the one-dose assay, compound 45 showed the highest mean percent growth inhibition (Ahsan, 2016).

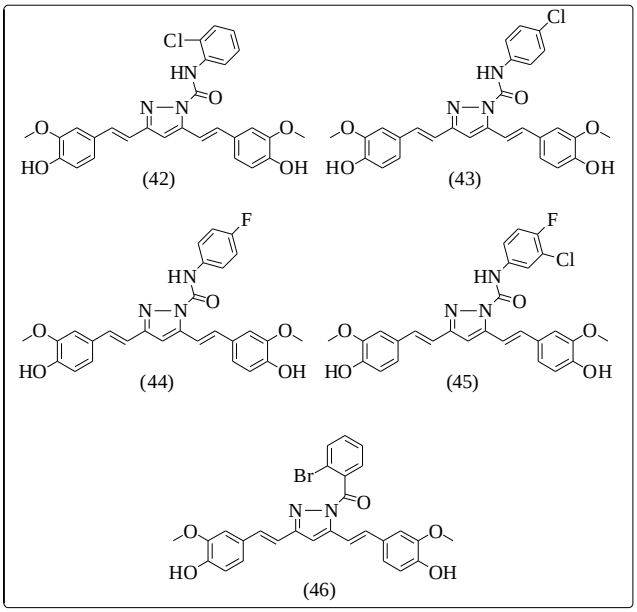


**Figure 9**: **Structures of pyrazole derivatives** 42-46**.**

**Table 1: Potent activity of compounds** 42-46 **against tumor cells**

| Compounds | Highest sensitivity ($GI_{50}$) | Least sensitivity ($GI_{50}$) |
|---|---|---|
| 42 | SR (leukemia) (0.03 µM) | OVCAR-5 (ovariancancer) (3.30 µM) |
| 43 | SR (leukemia) (0.06 µM) | HT29 (colon cancer) (2.52 µM) |
| 44 | MDA-MB 435 (melanoma) (0.23 µM) | SW620(colon cancer) (54.90 µM) |
| 45 | SR (leukemia) (0.04 µM) | COLO205 (coloncancer) (1.73 µM) |
| 46 | SR (leukemia) (0.03 µM) | OVCAR-5 (ovariancancer) (2.67 µM) |

Khatun and her team investigated the antitumor potential of compound 02 complexed with hydroxypropyl beta-cyclodextrin (HPbCD). The MTT assay was used to analyse the cytotoxicity of 02 and its cyclodextrin complex in A549 lung cancer cell lines. After 48 hours, the inclusion complex CPCD displayed better cytotoxicity against A549 cancer cells at a higher dose (100 g/ml) than curcumin 01 and compound 02 combined. The structural modification and additional complexationin curcumin did not appreciably alter its anticancer efficacy, according to the findings (Khatun *et al.*, 2020). It was reported that compound 02 encapsulated nanoparticles (NPs) could re-polarize tumor-associated macrophages (TAMs) from antiinflammatory (M2-like, tumorpromoting) to proinflammatory phenotype. 02 encapsuled nanoparticles could switch to M1-like phenotype, low IL-10, high IL-12, low TGF-β and the "re-educated" macrophages (M1-like macrophages) considerably demonstrated opposite effects on M2-like macrophages, especially the induction of 4T1 cells migration and invasion *in vitro* and suppression of tumor growth, angiogenesis and metastasis *in vivo*. 02 NPs were able to reverse TAM phenotype and could regulate their crosstalk between tumor cells and TAMs to suppress tumor progression (Zhang *et al.*, 2013).

Kumari and her team synthesized 02 loaded PEGylated galactomannan (GM) nanoparticles (PSGMHCNPs) and assessed their anticancer capacity to repolarize tumorassociated macrophages (TAMs) in 4T1 cells, EAC cells, and EAC-bearing mice by the participation of M1-like polarization in macrophages. The PSGM-HCNPs reduced tumor burden, increased survival time, reduced $CD206^{+}F4/80^{+}$ cells and enhanced TNF-$a^{+}F4/80^{+}$ cells signifying decrease in M2- and increase in M1-like dissymmetry among ascitic TAMs (Kumari *et al.*, 2019).

## 2.2 Curcumin pyrazole and isoxazole analogues as anti-neurodegenerative agents

Anti-Parkinson and anti-Alzheimer medications, anticonvulsants, and analgesics are all associated to anti-neurodegenerative drugs. Alzheimer's disease (AD) is the most common type of dementia. It is an irreversible, degenerative brain ailment that gradually destroys memory and thinking abilities. Major symptoms of this disease include the brain, senile plaques, and neurofibrillary tangles, which are aberrant aggregation of amyloid β (Aβ) peptide and tau protein (Okuda *et al.*, 2016). The accumulation of amyloid β (Aβ) and tau plays a key role in the onset and progression of Alzheimer's disease. As a result, inhibiting amyloid formation and tau aggregation could be considered a possible treatment target for Alzheimer's disease. Parkinson's disease is the second-fastest-progressing chronic neurodegenerative illness after Alzheimer's disease. Parkinson's disease is defined by the progressive degradation of nigrostriatal dopaminergic neurons due to apoptosis and inflammation, resulting in a variety of behavioural abnormalities. As a result, an antiapoptotic and anti-inflammatory regimen may be effective in the treatment of Parkinson's disease (Jayaraj *et al.*, 2014).

Phenylpyrazole derivative 11, CNB-001 is a new hybrid compound made from curcumin and phenyl hydrazine. Compound 11 has been shown to have neuroprotective and memory-improving effects. $Ca^{2+}$/calmodulin dependent protein kinase II (CaMKII), which is involved in long-term potentiation (LTP) and memory, was activated by 11 (Maher *et al.*, 2010).

It has been reported that 11 can cross the blood-brain barrier and exert neuroprotective effects against various types of toxic substances, including L-glutamate and amyloid α protein, the main constituent of senile plaques found in the brain of patients with Alzheimer's disease. Compound 11 possesses neurotrophic factor-like action that outperforms curcumin. Compound 11 replicated the impact of BDNF and increased cell survival in the HT22 oxidative stress experiment. Curcumin was inert in this assay, and 11's actions were TrkB receptor independent. In cell culture experiments for trophic factor withdrawal, oxidative stress, excitotoxicity, and glucose starvation, as well as toxicity from both intracellular and extracellular amyloids, compound 11 was found to be neuroprotective (Liu *et al.*, 2008).

Neuroprotective and memory-enhancing effects were shown for 11 and thus, it may be effective for the treatment of Alzheimer's disease. The compound not only subdued lipopolysaccharide (LPS)-induced nitric oxide (NO) production but also concealed LPS-induced nuclear translocation of nuclear factor κB (NF-κB), and expression of inducible NO synthase (iNOS). Thus, the efficacy of the pyrazole derivative

was superior to curcumin. The compound displayed anti-inflammatory effects based on the inhibition of NF-κB and p38 MAPK pathways in microglia, and the suppression of iNOS. These results propose a therapeutic potential for a variety of neurodegenerative diseases related to inflammatory conditions (Akaishi *et al.*, 2018).

In a rigorous rabbit ischemic stroke model, Lipchakand his team evaluated 11 and confirmed the molecular basis of its *in vivo* efficacy. Both cell culture and animal stroke models showed that 11 was effective. The calcium/calmodul independent kinase (CaMK) signalling pathways linked with neurotrophic growth factors, which are essential for brain function, were conserved in 11. Compound 11 has a lot of potential for treating ischemic stroke, as well as other CNS disorders (Lapchak *et al.*, 2011).

Compound 11 protected neuronal cells by antioxidant, antiapoptotic mechanisms and by its action on mitochondria. 11 (100 nM) increased SK-N-SH cell *via* ability, decreased reactive oxygen species (ROS) formation, maintained normal physiological mitochondrial membrane potential, and reduced apoptosis in Parkinson's disease. Moreover, 11 inhibited downstream apoptotic cascade by enhanced the expression of Bcl-2 and reduced the expression of Bax, caspase-3 and cytochrome C (Jayaraj *et al.*, 2013).

Compound 11 also exhibited biological activity in the glutamate based oxytosis assay and extracellular amyloid toxicity. It showed an $EC_{50}$ values of 460 nM (amyloid α, Aα) and 1.8 µM (HT22 cells). 11 is an orally active, neurotrophic molecule that facilitated memory in normal rodents and prevented the loss of synaptic proteins and cognitive decline in a transgenic AD mouse model (Chen *et al.*, 2011).

The anti-inflammatory and antiapoptotic neuroprotection by 11 was investigated on the 1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine (MPTP) model of Parkinson's disease (PD), too. 11 normalized neuro-inflammatory stress induced by MPTP. Co-treatment of MPTP with 11 notably reduced motor impairments and pathological changes caused by MPTP administration. 11 also protected dopaminergic neurons against MPTP toxicity by regulation of various molecular and cellular mechanisms (Jayaraj *et al.*, 2014).

Human 5-lipoxygenase and 15-lipoxygenase were inhibited by compound 11 and the ischemia-induced inflammatory response was reduced. Compound 11 could be a promising new treatment option for aortic occlusion-induced spinal cord ischemia (Lapchak *et al.*, 2019). It inhibits 5-LOX and 15-LOX, balances neurotrophic factor and synaptic plasticity pathways and slows the spread of the ischemic penumbra in NHPs with a permanent occlusion. *In vitro*, compound 11 was a powerful 5-LOX inhibitor that also inhibited 15-LOX. Both enzymes have been identified as possible stroke therapeutic targets for vascular and neuronal protection (Lapchak *et al.*, 2019).

Calcium/calmodulin dependent protein kinase II (CaMKII) plays an important role for pathological glutamate signalling. Brain functions such as learning and memory are activated by calcium influx through the N-methyl-d-aspartate type glutamate receptor (NMDAR). To identify calcium/calmodulin dependent protein kinase II in pathological glutamate signaling, Mayadevi and her team synthesized compounds 02, 03 and 11. Compound 02 was the most effective inhibitor of CaMKII and more active than curcumin. It exhibited better CaMKII autophosphorylation ($IC_{50}$ 6.5 ± 3.38µM) than curcumin ($IC_{50}$ 33 ± 9.0 µM), 03 ($IC_{50}$ = 18.01 ± 1.61 µM) and 11 ($IC_{50}$ = 111 ± 11.49 µM). 02 as well as natural curcumin could offer neuroprotective action in the excitotoxic cascade by inhibiting CaMKII activity (Mayadevi *et al.*, 2012).

Airoldi and his team synthesized pyrazoles 47-50 (Figure 10) which were tested for their ability to interact with Aβ peptide oligomers and to stain amyloid deposits in TgCRND8 mice. All compounds interacted with Aβ peptide oligomers without inducing their aggregation similar to curcumin. Due to their potential to interact with Aα peptides-oligomers and plaques these compounds could be very good and promising candidates for possible future applications both for the therapy and for the diagnosis of Aβ related diseases (Airoldi *et al.*, 2011).

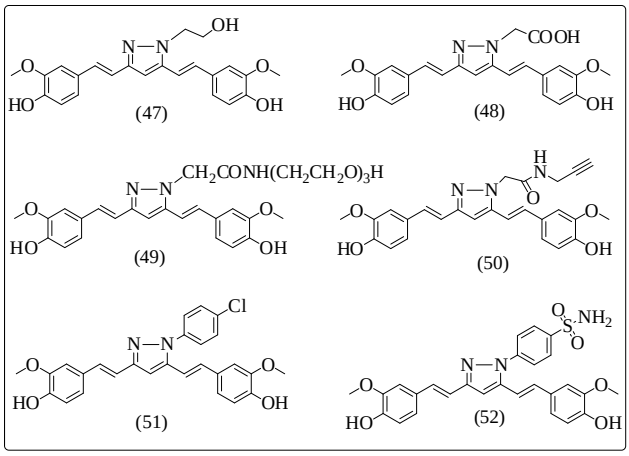


**Figure 10: Structures of pyrazole derivatives** 47-52.

Cell survival and LDH release were used to assess the neuroprotective effect of pyrazole compounds 04, 14, 26, 28, 51 and 52 on sodium nitroprusside (SNP)-induced PC12 cell damage. When compared to curcumin and edaravone, compounds 14, 26, 28 and 51 show a higher protective effect. In PC12 cells, compounds 14, 26, 28 and 51 lowered intracellular ROS generation, with compound 28 being the most efficient, with high antioxidant activity backed up by suppression of mitochondrial membrane potential loss and increased nuclear translocation of Nrf2 (Liao *et al.*, 2019). Effects of curcumin derivatives 02, 18-23, 27-28, 47 and 53-56 (Figure 11) on synuclein aggregation, fibril dissociation and toxicity were studied by Ahsan and his team. Using a combination of biochemical, biophysical and cell-based analysis, they stated that pyrazole 02 and its N-3-nitrophenylpyrazole derivative of curcumin 55 destroyed pre-formed fibrils and prevented the development of A11 conformation in the protein that conveys toxic effects. These works put forth that curcumin and its derivatives can dissolve amyloid fibrils into non-poisonous species and counter existing amyloid pathology. This approach of fibril separation into non-toxic species could lead to more effective clinical therapies for healing neurodegenerative diseases and other pathologies related to protein fibrillation. Compounds 02 and 55 decreased neurotoxicity associated with the fast aggregating A53T mutant form of α-aynuclein (Ahsan *et al.*, 2015).

Narlawar and his team reported that isoxazole 03, pyrazoles 02, 11, 17-18, 23, 47, 55, 57-61 (Figure 11) inhibited Aα secretion and the formation of fibrillary Aα42 and tau aggregates 10-100 folds more potent than curcumin. Several compounds were potent tau protein

aggregation inhibitors, excellent α-secretase inhibitors, had a high affinity for fibrillary Aα 42, and depolymerized tau protein clumps at low micromolar doses. When an aryl ring was added to the N-aryl pyrazole system, the inhibition of Aα secretion was enhanced by twofold. The most active compounds were 57 and 61, which had a lower cellular toxicity than curcumin (Narlawar *et al.*, 2007, 2008).

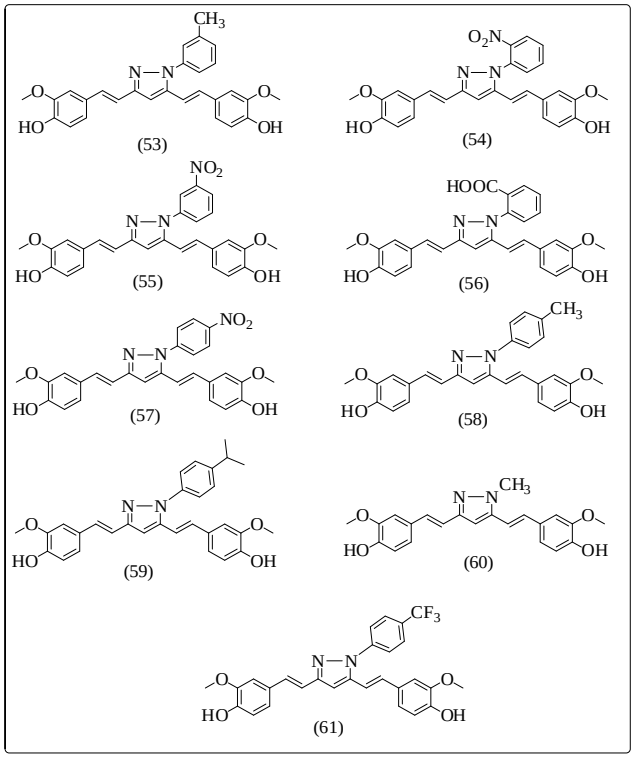


**Figure 11: Structures of pyrazole derivatives** 53-61.

## 2.3 Curcumin pyrazole and isoxazole analogues as antioxidant and anti-inflammatory agents

In lipopolysaccharide (LPS)-activated RAW 264.7 macrophages, Nathnarin and his team evaluated the anti-inflammatory effects of both curcumin 01 and pyrazole analogue 02 in RAW 264.7 macrophages. LPS-induced NO secretion in RAW 264.7 macrophages were inhibited by 02 ($IC_{50}$ = 3.7 ± 0.16 µM) at a greater efficacy than by curcumin ($IC_{50}$ = 11.0 ± 0.59 µM). 02 blocked lipopolysaccharide-induced inflammation *via* suppression of JNK activation in RAW 264.7 macrophages. Compound 02 significantly reduced the production of iNOS and COX-2, whereas curcumin only inhibited COX-2 at the same dose (Nathnarin *et al.*, 2018).

Analogues 02 and 03 showed antioxidant activity $IC_{50}$ values of 9.70 µM and 10.71 µM, respectively. These analogues significantly enhanced COX-2/COX-1 selectivity and possessed significant anti-inflammatory activity in the carrageenan induced rat paw edema assay. Compounds 02 and 03 exhibited anti-inflammatory activity at a dose of 75 mg/kg (68.8 ± 2.9 % inhibition for 02 and 60.3 ± 2.9 % inhibition for 03, carrageenan induced rat paw edema assay). Pyrazole analogue 02 was more potent than curcumin 01 while the isoxazole analogue 03 was equipotent to curcumin (Selvam *et al.*, 2005). Matrix metalloproteinase (MMP) inhibition by 02 was evaluated by zymographic analysis which revealed that 02 significantly down-regulated MMP-9 activity in inflammation-induced intestinal epithelial cells at a concentration of 50 µM (Claramunt *et al.*, 2009).

The effects of pyrazole 02 and isoxazole 03 on free radical scavenging was investigated using different free radicals assays and the results were compared with curcumin. It was shown that replacement of the 1,3-diketo moiety of curcumin with the pyrazole moiety not only ameliorated the peroxyl scavenging but also the stability of the resulting radical, serving the pyrazole moiety as a beneficial template for the rational design of new antioxidants that are more effective than the curcumin (Shaikh *et al.*, 2019).

The thiobarbituric acid reactive substances (TBARS) assay showed that compound 02 has potent activity $IC_{50}$= 0.6 ± 0.02 µM which was higher than the activity of curcumin, α-tocopherol and quercetin. The results were compared with values found in a DPPH assay showing that compounds 02 and 03 exhibited antioxidant activity mainly by lipid peroxidation inhibition (Lozada-García *et al.*, 2017).

Sherin and her team evaluated the antioxidant activities of 02-04, 11, 26, 51 and 56 based on DPPH, FRAP and β-carotene bleaching assays. The results showed that these compounds were stronger antioxidants than curcumin. For isoxazole derivative 03, the DPPH assay showed an $EC_{50}$ value of 8 ± 0.11 µM and, thus, 03 was a much more antioxidant than curcumin ($EC_{50}$ = 40 ± 0.06 µM) and 02 (14 ± 0.18 µM) (Sherin *et al.*, 2015).

With the use of spectroscopic methods, Jayaraj and his team examined the *in vitro* antioxidant capacity of compound 11 by examining its ability to scavenge DPPH, ABTS, nitric oxide, superoxide, hydrogen peroxide, superoxide anion, hydroxyl, hydrogen peroxide radicals and reducing power. Plasmid DNA (pUC19) was treated to hydroxyl radicals and conventional agarose gel electrophoresis to assess DNA protective activities of compound 11. It was discovered that 11 effectively scavenged free radicals in a dose-dependent manner. It was found that 11 scavenged nitric oxide ($IC_{50}$ = 1.36 µg/ml), 2,2-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) ($IC_{50}$ = 17.99 µg/ml), superoxide ($IC_{50}$ = 36.92 µg/ml), DPPH ($IC_{50}$ = 44.99 µg/ml), superoxide radical ($IC_{50}$ = 77.17 µg/ml), hydroxyl ($IC_{50}$ = 456.5 µg/ml) and hydrogen peroxide ($IC_{50}$ = 492.7 µg/ml) radicals. The reducing power was 11.53 µg/ml. 11 exhibited plasmid DNA from strand scission by OH in a dose dependent manner (Jayaraj *et al.*, 2014).

Puneeth and his team compared the antioxidant activity of pyrazole derivatives 11-12, 22, 26 and 28 to that of the conventional antioxidant ascorbic acid utilising superoxide anion scavenging, DPPH, nitric oxide and lipid peroxidation assays. Compounds 11, 22 and 26 demonstrated anti-lipid peroxidation action by quenching superoxide anion radicals, DPPH, and nitric oxide. The actions of compounds 12 and 28 were only mild. Superoxide anions were also scavenged by compounds 11, 22 and 26 (Puneeth *et al.*, 2015).

Jha and his team disclosed the antioxidant activity, redox behaviour of curcumin and its modified derivatives 02, 11, 19-20, 56, 62-63 (Figure 12). The conversion of the 1,3-dicarbonyl moiety of curcumin into pyrazoles which reduced its rotational freedom, led to improved redox properties as well as antioxidant activities (Jha *et al.*, 2015).

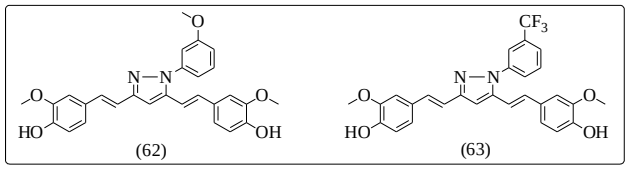


**Figure 12: Structures of pyrazole derivatives** 62-63.

Sahu and his team evaluated pyrazole derivatives 12 and 29-31 for their antioxidant activities. Compounds 12, 29-31 exhibited higher activity than curcumin. Among the tested compounds, 31 showed the highest DPPH scavenging activity (89.2%) (Sahu *et al.*, 2016).

1,3-diketo modified derivatives 02-03, 11-12, 29-30, 36 and 64 were evaluated for their anti-inflammatory and antinociceptive activities in experimental animal models. Additionally, inhibition of cyclooxygenase-2 (COX-2) enzyme was tested through *in vitro* assays. At 10 µM dose the test compounds showed 31.0 to 49.3 % COX-2 inhibition. Isoxazole 03 showed a higher inhibition of COX-2 than the pyrazole derivatives. Compound 09 exhibited the highest antinociceptive activity (74.9 %) compared to the standard drug diclofenac sodium and closely followed by compound 07 (73.2%) (Ahmed *et al.*, 2018).

## 2.4 Curcumin pyrazole and isoxazole analogues as antibacterial and antifungal

Compounds 12, 29-31 were evaluated for their antibacterial activities 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.*, *Aspergillusniger*, *Aspergillus fumigates*, *Aspergillusûavus*. Derivative 29 with an amide moiety at the hydrazine scaffold showed no significant activity while substitution of oxygen by a bigger sulphur atom showed immense antibacterial activity since 30 was active against all species except for *E. coli*. SAR study also showed that isoniazide 31 displayed equipotent antibacterial activity as ciprofloxacin against *S. aureus* (1.25 µM/ml) and *P. aeruginosa* (1.25 µM/ml). Electron withdrawing substituents at ortho and para positions such as a 2,4-dinitro phenyl group 12 have led to excellent activity against *S. aureus* and *B. cereus*. SAR study showed that a pyrazole moiety is additive to antibacterial activity (Sahu *et al.*, 2012). Curcumin derivatives 11-13 and 64-65 (Figure 13) were also evaluated for their antibacterial activities against gram-positive (*S. aureus*) and gram-negative bacteria (*P. mirabilis*, *E. coli*, *P. aeruginosa*). The compounds inhibited gram-positive microorganisms with a zone of inhibition ranging from 14-18 mm, and MIC ranging between 0.0625 and 0.25 mg/ml. All tested derivatives showed remarkable activity against gram-positive *S. aureus* bacteria. Compounds 13, 64 and 65 were more active than curcumin (Hamed*et al.*, 2013).

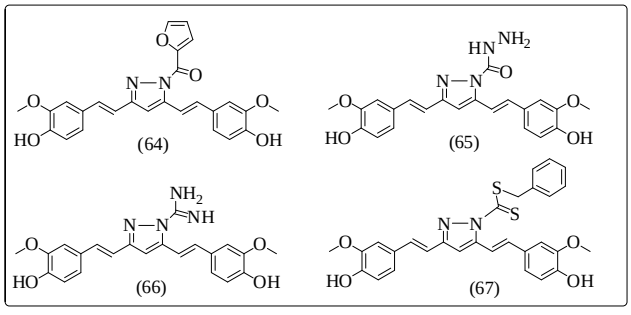


**Figure 13: Structures of pyrazole derivatives 64-67.**

N-substituted pyrazolecurcumin derivatives 29-30, 37 and 66-75 (Figure 14) were tested as antibacterial drugs. These pyrazole derivatives showed higher activities than curcumin against *B. subtilis*, *S. aureus*, *E. coli*, *A. niger* and *Penicillium*. The compounds 66, 73 and 75 showed significant antibacterial activities with inhibition zones ranging from 16.34 to 23.81 mm at a concentration of $1\times10^{-4}$ mol/l. Thiazole, guanyl and coumarin ring substituents enhanced the activities of N-substituted pyrazole curcumin derivatives when compared with their parent compound curcumin (Liu *et al.*, 2012).

## 2.5 Curcumin pyrazole and isoxazole analogues as Anti-mycobacterial tuberculosis agents

Antimycobacterial activity of 02, 03 and 11 was evaluated against *Mycobacterium tuberculosis*. Isoxazoleanalog 03 was highly active against *M. tuberculosis* strains; its MIC value for *in vitro* activity against *M. tuberculosis* H37Ra strain was 1.56 mg/ml, which was about 64-fold more active than the parent curcumin. 02 and 11 showed MIC 200 mg/ml and 25 mg/ml, respectively (Changtam *et al.*, 2010).

Similarly, compounds 02, 03, 24, 61 and 76 were evaluated for their *in vitro* and *in vivo* antimycobacterial activities against *M. tuberculosis*. Minimum inhibitory concentration drug-susceptible *M. tuberculosis* H37Rv greater than 60 g/ml for all compound except 03 showed it as 8 mg/ml (Singh *et al.*, 2017).

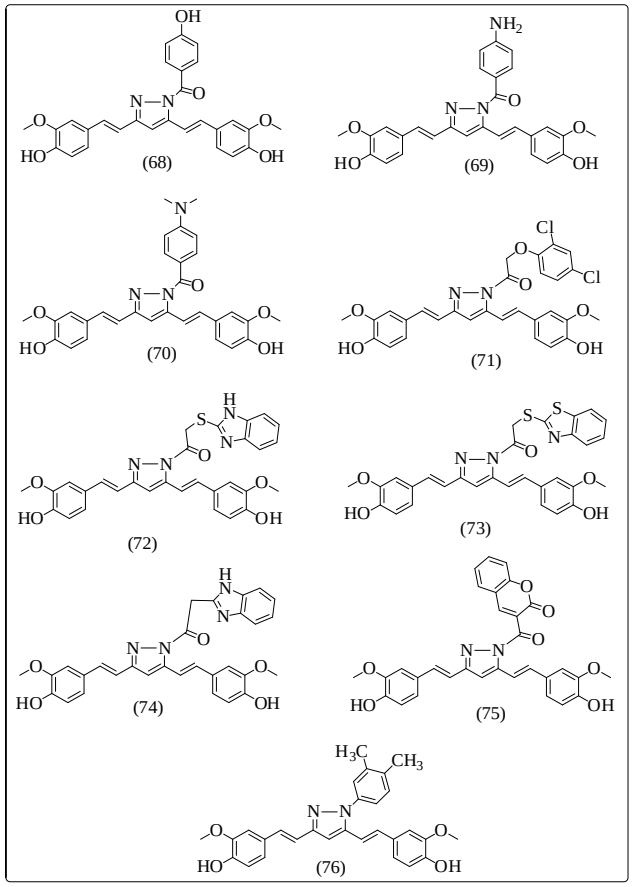


**Figure 14: Structures of pyrazole derivatives 68-76.**

## 2.6 Curcumin pyrazole and isoxazole analogues as antimalarial agents

The antimalarial activity of pyrazolecurcumin analogues 29, 34-44 and 77-80 (Figure 15)was investigated. All compounds showed parasiticidal activity with minimum killing concentrations (MKCs) between 4.18 and 19.86 µM and schizonticidal activity with $IC_{50}$ values between 4.21 and 19.72 µM. Compound 80 showed the

highest schizonticidal activity ($IC_{50}$ = 4.21 ± 0.62 µM) while 42 showed the highest parasiticidal activity (MKC = 4.18 ± 0.08 µM). 34 exhibited the lowest schizonticidal and parasiticidal activity of all test compounds (Balaji *et al.*, 2019).

Isoxazole derivative 03 and a series of pyrazole derivatives 02, 11, 14, 23, 26 and 55 were evaluated for their abilities to inhibit *Plasmodium falciparum* growth *in vitro*. Some of derivatives were more effective inhibitors of *P. falciparum* growth than curcumin. Compounds 02 and 55 were found to be the most efficient pyrazoles for CQ-S (chloroquine-sensitive), *P. falciparum* ($IC_{50}$ = 0.48, 0.87 µM) and CQ-R (chloroquine-resistant) *P. falciparum* ($IC_{50}$ = 0.45 µM, 0.89µM), respectively. 02 revealed seven times higher activity against the CQ-S strain and nine times higher activity against CQ-R than curcumin. In contrast to that, isoxazole 03 was less active than curcumin(Mishra *et al.*, 2008). Thus, the described curcumin pyrazole analogues may be promising lead structures for the design of new antimalarial agents.

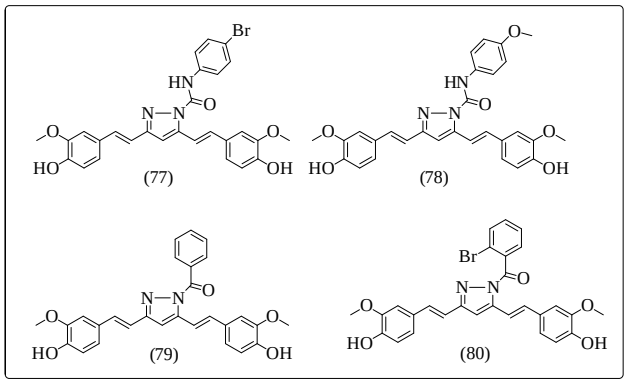


**Figure 15: Structures of pyrazole derivatives 77-80.**

## 2.7 Curcumin pyrazole and isoxazole analogues as antidiabetic agents

Curcumin had been studied in animal models to have the ability to lessen the effects of diabetes on key organs such as the heart and kidneys. Tetrahydrocurcumin was found to be more effective than curcumin at lowering blood glucose, improving carbohydrate metabolism, alleviating liver and kidney injury, and restoring the activities of multiple antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, catalase and glutathione S-transferase *in vitro* and *in vivo* experiments. The antidiabetic effect of 1,3 diketone-masked curcumin compounds is currently being studied (Rivera-Mancía *et al.*, 2015).

In mice fed a high-fat diet, compound 11 reduced glucose intolerance and insulin resistance. In addition, compound 11 decreased blood triglycerides, hepatic steatosis, interleukin-6 (IL-6) expression, muscle glucose absorption, and insulin signalling. Compound 11 increased insulin receptor and protein kinase B phosphorylation while suppressing the expression of protein tyrosine phosphatase 1 (PTP1B), a negative regulator of insulin signalling (Panzhinskiy *et al.*, 2014).

The effects of a series of curcumin pyrazole derivatives 11-12, 22, 26 and 28 on sucrose and inhibition of digestive enzymes including alpha-amylase and rat intestinal alpha-glucosidase were investigated. In the *in vitro* models used, all the compounds had hypoglycemic properties. The compounds elevated glucose absorption and insulin activity. Compounds 11 and 22 were the most effective in enhancing glucose absorption among the curcumin pyrazole derivatives examined. The hypoglycemic effects of 11 and 22 were found to be more pronounced. Compound 22 had the highest enzyme inhibitory activity and was a powerful inhibitor of carbohydrate hydrolysing enzymes (Ramesh *et al.*, 2015).

Inhibition of gluconeogenesis is a promising approach for an antidiabetic drug. The hypoglycemic potential by gluconeogenesis inhibition studies was investigated and all compounds of the series inhibited gluconeogenesis at different concentrations. Compounds 11 and 22 exhibited significant glucose lowering effects by inhibition of gluconeogenesis in rat liver slices. It was concluded that compound 22 possesses potent hypoglycemic properties and can be selected for further *in vitro* and *in vivo* antidiabetic investigations (Honnalagere *et al.*, 2015).

## 2.8 Miscellaneous activities of curcuminpyrazole and isoxazole analogues

1,3-diketo modified heterocylic curcuminoid pyrazole derivative 51 was tested for antiviral activity. Compound 51 showed antiviral activity against respiratory syncytial virus-RSV ($IC_{50}$ = 12.5 µM), which was distinctly more active than curcumin ($IC_{50}$> 50 µM) (Jiang *et al.*, 2015).

Human vascular endothelial growth factor (VEGF)-induced rabbit corneal neovascularization was inhibited by compound 02. On CorNV, topical treatment exhibited a remarkable therapeutic impact. In terms of vessel length and levels of cluster of differentiation 31 (CD31) proteins or angiogenesis-related genes such as VEGF, matrix metalloproteinase-2 (MMP2) and matrix metalloproteinase-9, the compound 02 was more efficient in decreasing CorNV (MMP9) (Zhan *et al.*, 2016).

Compound 02 was investigated for *in vivo* antinociceptive activity using the acetic acid induced writhing test while central antinociceptive activity was investigated using the hot plate method. 02 showed peripheral and delayed centrally mediated antinociceptive activity. These activities make it a potential lead compound for the development of new analgesics agents (Okalebo *et al.*, 2013).

Pyrazole and isoxazole analogues 02 and 03 were evaluated for urease inhibitory activity using the indophenol method. Compound 02 inhibited urease with an $IC_{50}$ value of 55.45 ± 0.35 µM, no inhibition was observed for 03 (Ahmed *et al.*, 2017).

Lee and his team tested compounds 02 and 52 as antiplatelet inhibitors. The compounds were evaluated against thrombin, ADP and collagen using an aggregometer. Compound 02 showed higher inhibition percentages for thrombin, ADP and collagen than the substituted pyrazole compound 52 (Lee *et al.*, 2014).

*In vitro* hypolipidemic activities of 11-12, 22, 26 and 28 were investigated by Puneeth and his team. The compounds were screened for the inhibition of enzymes such as pancreatic lipase, glucose-6-phosphate dehydrogenase and malate dehydrogenase which are actively involved in lipid metabolism. Curcumin and compound 22 showed prominent pancreatic lipase inhibitory activity with $IC_{50}$ values of 17.39 and 16 µM, respectively. Curcumin, 11 and 22 had considerable malic dehydrogenase inhibitory activity and the $IC_{50}$ values were 23.42, 18.54 and 22.82 µM, respectively. Glucose-6-

phosphate dehydrogenase was inhibited significantly by curcumin, 11, 22 and 26 with $IC_{50}$ values of 17.41, 17.11, 14.02 and 18.7 µM, respectively (Puneeth *et al.*, 2016).

Taking into consideration, curcumin's low bioavailability and stability, Gupta and his team tested 3,4-dichlorophenyl pyrazole 24 for antiadipogenic activity. 24 was a potent *in vitro* inhibitor of adipogenesis. It blocked mitotic clonal expansion by induction of cell cycle arrest. 24 showed improved gastrointestinal stability and bioavailability as well as *in vivo* antiadipogenic activity when compared to curcumin. 24 demonstrated antiadipogenic potential in three different cell models (3T3-L1, C3H10T1/2 and hMSC cells) of adipogenesis. 24 inhibited adipogenesis and ameliorated dyslipidemia by activation of reverse cholesterol transport (Gupta *et al.*, 2017).

Suppressive effects of 11 on airway inflammation and remodelling were reported by Narumoto and his team. Compound 11 extensively obscured IL-6, TNF-α, GM-CSF production by NHBE cells and downregulated the level of active serine peptidase inhibitor. 11 was more active than curcumin or dexamethasone (DEX). The level of active serine peptidase inhibitor clade E member (SERPINE) was significantly downregulated by 11, which is related to airway remodelling (Narumoto *et al.*, 2012).

## 3. Six membered heterocyclic analogues

Curcumin modifications as six membered heterocycles are uncommon compared to five membered heterocycles.The reaction with urea, guanidine, or thiourea yielded six-membered pyrimidines.

On nine separate cell panels, compound 81 was tested for anticancer activities (leukemia, non-small cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer and breast cancer). Compound 81 showed highest activity against HT-29 cells (colon cancer) with a $GI_{50}$ value of 1.30 µM and lowest activity against NCI ADR-RES cells (ovarian cancer) with a $GI_{50}$ value of 16.7 µM. The best value of total growth inhibition (TGI) was noted in HCT-116 (colon cancer) with 1.24 µM (Ahsan, 2016).

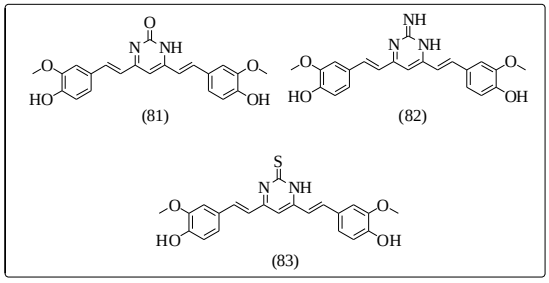


**Figure 16: Structures of pyrimidines 81-83.**

Pyrimidine derivatives 81-83 (Figure 16) were investigated for urease enzyme inhibition. Compound 83 was found to be the most potent derivative ($IC_{50}$ = 2.44 ± 0.07 µM). Compound 81 showed an $IC_{50}$ value of 35.83 ± 0.34 µM, whereas 82 showed no urease inhibition. In addition, pyrimidines 81-83 were tested for their anti-inflammatory, antinociceptive and cyclooxygenase-2 inhibitory activities. COX-2 *in vitro* inhibition assays results revealed that compound 82 showed 75.3 % inhibition being the most active compound (Ahmed *et al.*, 2018; Hamed *et al.*, 2020).

Balaji and his team tested 81, 83 for their antimalarial activity. Compound 81 showed significant maximum schizonticidal ($IC_{50}$ = 1.48 ± 0.10 µM) and parasiticidal activities (MKC; 3.87 ± 0.36 µM) and was identified as a promising lead compound for further investigations (Balaji *et al.*, 2019).

Nabil and his team tested compounds 81-83 for their antidiabetic activity (amylase inhibition assay) and antihistamine activity (histamine release activity assessed from U937 human monocytes). Compound 81 exhibited significant inhibitory activity against amylase and antihistamine activity (Nabil *et al.*, 2018).

## 4. Other heterocyclic analogues

Diazepine compound 84 was prepared and evaluated for its antibacterial activity. Compound 84 showed remarkable activity against *S. aureus* with zone of inhibition of 27 mm, which meant higher activity than ampicillin. The minimal bactericidal concentration (MBC) for compound 84 was 0.0075 mg/ml (Liu *et al.*, 2012). In continuation of this research 1,4-benzodiazepines 85-89 (Figure 17) were synthesized along with 84 and evaluated for their *in vitro* antimicrobial activity against gram-positive (*S. aureus* and *S. epidermidis*) and gram-negative (*E. coli* and *P. aeruginosa*) bacteria. Minimum inhibition concentration (MIC) results showed that halogenated compounds (except for the fluorinated one) showed excellent activity against *S. aureus*. The highest activity and lowest total inhibition of gram-positive bacterial growth (MBC) values were determined for compounds 84 and 89 (7.5 µg/ml and 12.0 µg/ml, respectively). Dichlorinated benzodiazepine derivative 89 destroyed the cell membrane of *E. coli* and showed potent genotoxic activity against *E. coli* (Hamed *et al.*, 2020).

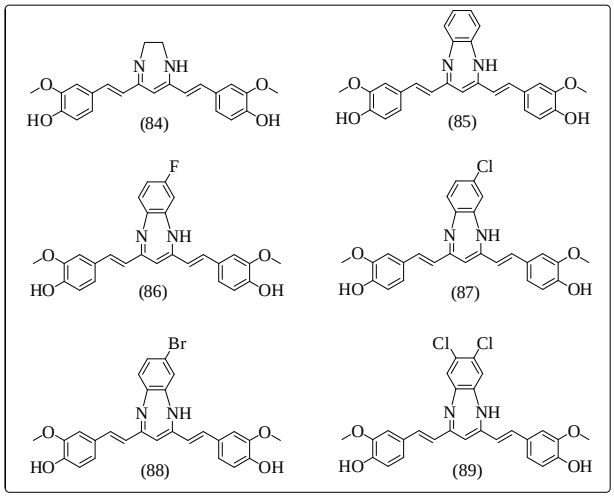


**Figure 17: Structures of pyrimidines 84-89.**

The inhibition of the biophysical gating properties of GluA2 and GluA2/A3 AMPA receptors by curcumin derivatives 85-88 was assessed. The biophysical parameters of compounds 85-88 such as desensitization, deactivation, and peak currents were calculated by using whole cell patch clamp electrophysiology with and without the administration of the derivatives onto HEK293 cells (Qneibi *et al.*, 2019).

## 5. Clinical studies

The clinical trials related to curcumin and their derived products have demonstrated that these compounds are effective on different types of cancers, such as chronic myeloid leukemia, multiple

myeloma, prostate, colorectal and pancreatic cancer. Clinical trials have also demonstrated curcumin's effectiveness as an anti-inflammatory agent. The emerging data from the clinical trials confirm that curcumin has the potential for cancer prevention and intervention. However, it is not yet clear whether long-term curcumin supplementation has similar benefits (Arslan *et al.*, 2022).The clinical trials have established that curcumin does not show any adverse effect up to a daily dose of 12 g. However, issue related to poor solubility, lower bioavailability and less stability in physiological conditions during human trials are yet to be resolved (Shaikh *et al.*, 2021). It is also reported that administration of oral curcumin with piperine as an adjuvant symptomatic therapy in COVID-19 treatment could substantially reduce morbidity and mortality on the healthcare system. Curcumin could be a safe and natural therapeutic option to prevent post COVID-19 thromboembolic events (Pawar *et al.*, 2021). Although, the effect of curcumin and its various derivatives have been studied under clinical trials in patients with chronic pancreatitis, psoriasis, hyperlipidemia, and cancers, it is imperative that well-designed clinical trials of curcumin heterocyclic derivatives be conducted in the near future (Hsu *et al.*, 2007).

## 6. Conclusion

The current review is focused on the discussion of heterocyclic curcumin derivatives having various pharmacological properties. The modification of curcumin's chemical structure resulting in important derivatives show enhanced pharmacokinetic characteristics and biological activities. Pyrazole and isoxazole compounds showed a wide range of biological activities such as antimalarial, anti-neurodegenerative, antibacterial, and anticancer properties. When compared to the parent compound curcumin, the design and synthesis of potent curcumin derivatives was highlighted as an approach for obtaining more soluble, more bioactive, and/or more bioavailable substances. These bioactive compounds could be used as models for developing better drug candidates. In the review, a large number of 1,3-diketo modified heterocyclic derivatives of curcumin have been mentioned having more potent medications to treat a variety of human ailments.Curcumin modifications as six membered heterocycles are uncommon compared to five membered heterocycles. From the literature, it has been found that in spite of having good scope of applications, pyrimidine and diazepine modifications of curumin are studies to a lesser extent.

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## Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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