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Curcumin Analogues With Improved Stability: Structure Activity Trends From Two Decades of Work

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Abstract

Curcumin has been studied more intensively than almost any other natural product, and it remains a poor drug candidate for a simple reason: the molecule does not survive long enough in neutral aqueous solution or in the body to reach most of its proposed targets. Since the mid-2000s medicinal chemists have responded by redesigning the scaffold. This narrative review brings together the main lines of that work and the structure activity trends that have emerged from it. It begins with the chemical and metabolic routes by which curcumin is lost, namely autoxidation and alkaline degradation centred on the β -diketone and the phenol, reduction of the alkene bridges and conjugation of the phenolic groups. It then considers the analogue families designed to block each route: monocarbonyl dienones, heterocyclic replacements for the diketone, modified aryl rings, and substituted or saturated linkers. Across these families, removal of the active methylene and enol reliably improves stability in buffer, while protection of the phenol slows conjugation. The review argues, however, that stability in a buffer is not the same as suitability as a drug, since many stabilised analogues retain reactive enone groups and the assay liabilities of the parent. Priorities for future work are set out.

Keywords: Curcumin analogues, Chemical stability, Structure activity relationship, Monocarbonyl analogues, β -Diketone, Drug metabolism

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1. Introduction

Curcumin, the yellow diarylheptanoid of turmeric (*Curcuma longa* L.), is 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione. Its structure can be read in three parts: two guaiacol rings, two *trans* alkene bridges, and a central β -diketone that exists in solution almost entirely as the hydrogen-bonded keto-enol tautomer (Payton et al., 2007). Each part contributes to the long list of activities reported for the compound in cell culture, and each is also a point of weakness (Priyadarsini, 2014).

The gap between that list of activities and clinical usefulness has been recognised for a long time. Early

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clinical pharmacology found very low concentrations of the parent compound in plasma after oral doses measured in grams (Sharma *et al.*, 2005), and an influential review attributed the problem to poor absorption, rapid metabolism and rapid elimination acting together (Anand *et al.*, 2007). Two responses followed. One was formulation: phospholipid complexes, nanoparticles, micelles and co-administration with inhibitors of conjugation. The other, the subject of this review, was to change the molecule.

The literature on synthetic curcumin analogues is now very large, and several surveys have catalogued it by biological activity (Anand *et al.*, 2008). This article takes a narrower view. It asks which structural changes have made the scaffold more stable, by what mechanism, and what happened to activity when they were made.

2. Scope and Approach

This is a narrative review of the medicinal chemistry literature published from roughly the mid-2000s onward, with earlier papers on degradation and metabolism included where they explain the design logic. It is organised by the site of modification, not by disease area. Stability is taken in two senses that the literature often runs together: chemical stability in aqueous media at physiological pH, and metabolic stability towards reduction and conjugation. Formulation approaches are outside the scope. No claim of exhaustive coverage is made, and potency values from individual papers are not tabulated, because they were obtained in different cell lines and assay formats and cannot be compared across laboratories.

3. How Curcumin Is Lost

Design for stability presupposes an account of instability. Three processes are well documented, and they act on different parts of the molecule.

3.1. Degradation in aqueous solution

Curcumin is reasonably stable in acid and decomposes quickly as the pH rises above neutrality, as kinetic studies established in the 1980s (Tønnesen and Karlsen, 1985). The observation most often quoted comes from Wang *et al.* (1997), who found that most of the compound disappeared within half an hour in serum-free phosphate buffer at physiological pH and temperature, and who identified vanillin, ferulic acid and feruloylmethane among the products. For some years these cleavage products were taken to be the main fate of the molecule.

Later mechanistic work changed that picture. The dominant reaction at physiological pH is an autoxidation: hydrogen abstraction from a phenolic hydroxyl gives a radical that is delocalised through the conjugated chain, oxygen is incorporated, and the heptadienedione chain cyclises to a bicyclopentadione (Griesser *et al.*, 2011). The cleavage products are minor. The same studies showed that the reaction depends on the phenol and on the unsaturated diketone together, and that the methoxy groups accelerate it, which is why bisdemethoxycurcumin is far more resistant to autoxidation than curcumin itself (Schneider *et al.*, 2015). Curcumin is also degraded by light.

3.2. Metabolic conversion

In animals and in human tissue preparations curcumin is metabolised along two routes. The alkene bridges are reduced stepwise to dihydro-, tetrahydro- and hexahydrocurcumin, and the phenolic hydroxyls of the parent and of its reduced forms are conjugated with glucuronic acid and sulfate (Pan *et al.*, 1999; Ireson *et al.*, 2001). The conjugates are the principal circulating species after oral dosing. A comprehensive pharmacological review concluded that the pharmacokinetics of the parent compound are difficult to reconcile with many of the systemic effects attributed to it (Heger *et al.*, 2014).

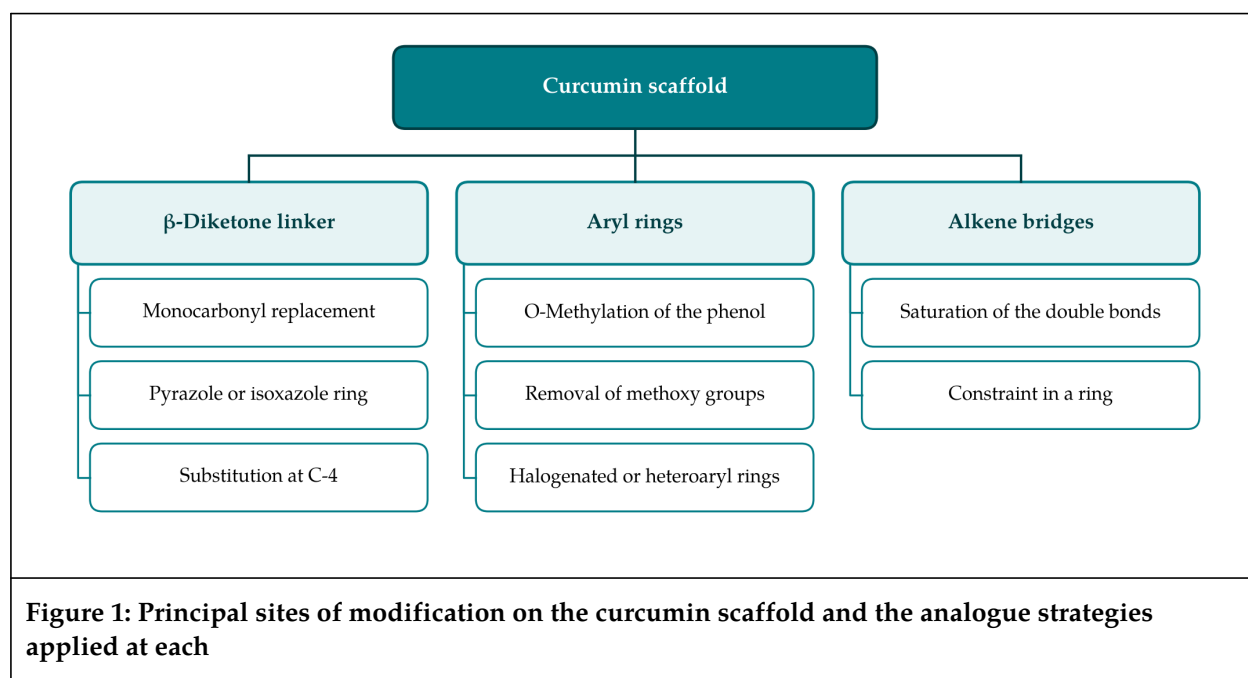
These findings define the design problem. The active methylene and enol of the diketone, the free phenol and the conjugated dienone are each implicated in loss of the compound, and the same groups have each been proposed as essential for one activity or another. The structural liabilities, the strategies used against them and the price paid for each are summarised in Table 1.

Table 1: Structural liabilities of curcumin, the analogue strategies directed at them and the usual trade-off

Liability	Structural origin	Analogue strategy	Usual trade-off
Autoxidation at neutral pH	Phenol plus conjugated enolised diketone	Monocarbonyl linker; removal of methoxy groups	Dienone remains a reactive Michael acceptor
Alkaline cleavage	Active methylene and β -diketone	Pyrazole or isoxazole in place of the diketone	Metal chelation and enol chemistry are lost
Glucuronidation and sulfation	Free phenolic hydroxyl groups	O-Methylation or replacement of the phenol	Lower aqueous solubility; radical scavenging reduced
Reduction of alkenes	Conjugated double bonds	Ring constraint or hindered enones	Gain is modest and seldom measured directly
Keto-enol reactivity	Acidic C-4 hydrogens	Mono- or disubstitution at C-4	Planarity and conjugation are altered
Photodegradation	Extended chromophore	Shortened or saturated chromophore	Loss of colour and of photodynamic activity

4. Analogue Strategies by Site of Modification

The modifications that have been tried fall naturally into three groups according to the part of the scaffold they change, as Figure 1 shows. The groups are not exclusive, and the most studied compounds combine changes at two sites.



4.1. Removing the β -diketone: monocarbonyl analogues

The most productive single idea has been to delete one carbonyl and the methylene between them, leaving a 1,5-diaryl-1,4-pentadien-3-one. The dienone may be acyclic or built on a cyclopentanone, cyclohexanone or 4-piperidone ring. A series from Emory University introduced the fluorinated piperidone later known as EF24 and showed that compounds of this type could exceed curcumin in potency in tumour cell and angiogenesis screens (Adams *et al.*, 2004). Working independently, Ohori *et al.* (2006) prepared a set of symmetrical diarylpentadienones, among them the compound designated GO-Y030, with markedly greater growth-suppressive activity than the parent.

The stability argument for this class was made explicitly by [Liang et al. \(2009\)](#), who reasoned that the active methylene was the source of instability, synthesised monocarbonyl analogues lacking it, and reported both improved persistence in buffer and a better pharmacokinetic profile in rodents. Their result is consistent with the autoxidation mechanism: without the enolisable diketone the radical chain cannot proceed as it does in curcumin. Subsequent reviews of the class describe several hundred members and a broadly consistent pattern in which the central ring and the aryl substituents tune potency while stability in buffer is a property of the class as a whole ([Mosley et al., 2007](#); [Shetty et al., 2015](#)).

4.2. Masking the diketone as a heterocycle

Condensation of curcumin with hydrazines or hydroxylamine converts the diketone into a pyrazole or an isoxazole. The heterocycle locks the two carbons that carried the carbonyls into an aromatic ring, removes the acidic methylene, and abolishes both the enol and the ability to chelate metal ions, while keeping the two styryl arms in conjugation. [Selvam et al. \(2005\)](#) prepared such compounds and found antioxidant and cyclooxygenase-inhibitory activity retained or increased. In work directed at neurodegeneration, [Narlawar et al. \(2008\)](#) showed that curcumin-derived pyrazoles and isoxazoles inhibited tau aggregation and amyloid-related processes, sometimes more effectively than curcumin, which demonstrated that the diketone is not required for those effects.

4.3. Changing the aryl rings

The phenolic hydroxyl is both the handle for conjugation and the starting point of autoxidation, so its protection addresses two liabilities at once. Dimethoxycurcumin, in which both phenols are methylated, proved considerably more stable than curcumin in cells and in mice and was at least as active against tumour cells ([Tamvakopoulos et al., 2007](#)). A systematic programme on anti-prostate cancer agents varied the ring substituents and the linker together and identified methylated and otherwise protected analogues with improved activity ([Lin et al., 2006](#)).

The natural congeners offer a complementary lesson. Demethoxycurcumin and bisdemethoxycurcumin differ from curcumin only in lacking one or both methoxy groups, and comparison of symmetric and asymmetric curcuminoids found clear differences between them in hydrolytic stability ([Tomren et al., 2007](#)). The methoxy group *ortho* to the phenol stabilises the phenoxyl radical and so promotes the first step of autoxidation; its removal slows degradation while leaving the phenol open to conjugation. Halogenated rings, as in EF24, and pyridyl or other heteroaryl rings have been used in the monocarbonyl series to adjust electron density at the enone and to improve solubility ([Shetty et al., 2015](#)).

4.4. Altering the linker carbons

Substitution at the central carbon, C-4, removes one or both acidic hydrogens. A single substituent shifts the tautomeric balance, and two substituents prevent enolisation altogether and force the molecule out of planarity. Analogues of this kind appear in several of the series already cited ([Lin et al., 2006](#); [Anand et al., 2008](#)). Saturation of the alkenes is the opposite extreme. Tetrahydrocurcumin, itself a metabolite, lacks the conjugated dienone, is colourless, and is considerably more stable in neutral buffer than curcumin ([Pan et al., 1999](#)). It retains antioxidant activity attributable to the phenols and the diketone but loses the activities that depend on the electrophilic enone.

5. Structure Activity Trends That Recur

Four trends appear repeatedly across independent series. First, the β -diketone is dispensable for cytotoxic and anti-inflammatory activity in cell assays: both the monocarbonyl dienones and the heterocyclic analogues retain or exceed the potency of curcumin. Second, at least one α,β -unsaturated carbonyl is required for most of the cell-based activities; analogues in which the alkenes are saturated are consistently weaker in those assays. Third, a free phenol is not necessary for cytotoxic potency, though it is necessary for direct radical-scavenging activity. Fourth, electron-withdrawing substituents on the aryl rings of monocarbonyl analogues tend to raise potency, in line with a mechanism involving conjugate addition of

cellular thiols to the enone ([Adams et al., 2004](#); [Mosley et al., 2007](#)).

Taken at face value these trends describe a pharmacophore that is essentially a bis-aryl enone. That conclusion is chemically coherent and has been reached by several groups, but it also raises the central difficulty of the field.

6. Stability Is Not the Same as Developability

The feature that most analogue series preserve, a doubly activated Michael acceptor, is the feature that makes the compounds react with glutathione and with cysteine residues across many proteins. Potency that rises with electrophilicity is as likely to reflect indiscriminate covalent reactivity as selective target engagement. Curcumin itself matches several of the substructure patterns that [Baell and Holloway \(2010\)](#) identified as characteristic of pan-assay interference compounds, and a detailed critical review described it as unstable, reactive and not a viable lead, noting in addition that it aggregates, fluoresces and chelates metals in ways that distort assay readouts ([Nelson et al., 2017](#)).

Stabilised analogues answer the first of those charges and not necessarily the others. A monocarbonyl dienone that persists for hours in phosphate buffer may still be consumed in minutes by thiols in a cell or in plasma, and persistence in buffer has too often been reported as though it settled the question of metabolic fate. Few papers measure reactivity towards glutathione, stability in liver microsomes or hepatocytes, and plasma protein binding alongside potency. Fewer still identify the metabolites of the analogue, as was done for dimethoxycurcumin ([Tamvakopoulos et al., 2007](#)). A further complication is that the degradation products of curcumin are themselves biologically active, and some of the effects attributed to the parent in long cell incubations may belong to its oxidation products ([Gordon et al., 2015](#)). An analogue that cannot autoxidise may therefore lack an activity for reasons that have nothing to do with target affinity.

7. Gaps and Future Work

Three gaps stand out. The first is measurement. Stability should be reported under stated and comparable conditions, covering buffer, plasma and a metabolically competent system, with curcumin run alongside as a reference and with thiol reactivity determined explicitly. The second is selectivity. Claims of target engagement for enone-containing analogues need support from orthogonal assays, from counter-screens for aggregation and interference, and where possible from analogues in which the electrophile is removed while the shape is kept. The third is translation: very few analogues have progressed to rigorous pharmacokinetic and toxicological evaluation in animals, and none has become an approved medicine, so the clinical value of the whole approach is unproven.

There is also a case for asking a different question. If the reproducible activities of the scaffold reduce to those of a tunable electrophile, then the more promising route may be to design that reactivity deliberately, with a defined target and a reversible or weakly reactive warhead, and to treat the natural product as a starting point of historical interest.

8. Conclusion

Two decades of analogue work have shown convincingly how to make the curcumin scaffold last longer. Removing the active methylene and the enol, by deleting a carbonyl or by building the diketone into a heterocycle, suppresses the autoxidation and cleavage that destroy the parent at physiological pH, and masking the phenol slows conjugation. The associated structure activity trends are consistent between laboratories. What the work has not yet shown is that a stabilised analogue is a selective and well-behaved drug candidate. The field's next advances are more likely to come from stricter characterisation of the compounds already in hand than from further additions to an already long list.

Conflict of interest

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