Synthesis and Biological Evaluation of Curcumin Analogues

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

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

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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 glucuronides 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 C7 chain of linear diarylheptanoids contains unsaturation, oxo functions, enone moiety and a 1,3-diketone group. The C7 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 oxo 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.

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 recap 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-CH3-CO-C-C- linker and the oxy substituents on the benzene rings, that maintain the fundamental structural features of curcumin are termed 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 aryldiene 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 C7 chain.
Table 1: Biological properties of synthetic analogues of curcumin

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<thead>
<tr>
<th>Biological activity</th>
<th>Functional groups and types of curcumin analogues promoting the biological activity</th>
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<tr>
<td><strong>Anticancer and antiangiogenic</strong></td>
<td>Cyclic curcumin analogues have stronger cytostatic, antitumor and radical-scavenging activities than curcumin (Yousef et al., 2004, 2007; Yousef and El-Sherbini, 2005). Curcumin has lesser anticancer and antiangiogenic activities than the synthesized EF24 and other associated compounds (Lin et al., 2006; Mazarudeh et al., 1997). Hydroxycurcumin 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 ERK/MAK function (Webber 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 toxic than asymmetrical bis-alkyl derivatives or alkyl pyridine and thiophene derivatives (Venkateswarlu et al., 2005). Increased antioxidant activity (growth inhibition and apoptosis) was found with the isoxazole analog in the hepatocellular carcinoma H22T/VGH cells, as well as in the MCF-7 breast cancer cell line and its multidrug resistant (MDR) variant MCF-7/DR (Simoni et al., 2008). Dimethylaminoethyl-substituted curcumin derivatives analogous inhibited four tumor cell lines proliferation hepatocellular carcinoma cell line (HepG2), human gastrointestinal cancer cell line (SGC-7901), human non-small lung cancer cell line (A549) and human colorectal cancer cell line (HCT-116) (Fang et al., 2013).</td>
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<td><strong>Antibacterial and antifungal</strong></td>
<td>Diacetyl, diglycycol, diglycyol-di-piperoyl, dipiperoyl and diacetyl derivatives and curcumin-4,4-di-O-D-b-D glucopyranoside have superior antibacterial and antifungal activities as of curcumin (Kumar et al., 2006; Mukhopadhyay et al., 1982; Mishra et al., 2005). Curcumin has perhaps the same or slightly lesser antibacterial activity than Mono-carboxyl analogues (Adams et al., 2003; Al-Omari et al., 2005) 3,4-Dihydroxypropylnitrosofurans derivatives of curcumin showed significant antimirbrial activity against tested bacteria (Staphylococcus aureus, Escherichia coli, Salmonella typhi and Pseudomonas aeruginosa) and antifungal activity against human pathogenic fungal cultures viz. Aspergillus niger, Aspergillus flavus, Trichoderma viride and Curvularia lunata (La et al., 2012).</td>
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<td><strong>Antiproliferative</strong></td>
<td>If antiproliferative effects are brought into line of sight, Cyclopalladated complexes of curcumin show the best activity (Pucci et al., 2007). Bisdemethoxycurcumin and bisepolongo analogues of curcumin are more potent anti-inflammatory as an anti-proliferative agent than curcumin (Jayaraj Ravindra). Dimethoxycurcumin, bisdemethoxycurcumin, tetrahydrocurcumin and turmerone, modulate cell proliferation signaling as well as curcumin was investigated (Sandor et al., 2007). Pyrrole analogues and a curcumin Knoevenagel condensate have better antioxidant, anti-oxidant and COX-1- and COX-2- inhibitory activities than curcumin (Mishra et al., 2008; Selvakumar et al., 2005). Curcumin has less potent antioxidant activity than its Fused pyridine analogues (Bukkamani et al., 2004). Curcumin has better antiradical activity than its Semicarbazone, but the antitumor activity of curcumin is lesser (Dutta et al., 2005). Compounds with ortho-diphenol functionality display greater antioxidant activity than curcumin (Adams et al., 2005). Dimethylaminoethyl-substituted curcumin analogues have higher free radical scavenging activity than curcumin towards both DPPH and galloyl radicals (Fang et al., 2013) curcumin analogues bearing o-diphenol and o-dimethoxyphenol groups exhibited significantly higher DPPH scavenging and anti-oxidation (Shang et al., 2010).</td>
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<td><strong>Inhibitors of tumor-induced angiogenesis</strong></td>
<td>Symmetrical curcumindis, 1,7-bis(1-hydroxy-5-methoxy-3-nitrophenyl)-1,6-heptadiene-3,5-dione 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 (Hahn et al., 2004; Hahn et al., 2002). Synthetic analogues with customized aromatic ring and/or adapted o-esteridene bridge among rings have more effective antiangiogenic and COX-1 reducing activity than curcumin (Handier et al., 2017; Furness et al., 2005; Adams et al., 2004).</td>
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<td><strong>Inhibitors of TPA-induced NF-κB activation</strong></td>
<td>Curcumin analogues that retain the 7-carbon spacer between the acyl rings, with a 5-carbon spacer and with a 3-carbon spacer, inhibit TPA-induced AP-1 (activator protein-1) and NF-κB (nuclear factor kappa B) activation better than curcumin and are improved antioxidants (Weber et al., 2005; Weber et al., 2006). TPA-induced NF-κB activation and proliferation is inhibited better by the Copper (II) conjugate of a synthetic analogue with non-oxidizable diketone than curcumin (Zambrer et al., 2006). Curcumin analogues, dibenzoylmethane, dibenzoylpropene, and dibenzylideneacetone (DBA) have ability to suppress TPA-induced NF-κB activation (Anand et al., 2008).</td>
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<td><strong>Radical-scavenging activities</strong></td>
<td>Cyclic curcumin analogues have best cytostatic, antitumor and radical-scavenging activities (Yousef et al., 2007; Yousef et al., 2004; Yousef and El-Sherbini, 2005). Curcumin has lesser SOD (superoxide dismutase) mimicking, radiation-induced lipid peroxidation and radical-scavenging activities than Synthetic copper (II)-curcumin complexes (Barki 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., 2007; Vagaputra et al., 2004). Cu(II)-curcumin complex possesses SOD mimicking activity, free radical neutralizing ability and antioxidant potential (Barki et al., 2005).</td>
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<td><strong>Cytochrome P450-inhibitory activity</strong></td>
<td>Cinnamoyl derivatives of curcumin are better than curcumin in inhibiting HIV-1 (human immunodeficiency virus) integrase (Srinivasan et al., 2003). HIV-1 and HIV-2 proteases are inhibited better by Curcumin-boron complexes than curcumin (Sui et al., 1993). Dicaffeicarboxyl and rosmanic acid derivatives of curcumin, inhibited both activities of integrase and inhibit binding of the enzyme to the viral DNA. (Mazardueh et al., 1997).</td>
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<td><strong>Inhibitors of growth and tube formation</strong></td>
<td>Aromatic cinnamonic 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 lip-oxidized units such as a phenyl group with alkyl amide, chloro-sulfonate of mandine, or heterocyclic amide moieties in inhibiting growth and tube formation (Woo et al., 2005).</td>
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<td><strong>Antidiabetic and hypolipidemic</strong></td>
<td>Vanadium complex of curcumin has antidiabetic and hypolipidemic properties and also recovers the cardiovascular complications associated with diabetes (Thompson et al., 2004).</td>
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<td>Oxidative stress</td>
<td>Bisdemethoxycurcumin is the better option than curcumin in suppressing nicotine, alcohol and polyunsaturated fatty acid induced oxidative stress, CCH-induced hepatotoxicity and alcohol- and polysaturated fatty acid hyperlipidemia in rats (Devasena et al., 2002; Kalpana et al., 2007; Kamalakkaan et al., 2005).</td>
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<td>Inhibitors of testosterone biosynthesis a</td>
<td>Inhibit the biosynthesis of testosterone by inhibiting 17β-hydroxysteroid dehydrogenase isoform 3 (17β-HSD3), an enzyme catalyzing the final step in testosterone biosynthesis. Some derivatives of curcumin are more potent than curcumin in the inhibition of human 17β-hydroxysteroid dehydrogenase (Hu et al., 2010).</td>
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<td>Gastroprotective and antidepressant effects</td>
<td>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).</td>
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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)-CH₃ to methyl ferulate. Analogues such as DHC, THC, HHC and OHHC are given by the hydrogenation of the C, linker double bonds and the carbonyl groups, which are attained by the reduction of curcumin (Fig. 3) (Sompm 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).
Wang et al. (2012) reported a series of nonsteroidal mono-carbonyl analogs 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 hydrophilic 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 pyrido 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.

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-n) were prepared by acylation of 3-aminoacetoephene with different acylchlorides in basic medium. Compounds (9.1a-m) on Claisen-Schmidt condensation with 3-bromo-2,4,6-trimethoxy benzaldehyde under basic media afforded a residue, which on purification by column chromatography with 0.5% 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

Fig. 7(a-c): Reaction protocol for the synthesis of 7a-g and 4: (a) \((\text{CH}_3)_2\text{SO}_4, \text{K}_2\text{CO}_3\), DMSO/THF (b) NaOH, EtOH and (c) \((\text{C}_2\text{H}_5)_2\text{SO}_4\), acetone, \(\text{K}_2\text{CO}_3\).

Fig. 8(a-d): Reaction protocol for the synthesis of 8.1a-j, 8.2a-g, 8.3a-g, 8.4a-e and 8.4h-j: (a) NaOH, EtOH (b) malonitril, 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-
Fig. 9: Synthesis of curcumin analogues

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-nitrophennylazo)-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 soda 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) molar ratio in boiling ethanolic sodium ethoxide. Similarly, it has been found that N-[bis-(5-(4-hydroxy-3-methoxy-phenyl)-2,5-dihydro-isoaxazol-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, rubrocumin. 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 Knovenagel 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 difluoroamine, 24 h, piperidine, methanol, room temp; (d) CuCl₂·2H₂O, 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.

ACKNOWLEDGMENTS

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REFERENCES


