REVIEW

Novel synthetic curcuminoids: Not merely an anticancer agent

Hailei Zhang[2], Xiaonan Jiang[1], Weihua Song[1]* and Zhangqun Yang[1]*

[1]Department of Pharmacy, Affiliated Hospital of Hebei University, Hebei University, Baoding, Hebei, PR China
[2]College of Chemistry and Environmental Science, Hebei University, Baoding, PR China

Abstract: Curcumin, a natural polyphenolic compound derived from turmeric (*Curcuma longa L*), has proven to exhibit biological activity towards different kinds of diseases. But the low oral bioavailability results in a limited application in clinic treatment. Recently, numerous curcumin derivatives were synthesized by the modification of three important functional groups: The aromatic *o*-methoxy phenolic group, a seven conjugated carbon linker and the *β*-diket one moiety. However, many people know curcumin only as an anticancer agent and overlook the diverse biological activities of curcumin and curcumin-based derivatives. In this article, we summarized the novel synthetic curcuminoids by different therapeutic activities including antioxidant activity, anti-HIV activity, stimulating activity of gastric emptying, anti-inflammatory activity, ACE inhibition activity, prevention of Parkinson's disease, anti-parasitism, anti-obesity, prevention of Alzheimer's disease, and antibacterial activity. The relation between structural features and activities were also investigated.

Keywords: Curcumin, curcuminoid, therapeutic activity, structure.

INTRODUCTION

Curcumin (diferuloylmethane) is a natural yellow-orange dye extracted from the rhizomes of the *Curcuma longa* L (Magro *et al*., 2015, Naksuriya *et al*., 2014). Generally, the extractive fraction of *Curcuma longa* is made up of various curcuminoids, which are chemically related to 1,6-heptadiene-3,5-dione-1,7-bis(4-hydroxy-3-methoxyphenyl)-(1*E*,6*E*)(Kunnumakkara, Anand *et al*., 2008). The commercially available curcumin is not a pure curcumin but a mixture of curcumin (1,77%), demethoxycurcumin (2, 17%) and bisdemethoxycurcumin (3, 3%). For many centuries, curcumin in its crude form has been used as spice and dietary supplement as well as component of many herbs (Sharma *et al*., 2005). Recently, it has been shown that curcumin shows different kinds of biological activities including anticancer activity (Wei *et al*., 2014), anti-inflammatory activity (Beloqui *et al*., 2014), anti-HIV activity (Mazumder *et al*., 1997), antiprotozoal activity (Changtam *et al*., 2010), antioxidant activity (Barry *et al*., 2009), antibacterial activity (Changtam *et al*., 2010) and preventative activity against A *β* aggregation in Alzheimer's models (Shi *et al*., 2007, Zhang *et al*., 2013). The applications of curcumin were limited by its very poor water and plasma solubility. In addition, curcumin possesses a low cellular uptake and a fast metabolism once inside the cell. As a result, various approaches have been attempted to address the problems of curcumin by the incorporation of curcumin intodelivery vehicles, including liposomes (Karewicz *et al*., 2011), nanoparticles (Shaikh *et al*., 2009), cyclodextrins (Yallapu *et al*., 2010), micelles (Gong, *et al*., 2013), micro emulsions (Hu *et al*., 2012) and solid dispersions (Hegge *et al*., 2013).

On the other hand, there are more researches on exploring the action mechanisms for various pharmacological activities. It has been shown that curcumin can physically bind to more than 30 different proteins including protein kinase C (PKC), human alpha1-acid glycoprotein, thioredoxinreductase, cyclooxygenase-2 (COX2), tubulin and 5-lipoxygenase (5-LOX) (Kunnumakkara *et al*., 2008).

Significantly, it has been reported that the potency for the suppression of tumornecrosis factor-induced nuclear factor-kappa Bactivation ranked curcumin> desmethoxycurcumin >bisdesmethoxycurcumin (Sandur *et al*., 2007). Moreover, curcumin has the highest cardio protective, neuroprotective and antidiabetic activities of the three curcuminoids shown in fig.1 (Nishiyama *et al*., 2005). Therefore, it is a meaningful strategy to synthesize novel kinds of curcuminoids from curcumin in its pure form.

Curcumin is one of the diarylhepatanoid compounds. Two aromatic rings are linked by conjugated alkyl chain made up of seven carbons. The quantum chemical studies demonstrated that the transconformer having the lowest energy where two phenol-methoxy groups locate in the opposite flanks of the curcumin backbone. The phenolic -OH group has intramolecular hydrogen bonding with the *o*-methoxy group. The 1,3-diketone usually possesses a keto-enoltautomerism (Shen and Ji, 2007). Extensive NMR studies in solution confirmed that in most of the

**Corresponding author:* e-mail: hdfysongweihua@sina.com

non-polar organic solvents curcumin is predominantly in the enolform (Payton *et al*., 2007). The recent studies for synthesizing novel kinds of curcuminoids are mainly based on the modification of phenolic -OH groups, enone moieties and 1,3-keto-enol moiety (shown in fig. 2). The influences of the change of structure on biological activities of curcumin are discussed in this article. In addition, we are interested in the novel curcuminoids synthesized by the modification of functional group in curcumin structure. Some curcuminoids synthesized from vanillic aldehydean alogue or other compounds are not in our scope. Recent numerous investigations and reviews have revealed the influences of the change of structure on anti cancer activities of curcumin. Therefore, the curcuminoids used in anticancer studies in our scope. Herein, we summarized a series of synthesized curcuminoids categorized by different biological activities including antioxidant activity, anti-HIV activity, stimulating activity of gastric emptying, anti-inflammatory activity, ACE inhibition activity, prevention of Parkinson's disease, anti-parasitism, anti-obesity, prevention of Alzheimer's disease, and antibacterial activity.

Antioxidant activity

There are conflicting reports concerning the structural/electronic basis of the anti-oxidant activity of curcumin (Barclay *et al*., 2000, Jovanovic *et al*., 2001, Priyadarsini *et al*., 2003). In addition, some of the biological activities, including anti-cancer, anti-inflammatory, and anti-angiogenesis, may derive from its anti-oxidant properties. Some reports argued that the anti-oxidant activity of curcumin depends on the presence of the phenolic OH groups. One of the necessary requirements of an antioxidant is to efficiently convert the reactive oxygen species (ROS) responsible for the induction of oxidative stress into less reactive species. ROS scavenging activity of curcumin was attributed either due to hydrogen atom transfer (HAT) or sequential electron and proton transfer (SET) from the phenolic OH groups. The resultant phenoxyl radicals, produced on account of this reaction, can acquire stabilization due to the extended conjugation (Gorman, Hamblett *et al*., 1994, Priyadarsini, 1997). However, there are some other views about the antioxidative mechanism of curcuminoids after the modification of curcumin structure.

Some synthesized curcuminoids shown in table 1 were associated with anti-oxidant activities. Tetrahydrocurcumin (THC, 1a), a metabolic product of curcumin *in vivo*, was synthesized by hydrogenation with Pt_2O as the catalyst firstly reported by Uehara *et al* (1987). Osawa *et al* (1996) investigated the antioxidative activity of curcumin and 1a by examining the inhibitory effects on *tert*-butyl hudroperoxide-induced lipid peroxidation. The results showed that 1aexhibited a greater inhibitory effect than curcumin. The investigations relating to the mechanism of antioxidative activity suggested that the *β*-diketonemoiety of 1a must exhibit antioxidative activity by cleavage of the C-C bond at the active methylene carbon between two carbonyls in the *β*-diket one moiety. The *β*-diketonemoiety may play a significant role in antioxidative activity as well as phenolichydroxy groups.

More over, the superiority of antioxidative activity of 1a was verified by Jagt *et al* (2005). In this study, anti-oxidant activity was tested as the ability of the compounds to react with the preformed radical monocation of 2, 2'-azinobis-(3-ethylbenzothiazoline-6-sulfonicacid), where Trolox was used as reference standard. Analogue 1a was more active than curcumin in the TRAP assay. Significantly, both curcumin and 1a exhibited a much more antioxidative activity than Trolox in same concentration.

Abraham *et al* (2012) synthesized salicylidenecurcumin (2a), and benzalidene curcumin (3a) by the Knoevenagel condensation of curcumin with the aldehydes-salicylaldehyde or benzaldehyde. Their antioxidant properties were compared with curcumin in the presence of DPPH. The result indicated the antioxidant property increased in the order curcumin<2a<3a.The authors demonstrated that the additional -OH group in the salicylidene may increase the antioxidant property.

Anti-HIV activity

Several reports indicated that curcumin possess desirable inhibitory activity against HIV-1integrase (Burke *et al*., 1995, Mazumder *et al*., 1995, Mazumder *et al*., 1995, Sui *et al*., 1993).

Socurcumin exhibits a great potential for developing as a treatment for AIDS. Pommier *et al* (1997) synthesized two curcuminoids after demethylation of curcumin. Curcumin was demethylated by $AlCl_3$/pyridine in CH_2Cl_2 to furnish 1b and 2b. In this study they found curcumin to inhibit integrase with an IC_{50}about 150 μM. The two analogs (1b and 2b) of curcumin were found to possess a much higher inhibitory effect than that of curcumin (IC_{50}= 18 for 1b, IC_{50}= 6 for 2b). These result suggested that the phenolic OH groups play a significant role in inhibitory activity. In addition, the inhibitory activity against HIV-1 integrase of curcuminoid1a was evaluated. Compounds 1a showed no activity against integrase even at concentrations of 300μM, suggesting the importance of both the hydroxyls and the unsaturated linker present in curcumin structure. Some synthesized curcuminoids associated with anti-HIV activities were listed in table 2.

Tanaka *et al* (2009) synthesized a series of curcuminoids by conjugating one or two molecules triterpenoid (3α-Methoxyserrat-14-en-21β-ol or 3β-methoxyserrat-14-en-21β-ol) to one molecule of curcumin using succinic acid or malonicacidas linker.

Table 1: Curcumin derivatives in antioxidativeinvestigations

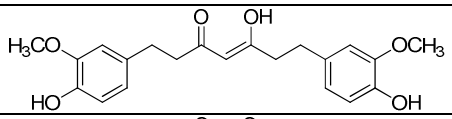
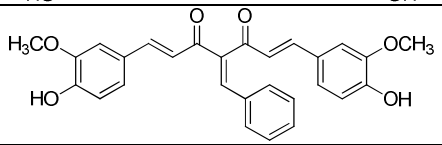
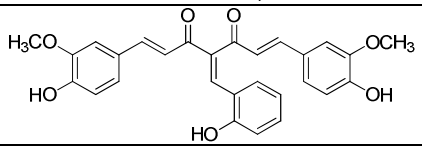
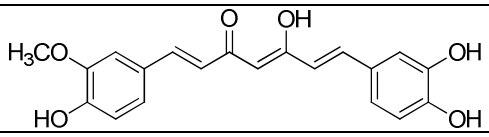
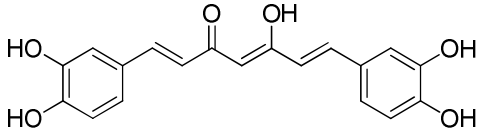
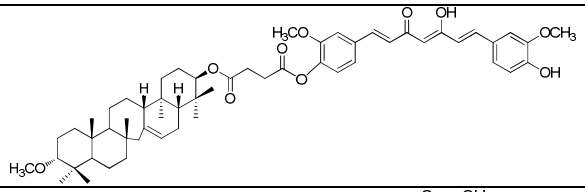
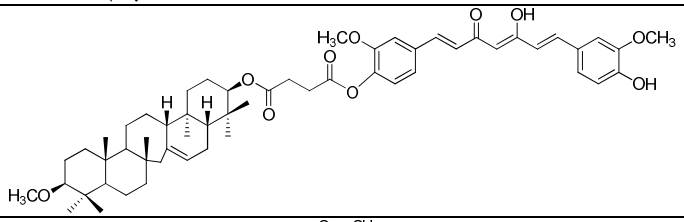
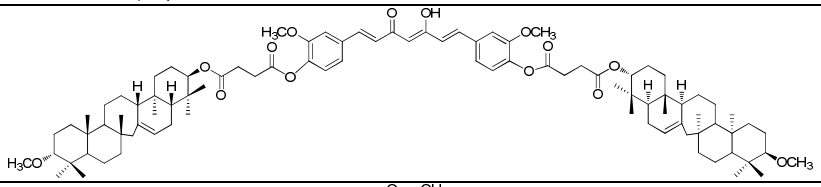
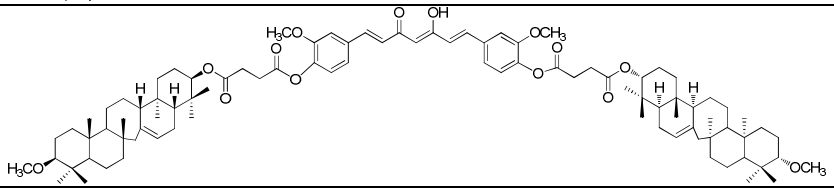
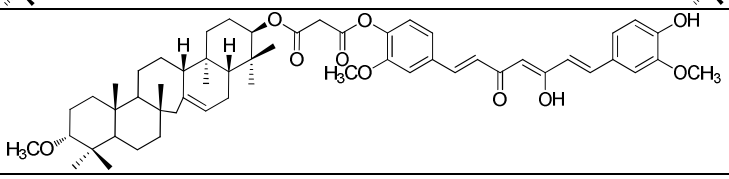
No.	Structural formula
1a	
2a	
3a	

Table 2: Curcumin derivatives in anti-HIV investigations

No.	Structural formula
1b	
2b	
3b	
4b	
5b	
6b	
7b	

Continue…

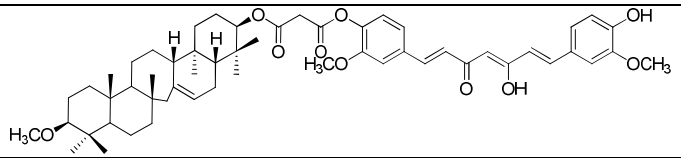
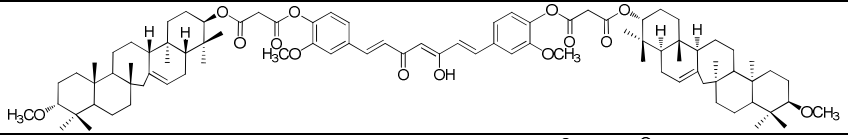
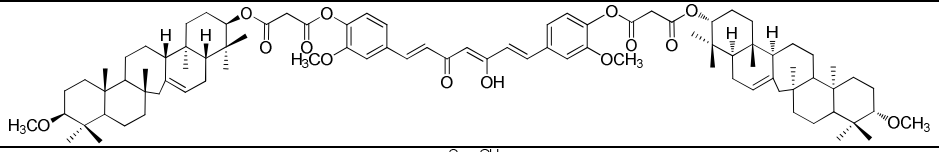
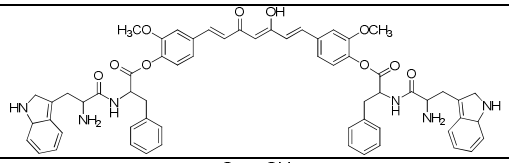
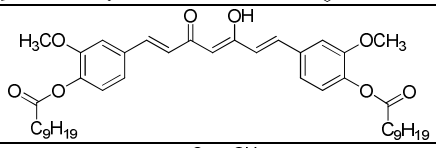
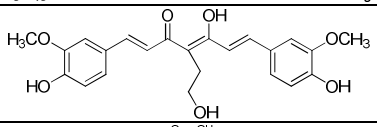
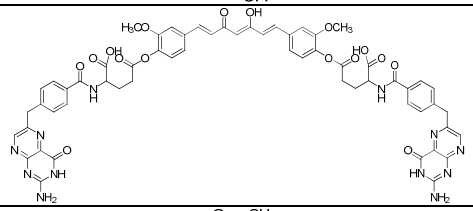
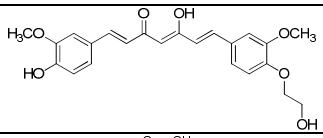
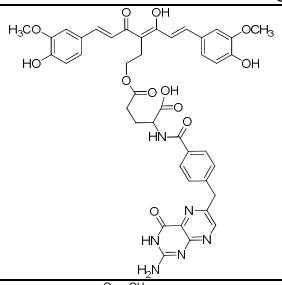
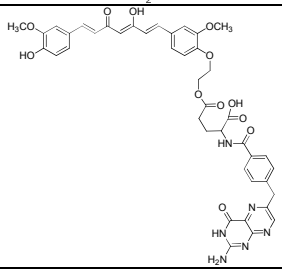
No.	Structural formula
8b	
9b	
10b	
11b	
12b	
13b	
14b	
15b	
16b	
17b	

Table 3: Curcumin derivatives in stimulating activity investigations of gastric emptying

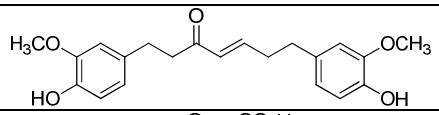
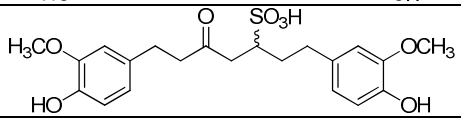
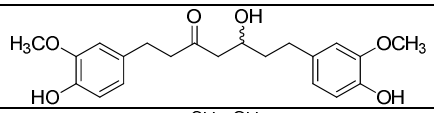
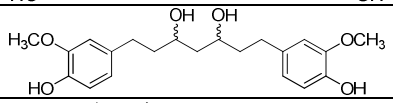
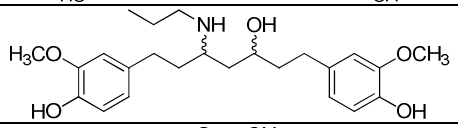
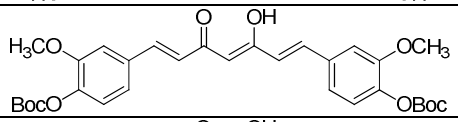
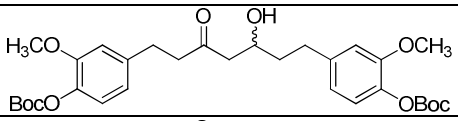
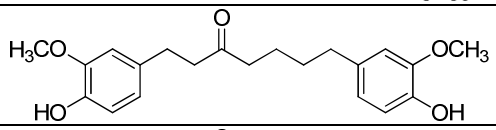
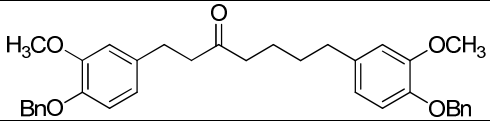
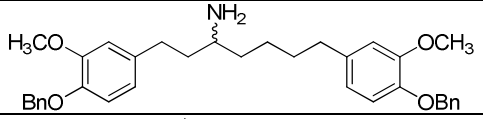
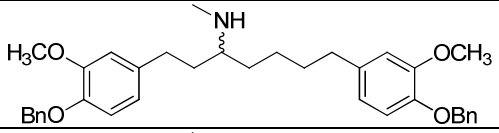
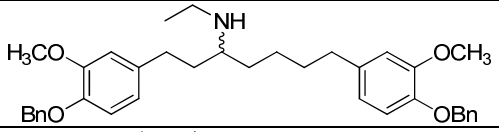
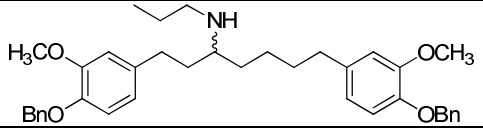
No.	Structural formula
1c	
2c	

Table 4: Curcumin derivatives in anti-inflammatory activity investigations

No.	Structural formula
1d	
2d	
3d	
4d	
5d	
6d	
7d	
8d	
9d	
10d	
11d	

Continue…

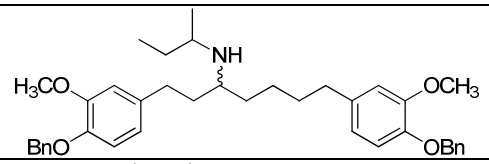
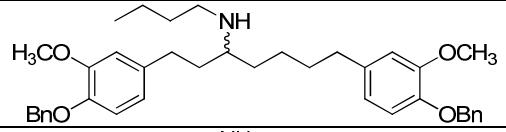
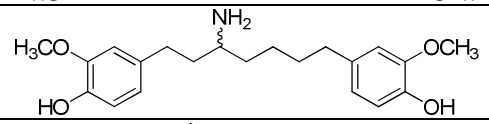
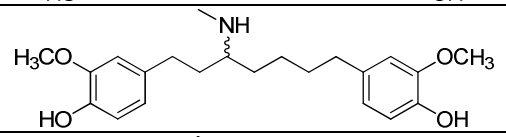
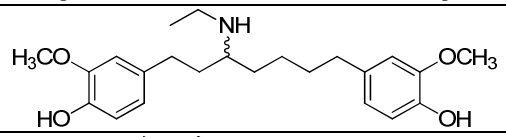
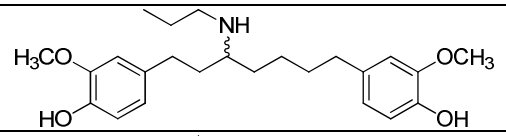
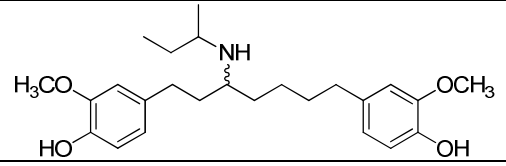
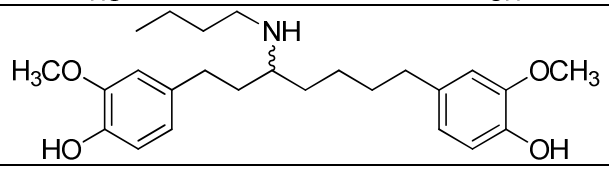
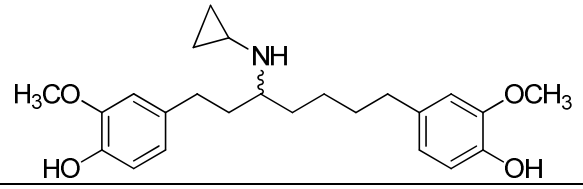
No.	Structural formula
12d	
13d	
14d	
15d	
16d	
17d	
18d	
19d	
20d	

Table 5: Curcumin derivative in ACEI activity investigations

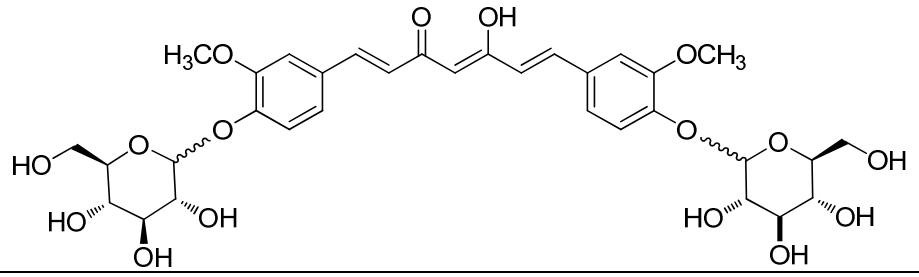
No.	Structural formula
1e	

Table 6: Curcumin derivatives in Parkinson's disease investigations

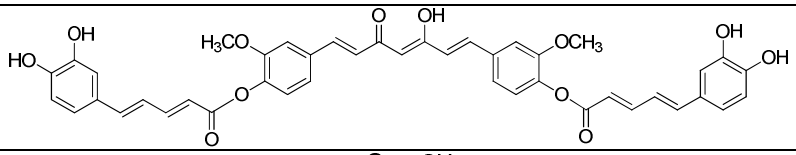
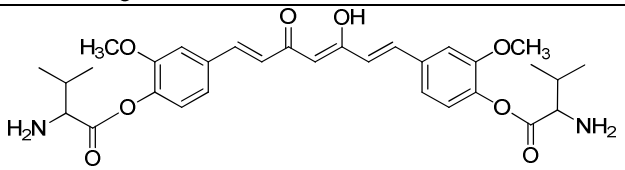
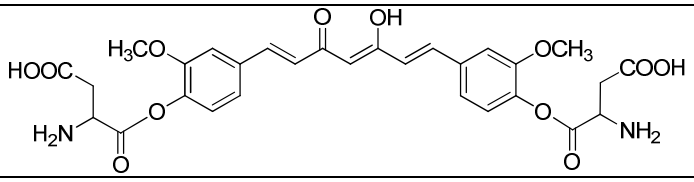
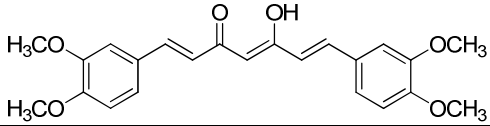
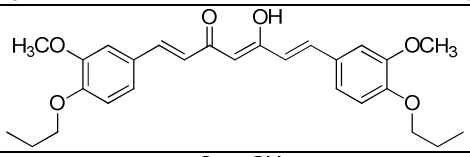
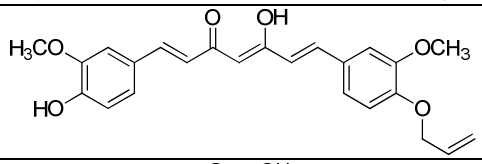
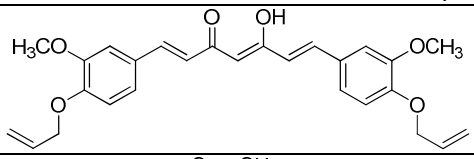
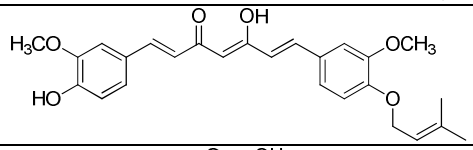
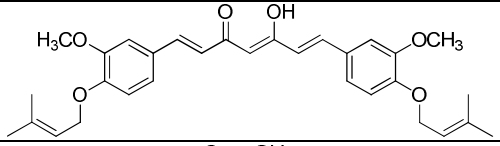
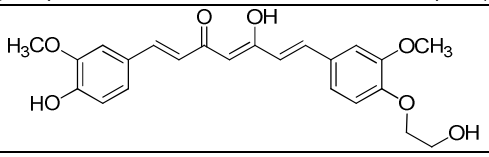
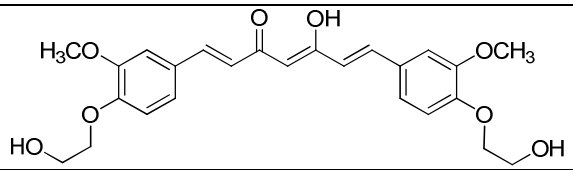
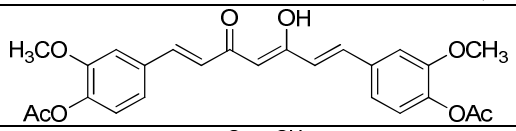
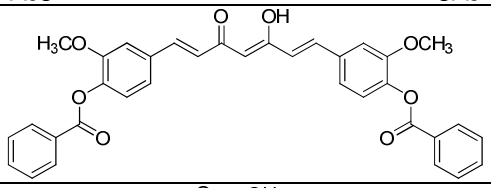
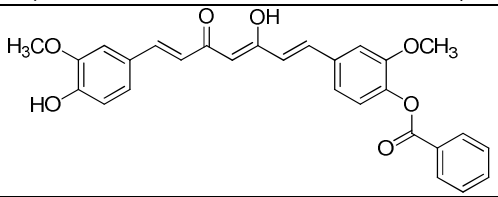
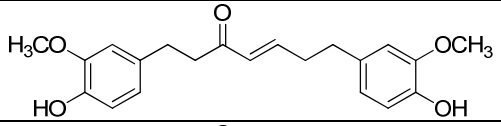
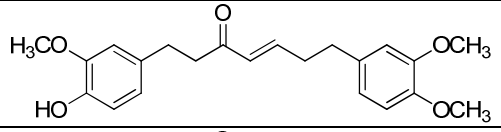
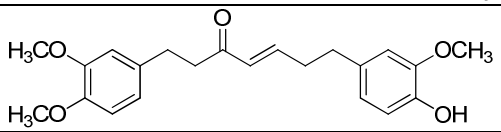
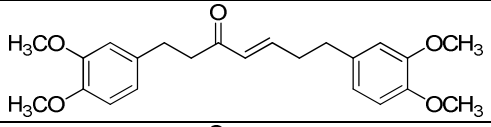
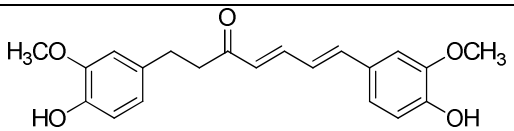
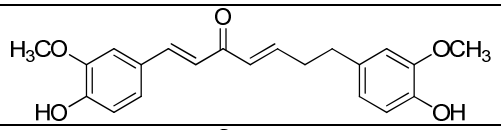
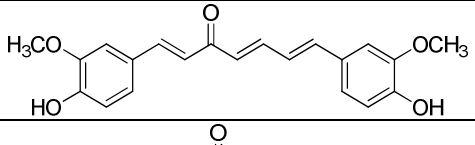
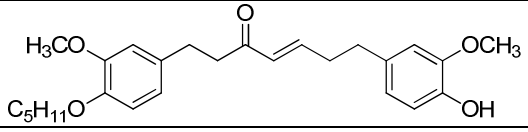
No.	Structural formula
1f	
f	
3f	

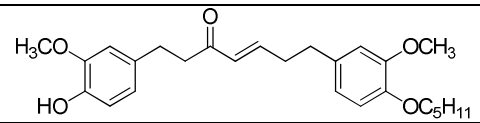
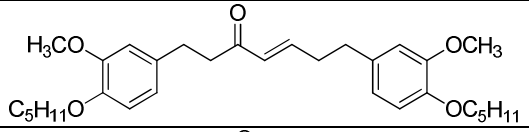
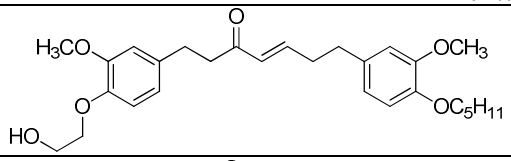
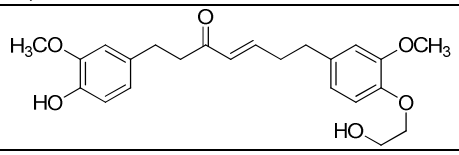
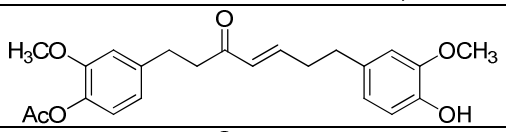
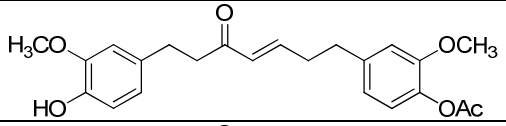
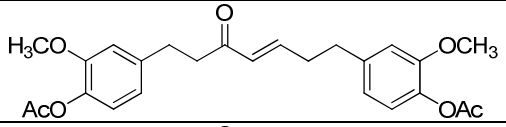
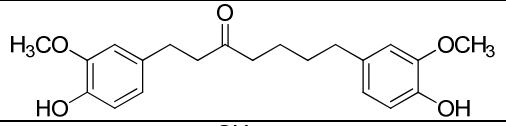
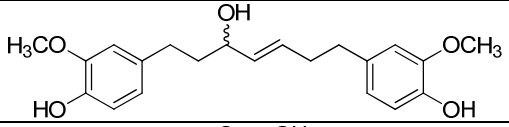
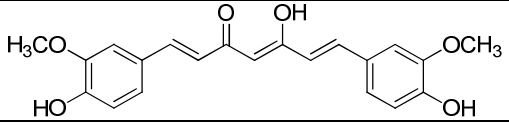
Table 7: Curcumin derivatives in antitrypanosomiasis and antileishmaniasis investigations

No.	Structural formula
1h	
2h	
3h	
4h	
5h	
6h	
7h	

Continue…

No.	Structural formula
8h	
9h	
10h	
11h	
12h	
13h	
14h	
15h	
16h	
17h	
18h	
19h	

Continue…

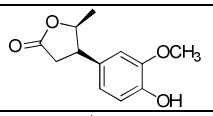
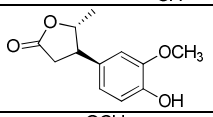
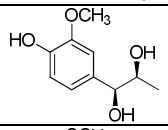
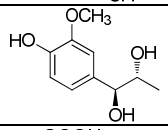
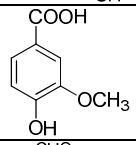
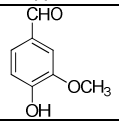
No.	Structural formula
20h	
21h	
22h	
23h	
24h	
25h	
26h	
27h	
28h	
29h	

The HIV infection was evaluated by reverse transcript aseassay using C8166-CCR5 cells. The triterpenoids and obtained curcuminoids (2b-10b) exhibited no reverse transcriptase activity. These results indicated that the phenolic OH groupmay be the essential functional group in anti-HIV activity.

A series of curcumin bioconjugates were synthesized by Singh *et al* (2010). The phenolichydroxyls and active methylene group on curcumin have been utilized. Curcuminoid 11b, 12b and 14b were yielded by treating curcuminwitht-boc–N-trp–phe-COOH, decanoyl chloride and*p*-nitrophenyl ester of folic acid, respectively, in the presence of dicyclohexylcarbodiimide and dimethylaminopyridine. The intermediate compound 15b was prepared following a similar procedure by treating curcumin with 2-chloroethanol. Curcuminoid13b was obtained by conferring di-*O*-benzoyl curcuminon a carbanionic character at the active methylene site by NaOEtin the presence of 2-chloroethanol. The intermediate compounds 13b and 15b were treated with *p*-nitrophenyl ester of folic acid to yield 16b and 17b, respectively. The anti-HIV-1 activities of curcuminbioconjugates11b, 12b, 14b, 16b and 17b were investigated. However, the bioconjugates did not show any better activity against HIV-1 than curcumin. The results showed the phenolichydroxyls and active methylene group on curcumin may be the essential

functional group in anti-HIV activity.

Table 8: Curcumin derivatives in diet-induced obesity investigations

No.	Structural formula
1i	
2i	
3i	
4i	
5i	
6i	

Stimulating activity of gastric emptying

Shogasulfonic acid A (1c) was isolated from the Zingiberisrhizome and reported to have stimulating activity of gastric emptying (Structure was shown in table 3). Ida *et al* (Hori, Miura *et al*., 2003) explored a three steps involved feasible approach to synthesize 1cusing curcumin as the starting material. Curcumin was hydrogenated with Pd/C in EtOH (100 ml) to give 1a as an intermediate product. 1awas then dehydrated by reflux with p-TsOH monohydrate in dry benzene to afford 2c. 1c was obtained by treating 2c with sodium hydrogen sulfite and tert-butyl perbenzoate in MeOH. The authors suggested that sulfonated groups may be essential for the stimulating activity of gastric emptying.

Anti-inflammatory activity

In various chronic illnesses, inflammation is known to play a significant role. Curcumin was found to possess strong anti-inflammatory activity. Chen *et al* (2005) synthesized various kinds of reductive state products (1d-20d) starting from curcumin. The hexahydro curcumin (1d) and octahydro curcumin (2d) were obtained through Pt/C-catalyzed hydrogenations. The direct reductive amination of 1dwith propylamine yielded 3d. To improve the yield, two phenolic groups were protected to yield 4d as an intermediate. 4dwas hydrogenated under a neutral condition (EtOAc) to give 5d in a high yield. A facile reaction condition was conducted to achieve deprotection, dehydration, and hydrogenation sequencely to yield6d. Then 6d was *O*,*O*-dibenzylated via a rapid microwave reaction to yield dibenzylmonoketone 7d. Intermediates 8d-13dwere synthesized by reductive aminationof7d with six primaryamines, deprotected curcuminoids 14d-19d were obtained. Curcuminoid 20d was prepared directly from 6d through reductive amination. The inhibitions of iNOS expression, NO production and biosynthesis ofCOX-2 downstream product $PGE_2$of 1a, 1d, 2d,6dand 14d-20d were evaluated in LPS(1μg/mL)-stimulated RAW264.7 macrophages; in addition, the MTT assay was also conducted to evaluated the cytotoxicity. Curcuminoids1a, 1d, 2d, 6d and 15d had no significant effect on cell viability when concentrations up to 100μM. Among the five curcuminoids, 1d and 2d showed the most superior inhibition effect in LPS (1μg/ml)-induced NO production and LPS (1μg/ml)-induced PGE_2 production, respectively. However, it should be noted that 1d and 2dexistedas mixtures of enantiomeric and diastereomeric isomers, respectively. The influence of isomers on the anti-inflammatory activities is still not clear (table 4).

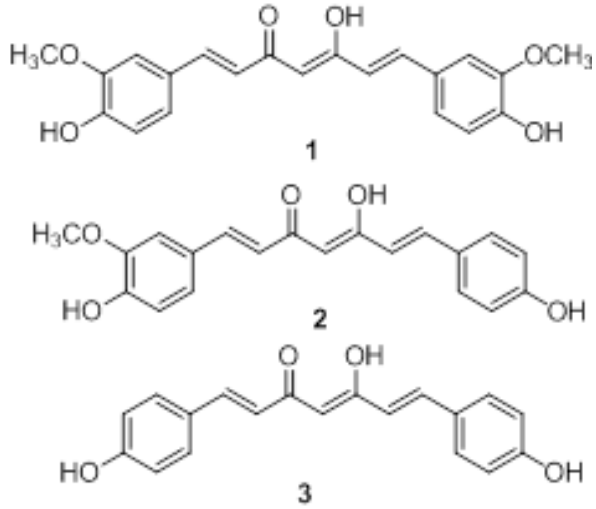


Fig. 1: Chemical structure of curcumin and its analogues in commercially available curcumin

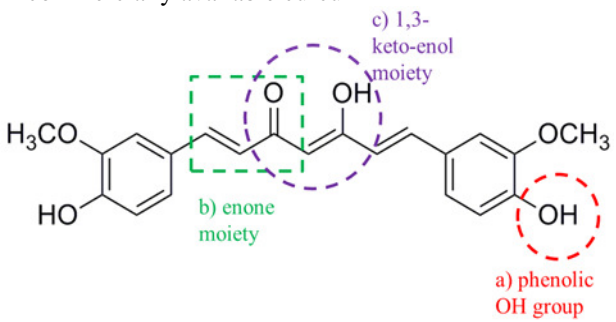


Fig. 2: Modifiable functional groups in curcumin structure

ACE inhibition activity

Angiotensin converting enzyme (ACE), a zinc containing nonspecific dipeptidylcarboxypeptidase, can regulate the blood pressure by modulating renin–angiotensin system.

Several bio-molecules including glycosides are available for ACE inhibition (Li, Li *et al*., 2004). Curcuminyl-bis-α-D-glucoside (1e) (table 5) was synthesized by Divakar *et al* via a classical glycosylation reaction in presence of appropriate quantity of amyloglucosidase. Underivatized curcumin and glucose were tested for ACE inhibition as controls and they did not show any ACE inhibitory activities. Obtained curcuminoid1eexhibited an IC_{50} value of 1.5±0.13mM, suggesting that 1e possessed potentials as hypotensive drugs.

Parkinson's disease

Parkinson's diseases a neurodegenerative disorder which is associated with the loss of dopamine in the basal ganglia (Beal, 1992). Some scholars surmised that restoration of intracellular glutathione levels may prevent causing of the early events of Parkinson's disease (Jha *et al*., 2000, Vali *et al*., 2007). Curcumin was found to be able to protect mitochondria against oxidative stress and nitrosative stress (Mythri *et al*., 2007), result in the protection effect on GSH metabolism (Mishra *et al*., 2005). Bharath *et al* (2010) synthesized three bioconjugates of curcumin by covalent linking of different acids including piperic acid, valine and glutamic acid through the two phenolic groups to yield 1f, 2f and 3f, respectively (table 6). The results indicated that administration of 3fcan enhance the cellular GSH levels and bioavailability. The introduction of the carboxylic groups may play an important role in neuro protective ability. Curcuminoid 3f possess a capacity to cross blood brain barrier could serve as potential neuro protective estrategiesin disorders such as Parkinson's disease.

Antitrypanosomal and antileishmania

Trypanosomiasis and leishmanias are among the mostneglected diseases all around the world (Barrett, 2000). They are caused by related protozoan parasites, *Trypanosoma* and *Leishmania species*, respectively. It has been reported that curcumin possessed moderate-to-lowactivity against *Trypanosoma brucei brucei* (Nose, Koide *et al*., 1998) and against promastigotes of *Leishmania major* (Koide *et al*., 2002). A series of curcuminoids (1h-29h, shown in table 7) were synthesized by Suksamrarn *et al* (Changtam, de Koning *et al*., 2010) and the antitrypanosomal and antileishmanial activities were investigated. The methylated analog1h was achieved by treating curcumin with methyl iodide in acetone in the presence of potassium carbonate. Higher alkyl ether analogsincluding 2h, 3h, 4h, 5h, 6h, 7h and 8h were synthesized using differentalkyl bromide or iodide. Di-*O*-acetyl analog (9h) was synthesized by treating curcumin with excess acetic anhydride. Benzoylation of curcumin with benzoic anhydride in pyridine furnished the monobenzoate (11h) and the dibenzoate (10h). Above-mentioned curcuminoids1a, 2d and 5d were also included in this study and served as intermediates. Curcuminoid1d was subjected to dehydration, with *p*-toluenesulfonic acid as a catalyst, to afford the enone12h. Curcuminoids13h-15h and 19h-23h were furnished by treating12h with different alkyl bromide or iodide.Curcuminoids16h-18h were given via dehydrogenation by treating 12h with 4,5-Dichloro-3,6-dioxo-1,4-cyclohexadiene-1,2-carbonitrilein THF. Curcuminoids24h-26hwere synthesized after acetylation of the12h. To see the influence of olefinic function in the conjugated enone system and the keto function in biological activity, 27h and 28h were prepared after hydrogenation of 12h. Curcuminoid29h was obtained following a benzoylation of curcumin with benzoic anhydride.

The trypanocidal effect and antileishmanial activity of the obtained curcuminoids were evaluated. The natural curcuminoids including curcumin exhibited fairly low trypanocidal effect and antileishmanial activity when compared with the drug diminazeneaceturate. After the substitution of phenolic hydroxyl groups, 2h-11h displayed higher trypanocidal effect and antileishmanial activity. The result indicated that the phenolic hydroxyl group was not the active group of trypanocidal effect and antileishmanial activity. It's worth noting that both trypanocidal effect and antileishmanial activity dramatically decreased for 1a, 2d and 5dcomparing with those of curcumin. Curcuminoid 19h exhibited the optimal trypanocidal effect and antileishmanial activity among all the curcuminoids in this study and a markly higher effect than diminazene aceturate. But the trypanocidal effect and antileishmanial activity significantly decreased after hydrogenation of 19h. It can be surmised that the enone motif group may play a significant role in trypanocidal effect and antileishmanial activity. The authors considered 19h as the most promising lead compound because of its optimal activity, desirable solubility and simple synthetic route.

Diet-induced obesity

Obesity is widely regarded as a major public health problem which can give rise to hypertension, hyperlipidemia, arteriosclerosis and some other complications. Recent studies have demonstrated that pancreatic lipase inhibitors are significant therapeutic reagents for treating diet-induced obesity (Lowe, 1994). Jo *et al* (2011) obtained some degraded products (1i-6i, shown in table 8) derived from curcumin by γ-irradiation. The compounds isolated from irradiated curcumin were evaluated for their pancreatic lipase inhibitory activity. The obtained derivatives displayed higher inhibitory activity toward pancreatic lipase than that of parent curcumin except for 5i. Two phenylpropanoid-type byproducts (3i and 4i) exhibited the most potent pancreatic lipase inhibitory activities with IC_{50} values of 9.1±0.2 and 12.1±0.3 μM, respectively, suggesting a much higher lipase inhibitory than curcumin. But the lipase inhibitory activities are still lower thanorlistat, a classical pancreatic lipase inhibitor (Hill *et al*., 2005).

Alzheimer's disease

Alzheimer's disease is the most common cause of dementia among the elderly population (Brook meyer, Gray *et al*., 1998, Masters, Cappai *et al*., 2006, Selkoe, 2001). Recent research indicates that Amyloid-*β*-peptide aggregation plays an important role in Alzheimer's disease (Roberson and Mucke, 2006). It has been reported that curcumin exhibited effective binding and dissolution properties against amyloid fibrils, suggesting its potent application for treatment of Alzheimer's disease. A study conducted by Raja *et al* (2007) was carried out to assess whether the monofunctional curcumin derivatives can retain the ability to bind and dissolve amyloid fibrils. Curcumin monocarboxylicacid 1j was synthesized by treating curcumin with glutaricanhydridein the presence of dimethylaminopyridine. In a polarized light microscope observation, 1j can effectively label fibrils at a much lower concentration than Congo Red, a commonly used biological stain. Moreover, the monofunctional curcumin derivative 1j also exhibited an effective dissolution of amyloid fibrils.

One important aspect in the treatment of Alzheimer's disease is the delivery of drugs to the brain. So the drug must be able to pass the blood brain barrier. Ferla *et al* (2011) synthesized a series of labeled curcumin derivatives as tools for *in vitro* blood brain barrier trafficking studies. Pyrazole derivative 2j was synthesized by treating the curcumin with ethyl 2-hydrazinylacetate hydrochloride in refluxingtoluene. Curcuminoid3j was obtained from 2j by basic hydrolysis of the ethyl ester.Curcuminoid4j was obtained from 3j through coupling with propargylamine. Curcuminoid 5j and 6j were prepared following a similar labeling procedure using [^{2}H] water and [^{3}H] water in dry THF, respectively. The curcuminoids1j-6j were shown in table 9. The resulting specific activities of obtained curcuminoids were sufficient for the trafficking studies when using an *in vitro* blood brain barrier model.

Antibacterial activity

Curcumin has been show to possess antibacterial activities towards various bacterial strains. The synthesized curcuminoids relating to antibacterial activities were briefly introduced in this section (table 10). Curcuminoids1k, 2k and 3k were synthesized by Mishra *et al* (2005) by conjugating glycine, D-alanine and piperic acid respectively. The activate dpiperic acid was then reacted with 1k to yield 4k as a bioconjugate of curcumin, glycine and piperic acid. Above mentioned 1e and 9h were also included in Mishra's study. Curcuminoid4k showed the most positive results and much higher antibacterial activity than curcumin against *E. coli*, *S. aureus*, *P. aeruginosa*, *P. pyocynin*, *E. cloacae*, *Staphylococcus saprophyticus*, *Micrococcus* and *E. aerogen*. Significanly, Curcuminoid4k exhibited a higher antibacterial activity than Cefeprime against *E. coli*, *S. aureus*, *P. aeruginosa*, *P. pyocynin*, *E. cloacae* and *Staphylococcus saprophyticus*.

The excellent activity of 4k can be attributed to the fact that the enhanced bio availability. Moreover, the curcumin-bioconjugates all showed higher antibacterial activity than curcumin. The results can be due to that the introduction of glucose, D-alanine, acetic acid, piperic acid or glycinein curcumin may ease the transmembrane passage and reduce the rate of metabolism. All the results suggested that the phenolic hydroxyl group is not a determining factor of antibacterial activity.

Suksamrarn *et al* (2010) synthesized a series of curcuminoids and the antimycobacterial activity against *M. tuberculosis* has been evaluated. Curcuminoid 5k was synthesized by reduction of curcumin with zinc-acetic acid. Pyrazole analog6k was synthesized by treating curcumin with hydrazine hydrate in presence of AcOH. The N-substituted analog 8k was also prepared following a similar procedure. Isoxazole analog 7k was synthesized by treating curcumin with $NH_2OH{\cdot}HCl$. The pyrazole analog6k (MIC = 200μg/mL) didn't show better activity than curcumin (MIC = 100μg/mL) against *M. tuberculosis* H37Ra strain. However, the isoxazole analog 7k exhibited a much lower MIC (MIC = 1.56μg/mL) than curcumin and a better activity than Kanamycin (MIC = 2.5μg/mL). So the isoxazole analogs possess great potentials for use of antitubercular agent. A series of isoxazole-based curcuminoids were prepared in the following study. Compound 9k, 10k and 11kwere synthesized by treating 5k and 1a with $NH_2OH{\cdot}HCl$, respectively. Isoxazole-based curcuminoids 12k-26k were prepared by treating 7k with corresponding iodide or bromide. Among the all curcuminoids in this study, mono-*O*-methylcurcuminisoxazole (24k) was the most active compound (MIC = 0.09 μg/mL), exhibiting 1131-fold more active than curcumin. Significantly, it was approximately 18 and 2-fold more active than the standard drugs kanamycin and isoniazid, respectively. The detailed results confirmed the introduction of two unsaturated bonds and an isoxazolering on the unsaturated alkyl chain can be positive for antimycobacterial activity. The introduction of a suitable alkoxyl group on an aromatic ring near the nitrogen function and a free phenolic hydroxyl group on the other aromatic ring may enhance the antimycobacterial activity inisoxazole-based curcuminoids.

The antibacterial activities of curcumin bioconjugates, 11b, 12b, 14b, 16band 27k were compared with that of curcumin in Singh's study (2010). The curcumin bioconjugates 11b, 12b, 14b, 16b and 27k exhibited remarkable anti-bacterial activities with MIC ranging between 0.09 and 0.67μMagainst *Streptococcus virudans* as well as *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabeilis* bacterial strains, was 3.7-27 times higher than that of curcumin. The introduced groups, including amino acids, lipids and folic acid, possess

structural similarity with the bacterial cell wall, resulting in enhanced bioavailability and higher cellular uptake. Moreover, the biodegradable ester bonds lead to the compounds can get hydrolysed *in vivo*. On the other hand, 16b exhibited a much better antibacterial activity than others, suggesting the importance of phenolic hydroxyl group in antibacterial activities.

Lal *et al* (2012) synthesized a series of curcuminoids (28k-41k) by treating curcumin with substituted aryl aldehyde and urea/thiourea in presence of $SnCl_2 \cdot 2H_2O$. The zone of inhibition and MIC of synthesized curcuminoids were measured to evaluate their antibacterial activity against *Staphylococcus aureus*, *Escherichia coli, Burkholderia pseudomallei*, *Salmonella typhi* and *Pseudomonas aeuriginosa*. The antibacterial activity was compared with curcumin and ampicillin. In case of all the bacterial strains, curcuminoid34kdisplayed a much better antibacterial activity than curcumin and other curcuminoids. These result also suggested the importance of phenolic hydroxyl group in antibacterial activities.

Sahu *et al* (2012) demonstrateda feasible method for synthesizing novel benzothiazole derivatives (42k-49k) of curcumin. Benzylidene derivatives (2a, 3a, 54k and 55k) and pyrazole derivatives (50k-53k) of curcumin were also synthesized.

The benzothiazole derivatives (42k-49k) of curcumin were prepared through the reaction of curcumin, substituted aromatic aldehydes and 2-amino benzothiazol eat 60-65^oC in the presence of pyridineas a catalyst. In addition, the benzothiazole derivatives were also synthesizedin microwave under solvent free conditions.

The pyrazolederivatives (50k-53k) were prepared by treating curcumin with hydrazinesat 65-70^oC in the presence of acetic acid as solvent. The pyrazole derivatives (50k-53k) of curcumin were prepared by a reaction of curcumin and substituted aromatic aldehydes at 60-65^oC in the presence of pyridine.

Antibacterial activity was tested *in vitro* against *Staphylococcus aureus*, *Bacillus cereus, Pseudomonas aeruginosa*, *Salmonella typhi*, *Escherichia coli* and *Providencia rettgeri*. As for benzothiazole derivatives (42k-49k), curcuminoid 47k displayed the best activity on microorganism. The data also revealed that the activity of all compounds follow the order 47k>46k>45k>42k>49k> 48k>44k>43k> curcumin.
The antibacterial study showed that the introduction of hydroxyl group at para position exhibited a better activity than other positions. Pyrazolederivatives (50k-53k) showed much better antibacterial activity than curcumin and benzothiazole derivatives, which may due to the difference between atomicsize of sulphur and oxygen atoms. Electron withdrawing substituent at ortho and parapositions as 2,4-dinitro phenyl group (53k) have shown excellent activity against *Staphylococcus aureus* and *Bacillus cereus*.

This result indicated that the presence of pyrazole group is additive for the antibacterial activity. As for benzylidene derivatives (2a, 3a, 54k and 55k), they also displayed much better antibacterial activity than curcumin and benzothiazole derivatives. 2a displayed the best antibacterial activity in this group.

The chelating ability of diketone moiety has been widely investigated especially towards different kinds of metal ions. In Refat' study (2013), complexes of Co(II), Zn(II), Fe(III), Cr(III), Ni(II), Mn(II) and Cu(II) with curcuminlig and were prepared. The complexes were synthesized at 60^oC in water/methanol solution. Two times amount of each $CoCl_2 \cdot 6H_2O$, $ZnBr_2$, $FeCl_3$, $CrCl_2 \cdot 6H_2O$, $NiCl_2 \cdot 6H_2O$, $MnCl_2 \cdot 4H_2O$ and $CuCl_2 \cdot 2H_2O$, were added to the solution respectively to favor products as preparations. The antibacterial data of curcumin and complexes were introduced as inhibition zone diameter. Only 59k exhibited a mild antibacterial activity towards three kinds of bacteria *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

Curcuminoid (1a) was used as a starting material in Srinivas's study (2013). Reaction of 2-amino acetophenone or substituted 2-aminobenzophenoneswith 1a was carried out using trifluoroacetic acid at 100^oC to afford quinoline derivatives (63k-68k). The antibacterial activity was tested against *Bacillus cereus*, *Staphylococcus aureus*, *Escherichia coli* and *Yersinia enterocolitica*. The results showed that the quinoline derivatives exhibited better activity than curcumin, suggesting the superiority of quinolonemoiety. 65k was the most effective especially against Gram-negative bacteria. The nitro group may be additive for the antibacterial activity just like dinitro.

CONCLUSION

The research over the last decades has revealed that curcumin exhibits diverse activity against several common diseases. Although curcumin possess hypotoxicity in humans, its limited oral bioavailability is one of the major reasons why curcumin has been unsuccessful in achieving therapeutic outcomes. Therefore, numerous attempts were made to explore a more diverse application by synthesizing novel curcuminoids. In our study, novel synthesized curcuminoids were summarized and categorized by different biological activities. Future investigations on the complete biological studies and physico-chemical of the curcumin oids are essential so that the molecular role of curcumin in the targeted activity can be understood in a comprehensive way. We hope our review can serve as a guiding tool for related scholars.

Table 9: Curcumin derivatives in binding and dissolving amyloid fibrils investigations

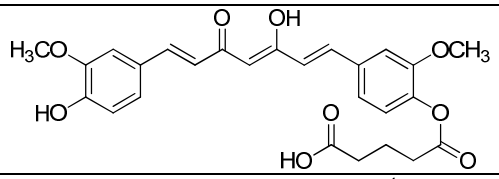
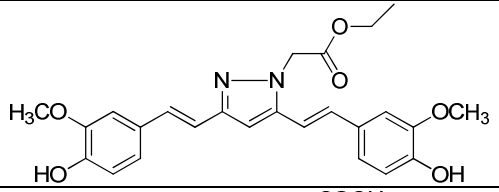
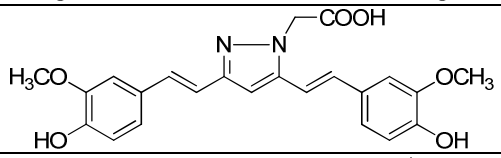
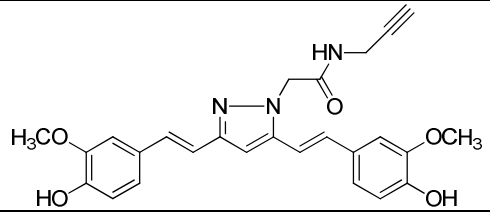
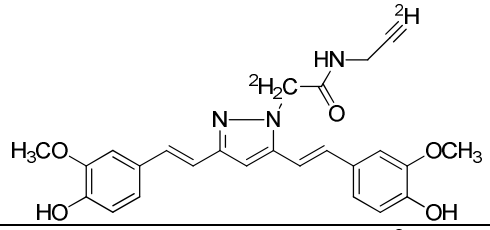
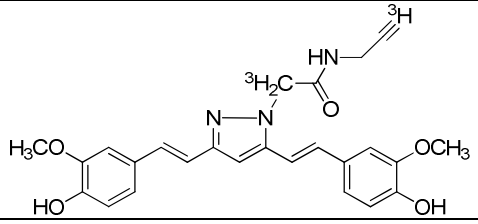
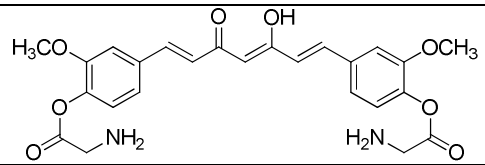
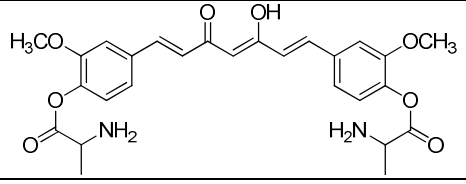
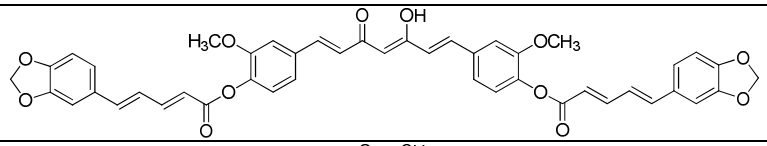
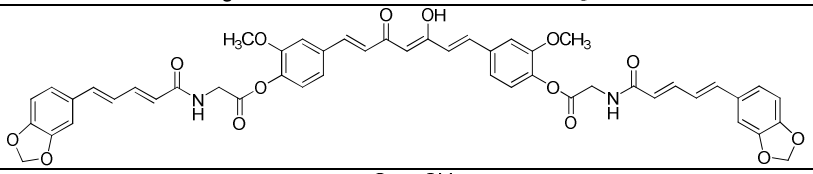
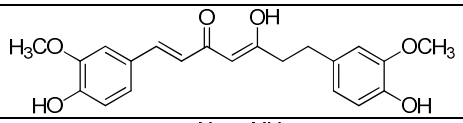
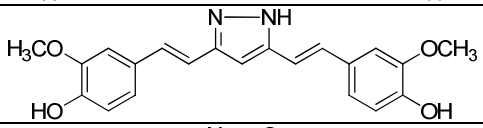
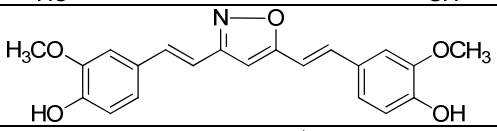
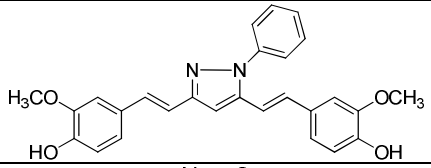
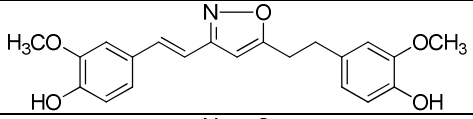
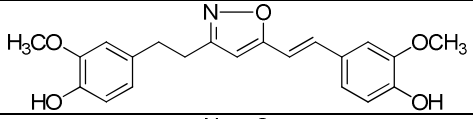
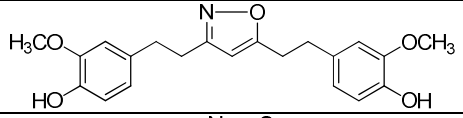
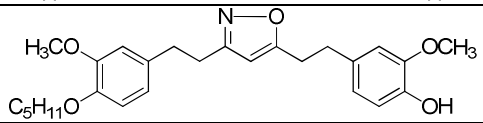
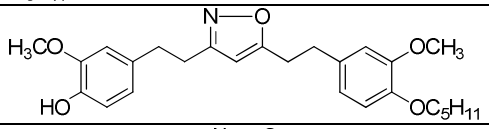
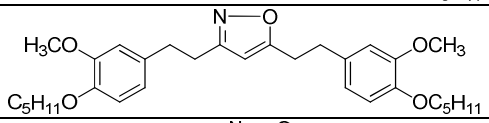
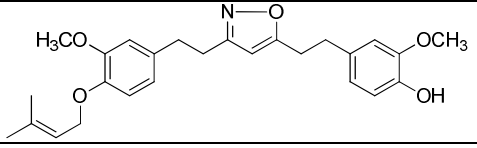
No.	Structural formula
1j	
2j	
3j	
4j	
5j	
6j	

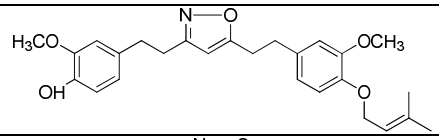
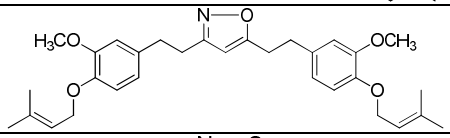
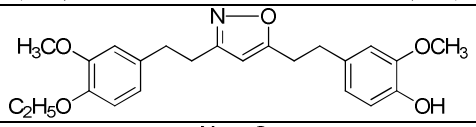
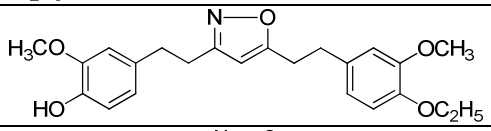
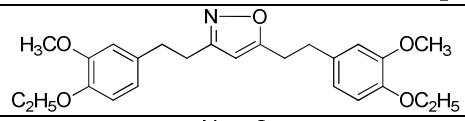
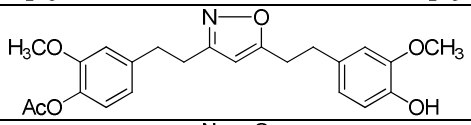
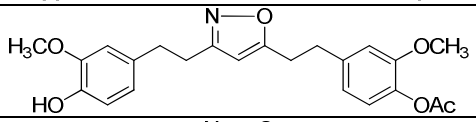
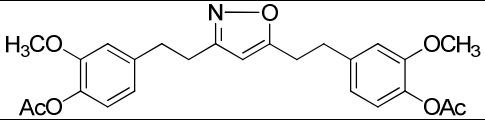
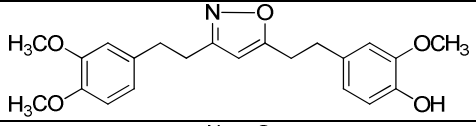
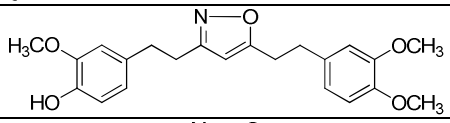
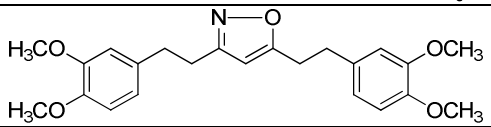
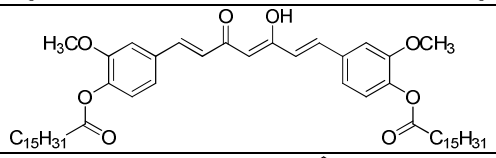
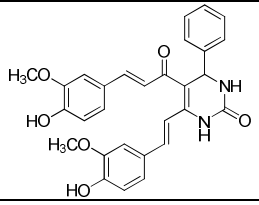
Table 10: Curcumin derivatives in antibacterial investigations

No.	Structural formula
1k	
2k	

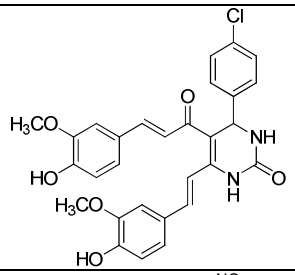
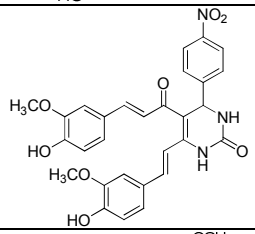
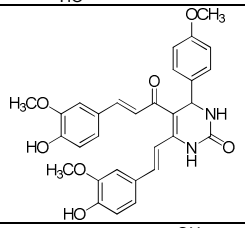
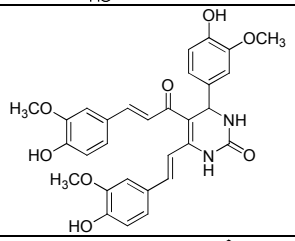
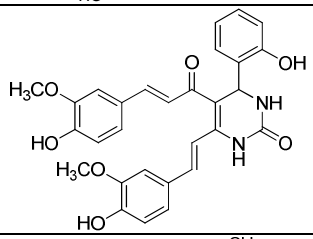
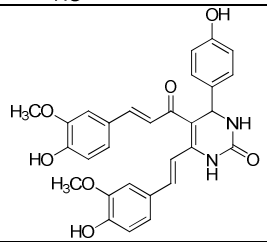
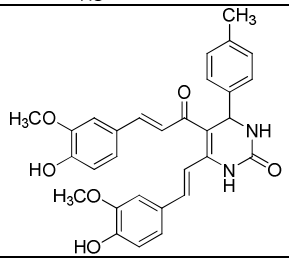
Continue…

No.	Structural formula
3k	
4k	
5k	
6k	
7k	
8k	
9k	
10k	
11k	
12k	
13k	
14k	
15k	

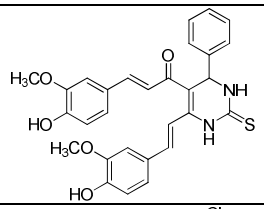
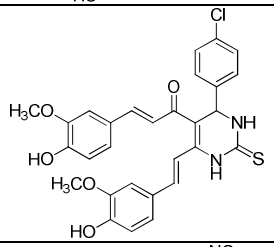
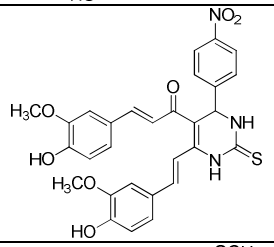
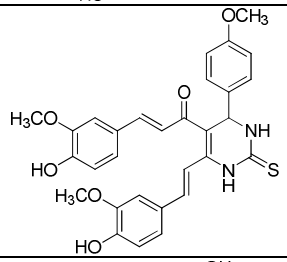
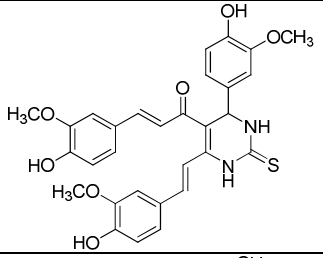
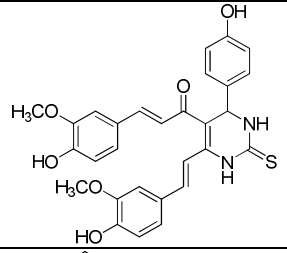
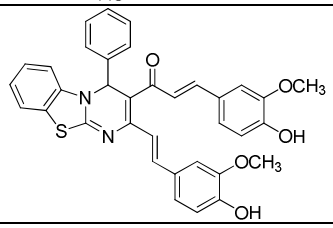
Continue…

No.	Structural formula
16k	
17k	
18k	
19k	
20k	
21k	
22k	
23k	
24k	
25k	
26k	
27k	
28k	

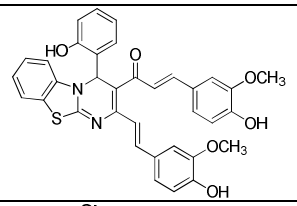
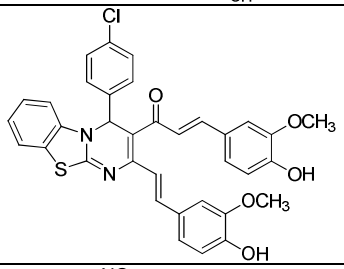
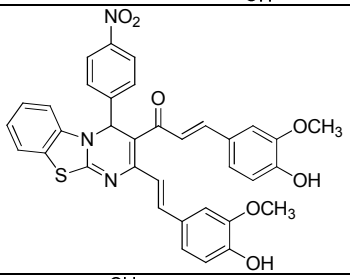
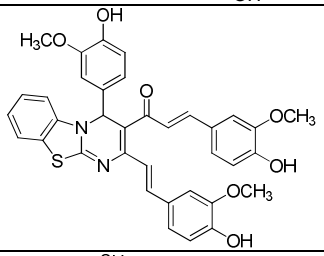
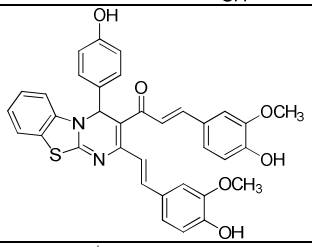
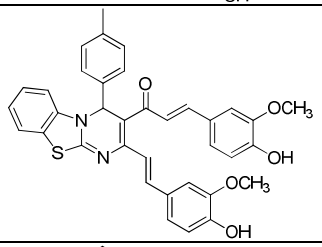
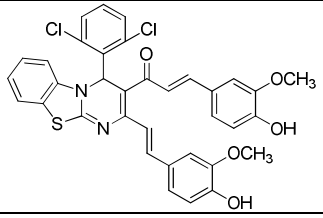
Continue…

No.	Structural formula
29k	
30k	
31k	
32k	
33k	
34k	
35k	

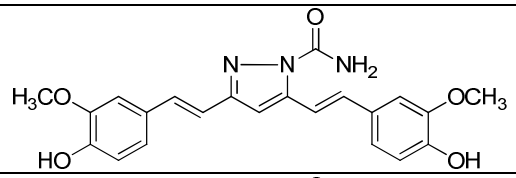
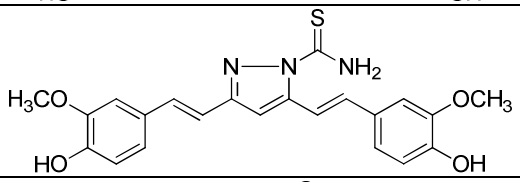
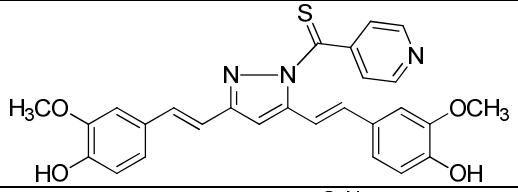
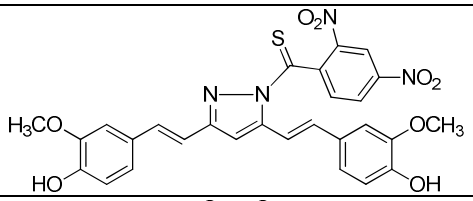
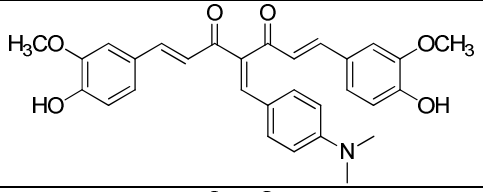
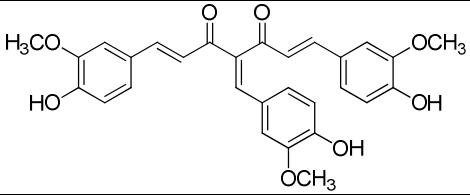
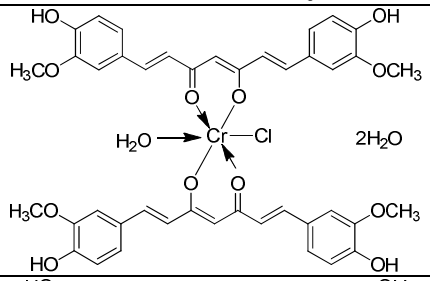
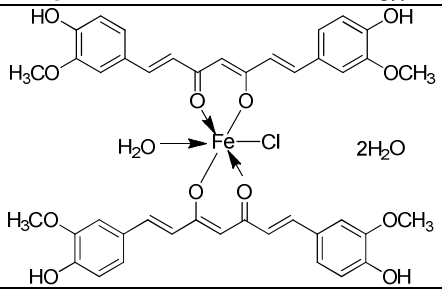
Continue…

No.	Structural formula
36k	
37k	
38k	
39k	
40k	
41k	
42k	

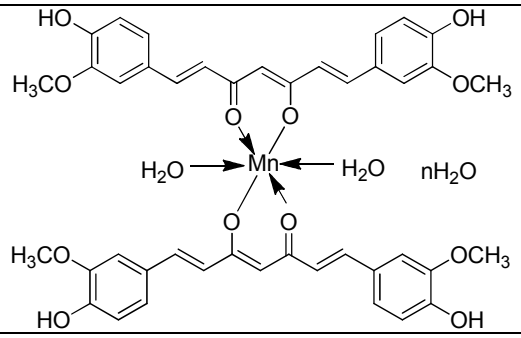
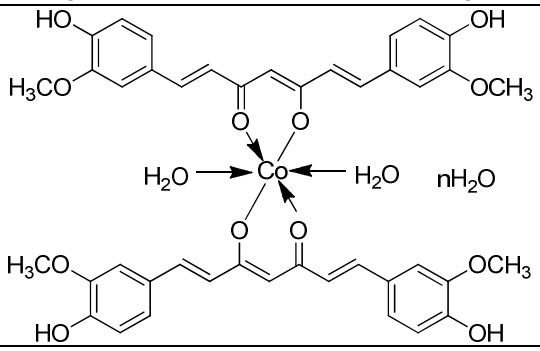
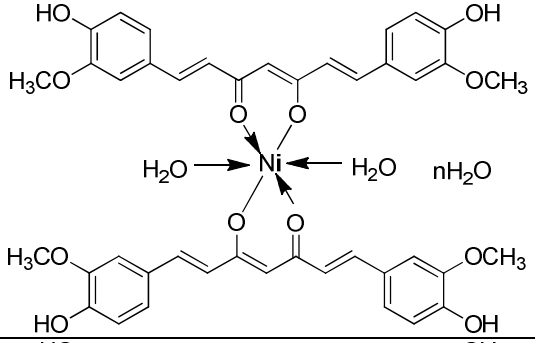
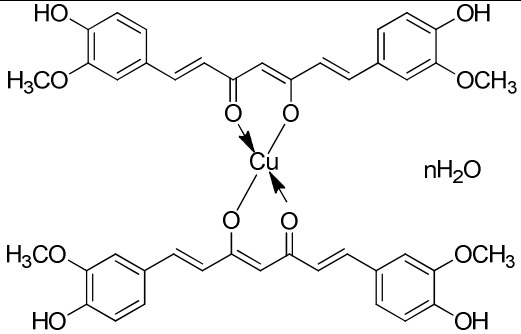
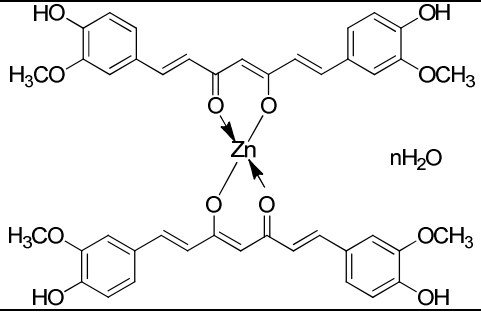
Continue…

No.	Structural formula
43k	
44k	
45k	
46k	
47k	
48k	
49k	

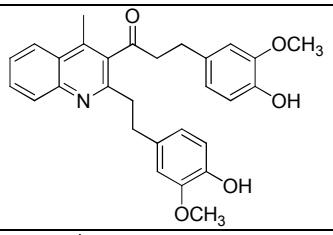
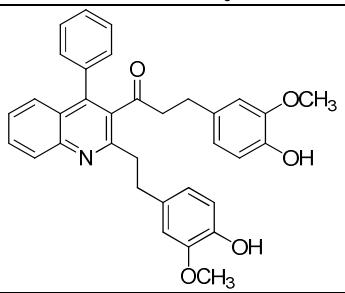
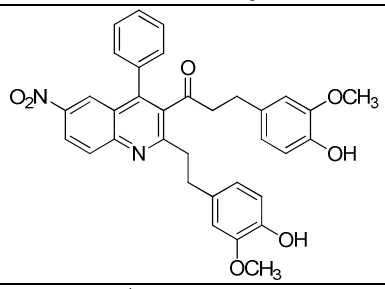
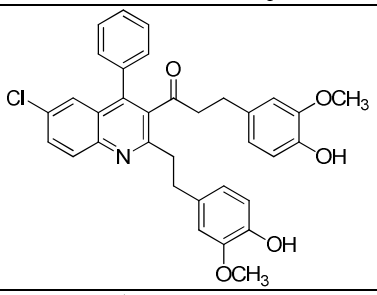
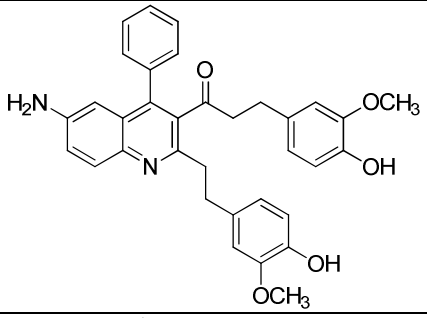
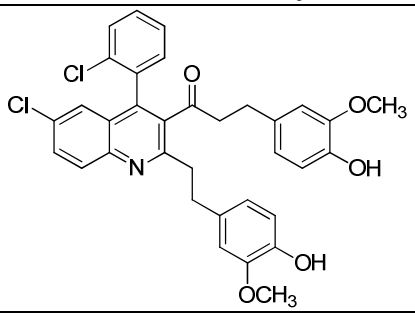
Continue…

No.	Structural formula
50k	
51k	
52k	
53k	
54k	
55k	
56k	
57k	

Continue…

No.	Structural formula
58k	
59k	
60k	
61k	
62k	

Continue…

No.	Structural formula
63k	
64k	
65k	
66k	
67k	
68k	

REFERENCE

Barclay LR, Vinqvist MR, M ukai K, Goto H, Hashimoto Y, Tokunaga A and Uno H (2000). On the antioxidant mechanism of curcumin: Classical methods are needed to determine antioxidant mechanism and activity. *Org. Lett.,* **2**(18): 2841-2843.

Barrett MP (2000). Problems for the chemotherapy of human African trypanosomiasis. *Curr. Opin. Infect. Dis.* **13**(6): 647-651.

Barry J, Fritz M, Brender JR, Smith PES, Lee DK and Ramamoorthy A (2009). Determining the effects of lipophilic drugs on membrane structure by solid-state NMR spectroscopy: The case of the antioxidant curcumin. *J. Am. Chem. Soc.,* **131**(12): 4490-4498.

Beal MF (1992). Does impairment of energy metabolism result in excitotoxic neuronal death in neuro-degenerative illnesses? *Ann. Neurol.,* **31**(2): 119-130.

Beloqui A, Coco R, Memvanga PB, Ucakar B, des Rieux A and Preat V (2014). pH-sensitive nanoparticles for colonic delivery of curcumin in inflammatory bowel disease. *Int. J. Pharmaceut.* **473**(1-2): 203-212.

Brookmeyer R, Gray S and Kawas C (1998). Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. *Am. J. Public Health,* **88**(9): 1337-1342.

Burke TR, Fesen MR, Mazumder A, Wang J, Carothers AM, Grunberger D, Driscoll J, Kohn K. Pommier Y (1995). Hydroxylated aromatic inhibitors of hiv-1 integrase. *J. Med. Chem.,* **38**(21): 4171-4178.

Changtam C, de Koning HP, Ibrahim H, Sajid MS, Gould MK and Suksamrarn A (2010). Curcuminoid analogs with potent activity against Trypanosoma and Leishmania species. *Eur. J. Med. Chem.,* **45**(3): 941-956.

Changtam C, Hongmanee P and Suksamrarn A (2010). Isoxazole analogs of curcuminoids with highly potent multidrug-resistant antimycobacterial activity. *Eur. J. Med. Chem.,* **45**(10): 4446-4457.

Gong CY, Deng SY, Wu QJ, Xiang ML, Wei XW, Li L, Gao X, Wang BL, Sun L, Chen YS, Li YC, Liu L, Qian ZY and Wei YQ (2013). Improving antiangiogenesis and anti-tumor activity of curcumin by biodegradable polymeric micelles. *Biomaterials,* **34**(4): 1413-1432.

Gorman AA, Hamblett I, Srinivasan VS and Wood PD (1994). Curcumin-derived transients: A pulsed laser and pulse radiolysis study. *Photochem. Photobiol.* **59**(4): 389-398.

Harish G, Venkateshappa C, Mythri RB, Dubey SK, Mishra K, Singh N, Vali S and Bharath MMS (2010). Bioconjugates of curcumin display improved protection against glutathione depletion mediated oxidative stress in a dopaminergic neuronal cell line: Implications for Parkinson's disease. *Bioorg. Med. Chem.,* **18**(7): 2631-2638.

Hegge AB, Vukicevic M, Bruzell E, Kristensen S and Tonnesen HH (2013). Solid dispersions for preparation of phototoxic supersaturated solutions for antimicrobial photodynamic therapy (aPDT) Studies on curcumin and curcuminoides L. *Eur. J. Pharm. Biopharm.,* **83**(1): 95-105.

Hill JO, Hauptman J, Anderson JW, Fujioka K, O'Neil PM, Smith DK, Zavoral JH and Aronne LJ (1999). Orlistat, a lipase inhibitor, for weight maintenance after conventional dieting: A 1-y study. *Am. J. Clin. Nutr.,* **69**(6): 1108-1116.

Hori Y, Miura T, Hirai Y, Fukumura M, Nemoto Y, Toriizuka K and Ida Y (2003). Pharmacognostic studies on ginger and related drugs - part 1: Five sulfonated compounds from Zingiberis rhizome (Shokyo). *Phytochemistry,* **62**(4): 613-617.

Hu LD, Jia YH, Niu F, Jia Z, Yang X and Jiao KL (2012). Preparation and enhancement of oral bioavailability of curcumin using microemulsions vehicle. *J. Agric. Food Chem.,* **60**(29): 7137-7141.

Jha N, Jurma O, Lalli G, Liu Y, Pettus EH, Greenamyre JT, Liu RM, Forman HJ and Andersen JK (2000). Glutathione depletion in PC12 results in selective inhibition of mitochondrial complex I activity. Implications for Parkinson's disease. *J. Biol. Chem.,* **275**(34): 26096-26101.

Jovanovic SV, Boone CW, Steenken S, Trinoga M and Kaskey RB (2001). How curcumin works preferentially with water soluble antioxidants. *J. Am. Chem. Soc.,* **123**(13): 3064-3068.

Karewicz A, Bielska D, Gzyl-Malcher B, Kepczynski M, Lach R and Nowakowska M (2011). Interaction of curcumin with lipid monolayers and liposomal bilayers. *Colloid. Surface. B.,* **88**(1): 231-239.

Kim TH, Kim JK, Ito H and Jo C (2011). Enhancement of pancreatic lipase inhibitory activity of curcumin by radiolytic transformation. *Bioorg. Med. Chem. Lett.,* **21**(5): 1512-1514.

Koide T, Nose M, Ogihara Y, Yabu Y and Ohta N (2002). Leishmanicidal effect of curcumin *in vitro*. *Biol. Pharm. Bull.,* **25**(1): 131-133.

Kunnumakkara AB, Anand P and Aggarwal BB (2008). Curcumin inhibits proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell signaling proteins. *Cancer Lett.,* **269**(2): 199-225.

Lal J, Gupta SK, Thavaselvam D and Agarwal DD (2012). Design, synthesis, synergistic antimicrobial activity and cytotoxicity of 4-aryl substituted 3,4-dihydropyrimidinones of curcumin. *Bioorg. Med. Chem. Lett.,* **22**(8): 2872-2876.

Lee SL, Huang WJ, Lin WW, Lee SS and Chen CH (2005). Preparation and anti-inflammatory activities of diarylheptanoid and diarylheptylamine analogs. *Bioorg. Med. Chem.,* **13**(22): 6175-6181.

Li CQ, Li BG, Qi HY, Li QL, Wang FP and Zhang GL (2004). Three cyclooctapeptides and one glycoside from Microtoena prainiana. *J. Nat. Prod.,* **67**(6): 978-982.

Lowe ME (1994). Pancreatic triglyceride lipase and colipase: Insights into dietary fat digestion. *Gastroenterology,* **107**(5): 1524-1536.

Magro M, Campos R, Baratella D, Ferreira MI, Bonaiuto E, Corraducci V, Uliana MR, Lima GPP, Santagata S, Sambo P and Vianello F (2015). Magnetic purification of curcumin from curcuma longa rhizome by novel naked maghemite nanoparticles. *J. Agric. Food Chem.* **63**(3): 912-920.

Manjunatha JR, Bettadaiah BK, Negi PS and Srinivas P (2013). Synthesis of quinoline derivatives of tetrahydrocurcumin and zingerone and evaluation of their antioxidant and antibacterial attributes. *Food Chem.,* **136**(2): 650-658.

Masters CL, Cappai R, Barnham KJ and Villemagne VL (2006). Molecular mechanisms for Alzheimer's disease: Implications for neuroimaging and therapeutics. *J. Neurochem.,* **97**(6): 1700-1725.

Mazumder A, Gazit A, Levitzki A, Nicklaus M, Yung J, Kohlhagen G and Pommier Y (1995). Effects of tyrphostins, protein kinase inhibitors, on human immunodeficiency virus type 1 integrase. *Biochemistry*, **34**(46): 15111-15122.

Mazumder A, Neamati N, Sunder S, Schulz J, Pertz H, Eich E and Pommier Y (1997). Curcumin analogs with altered potencies against HIV-1 integrase as probes for biochemical mechanisms of drug action. *J. Med. Chem.* **40**(19): 3057-3063.

Mazumder A, Raghavan K, Weinstein J, Kohn KW. Pommier Y (1995). Inhibition of human immunodeficiency virus type-1 integrase by curcumin. *Biochem. Pharmacol.,* **49**(8): 1165-1170.

Mishra S, Narain U, Mishra R and Misra K (2005). Design, development and synthesis of mixed bioconjugates of piperic acid-glycine, curcumin-glycine/alanine and curcumin-glycine-piperic acid and their antibacterial and antifungal properties. *Bioorg. Med. Chem.,* **13**(5): 1477-1486.

Mythri RB, Jagatha B, Pradhan N, Andersen J and Bharath MM (2007). Mitochondrial complex I inhibition in Parkinson's disease: How can curcumin protect mitochondria? *Antioxid. Redox Sign.,* **9**(3): 399-408.

Nakai M, Fukui Y, Asami S, Toyoda-Ono Y, Iwashita T, Shibata H, Mitsunaga T, Hashimoto F and Kiso Y (2005). Inhibitory effects of oolong tea polyphenols on pancreatic lipase *in vitro*. *J. Agric. Food Chem.,* **53**(11): 4593-4598.

Naksuriya O, Okonogi S, Schiffelers RM and Hennink WE (2014). Curcumin nanoformulations: A review of pharmaceutical properties and preclinical studies and clinical data related to cancer treatment. *Biomaterials* **35**(10): 3365-3383.

Nishiyama T, Mae T, Kishida H, Tsukagawa M, Mimaki Y, Kuroda M, Sashida Y, Takahashi K, Kawada T, Nakagawa K and Kitahara M (2005). Curcuminoids and sesquiterpenoids in turmeric (Curcuma longa L.) suppress an increase in blood glucose level in type 2 diabetic KK-A(y) mice. *J. Agric. Food Chem.,* **53**(4): 959-963.

Nose M, Koide T, Ogihara Y, Yabu Y and Ohta N (1998). Trypanocidal effects of curcumin *in vitro*. *Biol. Pharm. Bull.,* **21**(6): 643-645.

Payton F, Sandusky P and Alworth WL (2007). NMR study of the solution structure of curcumin. *J. Nat. Prod.,* **70**(2): 143-146.

Priyadarsini KI (1997). Free radical reactions of curcumin in membrane models. *Free Radic. Biol. Med.,* **23**(6): 838-843.

Priyadarsini KI, Maity DK, Naik GH, Kumar MS, Unnikrishnan MK, Satav JG and Mohan H (2003). Role of phenolic O-H and methylene hydrogen on the free radical reactions and antioxidant activity of curcumin. *Free Radic. Biol. Med.,* **35**(5): 475-484.

Radha A, Rukhmini SD, Vilasini S, Sakunthala PR, Sreedharan B, Velayudhan MP and Abraham A (2012). Bioactive derivatives of curcumin attenuate cataract formation *in vitro*. *Chem. Biol. Drug Des.,* **80**(6): 887-892.

Refat MS (2013). Synthesis and characterization of ligational behavior of curcumin drug towards some transition metal ions: Chelation effect on their thermal stability and biological activity. *Spectrochim. Acta A.,* **105**: 326-337.

Roberson ED and Mucke L (2006). 100 years and counting: prospects for defeating Alzheimer's disease. *Science,* **314**(5800): 781-784.

Sahu PK, Sahu PK, Gupta SK, Thavaselvam D and Agarwal DD (2012). Synthesis and evaluation of antimicrobial activity of 4H-pyrimido[2,1-b] benzothiazole, pyrazole and benzylidene derivatives of curcumin. *Eur. J. Med. Chem.,* **54**: 366-378.

Sandur SK, Pandey MK, Sung B, Ahn KS, Murakami A, Sethi G, Limtrakul P, Badmaev V and Aggarwal BB (2007). Curcumin, demethoxycurcumin, bisdemethoxycurcumin, tetrahydrocurcumin and turmerones differentially regulate anti-inflammatory and anti-proliferative responses through a ROS-independent mechanism. *Carcinogenesis,* **28**(8): 1765-1773.

Selkoe DJ (2001). Clearing the brain's amyloid cobwebs. *Neuron.,* **32**(2): 177-180.

Shaikh J, Ankola DD, Beniwal V, Singh D and Kumar MNVR (2009). Nanoparticle encapsulation improves oral bioavailability of curcumin by at least 9-fold when compared to curcumin administered with piperine as absorption enhancer. *Eur. J. Pharm. Sci.,* **37**(3-4): 223-230.

Sharma RA, Gescher AJ and Steward WP (2005). Curcumin: The story so far. *Eur. J. Cancer,* **41**(13): 1955-1968.

Shen L and Ji HF (2007). Theoretical study on physicochemical properties of curcumin. *Spectrochim. Acta A.,* **67**(3-4): 619-623.

Shi W, Dolai S, Rizk S, Hussain A, Tariq H, Averick S, L'Amoreaux W, El Ldrissi A, Banerjee P and Raja K (2007). Synthesis of monofunctional curcumin derivatives, clicked curcumin dimer, and a PAMAM dendrimer curcumin conjugate for therapeutic applications. *Org. Lett.,* **9**(26): 5461-5464.

Singh RK, Rai D, Yadav D, Bhargava A, Balzarini J and De Clercq E (2010). Synthesis, antibacterial and antiviral properties of curcumin bioconjugates bearing dipeptide, fatty acids and folic acid. *Eur. J. Med. Chem.,* **45**(3): 1078-1086.

Sugiyama Y, Kawakishi S and Osawa T (1996). Involvement of the beta-diketone moiety in the antioxidative mechanism of tetrahydrocurcumin. *Biochem. Pharmacol.,* **52**(4): 519-525.

Sui Z, Salto R, Li J, Craik C and Ortiz de Montellano PR (1993). Inhibition of the HIV-1 and HIV-2 proteases by curcumin and curcumin boron complexes. *Bioorg. Med. Chem.,* **1**(6): 415-422.

Tanaka R, Tsujii H, Yamada T, Kajimoto T, Amano F, Hasegawa J, Hamashima Y, Node M, Katoh K and Takebe Y (2009). Novel 3 alpha-methoxyserrat-14-en-21 beta-ol (PJ-1) and 3 beta-methoxyserrat-14-en-21 beta-ol (PJ-2)-curcumin, kojic acid, quercetin, and baicalein conjugates as HIV agents. *Bioorg. Med. Chem.,* **17**(14): 5238-5246.

Uehara SI, Yasuda I, Akiyama K, Morita H, Takeya K and Itokawa H (1987). Diarylheptanoids from the Rhizomes of Curcuma xanthorrhiza and Alpinia officinarum (Pharmacognosy, Chemical). *Chem. Pharm. Bull.* P.35.

Vali S, Mythri RB, Jagatha B, Padiadpu J, Ramanujan KS, Andersen JK, Gorin F and Bharath MM (2007). Integrating glutathione metabolism and mitochondrial dysfunction with implications for Parkinson's disease: a dynamic model. *Neuroscience,* **149**(4): 917-930.

Weber WM, Hunsaker LA, Abcouwer SF, Deck LM and Vander Jagt DL (2005). Anti-oxidant activities of curcumin and related enones. *Bioorg. Med. Chem.* **13**(11): 3811-3820.

Wei X, Senanayake TH, Bohling A and Vinogradov SV (2014). Targeted Nanogel Conjugate for Improved Stability and Cellular Permeability of Curcumin: Synthesis, Pharmacokinetics, and Tumor Growth Inhibition. *Mol. Pharmaceut.,* **11**(9): 3112-3122.

Yallapu MM, Jaggi M and Chauhan SC (2010). Poly(beta-cyclodextrin)/Curcumin Self-Assembly: A Novel Approach to Improve Curcumin Delivery and its Therapeutic Efficacy in Prostate Cancer Cells. *Macromol. Biosci.,* **10**(10): 1141-1151.

Zhang X, Tian Y, Li Z, Tian X, Sun H, Liu H, Moore A and Ran C (2013). Design and Synthesis of Curcumin Analogues for in Vivo Fluorescence Imaging and Inhibiting Copper-Induced Cross-Linking of Amyloid Beta Species in Alzheimer's Disease. *J. Am. Chem. Soc.,* **135**(44): 16397-16409.

Zona C and La Ferla B (2011). Synthesis of labeled curcumin derivatives as tools for *in vitro* blood brain barrier trafficking studies. *J. Labelled Compd. Rad.,* **54**(9-10): 629-632.