Facile Synthesis of Curcumin and Curcuminoid-like Derivatives at Microwaves

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Seven curcumin derivatives were synthesized by an ecological method, in a microwave field. The compounds obtained were purified and characterized by means of elemental analysis, UV-VIS, fluorescence, IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy. Structure-property relationship in the β-diketone derivatives are discussed with respect to the structure and nature of the substituents for possible applications in optical sensors and luminescent materials.

Keywords: curcumin derivatives, microwave, β-diketone, fluorescent properties, luminescent materials

Curcumin is a strong antioxidant that offers a good protection against injuries caused by free radicals and it also possesses antibacterial, antiseptic [1-4] and strong anti-inflammatory and anticancer properties [5-8]. The literature on this matter reported several acetylacetone derivatives, compounds with improved photochemical properties, for non-conventional applications. Thus, the compounds of β-diketone derivatives have applications in the field of labeling, for the identification of heavy metals or nitroderivatives from an aqueous medium [9-11], photocatalysis (TiO_2-curcumin) [12], sensors [13,14] and lasers [15,16]. The β-diketones are the most suitable for obtaining luminescent materials due to the large delocalization of π electrons that contributes to the strong absorption bands [17] and for obtaining high emission peaks and quantic efficiency. However, factors such as low stability under high temperature or humidity conditions and low resistance to light of the β-diketone compounds led to the search of new methods for dyestuffs typing by their incorporation in mesoporous materials [18], gel silica [19] or organic modified silicates [20], polymers [21], and zeolites [22]. Based on these considerations, this study is intended to provide data on extending the range of curcumin derivatives by a simple eco-friendly method.

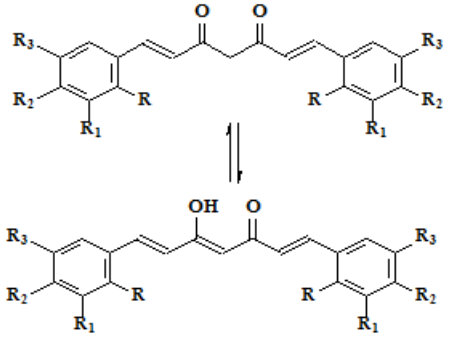
Experimental part

The present paper illustrates experimental data regarding synthesis and characterization of seven curcumin compounds (fig.1) with β-diketone structure obtained under microwave irradiation of a mixture of further components: boron trioxide, acetylacetone, tri-butyl borat, dodecylamine and an aromatic aldehyde as: 4-hydroxy-, 4-methyl-, 3-methoxy-4-hydroxy-, 4-acetamido-, 4-N,N-dimethyl-, 4-N,N-diethyl-benzaldehyde and unsubstituted benzaldehyde.

All chemicals used were of laboratory reagent grade and were obtained from Merck (Germany) and Aldrich (USA). Boron trioxide (B_2O_3), acetylacetone, tri-butyl borate, aromatic aldehydes, dodecylamine, acetic acid, ethyl-acetate, methanol (MeOH), and hydrochloric acid (0.1 N) were used as they were received without further purification.

General method of curcumin derivatives synthesis

A mixture of B_2O_3 (4 mmol), acetylacetone (8 mmol) and tri-butyl borate (3.2 mmol) was introduced in a porcelain capsule and was kept in a microwave oven at 30% power for 10 min. After the formation of the boron complex of acetylacetone, aromatic aldehyde (7 mmol) and dodecylamine (0.162 mmol) were added. The reaction components were mixed using a glass rod and then it was irradiated in a microwave oven for 20-60 minutes at 10-50% power. To the reaction mixture which was removed from the oven and cooled to the room temperature was added 10% acetic acid solution (50 mL) and the reaction mass was kept cold overnight. The obtained suspension was filtered off, and the product was washed with cold water and dried. The obtained product was purified by dissolution and recrystallized from a mixture of ethyl-acetate : methanol = 3:2 (v/v). Yellow to red powders were obtained in 75-87% yields (table 1).



cc1: R, R_1, R_2, R_3 = H
cc2: R, R_1, R_3 = H; R_2 = OH
cc3: R, R_2 = CH_3; R_1, R_3 = H
cc4: R, R_1 = H; R_2 = OH; R_3 = OCH_3
cc5: R, R_1, R_3 = H; R_2 = $NHCOCH_3$
cc6: R, R_1, R_3 = H; R_2 = $N(CH_3)_2$
cc7: R, R_1, R_3 = H; R_2 = $N(C_2H_5)_2$

Fig.1 Structural formula of curcumin derivatives

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Table 1
CURCUMIN DERIVATIVES OBTAINED IN THE MICROWAVE FIELD AND RESULTS OF ELEMENTAL ANALYSIS

Compound	Molecular formula	Melting point, ^{0}C	Color	Yield %	Elemental analysis, %		
					C found (calculated)	H found (calculated)	N found (calculated)
cc1	$C_{19}H_{16}O_2$	129-132	light yellow	75	82.69 (82.58)	5.75 (5.84)	-
cc2	$C_{19}H_{16}O_4$	176-177	yellow	78	73.85 (74.09)	5.36 (5.23)	-
cc3	$C_{21}H_{20}O_2$	140-143	yellow	87	83.03 (82.86)	6.86 (6.62)	-
cc4	$C_{21}H_{20}O_6$	181-183	orange	83	68.26 (68.47)	5.31 (5.47)	-
cc5	$C_{23}H_{22}N_2O_4$	183-185	dark orange	84	70.55 (70.83)	5.82 (5.68)	6.98 (7.18)
cc6	$C_{23}H_{26}N_2O_2$	150-152	red	80	76.29 (76.31)	7.51 (7.16)	7.62 (7.74)
cc7	$C_{27}H_{34}N_2O_2$	135-138	red	82	77.81 (77.58)	8.03 (8.20)	6.95 (6.70)

Table 2
R_f VALUES FOR CURCUMIN DERIVATIVES

		Rf value						
Compound		**cc1**	**cc2**	**cc3**	**cc4**	**cc5**	**cc6**	**cc7**
Mobile phase	C_6H_{14}:$C_2H_4O_2$ 3:1	0.6	0.56	0.58	0.45	0.73	0.62	0.61
	C_6H_6:C_2H_5OH:C_6H_{14} 27:11:12	0.93	0.72	0.97	0.84	0.88	0.98	0.96
Stationary phase Silica gel Merck 60 F254	**Spot color (UV)**	yellow	yellow	yellow-green	yellow-orange	orange	orange	red

Synthesis reactions were conducted into a microwave oven PLATINUM (Power - 1000 W; Frequency -2.45 GHz; Volume - 31 L, multimode cavity), the power of the microwaves being adjusted by modifications of the irradiation time and microwaves power.

Purified substances were subject for elemental analysis. Experiments were made with a Carlo Erba M 1106 apparatus. Results obtained are presented in table 1 and are in good agreement with those theoretically calculated. UV-VIS absorption spectra were acquired for solutions in methanol at $3 \cdot 10^{-4}$ mol/L concentrations, at 25± 0.5^{0}C, in rectangular quartz cuvettes with a thickness of 1 cm, in the range 350-650 nm using an UV-Vis-NIR Jasco V-570 spectrometer; fluorescence spectra were recorded for solutions in methanol at $1 \cdot 10^{-5}$ mol/L concentrations with a JASCO FP 6500 spectrofluorimeter, at 25^{0}C, using 10 mm path-length quartz cuvettes for liquids or the device for solid samples, at an excitation wavelength of 435 nm; IR spectra were registered in solid samples on a Jasco FT-IR 6300 spectrometer equipped with a Specac ATR Golden Gate (KRS5 lens), in the 400-4000 cm^{-1} range (32 accumulations at a resolution of 4 cm^{-1}); ^{1}H-NMR and ^{13}C-NMR spectra were registered on a BRUKER AVANCE 400 MHz spectrometer at 25^{0}C, as solutions in $CDCl_3$ and tetramethylsilane as the internal reference.

Results and discussions

In this study seven derivatives of acetylacetone (**cc1-cc7**) were obtained by a simpler and cheaper method compared to the classic one in solvent. A series of parameters for the condensation reaction were investigated: the molar ratio of reactants, the catalyst, microwaves power and irradiation time. The compounds synthesized at microwaves were obtained in high yields and with shorter time of reaction, the results being presented in table 1.

Purity of synthesized curcumin compounds and testing during synthesis were controlled by thin layer chromatography, thus for each compound were established stationary and mobile phases. Solubility of samples was done in methyl alcohol at a concentration of 0.25% and the identification of individual spots was made by direct visualization of colored spots, after their exposure to ultraviolet light (365 nm). R_f values for all compounds are presented in table 2.

There are studies [23] that confirm the high level of conjugation throughout the molecular structure of curcumin. The first conjugation is into the keto-enolic system of di-keto conformers and the second is cis-trans conjugation to the heptadiene system, also involving phenyl groups with various auxochromes. All these tautomeric states and their interaction with solvents of different polarities influence directly the spectral absorption and fluorescence emission properties. Analyzing the UV absorption spectra result that for all the compounds recorded in the same type of solvent (table 3), the transition corresponding of $\pi \rightarrow \pi^*$ type from about 300 nm was a bathochromic shift ($\Delta \approx$ 87-109 nm), the peaks were strongly influenced by the chemical structure, the conjugation with auxochromes characterized by low levels of extinction. A further factor that increases the absorption peaks for unsaturated carbonyl compounds was double bonds from benzene rings by extending conjugation on the entire molecule. Compound **cc2**, which has the auxochrome hydroxyl group with electron donor effect and compound **cc6** containing an auxochrome with inductive effect, repulsive electron records a bathochromic shift more pronounced due to a transition energy reduction, as a result of increased excitability π electrons. Due to the presence of the second auxochrome OCH_3 respectively, compound **cc4** shows bathochromic and hyperchromic effects which depend on solvent polarity. Compounds **cc4** and **cc7** show more pronounced bathocrome and hyperchrome effects due to electron donor auxocroms that produce an increase of electron density, both on aromatic rings and on the entire molecule.

In the case of compound **cc4**, the results of electronic spectra recorded in different solvents show the phenomenon by positive solvatochromism. In all studied cases a bathochromic shift of the maximum absorption was recorded by increasing the polarity of the solvent. The highest value was obtained by recording the electronic spectrum in a methanol solution, due to the possibility of the dye to form hydrogen bonds with the solvent.

Table 3

UV–Vis ABSORPTION BANDS OF CURCUMIN ANALOGUES IN DIFFERENT SOLVENTS

Compund	Solvent (polar)														
	CCl_4 (1.6)			CH_2Cl_2 (3.1)			THF (4)			CH_3OH (5.1)			DMF (6.4)		
	λ_{max}, nm	A	lgλ	λ_{max}, nm	A	lgλ	λ_{max} nm	A	lgλ	λ_{max} nm	A	lgλ	λ_{max} nm	A	lgλ
1	389	1.41	1.3129	392	1.39	1.3067	390	1.31	1.2807	389	1.34	1.2906	394	1.36	1.2971
2	416	1.38	1.3035	415	1.29	1.2741	415	1.49	1.3371	415	1.31	1.2808	419	1.40	1.3098
3	399	1.33	1.2874	401	1.42	1.3160	399	1.30	1.2774	400	1.38	1.3035	411	1.28	1.2706
4	418	1.37	1.3003	421	1.40	1.3098	424	1.49	1.3371	425	1.56	1.3571	431	1.46	1.3282
5	415	1.39	1.3067	415	1.30	1.2774	419	1.43	1.3191	413	1.32	1.2841	424	1.48	1.3341
6	408	1.34	1.2906	415	1.32	1.2841	410	1.27	1.2672	413	1.29	1.2740	400	1.23	1.2532
7	484	1.74	1.4050	499	1.68	1.3900	487	1.62	1.3737	498	1.42	1.3160	481	1.47	1.3312

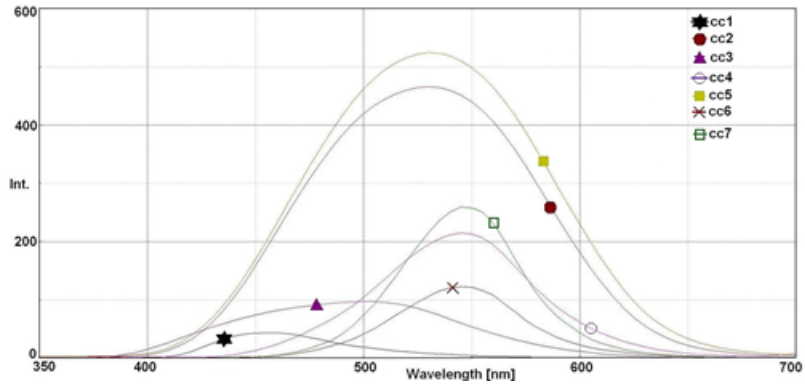

Fig.2. Fluorescence spectra of curcumin derivatives in methanol, 1.10^{-5}mol/L

Fluorescence was due mainly to the appearance of polar mesomer structures in the interaction with bright radiation. The samples were measured at 435 nm excitation wavelength, and the highest intensities were recorded for derivates **cc2** and **cc5** at a wavelength of 530 nm. Of the seven acetylacetone derivatives, compounds **cc4** and **cc6** show the largest Stokes displacements (Δ = 120 nm, respectively 132 nm) with bathofluor displacement (fig. 2).

There are literature studies [24] that show fluorescence emission spectra being influenced, on the one hand, by the hydrogen bonds established between the protic solvent and dyestuff molecules, which may explain the higher fluorescence intensities for compounds **cc2** and **cc5**, and on the other hand, the electron load has an important role on the structure of the molecule due to the p-π conjugation effect. This can be observed by the bathofluor displacement in the case of compounds **cc4** and **cc6**. The existence of a single peak indicates a high purity color emission which gives the opportunity of using such compounds and in unconventional fields.

The analysis of the FTIR spectra shows (fig. 3) the stretching vibration of OH groups involved in hydrogen bonds located at 3350-3245 cm^{-1} and at 3010-3050 cm^{-1} was found the aromatic C-H stretching vibration. The absorption bands range around 1740 cm^{-1} due to hydrogen bonds, while the intense band located at 1630-1650 cm^{-1} corresponds to the stretching vibration of C=O, characteristic of α,β-unsaturated compounds.

Depending on the auxochromes grafted on the aromatic rings, characteristic signals are obtained. Thus, the spectrum of compound **cc5** shows characteristic absorption bands around 1510-1585 cm^{-1} due to amide stretching vibrations, while compound **cc4** shows the absorption bands around 2942 cm^{-1}, attributed to the stretching vibration of methylene group. The absorption bands around 1262-1287 cm^{-1} correspond to the stretching vibration of C-N and are present in the spectra of compounds **cc5**, **cc6** and **cc7**.

The signal attribution in nuclear magnetic resonance spectrum ^{1}H-NMR spectra was done considering intensity, multiplicity and shift values verified with the reported literature values [25,26].

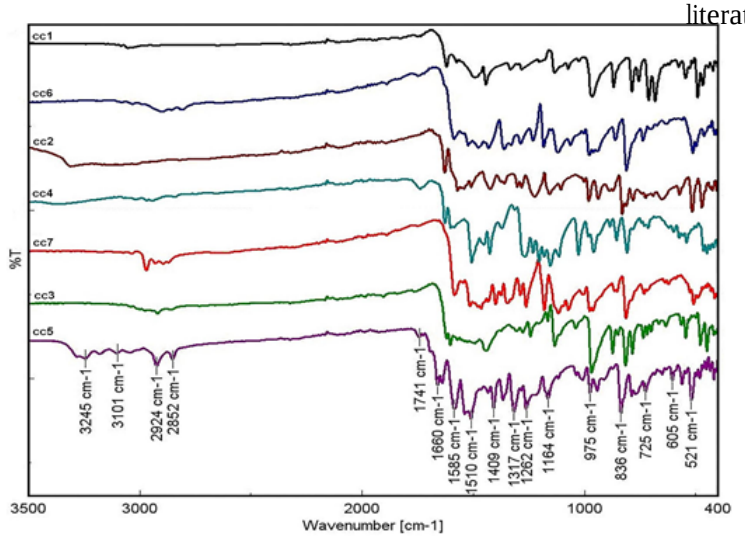

Fig.3. FTIR-ATR spectra of curcumine derivatives

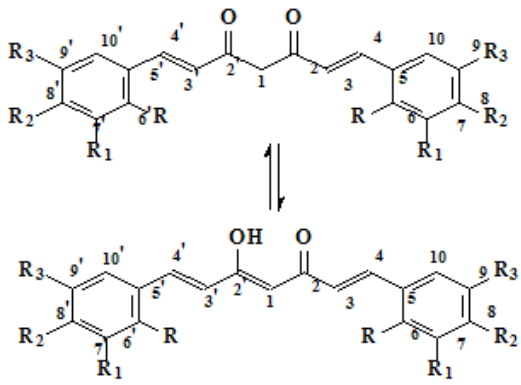

Fig. 4. Atoms localization for NMR spectra

Compound	Chemical shift δ, ppm (multiplicity)						
	cc1	cc2	cc3	cc4	cc5	cc6	cc7
H1	5.86(s)	5.63(s)	5.80(s)	5.88 (s)	5.64(s)	5.65(s)	5.62
H2	-	15.55(d)	-	-	15.46(s)	15.5(d)	15.69(d)
H33'	6.66(d)	6.36(d)	6.54(d)	6.49 (d)	6.41(d)	6.42(d)	6.29(d)
H44'	7.69(d)	7.57(d)	7.95(d)	7.61 (d)	7.58(d)	7.57(d)	7.57(d)
H66'	7.58(d)	7.44(d)	7.52(t)	7.13(dd)	7.48(d)	7.54(d)	7.53(d)
H77'	7.42(m)	7.26(s)	7.25(s)	7.05(d)	7.26(s)	7.26(s)	7.26(s)
H88'	7.40(d)	6.85(d)	-	-	-	-	-
H99'	7.39(m)	-	7.04(d)	-	-	7.34(s)	6.67(d)
H1010'	7.56(d)	-	-	7.26(d)	-	-	-
OH	-	5.63(s)	-	5.80(s)	-	-	-
OCH3	-	-	-	3.95(s)	2.17(s)	-	-
CH3 (orto) **CH3** (para)	-	-	2.45(d) 2.37(s)	-	-	- 2.17(s)	- 1.20(d)
NH	-	-	-	-	2.20(s)	-	-
CH2	-	-	-	-	-	-	2.15(m)

s=singlet, d=doublet, dd=doublet of doublet, m=multiplet

Table 4
RESULTS FOR ^{1}H-NMR SPECTROMETRY

Due to the symmetry of the structure of the β-diketone molecule to methylene group, the positions 2-2', 3-3' and 4-4' were equivalent and have chemical shifts values near (fig.4).

Methylene protons in the center of the molecule were situated at a chemical shift value of δ =5.62-5.88 ppm as a singlet. The corresponding protons 3-3' and 4-4' of carbon atoms of the double bonds of the diketone skeleton were situated at a shift value δ =6.29-6.66 ppm and δ =7.57-7.95 ppm, respectively, as well defined and intense doublets. ^{1}H-NMR shows that the protons of aromatic rings from the acetylacetone derivates were found at a shift values situated at δ =6.67-7.58 ppm depending on the presented substituent's. Thus at the compound **cc7** it can be seen that, due to higher electronic density as a result of the effect of conjugation occurs shielding those protons, leading to lower chemical shift values (table 4).

Table 5
RESULTS FOR ^{13}C-NMR SPECTROMETRY

Compound	Chemical shift δ, ppm						
	cc1	cc2	cc3	cc4	cc5	cc6	cc7
C1	101.81	-	101.85	101.19	101.10	101.29	-
C2	183.31	-	183.46	183.26	197.70	197.70	-
C33'	124.06	-	124.00	122.88	119.72	122.60	-
C44'	140.65	-	140.22	140.56	168.44	138.33	-
C55'	128.94	-	131.67	127.69	128.81	117.60	-
C66'	128.13	-	137.99	109.62	139.46	130.52	130.80
C77'	130.12	-	131.10	146.78	131.14	129.90	129.73
C88'	134.98		137.88	147.84	121.66	146.98	

C99'	130.12	-	126.17	114.83	130.90	129.62	-
C1010'	128.13	-	127.16	121.77	139.08	130.25	-
OCH3	-	-	-	55.97	-	-	-
CO	-	-	-	-	29.58	-	-
CH3 (orto)	-	-	21.34	-	-	-	-
CH3 (para)			19.77		14.13	27.08	12.29
CH2	-	-	-	-	-	-	26.86

Table 5
CONTINUATED

The results of the NMR studies form literature show with certainty that curcumin exists in solution as keto"enol tautomers [27]. With the aid of ^{13}C-NMR spectra ketone groups were found at a shift value of δ = 197.70 ppm.

The presence of these groups, was confirmed by IR spectra at 1630-1650 cm^{-1}, corresponds to the stretching vibration of C=O, characteristic of α,β-unsaturated compounds and by means of ^{1}H-NMR spectra by the absence of the signal at δ = 15.50 ppm. Considering these results, we can say that the compounds **cc1**, **cc3** and **cc4** were found in the keto tautomeric form. All the values obtained for the chemical shifts confirm the structures proposed for the studied compounds (table 4 and 5). These results indicate the seven analogs were successfully synthesized and characterized with yield and purity higher.

Conclusions

The microwave irradiation was appropriate method for obtaining acetylacetone derivatives as an energy-saving process and a useful method belonging to green chemistry. Compared to the classical method used for obtaining acetylacetone derivatives, microwave synthesis has the following advantages: reduced reaction time, higher yield and higher purity of the final product, operation conditions without solvent. Seven compounds were obtained by this method, three structures of which were not cited in the literature. All the structures of the synthesized compounds were characterized by elemental analysis, fluorescence emission/ adsorption studies, UV-Vis, FTIR, ^{1}H-NMR, ^{13}C-NMR spectral studies. Structural analysis confirms structures of β-diketone compounds derived synthesized.

The obtained curcumin derivatives will be used to produce high efficiency luminescent hybrid systems for photoactive and signaling coatings.

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