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Curcumin analogues for possible cancer treatment A QSAR and partial ordering study

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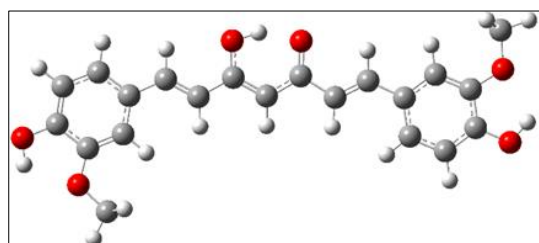
Abstract

The possible effect of curcumin as a potential natural cancer treatment drug has been intensively discussed. In the present study the probabilities of a series of curcumin analogues to possess potential as antineoplastic, prostate cancer treatment and anticarcinogenic agents has been studied theoretically applying a selection of quantitative structure-activity relation and absorption, distribution, metabolism, and excretion (ADME) approaches. From spectroscopic studies it is evident that these compounds can be found in both enol and diketo forms, the former in general the more predominant in non-polar solvents, whereas in polar solvents, like water an increasing amount of the diketo form can be noted. Hence, the probabilities for both the enols and diketo forms to possess the above-mentioned effects were studied. In most cases the enol form shows the highest probabilities for being effective although the differences are not significant. Thus, it is suggested to look at the sum of effects of the keto and the enol forms in relation to the possible therapeutic effects of the compounds here studied.

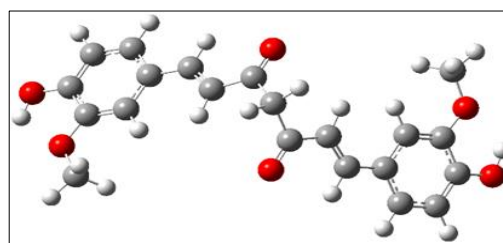
Keywords: Curcumin; Curcuminoids; Antineoplastic effects; Prostate cancer treatment; Anticarcinogenic effects

1. Introduction

Curcumin ((1E,6E)-1,7-Bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione; CAS 458-37-7) (Fig. 1) is a natural product extracted from Turmeric (*Curcuma longa*) of the ginger family. Curcumin has over the years been reported to have a variety of positive health effects among others anti-inflammatory and anti-carcinogenic effects [1], especially the possibly effect on prostate cancer has received attention [2]. The presence of extra methoxy groups have been shown to have beneficial effects [1, 3]. In addition to curcumin, small amounts of demethoxy- and didemethoxycurcumin are also found. It is interesting to test their potential as drugs.



Enol form



Diketo form

Figure 1 a) Enol and b) diketo forms of curcumin

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The actual use of curcumin as a drug has been rather limited [4] due to a rather low solubility (3.12 mg/L [5], and bioavailability [6]. Studies by several groups showed that curcumin doses administrated orally gave exceptionally low levels of 0.006(0.005 μ g /mL [7], 0.4–3.6 μ M [8], 51.2 ng/mL [9] in serum, 11.1 ± 0.6 nmol/mL [10] in plasma and 7-20 nmol/g [11] (in colorectum).

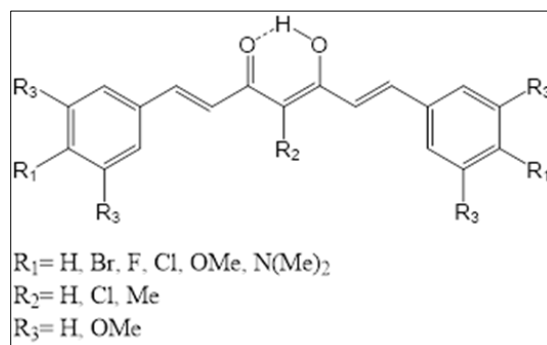


Figure 2 General substitution pattern for the curcumin analogues (enol form)

Table 1 Substitution patterns for the curcumin analogues

ID	R1	R2	R3	ID	R1	R2	R3
H1	H	H	H	OMe1	H	H	OMe
H2	Br	H	H	OMe2	Br	H	OMe
H3	F	H	H	OMe3	F	H	OMe
H4	Cl	H	H	OMe4	Cl	H	OMe
H5	OMe	H	H	OMe5	OMe	H	OMe
H6	N(Me) ₂	H	H	OMe6	N(Me) ₂	H	OMe
H7	H	Cl	H	OMe7	H	Cl	OMe
H8	Br	Cl	H	OMe8	Br	Cl	OMe
H9	F	Cl	H	OMe9	F	Cl	OMe
H10	Cl	Cl	H	OMe10	Cl	Cl	OMe
H11	OMe	Cl	H	OMe11	OMe	Cl	OMe
H12	N(Me) ₂	Cl	H	OMe12	N(Me) ₂	Cl	OMe
H13	H	Me	H	OMe13	H	Me	OMe
H14	Br	Me	H	OMe14	Br	Me	OMe
H15	F	Me	H	OMe15	F	Me	OMe
H16	Cl	Me	H	OMe16	Cl	Me	OMe
H17	OMe	Me	H	OMe17	OMe	Me	OMe
H18	N(Me) ₂	Me	H	OMe18	N(Me) ₂	Me	OMe
OH1	OH	H	H	OH2	OH	H	OMe

In the present theoretic study curcumin and a series of curcumin analogues have been investigated with the aim to test compounds that can easily be synthesized, but also to test how simple substituents can change the structure. Focus is on the possible positive effect on prostate cancer treatment as well as general anti-carcinogenic and anti-neoplastic

effects. The theoretical study enables the screening of a large number of compounds. Thus, the probabilities that the studied compounds possess or don't possess a given effect have been calculated for both the enol and diketo forms. The possible effects of the two forms have been compared as function of the substitution pattern. Subsequently, partial ordering was applied to verify the most beneficial substitution pattern assuming a wish for an optimal combined effect of, e.g., anti-neoplastic, anti-carcinogenic and prostate cancer treatment. Eventually the ADME characteristics are discussed for compounds with selected substitution patterns. In Table 1 and Fig. 2 the structures of the investigated compounds are summarized. In all cases, both the enol and the diketo forms were studied, the general formula being depicted in Fig. 2. In the following, the enol and diketo form will be denoted with an e and k prescripts respectively, as e.g., eH1 and kH1.

In addition, three isocurcumines (Fig. 3) have also been investigated.

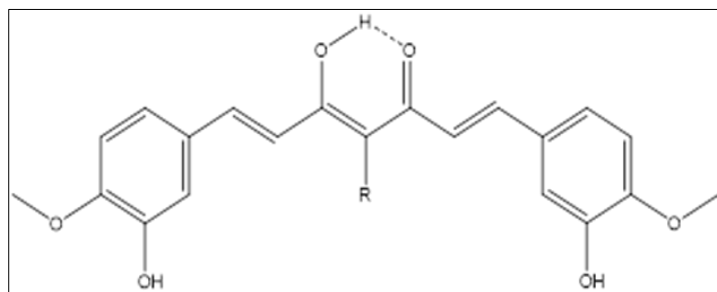


Figure 3 Isocurcumines. iC1: R = H, iC2: R = Cl and iC3: R = Me

As the amounts of enol and keto-forms matter, NMR and UV experiments have been performed to investigate this for the new isocurcumins and experiments have been done to get an impression of the importance of the solvent.

2. Methods

2.1. Quantitative Structure-Activity Relationships (QSAR)

Structural QSAR calculations including energy considerations were calculated applying the semi-empirical AM1 method as implemented in the OASIS software [12]. The probabilities for the compounds to possess (Pa) or not to possess (Pi) a given effect were calculated using the PASS Online software (newest online version) [13] and the Physico-chemical characteristics as well as Pharmacokinetic calculations were estimated applying the PK-explorer of the Percepta software from ACD/Labs [14]. An evaluation of the druglikeness of the different structures, based the Lipinski, Ghose, Veber, Egan and Muegge methods was carried out by the Swiss ADME software [15]. In all cases detailed description of the models are outside the scope of the present study and are available in the given references and will thus not be repeated here. In all cases, SMILES notations for the single compounds were used as input in the calculations.

2.2. Density Functional Calculations (DFT)

Density functional theory calculations (DFT) with the standard B3LYP [16, 17] approach have been carried out by using the Gaussian16 software [18]. The studied molecules were freely optimized either in the gas phase or in the solvent using the 6-311++G (2d,p) basis set. It has been shown that the B3LYP functional is suitable for studying both inter- and intramolecular hydrogen bonds if it is conducted with a basis set including diffuse functions [19,20].

For simulation in solution, e.g., water, chloroform or DMSO the Integral Equation Formalism Polarizable Continuum Model (IEFPCM) [21] was used.

2.3. Partial ordering

In its basis partial ordering appears pretty simple as the only mathematical relation among the objects is " \leq " [22,23]. The basis for a comparison of objects, here curcumin analogues, characterized by the subset of indicators describing their probabilities for being an active prostate cancer drug as well as the probabilities for exhibiting anti-neoplastic and anti-carcinogenic activity. These indicators, r_j , characterizes the single compounds. Thus, characterizing one compound (x) by a set of indicators $r_j(x)$, $j = 1, \dots, m$, where m is the number of indicators, can be compared to another compound (y), characterized by the indicators $r_j(y)$, when

$$r_j(y) \leq r_j(x) \text{ for all } j = 1, \dots, m \quad (1)$$

Eq. 1 is a very hard and strict requirement for establishing a comparison. It demands that all indicators of x should be better (or at least equal) than those of y . Further, let X be the subset of compounds included in the analyses, x will be ordered higher (better) than y , i.e., $x > y$, if at least one of the indicator values for x is higher than the corresponding indicator value for y and no indicator for x is lower than the corresponding indicator value for y . On the other hand, if $r_j(x) > r_j(y)$ for some indicator j and $r_i(x) < r_i(y)$ for some other indicator i , x and y will be called incomparable (notation: $x \parallel y$) expressing the mathematical contradiction due to conflicting indicator values. A set of mutual incomparable objects is called an antichain. When all indicator values for x are equal to the corresponding indicator values for y , i.e., $r_j(x) = r_j(y)$ for all j , the two objects/nations will have identical rank and will be considered as equivalent, i.e., $x \sim y$. The analysis of eq. 1 results in a graph, the Hasse diagram. Hasse diagrams are unique visualizations of the order relations due to eq. 1.

2.3.1. The Hasse diagram

The eq. 1 is the basic for the Hasse diagram technique (HDT) [22, 23]. Hasse diagrams are visual representation of the partial order. In the Hasse diagram comparable objects are connected by a sequence of lines [24-26].

2.3.2. The more elaborate analyses

In addition to the basic partial ordering tools some more elaborate analyses have been used including average ranks [27-29] and sensitivity analysis [23,30], the latter gives an insight in the relative importance of the included indicators [23,30]. For detailed information on the single tool, the cited literature should be consulted as a detailed description is outside the scope of the present paper.

2.3.3. Software

All partial order analyses were carried out using the PyHasse software [30]. PyHasse is programmed using the interpreter language Python (version 2.6). Today, the software package contains more than one hundred specialized modules and is available upon request from the developer, Dr. R. Bruggemann.

3. Results and discussion

3.1. Structure

Curcumin and its derivatives may exist as both an enol and a diketo-form (see Fig. 1). The structure of the enol-form has a strong intramolecular hydrogen bond, whereas the diketo-form, although traditionally drawn like Fig. 1b, is more on a trans-like form as seen in Fig. 4

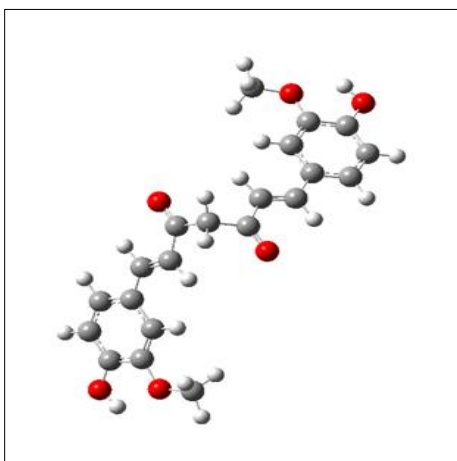


Figure 4 Calculated structure of the diketo-form of curcumin

3.2. Diketo-enol ratio

The ratio between the enol and the diketo-form depends on the substituent at C-4 and on the polarity of the solvent. Large alkyl substituents and polar solvents increase the amount of diketo-form [31]. The amount of the diketo-form for

curcumin in water/ethanol mixture showed a predominance of the keto form in 90% water [32]. A similar experiment done on eOMe5 also showed an increase in the amount of the keto-form, when increasing the percentage of water (see Fig. S3). An NMR experiment using D₂O/DMSO-d₆ as solvent showed no keto-form [33]. This was also studied in DMSO-water buffers from pH 3 to 9 again finding no keto-form [33]. A repetition of this experiment showed at 55% water the amount of keto-form to be 18±5 % (see Suppl. Mat. Fig. S2).

In case of the isocurcumins the ratios in DMSO-d₆ were determined from ¹H NMR spectra. For the isocurcumin itself no keto-form could be detected, for the 4-chloro-derivative the keto percentage is measured as 20%, whereas for the 4-methyl-derivative, the percentage is as high as 55% (Figs. S4-S10).

Theoretical DFT calculations, B3LYP/6-311++G(2d, p) in the Polarizable Continuum Model, confirm the solvent effect, but the calculations give much lower amounts of the diketo-form (Table 2) in agreement with the NMR experiments.

Table 2 Calculated total energies (Hartree) of substituted curcumins in different solvents, B3LYP/6-311++G(2d,p)

Molecule, Total energy,	Gas phase	Water	DMSO	CHCl ₃
Curcumin-enol	-1263.977485	-1263.996225	-1263.995866	-1263.990449
Curcumin-diketo-trans	-1263.967328	-1263.987823	-1263.987534	-1263.981908
DeltaE, ha	0.010157	0.008402	0.008332	0.008541
DeltaE, kJ/mol	26.7	22.0	21.9	22.4
Chloro-curcumin-enol (H7)	-1723.594307	-	-1723.610653	-
Chloro-curcumin-diketo-trans	-1723.585394	-	-1723.606072	-
ΔE, kJ/mol	23.4	-	12.0	-
Methyl-curcumin-enol (H13)	-1303.296165	-	-1303.314579	-
Methyl-curcumin-diketo-trans	-1303.291764	-	-1303.311699	-
ΔE, kJ/mol	11.5	-	7.6	-
Butyl-curcumin-enol	-1421.392430	-	-1421.289832	-
Butyl-curcumin-diketo-trans	-1421.401257	-	-1421.282518	-
DeltaE, kJ/mol	23.2	-	19.2	-

3.3. Barrier to interconversion

The barrier to interconversion between the enol and the diketo-form is rather high, as both forms could be observed in the ¹³C NMR spectrum at low magnetic field (80 MHz NMR instrument) [33]. From a study of acetylacetone, the barrier was calculated as 62 Kcal, but with water present it reduced to ~30 Kcal [34].

3.4. Structural analysis

Curcumin and its analogue can take up a number of conformations. Thus, it can be seen that the enol form can take up many different orientations with only a small energy difference. This should facilitate the binding to a receptor. For a structural view, including the energy differences we refer to the supplementary material (Fig. S1).

3.5. Solubility

Applying the ACD Percepta software [14], the predicted value (enol form) for the solubility in the gastrointestinal tract, Sol_{GI}, to 0.11 mg/ml. The Cp(Max) was found to be 0.29 µg/mL, the oral bioavailability, F, to 96.8 % taking into account a first pass of 1.9 % and the AUC (0 - INF) (oral): 4.57 µg×h/ml for Tmax 152 min. Not surprisingly, due to the pH effect in the gastrointestinal tract, the corresponding values for the diketo form were found to be significantly lower. Thus, we find Sol_{GI} : 0.064 mg/mL, Cp(Max): 0.25 µg/mL, F: 81.3 % taking a first pass of 16 % into account and an AUC (0 - INF) (oral): 3.95 µg × h/ml for Tmax 201 min, respectively.

As evident from the ADME figures for the enol and diketo form of curcumin given above in the introduction as well as the above discussion similar differences between enol and diketo form may prevail in the case of the here investigated substances (cf. Fig. 2 and Table 1). Furthermore, it may well be expected that from a drug point of view differences between enol and diketo form will be seen as being expressed by the probabilities for the studied effect for the two forms, respectively, i.e., the possible positive effect on prostate cancer treatment, and general anti-carcinogenic and anti-neoplastic effects, respectively.

Obviously, it is possible to rank the single compounds based on the single effects. In Fig. 5 the ranking of the 3 enol and diketo forms is visualized graphically based on the probability that the compounds possess prostate cancer treatment (PCT) ability, anti-neoplastic (AnNeo) and anti-carcinogenic (AnCar) activity, respectively.

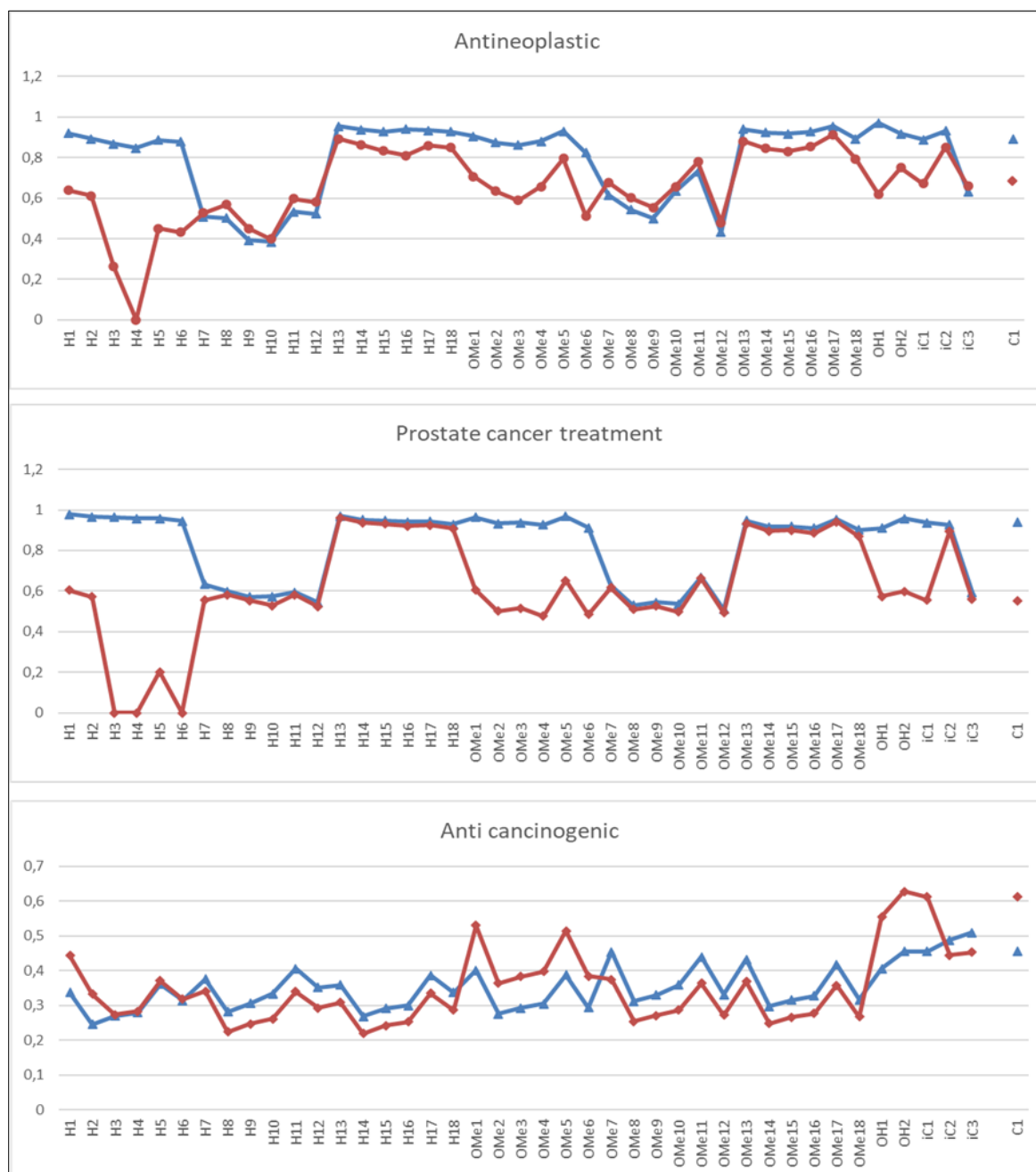


Figure 5 Ranking of the 23 enol (blue triangles) and 23 diketo (red diamonds) forms according to their calculated prostate cancer treatment (PCT) ability, anti-neoplastic (AnNeo) and anti-carcinogenic (AnCar) activity. For comparison, the values for the enol form (eC1) and the diketo form (kC1) of curcumin has been included

Immediately several interesting features become obvious. First, it is noted, that in the case of PCT and AnNeo the probabilities for the diketo forms in virtually all cases are lower or equal to those for the enol forms, whereas in the case of AnCar the probabilities for the two forms appear rather similar with no clear overall distinction between enol and diketo forms. For the PCT and AnNeo some distinct variations between the enol and diketo forms are noted. Thus, for the compounds H1 - H6 and OMe1 - OMe6, i.e., compounds with $R_2 = H$ (Fig. 2/Table 1) the diketo forms display significantly lower probabilities than the enol forms and further for the compounds H7 - H12 and OMe7 - OMe12, i.e., $R_2 = Cl$, enol and diketo forms display pronounced lower, although almost identical probabilities. Also, in the cases of the OH1, OH2 and iC1 a preference for the enol form is noted, whereas for the anticarcinogenic effect the reverse trend can be noted.

Based on the above results (Fig. 5) it is obviously rather simple to select possible compounds for, e.g., prostate cancer treatment. Although many prostate cancers are benign, they can spread. A drug that can act more generally is therefore useful. So, if we want a drug that in addition to select a compound with a high probability for being a prostate cancer treatment drug also want to maximize the selection by looking at the probabilities for being active anti-neoplastic and anti-carcinogenic, we are facing a multi-indicator system (MIS). Thus, we have a MIS consisting of 84 compounds and 3 indicators. Often such challenges are treated by combining the indicators through some arithmetic procedure, possibly including weight for the single indicators. However, such an aggregation process is obviously subject to compensation effect [35], which may lead to less transparent results. To overcome this, we apply partial ordering to analyze the MIS [22, 23]. In Fig. 6 the resulting Hasse diagram is shown displaying the best combination in the top of the diagram.

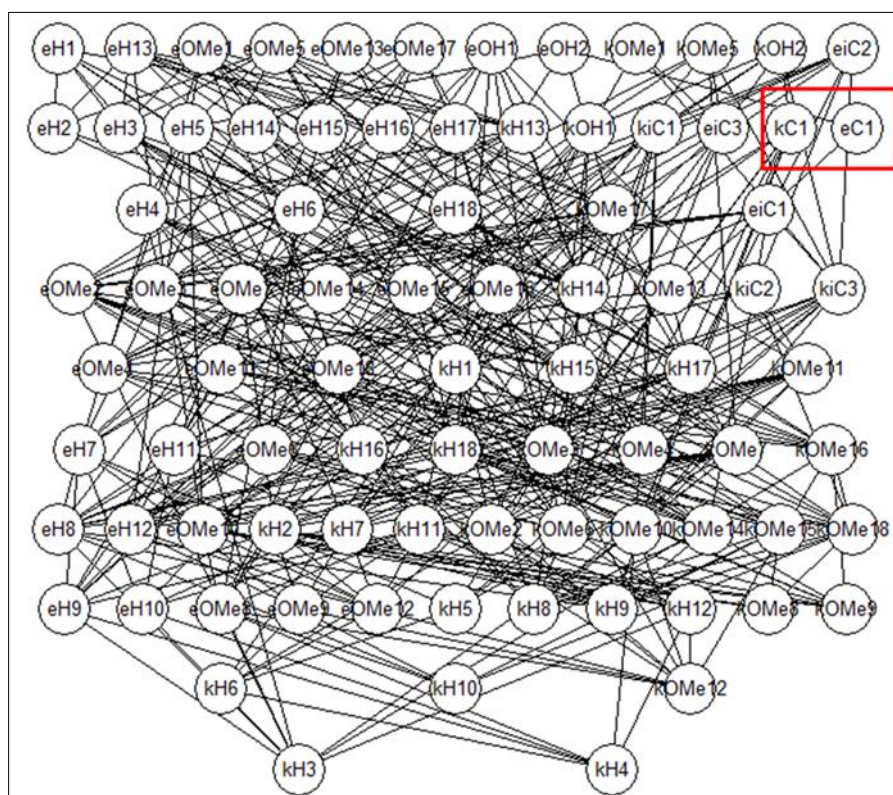


Figure 6 Hasse diagram based on probabilities for the 41 enols and 41 keto forms to be a prostate cancer treatment drug as well as the probabilities for being active anti-neoplastic and anti-carcinogenic. For comparison the enol form (eC1) and the diketo form (kC1) of curcumin has been included (red box)

The diagram is somewhat crowded, and it may be difficult to get a view of all details. To circumvent this, the average ranks of the single compounds are helpful. In Table 3 the average ranks for the 12 top ranked compounds is given.

It is noticed that the 12 compounds in the top level actually are found among the 13 highest ranks. At rank 8, the enol form of the original curcumin (eC1) is found. It should be noted that it is not necessarily a general trend that, e.g., the top level consists of the compounds with highest ranks [29]. It is further noteworthy that among the here mentioned compounds, the enol forms are dominating. Thus, the top 9 compounds, incl. the eC1, are all enols.

With reference to Fig. 5 it is not surprising that the enol forms are dominating here. However, it may seem to be in contradiction with the above discussed variation in PCT and AnNeo, where we here find eOMe5, eOMe1, kOMe5, eH1, kOMe1 and eOMe11, which all appeared to have a decreased probability for these two indicators. However, looking at the relative importance of the three indicators the answer is clear. The relative importance of the three indicators is 0.101, 1.192 and 0.707 for AnNeo, PCT and AnCar, respectively. Thus, the AnCar indicator apparently in this MIS is by far the indicator with the highest impact. Turning to the probability variation of AnCar (Fig. 5) it can be seen that for the compounds that at first sight appeared surprising to find in the top nine, relative high probabilities for AnCar are found for these compounds apparently bringing them to the top of the Hasse diagram.

Table 3 The top 12 highest ranked compounds

eOH2	1
eOMe5	2
eOMe17	3
eOMe13	4
eH13	5
eiC2	6
eOMe1	7
eH1	9
kOH2	10
kOMe5	11
eOH1	12
kOMe1	13

In addition to the calculation of the probabilities for having a given effect, here to be a prostate cancer treatment drug as well as being active as anti-neoplastic and anti-carcinogenic drugs, also the probabilities for the single compounds not exhibiting these effects, P_i , has been calculated [13]. Typically, the P_i values was found in the range from approx. 0.002 to 0.05. A partial order analysis verified that none of above top nine compounds exhibit P_i values above 0.03. Thus, the top compounds based on the P_a values, i.e. eOMe5, eOMe17 and eOMe13 are found at rank 65, 71 and 72, respective based on the P_i values, i.e., rather inferior combined probabilities for not exhibiting the studied effects.

Based on the above a selection of potential candidates can be made. To illustrate this, the top six compounds, i.e., eOH2, eOMe5, eOMe17, eOMe13, eH13 and eiC2 have been selected. In Table 3 the ADME data for the three compounds are summarized together with that of curcumin. It is noted that eOMe5 and eOMe17 are quite similar, whereas eOMe13 and eH13 differ significantly, by pronounced lower values for solubility, $C_p(\text{Max})$, AUC and oral bioavailability, F . For eOH2 F was found at an intermediary level. In the case of eOMe13 the $R_1 = H$ in contrast to eOMe5 and eOMe17 with $R_1 = \text{OMe}$. On the other hand, the variation in R_2 , i.e., H for eOMe5 and OMe for eOMe13 and eOMe17 (Table 1) apparently does not play a role.

Table 4 ADME data for the top six compounds found by the partial order analysis plus curcumin. Initial dose = 50mg

Compound	Sol _{GI} (mg/mL)	First pass (%)	Tmax (min)	Cp(Max) µg/mL	AUC(0- INF) at Tmax	F (oral) % at Tmax
eOH2	0.025	1.2	298	0.21	2.84	67.3

eOMe5	0.096	1.8	159	0.31	3.51	96.8
eOMe17	0.089	1.8	168	0.19	2.32	96.5
eOMe13	0.01	1.9	383	0.04	0.86	36.9
eH13	0.0053	1.6	405	0.02	0.33	22.8
eiC2	0.058	3.0	216	0.17	2.74	92.7
Curcumin	0.11	1.9	152	0.29	4.57	96.8

In addition to the ADME data (Table 4) it is worthwhile to have a look at the druglikeness of the three compounds. Druglikeness has been suggested by several researchers like Lipinsky, Ghose, Veber, Egan and Muegge [15]. In Table 4 the druglikeness for the three compounds are summarized. It can be seen that none of the compounds actually fulfill all five criteria. It is noted that the violation for eOMe13 according to Muegge, i.e., a XLOGP value too high is consistent with the rather low solubility of the compound. This substantiate further that eOMe13 apparently is not the optimal choice.

On the other hand, the reported data, i.e., the partial ordering in combination with the ADME (Table 3) and druglikeness estimations (Table 5) suggest eOMe5 as the preferable candidate for further experimental studies.

Table 5 Druglikeness [15] (Swiss ADME, 2019) for the top six compounds and curcumin found by the partial order analysis. For comparison, the enol and diketo form of curcumin has been included (eC1 and kC1, respectively)

Rule	eOH2	eOMe5 ¹	eOMe17 ²	eOMe13 ³	eH13	eiC2 ³	eC1 ⁴	kC1 ⁵	remarks
Lipinsky	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
Ghose	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	² Molecular refractivity >130
Veber	Yes	No	No	Yes	Yes	Yes	Yes	Yes	^{1, 2} Rotors >10
Egan	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
Muegge	Yes	yes	Yes	No	No	Yes	Yes	Yes	³ XLOGP >5

4. Conclusion

From the NMR and UV studies, the enol form is usually dominant in non-polar solvent. Substitution at C-2 with a large substituent increases the amount of the diketo-form. In addition, a polar solvent like water will increase the amount of the diketo-form. As the barrier between the enol and the keto-form is rather high, these two forms will only equilibrate very slowly. In relation to effect vs. the three forms (prostate cancer, anti-neoplastic and anti-carcinogenic) the enol form is in most cases show the highest probabilities for being effective. However, in some cases like OMe5 both the enol and the diketo forms have rather similar ranking which means, that the fact that the diketo-form increases in water apparently does not decrease its probability for being effective. In more general term it is suggested that the actual enol-keto ratio will not cause any significant variation on the possible therapeutic effects of the compounds here studied. However, some compounds will be favored as both forms show activity. It may seem somewhat surprising that the position of OH and OCH₃ groups does not seem to have any significant effect on the probability. Thus, it looks like the more the better.

Compliance with ethical standards

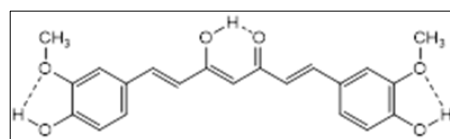
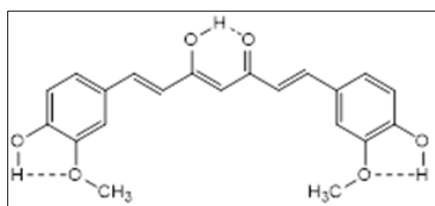
Disclosure of conflict of interest

No conflict of interest.

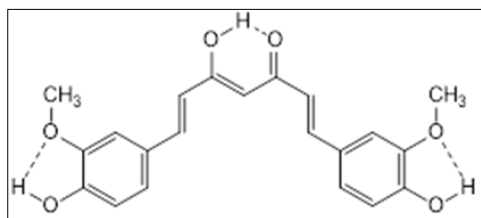
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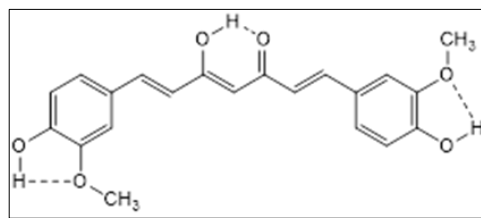
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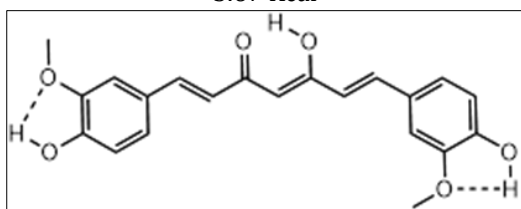
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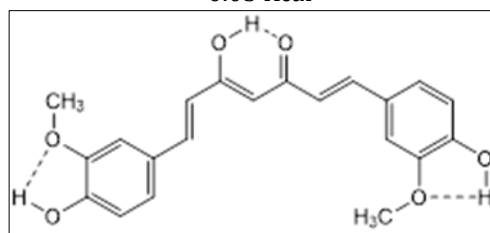
3.67 Kcal



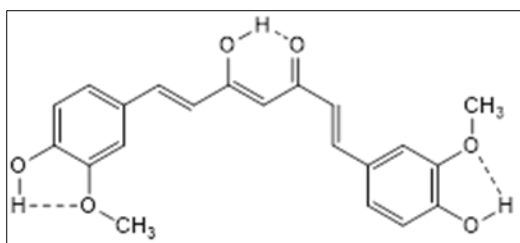
-0.05 Kcal



0.02 Kcal



2.20 Kcal



1.33 Kcal

Figure S1 Conformations of the enol form of curcumin. Geometry optimization: B3LYP/6-311++(2d,p). Values relative to the top compound

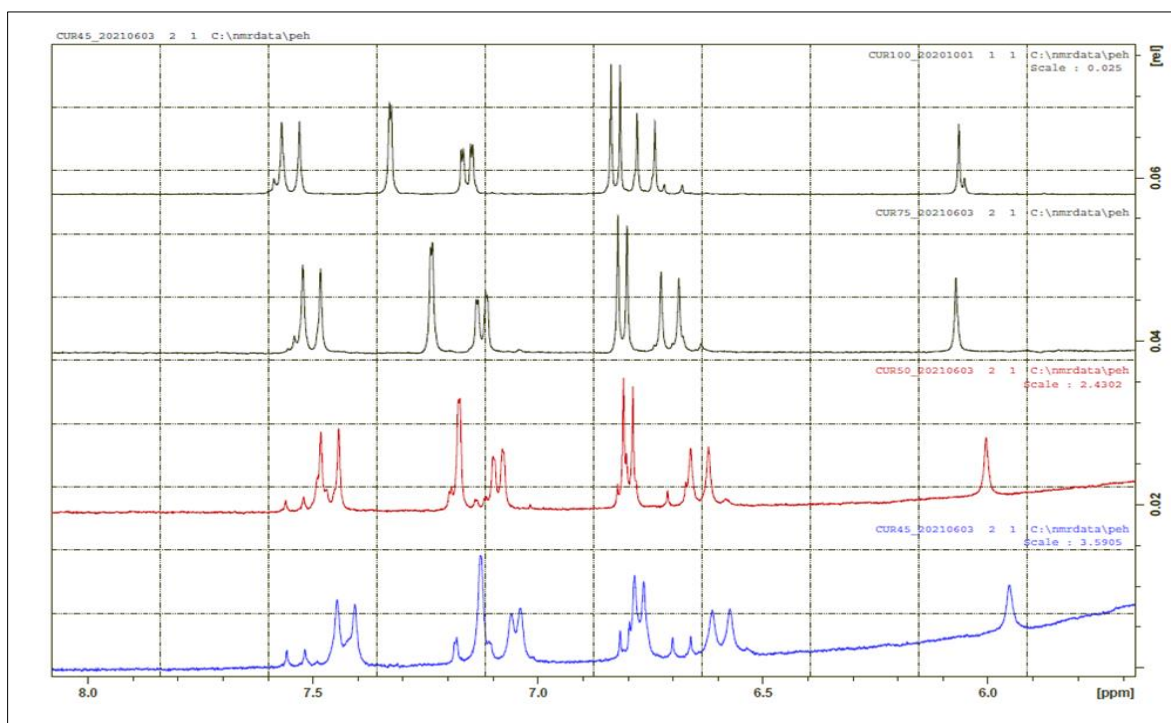


Figure S2 ^1H NMR spectra of curcumin. Top trace DMSO- d_6 , second 25% water, third 50% water, bottom 55% water. The smaller doublet are due to the keto-form

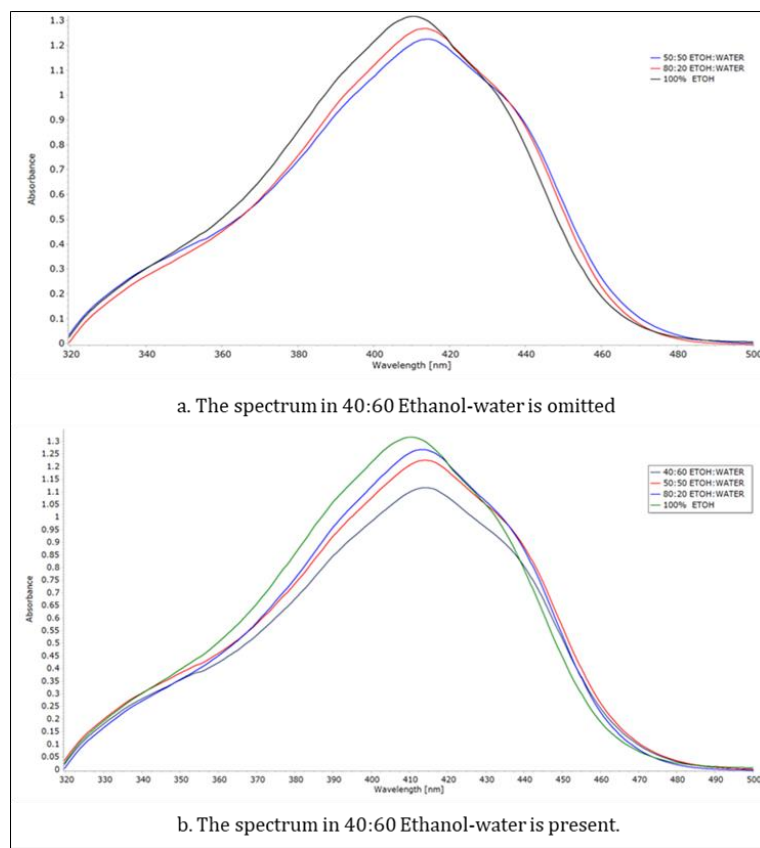


Figure 3S UV spectra of trimethoxycurcumin, R_1 and $R_3 = \text{CH}_3$, $R_2 = \text{H}$ (OMe5). Solvent EtOH with water added

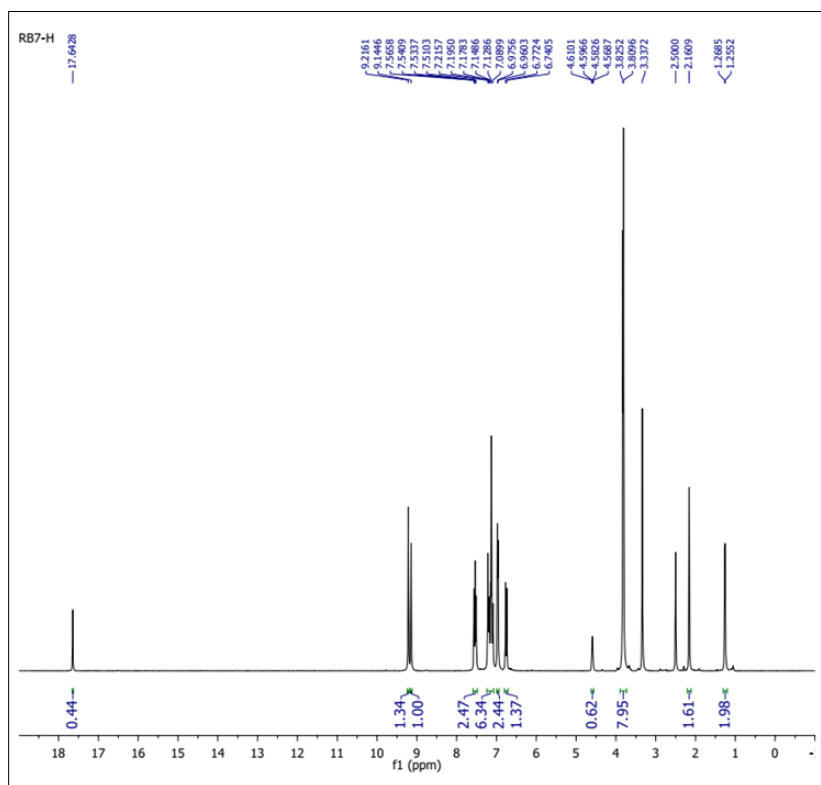


Figure 4S ^1H NMR spectrum of α -methylisocurcumin

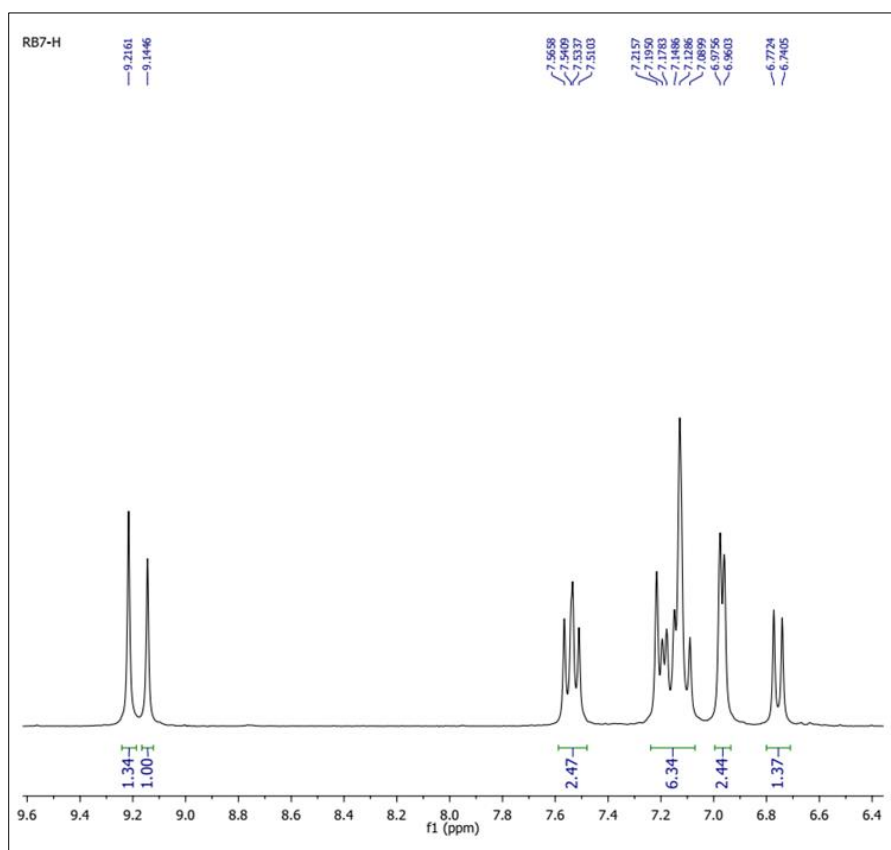


Figure 5S Expansion of ^1H NMR spectrum of α -methylisocurcumin

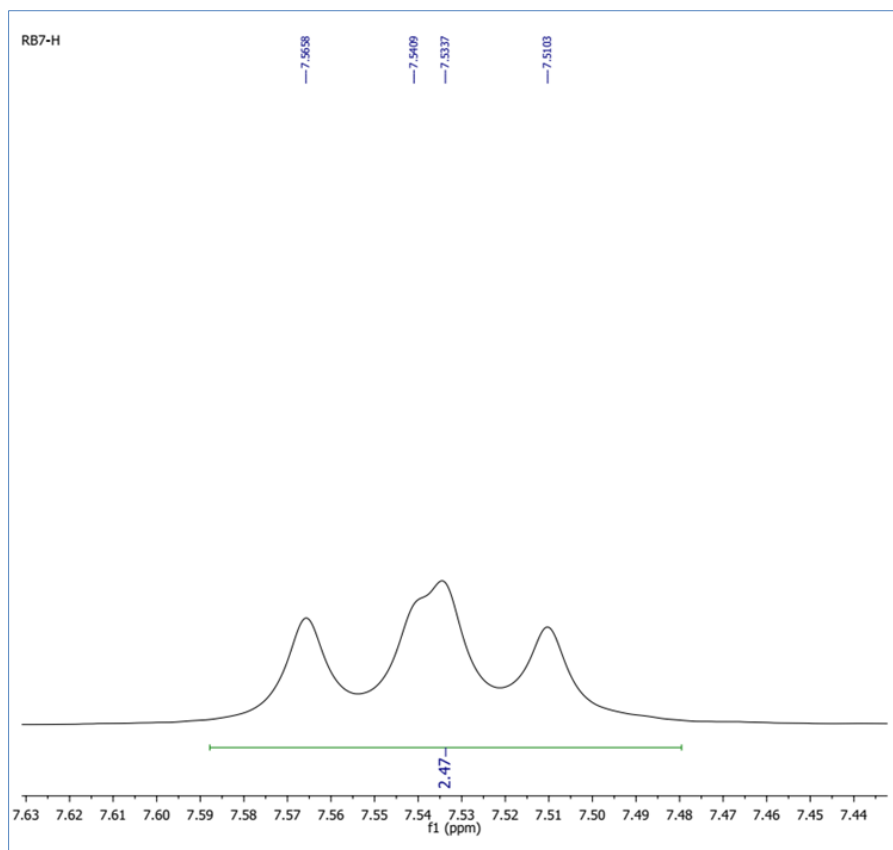


Figure 6S Expansion of ^1H NMR spectrum of α -methylisocurcumin

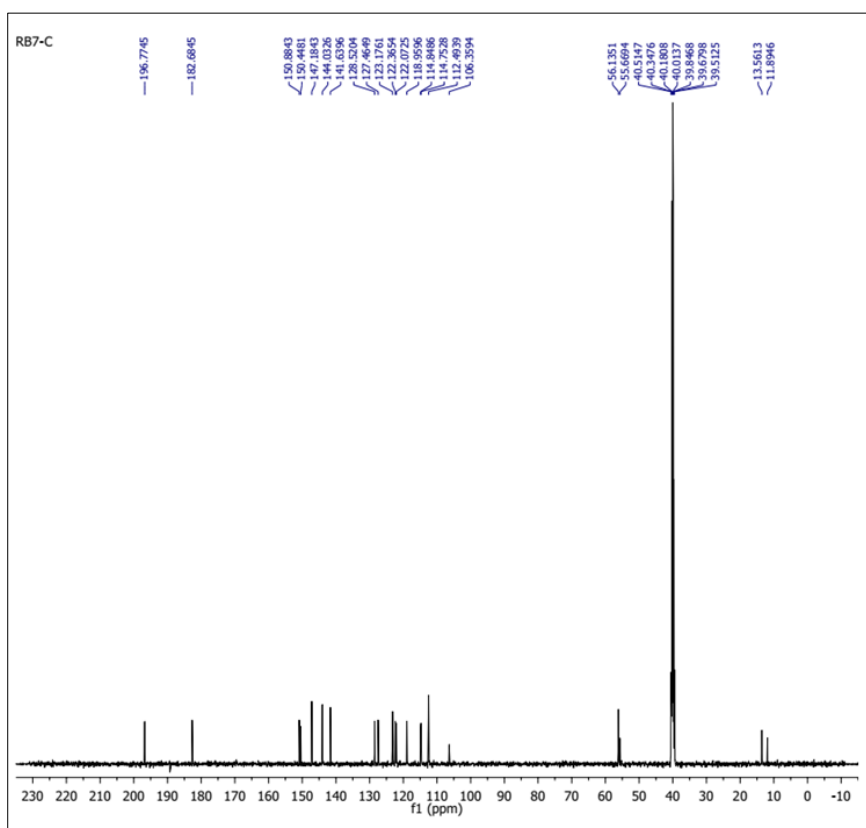


Figure 7S ^{13}C NMR spectrum of α -methylisocurcumin

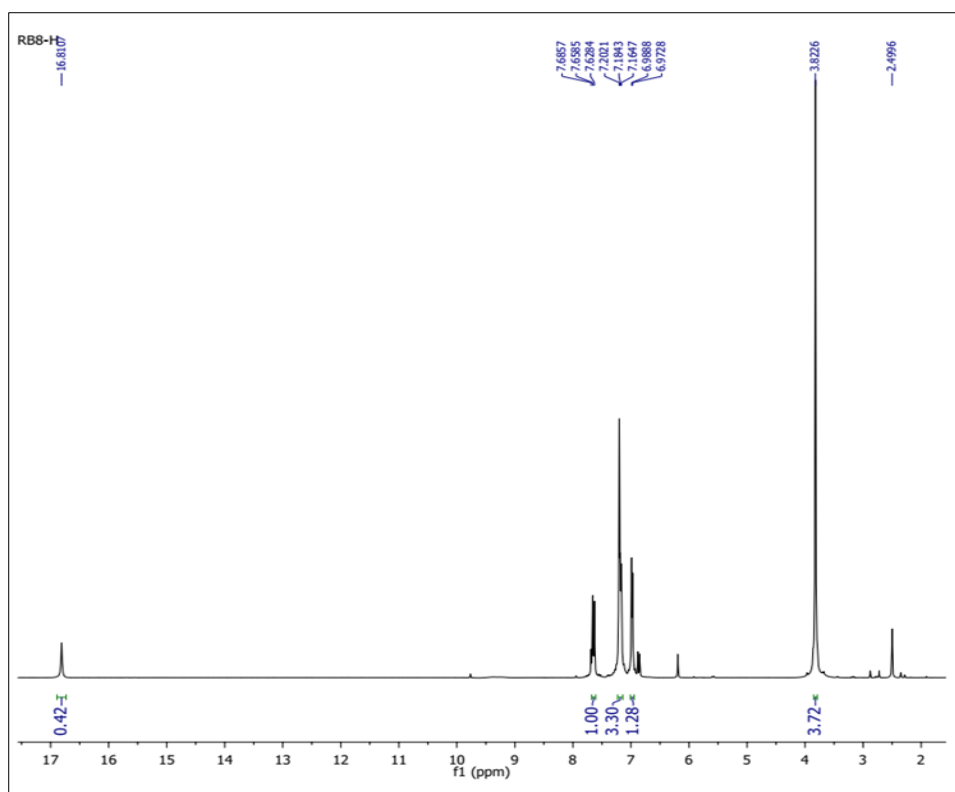


Figure 8S The ^1H NMR spectrum of α -chloroisocurcumin

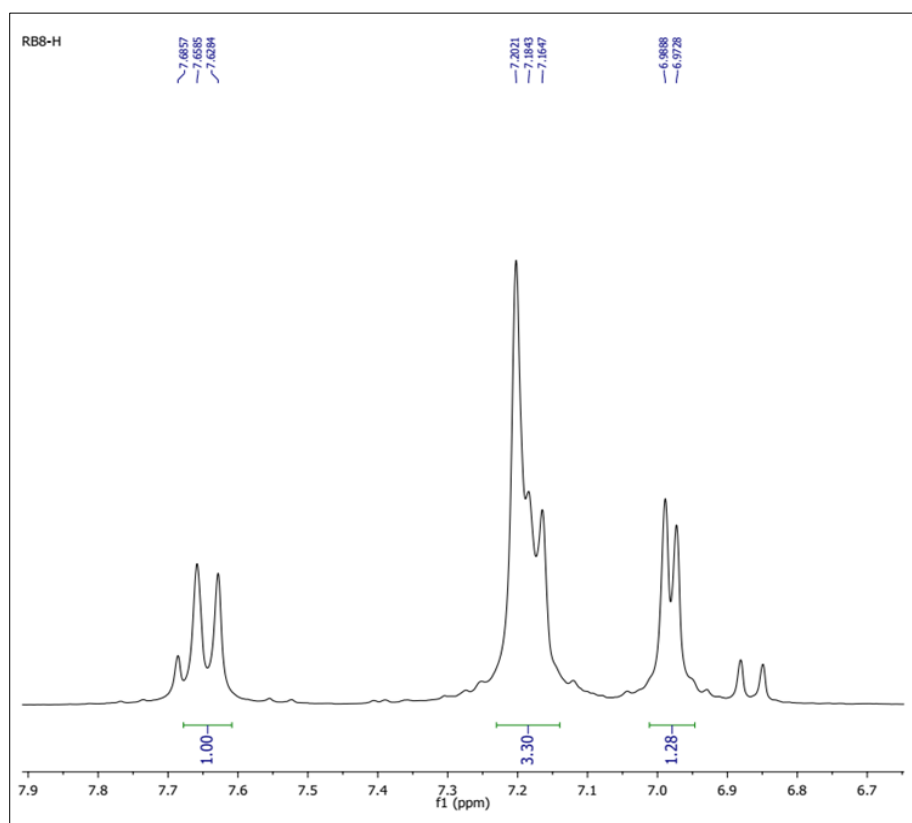


Figure 9S Expansion of ^1H NMR spectrum of α -chloroisocurcumin

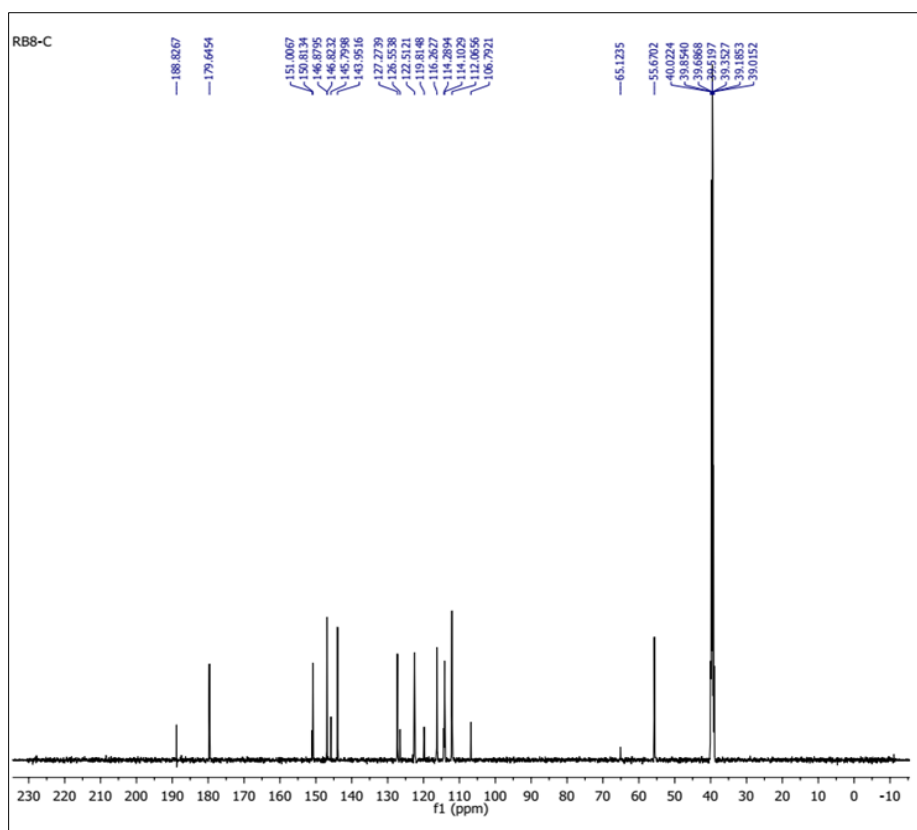


Figure 10S The ^{13}C NMR spectrum of α -chloroisocurcumin

Table S1 Spectroscopic characteristics of curcumin in different solvents

phase	λ_{max} (nm)	absorbance	λ (Shoulder)	absorbance
100% ethanol	411	1.317	355	0.443
80:20 Ethanol-water	413	1.268	355	0.398
50:50 Ethanol-water	413	1.22	355	0.42
40:60 Ethanol-water	413	1.12	355	0.39