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Anti-oxidant activities of curcumin and related enones

Waylon M. Weber,[a] Lucy A. Hunsaker,[b] Steve F. Abcouwer,[b] Lorraine M. Deck[a,*] and David L. Vander Jagt[b,*]

[a]*Department of Chemistry, University of New Mexico, Albuquerque, NM 87131, USA*
[b]*Department of Biochemistry and Molecular Biology, University of New Mexico School of Medicine, Albuquerque, NM 87131, USA*

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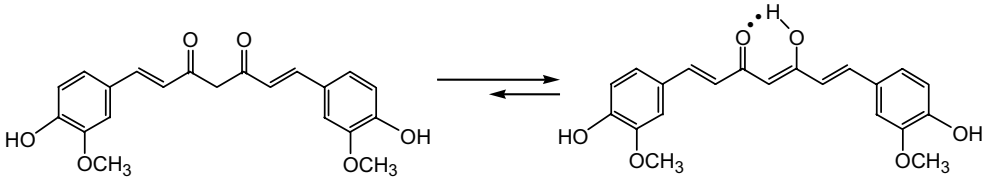
Abstract—The natural product curcumin (diferuloylmethane, 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), obtained from the spice turmeric, exhibits numerous biological activities including anti-cancer, anti-inflammatory, and anti-angiogenesis activities. Some of these biological activities may derive from its anti-oxidant properties. There are conflicting reports concerning the structural/electronic basis of the anti-oxidant activity of curcumin. Curcumin is a symmetrical diphenolic dienone. A series of enone analogues of curcumin were synthesized that included: (1) curcumin analogues that retained the 7-carbon spacer between the aryl rings; (2) curcumin analogues with a 5-carbon spacer; and (3) curcumin analogues with a 3-carbon spacer (chalcones). These series included members that retained or were devoid of phenolic groups. Anti-oxidant activities were determined by the TRAP assay and the FRAP assay. Most of the analogues with anti-oxidant activity retained the phenolic ring substituents similar to curcumin. However, a number of analogues devoid of phenolic substituents were also active; these non-phenolic analogues are capable of forming stable tertiary carbon-centered radicals.

1. Introduction

Curcumin (Fig. 1) is a non-nutritive, non-toxic chemical in turmeric that has been used for centuries in India and elsewhere as a dietary spice and as a herbal medicine for treatment of wounds, jaundice, and rheumatoid arthritis.[1] In addition, curcumin inhibits the proliferation of a variety of tumor cells[2] and has anti-metastatic activity,[3] possibly owing to its ability to induce apoptosis by inhibiting the activation of the prosurvival transcription factor NFκB.[2] Curcumin exhibits anti-inflammatory activity that may be related to its ability to inhibit up-regulation of COX-2.[4] Curcumin has anti-angiogenesis activity, which has been ascribed to the ability of curcumin to irreversibly inhibit CD13/aminopeptidase N, a membrane-bound metalloproteinase that is



Curcumin

Figure 1. Curcumin exists in solution as an equilibrium mixture of the symmetrical dienone and the keto-enol tautomer stabilized by intramolecular H-bonding.

Keywords: Curcumin; Anti-oxidants.
* Corresponding authors. Tel.: +1 505 277 5438 (L.M.D.); +1 505 272 5788 (D.L.V.J.); e-mail addresses: ldeck@unm.edu; dlvanderjagt@salud.unm.edu

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important in angiogenesis.[5a] Curcumin also exhibits potent anti-oxidant activity.[6] It is unclear whether the anti-oxidant activity of curcumin is the basis for most of its reported biological activities.

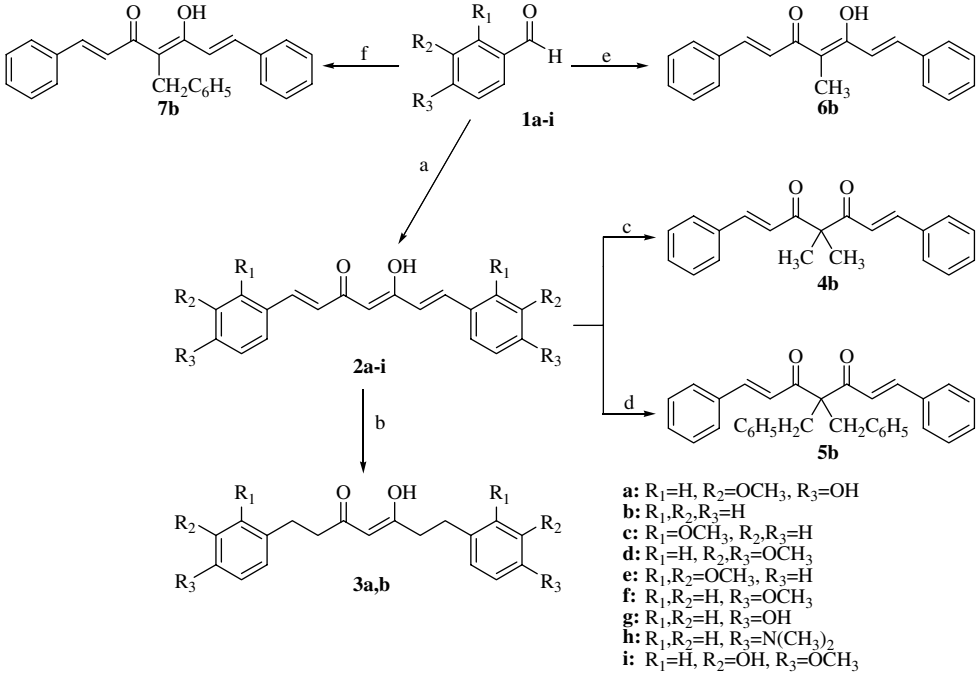
It has been suggested that the anti-oxidant activity of curcumin depends upon the presence of the phenolic functional groups.[6,7] However, other studies support the conclusion that the central methylene hydrogens of curcumin are important for anti-oxidant activity.[8] More recently, it has been demonstrated that both the central methylene hydrogens and the phenolic hydrogens may be involved in the mechanism of formation of the phenoxy radical, depending upon reaction conditions.[9] In the present study, three series of analogues of curcumin were synthesized and their anti-oxidant activities were compared using two different procedures. These three series examined the role of the enone functionality in aryl systems where the spacer is 7-carbons (as in curcumin), 5-carbons, or 3-carbons in length (as in a chalcone). In addition, the importance of ring substituents including phenolic groups was assessed as well as the importance of the central methylene hydrogens of curcumin.

2. Chemistry

Curcumin exists in equilibrium between the diketo and keto-enol forms; the keto-enol form is strongly favored by intramolecular H-bonding[9] (Fig. 1). Curcumin is a relatively simple bis-phenolic compound that can be prepared in a single reaction. The following schemes summarize the procedures used to prepare the three series of curcumin analogues. Compounds in series 1, which retain the 7-carbon spacer contained in curcumin, were prepared as shown in Scheme 1. Compounds **2a-i** contain two aryl rings separated by an unsaturated seven carbon spacer having two carbonyls. The aryl rings contain different substituents in various positions on the ring. These compounds were designed to test the importance of the type of functional group and location of the group on the aryl ring. Compounds **2a**–**i** were prepared following the procedure described by Pabon.[10] 2,4-Pentanedione was reacted with a substituted benzaldehyde in an aldol-type reaction to give curcumin (**2a**) or one of its analogues **2b**–**i**.

Two curcumin analogues, **3a** and **3b**, were prepared as shown in Scheme 1. Compounds **3a** and **3b** contain two aryl rings separated by a saturated seven carbon spacer having two carbonyls. These compounds were designed to test the importance of unsaturation in the seven carbon spacer. Compounds **3a** and **3b** were prepared by reduction of **2a** and **2b**, respectively, as described by Venkateswarlu et al.[11]

Four additional curcumin analogues, **4b**, **5b**, **6b**, and **7b**, were prepared as shown in Scheme 1. Compounds **4b**, **5b**, **6b**, and **7b** contain two aryl rings separated by an unsaturated seven carbon spacer. All four compounds have either one or two substituents attached to the central methylene carbon and were designed to test the importance of the central methylene hydrogens. Compounds **4b** and **5b** were prepared from **2b** using a base and an alkyl halide as described by Pederson et al.[12] In our hands the disubstituted compound **5b** was formed rather than the monosubstituted compound **7b** as reported by Pederson. Compounds **6b** and **7b** were prepared following the procedure described by Pabon.[10] 3-Methyl-2,4-pentanedione and 3-benzyl-2,4-pentanedione



Scheme 1. Reagents: (a) $CH_3C(O)CH_2C(O)CH_3$ (0.5 equiv), B_2O_3, $B(OC_4H_9)_3$, *n*$BuNH_2$, EtOAc; (b) H_2, Pd/C, EtOAc; (c) CH_3Br (2.0 equiv), NH_4Cl, NaOH, CH_2Cl_2; (d) $C_6H_5CH_2Br$ (2.0 equiv), NH_4Cl, NaOH, CH_2Cl_2; (e) $CH_3C(O)CH(CH_3)C(O)CH_3$ (0.5 equiv), B_2O_3, $B(OC_4H_9)_3$, *n*$BuNH_2$, EtOAc; (f) $CH_3C(O)CH(CH_2C_6H_5)C(O)CH_3$ (0.5 equiv), B_2O_3, $B(OC_4H_9)_3$, *n*$BuNH_2$, EtOAc.

were reacted with benzaldehyde in an aldol type reaction to give **6b** and **7b**, respectively.

Compounds in series 2, which contain a 5-carbon spacer, were prepared as shown in Scheme 2. Compounds **9a**–**w** contain two identical aryl rings separated by an unsaturated five carbon spacer having a single carbonyl whereas compounds **9x** and **9y** have two different aryl rings. These compounds were designed to test the importance of the length of the spacer between the two aryl rings. Compounds **9a**–**w** were prepared from acetone and a substituted benzaldehyde in a base catalyzed aldol reaction as described by Masuda et al.[13] In the case of phenolic benzaldehydes, the phenol was protected with a methoxymethyl group prior to the aldol reaction and deprotected later to give the free phenol.[13] Compounds **9u** and **9v** were prepared from **9a** and **9r**, respectively, by reaction with acetic anhydride as described by Ali et al.[14] Compounds **9x** and **9y** were prepared using two consecutive base catalyzed aldol reactions.[13]

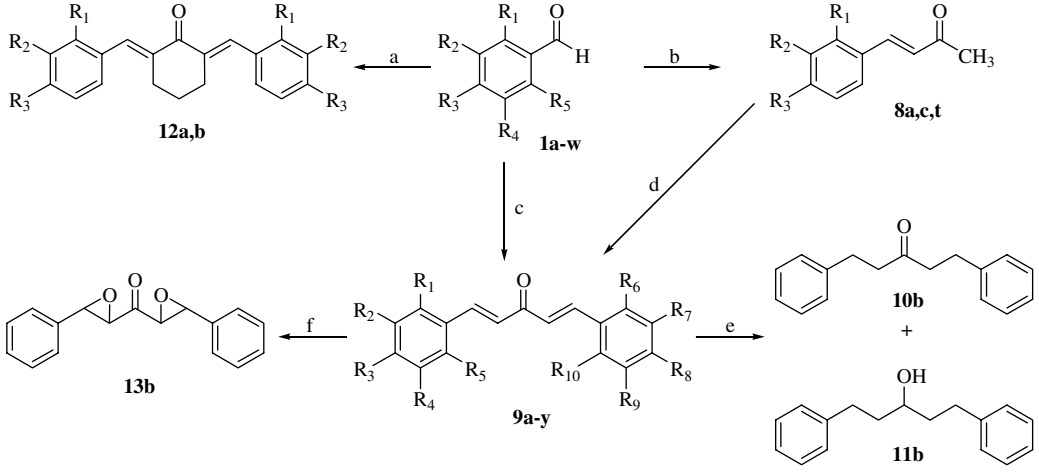
Compounds **8a**, **8c**, and **8t** were prepared as shown in Scheme 2. These compounds contain a single aryl ring with an unsaturated 3-carbon chain and a single carbonyl. These compounds were designed to test the necessity of two aryl rings. Compounds **8a**, **8c**, and **8t** were prepared from excess acetone and a substituted benzaldehyde in a base catalyzed aldol reaction following the procedure of Masuda et al.[13]

Compounds **10b** and **11b** were prepared as shown in Scheme 2. These compounds contain two identical aryl rings separated by a saturated five carbon spacer and were designed to test the importance of unsaturation and the necessity of a carbonyl in the spacer of series 2 compounds. Compounds **10b** and **11b** were prepared by reduction of **9b**.[11]

Compounds **12a** and **12b** were prepared as shown in Scheme 2. These compounds contain two identical aryl rings separated by an unsaturated five carbon spacer having both a carbonyl and a saturated ring and were designed to test the importance of a ring in the spacer. They were synthesized following the procedure of Masuda et al.[13] by reaction of a substituted benzaldehyde with cyclohexanone in a base catalyzed aldol reaction.

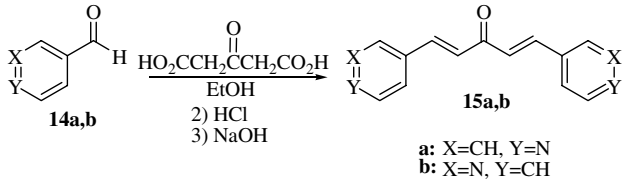
Compound **13b** was prepared as shown in Scheme 2. This compound contains two identical aryl rings separated by a five carbon spacer containing both a carbonyl and two epoxide rings. This compound was designed to test the importance of an epoxide on the spacer. Compound **13b** was synthesized following the procedure of Yadav and Kapoor[15] by the reaction of **9b** with *tert*-butyl hydroperoxide.

Compounds **15a** and **15b** were prepared as shown in Scheme 3. These compounds have an unsaturated five carbon spacer between two nitrogen containing aryl rings. These compounds were designed to test the importance of a heterocyclic ring. Compounds **15a** and **15b** were synthesized according to the method of Zelle[16] by the reaction of a pyridinecarboxaldehyde with 1,3-acetonedicarboxylic acid.



a: $R_1,R_4,R_5,R_6,R_9,R_{10}$=H, R_2,R_7=OCH_3, R_3,R_8=OH
b: $R_1,R_2,R_3,R_4,R_5,R_6,R_7,R_8,R_9,R_{10}$=H
c: $R_1,R_2,R_4,R_5,R_6,R_7,R_9,R_{10}$=H, R_3,R_8=OCH_3
d: $R_1,R_3,R_4,R_5,R_6,R_8,R_9,R_{10}$=H, R_2,R_7=OCH_3
e: R_1,R_6=OCH_3, $R_2,R_3,R_4,R_5,R_7,R_8,R_9,R_{10}$=H
f: R_1,R_2,R_6,R_7=OCH_3, $R_3,R_4,R_5,R_8,R_9,R_{10}$=H
g: $R_1,R_4,R_5,R_6,R_9,R_{10}$=H, R_2,R_3,R_7,R_8=OCH_3
h: R_1,R_4,R_6,R_9=OCH_3, $R_2,R_3,R_5,R_7,R_8,R_{10}$=H
i: R_1,R_3,R_6,R_8=OCH_3, $R_2,R_4,R_5,R_7,R_9,R_{10}$=H
j: $R_1,R_3,R_5,R_6,R_8,R_{10}$=H, R_2,R_4,R_7,R_9=OCH_3
k: R_1,R_5,R_6,R_{10}=OCH_3, R_2,R_3,R_4,R_7,R_8,R_9=H
l: $R_1,R_2,R_4,R_5,R_6,R_7,R_9,R_{10}$=H, R_3,R_8=CH_3
m: $R_1,R_3,R_4,R_5,R_6,R_8,R_9,R_{10}$=H, R_2,R_7=CH_3
n: R_1,R_6=CH_3, $R_2,R_3,R_4,R_5,R_7,R_8,R_9,R_{10}$=H
o: $R_1,R_2,R_4,R_5,R_6,R_7,R_9,R_{10}$=H, R_3,R_8=Cl
p: $R_1,R_3,R_4,R_5,R_6,R_8,R_9,R_{10}$=H, R_2,R_7=Cl
q: R_1,R_6=Cl, $R_2,R_3,R_4,R_5,R_7,R_8,R_9,R_{10}$=H
r: $R_1,R_2,R_4,R_5,R_6,R_7,R_9,R_{10}$=H, R_3,R_8=OH
s: $R_1,R_3,R_4,R_5,R_6,R_8,R_9,R_{10}$=H, R_2,R_7=OH
t: R_1,R_6=OH, $R_2,R_3,R_4,R_5,R_7,R_8,R_9,R_{10}$=H
u: $R_1,R_4,R_5,R_6,R_9,R_{10}$=H, R_2,R_7=OCH_3, R_3,R_8=$OC(O)CH_3$
v: $R_1,R_2,R_4,R_5,R_6,R_7,R_9,R_{10}$=H, R_3,R_8=$OC(O)CH_3$
w: $R_1,R_2,R_4,R_5,R_6,R_7,R_9,R_{10}$=H, R_3,R_8=$C(O)OCH_3$
x: $R_1,R_2,R_4,R_5,R_6,R_7,R_8,R_9,R_{10}$=H, R_3=OCH_3
y: $R_1,R_4,R_5,R_6,R_7,R_8,R_9,R_{10}$=H, R_2=OCH_3, R_3=OH

Scheme 2. Reagents: (a) cyclohexanone (0.5 equiv), NaOH, EtOH, H_2O; (b) $CH_3C(O)CH_3$ (1.0 equiv), NaOH, EtOH, H_2O; (c) $CH_3C(O)CH_3$ (0.5 equiv), NaOH, EtOH, H_2O; (d) PhCHO, NaOH, EtOH, H_2O; (v) H_2, Pd/C, EtOAc; (e) Al_2O_3-KF, $(CH_3)_3COOH$, CH_3CN, $ClCH_2CH_2Cl$.



Scheme 3.

Compounds in series 3, called chalcones, which contain a 3-carbon spacer, were prepared as shown in Scheme 4. Compounds **17a**–**h** contain two aryl rings separated by an unsaturated 3-carbon spacer having a single carbonyl. These compounds were designed to test the importance of the length of the spacer and symmetry in series 3 compounds. Compounds **17a**–**h** were prepared from a substituted benzaldehyde and a substituted acetophenone in a base catalyzed aldol reaction as described by Kohler and Chadwell.[17]

3. Results and discussion

The anti-oxidant activities of curcumin and analogues (Schemes 1–4) were determined in two standard assays. Anti-oxidant activity was measured as the ability of the analogues to react with the preformed radical monocation of 2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) ($ABTS^{\bullet+}$). This assay is also known as the *total radical-trapping anti-oxidant parameter* assay (TRAP assay). Anti-oxidant activity was also measured in the *ferric reducinglanti-oxidant power* assay (FRAP assay) in which the compounds are reacted with ferric tripyridyltriazine complex. In both colorimetric assays, the vitamin E analogue Trolox was used as a control.

The results of the TRAP assay of anti-oxidant activity are shown in Figure 2. There were active compounds in all three series. Generally, activity was observed with analogues that retained a phenolic substituent. In series 1, this included **3a**, which is the reduced form of curcumin (**2a**) in which both of the enone double bonds have been reduced. Analogue **3a** was the most active compound in the TRAP assay. Clearly, it is not necessary to retain the enone or dienone structure of curcumin in order to retain activity. Other phenolic analogues in series 1 included analogue **2g**, where the methoxy groups of curcumin have been removed, and **2i**, which is an isomer of curcumin. Active analogues in series 2 (**9r**, **9t**, and **12a**) also retained phenolic groups, although not all phenolic analogues were active including **9a**, **9s**, and **9y**. Active analogues in series 3 (**8a**, **8t**, **17f**, **17g**, and **17h**) retain phenolic groups.

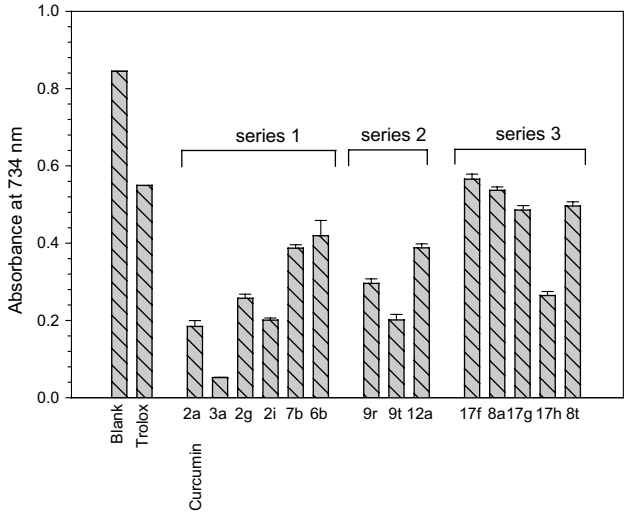
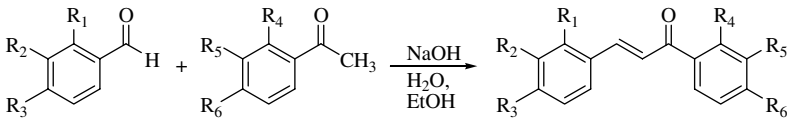


Figure 2. Activities of curcumin and analogues in the TRAP assay. All compounds were tested in triplicate at 10 μM concentrations, with Trolox, 10 μM, as reference standard. All of the remaining analogues were indistinguishable from the blank.

Most interesting is the activity of analogues that do not retain phenolic groups. Two analogues in series 1 (**6b** and **7b**) are dienones, similar to curcumin. However, both **6b** and **7b** are devoid of ring substituents but contain a single alkyl group attached to the central methylene carbon. By comparison, analogue **2b**, which has no ring substituents or an alkyl group attached to the central methylene carbon, and analogues **4b** and **5b**, which are similar to **6b** and **7b** but with dialkylation of the central methylene, are inactive. An explanation of these properties is shown in Figure 3. Curcumin (**2a**, Fig. 3, top) has been proposed to form the stable phenoxy radical in radical trapping reactions either through direct abstraction of the phenolic hydrogen, or by way of initial ionization of an acidic proton from the central methylene, followed by electron transfer to form a carbon-centered radical that can isomerize to the phenoxy radical.[9] The pathway is dictated by reaction conditions. In the case of analogues **6b** and **7b** (Fig. 3, bottom), stabilized tertiary carbon-centered radicals can form in the



1 **16** **17a-h**

a: R_1,R_2,R_3,R_4,R_5,R_6=H
b: R_1,R_2,R_4,R_5,R_6=H, R_3=COOH
c: R_1,R_2,R_3,R_4,R_5=H, R_6=COOH
d: R_1,R_2,R_3,R_4,R_5=H, R_6=CN
e: R_1,R_2,R_3,R_5=H, R_4,R_6=CH_3
f: R_1,R_4,R_5,R_6=H, R_2=OCH_3, R_3=OH
g: R_1,R_2,R_3,R_4=H, R_5=OCH_3, R_6=OH
h: R_1,R_4=H, R_2,R_5 = OCH_3, R_3,R_6 = OH

Scheme 4.

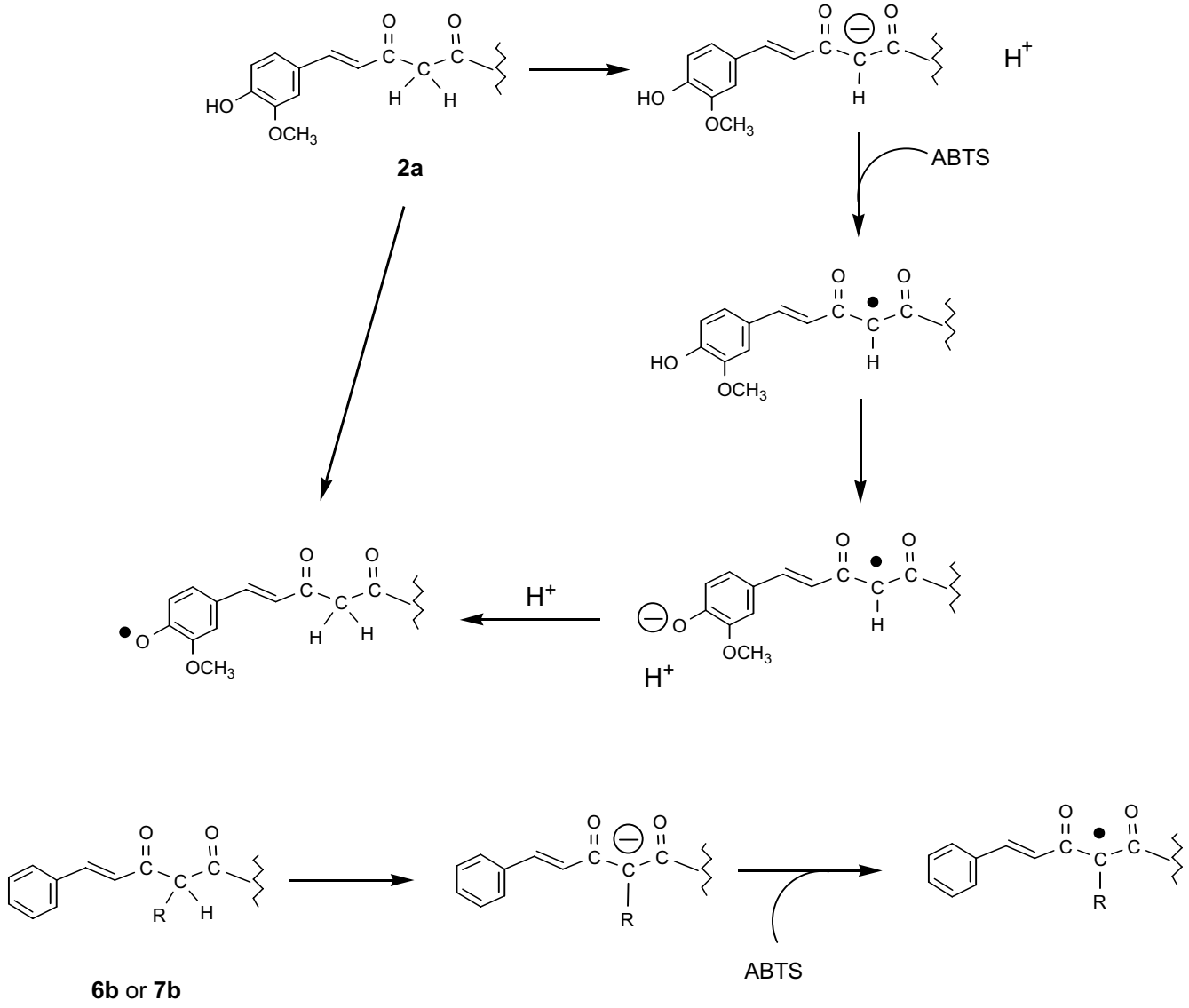


Figure 3. Mechanisms of the radical trapping reactions of curcumin (top) and non-phenolic analogues of curcumin (bottom).

reaction of **6b** or **7b** with ABTS in the TRAP assay. This is not possible with the dialkylated analogues **4b** and **5b**. Analogue **2b** likely is inactive because formation of a secondary carbon-centered radical is less favored than formation of tertiary radicals.

The FRAP assay measures the ability of a compound to reduce the ferric tripyridyltriazine complex to the colored ferrous complex. The results of the FRAP assay of anti-oxidant activities of curcumin and analogues are shown in Figure 4. The results show similarities as well as differences compared to the TRAP assay. In series 1, curcumin (**2a**) is most active, and other phenolic analogues including **3a**, **2g**, and **2i** are active. Likewise, in series 2 and 3, active analogues **12a**, **8a**, **17h**, and **17f** are phenolic compounds that also were active in the TRAP assay. Analogue **7b**, which is devoid of phenolic groups but contains a benzyl group attached to the central methylene of the curcumin basic structure and was active in the TRAP assay, is also active in the FRAP assay whereas the related **6b** was active only in the TRAP assay. Especially interesting are the results with analogues **2h** and **9l**, which are devoid of phenolic groups. Analogue **2h** which is comparable to curcumin in the FRAP assay, contains dimethylamino groups in place of phenolic groups in the basic curcumin structure and contains no other functional groups. This raises the possibility of developing analogues that are more active than curcumin. The mechanism of the anti-oxidant activities of **7b** and **2h** in the FRAP assay may involve formation of carbon-centered radicals, however this remains to be investigated.

4. Conclusions

We conclude, therefore, that selected analogues of curcumin that are devoid of phenolic groups are active in both the TRAP assay and the FRAP assay, and that some of these are active based on their abilities to form stable carbon-centered radicals. Other analogues that are devoid of phenolic groups also exhibit activity by

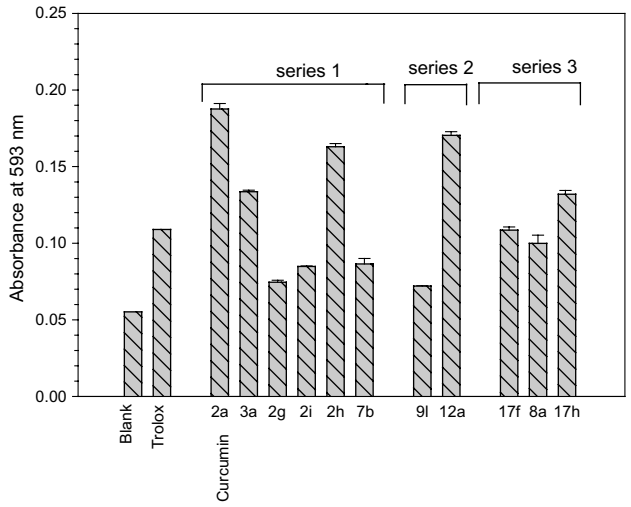


Figure 4. Activities of curcumin and analogues in the FRAP assay. All compounds were tested at 10 μM with Trolox, 1 μM, as reference standard. All of the remaining analogues were indistinguishable from the blank.

mechanisms that must still be determined. Most of the active analogues of curcumin, however, are able to form phenoxy radicals, and this is likely the basis of their anti-oxidant activities. With this set of analogues, we are now in a position to investigate the role of anti-oxidant activity in the multiple biological activities reported for curcumin.

The most extensive recent studies of the biological activities of curcumin and its analogues have focused on the anti-angiogenic properties of these compounds.[5a–d,37] Curcumin and analogues inhibit activator protein-1 (AP-1) transcription, resulting in the down-regulation of a number of pro-angiogenic genes.[5b] Synthetic analogues that are quite far removed from curcumin but retaining the same ring substituents, including the phenolic functional groups, were shown to be more active than curcumin in their anti-angiogenic activities involving cell proliferation and tube formation with human umbilical vein endothelial cells.[5c] Other analogues of curcumin were shown to exhibit anti-cancer activity against a wide range of cells, and the most active analogues also inhibited angiogenesis;[37] this includes a novel analogue, designated EF24, that was recently shown to induce apoptosis in a number of breast and prostate cell lines by a redox-dependent process.[5d] Interestingly, ER24 does not contain phenolic groups and is structurally related to the analogues with the 5-carbon spacer (Scheme 2). It is likely, therefore, that analogues of curcumin may exhibit a range of activities, not all of which are related to the anti-oxidant properties of curcumin.

5. Experimental

5.1. Chemical synthesis

Reagent quality solvents were used without purification. Melting points were determined on a Thomas–Hoover Uni-Melt apparatus and are uncorrected. NMR spectra were recorded on a Bruker AC250 NMR spectrometer in $CDCl_3$ unless otherwise noted. Chemical shifts are in ppm (δ) relative to TMS. High resolution mass spectra were recorded on a Waters APcI MS. Compounds **2a**–**i**, **6b**, and **7b** were prepared using a modification of Pabon's method.[10] Compounds **3a**, **3b**, **10b**, and **11b** were prepared following the method of Venkateswarlu et al.[11] Compounds **4b** and **5b** were prepared following the method of Pederson et al.[12] Compounds **9a**–**t**, **9w**, **8a**, **8c**, **8t**, **12a**, and **12b** were prepared following the method of Masuda et al.[13] Compounds **9u** and **9v** were prepared following the procedure of Ali et al.[14] Compound **13b** was prepared following the method of Yadav and Kapoor.[15] Compounds **15a** and **15b** were prepared following the method of Zelle and Su.[16] Compounds **17a**–**h** were prepared following the procedure of Kohler and Chadwell.[17]

5.1.1. 1,7-Bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione (2a). Orange-yellow solid: mp 182–184 °C [lit.[12] 182–183 °C].

5.1.2. 1,7-Diphenyl-1,6-heptadiene-3,5-dione (2b). Yellow solid: mp 140–142 °C [lit.[12] 139–140 °C].

5.1.3. 1,7-Bis(2-methoxyphenyl)-1,6-heptadiene-3,5-dione (2c). Yellow crystals: mp 121–123 °C [lit.[18] mp 121–122 °C]; ^{13}C NMR: δ 55.5, 101.4, 111.1, 120.6, 124.0, 124.7, 128.5, 131.1, 135.6, 158.3, 183.6.

5.1.4. 1,7-Bis(3,4-dimethoxyphenyl)-1,6-heptadiene-3,5-dione (2d). Orange solid: mp 129–131 °C [lit.[18] 128–130 °C].

5.1.5. 1,7-Bis(2,3-dimethoxyphenyl)-1,6-heptadiene-3,5-dione (2e). The compound was prepared according to the method of Pabon[10] by the reaction of 2,4-pentanedione and 2,3-dimethoxybenzaldehyde to give a yellow solid: mp 117–120 °C; ^{1}H NMR: δ 3.87 (s, 12H), 5.87 (s, 1H), 6.68 (d, 2H, J = 16.1 Hz), 6.92 (d, 2H, J = 8.2 Hz), 7.05 (t, 2H, J = 8.0 Hz), 7.18 (d, 2H, J = 6.8 Hz), 7.95 (d, 2H, J = 16.1 Hz), 15.88 (s, 1H); ^{13}C NMR: (DMSO) δ 55.7, 60.7, 101.9, 114.6, 118.7, 124.1, 125.1, 128.0, 134.2, 147.7, 152.6, 182.9. Anal. Calcd for $C_{23}H_{24}O_6$: C, 69.68; H, 6.10. Found: C, 69.43; H, 6.16.

5.1.6. 1,7-Bis(4-methoxyphenyl)-1,6-heptadiene-3,5-dione (2f). Yellow solid: mp 157–159 °C [lit.[18] mp 154–155 °C]; ^{13}C NMR: δ 55.4, 101.2, 114.4, 121.9, 127.9, 129.7, 140.0, 161.2, 183.2.

5.1.7. 1,7-Bis(4-hydroxyphenyl)-1,6-heptadiene-3,5-dione (2g). Red-orange crystals: mp 226–228 °C [lit.[12] mp 223–224 °C].

5.1.8. 1,7-Bis(4-*N*,*N*-dimethylaminephenyl)-1,6-heptadiene-3,5-dione (2h). Purple solid: mp 200–202 °C [lit.[19] mp 206 °C].

5.1.9. 1,7-Bis(3-hydroxy-4-methoxyphenyl)-1,6-heptadiene-3,5-dione (2i). Orange-yellow solid: mp 190–192 °C [lit.[20] 189–190 °C]; ^{1}H NMR: (DMSO) δ 3.78 (s, 6H), 6.09,

(s, 1H), 6.60 (d, 2H, $J = 15.9$ Hz), 6.49 (d, 2H, $J = 8.9$ Hz), 7.11 (m, 4H), 7.47 (d, 2H, $J = 15.9$ Hz), 9.19 (s, 2H); ^{13}C NMR: δ 55.6, 100.9, 112.0, 114.0, 121.2, 121.5, 127.5, 140.2, 146.6, 149.8, 182.8.

5.1.10. 1,7-Bis(4-hydroxy-3-methoxyphenyl)-heptane-3,5-dione (3a). White crystals: mp 93–95 °C [lit.[21] 92–93 °C].

5.1.11. 1,7-Diphenylheptane-3,5-dione (3b). Orange-yellow oil [lit.[22]].

5.1.12. 4,4-Dimethyl-1,7-diphenyl-1,6-heptadiene-3,5-dione (4b). The compound was prepared according to the method of Pederson et al.[12] by the reaction of **2b** with methyl iodide to give yellow oil: ^{1}H NMR: δ 1.46 (s, 6H), 6.77 (d, 2H, $J = 15.7$ Hz), 7.33 (m, 6H), 7.49 (m, 4H), 7.72 (d, 2H, $J = 15.6$ Hz); ^{13}C NMR: δ 21.1, 60.9, 121.4, 128.5, 128.7, 130.6, 134.1, 144.1, 197.9. Anal. Calcd for $C_{21}H_{20}O_2$: C, 82.86; H, 6.62. Found: C, 82.54; H, 6.83.

5.1.13. 4,4-Dibenzyl-1,7-diphenyl-1,6-heptadiene-3,5-dione (5b). The compound was prepared according to the method of Pederson et al.[12] by the reaction of **2b** with benzyl bromide to give **5b** as a white solid: mp 182–183 °C (lit.[12] 181 °C); ^{1}H NMR: (DMSO) δ 3.43 (s, 4H), 7.12 (m, 12H), 7.38 (m, 6H), 7.57 (d, 2H, $J = 15.5$ Hz), 7.67 (m, 4H); ^{13}C NMR: δ 37.0, 69.3, 123.6, 126.3, 127.8, 128.6, 128.7, 130.0, 130.5, 134.0, 136.3, 142.0, 196.4. Anal. Calcd for $C_{33}H_{28}O_2$: C, 86.81; H, 6.18. Found: C, 86.52; H, 6.24.

5.1.14. 4-Methyl-1,7-diphenyl-1,6-heptadiene-3,5-dione (6b). The compound was prepared according to the method of Pabon[10] by the reaction of 3-methyl-2,4-pentanedione and benzaldehyde to give an orange solid: mp 154–157 °C; ^{1}H NMR: δ 2.17 (s, 3H), 7.12 (d, 2H, $J = 15.5$ Hz), 7.38 (m, 6H), 7.58 (m, 4H), 7.74 (d, 2H, $J = 15.5$ Hz); ^{13}C NMR: δ 12.1, 106.2, 120.8, 182.1, 128.8, 129.9, 135.4, 141.3, 182.4. Anal. Calcd for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 82.69; H, 6.36.

5.1.15. 4-Benzyl-1,7-diphenyl-1,6-heptadiene-3,5-dione (7b). The compound was prepared according to the method of Pabon[10] by the reaction of 3-benzyl-2,4-pentanedione and benzaldehyde to give a yellow solid: mp 162–164 °C; ^{1}H NMR: δ (DMSO) 3.99 (s, 2H), 6.99 (d, 2H, $J = 15.6$ Hz), 7.34 (m, 15H), 7.77 (d, 2H, $J = 15.2$ Hz); ^{13}C NMR: δ 30.0, 110.6, 121.0, 125.8, 127.6, 128.3, 128.3, 128.7, 130.1, 134.7, 141.3, 141.6, 183.1. Anal. Calcd for $C_{26}H_{22}O_2$: C, 85.22; H, 6.05. Found: C, 85.48; H, 6.11.

5.1.16. 1-(4-Hydroxy-3-methoxyphenyl)-1-buten-3-one (8a). Orange-yellow solid: mp 120–122 °C [lit.[23] 124–125 °C].

5.1.17. 1-(4-Methoxyphenyl)-1-buten-3-one (8c). Yellow solid: mp 71–73 °C [lit.[24] 72–72.5 °C].

5.1.18. 1-(2-Hydroxyphenyl)-1-buten-3-one (8t). Yellow solid: mp 135–137 °C [lit.[25] 139–140 °C].

5.1.19. 1,5-Bis(4-hydroxy-3-methoxyphenyl)-1,4-pentadien-3-one (9a). Yellow solid: mp 84–86 °C [lit.[13] 82–83 °C].

5.1.20. 1,5-Diphenyl-1,4-pentadien-3-one (9b). Yellow crystals: mp 110–112 °C [lit.[26] 112–114 °C].

5.1.21. 1,5-Bis(4-methoxyphenyl)-1,4-pentadien-3-one (9c). Yellow solid: mp 128–130 °C [lit.[26] 133–134 °C].

5.1.22. 1,5-Bis(3-methoxyphenyl)-1,4-pentadien-3-one (9d). Yellow solid: mp 64–65 °C [lit.[27] 52–54 °C]; ^{1}H NMR: δ 3.83 (s, 6H), 6.94 (dd, 2H, $J = 8.1$ Hz, 2.4 Hz), 7.04 (d, 2H, $J = 15.9$ Hz), 7.15 (m, 4H), 7.32 (t, 2H, $J = 8.0$ Hz), 7.68 (d, 2H, $J = 16.1$ Hz); ^{13}C NMR: δ 55.2, 113.2, 116.2, 120.9, 125.5, 129.8, 136.0, 143.0, 159.8, 188.6.

5.1.23. 1,5-Bis(2-methoxyphenyl)-1,4-pentadien-3-one (9e). Yellow solid: mp 123–124 °C [lit.[28] 124 °C].

5.1.24. 1,5-Bis(2,3-dimethoxyphenyl)-1,4-pentadien-3-one (9f). Yellow solid: mp 106–108 °C [lit.[29] 108 °C]; ^{13}C NMR: δ 55.9, 61.3, 114.1, 119.3, 124.1, 126.8, 129.0, 137.8, 148.7, 153.0, 189.5.

5.1.25. 1,5-Bis(3,4-dimethoxyphenyl)-1,4-pentadien-3-one (9g). Yellow solid: mp 72–75 °C [lit.[30] 68–70 °C]; ^{13}C NMR: δ 55.9, 109.9, 111.0, 122.9, 123.5, 127.7, 142.8, 149.1, 151.2, 188.4.

5.1.26. 1,5-Bis(2,5-dimethoxyphenyl)-1,4-pentadien-3-one (9h). Yellow solid: mp 105–106 °C [lit.[31] 105–106 °C]; ^{1}H NMR: δ 3.79 (s, 6H), 3.85 (s, 6H), 6.88 (m, 4H), 7.11 (d, 2H, $J = 2.8$ Hz), 7.12 (d, 2H, $J = 16.1$ Hz), 8.01 (d, 2H, $J = 16.1$ Hz); ^{13}C NMR: δ 55.8, 56.1, 112.4, 113.1, 117.1, 124.5, 126.3, 137.9, 153.0, 153.4, 189.6.

5.1.27. 1,5-Bis(2,4-dimethoxyphenyl)-1,4-pentadien-3-one (9i). Yellow solid: mp 138–140 °C [lit.[32] 138–139 °C]; ^{13}C NMR: δ 55.4, 55.5, 98.3, 105.3, 117.1, 124.1, 130.0, 137.6, 159.9, 162.6, 189.7.

5.1.28. 1,5-Bis(3,5-dimethoxyphenyl)-1,4-pentadien-3-one (9j). Yellow solid: mp 126–128 °C [lit.[33] 124.5–125.5 °C]; ^{1}H NMR: δ 3.80 (s, 12H), 6.49 (s, 2H), 6.73 (d, 4H, $J = 2.0$ Hz), 7.00 (d, 2H, $J = 15.9$ Hz), 7.62 (d, 2H, $J = 15.7$ Hz); ^{13}C NMR: δ 55.4, 102.7, 106.2, 125.7, 136.8, 143.2, 160.9, 188.6.

5.1.29. 1,5-Bis(2,6-dimethoxyphenyl)-1,4-pentadien-3-one (9k). Yellow solid: mp 152–154 °C [lit.[28]]; ^{1}H NMR: δ 3.90 (s, 12H), 6.57 (d, 4H, $J = 8.5$ Hz), 7.26 (t, 2H, $J = 8.5$ Hz), 7.59 (d, 2H, $J = 16.3$ Hz), 8.17 (d, 2H, $J = 16.3$ Hz); ^{13}C NMR: δ 55.8, 103.7, 113.1, 129.0, 130.9, 133.3, 160.0, 192.4.

5.1.30. 1,5-Bis(4-methylphenyl)-1,4-pentadien-3-one (9l). Yellow solid: mp 174–176 °C [lit.[26] 171–172 °C].

5.1.31. 1,5-Bis(3-methylphenyl)-1,4-pentadien-3-one (9m). Yellow solid: mp 68–72 °C [lit.[34]]; ^{1}H NMR: δ 2.38 (s, 6H), 7.06 (d, 2H, $J = 15.9$ Hz), 7.26 (m, 4H), 7.40 (m, 4H), 7.70 (d, 2H, $J = 15.9$ Hz); ^{13}C NMR: δ 21.3,

125.1, 125.4, 128.6, 128.8, 131.1, 134.6, 138.4, 143.1, 188.6.

5.1.32. 1,5-Bis(2-methylphenyl)-1,4-pentadien-3-one (9n). Yellow solid: mp 98–100 °C [lit.[26] 94–96 °C].

5.1.33. 1,5-Bis(4-chlorophenyl)-1,4-pentadien-3-one (9o). Yellow crystals: mp 184–186 °C [lit.[26] 191–193 °C]; ^{1}H NMR: δ 7.00 (d, 2H, J = 15.9 Hz), 7.37 (d, 4H, J = 8.5 Hz), 7.52 (d, 4H, J = 8.5 Hz), 7.66 (d, 2H, J = 15.9 Hz); ^{13}C NMR: δ 125.7, 129.2, 129.5, 133.2, 136.4, 141.9, 188.1.

5.1.34. 1,5-Bis(3-chlorophenyl)-1,4-pentadien-3-one (9p). Yellow solid: mp 123–125 °C [lit.[35] 120–121 °C]; ^{13}C NMR: δ 126.3, 126.6, 127.9, 130.1, 130.3, 134.9, 136.5, 141.8, 188.0.

5.1.35. 1,5-Bis(2-chlorophenyl)-1,4-pentadien-3-one (9q). Yellow solid: mp 114–116 °C [lit.[36] 110 °C]; ^{1}H NMR: δ 7.04 (d, 2H, J = 16.1 Hz), 7.29 (m, 4H), 7.41 (m, 2H), 7.67 (m, 2H), 8.11 (d, 2H, J = 16.1 Hz); ^{13}C NMR: δ 127.0, 127.5, 127.6, 130.1, 131.1, 132.9, 135.3, 139.2, 188.4.

5.1.36. 1,5-Bis(4-hydroxyphenyl)-1,4-pentadien-3-one (9r). Yellow solid: mp 235–237 °C [lit.[37] 238–239 °C].

5.1.37. 1,5-Bis(3-hydroxyphenyl)-1,4-pentadien-3-one (9s). Brown solid: mp 199–201 °C [lit.[37] 198–200 °C].

5.1.38. 1,5-Bis(2-hydroxyphenyl)-1,4-pentadien-3-one (9t). Yellow solid: mp 156–157 °C [lit.[37] 155 °C].

5.1.39. 1,5-Bis(4-acetoxy-3-methoxyphenyl)-1,4-pentadien-3-one (9u). Yellow solid: mp 179–180 °C [lit.[38] 150 °C]; ^{1}H NMR: δ 2.31 (s, 6H), 3.87 (s, 6H), 6.98 (d, 2H, J = 15.9 Hz), 7.06 (d, 2H, J = 8.1 Hz), 7.18 (m, 4H), 7.67 (d, 2H, J = 15.9 Hz); ^{13}C NMR: δ 20.7, 56.0, 111.7, 121.4, 123.3, 125.5, 133.7, 141.6, 142.6, 151.4, 168.5, 188.3. Exact mass calcd for $C_{23}H_{22}O_7$: 410.4165, observed (M+H) 411.1444.

5.1.40. 1,5-Bis(4-acetoxyphenyl)-1,4-pentadien-3-one (9v). The compound was prepared by reaction of **9r** with acetic anhydride following the procedure of Ali et al.[14] to give a yellow solid: mp 167–168 °C; ^{1}H NMR: δ 2.30 (s, 6H), 7.00 (d, 2H, J = 15.9 Hz), 7.13 (d, 4H, J = 8.3 Hz), 7.60 (d, 4H, J = 8.2 Hz), 7.69 (d, 2H, J = 15.9 Hz); ^{13}C NMR: δ 21.1, 122.1, 125.4, 129.4, 132.4, 142.1, 152.2, 168.9, 188.3. Exact mass calcd for $C_{21}H_{18}O_5$: 350.3646, observed (M+H) 351.1232.

5.1.41. 1,5-Bis(4-carbmethoxyphenyl)-1,4-pentadien-3-one (9w). Yellow solid: mp 206–210 °C [lit.[39] 221–223 °C]; ^{1}H NMR: δ 3.92 (s, 6H), 7.12 (d, 2H, J = 16.1 Hz), 7.65 (d, 4H, J = 8.1 Hz), 7.73 (d, 2H, J = 15.9 Hz), 8.06 (d, 4H, J = 8.0 Hz); ^{13}C NMR: δ 52.3, 127.1, 128.1, 130.1, 131.6, 138.8, 142.1, 166.2, 188.0.

5.1.42. 1-(4-Methoxyphenyl)-5-phenyl-1,4-pentadien-3-one (9x). Yellow solid: mp 85–89 °C [lit.[40] 118–119 °C]; ^{1}H NMR: δ 3.82 (s, 3H), 6.91 (d, 2H, J = 8.5 Hz), 6.94 (d, 1H, J = 15.9 Hz), 7.06 (d, 1H, J = 16.1 Hz), 7.38 (m, 4H), 7.57 (m, 3H), 7.71 (dd, 2H, J = 15.9, 2.0 Hz); ^{13}C NMR: δ 55.4, 114.4, 123.3, 125.5, 127.4, 128.2, 128.8, 130.0, 130.2, 134.8, 142.6, 143.0, 161.5, 188.6.

5.1.43. 1-(4-Hydroxy-3-methoxyphenyl)-5-phenyl-1,4-pentadien-3-one (9y). The compound was prepared according to the method of Masuda[13] by the reaction of **8a** with benzaldehyde to give yellow oil: ^{1}H NMR: δ 3.92 (s, 3H), 6.08 (s, 1H), 6.91 (d, 1H, J = 16.1 Hz), 6.93 (d, 2H, J = 8.2 Hz), 7.07 (d, 1H, J = 15.9 Hz), 7.10 (s, 1H), 7.15 (d, 1H, J = 8.0 Hz), 7.38 (m, 2H), 7.59 (m, 2H), 7.67 (d, 1H, J = 15.9 Hz), 7.71 (d, 1H, J = 15.9 Hz); ^{13}C NMR: δ 56.0, 109.8, 114.9, 123.4, 125.3, 127.3, 128.3, 128.8, 130.3, 134.9, 142.8, 143.5, 146.8, 148.3, 188.7.

5.1.44. 1,5-Diphenylpentan-3-one (10b). Clear oil [lit.[41]].

5.1.45. 1,5-Diphenylpentan-3-ol (11b). White solid: mp 47–49 °C [lit.[42] 45–46 °C]. ^{13}C NMR: δ 32.1, 39.2, 70.8, 125.6, 128.3, 142.0.

5.1.46. 2,6-Bis(4-hydroxy-3-methoxybenzylidene)cyclohexanone (12a). Yellow solid: mp 177–178 °C [lit.[43] 179–181 °C]; ^{13}C NMR: δ 23.1, 28.5, 56.0, 113.2, 114.4, 124.4, 128.5, 134.2, 136.9, 146.2, 146.4, 172.8.

5.1.47. 2,6-Bis(benzylidene)cyclohexanone (12b). Yellow crystals: mp 117–119 °C [lit.[44] 117 °C].

5.1.48. *trans*,*trans*-1,2,4,5-Diepoxy-1,5-diphenylpentan-3-one (13b). White crystals: mp 117–119 °C [lit.[45] 117–119 °C].

5.1.49. 1,5-Bis(4-pyridyl)-1,4-pentadien-3-one (15a). Yellow solid: mp 145–146 °C [lit.[46] 149 °C]; ^{1}H NMR: δ 7.17 (d, 2H, J = 15.9 Hz), 7.42 (d, 4H, J = 5.6 Hz), 7.63 (d, 2H, J = 15.9 Hz), 8.67 (d, 4H, J = 5.6 Hz); ^{13}C NMR: δ 121.9, 128.6, 141.0, 141.6, 150.6, 172.5. Hydrochloride salt: yellow solid mp >250 °C; ^{1}H NMR: δ D_2O 7.54 (d, 2H, J = 16.3 Hz), 7.78 (d, 2H, J = 15.9 Hz), 8.15 (d, 4H, J = 6.6 Hz), 8.70 (d, 4H, J = 6.6 Hz); ^{13}C NMR: δ ^{13}C NMR: δ D_2O 128.2, 136.2, 141.3, 144.2, 154.4, 193.0.

5.1.50. 1,5-Bis(3-pyridyl)-1,4-pentadien-3-one (15b). Yellow solid: mp 148–149 °C [lit.[46] 150 °C]; ^{1}H NMR: δ 7.11 (d, 2H, J = 16.1 Hz), 7.32 (m, 2H), J = 7.71 (d, 2H, J = 15.9 Hz), 7.90 (d, 2H, J = 6.2 Hz), 8.61 (d, 2H, J = 4.6 Hz), 8.81 (s, 2H); ^{13}C NMR: δ 123.7, 126.7, 130.3, 134.4, 139.9, 149.9, 151.1, 198.6. Hydrochloride salt: yellow solid mp >250 °C; ^{1}H NMR: δ D_2O 7.40 (d, 2H, J = 16.3 Hz), 7.78 (d, 2H, J = 16.1 Hz), 8.02 (t, 2H, J = 7.9 Hz), 8.70 (d, 2H, J = 5.6 Hz), 8.79 (d, 2H, J = 7.9 Hz), 8.98 (s, 2H); ^{13}C NMR: δ 130.1, 132.8, 136.9, 139.9, 143.7, 144.3, 147.3, 193.0.

5.1.51. 1,3-Diphenylpropenone (17a). Pale yellow solid: mp 52–54 °C [lit.[47] 55–58 °C].

5.1.52. 3-(4-Carboxyphenyl)-1-phenyl-2-propen-1-one (17b). Yellow solid: mp 229–232 °C [lit.[48] 227–229 °C]; ^{13}C NMR: (DMSO) δ 124.2, 128.5, 128.7, 128.8, 129.6, 132.1, 133.2, 137.3, 138.7, 142.4, 166.7, 189.0.

5.1.53. 1-(4-Carboxyphenyl)-3-phenyl-2-propen-1-one (17c). Yellow solid: mp 217–220 °C; ^{13}C NMR: (DMSO) δ 121.9, 128.5, 128.8, 128.9, 129.4, 130.6, 134.3, 134.4, 140.6, 144.6, 166.4, 188.8.

5.1.54. 1-(4-Cyanophenyl)-3-phenyl-2-propen-1-one (17d). Yellow solid: mp 120 °C [lit.[49] 119–120 °C].

5.1.55. 1-(2,4-Dimethylphenyl)-3-phenyl-2-propen-1-one (17e). Yellow oil [lit.[50] 68 °C]; ^{1}H NMR: δ 2.37 (s, 3H), 2.44 (s, 3H), 7.05 (m, 2H), 7.16 (d, 1H, J = 16.1 Hz), 7.38 (m, 3H), 7.49 (d, 1H, J = 15.9 Hz), 7.54 (m, 3H); ^{13}C NMR: δ 20.4, 21.4, 126.0, 126.6, 128.2, 128.5, 128.8, 130.4, 132.2, 134.7, 136.1, 137.4, 140.8, 145.0, 195.6.

5.1.56. 3-(4-Hydroxy-3-methoxyphenyl)-1-phenyl-2-propen-1-one (17f). Yellow solid: mp 81–84 °C [lit.[51] 85–90 °C]; ^{13}C NMR: δ 56.1, 110.0, 114.8, 119.8, 123.3, 127.4, 128.4, 128.5, 132.5, 138.5, 145.1, 146.7, 148.2, 190.5.

5.1.57. 1-(4-Hydroxy-3-methoxyphenyl)-3-phenyl-2-propen-1-one (17g). Yellow solid: mp 61–64 °C [lit.[52] 63–66 °C]; ^{1}H NMR: δ 3.95 (s, 3H), 6.29 (s, 1H), 6.98 (d, 1H, J = 8.3 Hz), 7.38 (m, 2H), 7.53 (d, 1H, J = 15.5 Hz), 7.62 (m, 5H), 7.79 (d, 1H, J = 15.5 Hz); ^{13}C NMR: δ 56.1, 110.5, 113.8, 121.6, 123.6, 128.3, 128.8, 130.2, 130.9, 135.0, 143.8, 146.8, 150.4, 188.4.

5.1.58. 1,3-Bis(4-hydroxy-3-methoxyphenyl)-2-propen-1-one (17h). Yellow solid: mp 111–114 °C [lit.[51] 126–128 °C]; ^{1}H NMR δ 3.94 (s, 3H), 3.95 (s, 3H), 6.00 (s, 1H), 6.19 (s, 1H), 6.95 (m, 2H), 7.11 (d, 1H, J = 1.6 Hz), 7.20 (dd, 1H, J = 8.3, 1.6 Hz), 7.38 (d, 1H, J = 15.5 Hz), 7.61 (m, 2H), 7.73 (d, 1H, J = 15.7 Hz); ^{13}C NMR: δ 56.0, 56.1, 110.0, 110.5, 113.6, 114.8, 119.2, 123.0, 123.4, 127.6, 131.1, 144.2, 146.7, 146.8, 148.0, 150.1, 188.4.

5.2. Anti-oxidant activities

There are multiple standardized methods to determine anti-oxidant activities, and it is recommended that at least two different procedures be used.[53] For the TRAP assay,[54] 2,2′-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) was reacted with potassium persulfate in the dark, overnight, to generate the colored ABTS$^{\cdot+}$ radical cation, which has an absorption maximum at 734 nm. The activity of curcumin and analogues was determined by their abilities to quench the color of the radical cation. All analogues and the reference compound Trolox were used at 10 μM concentrations. For the FRAP assay,[55] the ferric complex of 2,4,6-tri-pyridyl-*s*-triazine was prepared at acidic pH, and the anti-oxidant activities of curcumin and analogues were determined at 10 μM concentrations by their abilities to reduce the ferric complex to the ferrous complex, monitored by formation of the ferrous complex at 593 nm. Trolox, 1 μM, was used as reference.

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