ISSN 2321-807X

Ultrasonic Waves Assisted Synthesis of Curcuminoids Based on 3-Methylacetylacetone and in Situ Synthesis of Gold Nanoparticles Capped with Curcuminoids

Faiz O. Neamah[1], Bahjat A. Saeed[1,*] and Rita S. Elias[2]

[1]Department of Chemistry, College of Education, University of Basrah, Iraq
[2] Department of Pharmaceutical Chemistry, College of Pharmacy, University of Basrah, Iraq
* Author to whom correspondence should be addressed; E-Mail: bahjat.saeed@yahoo.com
Tel.: +964-0780-2410050

Abstract

Ultrasonic irradiation was used to induce the Knuevenagle reaction between aromatic aldehydes and 3-methylacetylacetone to synthesize curcumin analogues with moderate to good yields. The structures of the compounds were established by elemental analysis and from their mass and ^{1}HNMR spectra. In situ curcumin-gold nanoparticles were synthesized. The solutions of the prepared nanoparticles have purple to deep-red colors and their UV-vis spectra were characterized by the Surface Plasmon Resonance bands within the range 538-554 nanometer.

Keywords: Curcumin analogues, ultrasonic-assisted synthesis; nanoparticles; surface Plasmon resonsnce

Council for Innovative Research

Peer Review Research Publishing System

Journal: Journal of Advances in Chemistry

Vol. 4, No. 3

editor@cirworld.com

www.cirworld.com, member.cirworld.com

ISSN 2321-807X

Introduction

Due to its practical benefits compared to conventional methods large numbers of compounds have been synthesized by ultrasound waves irradiation of the reactants. The benefits include higher yields, shorter reaction time and milder conditions. The synthesized compounds by this technique span over wide spectrum including organics [1-3]inorganics [4-6], polymers [7,8] and nanoparticles [9,10].

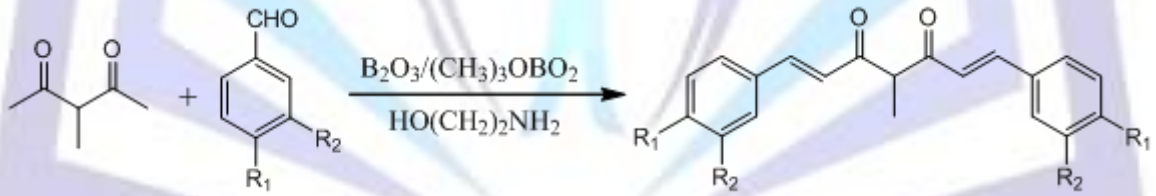
Curcumin is of considerable interest and is well-known compound because of its antioxidant [11-13], anti-inflammatory [14], antimicrobial [15] and anticarcenogenic activities [16-19]. In addition it is unique among active compounds because it is extremely safe even at very high doses. On the other hand and due to the presence of the olefinic groups in it structure this β-diketone of poor aqueous solubility rendering it of relatively low bioavailability [20]. This reason prevents curcumin to be approved as pharmaceutical agent. In order to overcome this shortage, synthesis of compounds with the same or even hopefully with better activities but with reasonable water solubility are continuously in progress. The best choice in this case is the synthetic analogues or derivatives less or more related to curcumin. Curcumin nanoparticles as pure curcumin or as adsorbed curcumin on gold surfaces were reported to enhance the solubility of curcumin in water and its biological activities [21-28].

In this work we report the synthesis of curcumin analogues via the reaction of aromatic aldehydes and 3-methylacetylacetone under ultrasound irradiation (Scheme I) as well as the synthesis of the nanoparticles of some curcuminoids.

2. Results and discussion

The curcumin analogues were synthesized by altrasonic-assisted Knuevenagle reaction of 3-methylacetylacetone with variety of aromatic aldehydes in the presence of boric oxide and aminoethanol. The reactions were done with relatively short times (20 min) as compared to the conventional reaction. The general synthesis procedure is shown in scheme I. The synthesized compounds were confirmed by elemental analysis and by mass and ^{1}H NMR spectra. The infrared spectra were characterized by a strong band within the range 1618 – 1625 cm^{-1} due to the stretching vibration of the carbonyl group which is shifted to lower frequencies due to both its conjugation with the unsaturated ethylinic system and participation in the intrahydrogen bonded chelated ring. This proved that the compounds are present mainly in the enolic form. The mass spectra showed the peak of the parent ion and a base peak results from the ion due to fragmentation at the methylene group of the chelated ring. The spectra were also characterized by a general peak due to the ion resulted by losing the Ar-CH=CH- fragment. The ^{1}H NMR spectra confirms the enolic structure of the compounds by two notes. First the absence of the methylene signal which must be present in the spectra of the keto form and such a signal presents at 2.34 ppm in the spectrum of the keto form of acetylacetone. Second the presence of the much more downfield peak (17.04 -17.84 ppm) which attributed to the intrahydrogen bonded chelated proton of the enolic OH group as it is the case with β-diketones [29].

Scheme 1. Synthesis of curcumin analogues, reaction conditions and prepared compounds.



1 R_1= OCH_3; R_2= H

2 R_1= Cl; R_2= H

3 R_1= R_2= H

4 R_1= OH; R_2= H

5 R_1= OH; R_2= H

6 R_1= OH; R_2= OCH_3

7 R_1= CH_3; R_2= H

8 R_1= F; R_2= H

9 R_1= Br; R_2= H

10 R_1= NO_2; R_2= H

11 R1= $N(CH_3)_2$; R_2= H

12= $NHCOCH_3$; R_2= H

ISSN 2321-807X

The curcuminoid capped gold nanoparticles (AuNPs) were synthesized *in situ* by the adsorption of compounds on the gold nanoparticles surface. The formation of the nanoparticles was confirmed by their electronic spectra as follows. The electronic spectrum of the gold solution is characterized by a long and strong band at 287.9 nanometers while the electronic spectra of the curcuminoids are characterized by long bands at 419.9 - 458.4 nm and accordingly has yellow colors. When the species were brought to contact their solutions changed to purple or deep-red color depending on the curcuminoid. These solutions are characterized by bands appear at longer wavelengths which are not present in the gold or the curcuminoid solutions. The resulting bands were interpreted as a Surface Plasmon Resonance (SPR) [30] that characterizes the electronic spectra of nanoparticles of organic compounds adsorbed on the gold surface and the optical properties of the nanoparticles depend strongly on their size, shape and interaction between the nanoparticles and the adsorbed species on the surface of the nanoparticles. Figs. 1-5 show the UV-vis spectra of chloroauric acid (1), the curcuminoid (2) and AuNPs (3). In all cases a new band at longer wavelength is appeared which attributed to surface Plasmon absorption maxima and situated at 554.6, 553.1, 538.4, 539.0, and nm for the curcuminoids 4, 5, 6, a, and b respectively. The difference of SPR bands is due to the varied level of size distribution of the nanoparticles in the solution and their aggregation [27]. It is worthy to note that efforts to prepare nanoparticles from curcuminoids that not have phenolic OH groups were failed with us.

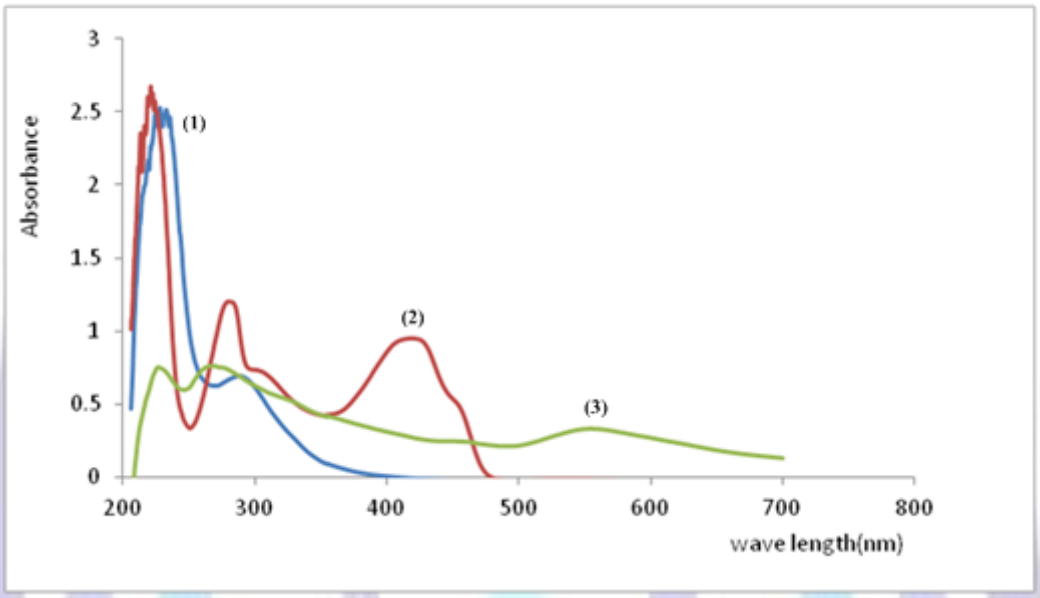


Fig. 1 UV-vis spectra of AuNPs synthesized by compound 4 and chloroauric acid (1.5 x 10^{-4} M).

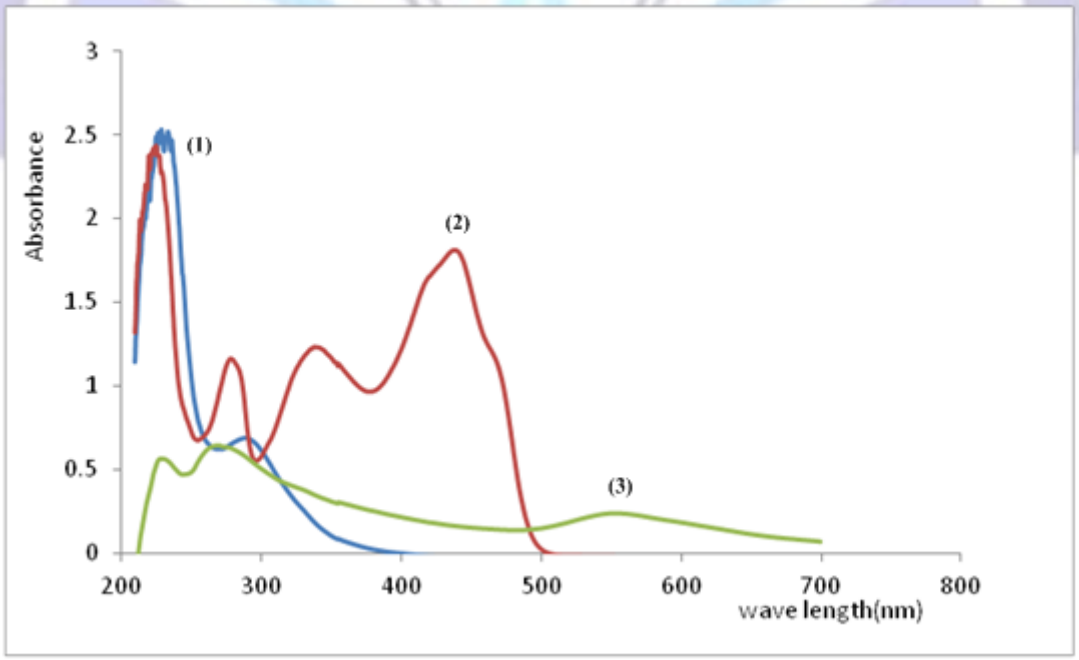


Fig. 2 UV-vis spectra of AuNPs synthesized by compound 5 and chloroauric acid (1.5 x 10^{-4} M).

ISSN 2321-807X

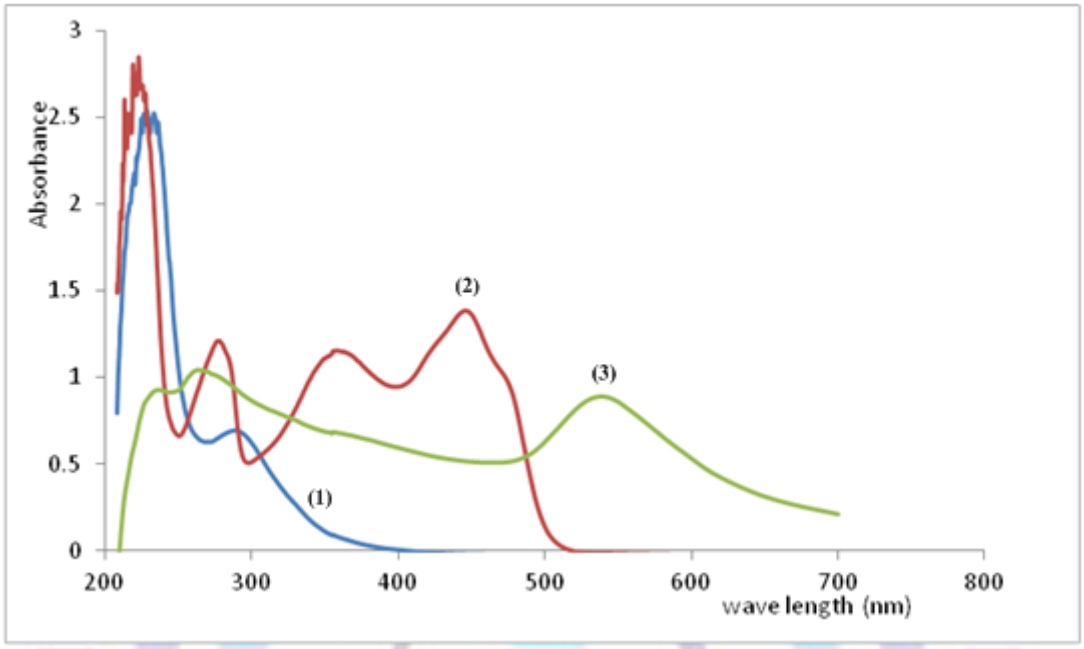


Fig. 3 UV-vis spectra of AuNPs synthesized by compound 6 and chloroauric acid (1.5 x 10^{-4} M).

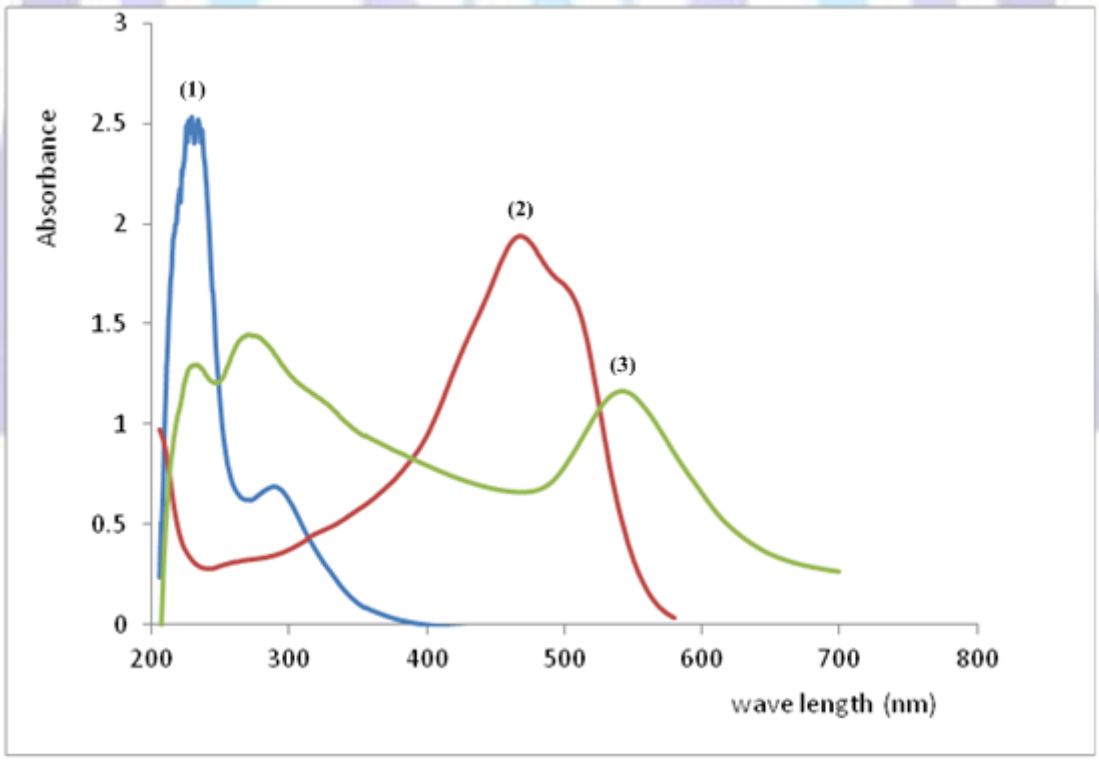


Fig. 4 UV-vis spectra of AuNPs synthesized by chlorocurcumin and chloroauric acid (1.5 x 10^{-4} M).

ISSN 2321-807X

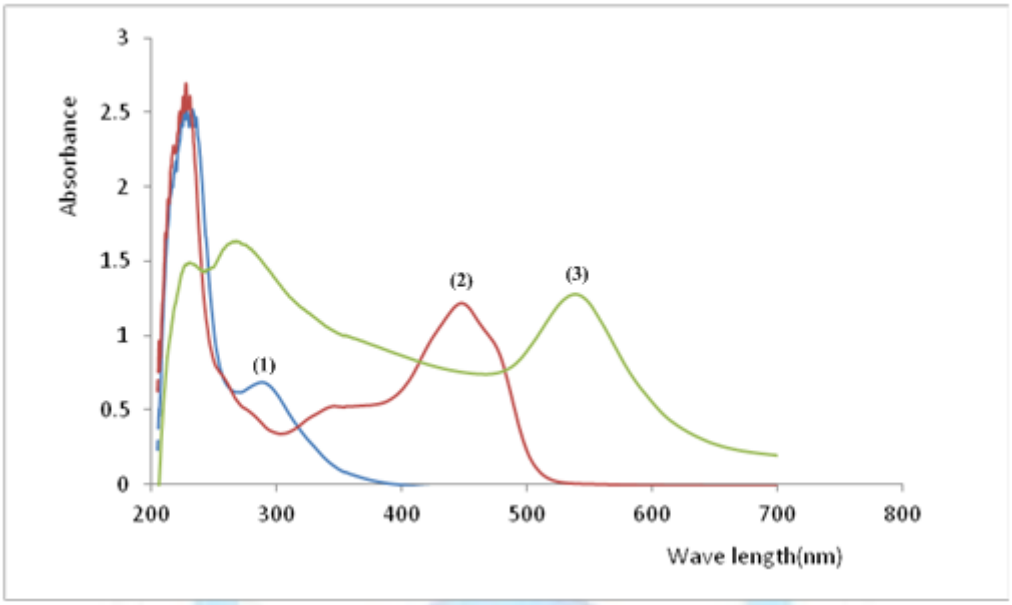


Fig. 5 UV-vis spectra of AuNPs synthesized by chloro-bisdemethoxycurcumin and chloroauric acid (1.5 x 10^{-4} M).

3. Experimental

3.1. General

NMR spectra were recorded on a Bruker 500 in deurated DMSO with tetramethylsilane as an internal standard. Mass spectra were determined on a Funigan instrument at 70 eV. Melting points were measured in open capillary tubes in a Thermo scientific apparatus. UV-vis spectra were measured with a CECIL CE7200 spectrophotometer in quartz matched cells of 1-cm pathlengths. Infrared spectra were recorded by Iraffinity-1 Shimadzu FTIR spectrophotometer. Elemental analyses were performed by Thermo Finnigan CHNS-O analyzer, 1112 series.

3.2. The Synthesis of curcuminoids

The compounds were synthesized according to the method described by Yingjie *et al.* [31]. A round-bottomed flask containing a mixture of boron oxide (0.013 mol), DMF (6 mL), monoethanolamine (0.37 mL) and trimrthylborate (2 mL) was set in an ultrasonic cleaner (40 kHz, 500 W). Aromatic aldehyde (0.025 mol) and 3-methyl-pentane-2,4-dione were added to the flask mixture and the contents were irradiated at 80 °C for 20 min. The progress of the reaction was monitored with TLC. After the completion of the reaction, the mixture was poured into 100 mL of 5% warm acetic acid. The crude product was filtered and separated by column chromatography on silica gel (200-300 mesh) using mixture of 1:3 hexane:diethylether as an eluent.

3.3. The synthesis of gold nanoparticles with curcumin (AuNPs)

Five curcumin analogues namely: 4, 5, 6, as well as 3-chlorocurcumin (a) and 3-chloro-bisdemethoxycurcumin (b) were used with gold to prepare the curcumin-capped gold nanoparticles.

The method described by Singh *et al.* [27] was employed. $HAuCl_4$ was added into 500 mL of water to make 1.5 x 10^{-4} M. The mixture held at 90°C under constant sterring, followed by the addition of the curcuminoid (4 mg). The heating was stopped after the mixing of the reactants and allowed to cool to room temperature to form deep red to purple colored solutions depending on the curcuminoid used. The solution colors were purple for compounds 4 and 5 and deep red for compounds 6, a and b.

4-Methyl-1,7-bis(4-methoxyphenyl)-1,6-hepta diene-3,5-dione **(1)**. Yellow crystals; Yield 68%; m.p. 175-177 ^{o}C; EI-MS: *m/z* =350 (M^+); IR (KBr disk) υ cm^{-1}: 1618; ^{1}H-NMR δ ppm: 2.15(3H, s, CH_3) ,3.78(6H, s, OCH_3), 6.86(2H,d, *J*= 15 Hz,CH=C),7.19(2H, d, *J*= 15 Hz, CH=C), 6.96-7.72(8H, m, Ar-H), 17.62(1H, s, enolic OH); Anal. Calcd. for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 75.32; H, 6.63.

4-Methyl-1,7-bis(4-Chlorophenyl)-1,6-hepta diene-3,5-dione **(2)**. Yellow powder; Yield 71%; m.p. 191-192 ^{o}C; EI-MS: *m/z* = 359 (M^+); IR (KBr disk) υ cm^{-1}: 1625; ^{1}H-NMR δ ppm: 2.18(3H, s, CH_3), 7.04(2H, d, *J*= 15 Hz, CH=C), 7.37(2H, d, *J*= 15 Hz, CH=C), 7.44-7.8(8H, m, Ar-H), 17.13(1H, s, enolic OH); Anal. Calcd. for $C_{20}H_{16}Cl_2O_2$: C, 66.87; H, 4.49. found: C, 66.98; H, 5.13.

4-Methyl-1,7-diphenyl-1,6-heptadiene-3,5-dione **(3)**. Yellow crystals; Yield 65%; m.p. 154-153 ^{o}C; EI-MS: *m/z* = 290 (M^+); IR (KBr disk) υ cm^{-1}: 1625; ^{1}H-NMR δ ppm: 2.18(3H, s, CH_3), 7.01(2H, d, *J*= 15 Hz, CH=C), 7.6(2H, d, *J*= 15 Hz,

CH=C), 7.4-7.76(10H, m, Ar-H), 17.40(1H, s, enolic OH). Anal. Calcd. For $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 82.92; H, 6.74.

4-Methyl-1,7-bis(3-hydroxyphenyl)-1,6-hepta diene-3,5-dione **(4)**. Yellow crystals; Yield 55%; m.p. 210-212 ^oC; EI-MS: *m/z* = 322 (M^+); IR (KBr disk) υ cm^{-1}: 1625; ^{1}H-NMR δ ppm: 2.15(3H, s, CH_3), 6.82-7.54(12H, m, olefinic + Ar-H), 9.50(2H, s, phenolic OH), 17.39(1H, s, enolic OH); Anal. Calcd. for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63. Found: C, 74.76; H, 5.32.

4-Methyl-1,7-bis(4-hydroxyphenyl)-1,6-hepta diene-3,5-dione **(5)**. Orange crystals; Yield 63%; m.p. 199-201 ^oC; EI-MS: *m/z* = 322 (M^+); IR (KBr disk) υ cm^{-1}: 1620; ^{1}H-NMR δ ppm: 2.12(3H, s, CH_3), 6.78-7.53(12H, m, olefinic + Ar-H), 10.03(2H, s, phenolic OH), 17,69(1H, s, enolic OH). Anal. Calcd. for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63. Found: C, 74.89; H, 5.79.

4-Methyl-1,7-bis(4-hydroxy-3-hydroxyphenyl)-1,6-heptadiene-3,5-dione **(6)**. Yellow powder; Yield 75%; m.p. 184-186 ^oC; EI-MS: *m/z* = 382 (M^+); IR (KBr disk) υ cm^{-1}: 1626; ^{1}H-NMR δ ppm: 2.12(3H, s, 2.20(3H, s, CH_3), 3.81(6H, s, OCH_3), 6.82(2H, d, J= 8 Hz, Ar-H), 6.88(2H, d, *J*= 15 Hz, CH=C), 7.15(2H, d, *J*= 8 Hz, Ar-H), 7.58(2H, d, *J*= 8 Hz, CH=C), 9.62(2H, s, phenolic OH), 17.77(1H, s, enolic OH). Anal. Calcd. for $C_{22}H_{22}O_6$: C, 69.10; H, 5.80. Found: C, 69.63; H, 5.58.

4-Methyl-1,7-bis(4-methylphenyl)-1,6-hepta diene-3,5-dione **(7)**. Yellow crystals; Yield 88%; m.p. 179-181 ^oC; EI-MS: *m/z* = 318 (M^+); IR (KBr disk) υ cm^{-1}: 1620; ^{1}H-NMR δ ppm: 2.16(3H, s, CH_3), 2.31(6H, s, CH_3), 6.95(2H, d, *J*= 16 Hz, CH=C), 7.21(4H, d, *J*= 9 Hz, Ar-H), 7.29(2H, d, *J*= 16, CH=C)), 7.66(4H, d, *J*= 9, AR-H), 17.84(1H, s, enolic OH); Anal. Calcd. For $C_{22}H_{22}O_2$: C, 82.99; H, 6.96. Found: C, 83.29; H, 6.71.

4-Methyl-1,7-bis(4-fluorophenyl)-1,6-hepta diene-3,5-dione **(8)**. Yellow crystals; Yield 77%; m.p. 187-189 ^oC; EI-MS: *m/z* = 326 (M^+); IR (KBr disk) υ cm^{-1}: 1625; ^{1}H-NMR δ ppm: 2.03(3H, s, CH_3), 6.98(2H, d, *J*= 16 Hz, CH=C), 7.30(2H, d, *J*= 16 Hz, CH=C), 7.33(4H, d, *J*= 9 Hz, Ar-H), 7.76(4H, d, *J*= 9 Hz, Ar-H); Anal. Calcd. For $C_{20}H_{16}F_2O_2$: C, 73.61; H, 4.94. Found: C, 73.98; H, 5.13.

4-Methyl-1,7-bis(4-bromophenyl)-1,6-hepta diene-3,5-dione **(9)**. Yellow powder; Yield 63%; m.p. 195-197 ^oC; EI-MS: *m/z* = 448 (M^+); IR (KBr disk) υ cm^{-1}: 1625; ^{1}H-NMR δ ppm: 2.17(3H, s, CH_3), 7.05(2H, d, *J*= 15 Hz, CH=C); 7.39(2H, d, *J*= 15 Hz, CH=C); 7.45-7.81(8H, m, Ar-H); 17.30(1H, s, enoilc OH). Anal. Calcd. For $C_{20}H_{16}Br_2O_2$: C, 53.60; H, 3.60. Found: C, 53.34; H, 3.88.

4-Methyl-1,7-bis(4-nitrophenyl)-1,6-hepta diene-3,5-dione **(10)**. Red crystals; Yield 66%; m.p. 215-217 ^oC; EI-MS: *m/z* = 380 (M^+); IR (KBr disk) υ cm^{-1}: 1622; ^{1}H-NMR δ ppm: 2.24(3H, s, CH_3); 7.24(2H, d, *J*= 15 Hz, CH=C); 7.58(2H, d, *J*= 15 Hz, CH=C); 8.08-8.26(8H, m, Ar-H); 17.04(1H, s, enolic OH). Anal. Calcd. for $C_{20}H_{16}N_2O_6$: C, 63.16; H, 4.24, N, 7.37. Found: C, 63.91; H, 4.89; N, 7.90.

4-Methyl-1,7-bis(4-(dimethylamino)phenyl)-1,6-hepta diene-3,5-dione **(11)**. Red powder; Yield 45%; m.p. 220-223 ^oC; EI-MS: *m/z* = 376 (M^+); IR (KBr disk) υ cm^{-1}: 1618; ^{1}H-NMR δ ppm: 2.10(3H, s, CH_3); 2.92(6H, s, $N(CH_3)_2$); 6.97(2H, d, *J*= 15 Hz, CH=C); 7.01-7.55 (10H, m, olefinic + AR-H); 17.10(1H, s, enolic OH). Anal. Calcd. for $C_{24}H_{28}N_2O_2$: C, 76.56; H, 7.50, N, 8.50. Found: C, 76.08; H, 7.73; N, 8.83.

4-Methyl-1,7-bis(4-acetoamidophenyl)-1,6-hepta diene-3,5-dione **(12)**. Red powder; Yield 60%; m.p. 248-249 ^oC; EI-MS: *m/z* = 404 (M^+); IR (KBr disk) υ cm^{-1}: 1662, 1625; ^{1}H-NMR δ ppm: 2.03(6H, s, $COCH_3$); 2.15(3H, s, CH3); 6.87(2H, d, *J*= 18 Hz, CH=C); 7.21(2H, d, *J*= 18 Hz, CH=C); 10.12(2H, s, NH); 17.56(1H, s, enolic OH); Anal. Calcd. for $C_{24}H_{24}N_2O_4$: C, 76.56; H, 7.50, N, 8.50. Found: C, 76.08; H, 7.73; N, 8.83.

4. Conclusions

The synthesis of curcumin analogues could be accelerated by synthesis under ultrasonic radiation conditions. The reaction time by this method is only 20 min compared to about 3 h in the conventional reflux method. Concerning nanoparticles the presence of the phenolic OH groups in curcumin analogues may be essential for the synthesis.

References

1. Sidorenko, D. Y.; Orlov, V. D. Synthesis of azoloquinazolinic systems using ultrasound. *Ultrason. Sonochem*. **2011**, *18*, 300-302.
2. Kitazume, T. Ultrasound-promoted stereocontrolled synthesis of fluorinated molecules. *Ultrasonics* **1990**, *28*, 322-325.
3. Ocampo, R. A.; Koll, L. C.; Mandolesi, S. D. Ultrasound promoted Barbier reactions and Csp3-Csp2 Stille coupling for the synthesis of diarylmethanes and substituted benzophenones. *Ultrason. Sonochem*. **2013**, *20*, 40-46.

4. Lang, E. S.; Tirloni, B.; de Oliveira, G. M.; Pereira, M. B. Synthesis, thermogravimetry, optical features and X-ray structural characterization of new Hg-Te dinuclear cluster compound obtained using an ultrasonic bath. *J. Organomet. Chem*. **2013**, *724*, 135-138.
5. Itatani, K.; Iwafune, K.; Howell, F. C.; Aizawa, M. Preparation of various calcium-phosphate powders by ultrasonic spray freeze-drying technique. *Material Res. Bull*. **2000**, *35*, 575-585.
6. Ni, Y.; Li, H.; Jin, L.; Hong, J.Synthesis of 1D Cu(OH)2 nanowires and transition to 3D CuO microstructures under ultrasonic irradiation, and their electrochemical property. *Cryst. Growth and Design* **2009**, *9*, 3868-3873.
7. Okitso, K.; Sharyo, K.; Nishimura, R. One-pot synthesis of gold nanorods by ultrasonic irradiation: the effect of pH on the shape of the gold nanorods and nanoparticles. *Langmuir*, **2009**, *25*, 7786-7790.
8. Belova, V.; Andreeva, D.; Mohwald, H.; Shchukin, D. Ultrasonic intercalation of gold nanoparticles into clay matrix on the presence of surface active materials. Part I: neutral polyethylene glycol. *J. Phys. Chem*. C, **2009**, *113*, 5381-5389.
9. Yang, W.; Nie, L.; Wang, Y.; Zhou, J.; Ma, L.; Wabg, Z.; Shi, W.Growth of oriented polycrystalline α-HgI_2 films by ultrasonic-wave-assisted physical vapour deposition. *J. Cryst. Growth* **2011**, *324*, 149-153.
10. Czubarow, P.; Sugimoto, T.; Seyferth, D. Sonochemical synthesis of a poly(methylsilane), a precursor for near-stoichiometric SiC. *Macromol*. **1998**, *31*, 229-238.
11. Priyadarsini, K.; Maity, D. K.; Naik, G. H.; Kumar, M.; Unnikrishnan, M.; Satav, J.; Mohan, H. Role of phenolic O-H and methylene hydrogen on the free radical reactions and antioxidant activity of curcumin. *Free Radical Biology and Medicine* **2003**, *35*, 475-484.
12. Jayaprakasha, G.; Rao, L.; Sakaria, K. Antioxidant activities of curcumin, demethoxycurcumin and bisdemethoxycurcumin. *Food Chemistry* **2006**, *98*, 720-724.
13. Yang, M.; Wu, Y.; Li, J.; Zhou, H.; Wang, X. Binding of Curcumin with Bovine Serum Albumin in the Presence of i-Carrageenan and Implications on the Stability and Antioxidant Activity of Curcumin. *J. Agric. Food Chem.*, **2013**, *61* , 7150–7155
14. Kastori, A.; Chatzopoulou, M.; Dimas, K.; Kontogiorgis, C.; Patsilinakos, A.; Trangas, T.; Hadjipavlou-Litina, D. Curcumin analogues as possible anti-proliferative & anti-inflammatory agents. *European Journal of Medicinal Chemistry* **2011**, *46*, 2722-2735.
15. Singh, P.; Kotia, V.; Ghosh, D.; Mohite, M.; Kumar, A.; Maji, S. Curcumin modulates α-synuclein aggregation and toxicity. *ACS Chem. Neurosci.*, **2013**, *4*, 393–407.
16. Tharakan, S.; Inamoto, T.; Sung, B.; Aggarwal, B.; Kamat, A. Curcumin potentiates the antitumor effects of gemcitabine in an orthotopic model of human bladder cancer through suppression of proliferative and angiogenic biomarkers. *Biochemical Pharmacology* **2010**, *79*, 218–228.
17. Notarbartolo, M.; Poma, P.; Perri, D.; Dusonchet, L.; Cervello, M.; D'Alessandro, A. Antitumor effects of curcumin, alone or in combination with cisplatin or doxorubicin, on human hepatic cancer cells. Analysis of their possible relationship to changes in NF-kB activation levels and in IAP gene expression. *Cancer Letters* **2005**, *224*, 53-65.
18. Khar, A.; Ali, A.; Pardhasaradhi, B.; Begum, Z.; Anjum, R. Antitumor activity of curcumin is mediated through the induction of apoptosis in AK-5 tumor cells. *FEBS Letters*, **1999**, *445*, 165-168.
19. Anand, P.; Thomas, S. G.; Kunnumakkara, A. B.; Sundaram, C.; Harikumar, K. B.; Sung, B.; Tharakan, S. T.; Misra, K.; Priyadarsini, I. K.; Rajasekharan, K. N.; Aggarwal, B. B. Biological activities of curcumin and its analogues (conjeners) made by man and mother nature. Biochem. Pharmacol., **2008**, *76*, 1590-1611.
20. Anand, p.; Kunnumakkara, A. P.; Newman, R. A.; Aggarwal, B. B. Bioavailability of curcumin, problems and promises. *Mol. Pharmaceutics*, **2007**, *4*, 807–818.
21. Jain, D. Curcumin nanoparticles, preparation, characterization, and antimicrobial activity. *J. Agric. Food Chem.*, **2011**, *59*, 2056–2061.
22. Ghosh, D.; Choudhury, T. S.; Ghosh, S.; Mandal, A. K.; Sakar, S.; Ghosh, A.; Saha, K. D.; Das, N. Nanocapsulated curcumin: Oral chemopreventive formulation against diethylnitrosamine induced hepatocellular carcinoma in rat. *Chemico-Biological Interactions*, **2012**, *195*, 206-214.
23. Liu, j.; Xu, L.; liu, C.; Zhang, D.; Wang, S.; Deng, Z.; Lou, W.; Xu, H.; Bai, Q.; Ma, J. Preparation and characterization of cationic curcumin nanoparticles for improvement of cellular uptake**.** *Carbohydrate Polymers*, **2012**, *90*, 16-22.
24. Manju, S.; Sreenivasan, K. Gold nanoparticles generated and stabilized by water soluble curcumin–polymer conjugate: Blood compatibility evaluation and targeted drug delivery onto cancer cells. *J. Colloid and Interface Science*, **2012**, *368*, 144-151.
25. Wang, X.; Jiang, Y.; Wang, Y-W.; Huang, M-T.; Ho, C-T.; Huang, Q. Enhancing anti-inflammation activity of curcumin through O/W nanoemulsions. Food Chemistry, **2008**, *108*, 419-424.
26. van de Luijtgaarden, W.; Milano, F.; Guha, S.; Krishnadath, K. K. Nano-Curcumin as a Promising New Therapy for Treatment of Esophageal Adenocarcinoma. *Gastroenterology*, **2011**, *140*, S-223-S-224.
27. Singh, D. K.; Jagannathan, R.; Khandelwal, P.; Abraham, P. M.; Poddar, P. *In situ* synthesis and surface functionalization of gold nanoparticles with curcumin and their antioxidant properties: an experimental and density functional theory investigation. *Nanoscale* **2013**, *5*, 1882-1893.

28. Gangwar, R. K.; Dhumale, V. A.; Kumari, D.; Nakate, U. T.; Gosavi, S. W.; Sharma, R. B.; Kale, S. N.; Datar, S. Conjugation of curcumin with PVP capped gold nanoparticles for improving bioavalability. Mat. Sci. Eng. C, **2012**, *32*, 2659-2663.

29. Jayaprakasha, G. K.; Rao, L. J. M.; Sakariah, K. K. Improved HPLC method for the determination of curcumin, demethoxycurcumin, and bisdemethoxycurcumin. J. Agric. Food. Chem. **2002**, *50*. 3668-3672.

30. Jain, P. K.; El-Sayed, J. M. Surface Plasmon Resonance Sensitivity of Metal Nanostructures: Physical Basis and Universal Scaling in Metal Nanoshells. *J. Phys. Chem. C*, **2007**, *111*, 17451–17454.

31. Yingjie, L.; Te, B.; Jie, O. Synthesis of some curcumin analogues under ultrasound irradiation. *Advanced Materilas Research* **2011**, *332-334*, 1623-1626.

.