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For further information about this article or if you need reprints, please contact:

Syed Nasir Abbas Bukhari
Faculty of pharmacy,
Universiti Kebangsaan Malaysia,
Jalan Raja Muda Abdul Aziz,
50300, Kuala Lumpur, Malaysia

Tel: 0060142765730

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Synthesis and Biological Evaluation of Curcumin Analogues

Syed Nasir Abbas Bukhari, Ibrahim Bin Jantan, Malina Jasamai,
Waqas Ahmad and Muhammad Wahab Bin Amjad

Among all the *Curcuma* species, Curcumin is the most studied curcuminoid. Curcumin is renowned for its plentiful biological and pharmacological activities. Synthesis of new curcumin analogues always gained attention by scientists in the area to solve the poor bioavailability problems associated with curcumin. Uncountable analogues of curcumin have synthesized in past decades. In this review, alterations in the fundamental structure of curcumin to access associated compounds by chemical synthesis are described. We have endeavoured to sum up the biological activities of only synthetic analogues of curcumin and also most popular types of synthetic analogues of curcumin. This overview of synthetic data will provide an ease for the future scientists to develop new synthetic strategies for curcumin analogues as well as it shows the pharmacological importance and need of novel analogues.

Key words: Curcumin, anti-inflammatory, anticancer, antioxidant, synthetic analogues

Drug and Herbal Research Centre, Faculty of Pharmacy, Universiti Kebangsaan Malaysia, Kuala Lumpur, 50300, Malaysia

INTRODUCTION

Among all the species of *Curcuma*, Curcumin (1,7-bis-(4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3,5-dione) has acquired most of the attention of researchers. Curcumin is well-known for its numerous pharmacological and biological activities (Itokawa *et al*., 2008; Gupta *et al*., 2011). Curcumin has been known to restrain the metabolism of arachidonic acid and the activities of cyclooxygenase-2 (COX-2), lipoxygenase, proinflammatory cytokines, inducible nitric oxide (iNOS), protein kinases, transcription factors which include nuclear factor-kB and release of steroids (Kohli *et al*., 2005; Shakibaei *et al*., 2007; Aggarwal and Sung, 2009). Additional activities of curcumin include inhibition of low-density lipoprotein oxidation, lowering of blood cholesterol level, inhibition of platelet aggregation, repression of thrombosis and myocardial infarction, treatment of rheumatoid arthritis, hanging up HIV replication, protection from liver injury as well as anticancer and Immunomodulatory activities correspondingly (Ahn *et al*., 2004; Allam, 2009; Gupta *et al*., 2010).

Bioavailability of curcumin is very destitute, as orally administered curcumin suffers hepatic conjugation, leading to the formation of glucoronides and sulphates and systematic administration causes it to undergo reduction (Anand *et al*., 2007). Many studies have been performed to perk up the bioavailability of curcumin by adapting its molecular structure, i.e. removing the unstable β-diketone moiety and altering the heptadiene linker even as keeping the phenolic OH groups (Straganz and Nidetzky 2005; Liang *et al*., 2009a). The presence of the β-diketone moiety will lead to rapid metabolism by aldo-keto reductase in the liver, therefore restraining the useful effects of curcumin in many types of diseases.

Curcumin is an affiliate of the linear diarylheptanoid category of natural products in which two oxy-substituted aryl moieties are joined mutually through a seven-carbon chain. The C_7 chain of linear diarylheptanoids contains unsaturation, oxo functions, enone moiety and a 1,3-diketone group. The C_7 chain is generally unsubstituted apart from oxo and hydroxy functions. This unsaturation in the linker possesses an E-configuration (trans C-C bonds). The aryl rings may be symmetrically or unsymmetrically substituted; for the most part natural substituents are of the oxy type, for instance hydroxy or methoxy elements. Curcumin analogues can be catalogued in three groups: analogues from turmeric, analogues from mother nature and synthetic analogues. In this review article we have strived to recapitulate the biological activities and types of just synthetic analogues of curcumin.

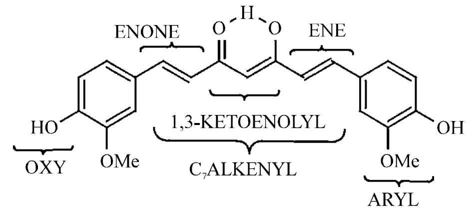


Fig. 1: Possible sites for structural modifications on curcumin

Curcumin and its analogues have been the subjects of computational studies, predominantly with the purpose of unravelling its exclusive structural characters and taking advantage of the information for further molecular design. Table 1 recaps the bioactivities of synthetic curcumin analogues. The typical structural features of curcumin comprise two o-methoxy phenol units, two enone moieties and a 1,3- diketone↔1,3-keto-enol system. The potentials for structural alteration on curcumin are shown in Fig. 1.

Alterations of structure have been attempted at all these molecular sites. The variation of the fundamental structure of curcumin to yield associated compounds by chemical synthesis may be of different types. We have tried our best to summarize most common and popular types of synthetic curcumin analogues in this review.

CURCUMIN DERIVATIVES

Compounds such as two dioxy-substituted benzene rings, the -C-C-CO-CH_2-CO-C-C- linker and the oxy substituents on the benzene rings, that maintain the fundamental structural features of curcumin are termed as curcumin derivatives. The curcumin derivatives are synthesized by and large by derivatization, initializing from curcumin. For instance, the phenolic hydroxy group can be acylated, alkylated, glycosylated and amino acylated (Fig. 2) (Kumar *et al*., 2000; Mishra *et al*., 2008; Barthelemy *et al*., 1998; Tong *et al*., 2006). The hydroxy groups may be synthesized by the demethylation of methoxy groups (Sharma, 1976). An arylidene group (Ar-CH-) may be used for acylation, alkylation or substitution of the reactive methylene group of the linker (Mishra *et al*., 2008), thus bringing in substituents on the C_7 chain.

Table 1: Biological properties of synthetic analogues of curcumin

Biological activity	Functional groups and types of curcumin analogues promoting the biological activity
Anticancer and antiangiogenic	Cyclic curcumin analogues have stronger cytostatic, antitumor and radical-scavenging activities than curcumin (Youssef *et al*., 2004, 2007; Youssef and El-Sherbeny, 2005). Curcumin has lesser anticancer and antiangiogenic activities than the synthesized EF24 and other associated compounds (Lin *et al*., 2006; Mazumder *et al*., 1997). Hydrazinocurcumin is a more powerful inhibitor of endothelial cell proliferation than curcumin and it restrains the cell cycle progression of colon cancer cells through antagonism of Ca2/CaM functions (Weber *et al*., 2005; Weber *et al*., 2006). Proportioned analogues with aromatic rings having an alkoxy replacement are more effective in repressing tumor enlargement than curcumin (Sui *et al*., 1993).As far as antiangiogenic activities are concerned, curcumin is less heady than symmetrical bis-alkynyl or alkyl pyridine and thiophene derivatives (Venkateswarlu *et al*., 2005). Increased antitumor activity (growth inhibition and apoptosis) was found with the isoxazole analog in the hepatocellular carcinoma HA22T/VGH cells, as well as in the MCF-7 breast cancer cell line and in its multidrug resistant (MDR) variant MCF-7R (Simoni *et al*., 2008). Dimethylaminomethyl-substituted curcumin derivatives/ analogues inhibited four tumor cell lines proliferation hepatocellular carcinoma cell line (HepG2), human gastrocarcinoma cell line (SGC-7901), human non-smallcell lung cancer cell line (A549) and human colorectal cancer cell line (HCT-116) (Fang *et al*., 2013).
Antibacterial and antifungal	Diacetyl, diglycinoyl, diglycinoyl-di-piperoyl, dipiperoyl and dialanoyl derivatives and curcumin-4,40-di-O-b-D glucopyranoside have superior antibacterial and antifungal activities as of curcumin (Kumar *et al*., 2000; Mukhopadhyay *et al*., 1982; Mishra *et al*., 2005). Curcumin has perhaps the same or slightly lesser antibacterial activity than Mono-carbonyl analogues (Adams *et al*., 2005; Al-Omar *et al*., 2005) 3,4-Dihydropyrimidinones derivatives of curcumin showed significant antimicrobial activity against tested bacteria (*Staphylococcus aureus*, *Escherichia coli*, *Burkholderia pseudomallei*, *Salmonella typhi* and *Pseudomonas aeuriginosa*) and antifungal activity agaist human pathogenic fungal cultures viz. *Aspergillus niger*, *Aspergillus flavus*, *Trichoderma viride* and *Curvularia lunata* (Lal *et al*., 2012).
Antiproliferative	If antiproliferative effects are brought into limelight, Cyclopalladated complexes of curcumin show the best activity (Pucci *et al*., 2007). Bisdemethylcurcumin and hispolon analogues of curcumin are more potent anti-inflammatory as an anti-proliferative agent than curcumin.(Jayaraj Ravindrana). Demethoxycurcumin, bisdemethoxycurcumin, tetrahydrocurcumin and turmerones, modulate cell proliferation signaling to same extent as curcumin was investigated (Sandur *et al*., 2007).
Antimalarial and antioxidant	Pyrazole analogues and a curcumin Knoevenagel condensate have better antimalarial, antioxidant and COX-1- and COX-2-inhibitory activities than curcumin (Mishra *et al*., 2008;; Selvam *et al*., 2005).Curcumin has less potent antioxidant activity than its Fused pyridine analogues (Rukkumani *et al*., 2004).Curcumin has better antiradical activity than its Semicarbazone, but the antioxidant activity of curcumin is lesser. (Dutta *et al*., 2005).Compounds with ortho-diphenoxyl functionality display greater antioxidant activity than curcumin (Adams *et al*., 2005). Dimethylaminomethyl-substituted curcumin analogues has higher free radical scavenging activity than curcumin towards both DPPH and galvinoxyl radicals (Fang *et al*., 2013) curcumin analogues bearing o-diphenoxyl and o-dimethoxyphenoxyl groups exhibited significantly higher DPPH scavenging and anti-haemolysis (Shang *et al*., 2010).
Inhibitors of tumor-induced angiogenesis	Symmetrical curcuminoids 1,7-bis(4-hydroxy-5-methoxy-3-nitrophenyl)-1,6-heptadiene-3,5dione and 1,7-bis(3,4,5-trimethoxyphenyl)-1,6 heptadiene-3,5-dione inhibit Fos-Jun, tumor-induced angiogenesis, migration and invasion better than curcumin (Hahm *et al*., 2004; Hahm *et al*., 2002). Synthetic analogues with customized aromatic ring and/or adapted enone/dienone bridge among rings have more effective antiangiogenic and COX-1 reducing activity than curcumin (Handler *et al*., 2007; Furness *et al*., 2005; Adams *et al*., 2004).
Inhibitors of TPA-induced AP-1 and TNF-induced NF-kB activation	Curcumin analogues that retain the 7-carbon spacer between the aryl rings, with a 5-carbon spacer and with a 3-carbon spacer, inhibit TPA-induced AP-1(activator protein-1) and TNF (tumor necrosis) induced NF-kB (nuclear factor kappa B) activation better than curcumin and are improved antioxidants (Weber *et al*., 2005; Weber *et al*., 2006). TNF-induced NF-kB activation and proliferation is inhibited better by the Copper(II) conjugate of a synthetic analogue with non-enolizable diketone than curcumin (Zambre *et al*., 2006). Curcumin analogues, dibenzoylmethane, dibenzoylpropane, dibenzylideneacetone (DBA) have ability to suppress TNF-induced NF-kB activation (Anand *et al*., 2008).
Radical-scavenging activities	Cyclic curcumin analogues have best cytostatic, antitumor and radical-scavenging activities (Youssef *et al*., 2007; Youssef *et al*., 2004; Youssef and El-Sherbeny, 2005). Curcumin has lesser SOD (superoxide dismutase) mimicking, radiation-induced lipid peroxidation and radical-scavenging activities than Synthetic copper(II)-curcumin complexes (Barik *et al*., 2005). Manganese complexes of curcumin and diacetylcurcumin are better than curcumin in preventing excitotoxicity and kainic acid-induced nitric oxide levels and neuronal cell damage in rats and are top nitric oxide radical scavengers and neuroprotectors (Sumanont *et al*., 2004; Sumanont *et al*., 2006; Sumanont *et al*., 2007; Vajragupta *et al*., 2004). Cu(II)- curcumin complex possesses SOD mimicking activity, free radical neutralizing ability and antioxidant potential (Barik *et al*., 2005).
Cytochrome P450-inhibitory activity	Cytochrome P450-inhibitory activity of 2,6-dibenzylidenecyclohexanone, 2,5-dibenzylidenecyclopentanone and 1,4-pentadiene-3-one substituted analogues of curcumin is better than curcumin (Sardijiman *et al*., 1997).
Inhibitors of HIV-1 integrase	Cinnamoyl derivatives of curcumin are better than curcumin in inhibiting HIV-1(human immunodeficiency virus) integrase (Srinivasan *et al*., 2003). HIV-l and HIV-2 proteases are inhibited better by Curcumin-boron complexes than curcumin (Sui *et al*., 1993). Dicaffeoylmethane and rosmarinic acid derivatives of curcumin, inhibited both activities of integrase and inhibit binding of the enzyme to the viral DNA. (Mazumder *et al*., 1997).
Anti-inflammatory	Curcumin has more or less the same anti-inflammatory and antibacterial activity as of its Mono-carbonyl analogues (Fang *et al*., 2013; Mishra *et al*., 2005; Jantan *et al*., 2012). Curcumin analogues are better inhibitors of 5-lipoxygenase and aldose reductase (ALR2) enzymes than curcumin both in vitro/in vivo than curcumin analogues bearing a variety of heterocyclic substituents in the aromatic part combine anti-inflammatory and anti-proliferative activity (Katsori *et al*., 2011) pyrazole derivative of curcumin reduce inflammation and airway remodeling in asthma (Narumoto *et al*., 2012).
Inhibitors of growth and tube formation	Aromatic enonic analogues are either similar or slightly more potent than curcumin in restraining cell growth and proliferation (Robinson *et al*., 2003, Robinson *et al*., 2005). Curcumin's activity is inferior to its synthetic analogues with lop-sided units such as a phenyl group with alkyl amide, chloro-substituted benzamide, or heteroaromatic amide moieties in inhibiting growth and tube formation (Woo *et al*., 2005).
Antidiabetic and hypolipidemic	Vanadium complex of curcumin has antidiabetic and hypolipidemic properties and also recovers the cardiovascular complications associated with diabetes (Thompson *et al*., 2004).

Table 1: Continue

Biological activity	Functional groups and types of curcumin analogues promoting the biological activity
Mitochondrial membrane permeability	Curcumin derivatives with a customized aromatic ring and a cyclohexanone bridge amid rings are better than curcumin in enhancing mitochondrial membrane permeability (Pucci *et al.*, 2007). Curcumin derivative induced mitochondrial swelling and release cytochrome C, resulted in opening of the permeability transition pore (PTP) (Ligeret *et al.*, 2004).
Oxidative stress	Bisdemethoxycurcumin is the better option than curcumin in suppressing nicotine, alcohol and polyunsaturated fatty acid-induced oxidative stress, CCl4-induced hepatotoxicity and alcohol- and polyunsaturated fatty acid hyperlipidemia in rats (Devasena *et al.*, 2002; Kalpana *et al.*, 2007, Kamalakkaunan *et al.*, 2005).
Inhibitors of testosterone biosynthesis a	Inhibit the biosynthesis of testosterone by inhibiting 17b-hydroxysteroid dehydrogenase isoform 3 (17b-HSD3), an enzyme catalyzing the final step in testosterone biosynthesis. Some derivatives of curcumin are more potent than curcumin in the inhibition of human 17b-hydroxysteroid dehydrogenase (Hu *et al.*, 2010).
Gastroprotective and antidepressant effects	The zinc complexes of curcumin showed significant gastroprotective and antidepressant effects compared with curcumin alone, reduced gastric lesions and H^+ -K^+-ATPase activity and increased antioxidant activity (Mei *et al.*, 2011)

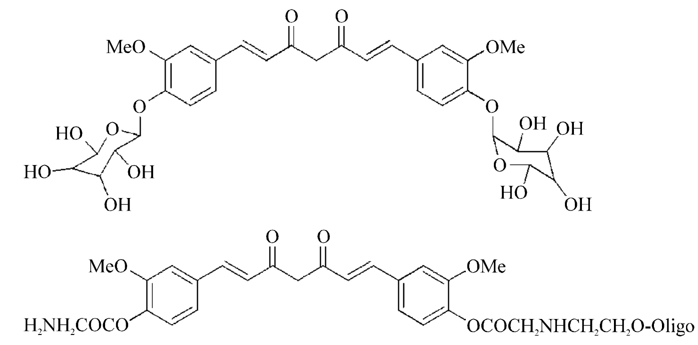


Fig. 2: Curcumin derivatives

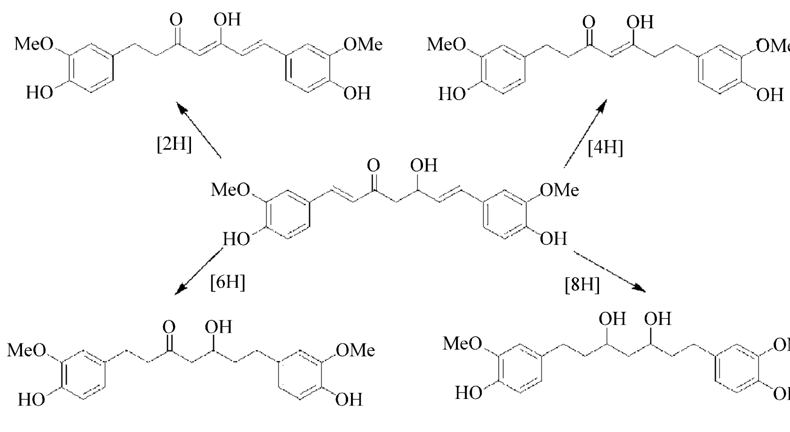


Fig. 3: Analogues synthesized by reduction of curcumin

CURCUMIN ANALOGUES

The next group, the curcumin analogues, which include all other compounds with some professed or stated structural correspondence to curcumin, now greatly outshine the first group. In their structural resemblance to curcumin, these so called analogues of curcumin differ on a broad scale, straddling a spectrum from structures such as (ferrocenyl-CH-CH-CO)$_2$ CH_2 to methyl ferulate. Analogues such as DHC, THC, HHC and OHC are given by the hydrogenation of the C_7 linker double bonds and the carbonyl groups, which are attained by the reduction of curcumin (Fig. 3) (Sompam *et al.*, 2007; Pan *et al.*, 2000; Hong *et al.*, 2004; Mukhopadhyay *et al.*, 1982).

Curcumin based analogues also include those acquired by utilizing the reactivity of the central β-diketone unit with hydrazine, its substituted derivatives and hydroxylamine. Such heterocyclizations lead to bisstyrylpyrazoles and isoxazoles in which the central 1,3-diketone↔1,3-keto-enol system has been shrouded and firmed (Fig. 4) (Mishra *et al.*, 2008; Shim *et al.*, 2004; Ishida *et al.*, 2002; Ohtsu *et al.*, 2002).

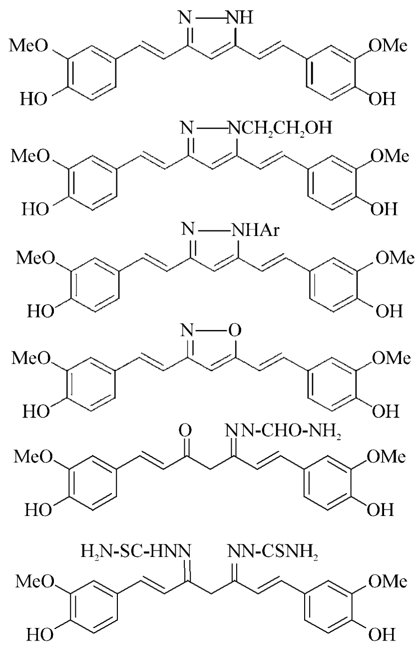


Fig. 4: Analogues synthesized by masking the central 3-diketone unit

Wang *et al.* (2012) reported a series of nonsteroidal mono-carbonyl analogues of curcumin, without the β-diketone moiety, possessing enhanced stability, improved pharmacokinetic profiles (Liang *et al.*, 2009b) and anti-inflammatory activity *in vitro* (Liang *et al.*, 2008; Zhao *et al.*, 2010).

Among the referred curcumin analogues (2E, 5E)-2,5-bis(4-(3-(dimethylamino)-propoxy)benzylidene) cyclopentanone , a hydrosoluble compound in the form of its quaternary ammonium salt (Fig. 5), exhibited strong inhibitory effects on lipopolysaccharide (LPS)-induced TNF-α and IL-6 release along with inflammatory gene expression in mouse macrophages (Liang *et al.*, 2009a).

Karthikeyan *et al.* (2011) suggested a new synthetic method (Fig. 6) in which ammonium acetate was used and result was the synthesis of monocarbonyl curcumin analogs (symmetrical aromatic moieties) with more stable chemical structures as well as their anticancer screening in various cell lines.

Bayomi *et al.* (2013) reported different series of Curcumin derivatives to be synthesized (Fig. 7, 8) and their antioxidant activity assessed by $ABTS^+$-scavenging and anti-haemolysis experiments. To explore the substituent effect, type and distribution pattern and the role of central active methylene hydrogens, compounds 7.1(a-g) and 7.2 were synthesized, where the seven carbon spacer was retained. Compounds 8.1a-g and 8.1h-j were prepared to test the effect of decreasing both length and flexibility of the seven carbon spacer. Fused pyrano ring systems were incorporated in compounds 8.2a-g to simulate coumarin and flavonoid ring systems, which are well known for their antioxidant and anticarcinogenic activities (Guthrie and Carroll, 1998). Finally, certain fused pyrazoles 8.3e-g, 8.4a-e and 8.4h-j, were included to reveal a more comprehensive structure-activity relationship, if any.

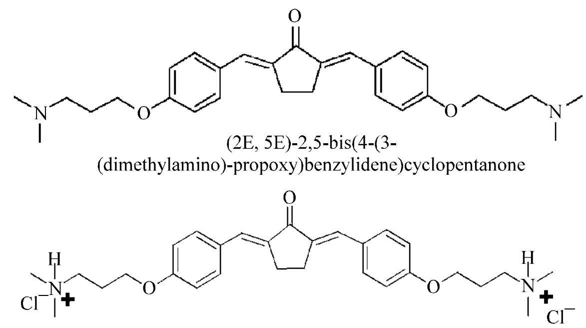
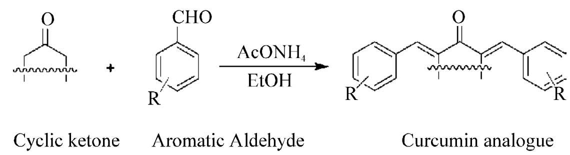


Fig. 5: Chemical structures of (2E,5E)-2,5-bis(4-(3-(dimethylamino)- propoxy) benzylidene) cyclopentanone and its quaternary ammonium salt

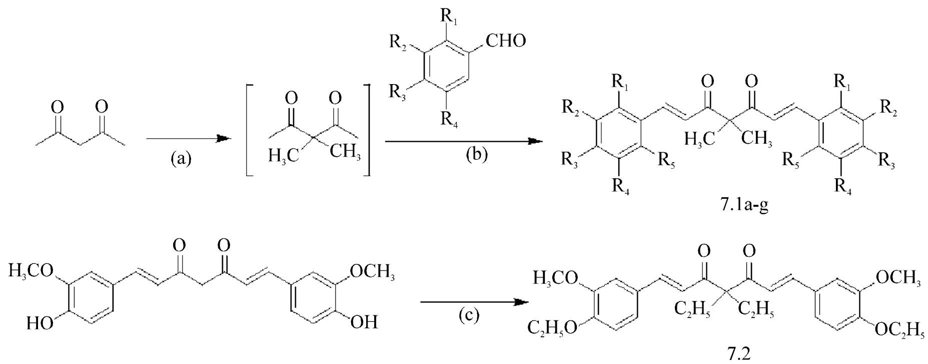


R = H, 4-Cl, 4-CH_3, 4-OCH_2CH_3, 4-$OCH_2CH = CH_2$, 3-OH, 2CH_3

Fig. 6: General synthesis of monocarbonyl curcumin analogs

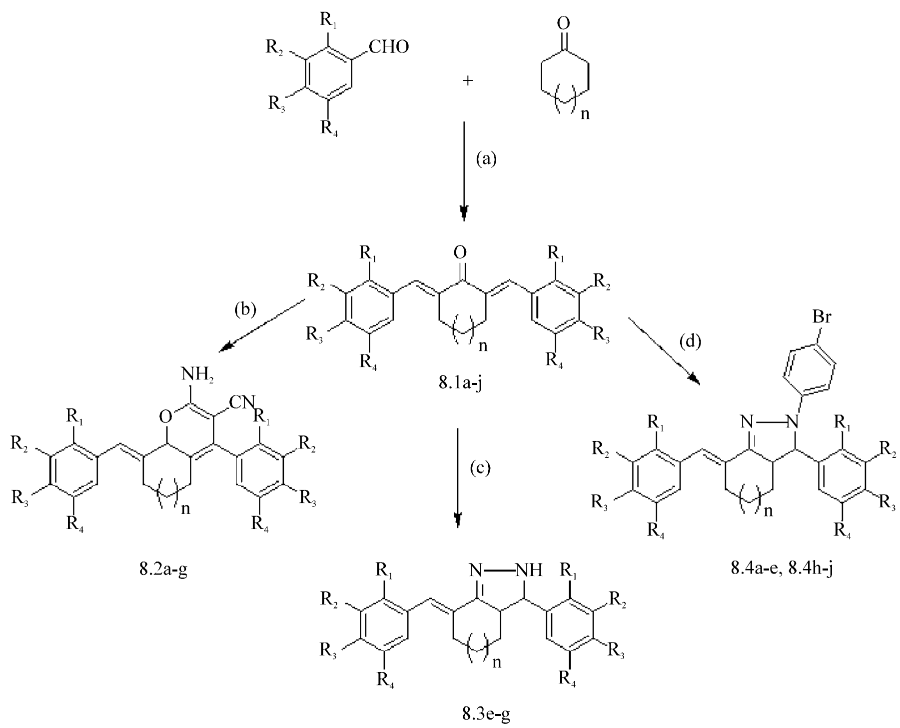
Babasaheb *et al.* (2012) synthesized the novel curcumin analogues containing enone and amide containing trimethoxy benzene moiety. The 1,3,5-trimethoxybenzene on Vilsmeier-Haack formylation gives 2,4,6-trimethoxy benzaldehyde, which yielded 3-bromo-2,4,6-trimethoxybenzaldehyde on bromination in glacial acetic acid. Compounds (9.1a-m) were prepared by acylation of 3-aminoacetophenone with different acylchlorides in basic medium. Compounds (9.1a-m) on Claisen-Schmidt condensation with 3-bromo- 2,4,6-trimethoxybenzaldehyde under basic media afforded a residue, which on purification by column chromatography with 1% ammonia and 0.5-1% methanol in chloroform as eluting solvent, furnished title compounds (9.2a-m) in good yield (Fig 9).

Fadda *et al.* (2010) decided to couple the diazonium salt of different aromatic amines with curcumin with a view to synthesize new azo-disperse dyes to explore the



a: R1 = R2 = R3 = R4 = H
b: R1 = R2 = R4 = H R3 = Cl
c: R1 = R2 = R4 = H R3 = OCH_3
d: R1 = R4 = H, R2 = R3 = OCH_3
e: R2 = R3 = H, R1 = R4 = OCH3
f: R1 = R2 = R4 = H, R3 = OH
g: R1 = R4 = H, R2 = OCH_3, R3 = OH

Fig. 7(a-c): Reaction protocol for the synthesis of 7a-g and 4: (a) $(CH3)_2SO_4$, K_2CO_3, DMSO/THF (b) NaOH, EtOH and (c) $(C_2H_5)_2SO_4$, acetone, K_2CO_3

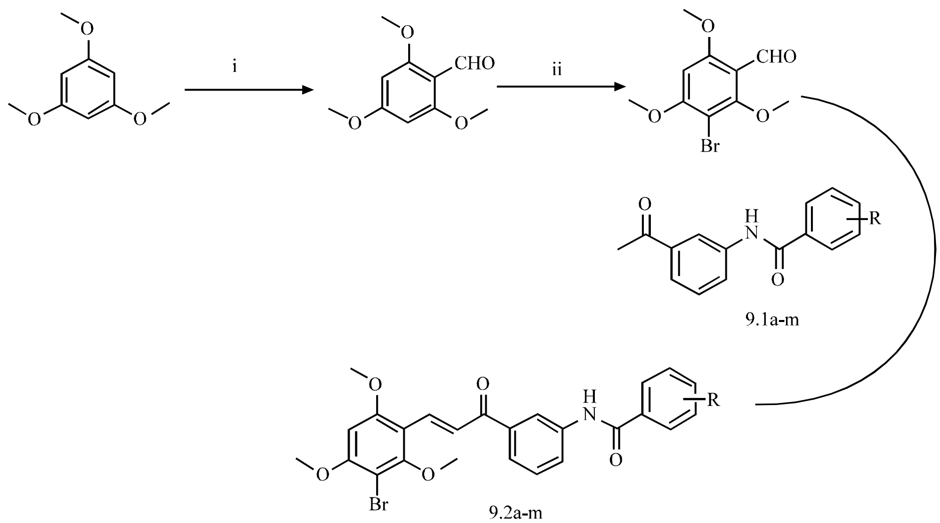


a: n = 1 R1 = R2 = R3 = R4 = H
b: n = 1 R1 = R2 = R4 = R3 = Cl
c: n = 1 R1 = R2 = R4 = H R3 = OCH_3
d: n = 1 R1 = R4 = H, R2 = R3 = OCH_3
e: n = 1 R2 = R3 = H, R1 = R4 = OCH_3
f: n = 1 R1 = R2 = R4 = H, R3 = OH
g: n = 1 R1 = R4 = H, R2 = OCH3, R3 = OH
h: n = 2 R1 = R2 = R4 = H R3 OCH_3
i: n = 2 R1 = R4 = H, R2 = H R3 OCH_3
j: n = 2 R2 = R3 = H, R1 = R4 = OCH_3

Fig. 8(a-d): Reaction protocol for the synthesis of 8.1a-j, 8.2a-g, 8.3e-g, 8.4a-e and 8.4h-j (a) NaOH, EtOH (b) malononitril, butanol or malononitril, DMF, piperidine (c) hydrazine hydrate, EtOH and (d) 4-bromo phenylhydrazine hydrochloride, Na ethoxide, EtOH

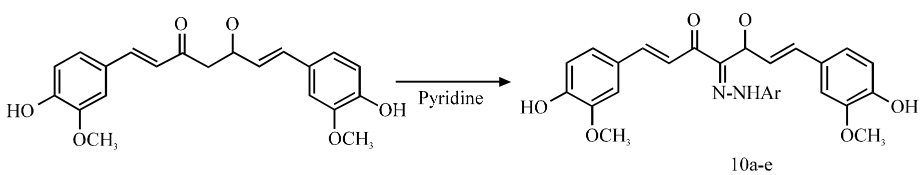
possibility of finding some new azodyes capable of dyeing different types of fibers and expected a wide spectrum of biological activity.

Diazonium salts undergo a coupling reaction with curcumin to give the corresponding 4-arylazo derivatives (10a-e) (Fig. 10). Treatment of 1,7-bis-(4-hydroxy-3-



9.2a = H
9.2b = 2-CF_3
9.2c = 3-CF_3
9.2d = 3-Cl
9.2e = 3-Br
9.2f = 4-F
9.2g = 4-tert. butyl
9.2h = 2.-F
9.2i = 3-F
9.2j = 3-Me
9.2k = 2-Me
9.2l = 4-OMe
9.2m = 2-Thiophene

Fig. 9: Synthesis of curcumin analogues



10a, Ar = C_6H_4-OCH_3-p
10b, Ar = C_6H_4-CH_3-p
10c, Ar = C_6H_5
10d, Ar = C_6H_4-Cl-p
10e, Ar = C_6H_4-NO_2-p

Fig. 10: Coupling of diazonium salt of different aromatic amines with curcumin

methoxy-phenyl)-4-[(4-nitro-phenyl)-hydrazono]- hepta-1,6-diene-3,5-dione (10e) with bromine in the presence of glacial acetic acid gave the corresponding 6,7-dibromo-1,7-bis-[3-(4-nitrophenylazo)-4-hydroxy-5-methoxy] hepta-1-ene-3,5-dione (11a). Condensation of (10e) with thiourea was performed in molar ratio (1:2), in boiling ethanolic sodium ethoxide to give the corresponding (Z)-4-(4-hydroxy-3-methoxy-phenyl)-6-[{6-(4-hydroxy-3-methoxy-phenyl)-2-thioxo-1,2,5,6-tetrahydro-pyrimidine-4-yl}(2-(4-nitrophenyl) hydrazono) methyl]-5,6 dihydropyrimidine-2(1H)-thione (11b).

Moreover(1Z,3E)-4-(4-hydroxy-3-methoxy-phenyl)-1-[6-(4-hydroxy-3-methoxy- phenyl)-2-thioxo-2,3,4,5-tetrahydro-pyrimidine-4-yl]-1-[2-(4-nitrophenyl) hydrazono]-but-3-ene-2-one (11c) was prepared by refluxing compound (10e) with thiourea (1:1) molarratio in boiling ethanolic sodium ethoxide. Similarly, it has been found that N-[bis-(5-(4-hydroxy-3-methoxy-phenyl)-2,5-dihydro-isoxazol-3-yl)-methylene]-N0-(4-nitro-phenyl)-hydrazine (11d) has been prepared by reaction of (10e) with hydroxylamine hydrochloride in refluxing pyridine (Fig. 11).

As an extension of their interest in the synthesis of new heterocycles by incorporating a pyrazole nucleus (Metwally *et al*., 1985), they report the behaviour of (10e) toward hydrazine hydrate and/or its derivatives as a facile route to some heterocyclic derivatives containing the pyrazole moiety. Therefore, the reaction of diferuloyl-(4-nitrophenyl) methane (10e) with hydrazine hydrate in (1:3) molar ratio in boiling mixture of ethanol-glacial acetic acid endowed the bis pyrazolyl derivative (11e).

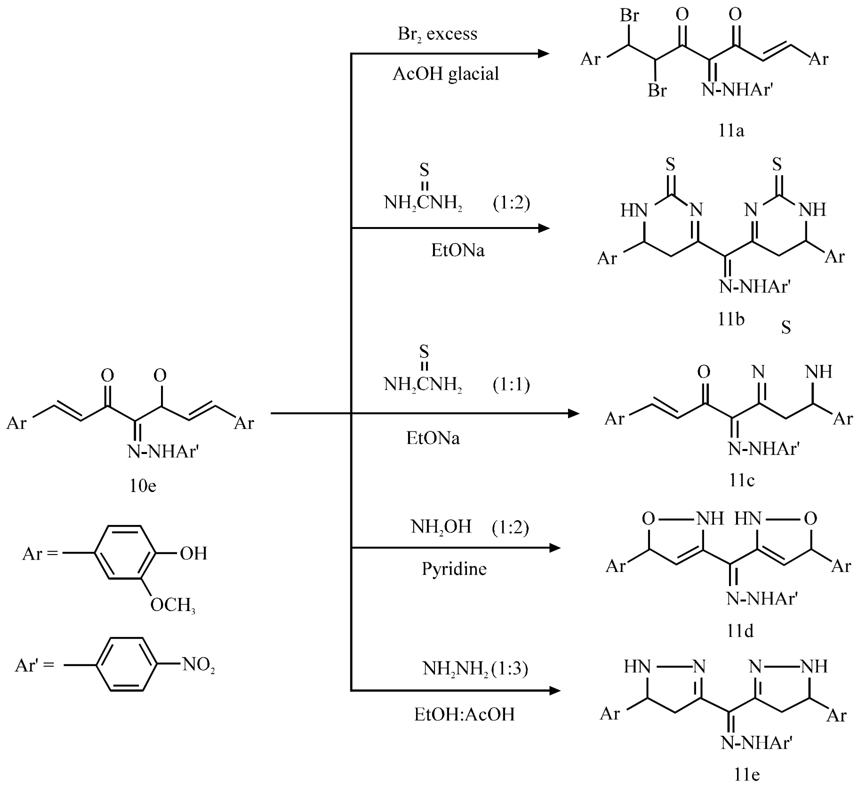


Fig. 11: Curcumin analogues synthesis

METAL COMPLEXES OF CURCUMIN

Metal complexes of curcumin and their analogues belong to the third group. A number of metal complexes of curcumin, derivatives of curcumin and analogues of curcumin have been detailed. They have normally been attained by the reaction of curcumin or one of its analogues with a metal salt. Boron has been known to form a complex with curcumin (Sui *et al.*, 1993). By combining a molecule of curcumin, oxalic acid and a boron atom (sourced from boric oxide or acid) yields a complex, rubrocurcumin. The complexation of two curcumin molecules with a boron atom produces rosocyanin. Moreover, complexes of copper (Barik *et al.*, 2005), iron, manganese (Sumanont *et al.*, 2004; Vajragupta *et al.*, 2003), palladium (Pucci *et al.*, 2007), vanadyl (Thompson *et al.*, 2004), gallium and indium (Majithiya *et al.*, 2005; Mohammadi *et al.*, 2005) have been stated.

The novel fluoro Knoevenagel condensates (Fig. 12) of Curcumin and their Schiff bases together with copper complexes, were evaluated for their proteasome inhibitory activity against a purified rabbit 20S proteasome, based on the observation that curcumin is a potent proteasome inhibitor as documented in colon cancer (HCT-116 and metastatic SW-480) cell lines (Milacic *et al.*, 2008). The results of their studies indicate that some of the new fluorocurcumin analogs are potent proteasome inhibitors as tested *in vitro* and in HCT116 cells in vivo and one amongst these compounds (CDF) moreover induced cell growth inhibition in both colon and pancreatic cancer cells. They also found CDF to be somewhat better in inducing apoptosis in BxPC-3 pancreatic cancer cells in initial screening. These preliminary findings suggest that CDF could be further developed by assessing its pharmacokinetics, tissue bioavailability and its mechanism of action for setting up the role of CDF as a chemo-preventive and/or therapeutic agent against cancer.

BIOLOGICAL ACTIVITIES

As man-made analogues of curcumin are renowned for their biological and pharmacological activities, so we have attempted to abridge these activities in Table 1.

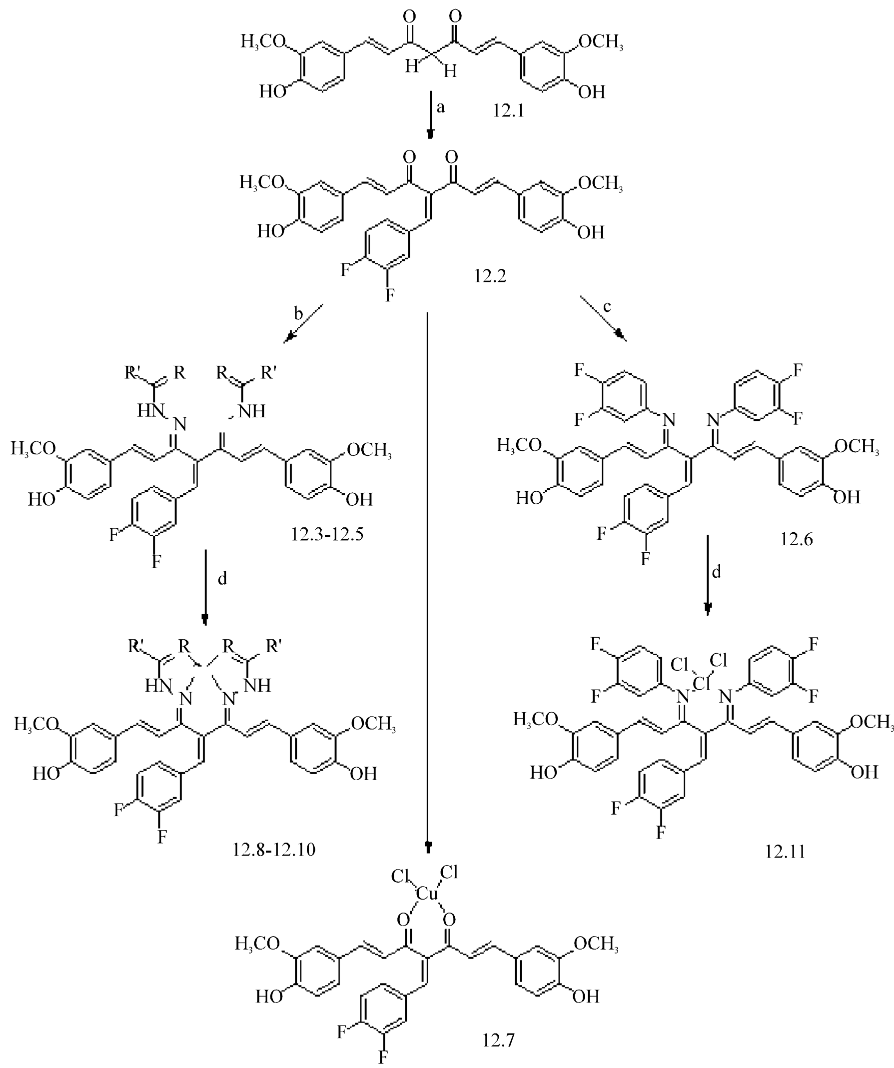


Fig. 12: Synthetic steps used in the preparation of copper conjugates of Knoevenagel condensates and Schiff bases of 1. The specific conditions followed for various steps include: (a) 3,4 diflouroaldehyde, piperidine, 48 h, methanol; (b) hydrazides, 24 h, piperidine, methanol, room temp. (1:2); (c) 3,4 diflouroamine, 24 h, piperidine, methanol, room temp; (d) $CuCl_2$. $2H_2O$, methanol, piperidine (1:1)

CONCLUSION

This extensive literature review on the synthesis and biological evaluation of curcumin analogues shows the pharmacological importance of these compounds and it gives an overview for the future scientists interested in development of new synthetic methods for synthesis of these analogues. Summarized data proves the pharmacological potential of curcumin analogues and encourages the discovery of new compounds with best biological activities and minimal issues related to the bioavailability of curcumin.

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